
Article:
Larsen, J., Wharton, S.B., Romanowski, C. et al. (4 more authors) (2017) Low grade glioma: An Update for Radiologists. British Journal of Radiology, 90 (1070). 20160600. ISSN 0007-1285

https://doi.org/10.1259/bjr.20160600

‘Low Grade Glioma’: An Update for Radiologists

Abstract

With the recent publication of a new World Health Organization (WHO) 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’ treatment. We will summarise these changes, give some context to the increased role of tumour genetics and discuss the associated implications for radiologists of their adoption. We will discuss the earlier and more radical surgical resection of low grade gliomas and what it means for imaging patients.

Background

Diffuse ‘low grade gliomas (LGG)’ are tumours of 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 are astrocytomas, oligodendrogliomas, and oligastrocytomas (although see below).[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 particularly, molecular findings are now integral to a full diagnostic categorisation 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 neuropathological 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 (ICD-0). 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 survival. 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 magnetic resonance imaging (MRI) based techniques have been explored for this purpose, including diffusion-weighted imaging[6–14], perfusion weighted imaging[6,8,10,15–21] and magnetic resonance spectroscopy[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 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 intra- and inter-observer reliability between pathologists[28,29]. This limits the usefulness of biopsy specimens which, combined with the apparent failure of MR imaging 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 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 summarise 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 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 LGG 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 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, $MTD=(2xV)^{1/3}$), and finally VDE 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 4mm/yr.[38] Further studies used changes in tumour volume. Tumour volumes are measured on fluid attenuation inversion recovery (FLAIR) series using semi-automated technique to contour the tumour margin on multiple axial images with manual editing as required to increase accuracy (see figure 1).[4,6] These studies found similar results to those measuring VDE: Rees et al. found in a study of 27 patients that stable LGG grow at a mean annualised percentage growth rate of 16%;[4] while Caseiras et al. demonstrated in 34 patients with LGG a mean growth over 6 months of 8.8ml[6] (approximately a 24% increase in volume per year).

Figure 1 here

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 greater than 3mm/year correlated with an increased risk of anaplastic progression.[16] Overall survival of patients was significantly longer in patients with a VDE of less than 8mm/year compared with those with a growth rate of greater than 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 six 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 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 biomarkers and the 2007 WHO Classification, whilst providing novel, more accurate, molecular biomarkers.

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 co-deletion 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] IDH1 mutations are more common than IDH2.[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 IDH1 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 younger patients, 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-wildtype 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-wildtype tumours.[42,52] An improved progression free survival has also been shown.[54,55]Grade II and III IDH-wildtype gliomas have a comparable survival to primary glioblastomas 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 versus 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 additional survival benefit demonstrated with IDH – mutated tumours when surgical resection is extended beyond the enhancing tumour margins, however this has only been shown in high-grade gliomas.[56]

IDH-mutated tumours have been shown to accumulate 2-hydroxyglutarate (2HG) and this can be detected non-invasively using magnetic resonance spectroscopy (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. (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 two cases that were negative for 2-HG despite progressive disease on conventional MRI.[59] 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 recognised 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 only occurs 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. found that overall survival was 97% at 3 years in tumours with codeletion compared with 89.9% in non-codeleted tumours.[54] Similarly it has been found that having a LGG with a combined 1p/19q codeletion and IDH mutation corresponds with a median overall survival of greater than eight years.[47]

1p/19q codeletion is also associated with an improved response to chemotherapy and chemo-radiotherapy as demonstrated in three randomised 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 includes 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 compared with 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] Due 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.

Figure 2 here

Implications for Neuropathological Classification and Diagnosis

The new (2016) classification now incorporates molecular genetics and histopathological findings into an integrated diagnosis.[2,30] The 4-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 co-deletion are in general astrocytic, whilst oligodendrogliomas are *ATRX* wildtype with 1p19q co-deletion. For the integrated diagnosis, the molecular findings take precedence over the morphological appearances in determining whether the tumour should be considered 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 finer sub-classification of tumour types. Where molecular typing cannot be fully assessed, the term NOS (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* wildtype (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 has been argued that in 'stable' LGG with well-controlled symptoms,

neurosurgery may cause greater morbidity than benefit due to the risk of secondary long-term neurological deficits.[4] In 2010, Soffietti et al. concluded the evidence for the timing of and extent of surgery in LGG to be inconclusive with no randomised trials in this field.[63] However, despite no prospective randomised 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., in their retrospective cohort study of patients with LGG undergoing early resection versus biopsy and then watchful waiting in two different centres, demonstrated that patients treated with early surgical resection have a better overall survival.[69] 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 greater than 90% of the tumour volume can produce overall 5 years 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 have 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 hasn't been consistently demonstrated, with other groups showing no significant differences in progression free survival with gross tumour resection versus subtotal resection/biopsy.[74,76] Seizure control is also reported to be improved by total resection, with more than 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 T2/FLAIR abnormality on MRI by up to 20mm[37] and the above findings on the benefit of aggressive

extent of resection, some have gone on further to suggest that, where possible, 'supra-total' resections (resecting beyond the MRI visible tumour margin) should be attempted and may also reduce the risk of anaplastic progression.[78,79]

Maximising 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 (EFNS) and European Association for Neuro-Oncology (EANO) recommend that 'surgical resection is the first treatment option, with the goal to maximally resect the tumour mass whenever possible, whilst minimising post-operative morbidity'.[63] The safest way to achieve this is by performing an awake craniotomy with intra-operative electrical stimulation, resecting according to functional boundaries. This is especially important as LGG are frequently located in eloquent areas of brain. In one study intra-operative 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 intra-operative 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 intra-operative neuro-navigational 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, PET and DTI.[82] However current imaging modalities available are not yet as reliable as intra-operative 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]

Due 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 intra-operatively,[70,76] which introduces a role for intra-operative 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. Haemostatic material used intra-operatively 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 categorisation 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 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 a LGG.

Accurate pre-operative imaging will be required to enable safe surgical planning. However, inter-individual variations have been shown to exist in 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 functional MRI in defining tumour boundaries and infiltration into functional brain tissue 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 intra-operative brain mapping along with possibly introducing intra-operative MRI where facilities exist. Accurately defining the tumour boundary is also important to enable maximal resection. Arbizu et al. suggest there may be role for metabolic imaging using 11C-methionine positron emission tomography (PET) for distinguishing the margins of LGG from perilesional oedema.[87]

Improved knowledge into pathways of tumour cell migration and infiltration along white matter tracts is also important and how this effects 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 the identification of recurrence/progression versus pseudo-progression 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.

1. Zhang C-M, Brat DJ. Genomic profiling of lower-grade gliomas uncovers cohesive disease groups: implications for diagnosis and treatment. Chin J Cancer [Internet]. BioMed Central; 2016 Jan 12 [cited 2016 Apr 19];35(1):12. Available from: http://cjcjournal.biomedcentral.com/articles/10.1186/s40880-015-0071-1
2. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol [Internet]. 2016 May 9 [cited 2016 May 12];131(6):803–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27157931
3. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol [Internet]. 2007 Aug [cited 2014 Jul 11];114(2):97–109. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1929165&tool=pmcentrez&rendertype=abstract
4. Rees J, Watt H, Jäger HR, Benton C, Tozer D, Tofts P, et al. Volumes and growth rates of untreated adult low-grade gliomas indicate risk of early malignant transformation. Eur J Radiol [Internet]. 2009 Oct [cited 2015 Apr 21];72(1):54–64. Available from: http://www.sciencedirect.com/science/article/pii/S0720048X08003410
5. Furnari FB, Fenton T, Bachoo RM, Mukasa A, Stommel JM, Stegh A, et al. Malignant astrocytic glioma: genetics, biology, and paths to treatment. Genes Dev [Internet]. 2007 Nov 1 [cited 2015 Feb 15];21(21):2683–710. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17974913
6. Caseiras GB, Ciccarelli O, Altmann DR, Benton CE, Tozer DJ, Tofts PS, et al. Low-grade gliomas: six-month tumor growth predicts patient outcome better than admission tumor volume, relative cerebral blood volume, and apparent diffusion coefficient. Radiology [Internet]. 2009 Nov [cited 2015 Mar 28];253(2):505–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19789244
7. Zonari P, Baraldi P, Crisi G. Multimodal MRI in the characterization of glial neoplasms: the combined role of single-voxel MR spectroscopy, diffusion imaging and echo-planar perfusion imaging. Neuroradiology [Internet]. 2007 Oct 10 [cited 2016 Apr 26];49(10):795–803. Available from: http://link.springer.com/10.1007/s00234-007-0253-x

8. Fan GG, Deng QL, Wu ZH, Guo QY. Usefulness of diffusion/perfusion-weighted MRI in patients with non-enhancing supratentorial brain gliomas: a valuable tool to predict tumour grading? [Internet]. The British Journal of Radiology. British Institute of Radiology; 2006 [cited 2016 Apr 26]. p. 652–8. Available from: http://www.birpublications.org/doi/full/10.1259/bjr/25349497
9. Yang D, Korogi Y, Sugahara T, Kitajima M, Shigematsu Y, Liang L, et al. Cerebral gliomas: prospective comparison of multivoxel 2D chemical-shift imaging proton MR spectroscopy, echoplanar perfusion and diffusion-weighted MRI. Neuroradiology [Internet]. 2002 Aug [cited 2016 Apr 26];44(8):656–66. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12185543
10. Bobek-Billewicz B, Stasik-Pres G, Hebda A, Majchrzak K, Kaspera W, Jurkowski M. Anaplastic transformation of low-grade gliomas (WHO II) on magnetic resonance imaging. Folia Neuropathol [Internet]. 2014 Jan [cited 2015 Apr 21];52(2):128–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25118898
11. Hu Y-C, Yan L-F, Wu L, Du P, Chen B-Y, Wang L, et al. Intravoxel incoherent motion diffusion-weighted MR imaging of gliomas: efficacy in preoperative grading. Sci Rep [Internet]. 2014 Jan [cited 2015 May 19];4:7208. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4248278&tool=pmcentrez&rendertype=abstract
12. Server A, Kulle B, Gadmar ØB, Josefsen R, Kumar T, Nakstad PH. Measurements of diagnostic examination performance using quantitative apparent diffusion coefficient and proton MR spectroscopic imaging in the preoperative evaluation of tumor grade in cerebral gliomas. Eur J Radiol [Internet]. 2011 Nov [cited 2015 May 19];80(2):462–70. Available from: http://www.sciencedirect.com/science/article/pii/S0720048X10003542
13. Chen S-D, Hou P-F, Lou L, Jin X, Wang T-H, Xu J-L. The correlation between MR diffusion-weighted imaging and pathological grades on glioma. Eur Rev Med Pharmacol Sci [Internet]. 2014 Jul [cited 2015 May 19];18(13):1904–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25010621
14. Arevalo-Perez J, Peck KK, Young RJ, Holodny AI, Karimi S, Lyo JK. Dynamic Contrast-Enhanced Perfusion MRI and Diffusion-Weighted Imaging in Grading of Gliomas. J Neuroimaging [Internet]. 2015 Apr 13 [cited 2015 Apr 21]; Available from:

http://www.ncbi.nlm.nih.gov/pubmed/25867683

15. Danchaivijitr N, Waldman AD, Tozer DJ, Benton CE, Brasil Caseiras G, Tofts PS, et al. Low-grade gliomas: do changes in rCBV measurements at longitudinal perfusion-weighted MR imaging predict malignant transformation? Radiology [Internet]. Radiological Society of North America; 2008 Apr 1 [cited 2015 Apr 21];247(1):170–8. Available from: http://pubs.rsna.org/doi/abs/10.1148/radiol.2471062089?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed
16. Hlaihel C, Guilloton L, Guyotat J, Streichenberger N, Honnorat J, Cotton F. Predictive value of multimodality MRI using conventional, perfusion, and spectroscopy MR in anaplastic transformation of low-grade oligodendrogliomas. J Neurooncol [Internet]. 2010 Mar [cited 2015 Apr 21];97(1):73–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19727562
17. Server A, Orheim TED, Graff BA, Josefsen R, Kumar T, Nakstad PH. Diagnostic examination performance by using microvascular leakage, cerebral blood volume, and blood flow derived from 3-T dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging in the differentiation of glioblastoma multiforme and brain me. Neuroradiology [Internet]. 2011 May [cited 2016 Apr 26];53(5):319–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20625709
18. Sugahara T, Korogi Y, Kochi M, Ikushima I, Hirai T, Okuda T, et al. Correlation of MR imaging-determined cerebral blood volume maps with histologic and angiographic determination of vascularity of gliomas. [Internet]. AJR. American journal of roentgenology. American Public Health Association; 2013 [cited 2016 Apr 26]. Available from: http://www.ajronline.org/doi/abs/10.2214/ajr.171.6.9843274
19. Law M, Young RJ, Babb JS, Peccerelli N, Chheang S, Gruber ML, et al. Gliomas: predicting time to progression or survival with cerebral blood volume measurements at dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging. Radiology [Internet]. Radiological Society of North America; 2008 May 1 [cited 2015 Apr 21];247(2):490–8. Available from: http://pubs.rsna.org/doi/abs/10.1148/radiol.2472070898
20. Caseiras GB, Chheang S, Babb J, Rees JH, Pecerrelli N, Tozer DJ, et al. Relative cerebral blood volume measurements of low-grade gliomas predict patient outcome in a

multi-institution setting. Eur J Radiol [Internet]. 2010 Feb [cited 2015 May 19];73(2):215–20. Available from: http://www.sciencedirect.com/science/article/pii/S0720048X08006293

21. Kim H, Choi SH, Kim J-H, Ryoo I, Kim SC, Yeom JA, et al. Gliomas: application of cumulative histogram analysis of normalized cerebral blood volume on 3 T MRI to tumor grading. PLoS One [Internet]. 2013 Jan [cited 2015 May 19];8(5):e63462. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3660395&tool=pmcentrez&rendertype=abstract
22. Hollingworth W, Medina LS, Lenkinski RE, Shibata DK, Bernal B, Zurakowski D, et al. A Systematic Literature Review of Magnetic Resonance Spectroscopy for the Characterization of Brain Tumors. AJNR Am J Neuroradiol [Internet]. 2006 Aug 1 [cited 2016 Apr 26];27(7):1404–11. Available from: http://www.ajnr.org/content/27/7/1404.short
23. Stadlbauer A, Gruber S, Nimsky C, Fahlbusch R, Hammen T, Buslei R, et al. Preoperative grading of gliomas by using metabolite quantification with high-spatial-resolution proton MR spectroscopic imaging. Radiology [Internet]. Radiological Society of North America; 2006 Mar 1 [cited 2016 Apr 26];238(3):958–69. Available from: http://pubs.rsna.org/doi/abs/10.1148/radiol.2382041896
24. Reijneveld JC, van der Grond J, Ramos LMP, Bromberg JEC, Taphoorn MJB. Proton MRS imaging in the follow-up of patients with suspected low-grade gliomas. Neuroradiology [Internet]. 2005 Dec [cited 2015 May 19];47(12):887–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16133483
25. Sahin N, Melhem ER, Wang S, Krejza J, Poptani H, Chawla S, et al. Advanced MR imaging techniques in the evaluation of nonenhancing gliomas: perfusion-weighted imaging compared with proton magnetic resonance spectroscopy and tumor grade. Neuroradiol J [Internet]. 2013 Oct [cited 2015 May 19];26(5):531–41. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4202829&tool=pmcentrez&rendertype=abstract
26. Tedeschi Gioacchino, Nina Lundbom, Ramesh Raman, Simona Bonavita, Jeff H. Duyn, Jeffrey R. Alger, et al. Increased choline signal coinciding with malignant degeneration of cerebral gliomas: a serial proton magnetic resonance spectroscopy imaging study.

Journal of Neurosurgery Publishing Group; 1997 Jun 10 [cited 2015 May 19]; Available from: http://thejns.org/doi/abs/10.3171/jns.1997.87.4.0516?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

27. Toyooka M, Kimura H, Uematsu H, Kawamura Y, Takeuchi H, Itoh H. Tissue characterization of glioma by proton magnetic resonance spectroscopy and perfusion-weighted magnetic resonance imaging: glioma grading and histological correlation. Clin Imaging [Internet]. 2008 Jul [cited 2016 Apr 26];32(4):251–8. Available from: http://www.sciencedirect.com/science/article/pii/S0899707108000272
28. Coons SW, Johnson PC, Scheithauer BW, Yates AJ, Pearl DK. Improving diagnostic accuracy and interobserver concordance in the classification and grading of primary gliomas. Cancer [Internet]. 1997 Apr 1 [cited 2016 Apr 26];79(7):1381–93. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9083161
29. van den Bent MJ. Interobserver variation of the histopathological diagnosis in clinical trials on glioma: a clinician's perspective. Acta Neuropathol [Internet]. 2010 Sep [cited 2016 Apr 26];120(3):297–304. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2910894&tool=pmcentrez&rendertype=abstract
30. Louis, DN, Ohgaki, H, Cavanee WK, Ellison, DW, Figarella-Branger, D, Perry, A, Reifenberger, G, von Deimling A. WHO Classification of Tumours of the Central Nervous System. Revised 4t. Lyon, France: International Agency for Research on Cancer; 2016.
31. Mandonnet E, Delattre J-Y, Tanguy M-L, Swanson KR, Carpentier AF, Duffau H, et al. Continuous growth of mean tumor diameter in a subset of grade II gliomas. Ann Neurol [Internet]. 2003 Apr [cited 2015 Apr 21];53(4):524–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12666121
32. Pallud J, Mandonnet E, Duffau H, Kujas M, Guillevin R, Galanaud D, et al. Prognostic value of initial magnetic resonance imaging growth rates for World Health Organization grade II gliomas. Ann Neurol [Internet]. 2006 Sep [cited 2015 Apr 21];60(3):380–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16983683
33. Ricard D, Kaloshi G, Amiel-Benouaich A, Lejeune J, Marie Y, Mandonnet E, et al. Dynamic history of low-grade gliomas before and after temozolomide treatment. Ann

Neurol [Internet]. 2007 May [cited 2015 May 19];61(5):484–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17469128

34. Peyre M, Cartalat-Carel S, Meyronet D, Ricard D, Jouvet A, Pallud J, et al. Prolonged response without prolonged chemotherapy: a lesson from PCV chemotherapy in low-grade gliomas. Neuro Oncol [Internet]. 2010 Oct [cited 2015 May 19];12(10):1078–82. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3018918&tool=pmcentrez&rendertype=abstract

35. Gozé C, Bezzina C, Gozé E, Rigau V, Maudelonde T, Bauchet L, et al. 1P19Q loss but not IDH1 mutations influences WHO grade II gliomas spontaneous growth. J Neurooncol [Internet]. 2012 May [cited 2015 May 19];108(1):69–75. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22392125

36. Pallud J, Llitjos J-F, Dhermain F, Varlet P, Dezamis E, Devaux B, et al. Dynamic imaging response following radiation therapy predicts long-term outcomes for diffuse low-grade gliomas. Neuro Oncol [Internet]. 2012 Apr [cited 2015 May 19];14(4):496–505. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3309865&tool=pmcentrez&rendertype=abstract

37. Pallud J, Varlet P, Devaux B, Geha S, Badoual M, Deroulers C, et al. Diffuse low-grade oligodendrogliomas extend beyond MRI-defined abnormalities. Neurology [Internet]. 2010 May 25 [cited 2015 May 19];74(21):1724–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20498440

38. Pallud J, Taillandier L, Capelle L, Fontaine D, Peyre M, Ducray F, et al. Quantitative morphological magnetic resonance imaging follow-up of low-grade glioma: a plea for systematic measurement of growth rates. Neurosurgery [Internet]. 2012 Sep [cited 2015 Mar 11];71(3):729-39-40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22668885

39. Pallud J, Blonski M, Mandonnet E, Audureau E, Fontaine D, Sanai N, et al. Velocity of tumor spontaneous expansion predicts long-term outcomes for diffuse low-grade gliomas. Neuro Oncol [Internet]. 2013 May [cited 2015 Apr 21];15(5):595–606. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3635513&tool=pmcentr

ez&rendertype=abstract

40. Potts MB, Smith JS, Molinaro AM, Berger MS. Natural history and surgical management of incidentally discovered low-grade gliomas. J Neurosurg [Internet]. American Association of Neurological Surgeons; 2012 Feb 1 [cited 2015 Apr 21];116(2):365–72. Available from: http://thejns.org/doi/abs/10.3171/2011.9.JNS111068

41. Majchrzak K, Kaspera W, Bobek-Billewicz B, Hebda A, Stasik-Pres G, Majchrzak H, et al. The assessment of prognostic factors in surgical treatment of low-grade gliomas: a prospective study. Clin Neurol Neurosurg [Internet]. 2012 Oct [cited 2015 Apr 21];114(8):1135–44. Available from: http://www.sciencedirect.com/science/article/pii/S0303846712001503

42. Network TCGAR. Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas. N Engl J Med [Internet]. Massachusetts Medical Society; 2015 Jun 10 [cited 2015 Jun 11]; Available from: http://www.nejm.org/doi/full/10.1056/NEJMoa1402121

43. Parsons DW, Jones S, Zhang X, Lin JC-H, Leary RJ, Angenendt P, et al. An integrated genomic analysis of human glioblastoma multiforme. Science [Internet]. American Association for the Advancement of Science; 2008 Sep 26 [cited 2014 Jul 25];321(5897):1807–12. Available from: http://science.sciencemag.org/content/321/5897/1807.abstract

44. Olar A, Sulman EP. Molecular Markers in Low-Grade Glioma-Toward Tumor Reclassification. Semin Radiat Oncol [Internet]. 2015 Jul [cited 2016 Mar 29];25(3):155–63. Available from: http://www.sciencedirect.com/science/article/pii/S1053429615000235

45. Balss J, Meyer J, Mueller W, Korshunov A, Hartmann C, von Deimling A. Analysis of the IDH1 codon 132 mutation in brain tumors. Acta Neuropathol [Internet]. 2008 Dec [cited 2016 May 5];116(6):597–602. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18985363

46. Liu X-Y, Gerges N, Korshunov A, Sabha N, Khuong-Quang D-A, Fontebasso AM, et al. Frequent ATRX mutations and loss of expression in adult diffuse astrocytic tumors carrying IDH1/IDH2 and TP53 mutations. Acta Neuropathol [Internet]. 2012 Nov [cited 2016 Apr 28];124(5):615–25. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/22886134

47. Taylor, JW; Chi, AS; Cahill D. Tailored therapy in diffuse gliomas: using molecular classifiers to optimize clinical management. | Harvard Catalyst Profiles | Harvard Catalyst [Internet]. Oncology 27 (6). 2013 [cited 2016 Mar 30]. p. 504–14. Available from: https://connects.catalyst.harvard.edu/Profiles/display/25895543
48. Siegal T. Clinical impact of molecular biomarkers in gliomas. J Clin Neurosci [Internet]. 2015 Mar [cited 2016 Mar 29];22(3):437–44. Available from: http://www.sciencedirect.com/science/article/pii/S0967586814006109
49. Hartmann C, Meyer J, Balss J, Capper D, Mueller W, Christians A, et al. Type and frequency of IDH1 and IDH2 mutations are related to astrocytic and oligodendroglial differentiation and age: a study of 1,010 diffuse gliomas. Acta Neuropathol [Internet]. 2009 Oct [cited 2016 Apr 4];118(4):469–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19554337
50. Lai A, Kharbanda S, Pope WB, Tran A, Solis OE, Peale F, et al. Evidence for sequenced molecular evolution of IDH1 mutant glioblastoma from a distinct cell of origin. J Clin Oncol [Internet]. 2011 Dec 1 [cited 2016 May 5];29(34):4482–90. Available from: http://jco.ascopubs.org/content/29/34/4482.full
51. Wick W, Hartmann C, Engel C, Stoffels M, Felsberg J, Stockhammer F, et al. NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and vincristine or temozolomide. J Clin Oncol [Internet]. 2009 Dec 10 [cited 2016 May 4];27(35):5874–80. Available from: http://jco.ascopubs.org/content/27/35/5874.short
52. van den Bent MJ, Brandes AA, Taphoorn MJB, Kros JM, Kouwenhoven MCM, Delattre J-Y, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. J Clin Oncol [Internet]. 2013 Jan 20 [cited 2016 Apr 28];31(3):344–50. Available from: http://jco.ascopubs.org/content/31/3/344.short
53. Hartmann C, Hentschel B, Wick W, Capper D, Felsberg J, Simon M, et al. Patients with IDH1 wild type anaplastic astrocytomas exhibit worse prognosis than IDH1-mutated glioblastomas, and IDH1 mutation status accounts for the unfavorable prognostic effect of higher age: implications for classification of gliomas. Acta Neuropathol [Internet]. 2010 Nov 19 [cited 2016 Mar 30];120(6):707–18. Available from:

http://link.springer.com/10.1007/s00401-010-0781-z

54. Sabha N, Knobbe CB, Maganti M, Al Omar S, Bernstein M, Cairns R, et al. Analysis of IDH mutation, 1p/19q deletion, and PTEN loss delineates prognosis in clinical low-grade diffuse gliomas. Neuro Oncol [Internet]. 2014 Jan 26; Available from: http://neuro-oncology.oxfordjournals.org/content/early/2014/01/25/neuonc.not299.abstract

55. Gozé C, Blonski M, Le Maistre G, Bauchet L, Dezamis E, Page P, et al. Imaging growth and isocitrate dehydrogenase 1 mutation are independent predictors for diffuse low-grade gliomas. Neuro Oncol [Internet]. 2014 Aug 1;16(8):1100–9. Available from: http://neuro-oncology.oxfordjournals.org/content/16/8/1100.abstract

56. Beiko J, Suki D, Hess KR, Fox BD, Cheung V, Cabral M, et al. IDH1 mutant malignant astrocytomas are more amenable to surgical resection and have a survival benefit associated with maximal surgical resection. Neuro Oncol [Internet]. 2014 Jan 1 [cited 2016 Apr 28];16(1):81–91. Available from: http://neuro-oncology.oxfordjournals.org/content/16/1/81.short

57. Choi C, Ganji SK, DeBerardinis RJ, Hatanpaa KJ, Rakheja D, Kovacs Z, et al. 2-hydroxyglutarate detection by magnetic resonance spectroscopy in IDH-mutated patients with gliomas. Nat Med [Internet]. NIH Public Access; 2012 Jan 26 [cited 2016 Oct 20];18(4):624–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22281806

58. Choi C, Raisanen JM, Ganji SK, Zhang S, McNeil SS, An Z, et al. Prospective Longitudinal Analysis of 2-Hydroxyglutarate Magnetic Resonance Spectroscopy Identifies Broad Clinical Utility for the Management of Patients With IDH-Mutant Glioma. J Clin Oncol [Internet]. American Society of Clinical Oncology; 2016 Oct 3 [cited 2016 Oct 20];JCO671222. Available from: http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2016.67.1222

59. Chen R, Salzman K, Prescot A, Maxwell A, Jensen R, Cohen A, et al. Evaluation of 2HG MR spectroscopy in relation to disease activity in gliomas [Internet]. 2015 [cited 2016 Oct 20]. Available from: https://soc-neuro-onc.conference-services.net/reports/template/onetextabstract.xml?xsl=template/onetextabstract.xsl&conferenceID=4558&abstractID=929979

60. Reifenberger J, Reifenberger G, Liu L, James CD, Wechsler W, Collins VP. Molecular

genetic analysis of oligodendroglial tumors shows preferential allelic deletions on 19q and 1p. Am J Pathol [Internet]. 1994 Nov [cited 2016 May 4];145(5):1175–90. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1887413&tool=pmcentrez&rendertype=abstract

61. KRAUS JA, KOOPMANN J, KASKEL P, MAINTZ D, BRANDNER S, SCHRAMM J, et al. Shared Allelic Losses on Chromosomes 1p and 19q Suggest a Common Origin of Oligodendroglioma and Oligoastrocytoma. J Neuropathol Exp Neurol [Internet]. The Oxford University Press; 1995 Jan 1 [cited 2016 May 4];54(1):91–5. Available from: http://jnen.oxfordjournals.org/content/54/1/91.abstract
62. Cairncross JG, Wang M, Jenkins RB, Shaw EG, Giannini C, Brachman DG, et al. Benefit from procarbazine, lomustine, and vincristine in oligodendroglial tumors is associated with mutation of IDH. J Clin Oncol [Internet]. 2014 Mar 10 [cited 2016 May 3];32(8):783–90. Available from: http://jco.ascopubs.org/content/32/8/783.short
63. Soffietti R, Baumert BG, Bello L, von Deimling A, Duffau H, Frénay M, et al. Guidelines on management of low-grade gliomas: report of an EFNS-EANO Task Force. Eur J Neurol [Internet]. 2010 Sep [cited 2015 Apr 20];17(9):1124–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20718851
64. Pouratian N, Schiff D. Management of Low-Grade Glioma. Curr Neurol Neurosci Rep [Internet]. 2010;10(3):224–31. Available from: http://dx.doi.org/10.1007/s11910-010-0105-7
65. Duffau H, Taillandier L. New concepts in the management of diffuse low-grade glioma: Proposal of a multistage and individualized therapeutic approach. Neuro Oncol [Internet]. 2015 Mar 1 [cited 2016 Mar 29];17(3):332–42. Available from: http://neuro-oncology.oxfordjournals.org/cgi/content/long/17/3/332
66. Wiestler B, Capper D, Holland-Letz T, Korshunov A, von Deimling A, Pfister SM, et al. ATRX loss refines the classification of anaplastic gliomas and identifies a subgroup of IDH mutant astrocytic tumors with better prognosis. Acta Neuropathol [Internet]. 2013 Sep [cited 2016 May 5];126(3):443–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23904111
67. Labussière M, Di Stefano AL, Gleize V, Boisselier B, Giry M, Mangesius S, et al. TERT promoter mutations in gliomas, genetic associations and clinico-pathological

correlations. Br J Cancer [Internet]. Cancer Research UK; 2014 Nov 11 [cited 2016 May 4];111(10):2024–32. Available from: http://dx.doi.org/10.1038/bjc.2014.538

68. Wiestler B, Capper D, Sill M, Jones DTW, Hovestadt V, Sturm D, et al. Integrated DNA methylation and copy-number profiling identify three clinically and biologically relevant groups of anaplastic glioma. Acta Neuropathol [Internet]. 2014 Oct [cited 2016 May 5];128(4):561–71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25008768

69. Jakola A, Myrmel K, Kloster R. Comparison of a strategy favoring early surgical resection vs a strategy favoring watchful waiting in low-grade gliomas. Jama [Internet]. 2012 [cited 2016 Apr 19]; Available from: http://archpedi.jamanetwork.com/data/Journals/JAMA/25482/joc120091_1881_1888.pdf

70. Capelle L, Fontaine D, Mandonnet E, Taillandier L, Golmard JL, Bauchet L, et al. Spontaneous and therapeutic prognostic factors in adult hemispheric World Health Organization Grade II gliomas: a series of 1097 cases: clinical article. J Neurosurg [Internet]. American Association of Neurological Surgeons; 2013 Jun 31 [cited 2016 Apr 16];118(6):1157–68. Available from: http://thejns.org/doi/abs/10.3171/2013.1.JNS121

71. Claus EB, Horlacher A, Hsu L, Schwartz RB, Dello-Iacono D, Talos F, et al. Survival rates in patients with low-grade glioma after intraoperative magnetic resonance image guidance. Cancer [Internet]. 2005 Mar 15 [cited 2016 May 11];103(6):1227–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15690327

72. Smith JS, Chang EF, Lamborn KR, Chang SM, Prados MD, Cha S, et al. Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. J Clin Oncol [Internet]. 2008 Mar 10 [cited 2015 May 14];26(8):1338–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18323558

73. McGirt MJ, Chaichana KL, Attenello FJ, Weingart JD, Than K, Burger PC, et al. Extent of surgical resection is independently associated with survival in patients with hemispheric infiltrating low-grade gliomas. Neurosurgery [Internet]. 2008 Oct [cited 2015 May 14];63(4):700-7-8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18981880

74. Ahmadi R, Rezvan A, Dictus C, Christine D, Hartmann C, Christian H, et al. Long-term

outcome and survival of surgically treated supratentorial low-grade glioma in adult patients. Acta Neurochir (Wien) [Internet]. 2009 Nov [cited 2016 May 11];151(11):1359–65. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19575144

75. Ius T, Isola M, Budai R, Giada P, Tomasino B, Fadiga L, et al. Low-grade glioma surgery in eloquent areas: volumetric analysis of extent of resection and its impact on overall survival. A single-institution experience in 190 patients. American Association of Neurological Surgeons; 2012 Nov 30 [cited 2016 May 11]; Available from: http://thejns.org/doi/abs/10.3171/2012.8.JNS12393

76. Shaw EG, Berkey B, Coons SW, Bullard D, Brachman D, Buckner JC, et al. Recurrence following neurosurgeon-determined gross-total resection of adult supratentorial low-grade glioma: results of a prospective clinical trial. J Neurosurg [Internet]. 2008 Nov [cited 2016 May 11];109(5):835–41. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3833272&tool=pmcentrez&rendertype=abstract

77. Chang EF, Potts MB, Keles GE, Lamborn KR, Chang SM, Barbaro NM, et al. Seizure characteristics and control following resection in 332 patients with low-grade gliomas. J Neurosurg [Internet]. American Association of Neurological Surgeons; 2008 Feb 1 [cited 2016 May 12];108(2):227–35. Available from: http://thejns.org/doi/full/10.3171/JNS/2008/108/2/0227

78. Yordanova YN, Moritz-Gasser S, Duffau H. Awake surgery for WHO Grade II gliomas within “noneloquent” areas in the left dominant hemisphere: toward a “supratotal” resection. Clinical article. J Neurosurg [Internet]. American Association of Neurological Surgeons; 2011 Aug 1 [cited 2016 May 12];115(2):232–9. Available from: http://thejns.org/doi/abs/10.3171/2011.3.JNS101333

79. Duffau H. Long-term outcomes after supratotal resection of diffuse low-grade gliomas: a consecutive series with 11-year follow-up. Acta Neurochir (Wien) [Internet]. 2016 Jan [cited 2016 Apr 10];158(1):51–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26530708

80. Duffau H, Lopes M, Arthuis F, Bitar A, Sichez J-P, Van Effenterre R, et al. Contribution of intraoperative electrical stimulations in surgery of low grade gliomas: a comparative study between two series without (1985-96) and with (1996-2003)

functional mapping in the same institution. J Neurol Neurosurg Psychiatry [Internet]. 2005 Jun 1 [cited 2016 Apr 19];76(6):845–51. Available from: http://jnnp.bmj.com/content/76/6/845.short

81. De Witt Hamer PC, Robles SG, Zwinderman AH, Duffau H, Berger MS. Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. J Clin Oncol [Internet]. 2012 Jul 10 [cited 2016 May 12];30(20):2559–65. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22529254
82. Duffau H. Lessons from brain mapping in surgery for low-grade glioma: insights into associations between tumour and brain plasticity. Lancet Neurol [Internet]. 2005 Aug [cited 2016 May 11];4(8):476–86. Available from: http://www.sciencedirect.com/science/article/pii/S147444220570140X
83. Ius T, Angelini E, Thiebaut de Schotten M, Mandonnet E, Duffau H. Evidence for potentials and limitations of brain plasticity using an atlas of functional resectability of WHO grade II gliomas: towards a “minimal common brain”. Neuroimage [Internet]. 2011 Jun 1 [cited 2016 May 11];56(3):992–1000. Available from: http://www.sciencedirect.com/science/article/pii/S1053811911002837
84. Leclercq D, Duffau H, Delmaire C, Capelle L, Gatignol P, Ducros M, et al. Comparison of diffusion tensor imaging tractography of language tracts and intraoperative subcortical stimulations. J Neurosurg [Internet]. American Association of Neurological Surgeons; 2010 Mar 1 [cited 2016 May 11];112(3):503–11. Available from: http://thejns.org/doi/abs/10.3171/2009.8.jns09558
85. Senft C, Bink A, Franz K, Vatter H, Gasser T, Seifert V. Intraoperative MRI guidance and extent of resection in glioma surgery: a randomised, controlled trial. Lancet Oncol [Internet]. 2011 Oct [cited 2016 May 24];12(11):997–1003. Available from: http://www.sciencedirect.com/science/article/pii/S1470204511701966
86. Graber JJ, Tabar V, Brennan C, Rosenblum M, Deangelis LM. Acute inflammatory reactions to hemostatic materials mimicking post-operative intracranial abscess. Interdiscip Neurosurg Adv Tech Case Manag. 2014;1(1):5–7.
87. Arbizu J, Tejada S, Marti-Climent JM, Diez-Valle R, Prieto E, Quincoces G, et al. Quantitative volumetric analysis of gliomas with sequential MRI and ^{11}C-methionine PET assessment: patterns of integration in therapy planning. Eur J Nucl Med Mol Imaging [Internet]. 2012 May [cited 2015 Apr 21];39(5):771–81. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/22258713

Figure 1

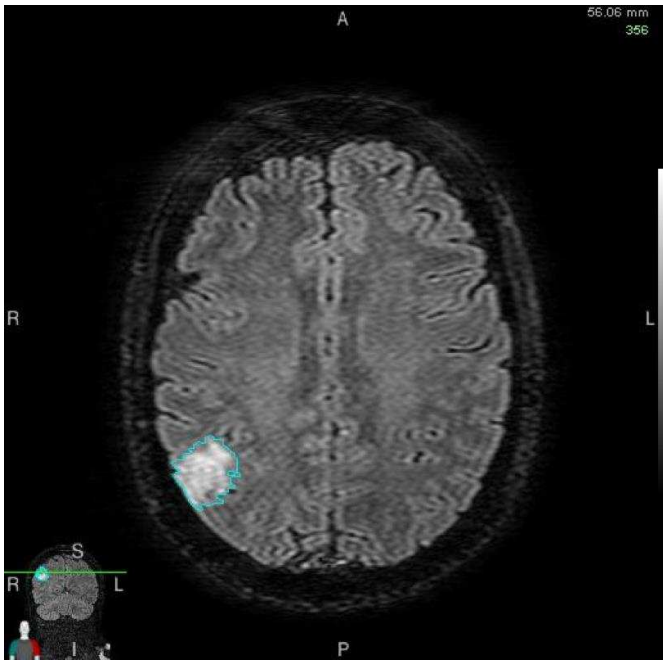
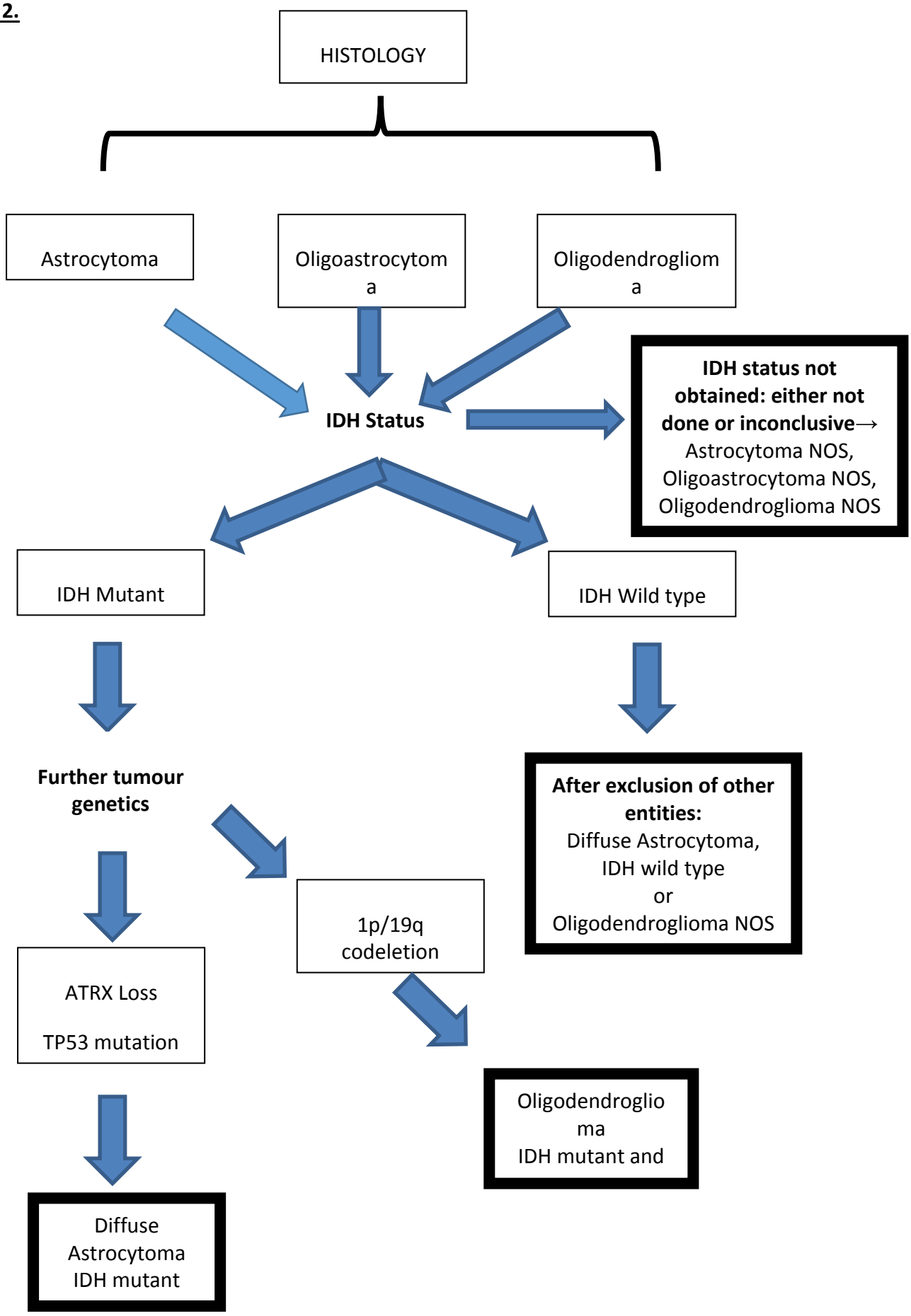


Figure 1: Axial FLAIR image with Gadolinium showing contour around the tumour margin used to calculate tumour volume. The overall tumour volume is the product of the contoured areas on each axial slice, the slice thickness and inter-slice gap.

Figure 2.


HISTOLOGY
Astrocytoma
Oligoastrocytoma
Oligodendroglioma
IDH Status
IDH status not obtained: either not done or inconclusive→ Astrocytoma NOS, Oligoastrocytoma NOS, Oligodendroglioma NOS
IDH Mutant
IDH Wild type
Further tumour genetics
After exclusion of other entities: Diffuse Astrocytoma, IDH wild type or Oligodendroglioma NOS
1p/19q codeletion
ATRX Loss
TP53 mutation
Oligodendroglioma IDH mutant and
Diffuse Astrocytoma IDH mutant