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Early Recurrences in Malignant Gliomas - Controversies and Consensus

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Introduction

Malignant gliomas, encompassing the continuum of higher-grade gliomas (WHO Grade 3) and WHO Grade 4 lesions (IDH-mutant astrocytomas and glioblastomas), continue to represent a formidable challenge in neuro-oncology due to their aggressive nature and dismal prognosis. For instance, the current standard of care with safe maximal resection followed by concurrent chemoradiation with temozolomide and subsequent adjuvant chemotherapy, yields a median overall survival (OS) of approximately 15 months and a median progression-free survival (PFS) of around 7 months for glioblastoma (GBM), the most prevalent and lethal subtype.[1,2] Thus, the quest for effective management strategies is both urgent and compelling.

The treatment landscape for early recurrences of malignant gliomas (MGs) is as complex as it is controversial. There is no established consensus on the optimal treatment approach for early recurrences of malignant gliomas, and multiple therapeutic modalities are actively being explored in clinical trials, as standalone interventions and in combination.[3,4] Broadly, these strategies can be categorized into "conventional" and "novel" therapeutic approaches. Conventional treatments include re-resection, chemotherapy, and re-irradiation. Re-resection, when feasible, has demonstrated significant survival benefits in appropriately selected patients, while chemotherapy with agents such as lomustine and temozolomide has been associated with improved overall survival (OS).[5,6] Additionally, re-irradiation via fractionated stereotactic radiotherapy (SRT) or stereotactic radiosurgery (SRS), has shown promise in prolonging progression-free survival (PFS) in select cases.[7]

In parallel, the advent of novel therapeutic modalities has stimulated hopes of achieving improved survival in these patients. Immunotherapeutic strategies, including immune checkpoint inhibitors (e.g., pembrolizumab, nivolumab), monoclonal antibodies (e.g., bevacizumab, cetuximab), and dendritic cell vaccines are some of the therapies currently under investigation.[8-10] Furthermore, approaches such as oncolytic virotherapy, adoptive cell transfer (CAR-T cell therapy), laser interstitial thermal therapy (LITT), tumour treating fields (TTF), and focused ultrasound (FUS) offer promising avenues for intervention.[10-13] Notably, early-phase clinical trials employing immunotherapy have generated compelling preliminary data, positioning it as a potentially transformative modality despite the modest improvements in OS and PFS observed to date.[14] The heterogeneous nature of glioblastoma recurrences - marked by diverse genetic aberrations, variable expression of molecular markers, and differences in the timing and location of lesions - presents a significant barrier to the development of universally effective treatments. As such, enrolment in clinical trials, when possible, is a cornerstone of management, facilitating the evaluation of personalised therapeutic regimens and the integration of multimodal strategies.[15]

In this review, we aim to highlight the progress and ongoing innovation that continue to shape the landscape of recurrent malignant glioma treatment, while maintaining a cautiously optimistic outlook about the future direction.

Recurrence Timing and Patterns

The pattern and timing of GBM and IDH-mutant WHO grade 4 astrocytoma recurrences (collectively referred to as Grade 4 gliomas – G4Gs) can vary widely and are insufficiently characterised, despite an extensive body of literature. While the majority of studies have emphasised spatial aspects of recurrence, particularly the predominance of local failures within or adjacent to the surgical or radiation field, recurrence as a temporal phenomenon has received comparatively limited attention. It is generally observed that local recurrences which occur more often, also tend to arise much earlier than distant ones; however, the associations between recurrence patterns and treatment modalities, tumour biology, or patient-specific factors remain inconsistent across studies.[16]

Temozolomide (TMZ)-based chemoradiotherapy has been shown to prolong OS, and most patients undergoing this regimen experience local rather than distant failure. Notably, patients with local recurrence tend to exhibit shorter PFS than those with distant recurrence. Paradoxically, patients with distant failure often have shorter OS, suggesting distinct temporal and biological underpinnings. Patients experiencing both

local and distant recurrences demonstrate intermediate PFS but the poorest OS outcomes, highlighting the complexity of recurrence dynamics.[17-21]

Moreover, O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, which is associated with higher responsiveness to TMZ, has been linked to a higher incidence of distant recurrence, adding another layer of nuance to recurrence characterization.[16,22] These apparent contradictions may in part be attributed to the reliance on PFS, which, while widely used, remains a coarse measure of disease dynamics.[16,19] Further complicating the picture are methodological limitations, including retrospective study designs, small cohort sizes, and the absence of standardised inclusion criteria.

The Response Assessment in Neuro-Oncology (RANO) criteria and its updates have improved diagnostic consistency by establishing objective thresholds for defining progression, but even within this framework, recurrence is typically described in terms of *location*.[23,24] A time-based framework could provide a valuable orthogonal dimension for characterising disease progression in a typically underrepresented cohort of patients. For example, patients who recur during or shortly after treatment may harbour intrinsically aggressive tumours or lesions that are primarily resistant to treatment. Similarly, patients who have longer times to progression may represent a fundamentally different disease entity characterised by biologically indolent subtypes or may reflect transformation during treatment owing to selection pressure.[25,26]

Although local recurrences are more frequent, distant failures, representing approximately 10–20% of cases, may occur later and are often underrepresented in PFS-centric analyses. Compounding this, patients may exhibit multifocal recurrences - local and distant - over time, further challenging traditional categorisation schemes.[18,21] However, the median PFS (mPFS), typically around 6.8-7.2 months in Stupp-era cohorts, offers a useful population-level reference and can serve as a cut-point to define early versus late recurrence.[2] Such dichotomisation enables stratification of patients not only by recurrence *location* but also by *timing*, allowing assessment of whether early versus late recurrences correlate with specific biological or treatment-related factors. Importantly, mPFS itself reflects cumulative treatment efficacy and patient heterogeneity; thus, its value is modifiable based on advancements in therapy. Incorporating recurrence timing into standard reporting practices may enhance prognostic modelling and guide therapeutic decision-making.

Diagnosis

Overview and recommendations

The current standard of care for diagnosing glioma recurrence involves serial contrast-enhanced magnetic resonance imaging (MRI).[27] Early recurrence, defined as recurrence occurring within 6–7 months of initial treatment, presents a frequent clinical challenge due to the limited ability of conventional anatomical MRI to distinguish true tumour progression from treatment-related effects, particularly pseudoprogression.[28] This diagnostic ambiguity can result in either over-treatment or under-treatment, raising important considerations regarding the optimal frequency of imaging. Consequently, the utility of advanced imaging modalities capable of accurately identifying early recurrences assumes significant clinical importance.

Immediate postoperative MRI, usually obtained within 48 hours after surgery, is used by most centres to evaluate the extent of resection and post-surgical changes. The first MRI performed following the completion of radiation therapy usually serves as the baseline post-treatment scan, since there is less likelihood of post-surgical changes being misinterpreted as residual or recurrent disease.[29] For *diagnosis* of recurrence, anatomical MRI supplemented with perfusion-weighted imaging sequences and/or positron emission tomography (PET) combined with CT or MRI (PET-CT or PET-MRI) is recommended.[27]

Evidence suggests that a follow-up MRI performed three months after the baseline post-treatment scan would provide optimal diagnostic value for identifying progression. If progression or recurrence is suspected earlier, treatment is typically continued, and an additional MRI is obtained at an interval of 4 or 8 weeks to confirm disease progression

or recurrence.[29] PET/CT hybrid imaging should be acquired at the same intervals as MRI scans, if available.[5] Following the 2021 revision of the WHO classification of CNS tumours, unified diagnostic guidelines have been established for both high-grade gliomas (HGG) and low-grade gliomas (LGG).[27]

Despite the availability of various advanced imaging techniques and modalities, each with distinct advantages and limitations (***Table 1***), clear consensus on the most appropriate modality for identifying early recurrence is lacking. Histopathological examination remains the gold standard for definitive diagnosis, and clinical decision-making should be guided by a patient-specific, individualised approach.[27]

Modalities of imaging

Baseline MRI

Immediate postoperative MRI is valuable for identifying surgical complications, including subacute ischemia, which may demonstrate contrast enhancement, and for estimating the extent of resection. To minimize confounding enhancement due to post-surgical changes, the scan should be performed within 48 hours of surgery, since postoperative changes typically begin to appear 48–72 hours postoperatively.[27,28]

Post-radiotherapy MRI can serve as the baseline scan in cases where the extent of resection is deemed adequate, the likelihood of recurrence prior to radiotherapy is low, and post-surgical complications are minimal. Follow-up MRI is recommended three months after the completion of high-dose radiotherapy. Importantly, studies have shown no survival benefit in patients undergoing imaging within the first three months post-radiotherapy.[27]

Recurrence evaluation

New contrast enhancement in the follow up MRI is suggestive of disease recurrence especially if it occurs outside the RT field or shows features like crossing the midline, callosal involvement or ependymal involvement. However, differentiating new tumour enhancement from pseudoprogression and radiation necrosis could still be a difficult task.

Pseudoprogression is apparent radiological progression without underlying disease resulting in spontaneous reversal or improvement without any intervention. Following adjuvant radiation and chemotherapy, areas of enhancement can occur and increase in size especially during the first 3-6 months after radiotherapy. The likely pathophysiology is increased vascular permeability following endothelial injury and upregulation of vascular endothelial growth factor (VEGF). MGMT methylation in gliomas is associated with increased occurrence of pseudoprogression and patients with MGMT promoter methylated lesions achieve superior outcomes. Radiation necrosis occurs notably later after radiation therapy, and is generally noted about 9-12 months after therapy. The pathophysiology is due to oligodendrocyte injury leading to fibrinoid necrosis, reactive gliosis and vascular hyalinisation. Radiation necrosis occurs in areas with lower vascular supply, such as periventricular white matter or adjacent to a radiation field. Conventional MRI would show a Swiss-cheese pattern of internal enhancement or peripheral enhancement with feathery margins.[28,30]

MRI

Advanced MR imaging techniques can facilitate the detection of increased cellular proliferation and vascular permeability, aiding in the identification of disease progression with above-average diagnostic accuracy.[6]

Perfusion MRI techniques, including dynamic susceptibility contrast (DSC), dynamic contrast-enhanced (DCE), and arterial spin labelling (ASL), provide essential data on tumour vascularity and angiogenesis. DSC measures relative cerebral blood volume (rCBV), aiding differentiation between viable tumour tissue and radiation necrosis. DCE quantifies capillary permeability (ktrans), allowing assessment of blood-brain barrier (BBB) integrity. ASL offers non-invasive cerebral blood flow (CBF) quantification without exogenous contrast, improving the distinction between tumour recurrence and pseudoprogression.[31]

Diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI) evaluate tumour cellularity and white matter tract integrity. Apparent diffusion coefficient (ADC) mapping

Table 1: Summary of imaging modalities for diagnosing recurrent GBM[223-226]

Modality	Mechanism	Parameters & advantage	Disadvantage
T1 weighted	Magnetic resonance	Anatomical tissue and tumour visualization	Difficulty in differentiating radiation necrosis and recurrence
T2/T2 FLAIR	Magnetic resonance	Anatomical tissue and tumour visualization • Hyperintensity on T2/FLAIR extending beyond the radiation field, involvement of the corpus callosum, signal that crosses midline, and subependymal involvement	Difficulty in differentiating radiation necrosis and recurrence Perilesional edema, gliosis and non enhancing tumour are hyperintense
DWI	Brownian motion of water molecules	Apparent diffusion coefficient maps show restricted diffusion in recurrence due to increased cellular density	Tumour heterogenicity and necrosis can alter ADC map findings
MR Spectroscopy (MRS)	Biochemical composition of areas of interest	High Choline peak, high Choline/Creatine and Choline/N-acetyl aspartate ratios suggests recurrence	Large lesion required within the voxel and less technical standardization
MR PERFUSION IMAGING			
Dynamic Susceptibility Contrast (DSC)	Measurement of temporary decrease in brain signal intensity in T2 post contrast imaging	rCBV (relative cerebral blood volume) - angiogenesis marker, helps in differentiating recurrence (increased perfusion) and post treatment changes	User dependent variability due to extraction of arterial input function required for rCBV calculation
Dynamic contrast enhanced (DCE)	Measurement of dynamic signal changes post contrast in T1 weighted imaging	Rate of capillary permeability, helps in differentiating recurrence (increased perfusion) and post treatment changes	Technically challenging
Arterial spin labelling (ASL)	Inverting the magnetization of water protons in blood	Cerebral blood flow (without exogenous contrast)	Low signal to noise ratio Unavailability of standardization
NUCLEAR MEDICINE IMAGING			
^{18}F-FET PET (FET – Fluoroethyltyrosine)	Taken up by tumour cells via L-transporters (amino acid transporters upregulated in tumour)	Raised tumour to background ratio (TBRmax) Metabolic tumour volume measured by areas showing SUV >1.6-1.8 of the mean value of healthy appearing brain	Due to disruption in blood brain barrier in post treatment regions the tracer uptake can increase in the areas of post treatment related changes and overlap with the tumour (especially during first 6 months after high dose radiotherapy) Increased uptake in infarcts up to 7 days and in hematoma up to 14 days after the occurrence Availability Slow renal elimination

Contd...

Table 1: Contd...

Modality	Mechanism	Parameters & advantage	Disadvantage
^{11}C-MET PET (MET – Methionine)	Taken up by tumour cells via L-transporters (amino acid transporters upregulated in tumour)	Raised tumour to background ratio (TBR) Metabolic tumour volume measured by areas showing SUV >13 of the mean value of healthy appearing brain	Increased uptake in hematoma up to 45 days after the occurrence. Availability Short half life
^{201}Tl SPECT Thallium Single positron emission computed tomography	Uptake via Na + -K + ATPase pump and blood brain barrier disruption in tumour leading to increased uptake • Gomez rio	Raised tumour to background ratio	Low spatial resolution and image quality Availability
^{18}F-FDG PET (FDG – Fluorodeoxyglucose)	Uptake via GLUT due to increased glucose metabolism in tumour cells	Increased uptake in the tumour	Raised background physiological activity
^{18}F-FDOPA PET (FDOPA-Fluorodopa)	Uptake via L-transporters (amino acid transporters upregulated in tumour) and dopamine reuptake transporter	Raised tumour to striatum ratio	Increased uptake in the striatum
NEWER IMAGING MODALITIES			
^{18}F-FLT (FLT – Fluorothymidine)	Uptake via nucleoside transporter (indicator of cellular proliferation)	Raised tumour to background ratio	Not standardized Cannot cross intact BBB
Treatment response assessment maps (TRAM)	Delayed contrast MRI to assess delayed contrast washout in tumour	>20% ratio of the wash-out volume to the sum of wash-out and wash-in volumes	Not standardized
Intravoxel incoherent motion (IVIM)	Acquires details on perfusion and diffusion of water molecules	Increased perfusion in the tumour	Not standardized
APT-CEST (Amide proton transfer - Chemical exchange saturation transfer)	Exchange of magnetization between liable protons in amide and surrounding water molecule	Higher spatial resolution than MRS in identifying compounds	Multiple compounds cannot be assessed
^{18}F-RGD (RGD – Arginine-Glycine-Aspartic acid)	Binds to $\alpha_v\beta_3$ integrin	Identification of areas of angiogenesis	Not standardized

helps differentiate highly cellular tumours from treatment-related edema. DTI provides fractional anisotropy (FA) data, which assists in surgical navigation by mapping fibre tracts near infiltrative tumour margins.

Susceptibility-Weighted Imaging offers high sensitivity to paramagnetic substances such as deoxyhaemoglobin and hemosiderin, enabling the identification of microhaemorrhages and calcifications associated with glioblastoma progression. This modality is particularly useful in assessing post-treatment effects, such as radiation necrosis.[31]

Magnetic resonance Spectroscopy (MRS) facilitates non-invasive tumour metabolic profiling. Elevated choline (Cho) and reduced N-acetylaspartate (NAA)levels indicate increased membrane turnover and neuronal loss in high-grade gliomas. Advanced MRS techniques can quantify 2-hydroxyglutarate (2-HG), a metabolic marker for IDH-mutant gliomas.[31]

Treatment Response Assessment Maps (TRAMs) are an advanced MRI technique designed to differentiate recurrent glioblastoma from radiation necrosis. TRAM MRI utilizes two contrast-enhanced T1-weighted sequences to assess contrast wash-in and wash-out dynamics, providing valuable insights into tumour viability. Vital tumour cells exhibit rapid contrast wash-out due to their high turnover rate and hypervascularization, whereas radiation necrosis shows gradual contrast accumulation. Studies indicate that a wash-out volume ratio exceeding 20% strongly correlates with recurrent glioblastoma. TRAM MRI enhances diagnostic reliability, particularly in cases where conventional imaging struggles to distinguish between tumour progression and post-treatment effects. Robust correlation has been demonstrated between contrast clearance and pathology in terms of radiation change versus recurrent tumour.[32,33]

Integration of Dynamic Contrast-Enhanced (DCE) MRI

DCE MRI complements TRAM MRI by providing quantitative measures of tumour vascular permeability and microcirculation.[34] This technique relies on T1-weighted imaging acquired dynamically after contrast administration, allowing for the calculation of kinetic parameters such as:

- Ktrans (volume transfer constant): Reflects the rate at which contrast agent moves from blood plasma into the extracellular extravascular space (EES), serving as a marker of BBB integrity and tumour angiogenesis.
- Ve (extracellular extravascular volume fraction): Indicates the proportion of tissue occupied by the EES, helping to assess tumour heterogeneity.
- Vp (plasma volume fraction): Represents the fraction of tissue occupied by blood plasma, aiding in the differentiation of high-grade gliomas from low-grade tumours.

Tracer kinetic models are essential for analysing dynamic contrast-enhanced (DCE) MRI data in glioma imaging. These models quantify contrast agent kinetics, providing insights into tumour vascular permeability, microcirculation, and blood-brain barrier (BBB) integrity. The most commonly used models include the Tofts model and Brix's Two-Compartment Model.

PET

Positron emission tomography (PET) demonstrates comparable diagnostic performance to advanced MRI (***Table 2***), although it relies on distinct molecular mechanisms, as outlined in Table 1.[35,36] Among the various advanced modalities, perfusion MRI is widely utilised due to its greater accessibility and superior anatomical resolution.

Table 2: Pooled sensitivity and specificity of imaging modalities with 95% CI shown in meta-analyses done recently[36,38]

Modality	Sensitivity	Specificity
CE-MRI	48-68%	77-85%
DSC	87-90%	85-88%
DCE	89-92%	85%
DWI	60-80%	77-93%
Cho/NAA of MRS	81-93%	76-93%
Cho/Cr of MRS	77-89%	74-90%
^{18}F-FET PET	75-90%	67-88%
^{11}C-MET PET	78-95%	25-95%
^{18}F-DOPA PET	86-98%	58-90%
^{18}F-FDG PET	80-94%	65-87%

Amino Acid PET Tracers

Amino acid PET tracers, such as 18F-FET and 18F-DOPA, are widely used for glioma imaging due to their ability to highlight increased amino acid transport in tumour cells. The study by Lapa *et al*. compared 18F-FET and 18F-DOPA in high-grade glioma (HGG) patients, demonstrating that both tracers provide comparable tumour delineation.[37] While 18F-FET exhibited higher SUVmean and SUVmax values than 18F-DOPA, visual analysis revealed no significant differences in uptake patterns. 18F-DOPA, despite its uptake in the basal ganglia, did not compromise tumour visualization, making both tracers viable options for glioma imaging.

Glucose Metabolism PET

18F-FDG PET, which measures glucose metabolism, was historically used for brain tumour imaging but has limitations due to high cortical uptake, making tumour-background differentiation challenging. Newer amino acid tracers, such as 11C-MET, 18F-FET, and 18F-DOPA, have largely replaced 18F-FDG for glioma imaging due to their superior tumour specificity.

Hypoxia and Proliferation PET

Hypoxia-targeted PET tracers, such as 18F-FMISO, provide prognostic data by identifying hypoxic tumour regions associated with aggressive glioblastoma behaviour. Additionally, 18F-FLT PET, which targets thymidine metabolism, serves as a marker for cellular proliferation, aiding in glioma grading and treatment response assessment.[37]

Emerging PET Tracers and Theranostics

Recent advancements in PET imaging include PSMA-targeted PET, fibroblast activation protein inhibitor (FAPI) PET, and translocator protein (TSPO) PET, which offer novel approaches for glioma characterization. These tracers provide insights into tumour microenvironment interactions, immune response, and potential therapeutic targets. Additionally, ligands used in molecular imaging with specific radionuclides can be conjugated with beta-emitting isotopes such as ^{90}Y and ^{177}Lu, forming the basis of a theranostic strategy. This approach has been explored in select cases and represents a novel avenue in the management of glioma recurrence. However, it remains limited by challenges in clinical trial implementation.[38]

Radiomics enables the extraction and analysis of quantitative parameters from imaging across various modalities, allowing the identification of features that significantly correlate with tumour recurrence, improving diagnostic accuracy. The application of radiomics in distinguishing post-treatment changes from true recurrence is an area of active research and has shown promising results.[39] Moreover, radiomics can provide insights into tumour heterogeneity and, when integrated with tumour genomics, may support more personalised clinical decision-making.[40]

Management

Re-resection

It is well established that the extent of surgical resection correlates positively with survival in MGs.[41-43] However, unlike first-line treatment, the role of radical resection in recurrent MGs is poorly defined and cannot be considered as standard practice.[44] Various studies suggest that only 20-30% of patients with recurrent glioblastoma are suitable candidates for repeated resection.[4,45,46] This relatively small percentage, compared to primary disease, is explained by multiple factors which contribute to higher surgery related morbidity including, but not limited to, deterioration in Karnofsky Performance Status (KPS) with disease progression. Tissue changes induced by adjuvant therapy make re-resection and wound healing challenging, and recurrence often occurs in proximity to eloquent areas which form the margin of a prior maximal safe resection, increasing the chances of neurological injury from a second surgery.[47,48]

The National Comprehensive Cancer Network (NCCN) guidelines indicate that a second surgery can be considered for local recurrence in malignant gliomas (level 2A evidence), but a consensus on how to select patients has not been established.[49] The key objective of the decision-making process should be to improve quality of life and overall survival. Various scales have been designed in an attempt to standardise selection of surgical

candidates in recurrent MGs. Park *et al*. developed a three-tier scale composed of additive scores for KPS and ependymal involvement, which stratified patients into groups with good (median survival 18 months), intermediate (median survival 10 months) and poor prognosis (median survival 4 months).[50] Similarly, the National Institutes of Health (NIH) recurrent glioma scale uses KPS, tumour involvement of prespecified eloquent/critical brain regions and tumour volume as variables to identify patients with good, intermediate and poor prognoses.[51] To summarise, the major factors which influence patient selection for a second surgery are as follows:

- KPS: Patients with a Karnofsky Performance Status (KPS) ≥70 are more likely to benefit from reoperation.[51,52]
- Age: Overall survival is longer in patients who are younger at the time of diagnosis.[53-55]
- Interval since initial surgery: A longer interval between initial surgery and recurrence may indicate more indolent tumour biology, potentially favouring re-resection. Patients with early recurrence have a greater risk of death than patients with prolonged PFS.[56]
- Tumour location: Lesions in non-eloquent brain regions are more amenable to surgical resection with lower risk of functional deficits.
- Extent of resection achievable: Gross total resection is associated with better outcomes compared to subtotal resection.

The effect of surgery on OS in recurrent MGs, though largely positive, is not conclusive. Robin *et al*. published a comprehensive literature review that included 33 studies evaluating the benefit of surgery on OS at progression after first line management using the Stupp protocol.[57] Most of them showed a positive impact on the OS after re-operation, with an estimated median OS of 9.9 months. In contrast, Sastry *et al*. reviewed a cohort of 368 patients and concluded that after accounting for potentially confounding factors, the benefit of resection in recurrent glioblastoma is not statistically significant.[58] The ongoing RESURGE study aims to compare survival outcome after surgery followed by adjuvant second-line therapy to no surgery followed by second-line therapy in recurrent glioblastoma. Nevertheless, the primary goals of re-resection extend beyond the prolongation of OS and include:

- Cytoreduction: Reducing tumour burden to enhance the efficacy of adjuvant therapies.[59,60]
- Symptom Relief: Alleviating mass effect and reducing intracranial pressure.
- Diagnostics: Obtaining tissue for histopathological and molecular analyses, which may differ from the initial tumour and influence subsequent treatment decisions.[61]

As mentioned previously, re-operation poses significant technical challenges due to changes in tissue characteristics, difficulty in delineating normal versus infiltrated tissue and proximity to eloquent areas. The use of technical adjuncts such as intraoperative neuromonitoring, fluorescence guided resection and intraoperative imaging have been shown to aid in achieving safer resection.[62-65] In addition, the implantation of carmustine wafers has also been shown to extend OS in recurrent MGs.[66] To conclude, re-operation may be considered for recurrent MGs, but its usefulness is significantly constrained due to the high risk of complications and mortality. This necessitates an open and clear discussion with the patient before proceeding with surgery.

Re-irradiation

Nearly all patients with grade 3-4 gliomas, and most grade 2 gliomas receive radiotherapy with or without chemotherapy as part of postoperative adjuvant management. A proportion of these patients may need re-irradiation (re-RT) at recurrence, either as the sole local therapy or after re-resection. Although re-RT has been used for recurrent malignant brain tumours since more than half a century, there is widespread variability in its practice.[67] The volume and location of brain tissue to be included in the re-RT treatment volume becomes the main determinant of safe delivery of re-RT, besides other critical neurological structures. Radiobiological experiments suggest a time-dependent tissue recovery (25% at 6 months and 50% at 1-2 years) after the first course of radiotherapy.[68,69]

The decision to offer re-RT should be made after a multidisciplinary tumour board (MDT) discussion considering patient (age, performance status), disease (histology at recurrence, expected prognosis, time from prior irradiation) and treatment (prior therapies, available systemic and local therapy options) factors.[7] Generally, only patients with a KPS of 70 or above and those with preserved neurologic status after

surgery would be considered for re-RT with radical intent.[6,70] An interval of 6-12 months from prior radiotherapy is necessary to allow the radiobiological recovery of normal neurological tissues.[71] Leptomeningeal disease, large lesions (>5-6 cm diameter) and multifocal lesions are not traditionally considered appropriate for re-RT.[72] Re-RT is most appropriate for small volume recurrences that can be treated with radiation fields that have minimum overlap with the initial radiation portals. Appropriate patient selection for Re-RT might improve local control without deterioration of neurological function and neuro-cognition as evidenced by small prospective studies with conventional and hypo-fractionation.[73,74] Patients with large recurrences and diffuse disease usually cannot be treated safely with the appropriate dose needed for local control and hence are not good candidates for re-RT. In-field recurrences and recurrences occurring within 6 months of radiotherapy suggest an inherently radioresistant disease that would not benefit from re-RT.[75,76] Only about 15% of recurrences may be candidates for re-RT based on these factors. Online calculators (re-RT risk score) that estimate survival after re-RT based on initial histology, performance status and age may aid decision-making.[70]

Most evidence supporting re-RT is retrospective, and systematic reviews suggest a median OS of 6-12 months after re-RT. Re-RT alone improves local control and PFS but not OS. Additional systemic therapeutic options (bevacizumab, chemotherapy, APG101) with re-RT have been evaluated in multiple prospective randomised studies; these also improve local control and PFS but not OS (Table 3).[69,73,77,78]

Various radiotherapy techniques and fractionation schema have been used. No direct robust comparisons between techniques exist but it is accepted that small volume recurrences do well with extreme or moderate hypofractionation (stereotactic radiosurgery (SRS) or fractionated stereotactic radiation therapy (FSRT)) while larger volumes tolerate conventional fractionation better with similar outcomes. Brachytherapy addressing re-resection cavity with I-125 (Gliasite), Cs-131 and Ir-192 has demonstrated improved local control in small studies.[81] Particle therapy (proton beam therapy, carbon ions) has also been used to minimise collateral damage to surrounding normal structures.[82,83]

Unlike primary radiotherapy where large margins of 1.5-2 cm are given to MRI-identified tumour or tumour bed (gross tumour volume, GTV) for dose prescription, re-RT volumes address only the residual tumour with a small margin for microscopic disease (clinical

Table 3: Summary of evidence for the clinical benefit of Reirradiation

Author (Year)	Type of evidence	Arms and intervention	RT dose	Outcome
Kazmi *et al* (2019)[79]	Meta-analysis	50 studies involving 2095 patients of recurrent GBM	Variable	OS at 6 and 12 months – 73% and 36% PFS at 6 and 12 months- 43% and 17%
Marwah *et al* (2023)[80]	Meta-analysis	31 studies involving 2084 patients of recurrent HGG – Re-RT vs systemic therapy vs Combination therapy	Variable	Combination therapy improved outcomes compared to Re-RT or systemic therapy alone
Bergman *et al*.[78]	Phase 2 Randomised study	*n*=35 FSRS + Bevacizumab vs FSRS + Chemotherapy in Bevacizumab resistant HGG	32 Gy in 4 fractions over 2 weeks	Median PFS better with chemotherapy=51. Vs 1.8 months Local control – 82% vs 27% OS Similar
Tsien *et al*.[7]	Phase 2 Randomised trial	*n*=182 Re-RT + Bevacizumab vs Re-RT alone in recurrent HGG	35 Gy in 10 fractions over 2 weeks	Median PFS – 7.1 vs 3.8 months in favour of bevacizumab OS similar
Wick *et al*.[73]	Phase 2 Randomised study	*n*=91 Re-RT + APG 101 vs Re-Rt alone in recurrent glioblastoma	36 Gy in 18 fractions over 3 ½ weeks	Median PFS – 4.5 vs 2.5 months in favour of APG 101 OS similar

target volume, 0-5 mm) and set up errors (planning target volume, 1-5 mm) depending on the technique used.[69,73,78] While delineating the GTV, additional MRI sequences (DWI, DCE) or other metabolic imaging modalities such as amino acid PET (AA-PET) may help distinguish tumour from post-treatment changes.[84]

Doses vary with techniques used (18-20 Gy in a single fraction with SRS, 32 Gy in 4 fractions or 35 Gy in 10 fractions with FSRT, or 36-50 Gy in 18-28 fractions with conventional fractionation).[70,71,85,86] Consensus recommendations have indicated preference for moderate hypofractionation owing to fair patient tolerance even amongst moderate to large sized lesions.[72] The decision regarding the dose fractionation and technique to be used must be made after cumulative equivalent dose in 2Gy fractions(EQD2) recalculation taking into account the possible recovery especially for critical organs at risk (OARs) such as the brainstem, spinal cord and optic neural structures.[87] Dose accumulation tools are now available that provide cumulative doses for OARs after deformable registration of radiotherapy plans.[88,89]

Stereotactic radiation techniques

Stereotactic radiosurgery (SRS) has gained traction as a salvage treatment for recurrent high-grade gliomas, offering a high-dose, focal irradiation approach that minimizes exposure to surrounding healthy tissue.[90] In SRS for recurrent high-grade gliomas, no margins would be involved – focal treatment to either enhancing areas of recurrent disease or proven FLAIR areas of tumour would be treated in a conformal fashion. Retrospective analyses indicate that SRS provides median overall survival (OS) of approximately 12.2 months post-reirradiation, with local progression-free survival (PFS) rates of 65.8% at six months.[91] Gamma Knife SRS has demonstrated efficacy in select cohorts, with local failure rates of 79.5%, predominantly in-field (53.1%) and marginal (45.1%), reinforcing the need for precise target delineation. The use of PET fused with anatomic imaging such as MRI and techniques such as TRAM, enhance the precision of SRS treatments.

Recent studies have explored the integration of systemic therapies with SRS, particularly the use of bevacizumab, which has been associated with improved PFS (HR 0.46) and OS (HR 0.42), while significantly reducing the incidence of radiation necrosis (RR 0.17).[92,93] Moreover, patients treated with a combination of bevacizumab and Gamma Knife SRS demonstrated longer post-recurrence PFS (7.7 months) and OS (11.5 months) compared with patients who received either bevacizumab or Gamma Knife as monotherapy.[94]

Additionally, fractionated stereotactic radiotherapy (FSRT) has been investigated as an alternative to single-session SRS, demonstrating comparable tumour control rates with potentially reduced toxicity.[95] Data from a recent study further underscores the importance of dose optimization and fractionation strategies in SRS for rHGG. This study highlights that higher radiation doses ($\geq$ 20 Gy) correlate with prolonged local control (HR 0.34) but also increase the risk of distant failure (HR 5.62). Moreover, advanced imaging techniques, including radiomics-based predictive modelling and artificial intelligence-driven treatment stratification, are being explored to refine patient selection criteria and improve treatment outcomes.

The toxicity profile of SRs for recurrent gliomas has been acceptable, with a third of patients in one study developing grade 2 radiation necrosis that could be managed in an out-patient setting with oral steroids.[96]

Patient selection remains critical, with factors such as tumour histopathology, prior surgical interventions, and systemic therapeutic regimens influencing outcomes. Emerging strategies, including adaptive radiotherapy protocols and biomarker-driven treatment personalization, hold promise for optimizing risk stratification in rHGG management. The main advantage of SRS in the recurrent setting remains the low spillage of radiation to uninvolved brain tissue, thus offering the opportunities to treat focal areas of recurrence as and when they are diagnosed.[97]

Overall, SRS represents a valuable tool in the multidisciplinary approach to rHGG, balancing tumour control with quality-of-life preservation. Future research should focus on prospective trials evaluating optimal dose fractionation, combination therapies, and advanced imaging biomarkers to further enhance treatment efficacy.

Systemic therapy

Chemotherapy is the most commonly used therapeutic option for recurrent gliomas. Unlike surgery or re-RT, the use of systemic therapy is not limited by the size or volume of the recurrent disease. Prerequisites for the use of systemic therapy include maintained performance status (KPS 60 or more) and preserved haematological, liver and renal function parameters. Although many agents are available for clinical use, head-to-head comparison between them is lacking.

Alkylating agents

Temozolomide (TMZ) is an alkylating agent that is commonly used in first line and recurrent settings. MGMT promoter methylation is a positive predictive factor for response to TMZ.[98] Prospective studies have shown that while TMZ is superior to procarbazine alone, it is non‐inferior to the PCV regime (procarbazine, lomustine and vincristine).[99,100] Various dose schedules of TMZ are used in clinical practice such as the original Stupp schedule, dose intensified schedule and a metronomic (low dose continuous) schedule.[98,101,102] Carmustine and lomustine are alkylating agents belonging to the nitrosourea class that penetrate the blood brain barrier (BBB). Lomustine has been evaluated as a single agent, as part of the PCV regime, and in combination with bevacizumab.[103,104] MGMT promoter methylation is a positive predictive factor for response for lomustine as well. The use of PCV has been limited due to its delayed and prolonged myelosuppression and pulmonary toxicity. However, it remains an important option and is usually the comparator arm in most trials studying newer agents.[105]

Anti-angiogenic therapy

Angiogenesis plays a crucial role in the progression of malignant gliomas. Tumour-induced hypoxia leads to the upregulation of proangiogenic factors like VEGF and angiopoetin-1 that lead to new blood vessel formation.[106] Bevacizumab, an anti-VEGF monoclonal antibody, is the most commonly used anti-angiogenic agent in recurrent malignant gliomas. A large meta-analysis by Lombardi *et al* reviewed 14 randomized trials with 4330 patients and found that while bevacizumab did not improve OS, it led to a significant benefit in PFS (HR – 0.60).[107] This PFS benefit was also associated with maintaining quality of life and neurocognition. Some researchers feel that the PFS benefit provided by bevacizumab is not a true clinical benefit but a consequence of its antiangiogenic effects masking radiological disease progression. Bevacizumab has been studied in combination with other agents like irinotecan and TMZ.[108,109] Bevacizumab in combination with lomustine was found to have a similar OS but improved PFS (4.2 months vs 1.5 months) as compared with lomustine alone in a phase 3 trial.[104] Bevacizumab in combination with re-RT has been evaluated in phase 2 trials and has led to an improved PFS without an OS improvement.[7,79] It is associated with adverse events like hypertension, proteinuria, thromboembolic events and haemorrhage.[110] Regorafenib is an oral anti-angiogenic multikinase inhibitor that affects VEGF, KIT, RET and RAF pathways. REGOMA was a phase 2 randomised study that compared regorafenib with lomustine in recurrent malignant gliomas and found that regorafenib significantly improved OS compared to lomustine.[111] However, this promising effect was not confirmed when comparing regorafenib with lomustine in the phase 3 Bayesian platform trial GBM AGILE.[112]

Other agents

Mebendazole is an anthelmintic drug that initially showed promise as an agent with anti-tumour activity against glioma cell lines. It was evaluated in a phase 2 trial in combination with TMZ or lomustine and was found to have a 9-month OS of 36.6% (TMZ-mebendazole) and 45% (lomustine-mebendazole) but failed to achieve the pre-set benchmark (55%).[113] Enzastaurin, an oral serine and threonine kinase inhibitor, showed response in pre-clinical studies but failed to improve OS or PFS when compared with lomustine in a phase 3 study.[114] Another oral pan-VEGFR tyrosine kinase inhibitor, cediranib, was evaluated in a phase 3 study and failed to improve PFS in combination with or versus lomustine.[115] Other molecules that failed to meet their endpoints in recurrent malignant gliomas include galunisertib and axitinib.[116,117] Depatuxizumab mafodotin (ABT 414), an anti-EGFR antibody-drug conjugate, has shown promising results in patients with recurrent glioma previously treated with TMZ in a small single arm study with a 6-month PFS of 28.8% and 6-month OS of 72.5%.[118]

Combined chemoradiotherapy

A meta-analysis of 31 studies with 2084 participants comparing re-RT, systemic therapy and combination therapy in recurrent high-grade gliomas, suggested that combination therapy improved PFS and OS compared to systemic therapy alone (PFS HR 0.57, OS HR 0.73) as well as re-RT alone (PFS HR 0.52, OS HR 0.69). Combinations of re-RT and TMZ (variable dose schedules of RT and TMZ) have yielded OS of 9–12 months with reported neurologic toxicity of 7–13%.[119,120] A phase 3 study evaluating lomustine alone vs combined with re-RT (35 Gy/10 fractions) is ongoing.[121] The combination of bevacizumab with re-RT was found to reduce the rates of radiation necrosis especially with SRS/FSRT doses.[79] In conclusion, systemic therapy is an option for patients with recurrent glioma that have preserved performance status, haematological and biochemical reserves. However, no single agent has emerged successful in improving outcomes compared to historical comparators such as lomustine. The time since previous therapy and volume of the disease are not deterrents for systemic therapy. In select groups of patients that are fit for both re-RT and systemic therapy, a combined approach appears to provide the most favourable outcomes. Summary of various chemotherapy agents used in the management of recurrent GBM can be found in Table 4.

Immunotherapy

In recent years, immunotherapeutic modalities have gained prominence in the treatment of various cancers, such as melanoma and lung cancer, and are now being explored for glioblastoma treatment as well.[122,123]

Factors affecting efficacy of immunotherapy in gliomas

Immunosuppressive tumour microenvironment (TME) is considered one of the most important factors affecting immunotherapy in glioma management. The TME is a complex interaction between the tumour and the immune system that contributes to immune escape and tumour cell survival in glioblastoma.

Immune suppression in glioblastoma occurs via several mechanisms, including recruitment and maintenance of immunosuppressive cells like glioma associated microglia/macrophages (GAMs) and myeloid-derived suppressor cells (MDSCs), secretion of immunosuppressive cytokines (TGF-β, IL-10), reduced expression of tumour-infiltrating

Table 4: Commonly used systemic therapeutic agents in the management of recurrent malignant gliomas

Drug and class	Study type	Dose regimen	Outcomes
Temozolomide (Triazene – Alkylating agent)	Phase 2 Weller *et al* Perry *et al*.	Stupp *et al*.[3] – 150-200 mg/sqm D1-D5 q 3 weekly Dose intensified – 75-100 mg/sqm D1-D21 q 4 weekly Low dose daily – 40-50 mg/sqm	Median OS – 9-10 months PFS higher in MGMT methylated
Lomustine (Nitrosoureas – Alkylating agent)	Retrospective Hochberg *et al*.	Lomustine (CCNU) – 80-110 mg/sqm q 6 weekly	Median OS – 11.5 months
Bevacizumab – (Antiangiogenic Agent) (Bev)	Meta-analysis Lombardi *et al*	10 mg/Kg iv q 2 weekly	Has PFS benefit – HR – 0.60 No OS benefit
Bevacizumab + Chemotherapy	Phase 2 Friedman *et al* (Bevacizumab + Irinotecan) Sepulveda *et al* (Bevacizumab + Temozolomide) (Single arm)	Irinotecan – 125-340 mg/sqm q 2 weekly TMZ – 150 mg/sqm D1-D7 and D15-21 q 4 weekly	Median OS – 9.2 months (Bev alone) vs 8.7 months (with Bev + Irinotecan) 6 months PFS – 42.6% vs 50.3% Median OS – 7.3 months Median PFS - 4.2 months MGMT status did not affect outcomes
Regorafenib (Antiangiogenic multikinase inhibitor)	Phase 2 Lombardi *et al* (Regorafenib vs Lomustine)	160 mg D1-D21 q4 weekly	Median OS – 7.4 months vs 5.6 months (Lomustine arm)

lymphocytes (TILs), high expression of inhibitory immune checkpoint molecules such as PD-1, TIM-3, and LAG-3.[124-126] GAMs also promote the proliferation of glioma stem cells (GSCs) which have the properties of self-renewal and multi-differentiation, leading to tumour occurrence, progression, drug resistance, recurrence and heterogeneity.[127] Blood–brain barrier (BBB) is another important determinant that contributes to the efficacy of immunotherapy. BBB limits immunotherapeutic effects by expressing low levels of APC and MHC molecules, expression of immunosuppressive cytokines like IL10 and TGF-β, acting as a barrier to drug delivery, and lacking traditional lymphatic structures. Furthermore, the properties of BBB are also regulated by components of the TME.[128-130]

The major immunotherapeutic strategies in glioma management include oncolytic virotherapy (OV), glioma vaccines, chimeric antigen receptor T (CAR-T) cell therapy and immune checkpoint blockade (ICB).[131,132]

OV therapy

OVs are genetically modified viruses with weakened pathogenicity which enhance the anti-tumour effects without damaging normal cells.[133] Broadly, OV genetic modification strategies include: deleting virulence genes to improve the safety of OVs, enhancing tumour cell tropism and selective targeting of tumour cells, and modification of OVs with different therapeutic genes to enhance anti-tumour effects.[134]

OVs act via self-replication in host cancer cells leading to their direct lysis, which helps activate innate and adaptive immune responses by releasing damage-related molecular patterns (DAMPs) and viral pathogen associated molecular patterns (PAMPs) leading to improvement in the immunosuppressive TME, inhibit GSCs which play an essential role in drug resistance, tumour neovascularisation, and immunosuppressive TME.[133-136]

Viruses used for OV therapy include oncolytic H-1 parvovirus, oncolytic reovirus, oncolytic poliovirus, oncolytic adenovirus, oncolytic zika virus, oncolytic herpes simplex virus.[135,137-140] Amongst all the OVs, oHSV has shown the most promising results.[141] The limited and conditional approval of G47D for treatment of malignant gliomas, a type of oHSV, in Japan indicates the huge potential of OVs. Further research and phase III trials with large samples are needed to verify its efficacy.

Glioma Vaccines

Peptide vaccines and dendritic cell (DC) vaccines constitute promising immunotherapeutic strategies under investigation. These approaches leverage tumour-associated antigens (TAAs) and tumour-specific antigens (TSAs) as immunogenic targets to stimulate a tumour-specific immune response.[142,143]

Peptide vaccines comprise 8-25 amino acids and carry epitopes which act as antigenic targets.[145] Frequently mutated or highly expressed proteins/antigens in glioblastoma include EGFRvIII, NF1, TERT, PDGFR, PTEN, RB1, IDH1, P53, PIK3R1 and PIK3CA, some of which can be explored as vaccine targets.[143,144] At present, EGFRvIII is one of the most studied TSAs and an important target for glioma vaccines.[145] However, a phase III trial of Rindopepimut, a peptide vaccine, in combination with Temozolomide in patients with EGFRvIII+ glioblastoma did not show improvement in median OS. The result also highlighted the need for multi-peptide vaccines against multiple targets to overcome the antigenic heterogeneity in tumour cells.[143,146]

Dendritic cells' role as antigen-presenting cells is the main mechanism of DC vaccines.[147] When immune cells (T cells) are activated by DCs, they can cross BBB and have antitumour effects.[148] DC vaccines are also believed to trigger innate and adaptive immune responses and facilitate the transformation of immunologically cold to immunologically hot gliomas.[149] Phase III trials of an autologous tumour lysate-loaded DC vaccine (DCVax-L) plus TMZ in patients with newly diagnosed and recurrent glioblastoma showed a significant improvement in median OS. DCVax-L-treated patients with newly diagnosed glioblastoma with methylated MGMT promoter had a significantly longer survival than those in the external control group.[150,151]

CAR-T cell therapy

This approach involves collecting T-cells from the patient's blood, followed by their modification, amplification and activation to express CAR molecules on their cell

membranes. These genetically engineered T-cells are then administered to the patient, allowing them to target specific tumour cell antigens.[152]

Several commonly used targeted antigens like EGFRvIII, IL13Ra2, and HER2 are being studied in this regard.[153-155] A phase I clinical trial of IL13Ra2-targeted CAR-T cell therapy in glioblastoma treatment explored two intracranial approaches to deliver CAR-T cells to a patient with recurrent multifocal glioblastoma, drug infusion into the resected tumour cavity and the ventricular system. The intraventricular therapy achieved wide regression of the multifocal disease including leptomeningeal and spinal disease. In comparison, the intracavitary infusion seemed to control only the local tumour recurrence.[154] Another phase I study investigated the use of HER2-targeting CAR-modified virus-specific T cells (HER2-CAR VSTs) in patients with recurrent glioblastoma which showed promising results.[155]

ICB

ICB acts by blocking the immune checkpoints like PD-1/PD-L1, and CTLA-4, causing reduction in immunosuppressive effects and having an antitumour effect. Anti PD-1 antibodies like Pembrolizumab and Nivolumab have been studied in treating recurrent glioma and GBMs. However, there aren't any successful phase III clinical trials or marketing authorizations of ICBs in GBM treatment.[156,157] Unlike other cancers, such as melanoma and lung cancer, the ICBs have not shown favourable results in treating gliomas.[158] Nevertheless, ICBs can be candidates for combination therapy by combining them with other treatment modalities, like chemoradiotherapy, targeted therapies, or other kinds of immunotherapies.[159]

Immunotherapy is a promising treatment modality for malignant and high-grade gliomas. However, further research is required to overcome challenges and to realise its full potential. These include understanding the molecular biology of malignant and high-grade gliomas, TME and the BBB, exploring TME-immunotherapy relationships, and the rational exploration of combination therapies (surgery, radiotherapy, chemotherapy) offering synergistic advantages. Personalised treatment based on the individual's genetic makeup is crucial to optimize therapeutic outcomes.

Newer Modalities

LITT

Laser interstitial thermal therapy is a minimally invasive modality proven to be effective in the management of various intracranial pathologies. The first use of thermal application to intracranial tissue was described by Bown in 1983.[160] Following this, however, there were only limited efforts to thermally ablate solid tumours. With the advent of magnetic resonance (MR) thermography, which allows real-time visualisation of the thermal effects of ablative lasers, enhanced control became possible, facilitating the widespread adoption of LITT.[161]

Recurrence in high-grade gliomas is inevitable. Patients with recurrent glioblastomas (rGBMs) have a mean progression-free survival (PFS) of approximately 5.5 months and a median overall survival (OS) of about 6.5 to 11.9 months, following surgery and second-line systemic therapy.[162,163] These individuals typically present with poorer Karnofsky performance scores (KPS), new onset or worsened neurological deficits, and face a greater risk of complications following redo-surgery.[51,163] The presence of a remote recurrence or multiple recurrences further complicates management in these patients.

Considering these factors, it is unsurprising that the rate of resection for rGBMs varies from 3% to 30% across studies and populations.[57] In this context, the role of LITT is well established.[164–166] LITT provides a minimally invasive method for patients to undergo a cytoreductive procedure, even when other factors hinder surgical debulking. Each lesion, even in cases of multiple recurrences, can be targeted through a small burr hole or bolt. Each trajectory is visualised in real-time, and important neurovascular structures are avoided. The addition of diffusion tensor tractography imaging in the planning of these trajectories further reduces the approach-related morbidity of this procedure.[167,168] This is especially beneficial for deep-seated lesions, where the effectiveness of LITT has been established due to its ability to access these areas with relative ease.[169] Furthermore, in

case of progression of the disease or a diagnostic dilemma, a stereotactic biopsy can be safely obtained, followed by the insertion of the LITT probe via the same trajectory.[170]

The planning of LITT involves acquisition of stereotactic MR imaging, followed by reconstruction of the three-dimensional tumour volume. Thermal damage threshold (TDT) lines are then marked across the volume, with the blue TDT line typically corresponding to a thermal dose of 43 °C for 10 minutes (or higher temperatures for shorter durations), and a yellow TDT line corresponding to a thermal dose of 43 °C for 2 minutes. Some systems also permit the creation of a white TDT line that corresponds to a dose of 43 °C for 60 minutes.[171] Preclinical studies indicate that tissue within the white TDT line suffers 100% death within 48 hours. Tissue within the blue TDT line experiences necrosis, while tissue within the yellow TDT line undergoes apoptosis. No irreversible damage was observed in tissue outside the yellow TDT line.[172]

The clinical appeal of LITT in rGBM lies in its potential to achieve a higher cytoreductive effect compared to resection in eloquent or deep-seated areas. Barnett *et al*.[173] noted in a systematic review that the median extent of ablation (EOA) was 85.4 ± 10.65% with LITT compared to the extent of EOR of 77.0 ± 40% after resection for rGBMs. This is associated with improved median OS.[165] Studies have identified EOA cut-offs of 85% - 90% and above to be associated with better outcomes.[169,174]

Recent pooled analyses estimate the median post-LITT OS to be between 10.1 and 12.4 months.[164,175] Median PFS in large series ranged from 5.0 to 7.3 months.[169,174,176,177] This is comparable to re-resection with adjuvant systemic therapy in rGBMs.[162] Factors associated with favourable outcomes included lesions <3 cm, predicted achievable EOA ≥80%, and patients with KPS ≥70.[168,169,178]

Complications are inherent with any procedure, including LITT. Older studies described rates of morbidity up to 30%, with more recent studies reporting fewer serious adverse events, including infections, ranging from 6.4 to 15%.[171,177,179] Lower rates of major complications have been observed in tumours near eloquent areas undergoing LITT compared to surgical resection (5.7% versus 13.8%) in a study evaluating primary and rGBMs.[173] The most prevalent complications include seizures, permanent or transient neurological deficits, wound infections and haemorrhage.[179] Up to 20% of patients in a series were noted to have worsening preoperative deficits in a series, the majority transient, attributed to the expected post-ablative oedema.[169] Rarer complications include deep venous thrombosis, hyponatremia and epicranial seeding at the probe entry site.[171] Deep-seated, larger tumours, margins near cortical fibres and poor preoperative KPS were found to be associated with adverse outcomes.[168,169,180]

Future studies on LITT for neoplastic lesions will undoubtedly consider the impact of thermal damage on blood-brain barrier (BBB) integrity. Leuthardt *et al*. observed that the peak disruption of the peritumoural BBB in rGBMs occurred between 1 and 3 weeks after LITT, decreasing to baseline levels at 6 weeks.[181] This creates a therapeutic window for administering BBB-impermeable second-line chemotherapeutics in rGBMs. Phase II trials have already shown longer OS in rGBM patients receiving doxorubicin following LITT.[182]

TTFs

Tumour Treating Fields (TTFs) are a novel, non-invasive treatment modality that employ low-intensity, intermediate-frequency alternating electric fields to target tumour cells.[183,184] TTFs are believed to disrupt rapidly dividing cells by interfering with mitotic spindle formation and inhibiting cytokinesis.[185] Emerging evidence highlights its promise in managing recurrent high-grade gliomas, particularly glioblastoma (GBM). Due to their non-invasive nature, TTFs may circumvent the adverse effects of conventional therapies, offering a viable alternative.[183,186]

Biophysics of TTFs

TTFs induce structural alterations in charged organelles essential for mitosis.[187] Their effects stem from two principles: dipole alignment and dielectrophoresis.[187,188] A dipole, having separated charges, aligns with an external alternating field.[189] TTFs interfere with this alignment, limiting mitotic function.[187,190] Dielectrophoresis causes charged macromolecules to migrate toward high-field regions, which disrupts their precise

spatial organization—crucial for mitosis.[191] TTFs, being non-uniform fields, interrupt this arrangement, thereby inhibiting cell division.[187,190]

Biological Effects

Beyond mitotic disruption, TTFs erode the nuclear envelope, forming cytosolic micronuclei clusters.[183] These activate DNA sensors like cyclic GMP AMP synthase (cGAS) and AIM2, triggering cGAS/STING and AIM2/caspase-1 inflammasomes, respectively—initiating inflammatory anti-tumour responses.[183] TTFs also enhance GBM cell membrane permeability, improving susceptibility to cytotoxic agents.[192] Furthermore, they downregulate VEGF, HIF-1α, and MMP-2/9, thereby inhibiting tumour angiogenesis.[193]

TTF Delivery

Optune (Novocure™) is the most widely used TTF delivery system, consisting of four transducer arrays, a field generator, and a power source.[183,194] The arrays are affixed in pairs to the shaved scalp.[194] Optimal array placement can be determined using software like NovoTAL™, which tailors positioning based on tumour location and head topology.[194,195] Skin reactions, such as dermatitis, may occur but are typically managed with topical corticosteroids.

Clinical Efficacy in Recurrent Glioblastoma

The efficacy of TTFs in recurrent GBM and high-grade gliomas (HGG) has been debated. A 2007 pilot study reported improved outcomes for TTFs, with a median time to progression of 26.1 weeks and overall survival (OS) of 62.2 weeks, compared to 9.5 ± 1.6 weeks and 29.3 ± 6 weeks in controls.[185] This catalysed subsequent investigations into TTFs for recurrent GBM.

The EF-11 trial, a multicentre phase III study, compared TTF monotherapy with 'physician's best choice' chemotherapy in recurrent GBM. Although median OS was not significantly different (6.6 vs. 6.0 months, $p = 0.27$), TTFs had a modestly higher response rate (14% vs. 9.6%, $p = 0.19$) and better six-month PFS (PFS6) (21% vs. 15%, $p = 0.13$). The trial concluded that TTFs were as effective as chemotherapy, with fewer adverse effects and improved quality of life (QoL).[196] The Federal Drug Administration (FDA) subsequently approved TTFs as monotherapy for recurrent GBM.

A post-hoc analysis of EF-11 revealed that patients who received at least one TTF treatment had significantly better OS than those receiving any active chemotherapy (7.8 vs. 6.0 months, HR 0.69; 95% CI 0.52–0.92, $p = 0.0093$).[197] These findings were reinforced by a meta-analysis showing prolonged TTF use improved survival. Regev *et al*. reported that patients using TTFs ≥75% of the day had a median OS of 10.3 months compared to 5.7 months for <75% use.[198]

The PRiDe registry, which tracked GBM patients treated with TTFs from 2011 to 2013, reported a median OS of 9.6 months—surpassing the EF-11 trial outcome. However, patients in PRiDe had earlier-stage follow-up, potentially contributing to better responses.[199]

TTFs have also been studied in combination therapies. A post-hoc analysis of the EF-14 trial (NCT00916409) showed that adding TTFs to second-line therapy in first-recurrence GBM significantly improved OS (11.8 vs. 9.2 months; HR 0.70; 95% CI 0.48–1.00; $p = 0.049$).[200]

More recently, interest has grown in integrating skull-remodelling (SR) surgeries with TTFs. Preclinical studies suggest SR may synergize with TTFs by enhancing field intensity. The OptimalTTF1 trial evaluated SR-surgery aimed at boosting TTF delivery. After a four-week recovery, patients began TTF therapy. Median TTF enhancement was 32% (range 25–59%). While mild adverse events occurred, there were no serious intervention-related complications. The cohort achieved a median PFS of 4.6 months and OS of 15.5 months.[201] The ongoing OptimalTTF2 trial compares standard TTF plus chemotherapy with SR-surgery plus TTF and chemotherapy.[202]

Predictive Biomarkers and Personalization

A key focus in TTF research is identifying predictive biomarkers. A recent retrospective study indicated that PTEN-mutant GBM patients experienced a significant progression-

free survival benefit with TTF therapy, suggesting PTEN status may help guide treatment selection.[203]

Adverse Events and Tolerability

Across multiple studies, TTFs demonstrate a favourable safety profile in recurrent HGGs, with most adverse events being mild to moderate and well-tolerated.[199,200] The most frequent are skin reactions beneath the transducer arrays. Though not typically serious, such reactions can reduce compliance. Therefore, ensuring patient comfort is essential for treatment adherence.

FUS

Focused ultrasound is an emerging, non-invasive therapeutic modality that leverages the mechanical and thermal properties of ultrasonic waves (>20 kHz) for both standalone and adjunctive treatment of intracranial pathologies. FUS has shown therapeutic promise in recurrent gliomas through targeted tissue ablation, blood-brain barrier (BBB) disruption, and facilitation of drug delivery.[204]

FUS systems typically employ phased-array transducers composed of piezoelectric elements, allowing precise modulation of ultrasound parameters, frequency, pulse duration, and intensity.[205-207] These systems are often MR-guided, providing real-time thermographic monitoring to optimize energy deposition and tissue response.[13,204,208] Based on intensity and mechanism, FUS is categorized into high-intensity focused ultrasound (HIFU) and low-intensity focused ultrasound (LIFU). HIFU, operating at 1000–10,000 W/cm² and 200–600 kHz, induces thermal effects that result in coagulative necrosis through localized hyperthermia.[208] In contrast, LIFU (<3 W/cm²; 220 kHz–1 MHz) exerts mechanical effects such as cavitation, which facilitate BBB disruption and drug delivery.

Blood-Brain Barrier Disruption

LIFU, combined with intravenously administered microbubbles, can transiently open the BBB. Oscillating microbubbles generate shear forces that selectively increase permeability, improving delivery of chemotherapeutic and biologic agents to gliomas while minimizing systemic toxicity.[209–211]

Clinical trials have demonstrated this capability in recurrent glioma patients. Phase I/II studies using microbubble-enhanced FUS with carboplatin confirmed safe, localized BBB disruption. A phase 0 study using fluorescein showed a 2.2-fold increase in dye accumulation in FUS-treated tumour regions, suggesting its potential for improved resectability.[212]

The largest study to date (N=33) employed an implantable ultrasound device activated repeatedly in conjunction with carboplatin administration, reporting a one-year overall survival of 58% and a median survival of 14 months post-surgery.[213]

Despite promising results, these studies remain exploratory. Contrast enhancement is typically used as a surrogate to verify BBB opening, but pharmacokinetic evidence of improved drug penetration is limited. Long-term benefits remain uncertain, and permeability windows vary with drug size and ultrasound parameters—ranging from minutes for large molecules to hours for smaller agents.[214]

Thermal Ablation

Initial evidence for FUS-induced thermal ablation came from a 2006 study in which three patients underwent over 30 sonications each, with histological confirmation of thermocoagulation. However, the need for craniotomy to overcome skull-related energy attenuation limited its appeal.[215] A 2010 follow-up study demonstrated FUS feasibility without craniotomy but failed to reach therapeutic temperatures.[216] The first non-invasive thermal ablation case was documented in 2014, with successful partial tumour ablation using 25 sonications in the subthalamic region.[217] Effective tissue coagulation via FUS requires temperatures exceeding 55°C.[218] However, the limitations outlined above restrict its applicability to centrally located tumours. Treating superficially situated tumours is prone to excessive scalp heating, while treating deeper tumours is difficult since converging the beam beyond the focal point to achieve sufficient temperatures leads to a drop in target precision, potentially damaging critical nearby structures. Additionally, the

therapeutic envelope of HIFU remains small (<1 cm^3), making larger tumour volumes a significant limiting factor. Consequently, direct thermal ablation for glioma cytoreduction has become less prominent.

Emerging Applications and Future Directions

Several adjunctive applications of FUS are under active investigation. Microbubble-enhanced ablation combines low-intensity ultrasound with microbubbles to induce ischemic necrosis via targeted vascular destruction, mitigating the limitations of conventional HIFU.[219] Histotripsy employs high-intensity, microsecond ultrasound pulses to induce nonthermal tissue liquefaction through cavitation.[220] Sonodynamic therapy (SDT) uses sonosensitizers that are activated by LIFU to produce cytotoxic reactive oxygen species (ROS), triggering apoptosis. Radiosensitization via FUS-induced hyperthermia may potentiate radiation therapy. Unlike traditional hyperthermia methods requiring invasive delivery, FUS offers non-invasive, focal heat induction. Preclinical and clinical studies continue to explore this synergy.[221] Diagnostic augmentation, particularly in liquid biopsies, is another promising avenue. FUS may enhance the release of tumour-derived biomarkers (e.g., cell-free DNA, extracellular vesicles) into biofluids, facilitating molecular profiling and treatment monitoring.[222]

While early studies support the safety and feasibility of FUS in glioma management, challenges persist. These include optimization of acoustic parameters, variability in drug delivery efficacy, and limited long-term clinical outcome data. However, advancements in transducer design, growing understanding of FUS biology, and its integration into multimodal glioblastoma treatment regimens continue to broaden its clinical utility.

FUS is a versatile and evolving modality with demonstrated potential in recurrent glioma therapy. Its non-invasive nature, coupled with the ability to enhance other treatments, positions it as a valuable tool in neuro-oncology. Ongoing clinical trials and technological refinements will determine its definitive role in future glioma management paradigms.

Conclusion

Despite extensive research and the emergence of multiple therapeutic avenues, there remains no consensus on the optimal management of early recurrences of malignant gliomas [Figure 1]. Treatment decisions are inherently patient-specific, influenced by factors such as performance status, tumour location, recurrence pattern, and prior interventions. Multimodal strategies, often combining surgery, re-irradiation, systemic therapy, and novel modalities, are increasingly adopted to tailor care. While numerous promising interventions, including immunotherapy and advanced image-guided techniques, are under investigation, none have conclusively demonstrated a clear and consistent survival benefit. Continued research, refinement of patient selection criteria,

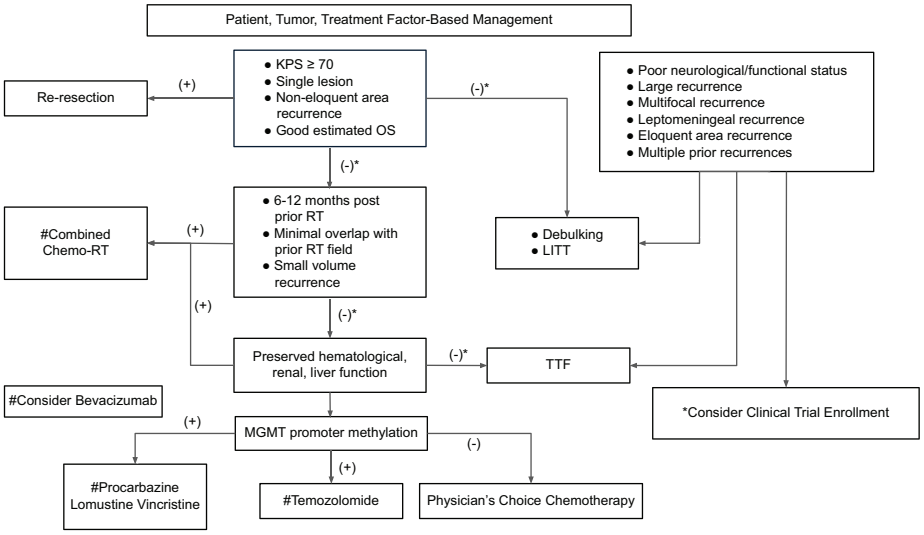

Figure 1: Algorithm summarizing management options for early recurrences

and integration of personalised approaches remain critical to improving outcomes in this challenging disease.

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