REVIEW ARTICLE

'Low grade glioma': an update for radiologists

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ABSTRACT

With the recent publication of a new World Health Organization brain tumour classification that reflects increased understanding of glioma tumour genetics, there is a need for radiologists to understand the changes and their implications for patient management. There has also been an increasing trend for adopting earlier, more aggressive surgical approaches to low-grade glioma (LGG) treatment. We will summarize these changes, give some context to the increased role of tumour genetics and discuss the associated implications of their adoption for radiologists. We will discuss the earlier and more radical surgical resection of LGG and what it means for patients undergoing imaging.

BACKGROUND

Diffuse low-grade gliomas (LGG) are tumours of the glial tissue, which are generally slow-growing, but have the potential to undergo anaplastic progression into more aggressive tumours. For the best part of the past century, glial tumours have been grouped based on histological appearance,[1,2] and this approach formed the basis of the 2007 World Health Organization (WHO) Classification of Tumours of the Central Nervous System.[3] This system graded diffuse gliomas based on morphological features, reflecting biological behaviour, into grades II–IV with grade II being low grade and grades III and IV being high grade.[3] WHO grade II tumours previously comprised astrocytomas, oligodendrogliomas and oligastrocytomas.[4] The recently published updated WHO classification, however, now contains some significant changes in the approach to the classification of LGG (and the higher grade gliomas). In particular, molecular findings are now integral to a full diagnostic categorization of these tumours.

It is important at this point to say something about terminology. The term "low-grade glioma (LGG)" is commonly used in the literature to refer to grade II gliomas as a group in both clinical and radiological literature. Whilst this is a useful grouping, it should be noted that LGG is not used in the WHO classification and is not a final neuro-pathological diagnosis. Furthermore, it should be appreciated that grade II gliomas are not benign tumours, given their infiltrative behaviour and eventual progression to more aggressive grade III and IV tumours with an associated poor prognosis. Thus, they have a/3 malignancy grading in the International Classification for Diseases of Oncology. Grade I tumours, such as pilocytic astrocytoma, are also often included in the term LGG. As these are benign and considered a separate entity, they are not included within the scope of this article, which is therefore restricted to the WHO grade II gliomas. LGG is used within this review to refer to WHO grade II gliomas, as this is the terminology currently used in clinical practice and widely understood by clinicians and radiologists alike, but it is important to note these caveats, and that it should not be considered as a final diagnostic label.

Despite LGG being sometimes indolent in behaviour, it is estimated that approximately 70% will undergo anaplastic progression into high-grade tumours within 5–10 years of diagnosis.[5] This progression is unpredictable and varied and consequently, the management of LGG has been debated for some time. Expectant management has been the norm in many centres for stable LGG showing no signs of

further anaplastic progression, particularly as LGG tend to occur in eloquent brain areas. This has arisen out of the supposition that intervention and treatment can cause greater adverse effects than benefits in these patients, as well as the conflict of opinions on the benefit of early surgical resection, radiotherapy or chemotherapy in improving overall and progression-free survivals. Many institutions have therefore adopted an imaging-based monitoring policy for LGG, with intervention being initiated when changes suggestive of anaplastic progression occur. Radiologists have played a key role, monitoring and identifying signs suggestive of anaplastic progression, traditionally by an increase in tumour diameter and new areas of contrast enhancement. Research has therefore also been focused in this area, aiming to identify non-invasive surveillance methods to allow early, yet sensitive and specific, detection of anaplastic progression. A variety of MRI-based techniques have been explored for this purpose, including diffusion-weighted imaging,[6–14] perfusion-weighted imaging[6,8,10,15–21] and MR spectroscopy (MRS).[10,12,16,22–27] However, despite the plethora of research into imaging biomarkers of anaplastic progression, the results have been varied with no definitive predictive marker being found that has been universally accepted.

Some grade II gliomas rapidly progress within a very short time period, whereas others remain stable for many years. It has therefore become readily apparent that the 2007 WHO histological typing and grading system does not always allow an accurate prediction of tumour behaviour, response to treatment and patient prognosis, despite being based on morphological features reflective of biological behaviours. There are several reasons why this may be the case. LGG are heterogeneous in nature both within a single tumour resulting in potential sampling errors at biopsy and also amongst each other reflecting genetic diversity within this group of tumours. There is also suboptimal intraobserver and interobserver reliability between pathologists.[28,29] This limits the usefulness of biopsy specimens which, combined with the apparent failure of MRI to provide a widely accepted and reliable biomarker of future tumour behaviour and progression risk, has led to recent research into the genetic make-up of LGG. The conflicting evidence reported for the various MR biomarkers previously studied as markers of progression is almost certainly attributable to the diverse nature of gliomas and differences in the molecular status of tumours within the same histological grading.

There have been significant advances in the understanding of molecular genetic abnormalities in the pathogenesis of brain tumours. The new update to the WHO Classification of Tumours of the Central Nervous System, published this year, incorporates molecular abnormalities into the neuropathological assessment of gliomas and as such is a departure from the primarily morphological approach used in the previous classification.[30] Key changes in the new classification have been recently reviewed.[2] This update has thus radically restructured the classification of gliomas, which is now based on integrated molecular and histological parameters.[2] This review article aims to summarize the recent key findings in LGG genetics research and how these findings have shaped the latest 2016 WHO classification,[2] as well as the shift towards a more aggressive surgical management. It will focus on the changing role of imaging and

the impact of this on the radiologist in the clinical management of LGG. Potential new imaging-based research areas that may emerge as a result of a shift towards using molecular markers in LGG management will also be discussed.

NEW KNOWLEDGE INFLUENCING THE CHANGING PRACTICE IN LOW-GRADE GLIOMA MANAGEMENT
Assessment of tumour growth
Studies investigating the growth rate of LGG have consistently demonstrated that LGG grow continuously prior to anaplastic progression, despite often appearing static on the subjective visual analysis of interval imaging examinations, demonstrating that LGG are actually not "stable" as initially thought.

The majority of studies use velocity of diametric expansion (VDE) as a measure of growth rate.[16,31–37] This is obtained from a series of measurements and calculations: the tumour volume is measured using axial images and manual segmentation, the volume (V) is used to calculate a mean tumour diameter (MTD) [$MTD = (2 \times V)^{1/3}$] and finally, the VDE is calculated from the linear regression of MTD over time.[38] Prior to anaplastic progression, LGG have been demonstrated to grow linearly at a mean VDE of 4 mm/year.[38] Further studies used changes in tumour volume. Tumour volumes are measured on fluid attenuation inversion-recovery series using semi-automated technique to contour the tumour margin on multiple axial images with manual editing as required to increase accuracy (Figure 1).[4,6] These studies found similar results to those measuring VDE: Rees et al[4] found in a study of 27 patients that stable LGG grow at a mean annualized percentage growth rate of

Figure 1. An axial fluid attenuation inversion-recovery image with gadolinium showing the contour around the tumour margin used to calculate tumour volume. The overall tumour volume is the product of the contoured areas on each axial slice, the slice thickness and interslice gap. A, anterior; I, inferior; L, left; P, posterior; R, right; S, superior.
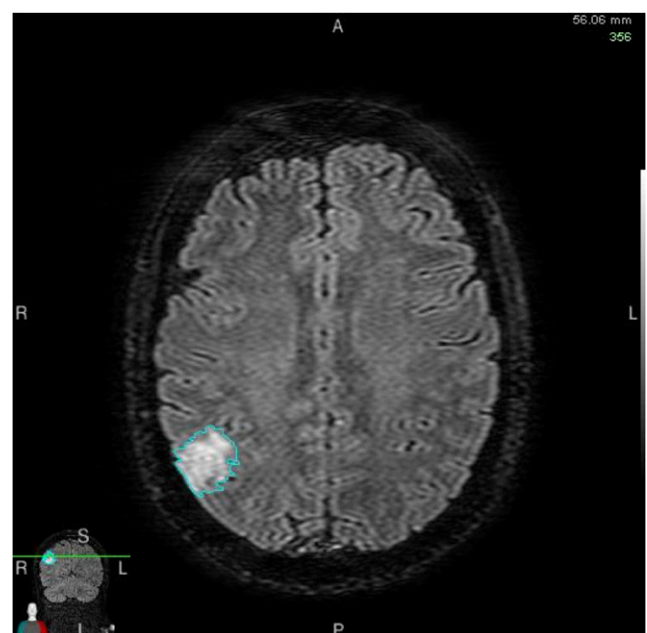
16%, whilst Brasil Caseiras et al[6] demonstrated in 34 patients with LGG a mean growth of 8.8 ml over 6 months (approximately a 24% increase in volume per year).

Tumour growth rate is a prognostic indicator of tumour grade, risk of anaplastic progression and overall survival.[4,6,16,32,38–41] A VDE >3 mm/year correlated with an increased risk of anaplastic progression.[16] Overall survival of patients was significantly longer in patients with a VDE of <8 mm/year compared with those with a growth rate of >8mm/year, as well as increased progression-free survival in the slower growth rate group.[39] There is often an acceleration in growth rate in the 6 months preceding anaplastic progression prior to any clinical deterioration or other imaging features suggestive of progression.[4,6] Similarly, tumour volume at

presentation has been demonstrated as an independent predictor of time to anaplastic progression.[4,6]

Despite growth rate and presentation tumour volume being reliable predictors of anaplastic progression and survival based on the handful of studies currently available, there is considerable overlap in the tumour volume and growth rates of LGG that remain stable for a long period and those that progress rapidly,[32] suggesting that there are other factors important for the prediction of progression risk and prognosis.

Molecular markers

The emerging understanding of glioma oncogenetics has started to explain the prognostic inaccuracies of radiological and clinical

Figure 2. A flow diagram of the new diffuse glioma classification system adapted from Louis et al.[2] The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol* 2016; 131: 803–20. ATRX, alpha thalassaemia/mental retardation syndrome X-linked; IDH, isocitrate dehydrogenase; NOS, not otherwise specified; TP53, tumour protein 53.
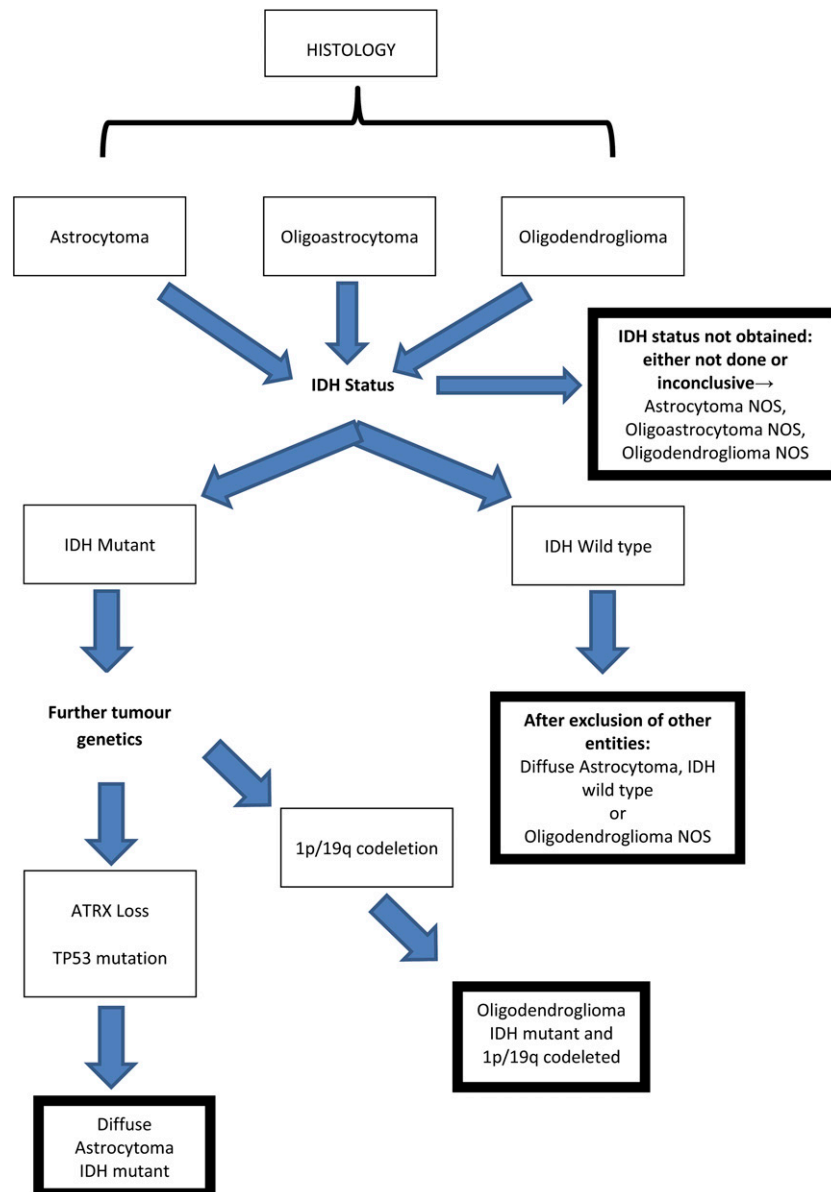
biomarkers and the 2007 WHO Classification, whilst providing novel, more accurate, molecular biomarkers (Figure 2).

Several molecular markers have been identified in diffuse gliomas (grades II–IV) with promising diagnostic and prognostic properties for stratification that could help guide clinical decision-making, as well as potential predictive properties which may influence treatment options. Genome-wide analyses have identified isocitrate dehydrogenase (IDH) mutations, 1p19q codeletion and genetic alterations in tumour protein 53 (TP53), telomerase reverse transcriptase (TERT) promoter and alpha thalassaemia/mental retardation syndrome X-linked (ATRX) as potential key markers.[42]

IDH mutations were first discovered in 2008 initially in glioblastoma (GBM)[43] and are heterozygous somatic point mutations in genes that encode for enzymes involved in the Krebs cycle.[44] IDH 1 mutations are more common than IDH 2 mutations.[44] IDH mutations (1 or 2) occur in 65–80% of grade II–III gliomas and secondary GBM (occurring as a result of progression of grade II/III tumours), whereas they are uncommon in primary GBM (occurring in approximately 5%).[44] It has been reported that 75% of astrocytomas, 80% of oligodendrogliomas and 80% of oligoastrocytomas display IDH 1 mutations.[45] It is believed that IDH mutations are consistent molecular events which occur early during tumour pathogenesis and can therefore often be associated with other mutations,[44] most commonly TP53 and ATRX in astrocytomas and 1p/19q in oligodendrogliomas.[46–48]

Gliomas with IDH mutations tend to occur in patients who are younger, have a predilection for the frontal lobes, are larger at diagnosis, are often non-enhancing and have prevalent cystic and diffuse components.[42,49,50] Despite being larger at presentation, IDH mutations in gliomas are strong independent predictors of improved overall prognosis. Several studies have demonstrated an improved median overall survival for IDH-mutated gliomas, compared with patients with IDH-wild-type tumours (*i.e.* without IDH 1 or 2 mutations).[51–55] The median overall survival for IDH-mutated tumours is reported as approximately 8–8.4 years, compared with 1.4–1.7 years in IDH-wild-type tumours.[42,52] An improved progression-free survival has also been shown.[54,55] Grade II and III IDH-wild-type gliomas have a survival comparable with primary GBMs and have been suggested to therefore behave similarly.[42,44,47,53] Interestingly, IDH status has no significant effect on the spontaneous growth rate of LGG, despite the tumours often being larger at presentation.[35,55]

It is not yet clear whether IDH status can predict sensitivity to chemotherapy or radiotherapy. A recent Phase III trial of radiotherapy *vs* chemotherapy showed a longer time to treatment failure associated with IDH mutations, but IDH status was not predictive of chemotherapy responsiveness.[51] IDH mutation may also prove to be a predictive marker in aggressive surgical management, with an additional survival benefit demonstrated with IDH-mutated tumours when surgical resection is extended beyond the enhancing tumour margins; however, this has been shown only in high-grade gliomas.[56]

IDH-mutated tumours have been shown to accumulate 2-hydroxyglutarate (2HG) and this can be detected non-invasively using MRS.[57] Concentrations of 2HG have been demonstrated to vary with tumour activity and increase with anaplastic progression, suggesting that 2HG measured by MRS could prove to be an accurate non-invasive biomarker in IDH-mutated gliomas.[58] However, Chen et al[59] (2015) found in their analysis of 2HG-MRS in 21 patients (blinded to IDH status) that there was a significant false-negative rate, most notably in 2 cases that were negative for 2HG despite progressive disease on conventional MRI. This suggests that 2HG cannot currently replace tissue diagnosis for determining IDH status; however, further research is needed in this area.

On the other hand, 1p/19q codeletion has been recognized for some time as being associated with oligodendroglial elements[60] and can be seen in both pure and mixed oligodendrogliomas.[44] There is combined loss of genetic material from the short arm of Chromosome 1 and the long arm of Chromosome 19, leading to an unbalanced translocation and loss of heterozygosity.[48] 1p/19q codeletion occurs only in the presence of concomitant IDH mutations[44] and is reported to occur in approximately 80% of oligodendrogliomas.[61]

The presence of 1p/19q codeletion can aid risk stratification in IDH-mutant gliomas and is associated with a significantly longer overall survival. Sabha et al[54] found that overall survival was 97% at 3 years in tumours with codeletion compared with 89.9% in non-codeleted tumours. Similarly, it has been found that having an LGG with a combined 1p/19q codeletion and IDH mutation corresponds with a median overall survival of greater than 8 years.[47]

1p/19q codeletion is also associated with an improved response to chemotherapy and chemoradiotherapy, as demonstrated in three randomized controlled trials;[51,52,62] however, the mechanism for this is still currently unknown. Furthermore, it has been demonstrated that 1p/19q codeletion correlated with a slower growth rate in LGG.[33,35] Isolated loss of 1p or 19q can also be seen, mainly in astrocytomas, but is not associated with the same degree of prognostic benefits as codeletion.[48]

Other molecular markers which are associated with diffuse gliomas include TP53, ATRX and TERT; however, these are less well established. TP53 mutation occurs in 50–60% of astrocytomas[46,63] and often follows IDH mutation.[42,48,63,64] It also occurs in oligodendrogliomas, but is comparatively rare, occurring in 5%.[63,65] It is not yet completely clear whether TP53 is a reliable prognostic predictor, either independently or in combination with other markers.

ATRX is also associated with astrocytic tumours.[46,47] It is rare for ATRX mutations to occur without concurrent IDH mutations and can be found in 36% of diffuse gliomas[46] and 86% of IDH-mutated tumours.[42] ATRX-mutated tumours may represent a subgroup of IDH-mutant astrocytomas with a better prognosis, as it has been demonstrated that they have a longer median time to treatment failure than those without the mutation.[66] However, the impact of ATRX mutation on survival and treatment response needs further investigation.

Mutation in TERT promoter tends to co-occur with 1p/19q codeletion and is therefore closely associated with oligodendrogliomas.[42,44,67,68] The Cancer Genome Atlas Research Network study found that 96% of diffuse gliomas with IDH mutation and 1p/19q codeletion also showed TERT promoter mutations, compared with only 4% in tumours with IDH mutation but no 1p/19q codeletion.[42] Owing to the close links between TERT promoter mutation and other molecular markers, it is unclear what elements of prognostic benefit are attributable to TERT status alone.

Implications for neuropathological classification and diagnosis

The new (2016) classification now incorporates molecular genetics and histopathological findings into an integrated diagnosis.[2,30] The four-point WHO grading scheme essentially remains unchanged, and the first step remains determination of the morphological subtype. LGG can be divided into IDH-mutant or wild-type tumours. Those with ATRX mutation but without 1p19q codeletion are in general astrocytic, whilst oligodendrogliomas are ATRX wild-type with 1p19q codeletion. For the integrated diagnosis, the molecular findings take precedence over the morphological appearances in determining whether the tumour should be considered an oligodendroglioma or astrocytoma in the final report. The implication of this is that tumours are defined by the molecular genetics as well as the histological features and that molecular typing allows a finer subclassification of tumour types. Where molecular typing cannot be fully assessed, the term not otherwise specified is used. The oligoastrocytoma remains in the classification as a morphological subtype, but with application of molecular subtyping, these would be resolved into either astrocytoma or oligodendroglioma in the integrated diagnosis. GBM is now classified into glioblastoma IDH-mutant or glioblastoma IDH wild-type (a number of morphological subtypes also remain in the classification).

Emerging surgical practice

Another emergent finding, particularly over the past decade, is that of the benefit of surgical resection of LGG, which further refutes the use of expectant management policies. Previously, it had been argued that in "stable" LGG with well-controlled symptoms, neurosurgery may cause greater morbidity than benefit owing to the risk of secondary long-term neurological deficits.[4] In 2010, Soffietti et al[63] concluded the evidence for the timing of and extent of surgery in LGG to be inconclusive with no randomized trials in this field. However, despite no prospective randomized trials in this area existing, multiple prospective observational/cohort and retrospective studies over recent years have repeatedly demonstrated increased survival and a reduced risk of anaplastic progression with early aggressive resection of LGG compared with biopsy alone/watch and wait programmes.

Jakola et al,[69] in their retrospective cohort study of patients with LGG undergoing early resection *vs* biopsy and then watchful waiting in two different centres, demonstrated that patients treated with early surgical resection have a better overall survival. The median overall survival in the biopsy and watchful waiting group was 5.9 years compared with an unreached median survival in the early resection group.[69] The French Glioma Network also concluded from their mixed retrospective and prospective study of 1097 LGG that resection gives superior survival compared with stereotactic biopsy and attribute this to a delay in anaplastic progression.[70]

Several studies have also demonstrated improved survival with increasing extent of resection.[71–76] Gross total resection or resection of >90% of the tumour volume can produce overall 5-year survival rates of 93–97%, compared with 41–84% for less extensive resections or biopsy.[72,73,75,76] The risk of recurrence and anaplastic progression has also been shown by some to improve with aggressive resective treatment.[71,73] This improvement in survival with extensive resection is also the case for repeat surgery following tumour recurrence.[74] However, this has not been consistently demonstrated, with other groups showing no significant differences in progression-free survival with gross tumour resection *vs* subtotal resection/biopsy.[74,76] Seizure control is also reported to be improved by total resection, with >90% of patients becoming seizure free or having a significant improvement in seizures following surgery for LGG.[77]

Following the demonstration that tumour cells can extend beyond the visible T_2/fluid attenuation inversion-recovery abnormality on MRI by up to 20 mm[37] and the above findings on the benefit of aggressive extent of resection, some have gone on further to suggest that where possible, "supratotal" resections (resecting beyond the MRI-visible tumour margin) should be attempted and may also reduce the risk of anaplastic progression.[78,79]

Maximizing survival chances by attempting the greatest extent of resection possible is obviously important, but only if balanced with no significant detrimental effect on the quality of life following aggressive surgery; after all, the risk of long-term deficit was the initial rationale for surveillance of stable LGG. The European Federation of Neurological Societies and European Association for Neuro-oncology recommend that "surgical resection is the first treatment option, with the goal to maximally resect the tumour mass whenever possible, whilst minimizing post-operative morbidity".[63] The safest way to achieve this is by performing an awake craniotomy with intraoperative electrical stimulation, resecting according to functional boundaries. This is especially important, as LGG are frequently located in eloquent areas of the brain. In one study, intraoperative functional brain mapping has been shown to reduce severe permanent neurological deficits from 17% to 6.5%;[80] however, a recent large-scale meta-analysis of 8091 patients from 90 studies reported permanent deficits in even fewer cases (3.4%).[81] The extent of resection is also improved with intraoperative mapping, as well as the ability to safely operate within eloquent areas.[80,81] It has also been shown in a retrospective study of 190 patients that adding pre-operative functional MRI (fMRI) or fibre-tracking diffusion tensor imaging (DTI) to an intraoperative neuronavigational system can further increase extent of resection.[75]

This highlights the role of imaging both pre- and post-operatively. With a drive to maximal resection as the optimal initial management of LGG, whilst still maintaining a low rate of long-term neurological sequelae, pre-operative imaging that clearly identifies anatomic structures and tumour boundaries and gives information on functional activity is increasingly important in aiding surgical planning. This can be achieved with a variety of modalities, including fMRI, positron emission tomography and DTI.[82] However, current imaging modalities available are not yet as reliable as intraoperative mapping, which is likely to remain the gold standard for the time being.[83] DTI when compared with intraoperative subcortical language mapping was concordant in 81% of cases, but negative tractography did not rule out the presence of white matter tracks in this area, particularly when invaded by tumour cells.[84]

Owing to the infiltrative nature of LGG and the potential for microscopic invasion beyond the visible tumour boundary,[37] it is very unlikely that LGG will be completely resected. Post-operative imaging is therefore also important. Studies have shown that it is very difficult to accurately predict the extent of resection intraoperatively,[70,76] which introduces a role for intraoperative MRI, as this has been shown to improve the extent of resection in gliomas when compared with conventional neurosurgery.[85] Initial post-operative imaging should be performed as early as possible to get an accurate baseline, before post-operative inflammation occurs. A haemostatic material used intraoperatively can also cause reactive enhancement, restricted diffusion and inflammatory responses.[86] Regular longer term post-operative imaging is also important for follow-up, monitoring for tumour recurrence and response to adjuvant chemotherapy or radiotherapy in subtotal tumour resections or where genetic make-up indicates the need for adjuvant treatment.

THE CHANGING ROLE OF THE RADIOLOGIST
As a result of the above findings, the role of the radiologist in imaging LGG is expected to change. Instead of imaging forming the mainstay for monitoring of patients with "stable" LGG for signs of anaplastic progression, patients are likely to undergo early aggressive surgical resection without prior biopsy to confirm the nature of the tumour. Genetic markers have radically changed the categorization of diffuse gliomas as is reflected in the updated 2016 WHO Classification.[2] MRI will therefore play a key role in the identification of LGG and distinguishing it from other non-neoplastic lesions, especially when the abnormality is small. Advanced MRI biomarkers may be developed and in the future provide reliable non-invasive methods for accurately

determining the genetic and molecular make-up of gliomas. Exploration is needed into the optimum management for indeterminate lesions, the ideal timing for interval imaging and the potential risks in delaying treatment if the lesion is later confirmed to be an LGG.

Accurate pre-operative imaging will be required to enable safe surgical planning. However, interindividual variations have been shown to exist in the anatomic location of various brain functions,[65] as well as a suboptimal concordance between DTI and intraoperative language mapping.[84] The role and accuracy of advanced imaging techniques such as DTI tractography and fMRI in defining tumour boundaries and infiltration into functional brain tissues needs exploring further, but should be available to supplement conventional anatomic imaging in surgical planning where believed to be beneficial in reducing the risk of long-term neurological deficit. This will complement the existing intraoperative brain mapping along with possibly introducing intraoperative MRI where facilities exist. Accurately defining the tumour boundary is also important to enable maximal resection. Arbizu et al[87] suggest that there may be role for metabolic imaging using carbon-11-methionine positron emission tomography for distinguishing the margins of LGG from perilesional oedema.

Improved knowledge into pathways of tumour cell migration and infiltration along white matter tracts is also important and how this affects appearances on DTI. Following early resection and the consequent improved overall survival, there will be prolonged follow-up of patients and so, identifying subtle and new areas of tumour recurrence or progression will become the predominant role of the radiologist. Investigation into the optimum timing and intervals for follow-up is needed and whether this should be modified according to the tumour genetics.

Depending on tumour genetics, patients may undergo chemotherapy and/or radiotherapy as well as surgery. This will bring further challenges in the interpretation of post-treatment imaging and in the identification of recurrence/progression *vs* pseudoprogression, but this is outside the scope of this article.

Overall, the role of the radiologist will change from one of monitoring for anaplastic progression to accurate early identification of LGG, delineation of tumour boundaries and facilitating safe aggressive surgical resection along with post-treatment follow-up imaging for tumour recurrence.

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