LOW GRADE GLIOMAS:

The WHO convention divides gliomas into 4 grades, with higher grades associated with worse prognosis. Knowledge of the heterogeneity of these tumours has led to a reconsideration of the sub-classifications that reflect a different prognostic spectrum and a therapeutic focus in which the grade on its own is insufficient for taking a decision. Genomic medicine has clarified a series of markers in these tumours that help to delimit the prognosis for low grade gliomas. Knowledge of IDH1 and IDH2 mutations, 1p/19q loss of heterozygosity and MGMT methylation help us predict the prognosis (along with all the patient's clinical features already described by Pignatti: aged over 40, astrocytoma histology, diameter > 6 cm, the tumour crossing the midline and the presence of neurological deficit) (1).

The diversity in anatomo-pathological decisions has been brought to light especially in low grade gliomas (2). Recent knowledge of the molecular characterisation of low grade gliomas will help to delimit clear subgroups of patients with therapies selected according to their prognosis (3,4,5). The new WHO classification has incorporated the importance of genetic alterations in the subdivision of the various gliomas (6).

Somatic mutations of the isocitrate dehydrogenase genes (IDH1 and IDH2) are very significant for the prognosis. These mutations are present in 50 to 80% of grade II-III gliomas. These mutated enzymes involve the conversion of a-ketoglutarate to D-2-hydroxyglutarate, an oncometabolite that directs oncogenetic activity. Regardless of the treatments, patients with these mutations have a better prognosis.

In oligodendrogliomas, the most common cytogenetic alteration is the 1,19 (q10;p10) translocation. Translocation results in the fusion of the 1p and 19q arms accompanied by loss of heterozygosity of 1p and 19q. This alteration has a prognostic significance that is clearly favourable.

Other biomarkers have been incorporated to delimit subgroups in low grade gliomas. Examples of this are telomerase reverse transcriptase (TERT) promoter mutations, mutations and losses of alpha thalassemia X-linked mental retardation syndrome (ATRX), BRAF and P53 (TP53) mutations.

Using these genetic alterations, the majority of low grade gliomas may be subdivided into three clearly reproducible categories (which is important in study design) and with clear prognostic, and consequently therapeutic, significance:

(1) LGG IDH1wt: Tumours with poor prognosis. These present deletions of chromosome 10 and gains of chromosome 7, EGFR amplification, PTEN and NF1 mutations.

(2) LGG IDH1 mutation without codeletion of 1p19q: Tumours with an intermediate prognosis. These present P53 mutation, ATRX mutation, amp(8q24).

(3) LGG IDH1 mutation with codeletion of 1p19q: Tumours with a good prognosis. These present CIC mut, FUBP1 mut, TERT mut and Notch1 mut. (This group will be considered and treated as oligodendrogliomas).

Recommendations for complementary treatment following surgery must contemplate this prognostic information from molecular studies. However, patients with a good prognosis and low risk, especially young patients and those with full resection, will not be candidates other than for follow-up (especially those with oligodendrogliomas).

SURGERY IN LOW GRADE GLIOMAS:

The role of surgery is fundamental in two ways: diagnostic and therapeutic. Historically, the diagnosis of the grade is best defined according to the volume of tissue available to the pathologist. Biopsies may not be fully representative (7). Some studies using biopsy and subsequent resection reported correct diagnostic correlation in only 49% of cases (8). Many authors support the maximum resection possible in these patients. Various large-scale retrospective studies and one non-randomised comparative study (biopsy versus maximum resection), point to the extent of resection (5 cm^3 of residual volume or >95%) as a prognostic indicator of survival (9).

The therapeutic role of resection in low grade gliomas has recently been studied. Studies tend to be retrospective and non-randomised but support the conclusion that resection for IDH1 mutation patients is associated with a higher number of complete resections (10). The RTOG 9802 study cohort with the highest survival rate was patients with a diameter less than 4 cm in the preoperative MRI, oligodendroglioma histology and with less than 1 cm of residual tumour following surgery (which reaffirms the role of surgery) (11).

CHEMOTHERAPY IN LOW GRADE GLIOMAS:

Given the relatively low rate of proliferation of these tumours, they have been typically considered chemoresistant. In one study by the Southwest Oncology group in patients with subtotal resection randomised to treatment with RT versus RT+lomustine, there were no clear differences (12). The RTOG -9802 study tested the role of combination PCV in patients with high-risk, low grade gliomas (considered as those over 40 and/or subtotal resection). When followed-up over 12 years, overall survival was clearly higher (13.3 years) in the combination (RT/PCV) arm versus RT (7.8 years). (13,14). The

significance of 1p19q, MGMT and IDH was unknown at the start of the study and several molecular analyses were carried out post hoc. IDH1 alteration was present in 61% of patients treated with RT+PCV and in 64% of those treated with RT. Patients with mutations showed higher progression-free survival and overall survival if they received the combined treatment. Overall survival for IDH mutated patients was 13.1 years versus 5.1 in the non-mutated The number of non-mutated is insufficient to extrapolate the benefit of the combination in non-mutated patients (13,14).

The RTOG 0424 study was a phase II study (129 patients with three or more poor prognosis factors). The patients were given a combination of radiotherapy and temozolomide. Overall survival at three years was 73.1%, significantly higher than in historic controls (15).

The EORTC 22033 (TMZ) trial tested RT versus temozolomide in a phase III study in high-risk, low grade gliomas. The PFS was 39 months for all patients, 30 months for patients with maintained 1p/19q, and 55 months for patients with codeleted 1p/19q. First line treatment with TMZ compared with RT did not increase the PFS in patients afflicted with high-risk, low grade glioma. Overall survival has not yet been reported with mature data (16).

RADIOTHERAPY IN LOW GRADE GLIOMAS:

Studies with radiotherapy have classically shown increased progression-free survival with reduced symptoms (especially seizures) but have not demonstrated increased overall survival (17). Increasing the dosage from 45 to 64 Gy did not improve the results (18).

The EORTC 22033-26033 study on low grade gliomas graded patients with 1p deletion, randomising them to receive RT versus temozolomide. A post hoc molecular analysis was reported for 407 patients. IDH1 and IDH2 mutations were detected in 85.8% of cases. 1p19q codeletions were identified in 33% of cases. MGMT methylation was observed in 90% of patients. IDH1 and IDH2 mutations, regardless of 1p19q codeletion was a positive prognostic factor. Patients with IDH mutation, without codeletion, had a lower SLP in patients treated with temozolomide versus those treated with RT (HR 1.86; 95% CI, 1.21–2.87; log rank p = .0043). No differences were observed in IDH non-mutated or IDH mutated patients when codeletion was present. (19).

In the minority of patients previously classified as having gliomatosis cerebri, not indicating radiotherapy should be considered because of the risk of secondary toxicity and the survival prognosis of the low grade glioma.

CONCLUSIONS:

1-There is evidence of the role of molecular markers in low grade gliomas (response-prediction and prognostic role).

2-The main molecular factors for subdividing low grade gliomas are IDH mutations, 1p19q codeletions, ATXR and TERT mutations.

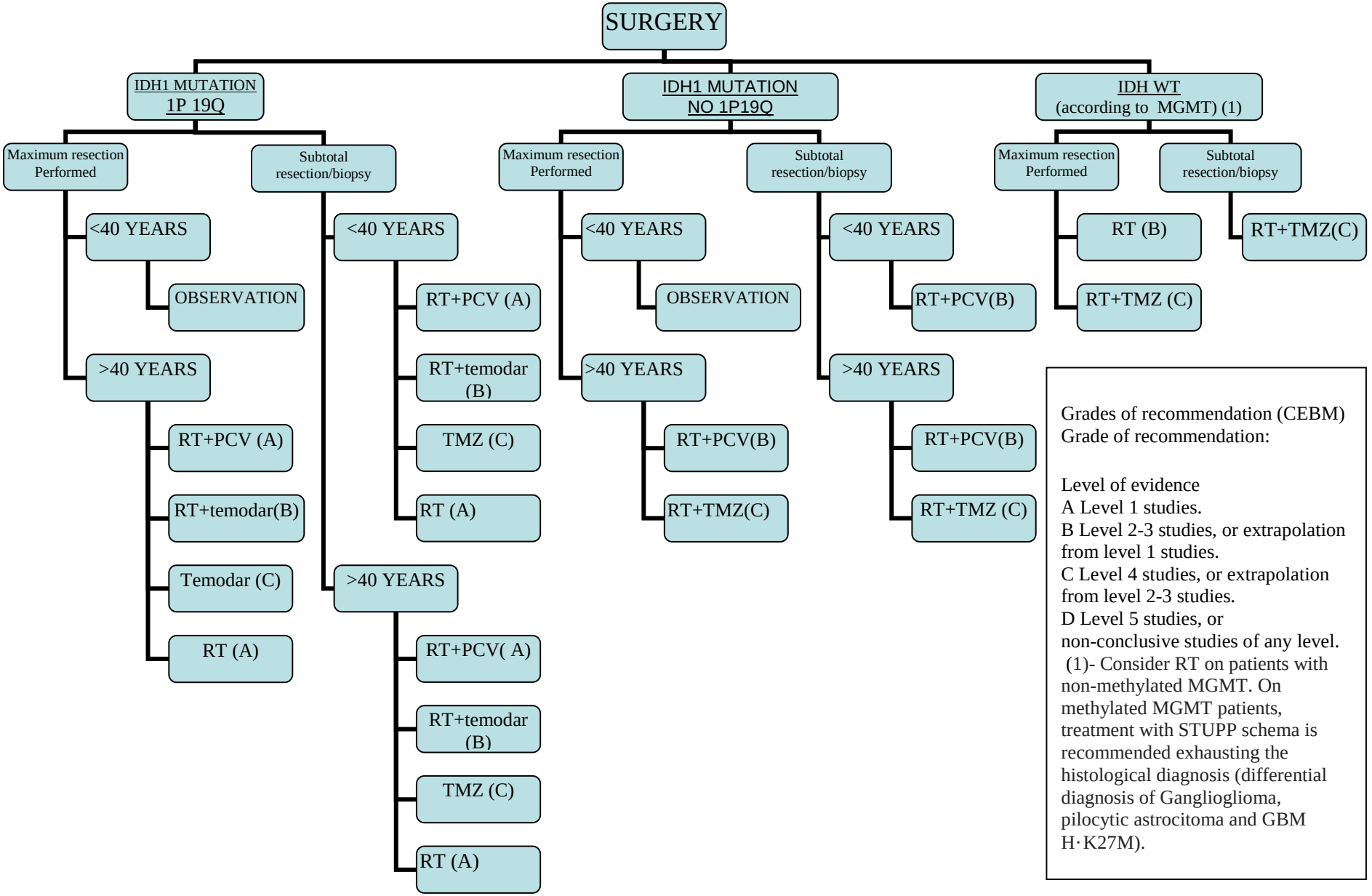
3-Low grade gliomas may be subdivided into three groups: 1) IDH wt 2) IDH mut + without 1p19q codeletion 3) IDH mut + 1p19q codeletion.

4-The prognosis and treatment should be a topic for research in prospective studies.

5-Current recommendations are based on moderate and controversial evidence but treatment should be more aggressive in patients with worse prognoses, particularly the IDH wt subgroup.

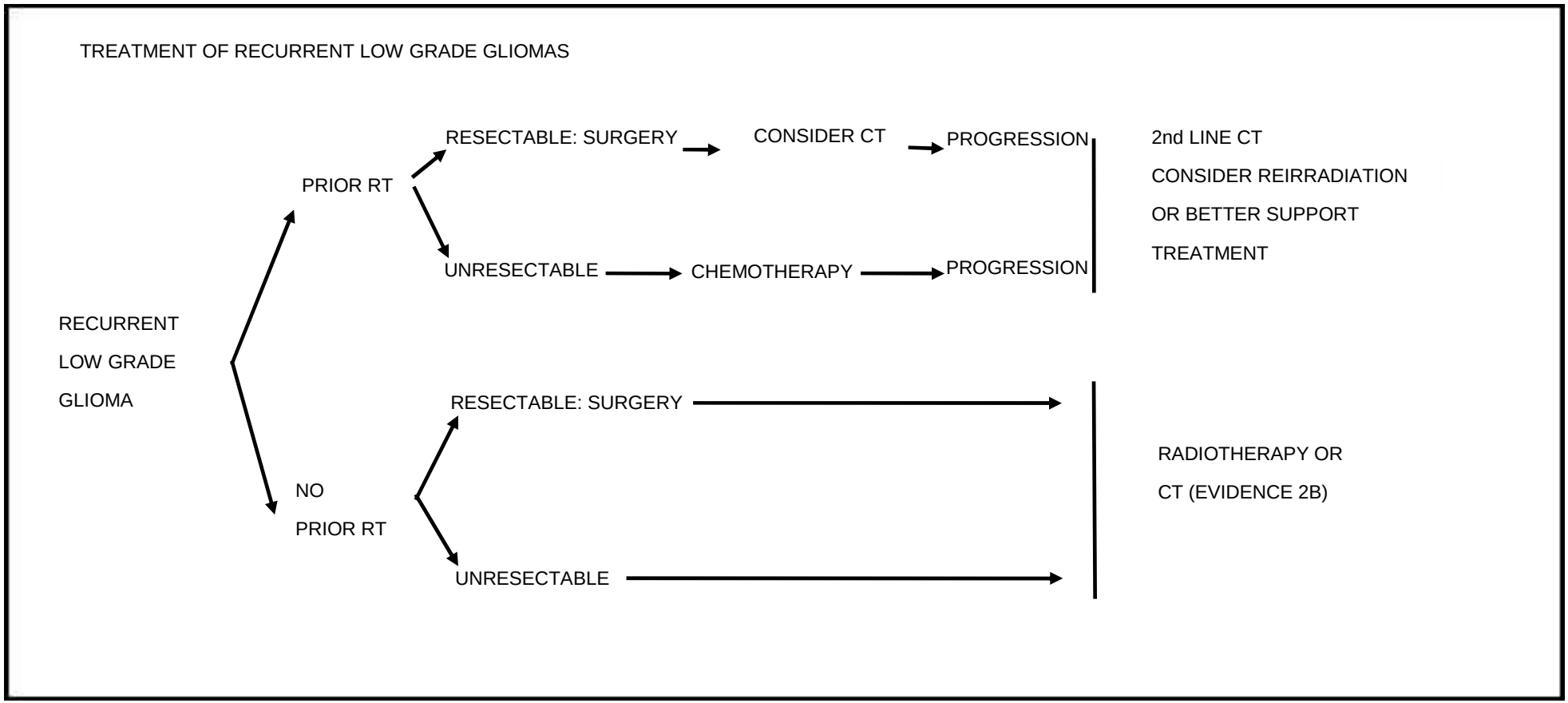
6-It is recommended that all cases of low grade glioma be discussed in a multidisciplinary committee before selecting a therapeutic option.

LOW GRADE GLIOMAS: FIRST LINE TREATMENT ALGORITHM.



*1: The EORTC 22033-26033 study reflected that the subgroup of IDH mutated patients without codeletion benefited more in the radiotherapy arm than in the arm of patients treated with temozolomide (TMZ). This would be an option.

LOW GRADE GLIOMAS: ALGORITHM FOR RELAPSE:



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