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Current management of low grade gliomas

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Abstract

Purpose of Review: The management of patients suffering from low-grade gliomas (LGG) remains a challenge in absence of a definite curative therapy. The median survival is highly variable, from 2 (high-risk disease) to over 15 years (low risk). The aim of this review is to provide a practical step by step evaluation of the patients and of the available treatment options.

Recent findings: Next to clinical prognostic markers, both the IDH mutation status and the status of 1p/19q codeletion are key prognostic factors for the optimal management of patients with LGG. Two recent randomized phase III clinical trials were performed in LGGs. The first compared the efficacy of radiation (RT) versus temozolomide chemotherapy in high risk LGGs. The second trial compared RT versus RT combined with PCV chemotherapy.

Summary: Regarding molecular prognostic factors IDH wild type LGG have the worst prognosis, independent of therapy, while patients with mutated IDH, codeleted 1p/19q LGGs fared best regarding progression-free survival. In high risk LGGs PFS is similar regardless of whether patients have been treated with RT or TMZ. In the second trial, patients that were treated with combination RT and chemotherapy showed significant longer overall survival.

Keywords:

low grade glioma, molecular markers, surgery, radiotherapy, chemotherapy, management

Introduction

Diffusely infiltrating gliomas are primary tumors of the central nervous system (CNS) that are classified into distinct entities based on the histopathological resemblance (phenotype) of the tumor cells and the genotype. According to the revised fourth edition of the WHO classification[1] these comprise 3 major subtypes, diffuse astrocytoma with mutation of the isocitrate dehydrogenase gene 1 or 2 (*IDH1*, *IDH2*; IDHmt), astrocytoma IDH wildtype (wt), and oligodendroglioma IDH mutant, and co-deleted for chromosomal arms 1p and19q (1p/19q codeleted); or in absence of genetic information into astrocytoma or oligodendroglioma not otherwise specified (NOS), respectively (FIGURE 1)

The median age of patients diagnosed with LGGs typically ranges from the late twenties to the mid forties, although some patients may be diagnosed after 60 years of age[2]. They are therefore relatively younger than patients diagnosed with an anaplastic astrocytoma or glioblastoma. The majority of patients present with seizures, sometimes that may have gone unrecognized for years. Given the widespread use of CT or MRI, an increasing number of patients are diagnosed with a suspected glioma for unrelated symptoms such as vertigo, migraine or head trauma. The appearance of a LGG is usually quite typical on MRI (FIGURE 2). Over 95% of them present in a supratentorial localization and appear hypointense on T1 without uptake of contrast in most cases and hyperintense on T2/FLAIR. Susceptibility-weigthed sequences may show calcifications. The center of the lesion is usually

localized in the white matter, although oligodendrogliomas may infiltrate or expand into the cortex[3].

Prognostic molecular markers

Recent advances in molecular characterization of gliomas have provided insights into their etiologic evolution, which is reflected in part in the new WHO classification (FIGURE 3)[1]. Mutation of *IDH1 or 2* is the hallmark of diffuse astrocytoma and oligodendroglima and has been associated with better outcome as opposed to IDHwt astrocytoma[4]. The most commonly identified mutant is IDH1 R132H, which represents >90% of all *IDH1 and 2* mutations and can be readily identified by immunohistochemistry[5]. Negative cases need to be subjected to sequence analyses of both *IDH1* and *2*. The mutations identified are gain of function mutations that alter the normal catalytic activity of the enzyme to produce 2-hydroxyglutarate, which accumulates to high concentrations in the tumors. This oncometabolite inhibits α-ketoglutarate dependent enzymes, including TET2 that is involved in DNA demethylation[6]. Thereby IDH mutants seem to mediate the formation of a CpG island methylation phenotype (CIMP)[7], associated with broad alteration of gene expression, resulting from silencing of genes including cancer relevant tumor suppressor genes.

The combined loss of one copy of chromosome arms 1p and 19q occurs in IDHmt tumors and is the hallmark of oligodendroglial tumors. This results from an unbalanced whole-arm translocation between chromosomes 1 and 19 with loss of the derivative chromosome t(1p:19q) and has been associated with

sensitivity to chemotherapy[8]. IDHmt and 1p/19q codeleted tumors are usually associated with *TERT* promoter mutations associated to increased expression, while the non-codeleted IDHmt tumors are associated with *TP53* mutations and mutations of alpha thalassemia/mental retardation syndrome X linked gene (*ATRX*). The latter can be assessed as loss of ATRX expression by immunohistochemistry[9]. Both TERT and ATRX are involved in maintenance of telomeres, which may drive the development of all gliomas[10].

In LGGs, the role of the methylation status of the repair gene O6-methyl-guanine-DNA methyltransferase (*MGMT*) is quite different from GBMs, where it is a known predictive factor for benefit from alkylating agent therapy[11]: IDHmt or CIMP+ tumors are highly associated with *MGMT* methylation, being positive in 100% of the 1p/19q codeleted LGGs and over 90% of the non-codeleted cases; In contrast, among IDHwt/CIMP- LGGs, only 40% were *MGMT* methylated[12, 13] (FIGURE 3). In other words, due to the nested relationship, the determination of the *MGMT* methylation status in IDHmt/CIMP+ tumors does not provide additional information. Furthermore, in contrast to GBM that loose the second allele of *MGMT* due to the common deletion of chromosome 10 (10q26 location of *MGMT*), in IDHmt gliomas a second allele is present, and residual MGMT expression may be expected, blunting the treatment effect even in *MGMT* methylated cases[13].

These retrospective observations have been confirmed in an international prospective randomized trial in patients with LGG (EORTC 22033-26033) where patients with IDHwt tumors had the worst prognosis, independent of

therapy, while patients with IDHmt/1p/19q codel tumors fared best regarding progression-free survival[14]. It is important to note that tumor grade has little impact on the outcome of patients with IDHmt tumors[15]. Although, this may be confounded by different initial treatment attitudes, as reported by Weller et al. where 90% of the patients with grade III tumors received immediate treatment in contrast to only 10% of grade II patients being treated immediately at diagnosis[16]. In contrast, in IDHwt LGGs, grade and age play an important role[17-19]. However, this subgroup is ill defined. Upon further molecular analysis most IDHwt astrocytoma may be classified as GBM, although this group also comprises less malignant tumors such as pilocytic astrocytoma[15, 20]

Management of patients with low grade gliomas

Clinical prognostic factors

The outcome of patients with LGGs may be extremely variable, spanning from as little as 2 years to over 15 years[21]. The identification of prognostic factors is thus critical for the optimal management of the patient. A prognostic score is available to help identifying patients being at risk for progression and thus needing a therapy. This score is derived from two large randomized EORTC studies[22]. In multivariate analysis, age ≥ 40 years, astrocytic tumour type, tumor size > 6 cm, tumor crossing the midline, and neurological deficit at diagnosis (before surgery) were identified as prognostic factors. A favorable (low-risk) prognostic score (< 2 factors present) was associated with a median survival of 7.7 years (95%CI=6.6-9.3). The presence of three to five

prognostic factors was associated with a median survival of 3.2 years (95%CI:3.0-4.0)[22]. More recently, this score was refined based on data from randomized trials from the EORTC and North American cooperative groups. Both PFS and OS were negatively influenced by the presence of baseline neurological deficits, a shorter time since first symptoms, an astrocytic tumor type, and tumors larger than 5 cm in diameter. In this more homogeneously defined patient population three risk groups were identified (low, intermediate, and high risk)[23].

1. Observation vs surgery

Once a lesion compatible with a LGG is identified on MR imaging, it should be decided whether to intervene surgically, and if so, whether to perform a biopsy or a resection. In certain situations, this decision might be quite easy: for instance in a patient that presents a small, easily resectable lesion or if the patient presents with neurologic deficits or has a significant mass effect. On the opposite, the decision is more difficult in a patient with an incidentally detected lesion or well-controlled seizures. To date, regarding outcome, there is no compelling evidence that early intervention is superior to observation with surgery reserved for the time point when the lesion grows. It must however be noted that LGGs grow continuously[24] and up to 50% of anaplastic gliomas do not enhance and can therefore not be distinguished from lower grade tumors. In this decision, not only patient preference, but also a number of prognostic factors must factored in as age, tumor size, location and surgical risks (see above). Imaging with FET-PET might represent an additional tool to help identify tumors that have a more aggressive

behavior[25]. If observation is selected, the patient must be carefully followed with serial MRIs and neurological observation. As soon as the tumor shows significant growth, signs of transformation or significant neurological deficits a definite diagnosis must be established. It is essential that the time point where a surgical resection is no longer feasible is not missed.

2. Biopsy versus surgery

Once the decision to obtain a definitive diagnosis has been reached, it must be decided whether to aim for a resection or a biopsy. It is obvious that larger resections minimize the risk of misdiagnosis or diagnosis to a lower level of aggessivity linked to the potential miss-sampling of a biopsy sample taken in a heteregenous tumor[26]. Regarding outcome, there is however no class I evidence available to differentiate between biopsy or resection. Several retrospective studies have tried to compare them. For instance, a retrospective review of 216 patients showed that the extent of resection correlated significantly with overall survival: patients that had >=90% resection showed a 5-year survival of >97%, versus 76% in those with larger residual tumors[27]. Similarly, another study showed a 5-year OS of 97% in patients with complete resection versus 70% if incomplete[28]. A Norwegian population-based parallel cohort study showed an improved overall survival in patients undergoing maximal safe resection versus those having undergone biopsy[29]. These retrospective studies are however likely to be biased by a number of factors, including smaller tumors, better localization, better performance scores for patients with more aggressive resections and a potential lead in bias as different doctors may decide differently at which time point treatment

must be started. Some studies have indeed found that although extensive resection predicts better outcome in univariate analysis, this finding is lost on multivariate analysis once data are controlled for other prognostic factors[22].

Practically, the general consensus is to recommend a maximal safe resection whenever possible. In cases where only a small portion of the tumor might be amenable to resection, a FET-PET scan may help to identify the most aggressive parts of the tumor that will be the ideal location for biopsy or for partial resection[25].

Postoperative management

Once the diagnosis is established, the optimal management of patients with LGGs remains challenging and controversial, as neither the time, nor sequence of treatment has been unambiguously resolved. A number of issues should be addressed, ideally in the setting of a multidisciplinary tumor board.

Postoperative follow-up?

The first question that usually arises is whether patients may be followed postoperatively without immediate postoperative treatment. This approach was mainly supported by the results of the randomized phase III EORTC22845 study that evaluated immediate postoperative radiotherapy versus delaying radiotherapy to the time point of progression in 157 patients with low grade astrocytoma and oligodendrogliomas. Whereas patients that underwent early RT had longer PFS, OS was similar in both groups[30]. This

option should be reserved for patients that underwent excellent resections and show no negative prognostic factors (age <=40, small initial tumor volume, absence of neurological deficit, and presence of favorable prognostic molecular markers (IDHmt, ideally 1p/19q codeleted). These patients will however need careful long-term surveillance with serial MRIs. Moreover comparisons will have to be made with the postoperative MRI. Indeed, it must be noted that in a prospective study 50% of patients with LGGs less than 40 years old that had undergone complete radiological resection, 50% showed disease progression 5 years after surgery[31].

Radiation therapy?

Patients being at a high risk to recurrence or progression (patients older than 40 years, after incomplete resection, with unresectable tumors or neurologic symptoms) are usually treated with radiation therapy. Radiotherapy is usually given in daily fractions of 1.8-2 Gy to a total dose of 45-50.4 Gy. Two randomized trials investigating radiation doses found no difference in overall survival for higher doses when comparing 45 Gy and 59.4 Gy, and 50.4 Gy and 64.8 Gy, respectively[32, 33]. However, toxicity is significantly worse with higher radiation dose levels: A 2-year actuarial incidence of grade ≥ 3 radiation necrosis of 2.5% has been observed in patients treated with a total dose of 50.4 Gy versus a 5% rate using 64.8 Gy[30, 32]. Approximately 30% of patients treated with RT will show tumor shrinkage. Of particular concern in patients with LGG is the development of long-term neurocognitive deficits. In a study of 195 patients with LGGs followed at a mean of 12 years after diagnosis showed that patients that had received no RT had stable

radiological and neurocognitive status, whereas patients that had undergone RT showed progressive neurocognitive decline associated with radiologic RT induced leukoencephalopathy[34]. The risk of long-term neurocognitive deficit must therefore be considered carefully for these patients, especially those with the longest expected outcomes (oligodendrogliomas IDHmt, 1p/19q codeleted), although most recent studies evaluating long term effects of radiation therapy suggest that there is only sporadic limited, neurocognitive damage from focal radiotherapy at the usually prescribed doses for low-grade gliomas[35].

In the EORTC 22844 trial, functioning concerning quality-of-life was lower for patients who received 54Gy compared to 45Gy in the EORTC22844 trial especially for fatigue, insomnia and emotional functioning[36], however, there was no difference in quality-of-live scales in the randomized EORTC 22033 trial between patients treated with RT or TMZ, although the follow up remains limited in this study[37].

It must be noted that following RT, determining further tumor progression might be challenging as RT may cause delayed white matter changes that may resemble tumor progression. The RANO group has devised a radiological assessment tool to assist in this evaluation[38].

Chemotherapy?

Given the risks associated with RT, using chemotherapy as a first line treatment option has been widely evaluated. This approach was further

validated by the observation that anaplastic and grade II oligodendrogliomas with 1p/19q codeletion were highly sensitive to chemotherapy[8]. These early studies were performed with a combination of procarbazine, lomustine and vincristine (PCV). This combination was then replaced by temozolomide as this agent showed a much better tolerability and fewer side effects. A number of small phase II studies showed similar response rates and OS than RT, typically in the range of 3-5 years[39]. To validate these findings, the EORTC launched a large phase III trial to randomize 477 patients with low grade gliomas and a high risk profile (defined as age>40, neurologic deficits or progredient lesions under supervision) between 12 cycles of temozolomide or standard RT (EORTC 22033)[14]. After a median follow up of 4 years there was no difference between the two modalities for PFS, with a median PFS of 39 months for patients treated with TMZ (CI95: 35-44 months) and 46 months (CI95: 40-56 months; HR for progression: 1.16 (CI95: 0.9-1.5); p=0.22) in the RT-arm. The data are not yet mature enough to evaluate OS. Molecular subgroup analyses suggest that for patients with IDHmt, 1p/19q codeleted tumors no difference was observed in PFS between TMZ and RT. Treatment with chemotherapy first would allow delay of RT and its associated risks for long term CNS toxicity. However, patients with IDHmt 1p/19q non-codeleted tumors showed significantly longer PFS when treated with RT as compared to temozolomide[14].

Combination of chemotherapy and radiation therapy?

The combination of radiation therapy and chemotherapy has resulted in significantly improved outcomes in glioblastoma[40] and anaplastic oligodendrogliomas with 1p/19q codeletions[41, 42].

In a randomized phase III trial, 251 patients with high risk LGG, defined as less than complete resection or that were >=40 at age of diagnosis were randomized to receive either RT alone or RT followed by PCV chemotherapy. The study was started in 1998. Preliminary results published in 2012 showed no survival advantage with the addition of chemotherapy[43]. A subsequent analysis with longer follow up showed a significant survival advantage for patients that were treated with the combination treatment (13.3 vs 7.8 years)[44]. Unfortunately, this study only provides incomplete information about the molecular status of the patients, as information about IDH1 R132H status was available for 60% of patients, but the 1p/19q codeletion status has not been evaluated. Hence, it remains difficult to determine which molecular subgroup of patients particularly benefits from this combination of treatments, especially as 2 large trials in grade III gliomas (high grade) showed no evidence for increased survival in patients that did not present the 1p/19q codeletion[42, 45]. Nevertheless, in absence of additional data and given the large difference in OS observed in the latter study, it is probably safe to recommend the addition of chemotherapy in patients that are scheduled to undergo RT.

PCV chemotherapy is associated with quite severe side effects and only 56% of the patients were able to actually complete the planned cycles of PCV[44]. Thus it remains a valid question as to whether PCV can be replaced by TMZ, an alkylating agent that was developed after the initiation of this trial and that has a much better safety profile. Unfortunately there are no prospective data available to answer this question. It must however be noted that patients with anaplastic gliomas, the NOA-04 trial, who received either PCV or TMZ in the chemotherapy arm found that PCV was better than TMZ for PFS (HR: 0.39 [95CI: 0.17-0.92]), although this was not an endpoint and the trial was not powered for this analysis[46], whereas Brada *et al* showed that patients with recurrent high grade gliomas showed identical outcomes whether treated with PCV or TMZ[47]. Based on these findings and the fact that TMZ is much better tolerated than PCV and that patients will be more likely to actually complete their planned treatment course, we feel that it is justified to propose the option of a combination treatment with RT and TMZ to patients after careful explanation of the available data.

Conclusions

As the life expectancy of LGGs is extremely variable with IDHmt tumors possibly with little growth over years whereas IDHwt tumors can grow faster and more aggressively, treatment of LGGs remains extremely challenging. As now implemented in the WHO classification, it is of high importance to determine both the IDH mutation status and the status of 1p/19q codeletion. These molecular markers should be part of the initial diagnostic workup for all patients with a LGG in order to define an individual treatment strategy. This

strategy is a careful balancing act between the selection of the right time point to start treatment, the choice of the optimal treatment and a careful risk assessment of the expected therapeutic efficacy of the treatment and its potential late term complications. In short: Initial observation may be a reasonable postoperative option in a subset of patients defined both by clinical and molecular factors. If it is decided that the patient must be treated, options include radiation therapy, chemotherapy or a combination of both. Recent data suggest that a combination of RT followed by chemotherapy is probably superior to RT alone. Further trials will be needed to fully establish the best treatment options.

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Conflicts of interest

The authors have no conflicts of interest to report.

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Figure legends

Figure 1

New 2016 WHO classification of brain tumors: Integration of histopatologic features with tumor genetics. Adapted from [1] with permission.

Figure 2

Typical MRI sequence of a left frontal oligodendroglioma showing T2 hyperintensity

Figure 3

Relationship of biomarkers in low grade glioma. The Venn diagram depicts the relationship of IDH mutations or CIMP status and coedeletion of 1p/19q and the *MGMT* methylation status in the low grade glioma cohort of the TCGA (N=206). Analyses were performed as described in Bady et al [13] (with permission).

Key points in the management of patients with low grade gliomas

- The optimal management of low grade gliomas remains controversial.
- To date, no compelling evidence demonstrates that early intervention with surgery improves outcome over observation in low grade gliomas. These patients must however be carefully followed with serial MRIs and comparisons must be made with the oldest MRI.
- Once progression is established, maximal safe resection should be favored over biopsy.
- Initial observation may be a reasonable postoperative option in a subset of patients defined both by clinical and molecular factors. These patients must however be carefully followed with serial MRIs. Comparisons should systematically be performed with the postoperative MRI.
- If it is decided that the patient must be treated, options include radiation therapy, chemotherapy or a combination of both. Recent data suggest that a combination of RT followed by chemotherapy is probably superior to RT alone
- The choice of treatment must include the assessment of clinical and molecular prognostic factors and a careful evaluation of potential late complications of the treatment

Figure 1

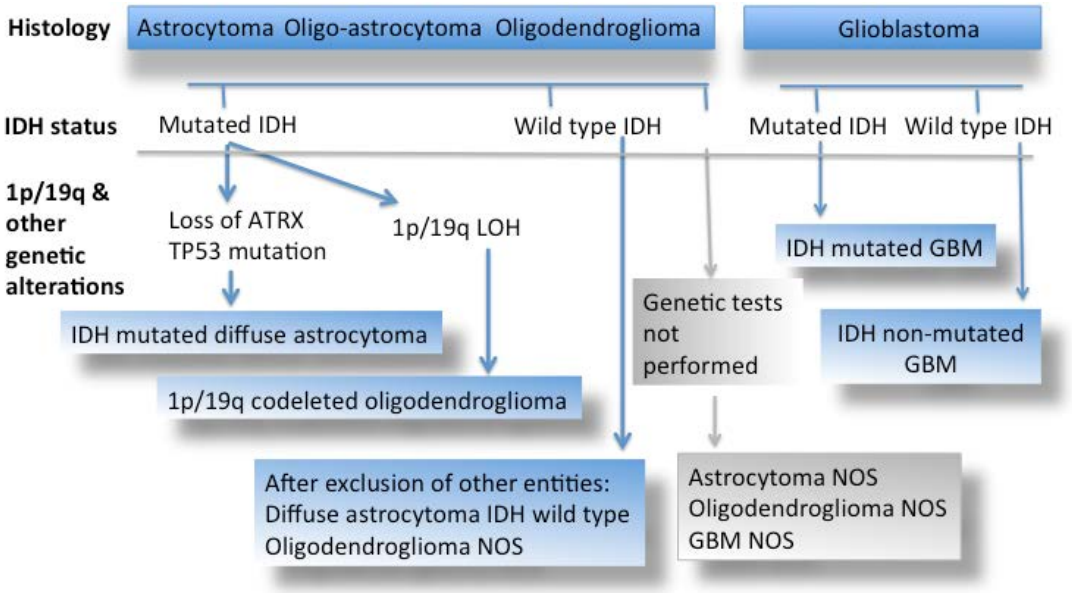

Histology
Astrocytoma Oligo-astrocytoma Oligodendroglioma
Glioblastoma
IDH status
Mutated IDH
Wild type IDH
Mutated IDH
Wild type IDH
1p/19q & other genetic alterations
Loss of ATRX TP53 mutation
1p/19q LOH
IDH mutated GBM
Genetic tests not performed
IDH non-mutated GBM
IDH mutated diffuse astrocytoma
1p/19q codeleted oligodendroglioma
After exclusion of other entities: Diffuse astrocytoma IDH wild type Oligodendroglioma NOS
Astrocytoma NOS
Oligodendroglioma NOS
GBM NOS

Figure 2:

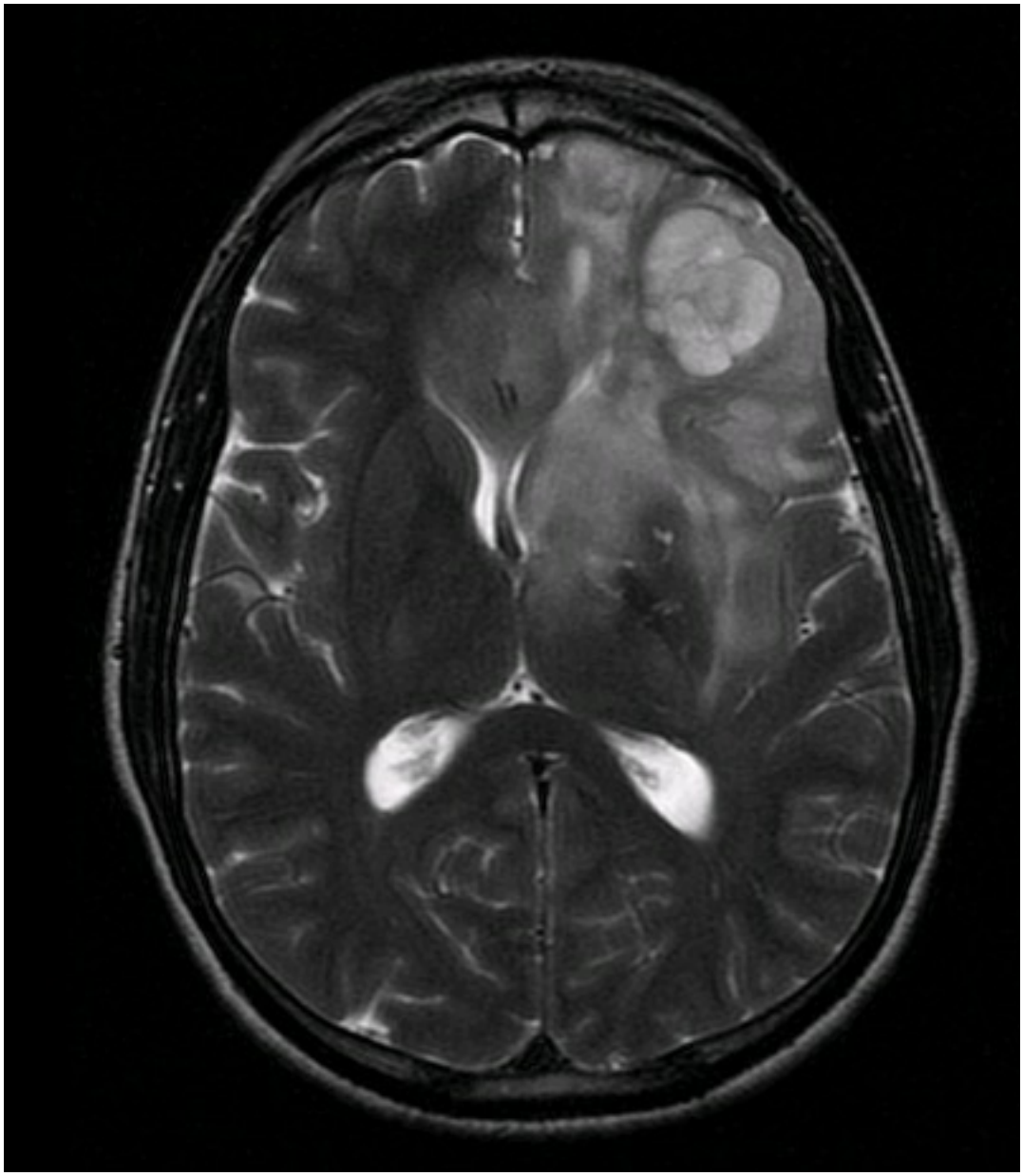
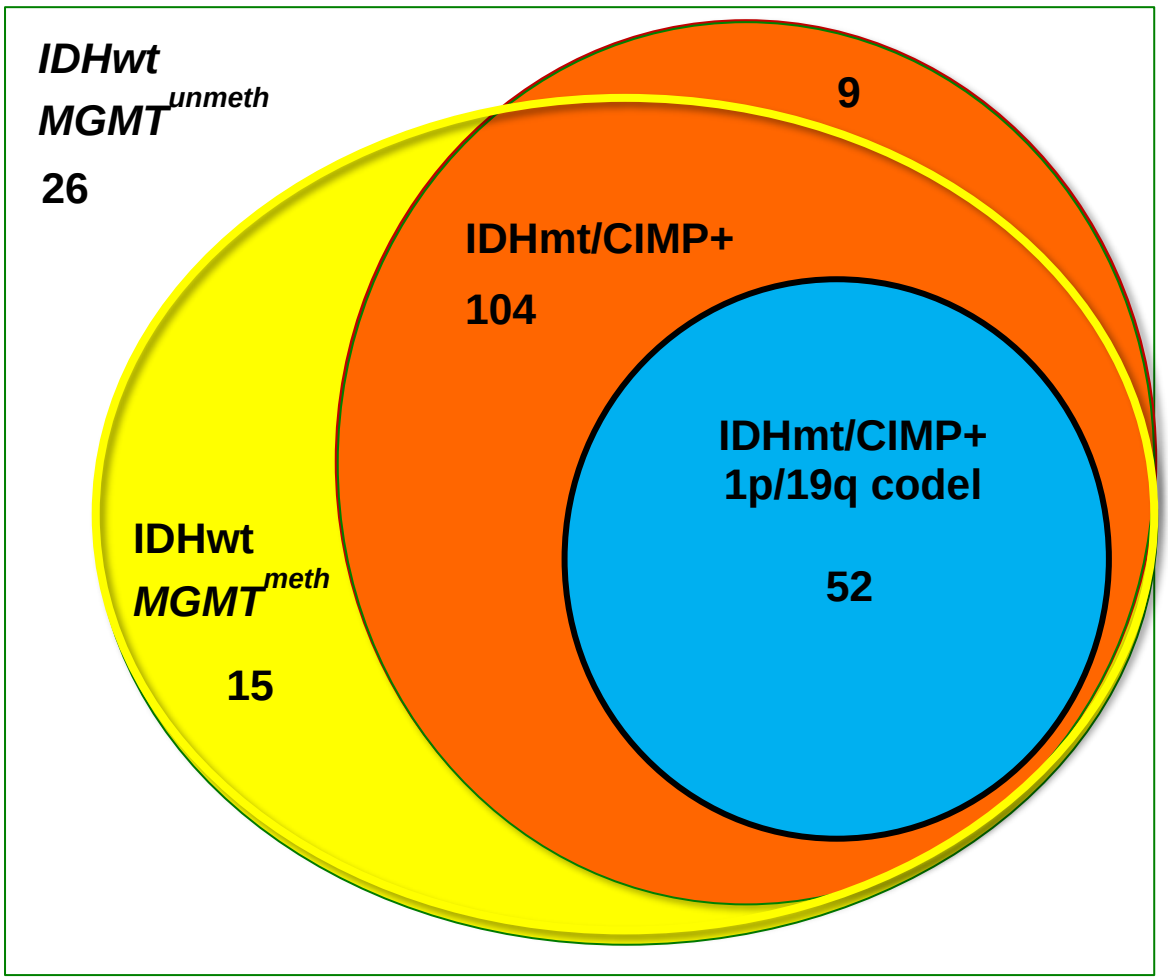


Figure 3:


IDHwt
MGMT unmeth
26
9
IDHmt/CIMP+
104
IDHmt/CIMP+
1p/19q codel
52
IDHwt
MGMT meth
15