Surgical resection of malignant gliomas —role in optimizing patient outcome

Ilker Y. Eyüpoglu, Michael Buchfelder and Nic E. Savaskan

Abstract | Malignant gliomas represent one of the most devastating human diseases. Primary treatment of these tumours involves surgery to achieve tumour debulking, followed by a multimodal regimen of radiotherapy and chemotherapy. Survival time in patients with malignant glioma has modestly increased in recent years owing to advances in surgical and intraoperative imaging techniques, as well as the systematic implementation of randomized trial-based protocols and biomarker-based stratification of patients. The role and importance of several clinical and molecular factors—such as age, Karnofsky score, and genetic and epigenetic status—that have predictive value with regard to postsurgical outcome has also been identified. By contrast, the effect of the extent of glioma resection on patient outcome has received little attention, with an 'all or nothing' approach to tumour removal still taken in surgical practice. Recent studies, however, reveal that maximal possible cytoreduction without incurring neurological deficits has critical prognostic value for patient outcome and survival. Here, we evaluate state-of-the-art surgical procedures that are used in management of malignant glioma, with a focus on assessment criteria and value of tumour reduction. We highlight key surgical factors that enable optimization of adjuvant treatment to enhance patient quality of life and improve life expectancy.

Eyüpoglu, I. Y. *et al. Nat. Rev. Neurol.* advance online publication 29 January 2013; doi:10.1038/nrneurol.2012.279

Introduction

Malignant gliomas—the most common primary brain tumours—account for about 2% of all cancers, and are a major cause of cancer-related mortality and morbidity.[1,2] These tumours are thought to originate from glial, stem or neuronal precursor cells, and are histologically classified, according to the WHO criteria, as grade III and grade IV tumours (so-called high grade or malignant gliomas).[3] Neuropathological analysis of malignant glioma reveals a diagnosis of glioblastoma in about 81% of cases.[4] Malignant gliomas all display characteristics of diffuse infiltration and high proliferation index, with glioblastoma—WHO grade IV tumours, also known as glioblastoma multiforme (GBM) owing to the variable characteristics observed at the macroscopic and microscopic level—exhibiting the highest malignancy rate. From the time of diagnosis, patients with glioblastoma have a median survival time of 14 months.[5]

Current multimodal treatment of patients with malignant glioma has been standardized on the basis of results from landmark randomized trials,[6,7] and has led to optimization of safety, and increased overall patient survival.[6,8] With the dual benefit of achieving cytoreduction and providing tissue for histopathological diagnosis, primary tumour surgery constitutes the cornerstone of the glioma therapy algorithm that enables treatment to be tailored to a given individual (Figure 1). The success of surgery has, unfortunately, long been underestimated owing to technical and methodological limitations in tumour imaging and visualization. In contrast to the active use of validated response assessment criteria for multimodal treatment regimens, implementation of neurosurgical assessment criteria has been minimal. In view of the poor prognosis and lack of validated treatments, attending physicians often have a nihilistic attitude when confronted with a diagnosis of a malignant glioma. To compound matters further, several reports seem to have fostered an 'all or nothing' approach to tumour resection,[9,10] and have led to questions about whether the extent of resection has any influence on the success of multimodal therapy and on overall patient outcomes.

In this Review, we explore the rationale behind—and clinical evidence to support—use of intraoperative imaging and objective preoperative and postoperative volumetric methods for maximal surgical removal of malignant brain tumours. The typical clinical course of glioma, from the onset of presenting symptoms to the point at which therapeutic options reach their limits, is described, followed by a discussion on the influence and prognostic value of tumour resection in terms of response to adjuvant therapy and patient life expectancy. We highlight advances in intraoperative imaging that have facilitated improved tumour surgery to enable resection to the maximal feasible extent, and that will eventually lead to marked improvements in outcome for patients with malignant glioma.

Malignant glioma

Clinical presentation

Malignant gliomas are characterized by a diffuse and infiltrative growth pattern, and generally do not exhibit

Competing interests
The authors declare no competing interests.

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Key points

- For patients with malignant glioma, maximal possible tumour resection (maximal surgical outcome) is critical to improve prognosis
- Objective preoperative and postoperative tumour volumetric methods and centre-independent validated assessment criteria should be implemented as part of the standard glioma management procedure
- Intraoperative or delayed postoperative MRI is presently the gold standard to evaluate success of malignant glioma resection
- Intraoperative imaging techniques enable surgeons to increase the extent of tumour resection, and can be used to quantify the success of tumour removal in an unbiased manner
- In future, patients will be stratified for inclusion in clinical trials for resection on the basis of functional tumour grading, surgical outcome (extent of tumour resection) and individual genetic characteristics

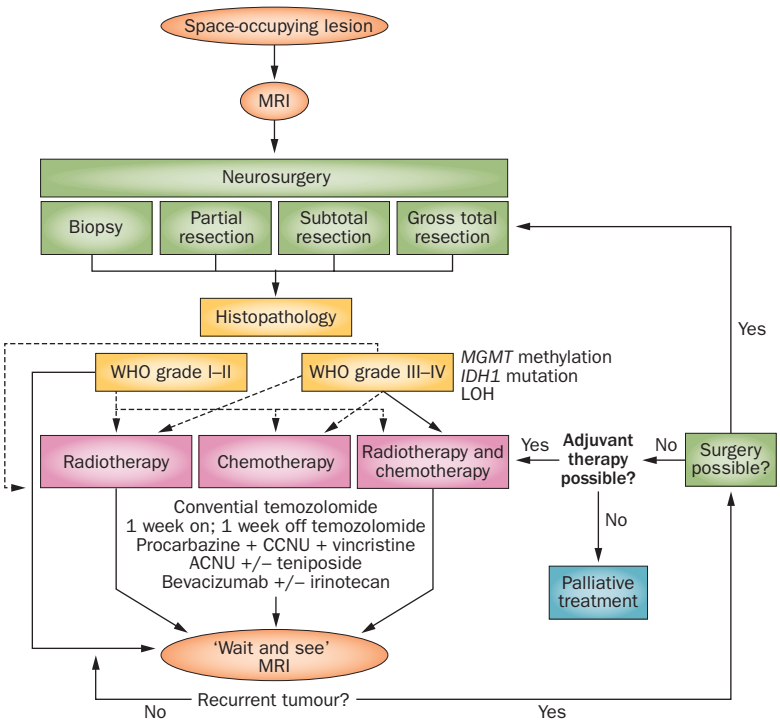

Figure 1 | Treatment algorithm for patients with glioma. Optimized treatment algorithm for patients diagnosed with intracranial space-occupying lesions from the time of initial clinical presentation to the point of exhaustion of therapy options. The dotted lines represent permutations and combinations of radiochemotherapy options according to individual case-specific needs. Solid lines represent standardized options. Molecular factors with known roles in tumour pathophysiology, but that exert no influence on treatment protocols, are also integrated. Abbreviations: *IDH1*, isocitrate dehydrogenase 1; LOH, loss of heterozygosity; *MGMT*, O^6-methylguanine-DNA methyltransferase.

a location preference. Although tumour growth can lead to signs of raised intracranial pressure, growth that occurs in eloquent areas often leads to highly variable symptoms, none of which is pathognomonic for brain tumours. These symptoms include location-dependent deficits, such as hemiparesis; Broca's, Wernicke's or combined defects; visual field deficits; nausea and/or vomiting; and gait disturbances, as well as general symptoms such as persistent headaches, epileptic seizures, confusion, memory loss, personality and cognitive changes, and generalized weakness.[11]

Following an initial investigation of the patient by a general practitioner, family physician or, depending on the acuteness of onset and severity of symptoms, by a neurologist or an emergency department attendant, the necessary imaging is carried out. Such imaging seems to be implemented at an increasingly early stage after presentation owing to general disposability and low costs of standard methodologies.[12] With the advent of high-resolution MRI scanners, improved and quicker visualization of detailed vascular structure, perfusion, spectroscopy and functional brain mapping is now possible.[13] Compared with CT scanning, MRI is superior for assessment of patients with glioma as it enables both initial tumour detection and radiological differentiation of recurrent tumours and treatment-related pseudoprogression. In the event of a diagnosis of a space-occupying lesion, neurosurgery is recommended, with either cytoreductive surgery (where possible) or biopsy often constituting the first step of therapy.

Neuropathological assessment provides information that enables classification of the tumour according to the WHO guidelines. About 30% of radiologically suspected low-grade (WHO grade I and II) gliomas—defined by their lack of contrast enhancement on MRI—are later histopathologically classified as malignant gliomas.[14,15] Such discrepancy between radiological and histopathological diagnosis indicates that high-resolution imaging alone is not a reliable tool in predicting the status of brain tumours. Histopathology must, therefore, be considered mandatory in any case of suspected glioma.

Follow-up imaging and treatment

Follow-up in cases of low-grade glioma typically involves observation with repeat MRI, whereas in high-grade glioma an adjuvant therapy is indicated. Randomized clinical trials found that a multimodal approach combining stereotactic fractionated radiation and concomitant chemotherapy (with the DNA-alkylating agent temozolomide) increased median patient survival to 14.6 months compared with 12.1 months with radiation alone.[6,16–18] Notably, temozolomide is better tolerated than are older chemotherapeutics such as ACNU, BCNU and CCNU.

Following treatment with concomitant chemotherapy and radiotherapy, novel, sophisticated metronomic or even uninterrupted chemotherapy dosage schemes—including a dose-dense intensified temozolomide monotherapy for a further 6 months to 1 year (or longer)—are now widely advocated, and are administered at the discretion of the treating centre.[19–21] Clinical trials indicate that, in terms of efficacy and patient outcome, achievement of maximal drug levels is superior to long duration of low-dose chemotherapy or total dosage intake.[19,22] Frequent MRI is also generally advised at this stage of patient management to facilitate early detection of tumour progression.

In the event of tumour recurrence, a thorough re-evaluation of the patient, including reassessment of their clinical condition, is carried out to enable tailoring of further treatment. Such treatment may consist of repeat surgery, radiotherapy and/or chemotherapy.[20,23] When making treatment decisions for patients with glioma,

adherence to the therapy algorithm (Figure 1) could markedly improve quality of life and increase overall survival.[24] Most of the current efforts aimed at improving this algorithm have focused on development and improvement of chemotherapy protocols.[25,26] The value of the first-line treatment—that is, maximal feasible surgical resection of the tumour—and clinical assessment criteria for this approach remain subjects for discussion.[27,28]

Assessing treatment success

The success of adjuvant treatment is defined using parameters such as the volume of tumour reduction, preoperative and postoperative patient performance, progression-free interval, quality of life, and overall survival. In neuro-oncology, a common dilemma when presented with glioma is whether biopsy alone is sufficient for treatment. Questions are raised about whether partial or subtotal tumour debulking should be carried out or if a forced gross total resection should be performed, and how to proceed with surgery for tumours in eloquent areas. As many neurological symptoms can be traced back to the space-occupying effect of the tumour itself, debulking even to a small extent can lead to a decrease in intracranial pressure and thus to improvement in acute symptoms, and improvement or elimination of seizures can be attained through resection of epileptogenic areas.[29,30] Taking these positive outcomes of surgery into account, it remains unclear whether surgical resection functions only to alleviate tumour mass effects, or whether it intervenes in the tumour disease itself and, if so, to what extent.

Glioma recurrence

An argument against therapeutic surgery?

Owing to their diffuse and infiltrative growth in the brain, malignant gliomas often recur after surgical therapy. These relapses constitute a setback for the patient and represent a formidable therapeutic challenge. One explanation for recurrences early after primary surgery may lie in nonstandardized—and hence unreliable—methods to determine the extent of glioma resection. Neurosurgeons often describe a 'macroscopic complete resection' or 'gross total resection' despite the fact that an objective measure to assess the resected and remaining volume is either absent or simply not defined.[31] Macroscopic complete resection usually implies removal of the preoperatively defined contrast-enhancing tumour portions. Postoperative MRI documentation represents the gold standard in surgical outcome assessment but, ideally, resection control should be performed using intraoperative imaging or, as an alternative, with postoperative MRI (preferably within 48 h following surgery). Assessment of tumour volume prior to and following surgery is instrumental for evaluation of surgical success and multimodal therapy outcome, but requires definition of accurate and validated volumetry methods to measure the extent of resection (Box 1).

Response-assessment criteria have been established for radiotherapy and chemotherapy in glioma; these criteria assist clinicians when making therapeutic adjustments and enable comparisons of clinical trials.[32,33] The RANO (Response Assessment in Neuro-Oncology) criteria[34] for measurement of surgical outcome in glioma include 2D tumour measurements on CT or MRI with T1 gadolinium-enhancement or T2 fluid-attenuated inversion recovery (FLAIR) sequences. Although methods to accurately measure preoperative and postoperative tumour volume exist, no established objective protocols to evaluate the extent of tumour resection have been defined. Many academic neurosurgical centres are using established preoperative and postoperative MRI with T2 FLAIR sequences to make 3D volumetric measurements in their clinical routine. Creation of computer-assisted tumour volume algorithms, which could enable comparison of surgical techniques and clinical trials, will lead to further progress in objective evaluation of tumour resection. Furthermore, the introduction of intraoperative imaging techniques such as intraoperative MRI, neurophysiologically and biologically active fluorescence markers, and their various combinations, now permits direct visualization of tumour tissue and enables intraoperative assessment.[35–41]

Box 1 | Advanced neurosurgical techniques

Introduction of new imaging techniques and combined use of these techniques has led to advances in neurosurgery. The following preoperative and intraoperative techniques have been shown to improve surgery for malignant glioma resection:

Preoperative techniques

- Arterial spin labelling
- Diffusion tensor imaging
- Diffusion-weighted imaging
- Perfusion, permeability diffusion MRI
- Magnetic reasonance spectroscopy
- Metabolic imaging

Intraoperative techniques

- Fluorescence-guided surgery
- Intraoperative MRI
- Functional imaging
- Intraoperative brain mapping
- Intraoperative ultrasound
- Dual intraoperative visualization approaches

Stem cell-like partisan cells

The battle to prevent glioma recurrence has a long history that began at a time when radiological imaging was in its infancy, and involved unsuccessful attempts at extensive lobectomies or hemispherectomy.[42,43] The failure of these approaches indicates that disseminated or tumour-initiating stem cell-like cells (collectively termed 'partisan cells') invade normal brain parenchyma and remain in the brain after tumour resection. Reports of malignant gliomas spreading outside the CNS are isolated, but the risk that glioma can be transmitted via organ transplantation is still considered and, thus, patients with malignant glioma are normally excluded as organ donors.[44–46]

The mechanisms behind the conjectured dissemination and transmission of glioma cells are unclear,

Box 2 | Postsurgical prognostic factors

- Age of patient
- Score on Karnofsky Performance Status Scale
- Presence of comorbidities (such as diabetes mellitus, chronic obstructive pulmonary disease, arterial hypertension, renal insufficiency, coagulopathies, and/or other neurological deficits)
- Tumour localization in relation to functionally eloquent areas (functional grade, benefit:risk ratio)
- Multilocal foci
- Extent of resection

but recent genetic data indicate that glioma heterogeneity may lie in its stem cell and neuronal precursor cell origins.[47–49] Importantly, stem cell-like neural precursors isolated from human glioblastoma biopsies have been shown to induce angiogenesis[47,50]—a hallmark of brain tumour malignancy.[51,52] Comprehensive profiling of glioblastoma tissue samples has revealed diagnostically relevant genetic aberrations, including somatic mutations in tumour suppressor protein p53 (*TP53*); neurofibromin 1 (*NF1*), which is involved in regulation of the oncogene Ras; human epidermal growth factor receptor 2 (*ERBB2*), which encodes a protein also known as HER2, Neu, or CD340; and the isocitrate dehydrogenase 1 (*IDH1*) gene.[53] These mutations all enhance glioma cell proliferation and suppress apoptosis, and are thus termed 'driver mutations'.[54] Of note, driver mutations in paediatric patients with glioblastoma differ from those found in adults.[55]

Although the genetic profile of recurring gliomas remains to be defined,[56] results of clinical trials stand in favour of surgery for debulking of these tumours, as modern reoperations are safe and do not necessarily reduce general well-being and daily life activities.

Preoperative prognostic factors

Evidence now indicates that several independent factors influence outcome following resective surgery in terms of quality of life and overall survival (Box 2). These parameters include age, patient performance status and general condition, comorbidities, imaging aspects (such as tumour localization, bihemispheric expansion or multifocal manifestation), and compliance on the part of the patient.[57,58] The two prognostic factors that are generally accepted as being the most crucial in survival of patients with malignant glioma are age, and performance status as measured using the Karnofsky Performance Status Scale (KPS).[59]

Age

Clinical trials of resection therapy for glioma unanimously show that patient age is inversely proportional to the period of overall survival: patients >40 years of age have a clear advantage over those with a comparable KPS score who are aged 45–65 years,[60,61] and elderly patients (>65 years of age) have the worst prognosis.[62] However, prolonged survival time can be achieved in elderly patients in otherwise good general condition when gross total resection is achieved.[63,64]

Clinical performance

Various scales for assessment of patient performance have been developed, of which the KPS is the most established and widely used. Several studies have consistently reported a positive association between KPS values and overall prognosis: patients with a KPS score >70 have the best prognosis whereas patients with a KPS scores <40 have a significantly reduced overall survival time.[65] Bihemispheric tumour expansion and gliomas in functionally eloquent areas of the brain are two factors that hamper achievement of gross total resection without incurring neurological deficits. Postoperative neurological deficits are associated with deterioration in KPS scores and, thus, lower survival time. Consequently, aggressive tumour resection in functionally eloquent areas carries a high risk of deterioration in clinical outcome.

Multifocality

Although malignant gliomas tend to grow as single-entity tumours, they can also appear at multiple locations within the brain. The prognosis in multifocal glioma manifestation is controversial, as often only one of the satellite tumours can be removed, and such partial removal is linked to a shorter survival time. Resection of all satellite tumours, even if several reoperations are necessary to achieve gross total resection, carries a prognosis comparable to that of standard gross total resection of solitary tumour manifestations.[66]

Central necrotic area

Another factor that exerts a negative influence on survival time for patients with malignant glioma is the presence of a central necrotic area.[67–69] Compared with patients who exhibit this lesion, patients with glioblastomas that lack a central necrotic area have better prognosis, with extension of survival time by up to several years.[70,71] These findings are corroborated by data showing a direct correlation between the presence of a central necrotic area and worse prognosis.[72,73]

Genetic markers

Traditional genomic and high-throughput microarray studies have revealed at least four markers with clinical predictive relevance.[69–71] These studies revealed absence of epidermal growth factor receptor (*EGFR*) gene amplification, loss of heterozygosity at chromosome arms 1p and 19q, methylation of the O^6-methylguanine-DNA methyltransferase (*MGMT*) promoter, and presence of *IDH1* mutations as molecular preconditions that are predictive of favourable outcome in patients with glioblastoma (Box 3).

Summary

Taking all aspects into account, a variety of factors other than surgical management can influence outcome in patients with glioblastoma. Given the results of clinical trials, a general consensus exists that surgical neuro-oncology must strike the optimum balance between the benefits of maximal extent of resection and the risks associated with clinical factors. Notably, postsurgical

deterioration of KPS scores could be as detrimental to quality of life and overall survival as incomplete resection. Despite numerous studies, however, the effects of the extent of resection on stratified clinical parameters, as well as on quality of life and overall survival, remain unclear.

Assessment of extent of resection

Over the past few years, the issue of whether the extent of tumour resection can affect survival has been controversial. Several studies indicate that the extent of resection exerts no influence on overall patient survival,[36,74,75] whereas others have shown a positive correlation between tumour resection volume and clinical course.[57,76–78] Notably, of those studies in which no positive correlation was found, almost all involved only a small number of patients.[27] A further drawback of these studies lay in limitations inherent to subjective estimation of the extent of resection; such assessment could easily be misleading, as macroscopic differentiation between pathological and normal tissue is difficult, even for experienced neurosurgeons. Suboptimal visualization into the resection cavity or an intervening layer of apparent healthy tissue could also give the erroneous impression of complete resection. Methods to assess the extent and success of surgery, therefore, are urgently needed.

Objective criteria for surgical success

Clinical trials have been performed to elucidate the effects of tumour resection on prognosis,[77,79–81] but certain aspects hamper extrapolation of results and prevent comparison of the studies. First, the criteria to determine extent of resection, preoperative and postoperative tumour volume, and the relationship of such factors with overall survival time, were often inhomogeneous. Second, as suboptimal numbers of patients were recruited, the evidence could not be considered as 'strong'. Third, each study utilized different imaging techniques and volumetric approaches. Despite these issues, interpretation of the results revealed a general impression that surgical therapy had less of an effect on overall survival time than did medical treatment.

Several novel intraoperative visualization techniques have now been developed that enable objective assessment of the extent of tumour resection. Excellent examples include intraoperative MRI (iMRI),[36,75,82] tumour visualization with 5-aminolevulinic acid (5-ALA),[38,83,84] intraoperative electrophysiological brain mapping,[41,85] intraoperative ultrasound,[86,87] and dual intraoperative imaging approaches.[40] Use of these new techniques should improve measurement of resection extent, and thus enhance the reliability of results of clinical trials that aim to assess how the extent of tumour resection influences outcome.

Tumour heterogeneity

As malignant gliomas show no location preference in the brain, the clinical presentation of patients with these tumours can vary enormously. For clinical trials, this variability presents complications with patient stratification approaches based on risk associated with tumour type and/or location. Besides traditionally accepted factors that may influence patient presentation such as general health[65] and age of the patient,[61] proximity of the tumour to functionally eloquent brain areas,[36] multifocal manifestation,[58] and the presence of a central necrotic area,[69] novel molecular factors have emerged that may underlie the polyclonal and heterogeneous character of glioblastomas. Such factors may also explain the heterogeneity of patient cohorts in randomized trials. To address this problem, large clinical trial cohorts are required to achieve a homogenous distribution of these limiting factors.

Box 3 | Genetic factors with predictive value in malignant glioma

Traditional genomic and advanced high-throughput microarray studies in malignant glioma have uncovered central canonical oncogenic pathways that enable stratification of patients into subgroups.[105–107] Several molecular anomalies have been consistently associated with primary glioblastomas.[108,109]

EGFR amplification and _TP53_ mutation

Epidermal growth factor receptor (*EGFR*) gene amplification leads to increased tumour proliferation and augmented resistance towards therapeutic apoptosis. Combined *EGFR* and tumour protein 53 (*TP53*) alterations were associated with poor patient survival.[110]

1p19q codeletion

1p19q codeletion is associated with an oligodendroglial morphology,[111] and such mutations are associated with a favourable prognosis and good response to radiochemotherapy.[112] Patients with a 1p19q codeletion who do not receive radiochemotherapy do not have prolonged survival time.[113]

Methylation status of the _MGMT_ promoter

MGMT (O^6-methylguanine-DNA methyltransferase) is a ubiquitously expressed DNA-repair enzyme that dealkylates DNA.[114–117] Accordingly, decreased MGMT protein levels correlate with accumulated DNA damage and susceptibility towards alkylating agents such as temozolomide.[118,119] Epigenetic silencing of *MGMT* via methylation of the *MGMT* promoter reduces the active MGMT-enzyme pool, leading to early DNA damage and a subsequent increase in tumour cell apoptosis.[116,118] In patients with glioma, methylation of the *MGMT* promoter is predictive of a favourable response to temozolomide.[116,120]

Presence of _IDH1_ mutations

In WHO grade II and III gliomas and in secondary glioblastomas, mutations in the isocitrate dehyodrogenase 1 (*IDH1*) gene are common, whereas primary glioblastomas seldom show such alterations.[105,121,122] *IDH1* mutations can be used to distinguish primary glioblastomas from secondary ones that are derived from grade II and III gliomas. *IDH1* mutations do not cause loss of function and may act through either oncometabolic hydroxyglutarate formation or reduction of wild-type enzymatic activities. *IDH1* mutations are also associated with the activation of hypoxia-inducible factor signalling, although it remains to be ascertained how this action would, in turn, affect prognosis.[123,124]

Clinical studies

As of December 2012, management of malignant glioma had been addressed in 102 studies, 10 of which were clinical trials that focused on the extent of resection (Table 1). As most neurosurgical trials on the role of glioma resection were retrospective and revealed heterogeneous outcomes, methodological considerations such as surgical techniques and imaging approaches must be taken into account.

Gross total resection is defined as the removal of visible contrast-enhancing tumour tissue visible on MRI alone. With this approach, however, microscopic deposits of tumour cells, which are not detectable with routine imaging techniques, often remain. This problem raises the question of what modality to use to

Table 1 | Clinical studies investigating effects of extent of glioma resection on survival

Study	*n*	Imaging or surgical tool	Definition of surgery or outcome	Resection extent and survival (days)	*P* value
Lacroix *et al.* (2001)[69]	416	Microsurgery	EOR (%)	<98% (264) ≥98% (390)	<0.0001*
Laws *et al.* (2003)[57]	413	Microsurgery	Biopsy vs resection	Biopsy (147) Resection‡ (317)	<0.0001
Vuorinen *et al.* (2003)[94]	30	Microsurgery	Biopsy vs GTR	Biopsy (85) GTR (171)	<0.035
Schneider *et al.* (2005)[90]	27	iMRI	EOR (%)	<100% (237) 100% (537)	<0.004
Stummer *et al.* (2006)[38]	243	5-ALA	Incomplete resection vs GTR	Incomplete (354) Complete (501)	<0.0001
McGirt *et al.* (2009)[93]	700	Microsurgery	STR vs NTR vs GTR	STR (240) NTR (330) GTR (390)	<0.05
Senft *et al.* (2010)[91]	41	iMRI	STR vs GTR	STR (322) GTR (518)	<0.001
Ewelt *et al.* (2011)[63]	103§	Microsurgery	Biopsy vs partial resection vs GTR	Biopsy (66) Partial resection (210) GTR (417)	<0.05
Kuhnt *et al.* (2011)[77]	117	iMRI	EOR (%)	<98% (270) ≥98% (420)	<0.001
Sanai *et al.* (2011)[81]	500	Microsurgery	EOR (%)	78% (375)‖ 80% (384) 90% (414) 100% (480)	<0.0001

*Statistically significant level was reached at 89% resection ($P = 0.04$). ‡Extent of resection not indicated. §All patients aged >65 years. ‖78% tumour resection identified as threshold at which any survival benefit is seen. Abbreviations: 5-ALA, 5-aminolevulinic acid; EOR, extent of resection; GTR, gross total resection; iMRI, intraoperative MRI; NTR, near-total resection; STR, subtotal resection.

determine efficacy of tumour resection. Introduction of fluorescence-guided cytoreductive surgery in the mid 1990s[83,88,89] provided an advanced method to visualize tumours at the cellular level, with submillimetre resolution—a resolution that is currently unattainable on standard magnetic resonance-based scanners. This new technology enabled discrimination of tumour tissue from surrounding tissue. However, as data from MRI can be used to generate 3D reconstructions of the brain with depiction of the interrelationship between the tumour and functionally eloquent areas, MRI is generally accepted as the method of choice for tumour volumetry.

Interestingly, from three clinical studies that utilized intraoperative visualization approaches to enable continuous monitoring of tumour volumetry,[30–32] a consensus was reached that resection of >98% or gross total resection is favourable whenever possible, with biopsy considered to be the worst treatment option. In two studies, statistically significant results with regard to survival were achieved with resection volumes of 78% ($P < 0.0001$)[81] and 89% ($P = 0.04$).[69] However, the fact that these studies involved collection of patient data over several years, and utilized different surgical, radiotherapy and chemotherapy protocols at various points in the study, raises concern about the validity of the results.

5-ALA-based fluorescence-guided surgery was used in one clinical study,[78] with iMRI being implemented in three others.[77,90–92] The fact that the longest patient survival times were achieved in these four studies (Table 1) unequivocally demonstrates that image-guided surgery leads to a more tailored resection than does white-light-aided surgery. Six studies utilized conventional white-light microsurgery, and thus were subject to the aforementioned assessment pitfalls that are inherent in this approach.[57,63,69,81,93,94]

Intraoperative imaging and surgery

The advantage of intraoperative imaging techniques lies in the detection of pathological tissue that is not visible with white light, and its capacity to enable direct visualization of the surgical procedure. Future combinations of intraoperative image-guided approaches should aim to increase the extent of glioma resection by enhancing the positive attributes and minimizing the disadvantages associated with each technique. For example, a dual intraoperative visualization approach involving fluorescence-guided surgery and iMRI with integrated functional neuronavigation could permit more-comprehensive planning and high-precision surgery, particularly in patients with functional grade II tumours that are located in the vicinity of eloquent brain areas.[40]

Functional grading of brain tumours

Collective analysis of the 10 clinical studies reveals that the extent of tumour resection does indeed show positive correlation with increased overall survival time (Table 1), with gross total resection (threshold >98%) increasing survival time by a mean of 150 days over incomplete resection.[24–29,33,50,52,94] The feasibility of gross total resection within the brain must be considered, however, as

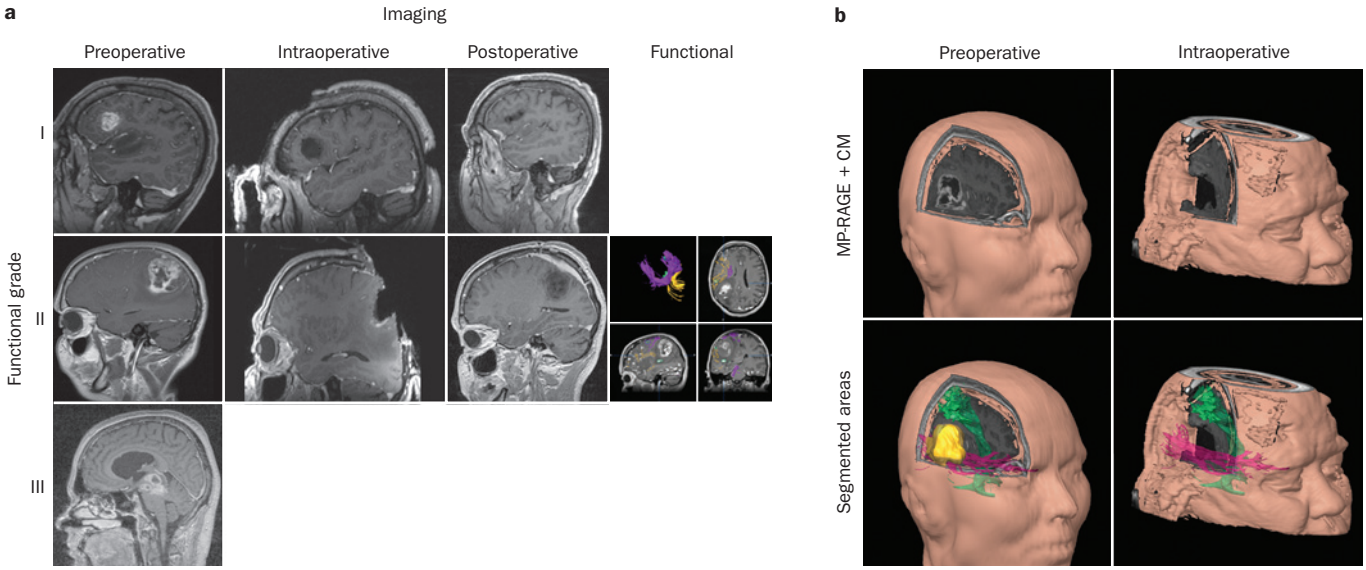

Figure 2 | Functional grading and imaging of malignant gliomas and surgical planning. **a** | Preoperative T1-weighted contrast-enhanced MRI depicting tumour location in relation to expected anatomical location of functionally eloquent brain areas. Functional grade I tumour: iMRI depicts gross total resection without the need for functional imaging studies. Functional grade II tumour: preoperative functional imaging defines tumour location with respect to functionally eloquent brain areas, thereby permitting gross total resection as documented in the iMRI scans. Functional grade III tumours: localization within eloquent areas, as shown in preoperative imaging in the case of a malignant brainstem glioma, makes radical surgery impossible. **b** | State-of-the-art functional neuronavigation depicting functionally eloquent brain areas and their relationship to the brain tumour for thorough surgical planning. Left panels: 3D depiction of the tumour using MP-RAGE+CM (top image) and the volumetrically segmented tumour (yellow regions) as well as visualization of the pyramidal (green regions) and visual (pink regions) fibre tracts (bottom image). Right panels: 3D depiction of the intraoperative resection control (top) and the postresectional visualization of the intact pyramidal and visual tracts (bottom). Such operative planning aids in determining the feasibility of gross total and/or possible extent of tumour resection. Abbreviations: iMRI, intraoperative MRI; MP-RAGE+CM, magnetization prepared rapid gradient-echo with contrast medium.

tumour location is one of the primary limiting factors in resection. Gross total resection of tumours in functionally silent brain areas is easily achievable and may even afford the luxury of a comfortable safety margin. Tumours in critical brain areas, however, cannot be resected at all. Tumours that lie between these two extremes pose a challenge to surgical neuro-oncology, as a thin line exists between inadequate resection owing to concerns of causing damage to the adjacent functionally eloquent brain areas, and radical resection with the inevitable postoperative neurological deficits.

In addressing the issue of resection feasibility, a simple but elegant classification devised by Sawaya *et al.* has shown merit.[95] With regard to the need for specialized diagnostic imaging prior to surgery, this system facilitates quick decisions on the basis of functional grade: grade I refers to tumours located in non-eloquent brain areas; grade II tumours are located in the vicinity of eloquent brain areas; and grade III tumours are located in eloquent brain areas (Figure 2a). In contrast to patients with functional grade I tumours, those with functional grade II or grade III tumours must undergo preoperative diagnostic imaging studies with representation of relevant, functionally eloquent brain areas (Figure 2b). Functional grading can, therefore, guide surgery or, in cases where only a biopsy is taken, aid in planning for safe access. Gross total resection can be easily achieved in functional grade I tumours through conventional microsurgery techniques and in all functional grade II tumours with the aid of functional visualization techniques (such as functional neuronavigation; Figure 2b). In the case of functional grade III tumours, however, only partial resection or biopsy can be carried out.

Postoperative considerations

Even with aggressive multimodal treatment, patients with glioblastoma have a poor prognosis, and all will eventually succumb to the disease or associated complications. Nevertheless, we have recently witnessed a gradual increase in patient survival time, which can be attributed to our increased understanding of tumour pathophysiology. The majority of clinical studies have focused on optimizing radiochemotherapy protocols on the basis of molecular and clinical factors.[96–98] Despite these efforts, inhomogeneity of cohort distribution with regard to age, KPS score, functional grade, and extent of resection, carries the danger that the data are not representative of all patients with malignant glioma. Although the role of the extent of glioma resection is often disregarded, several studies have shown a distinct association between increased cytoreduction and prolonged survival time.[81,93] In addition, several studies indicate an association between increased cytoreduction and favourable response to adjuvant treatment.[77,78,91,93] As these studies show, the remaining tumour volume is critical with regard to prognosis (Table 1); thus, when predicting

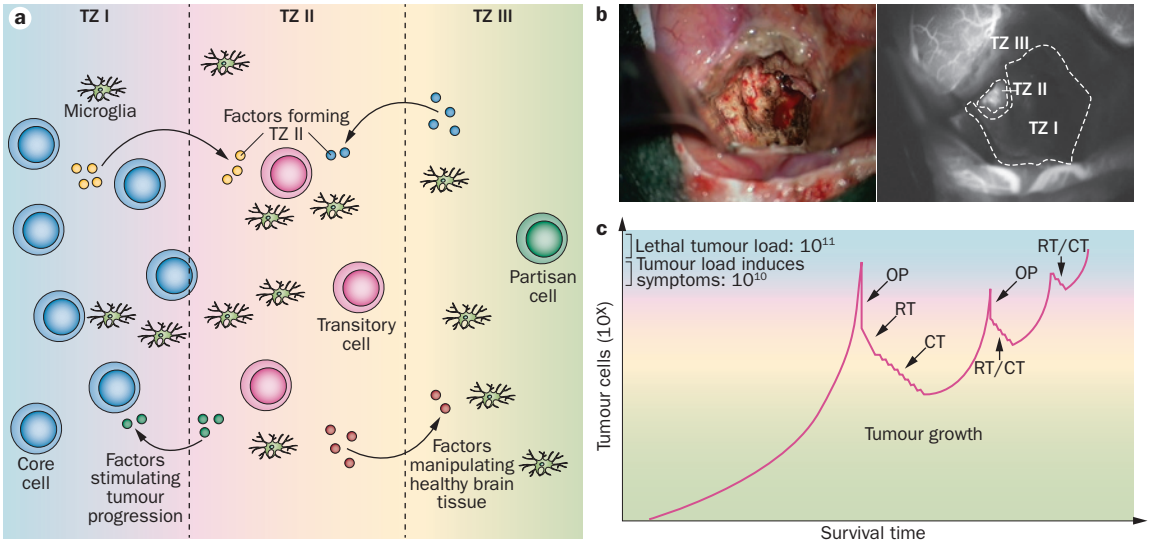

Figure 3 | The tumour zone model. **a** | Conceptual framework depicting the heterogeneity of malignant gliomas is encapsulated in a model classifying gliomas into three distinct tumour zones (TZs). TZ I consists of the main tumour bulk. TZ II represents tumour microenvironment or zone of perifocal oedema. TZ III represents macroscopically healthy brain parenchyma. Microglial cells accumulate most frequently in TZ II, although they can also be identified in TZs I and III. **b** | TZs in the context of an actual tumour. Imaging using white-light microscopy (left panel) does not enable differentiation of the individual zones. Imaging of vascularization by use of indocyanine green fluorescence (right panel) enables visualization of areas of hypervascularization (representing TZ II) that border TZ I and III. **c** | Model of the relationship between tumour cell mass and survival time. Tumour growth kinetics during the undetected preclinical phase and following neuro-oncological therapy. A tumour load of 10^{10} cells leads to clinical symptoms, even if the tumour is located in a functionally silent area of the brain. An increase in tumour load to $>10^{11}$ cells is incompatible with life. Abbreviations: CT, chemotherapy; OP, operation; RT, radiotherapy.

outcome, the extent of tumour resection should be considered to avoid the danger of nonrepresentative bias.

The tumour zone model

From the available literature, one can conclude that the most favourable outcomes following glioma surgery are achieved in cases of >98% resection. To explain this finding, we propose a theoretical model whereby the tumour microenvironment consists of at least three heterogeneous areas (Figure 3a,b).[99]

Comprising the main tumour bulk, tumour zone I consists of the 'core cells' or 'centre cells', and corresponds to the contrast-enhancing regions observed on MRI. Tumour zone II—also termed the peritumoural zone—includes glioma cells that are described as 'transitory cells' as they exhibit some, but not necessarily all, histological features of core glioma cells. This zone, which also contains microglial cells and displays hypervascularization and endothelial cell proliferates, is probably the most biologically active area of the tumour. In the case of malignant gliomas, despite accumulation of microglial cells, no competent immune response is generated.[100] Tumour zone II is depicted on MRI as an area of perifocal oedema.

Tumour zone III seems to be clinically silent and is, therefore, the most intractable region to manage therapeutically. This zone consists of macroscopically healthy brain parenchyma that comprises solitary tumour cells, tumour-initiating (stem cell-like) cells, or precursor cells that are collectively termed 'partisan cells'. Various factors that foster tumour growth and adapt the microenvironment in favour of the neoplasm are secreted and released in each of the zones. These factors promote glioma progression by inducing angiogenesis, intensifying the perifocal oedema, inducing neuronal cell death, paralysing immune cells, and stimulating proliferation and invasion (Figure 3a,b).[100–104]

At best, gross total resection entails complete resection of tumour zone I, with only partial resection of tumour zone II. In rare cases, complete resection of tumour zone II may also be achieved, but complete resection of all tumour zones is practically impossible. According to the mathematics, therefore, about 10^6–10^7 tumour cells will inevitably remain even in the case of a gross total resection (Figure 3c). Although postoperative radiochemotherapy leads to further tumour cell reduction, some radiochemoresistant partisan cells will remain from which tumour recurrences can develop. In this scenario, the cycle of surgery—now primarily performed to counter the space-occupying effect of the recurrence—and subsequent radiochemotherapy is repeated, and leads to selection of increasingly resistant tumour cells. Through this repetitive selection, the time from surgery to recurrence is reduced with each successive cycle. At some point, neither surgery (if possible) nor radiochemotherapy can control tumour progression any longer. Consequently, neuro-oncological treatment becomes a race against time until the limits of surgical treatment and acquired resistance to radiochemotherapy are superseded (Figure 3c).

Considerations and future directions

Results of studies that take all factors of glioma therapy into account are still in danger of bias owing to the

naturally suboptimal distribution of subgroups that is inherent to studies with low patient numbers. For class I evidence on the effects of tumour resection on patient outcome, an ideal but ethically challenging scenario would require deliberate cytoreduction to various predetermined extents, in order to maximize homogeneity in various subtotal (>80%), near-total (>95%) and total (>98%) resection groups. In reality, however, distribution into subgroups according to extent of resection has occurred only following maximal feasible resection in cases where a remaining tumour mass was not resected, probably owing to its localization in functionally eloquent brain areas. As this drawback cannot be avoided, we must continue to work with the data we have at hand.

Thus far, evidence suggests that maximal cytoreduction without resultant neurological deterioration is in the best interest of the patient, and that together with clinical and genetic factors, the functional grade of brain tumours has prognostic value for surgical outcome. Taking the extent of resection alone as a factor, data further indicate that gross total resection improves survival over incomplete resection by up to 5 months.[78]

Three decades ago, the dream of neurosurgeons was to achieve complete resection of tumour zone I without inflicting neurological deterioration. Today, advances in intraoperative imaging enable neurosurgeons to carry out precise tumour excisions, even for those tumours that are adjacent to eloquent brain areas, and to target tumour zone I and II with few complications. Advances in surgical and intraoperative imaging techniques are likely to enable surgical attempts at resection of the currently inoperable tumour zone III. The challenge will be to stratify patient cohorts for medical treatment on the basis of surgical outcome and in conjunction with individual genomic and tumour characteristics.

Conclusions

Despite concerted, intensive research efforts worldwide, the neuro-oncological fraternity still has a long road ahead in the search for a cure for malignant glioma. Current treatment protocols focus on extension of survival time through improvement of quality of life in a race against time. The gold standard therapy for malignant glioma consists of primary tumour surgery with the aim of achieving maximum possible resection, followed by radiochemotherapy then chemotherapy alone for 6 months. Although the surgical aspect of glioma management has a pivotal role in improving survival, with numerous studies showing that a resection of >98% of tumour volume is associated with maximum possible life expectancy, extreme caution must be exercised to prevent postoperative neurological deterioration. In this context, advances in surgical techniques, including improved integrated visualization of brain function, are continuously expanding the definition of 'safe' gross total resection. History has taught us that the surgeon's own intraoperative impression can no longer suffice as an acceptable determinant of the extent of resection: state-of-the-art visualization technology must be used to quantify tumour removal and improve surgical accuracy to enable resection to the maximal feasible extent. The days of microsurgery with the use of white light alone belong in the past. Integration of intraoperative visualization techniques with quantifiable assessment criteria will soon become standard practice in surgical neuro-oncology, bringing with it the hope of improved survival for patients with malignant glioma.

Review criteria

A literature search of PubMed and ClinicalTrials.gov served as a basis for the literature analysis. Articles were identified using the keywords "glioma" and "extent of resection", either alone or in combination. The relevant papers identified by this search (up to December 2012 and articles in English only) were reviewed and the references therein were also reviewed for other useful leads.

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Acknowledgements

We thank all members of our neuro-oncology laboratory team for continuous support and clinical and experimental data discussion. The Tumorzentrum Erlangen-Nürnberg, particularly P. Karl and S. Petsch, are acknowledged for continuous collaboration and clinical data exchange. K. Friedlein is gratefully acknowledged for initial comorbidity analysis. We further thank P. Grummich for functional imaging, F. Bittner for digital artwork, and J. Halstead (Syngenta, Basel, Switzerland) for helpful comments. N. Hore is gratefully acknowledged for editing and critical suggestions on the manuscript. This study was supported by the German Research Foundation (DFG Grant Ey94/2-1 awarded to I. Y. Eyüpoglu).

Author contributions

All authors contributed equally to researching data for the article, discussion of the content, writing the article, and to review and editing of the manuscript before submission.