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Review

# Prospective therapies for high-grade glial tumours: A literature review

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ABSTRACT

After three decades of intensive research, cytoreductive surgery remains the gold standard of treatment of malignant gliomas. Survivorship at both 1-year and 5-years has not drastically changed in the UK. Concomitant chemo- and radiotherapy has enhanced the efficiency of surgery, enabling more aggressive tumour resection whilst also preserving the surrounding healthy brain parenchyma. More accurate imaging techniques have also played a role in tumour identification, key to this has been pre- and intra-operative contrast enhancement and compounds that have a high affinity in binding to glioma cells. Intra-operative imaging has heralded the ability to give the operating surgeon continuous feedback to assess the completeness of resection. Research is shifting into investigating the complex cellular and molecular glial tumour-genesis, and has led to the development of efficacious chemotherapy agents and trial novel therapies. Oncolytic virotherapy has shown promise in clinical trials and gene therapy in-vitro studies. Surgery however remains the primary therapeutic option for the management of malignant gliomas removing the mass of proliferating malignant tumour cells and decompression of the space-occupying lesion.



## 1. Introduction

Glial cells unlike neurons undergo mitosis and any abhorrent deviation may result in glial tumours. The initiation is thought to originate from a common pluripotent neuro-ectodermal precursor cell whose progeny retains the ability to differentiate, along the astrocytic lineage to a Grade IV glioblastoma multiforme (GBM). Primary GBMs occur de-novo [1]. Only radiation exposure and certain genetic syndromes, for example Li-Fraumeni syndrome, are well defined risk factors for malignant glioma [2].

Subtype classification is dependent on which cell type the glial tumour most closely resembles including: Astrocytoma (astrocytes), Oligodendrogliomas (oligodendrocytes) or mixed gliomas (for example oligoastrocytomas) – the three of which account for more than 70% of all brain tumours [2].

Glial tumour grading is according to WHO classification grade I to IV, I least aggressive non-anaplastic gliomas and IV most aggressive anaplastic gliomas. High-grade gliomas (HGG), WHO grade III & IV, account for approximately 70% of all gliomas and predominantly affect patients between 40 and 70 years of age [3].

## 2. Epidemiology & current practise

In the UK, incidence rates of central nervous cancers are 12.4 per 100,000 of the population and not changed significantly in the last three decades [4]. The prognosis and survival remains bleak despite research including advances in cytoreductive surgery, imaging technology, chemotherapy and radiotherapy. The five-year survival in the early 1970s was 8% and this has plateaued at approximately 14% since the late 1980s [4]. There is also significant morbidity with HGG, as they are commonly located in or near to eloquent brain regions, i.e. language, memory, motor and visuo-spatial centres.

The current management for HGG aims to increase survivorship and provide a good quality of life during this short reprieve, before presumed reoccurrence including distal brain metastasis [4]. As briefly mentioned this has been in part due to the combination of cytoreductive surgery, imaging technology, chemotherapy and radiotherapy. It should also be emphasised the management decisions are reached through consensus by a multidisciplinary team

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including the neurosurgeons, oncologists, physiotherapists and specialist nurses taking into account the individual patients pre-morbid status in particular the WHO performance status.

The Stupp protocol is the gold standard regimen for Grade IV gliomas; involving gross-total resection of tumour bulk (equal to or greater than 95%) followed by radiotherapy with concomitant and adjuvant alkylating/methylation (of tumour cell DNA) chemotherapy agent temozolomide. There was a significant increase in 2-year survival from 10.4% to 26.5% [5]. The Stupp protocol has replaced the PCV adjuvant chemotherapy regimen (procarbazine, lomustine and vincristine) traditionally given due to it failing to improve survival in prospective randomised studies, both in grade III and IV tumours [6].

The placement of intra-operative carmustine wafers (Gliadel), if the resection cavity is greater than 90%, has shown modest increases in median overall survival of approximately two-and-half months [7].

It should be noted for the over 70 years of age cohort, that radiotherapy maybe the only post-operative therapy recommended at MDT although, this alone has shown to increases median survival by 3 months without altering the quality of life compared with best supportive care.

## 3. Recent intra-operative advances in practise

In the last decade there have been advancements in technology to enable greater and more accurate surgical resection of the HGG, these include:

- Fluorescence-guided surgery with 5-Aminolevulinic acid (5-ALA) given pre-operatively accumulates in HGG allowing for greater resection of tumour and a prolonging progression-free survival, twice as long at 6 months [8–10].
- High-magnification microscopes
- Intra-operative Magnetic Resonance Imaging (iMRI) – allows for real-time assessment of the tumour resection especially given intra-operative brain shift
- Intra-operative ultrasound – free hand intra-operative tumour visualisation and neuronavigation
- Neuronavigation with/without diffusion tensor imaging (DTI) – to intra-operatively localise and estimate tumour resection on a 2D-screen, while avoiding iatrogenic damage of eloquent structures as also DTI assists in defining the white matter tracts

A Cochrane review demonstrated that the extent of resection is significantly increased with 5-ALA iMRI and neuronavigation with DTI, however the data was insufficient to evaluate the overall benefit and effects of neuronavigation. There is no clear evidence whether 5-ALA or neuronavigation with DTI improved overall survival in patients with HGG. There is a theoretical concern that maximising the extent of resection may lead to more frequent adverse events but this was poorly reported in the included studies [11].

### 3.1. Robotic neurosurgery

General-purpose non-neurosurgical laparoscopy multi-manipulators such as the Da Vinci Surgical System have performed thousands of procedures [12]. The combination of robotic neurosurgery with intraoperative MRI is a logical progression for a telesurgical device, the NeuroArm. The Da Vinci Surgical System unlike the NeuroArm utilises a 3-D visual display unit to give the surgeon full stereoscopic vision. Surgical procedures performed with the NeuroArm have been just as accurate as conventional techniques in malignant glioma resection [13–15]. The integration of tele-operated robotics with surgery should reduce intra-operative error and iatrogenic trauma by decreasing tremor and improving accuracy, and precision. The NeuroArm is still experimental. The Da Vinci system is an example of a well-integrated robotic solution, however the clinical data has not supported the claim of improved patient outcomes and the procedure takes longer than traditional non-robotic surgery [14,15].

### 3.2. Targeted chemotherapy

Maximal surgical resection of the tumour removes all of the central core of hypoxic, proliferative cells as well as some of the migratory cells in the marginal region, providing a rapid kill of a significant number of tumour cells. Despite combination therapy, tumour reoccurrence is commonplace in most patients after initial successful treatment and consequent poor survival rates [4,5]. Gliomas can originate from neural stem cells, progenitor cells or from de-differentiated mature neural cells transformed into cancer stem cells [1,2]. Genetic sequencing has identified markers that support the diagnosis of a glioma sub-type, but more notably tumour behavioural characteristics especially to chemotherapy [16]. A chemotherapy regimen tailored to the molecular genetics would target residual glial cells and any proliferating Brain Tumour Stem Cells (BSC) responsible for proliferation-migration and differentiation of gliomas.

The molecular and cellular alterations observed in HGGs are strongly linked to signalling pathways involved in angiogenesis, cell-cycle control, cell metabolism (for example Isocitrate dehydrogenase), invasion, and signal transduction. There is also loss of chromosome-10, CDKN2A deletion and amplification of EGFR all linked to HGGs [5,16].

Isocitrate dehydrogenase 1 (*IDH1*; and rarely *IDH2*) mutations, important in cell metabolism, have been found in more than 60% of low-grade gliomas and HGGs. This mutation is favourable predictor for outcome irrespective of histological tumour type and grade [5,16].

Methyl-guanine methyl transferase (MGMT) gene is crucial in DNA damage repair and methylation of the MGMT gene promoter (epigenetic silencing) prevents the tumour cell repairing itself from chemotherapy-induced DNA damage. Temozolomide methylates DNA at the N-7 or O-6 positions of guanine residues rendering the HGG cells sensitive to DNA damage and the consequent apoptotic cascade [5,16].

Bevacizumab is a humanised monoclonal antibody, and was the first commercially available angiogenesis inhibitor to target and inhibit vascular endothelial growth factor (VEGF) [17]. The alternative development of immunomodulatory drugs including swainsonine, (inhibiting asparagine glycosylation) has shown therapeutic potential by stimulating the body's innate immune cells to attack tumour cells [18].

### 3.3. Stereotactic neuroradiosurgery

The Gamma Knife is a focused array of intersecting beams of gamma radiation to treat lesions within the brain and has been a gold standard method for delivery of stereotactic neuroradiosurgery [19]. The CyberKnife system was developed with the intention of delivering radiotherapy more accurately than standard protocols by combining the radiation produced from a small linear particle accelerator and a robotic arm that allows the energy to be directed at any part of the body from any direction [19]. The Gamma Knife requires a stereotactic frame placement that does not allow movement during treatment while CyberKnife allows for mobility and the integration of real-time imaging during radiotherapy session [20,21]. There has been no direct comparison of the aforementioned radiotherapy systems. Early trials of the CyberKnife have shown acceptable toxicity and increased accuracy in radiation