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Review article

The biological and clinical basis for early referral of low grade glioma patients to a surgical neuro-oncologist

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ABSTRACT

The discovery of IDH1/2 (isocitrate dehydrogenase) mutation in large scale, genomewide mutational analyses of gliomas has led to profound developments in understanding tumourigenesis, and restructuring of the classification of both high and low grade gliomas. Owing to this progress made in the recognition of molecular markers which predict tumour behavior and treatment response, the increasing importance of adjuvant treatments such as chemo- and radiotherapy, and the tremendous advances in surgical technique and intraoperative monitoring which have facilitated superior extents of resection whilst preserving neurological functioning and quality of life, contemporary management of low grade glioma (LGG) has switched from a passive, observant approach to a more active, interventional one. Furthermore, this has implications for the manner in which patients with incidentally discovered and/or asymptomatic LGG are managed, and this review of the biological behaviour of LGG, as well as its clinical investigation and management, should act as a timely reminder to all clinicians of the importance of referring LGG patients early to a surgical neuro-oncologist who is not only familiar and acquainted with the vagaries of this disease process, but who, in addition, is devoted to delivering care to these patients with the support of a multi-disciplinary clinical decision-making unit, comprising medical neuro-oncologists, radiation oncologists and allied health professionals.

The discovery of specific molecular aberrations that drive gliomagenesis has led to important modifications in the taxonomy of astrocytoma. The most recent edition of the WHO Classification of CNS Tumours has, for the first time, incorporated molecular parameters and traditional histological methods to stratify and define each tumour entity [1]. For instance, the diagnosis of oligodendroglioma is now made on the basis of presence of the characteristic 1p19q codeletion, and the oft-confusing former diagnosis of oligoastrocytoma has been largely abandoned. Although diffuse astrocytomas remain defined along previously established histological features, where grade II astrocytoma is hallmarked by nuclear atypia, anaplastic astrocytoma (grade III) by the presence of mitoses and glioblastoma (grade IV) by endothelial proliferation and palisading necrosis, genetic markers (i.e. ATRX loss, TP53 and IDH1/2 mutations) also impact brain tumour classification.

Therefore, supratentorial WHO grade II LGG are divided into two distinct histological categories: oligodendroglioma, and diffuse astrocytoma. (Table 1) As IDH1/2 mutations occur early in tumourigenesis [2,3], stratification into each group becomes dependent on subsequent genetic abnormalities: 1p19q codeletion

Abbreviations: 1p19q, short arm of chromosome 1, long arm of chromosome 19; 2-HG, 2-Hydroxyglutarate; α-KG, α (Alpha)-Ketoglutarate; ATRX, Alpha Thalassemia/mental Retardation syndrome X-linked; BBB, Blood-brain barrier; CDKN2A, Cyclin-Dependent Kinase inhibitor 2A; CDK4NA, Cyclin-Dependent Kinase inhibitor 4A; CNS, Central Nervous System; CNV, Copy Number Variations; CT, Computed Tomography; DNA, Deoxyribonucleic acid; DWI, Diffusion Weighted Imaging; EANO, European Association of Neuro-oncology; EGFR, Epithelial Growth Factor Receptor; EOR, Extent of resection; EORTC, European Organisation for Research and Treatment of Cancer; FET, Fluoroethyltyrosine; FLAIR, Fluid Attenuated Inversion Recovery; H3F3A, Histone H3.3A; HGG, High Grade Glioma; HR, Hazard ratio; IDH, Isocitrate Dehydrogenase; IDHmut, IDH mutant; IDHwt, IDH wildtype; IGFBP2, Insulin-like Growth Factor Binding Protein 2; KPS, Karnofsky Performance Score; LGG, Low Grade Glioma; MGMT, O-6-methylguanine-DNA methyltransferase; MR(I), Magnetic Resonance (Imaging); MRS, Magnetic Resonance Spectroscopy; NOS, Not otherwise specified; OS, Overall survival; PCV, Procarbazine/Lomustine/Vincristine; PET, Positron Emission Tomography; Pi3k, Phosphatidylinositol 3-Kinase; PFS, Progression-free survival; PTEN, Phosphastase and Tensin homologue; PWI, Perfusion Weighted Imaging; RTV, Residual Tumour Volume; TCGA, The Cancer Genome Atlas; TERT, Telomerase Reverse Transcriptase; TP53, Tumour Protein 53; UCSF, University of California San Francisco; WHO, World Health Organisation.

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Table 1
Algorithm of the integrated pathological diagnosis of gliomas. Please note that molecular signatures will outweigh histological characteristics in achieving an integrated diagnosis. The final diagnosis of oligoastrocytoma has thus been largely abandoned in the newest classification (adapted from 2016 WHO Classification of CNS Tumors [1]).

Traditional histopathology	Astrocytoma	(Oligoastrocytoma)	Oligodendroglioma	*Glioblastoma*	
IDH status	Mutant		Wildtype	*Mutant*	*Wildtype*
ATRX loss	Yes	No	No	*Yes*	*No*
1p19q codeletion	No	Yes	No	*No*	*No*
Final integrated diagnosis	Diffuse astrocytoma, IDH-mutant	Oligodendroglioma, IDH-mutant, 1p19q codeleted	Diffuse astrocytoma, IDH-wildtype	*Glioblastoma, IDH-mutant*	*Glioblastoma, IDH-wildtype*
WHO Grade	II or III	II or III	II or III	*IV*	*IV*
Inconclusive or unavailable genetic testing	Diffuse astrocytoma NOS	Oligoastrocytoma NOS	Oligodendroglioma NOS	*Glioblastoma NOS*	

(oligodendroglioma, as already mentioned), and ATRX loss/TP53 mutation for diffuse astrocytoma. However, this presumes that all LGG entities are IDHmut, which is not so; at least 10% of diffuse astrocytomas are IDHwt [4], with implications for genetic expression, tumour behaviour and prognosis. In fact, on that basis, this LGG subgroup has more in common with higher grade astrocytomas [5–7], whilst the clinical characteristics of IDHmut WHO Grade II and III astrocytomas appear almost to approach one another [8]. Thus, LGG represent a heterogeneous conglomeration of clinicopathological constructs, with repercussions for imaging, surgical management and adjuvant therapies.

Whilst CT and PET, respectively, play adjunct roles in detecting calcifications in the pre-operative diagnosis of oligodendroglioma and identifying 'hot' spots as a potential sign of tumour hyperactivity and/or progression [9], the mainstay of radiological diagnosis of LGG is MRI. The minimum required for adequate diagnosis is an anatomic MR exam (1.5 T or 3 T) with T2-weighted and pre- and post-gadolinium contrast enhanced T1-weighted imaging [10,11]. Typically, LGG is identified as a non-enhancing, T1-hypointense, T2- and FLAIR hyperintense mass lesion; contrast enhancement of as little as 1.2 cm^3 may be enough to distinguish glioblastoma from LGG, with very high specificity [12].

However, the controversy in LGG management, with regards to imaging, lies not in diagnosis; in practice, this is usually straightforward. Rather, the major debate revolves around the question of surveillance imaging over time, especially in those LGG patients who have not undergone treatment. Historically, LGG has been considered to be inactive or 'benign', at least on radiological grounds, however, longitudinal MRI studies, coupled with a deeper understanding of biological behaviour, has led to the development of a four step framework proposing to model the true natural history of LGG, all the way from MR silence, (with presumed occult glioma stem cell proliferation), to frank malignant transformation of LGG to glioblastoma [13,14]. There is also inconsistency regarding what the radiological radial growth rate of a given LGG might be, how that is affected by treatment, not to mention, of course, the explosive growth and development of enhancement characteristic of malignant progression [15–18]. These all potentially confound successive surveillance imaging over a protracted period as an adequate strategy for LGG management.

Surveillance imaging has been reflexively instituted by clinicians as the standard of care for LGG management, especially for incidentally discovered lesions or eloquent tumours, due to the perceived high risks of surgical resection, and fatalistic attitudes regarding the eventuality of low to high grade progression. However, especially in high volume quaternary centres, not only is surgical resection associated with low morbidity and mortality [19], maximising EOR is likely to convey significant PFS and OS benefit [20,21]. Moreover, intraoperative MRI [22] and the re-emergence of awake craniotomy with intraoperative monitoring and functional mapping in LGG surgery have proven themselves useful in helping achieve maximal safe resection for eloquent LGG [23,24], as well as spawning the concept of supramaximal LGG resection in order to prolong survival and preserve cognitive and neuropsychological function [25]. Consequently, advances in surgical technique, technologies and philosophy have rendered LGG far more amenable to operative management than previously envisaged.

This detailed synthesis of the salient literature aims to make the case for early referral of patients with presumed LGG to surgical neuro-oncologists for timely consideration of operative management. Making that case involves an appraisal of the biological and clinicoradiological characteristics of these tumours, and thorough critique of surgical LGG management, focusing on the value of functional mapping and intraoperative imaging in optimising extent of resection, survival, quality of life and efficacy of adjuvant treatments.

1. The biological behavior of low grade glioma

The discovery of IDH1/2 (isocitrate dehydrogenase) mutation across a number of sequencing analyses has transformed our understanding of gliomagenesis and glioma progression [4,7,26,27]. Identified in ~90% of LGG [4,28–31] using immunohistochemical and/or sequencing techniques, the most common mutations are found at codon 132 and 172 for IDH1 and IDH2, respectively [2]. These mutations occur early in tumourigenesis, thereby giving rise to both astrocytoma and oligodendroglioma, the resultant cell of origin possessing a Proneural genetic signature [2,3,32]. Such mutations reduce αKG production in the citric acid cycle, leading to the accumulation of a αKG antagonist, (2-HG) thus causing genome-wide histone and DNA methylation alterations and applying a brake to cellular differentiation [33–35]. Inactivating mutations of the ATRX gene are highly associated with IDH and TP53 mutations, but mutually exclusive with 1p19q codeletion [36]. ATRX mutations result in alternative telomere lengthening and a mechanistic link to genomic instability. Combining this property with inherent accentuated self-renewal, DNA hypermethylation and epigenetic instability [34] of IDH1/2 mutation provides a plausible pathogenic synergy capable of eventual malignant transformation of LGG, especially in the setting of TP53 mutation, almost ubiquitously observed in IDHmut LGG with ATRX loss [37].

Overall, IDHmut LGG, when compared to IDHwt LGG, generally occur in younger patients, and have superior prognosis; Metellus et al. found that the presence of IDH mutation in LGG patients was associated with a near doubling of the 5-year OS from 51% to 93% [5]. Leeper et al. found in their larger series of nearly 160 patients that the median survival of 1p19q-codeleted, IDHmut LGG patients was over fifteen years [30]. Etxanix et al. calculated that absence of IDH mutation was the only statistically significant poor prognostic factor, for both progression and death (hazard ratios of 3.1 and 6.4, respectively) on multivariate analysis [38]. In a more elaborate mutational analysis, Eckel-Passow et al. sought to gauge the effect of key genetic clusters on survival in patients with WHO Grade II (and III) glioma [39]. This group used the presence/absence of not only IDH mutations, but also TERT promoter mutations, and 1p/19q codeletion status to define five principal

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glioma groups; whilst median survival in the TERT-mutant/IDHmut group (regardless of 1p19q-codeletion status) was not reached at ten years, non-IDHmut gliomas had a median survival of less than four years, and non-1p19q-codeleted, non-IDHmut, TERT mutation only gliomas (nearly 10% of total cohort) had a dismal median survival of under two years, essentially mimicking the expected survival of IDHwt glioblastoma patients. Further, in a large 558-patient cohort, Olar et al. showed a statistically significant difference in outcome based on WHO grade for IDHwt gliomas (median OS: 4.82 years (grade II) v. 1.97 years (grade III), but not for IDHmut tumours. (Median OS ~ 13 years) [40].

It would seem fair to speculate that IDHwt LGG must share many of the biological properties of IDHwt glioblastoma, including EGFR amplification, PTEN loss and resultant Pi3k dysregulation [41]. Certainly, the inverse is true, as IDHmut glioblastoma shares many of the clinical and growth characteristics of IDHmut LGG [42]. Of 160 IDHwt astrocytomas (all grades) evaluated by Reuss et al., 78% were diagnosed as the molecular equivalent of IDHwt glioblastoma of the classical or mesenchymal subtype [43] (i.e. gain of chromosome 7, loss of chromosome 10, CDKN2A deletion, EGFR amplification and a TERT mutation rate of nearly 80%) and 17% with a DNA methylation pattern equivalent to IDHwt-H3F3A mutated glioblastoma [6]. Therefore, IDHwt LGG appears to share the poor survival associated with the Classical and Mesenchymal subtypes of glioblastoma, related to a growth advantage conferred by either rapid cellular turnover (possibly augmented by neovascularisation), whilst IDHmut LGG growth seems more reliant on subtle, paraphysiological amplification of canonical stem cell renewal. Certainly, this hypothesis is borne out by the work of Zeng et al., where IDHmut glioma (all grades) patients with low/moderate Ki-67 expression (as a marker of cellular turnover) had clearly superior median OS (1527 days) to IDHwt patients whose tumours expressed high Ki-67 expression. (355 days) [44].

However, the IDH mutant/wildtype dichotomy falls short in addressing the full characterisation of LGG behaviour, in particular, the phenomenon of rapidly progressive IDHmut LGG. Using a TCGA data set of 286 IDHmut LGG patients, Huang et al. found that IGFBP2 overexpression was the only inverse correlate with OS of IDHmut LGG patients, to the point where median survival was less than that seen for IDHwt lesions [45]. Increasingly gaining curiosity is the potential relationship between total number of CNV with PFS/OS in IDHmut LGG, especially as IDHwt LGG have been shown to develop nearly identical levels of CNV as glioblastoma [46]. Building on the work of Richardson et al., who found that rapidly progressive IDHmut LGG (defined as transformation to glioblastoma and death within three years) was directly associated with the presence of homozygous CDK4NA deletion and high CNV count [47,48], Shirahata et al. developed a novel grading system for IDHmut diffuse astrocytomas of all grades, incorporating the poor prognostic factors of CDK4NA gene deletion, high CNV load and histological necrosis [49].

Although the IDH mutation has made an impactful contribution to our understanding of LGG biology, it has begun to ask more questions than it has answered. It has initiated the progressive obsolescence of histological grading as the primary means of differentiating between glioma types, in favour of genetic, and possibly in future, epigenetic stratification. Thus, considerable intertumoural heterogeneity amongst all LGG determines that it is folly to predict the outcome or clinical course, merely on the basis of a single MRI scan, at a single time point.

2. Radiological properties

Whilst there is little conjecture regarding initial radiological diagnosis, the main controversies which will be addressed here revolve around chronological tumour growth rate on serial imaging, the accuracy of radiological imaging in predicting when a given LGG may switch to a more aggressive phenotype and the utility of imaging in predicting intrinsic lesional expression of relevant molecular markers. A small early report calculated a mean diameter growth rate (untreated LGG) of 4 mm/year; even after partial LGG resection, that growth rate remained remarkably stable [15,18]. This average growth rate was confirmed in a larger series of nearly 150 patients, although growth rates recorded ranged between 1 and 36 mm/year, an impressive fluctuation. Moreover, they calculated that LGG with mean tumour volume growth rate of > 8 mm/year carried inferior prognosis [16], a result supported by Hathout et al., who showed that the rate of expansion of contrast-enhancing tumour and FLAIR abnormality increased the likelihood of transformation of LGG to higher grade lesions; moreover, radial expansion rates of T2/FLAIR hyperintense regions higher than 45 μm/day (~16 mm/year) demonstrated an 82% sensitivity/86% specificity of identifying LGG experiencing malignant transformation [50].

Goze et al. measured median malignant PFS/OS in LGG cases of slow velocity of diametric expansion at 149 and 198 months, respectively, as opposed to cases in the fast velocity group, where the PFS and OS were just 46 and 82 months. Initial mean tumour volume > 100 cm^3 also portended poorer OS in univariate analysis of the same cohort [51]. An additional retrospective study by Pallud et al. calculated the asymptomatic 'silent phase' of LGG growth, with a median lead time of 11.6 years (with the longest calculated lead time of almost 40 years). They also found that velocity of tumour volume expansion, rather than tumour volume per se, correlated negatively with lead time, exploiting this data to advocate for an MRI screening program for early LGG identification [13].

However, whilst mean growth rates are a useful guide to overall LGG behavior, they fail to account for LGG that undergo explosive mean tumour growth and malignant transformation, or predict which patients will transform, after many years of steady, unspectacular growth [52]. Differentiating between better and poorer prognosis LGG from a radiological perspective is hardly an exact science, either. Darlix et al., in a retrospective LGG cohort of almost 200 patients, attempted to identify radiological signs which predict good prognostic molecular markers, like IDH mutation. A summary of their statistically significant findings indicate that IDHmut lesions have an anatomical frontal predilection, with 'sharp' borders, whereas IDHwt and 1p19q-codeleted tumours exhibited more 'indistinct' borders [53]. Clearly, subjective terminology such as this is of dubious clinical utility. Additional novel MRI sequences and techniques have been explored in efforts to stratify LGG prognosis, molecular expression and predict malignant transformation, such as DWI [54,55], PWI [56,57], amide proton transfer-weighted MRI [58] and MR spectroscopy [59–61], although a recent systematic review of imaging in the management of adult LGG patients suggests that their routine clinical use in LGG diagnosis, prognosis and follow up remains undefined [10].

PET scanning allows for quantification of tumour metabolism, helping identify potential histological upgrading in known LGG, which are usually hypometabolic on PET imaging with 18F-fluorodeoxyglucose. This practice of detecting malignant transformation in LGG is aided by the fact that malignant gliomas are usually hypermetabolic. Novel PET techniques utilising radiolabeled amino acids (FET) [62] have been shown to predict a higher diagnostic accuracy for LGG progression than contrast enhancement on MRI, especially if monitored with successive studies [63,64]. However, PET imaging remains a diagnostic tool of ambiguous clinical usefulness in LGG patients; tracer uptake values of non-neoplastic lesions, LGG and HGG often overlap across studies, and there is no evidence that PET imaging can distinguish between molecular subgroups of LGG [65].

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Therefore, the radiological mainstay of management of LGG patients remains MR imaging, with contrast-enhanced T1-weighted, T2-weighted and FLAIR image acquisition as a minimum requirement. However, in the absence of sequences, markers or techniques which categorically distinguish malignant transformation (in the absence of frank enhancement) and important molecular biomarkers, radiographical analysis of LGG patients therefore necessitates a nuanced, sophisticated approach. Although calculated radial LGG growth rates provide a valuable guide to expected radiological behavior, it remains an imperfect and inaccurate one. Whilst surveillance imaging spares LGG patients the immediate risks of surgical intervention, failure to understand that LGG is a forever evolving neoplastic process may breed unwitting clinical complacency, and certainly, may lead to inferior patient outcomes in the long term.

3. Clinical characteristics

LGG represent 15–20% of all primary brain tumours found in adults. They are most frequent among Caucasian men and typically affect patients at a younger age than HGG (4th vs 6th decade of life) [66,67]. LGG patients with lesions containing mutations in IDH, TP53, and ATRX (i.e. diffuse astrocytoma) are diagnosed at a median age of 34 years, as opposed to 44 years for patients whose tumours express IDH mutation, 1p/19q codeletion, and TERT promoter mutation (i.e. oligodendroglioma) [7,37,39]. IDHmut LGG, in particular, have a high tendency to involve the frontal lobe and supplementary motor area [68,69]. Capelle et al., in a comprehensive study of nearly 1100 patients, found that nearly 90% of all LGG, irrespective of mutational analysis, involved the frontal lobe, and/or temporal lobe and/or insula [70]. The only identified risk factor thus far for LGG formation is exposure to ionising radiation [71].

As LGG diffusely infiltrate normal brain structure at a relatively slow rate of progression, compensatory mechanisms involving the neuronal and astrocytic network enable the patient to tolerate insidious tumor growth, thus delaying overt clinical manifestations [72]. Seizures are a very common initial presentation in LGG patients, occurring when normal brain architecture is disrupted to an extent that perturbs electrical activity through the usual interconnected channels, a phenomenon which may be especially exacerbated in IDHmut LGG patients owing to the relationship between 2-HG accumulation and subsequent neuroexcitatory glutamate overload at the cellular level [73,74]. Occurring in ~ 90% of LGG patients [75], and in many instances pharmacoresistant, seizure incidence is highest in cortical lesions in the temporal or temporo-insular region, or those LGG in close proximity to the central sulcus; also, oligodendroglioma appears to be more epileptogenic than diffuse astrocytoma [76]. Once the extent of tumour infiltration becomes more pronounced, and overwhelm compensatory mechanisms, symptoms of mass effect soon supervene, such as headache (usually exacerbated by factors that raise intracranial pressure, such as cough or prolonged recumbent posture) and perturbations in cognitive, speech and sensorimotor function manifest. Neuropsychological deficits in at least one domain of memory, visuospatial capacity, executive function, attention, language and psychomotor speed may present in ~ 70% of LGG patients, even when basic history and examination reveal no abnormality, and/or in cases detected incidentally on imaging [77].

The Pignatti prognostic scoring system for LGG was extrapolated using the patient sets (over 600 in total) of the EORTC LGG radiotherapy trials 22,844 and 22845 [78]. The factors on multivariate analysis which predicted poorer prognosis in LGG patients included older age (40+), astrocytoma histology, tumour diameter > 6 cm, tumour crossing midline and presence of neurological deficit; patients with three or more unfavourable factors are classified as high-risk (median overall survival: 3.67 years), while low risk patients can expect a median overall survival of 7.8 years. Whilst this scoring system is important in identifying key LGG clinical and radiological features, its utility as a prognostic tool in future will likely be usurped by molecular markers of prognosis, including IDH1/2 mutation [38,40,79].

There are three fundamental features of LGG which need to be understood when considering the merits of surgical intervention. Firstly, these patients are generally younger adults; therefore, surgery needs to aim to maximise EOR as safely as is practicable, with preservation of neurological and cognitive function a primary goal, so as to maximise quality and productivity of life [24]. Secondly, whilst pharmacotherapy may temporise seizure control in LGG patients, many will eventually fail that therapy [80], accompanied by psychological anguish, functional impairment and unpleasant medical side-effects. Seizure control ought to be considered a surrogate marker for overall treatment response and tumour control [81]. Thirdly, a strategy of prompt surgical resection may help eliminate widely accepted and potentially modifiable risk factors of poor prognosis in LGG patients, such as reducing the incidence of larger diameter lesions and lesions which cross midline white matter structures, offering prophylaxis against future neurological deficit, and at least delaying the unpredictable longer term risk of malignant transformation [82].

4. The evolution of LGG surgical management

Goals of surgery have become cumulative and complementary, as our understanding of LGG behaviour improves, and surgical technique has become further refined. LGG-related seizure disorders are a common manifestation and intractable, medically refractory epilepsy became an early target for efforts to treat these patients surgically. In a heterogeneous LGG patient group, with a range of tumour histologies and children also represented, Berger et al. were able to eliminate the need for anti-epileptic medications altogether in half of patients who had intractable epilepsy; they described using electrocorticography during tumour resection [83]. Further studies showed that extent of lesional resection (including LGG), along with complementary epilepsy procedures such as amygdalohippocampectomy, significantly affected post-operative seizure control, to the point where at least 90% of these patients can be either seizure free or exhibit considerable improvement [76,84–89]. Xu et al. suggested an EOR threshold of 80% was significantly effective at reducing seizure occurrence in LGG-associated epilepsy [90].

This pivotal role of surgical EOR in controlling tumour-associated epilepsy led gradually to a change in mindset regarding the surgical management of LGG in general, especially for incidentally discovered and/or eloquent lesions. The most compelling evidence for advocating a more aggressive surgical approach was published in an elegant and imaginative study by Jakola et al. [91]. Examining survival in population-based parallel LGG cohorts from two Norwegian university hospitals (in adjacent geographical regions with separate regional referral practices) with different surgical treatment strategies was performed. Whilst one centre followed a biopsy and ‘watchful radiological waiting’ approach, the standard of practice in the second hospital was early safe surgical resection. Median survival in the watchful waiting group was 5.9 years, but had not been reached in the surgery group, and multivariate analysis revealed a relative HR of 1.8 when treated in the centre where watchful waiting was performed. Subsequent follow up of the long term survival data confirmed an ongoing survival benefit which persisted. Median OS in the surgery group eventually reached 14.4 years [92].

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However, this cohort study did not attempt to quantify EOR and its contribution to LGG PFS/OS, nor address the issue of avoiding post-operative deficits, especially in patients with eloquent or near-eloquent LGG. Attempts to quantify the extent of residual tumour required to impart a survival benefit in LGG patients have been made; Roelz et al. found in their series (126 patients), that RTV greater than 15 cm^3 imparted a near fourfold increase risk of worse survival [93]. This result reconfirmed the findings of the seminal paper by Berger et al., who found that RTV greater than 10 cm^3 led to a statistically significant increase in risk of malignant transformation (46% v. 3.7%) [94]. The minimum overall EOR thought to impart a survival advantage in LGG has been reported anywhere between 40 and 76% [20,70,95]. Most importantly, in line with the data collated in HGG patients [96,97] the best OS and PFS advantage in LGG management is imparted when EOR is 100% [20,70,95,98,99]; this concept has been maximally developed in the form of so called 'supratotal' or 'supramaximal resection' for LGG, using awake craniotomy and intraoperative electrical stimulation to excise tumours and surrounding non-eloquent tissue beyond the macroscopic tumour margin in order to preserve neurological function and further negate the risk of malignant transformation, as well as take advantage of intrinsic neurocompensatory mechanisms which allow function to be reacquired [25,100–102].

Achieving GTR for LGG which invade eloquent regions of the brain such as the motor cortex and dominant frontal operculum, owes much to the burgeoning usage of intraoperative monitoring, with both cortical and subcortical mapping, via awake craniotomy [103]. The main finding of a meta-analysis of ninety articles which investigated the effect of intraoperative monitoring on adult supratentorial glioma (WHO Grades II-IV) outcomes was that monitoring was significantly associated with a halving of the rate of late or permanent severe neurological deficit. Moreover, not only were eloquent (and thus, surgically more challenging) tumours more commonly represented in the intraoperative monitoring arm, but the GTR rate was higher, too. (74.8% v. 58.3%) [23] Specifically, persistent language deficit was caused in less than 2% of the 250 LGG patient cohort out of UCSF, with GTR achieved in just over half of all LGG patients [104]. Of 300 LGG patients (same centre) with eloquent, perirolandic lesions, surgical resection coupled with intraoperative electrical stimulation carried a risk of permanent motor deficit of ~ 5% [105]; similar rates of permanent language and sensorimotor have been reported elsewhere in patients with eloquent LGG [106,107].

Although beyond the scope of this review, the regular use of intraoperative stimulation has enabled neurosurgeons and neuroscientists to uncover extraordinary structural and functional insights into cerebral white matter tract and regional anatomy, including the supplementary motor area [108], expressive and receptive speech pathways [109,110], visual representation [111], executive and cognitive function [112,113]. Thus, this rapid progress in understanding of brain structure and function, coupled with the armamentarium of intraoperative stimulation, has greatly improved surgical resectability and oncological clearance of LGG lesions previously considered to be too high risk for causing severe post-operative neurological deficit, meaning quality of life can now be realistically salvaged, dispelling previously nihilistic attitudes towards the surgical management of LGG patients [24].

5. Adjuvant therapies in LGG – chemotherapy and radiotherapy

Extrapolation of data from numerous randomised controlled trials into the effect of concomitant chemo- and radiotherapy for anaplastic oligodendroglioma [114–117], IDHwt anaplastic astrocytoma [118] and glioblastoma [119,120] has permitted the formulation of comprehensive guidelines for post-surgical therapy in LGG [121] (Fig. 1). Furthermore, Buckner et al. showed that a treatment regimen consisting of adjuvant irradiation and a chemotherapy protocol (PCV) also improved outcome in a 254 patient LGG cohort, with benefits persisting irrespective of histological subtype or IDH mutation status. The median OS was 13.3 years with irradiation plus chemotherapy, versus 7.8 years with radiation therapy alone [122]; this now constitutes the new standard of care for WHO (1p/19q-non-codeleted) Grade II astrocytomas [121]. Adjuvant therapies are also effective at imparting improved seizure control in LGG patients, whilst a recrudescence of seizure frequency may act as a surrogate harbinger for tumour progression and treatment failure [81,123].

Thus, recognition of the prognostic impact in LGG patients of 1p19q codeletion [122], IDH1/2 mutation [124,125] and MGMT methylation status [126], as well as clinical factors such as age [78] and KPS [127], in terms of response to adjuvant therapy, has resulted in the recent adoption of a more aggressive multi-modal approach to LGG management. Retrospective analyses validating the superior outcomes seen in higher risk LGG patients treated with surgery and concurrent chemoirradiation help reinforce this management paradigm [128]. Indeed, owing to the unfavourable side-effect profile of PCV, the negligible BBB penetrance of vincristine [129] and the improved tolerability and patient preference for orally-administered chemotherapy, temozolomide has slowly (and not without controversy, one might add) superseded PCV in the day-to-day clinical practice of LGG patients in many Neuro-oncology departments [130]. Keenly awaited are the results of the randomised Phase III clinical trial comparing radiotherapy/temozolomide and radiotherapy/PCV in 1p/19q (WHO Grades II/III) co-deleted patients, which ought to provide some clarity on the matter. (NIH ClinicalTrials.gov Identifier: NCT0887146)

A post-operative 'watch and wait' approach for LGG patients ought to be reserved only for those who are young (age < 40), with high KPS (70+), whose tumours express the IDH1/2 mutation and whose surgical management constitutes GTR [121], especially given the long term risks of radiotherapy-induced neurocognitive dysfunction [131]. MGMT methylation status, as well as patient tolerance, may be a factor in the selection of temozolomide over PCV as chemotherapy of choice, although adjuvant treatment of IDHwt LGG now mimics that of glioblastoma. Adjuvant radiotherapy alone has been shown only to improve PFS (not OS) in LGG patients and thus, irradiation as a stand-alone treatment is only ever instituted in select or palliative LGG cases [132–134]. Chemotherapy only regimens (usually temozolomide) are limited to those patients for whom radiotherapy entails a large treatment volume and thus increased risk of delayed cognitive effects of treatment, although, in future, may yet prove to have a specific role in high risk and/or IDHwt LGG adjuvant treatment [135].

This switch from a relatively passive to a more proactive approach in adjuvant LGG management has consequences for how LGG patients are managed from time of diagnosis. Even higher risk, less surgically amenable LGG patients have been demonstrated to derive benefit from adjuvant therapy, which means, of course, that obtaining a tissue diagnosis, as a baseline, is imperative to instigating said treatments. Thus, the case for "sitting tight" indefinitely on LGG patients, using serial imaging to monitor radiological progress, is losing ground to the notion of instituting earlier management of an ever growing evidence base, across all modalities.

6. Illustrative case

A 25-year-old otherwise fit, right hand dominant woman was referred to a neurologist at a peripheral centre for investigation

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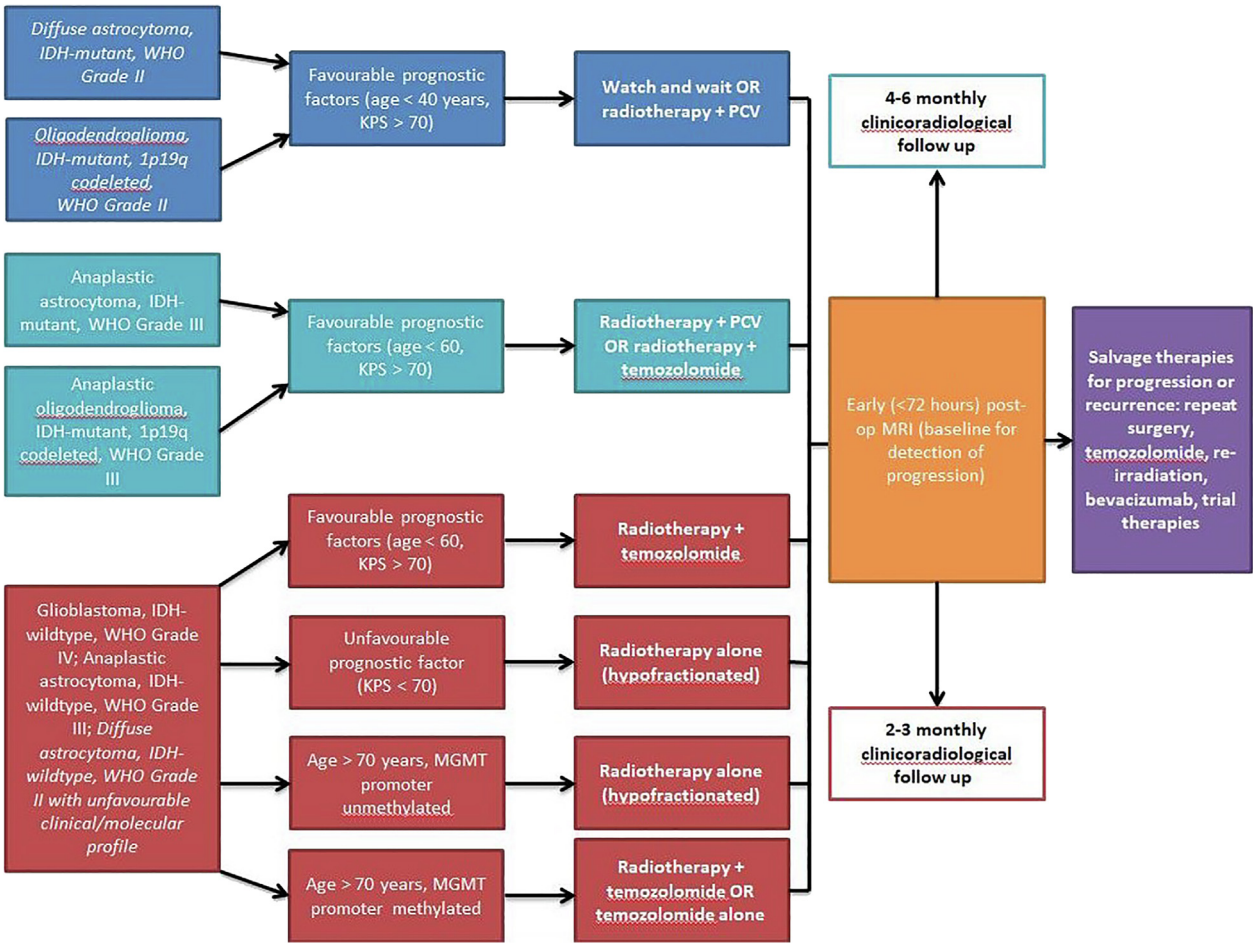

Fig. 1. Clinical pathway for glioma (adapted from EANO Guidelines on Glioma Diagnosis and Treatment [121]). Maximum safe surgical resection is recommended whenever feasible in all patients with newly diagnosed gliomas. Note that the current recommendation for management of WHO Grade II gliomas which are IDHwt is identical to the treatment pathway for glioblastoma, and upfront radiotherapy with PCV chemotherapy should at least be considered in all patients with IDHmut gliomas.

of persistent headaches. No pertinent neurological findings were evident and MRI of the brain was performed in October 2010. This somewhat surprisingly showed a small T2- and FLAIR hyperintense right superomedial frontal lesion, with the reported differential diagnosis of cortical dysplasia, encephalomalacia or incidental LGG. Table 2 outlines the surveillance MR imaging (and accompanying tumour features, volume measurements and key images) to which this patient was subjected over the following eight years, with no alteration in symptoms or signs during that intervening period. Although the lesion was officially reported as stable in size and appearance, on retrospective analysis, subtle changes in the T2 and FLAIR abnormality are apparent on comparison of successive images, especially between scans done in February 2015 and February 2016. Nevertheless, surveillance imaging for this patient was relaxed to biannual monitoring. On the MRI brain performed in August 2018, the lesion expanded markedly, measuring 5.7 × 4.4 × 3.3 cm, with avid peripheral enhancement and evidence of callosal invasion. Additionally, a satellite enhancing nodule measuring 11 mm in maximal diameter had also developed within the right superior frontal gyrus; fearing malignant transformation, the patient was subsequently referred to our centre, the first time she had ever been sent for neurosurgical assessment. Shortly thereafter, the patient underwent craniotomy and excision of the right frontocallosal lesion, and GTR of the contrast-enhancing and T2-hyperintense portions of the tumour was achieved. The final pathological diagnosis confirmed WHO Grade IV glioblastoma, (final molecular analysis: IDH1-mutant, ATRX lost, MGMT methylated, TP53 mutant) and the patient was referred for chemoirradiation, as per the Stupp protocol [119]. Crucial to note is that the technical complexity of this case was significantly heightened by the tumour's progression into the corpus callosum, irrespective of the excellent EOR achieved, and the patient in fact required further surgical intervention approximately six months later after developing intraventricular septations and delayed hydrocephalus.

7. Conclusion and recommendations

By highlighting the increasingly nuanced nature of LGG management, this article's primary objective is to recommend that all patients diagnosed with a likely LGG on either CT or MR imaging be referred, as soon as practicable, to a surgical neuro-oncologist who is familiar and acquainted with the vagaries of this disease process, as well as attached to and invested in a multidisciplinary clinical decision-making unit, with medical neuro-oncologists, radiation oncologists and allied health professionals involved. In light of progress made in understanding molecular biology, the emerging importance of adjuvant chemo- and radiotherapy, and tremendous advances in surgical technique which have facilitated superior EOR whilst preserving neurological functioning and quality of life, adhering to the traditional (yet misguided and erroneous) mantra, that LGG are "stable" lesions with "low" risk of progression or malignant transformation, no longer can be argued to serve the best interests of this patient cohort.

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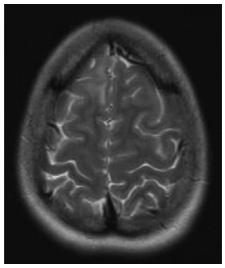
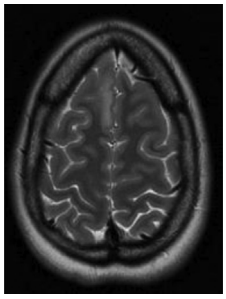
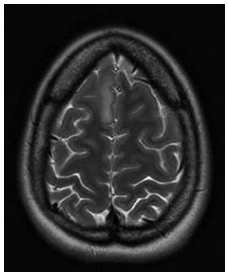
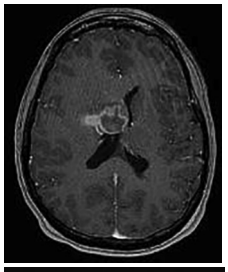
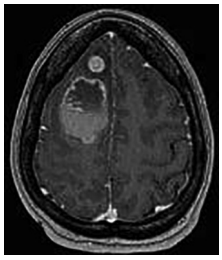
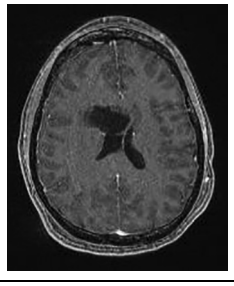
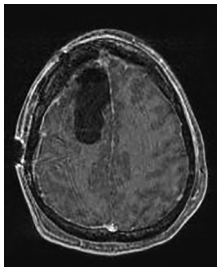
Table 2
MRI characteristics of the glioma of the illustrative case, in terms of size, growth rate, callosal involvement and presence of enhancement over time. Mean annualised growth rate in brackets. Key images also included: T2-weighted images displayed for scans performed from 2010 to 2016; T1-weighted (contrast enhanced) images shown for scans done in 2018. (tumour volumes calculated using Horos™ software [Purview; Annapolis, MD, USA]); *denotes all enhancing/macroscopic tumour within the corpus callosum excised.

Date of MRI	Size (T2/FLAIR) – cm^3	Annualised growth rate (cm^3/annum)	Callosal involvement?	Enhancement?	Key images
22.10.2010	3.95	–	No	No	
23.11.2011	4.31	0.33	No	No	–
11.04.2012	4.64	0.85	No	No	–
24.12.2012	5.51	0.87	No	No	–
14.02.2015	5.73	0.10	No	No	
24.02.2016	6.27	0.52	No	No	
02.08.2018	78.37	29.53 (Mean: 9.55)	Yes	Yes	 
12.08.2018 (post-op)	0	–	No*	No*	 

Conversely, it can be contended that such a mindset is in fact a proxy advocate for managing these complex patients in a complacent and falsely reassuring manner.

This review has no designs to repudiate altogether a place for surveillance imaging, over an unspecified period, for any given LGG patient. However, when (frequently young and well-functioning) LGG patients have been referred by specialists generally unacquainted with the inherent caprice that underpins LGG clinicoradiological behaviour, it is a source of unending frustration for surgical neuro-oncologists to discover, when reviewing the patient's history, medical record and catalogue of previous imaging (sometimes a decade or more in its accumulation) and with the

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benefit of 20:20 hindsight, that operative intervention, or at least its contemplation, ought to have been instigated months, or even years, sooner. Relatively commonly seen in the neurosurgical or neuro-oncological setting, the incidence of LGG in the community remains nonetheless relatively rare, and it is unreasonable to expect those not expert in treating this neoplastic disease to understand how best to tailor management for this patient group. Certainly, a blind and passive reliance on the radiologist's report which accompanies the annual MRI report should no longer masquerade as "best practice". Therefore, in exactly the same way a putative diagnosis of glioblastoma on MR imaging prompts a rapid neurosurgical referral for timely consideration of surgery, so too, should a radiological verdict of LGG pre-empt an early consultation from a surgical neuro-oncologist, with a view to subsequent takeover of patient care.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2020.04.119.

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