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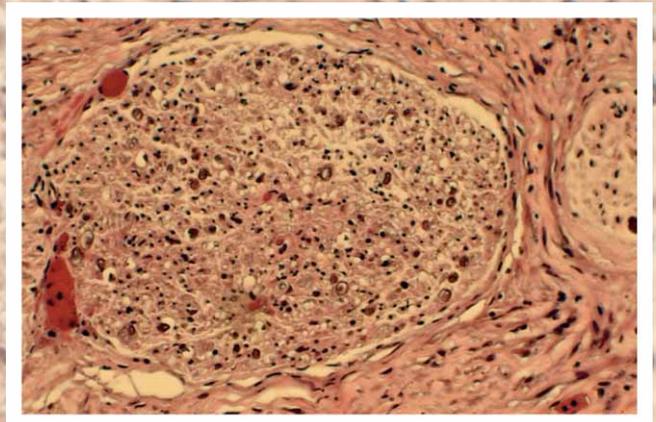
## WHO Guidelines for Diagnosis of Glial Tumours: What Is Old and What Is New?

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# WHO Guidelines for Diagnosis of Glial Tumours: What Is Old and What Is New?

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**Abstract:** Histopathology remains crucial for basic classification and grading of CNS tumour entities. The usefulness of particular histological features has been proven while that of others appears not very reliable for classification, prognostication, or prediction. By now, integration of histopathology with molecular characteristics with prognostic or predictive value is at stake. Candidate histological and molecular parameters

need to be tested for their relevance, reliability, and interdependency in prospective settings in order to optimize test batteries. For the relevant molecular changes, affordable tests which are practically applicable should be developed. The recent WHO editions have proven to be good guides in classification of CNS tumour entities and started to integrate molecular signatures into the definition of the entities. The gradual

availability of evidence-based prognostic and predictive histological and molecular parameters will certainly affect the content of the editions in the near future. **Eur Assoc Neurooncol Mag 2011; 1 (1): 9–12.**

**Key words:** glioma, WHO classification, molecular marker, prognosis, predictive factors

## ■ The WHO Edition on Tumours of the Central Nervous System

The most recent version of the WHO classification for brain tumours dates from 2007 [1]. In 1997, the concept of this book was published by the IARC in Lyon, initiated and edited by Dr Kleihues [2]. The format appeared to be successful and soon a revised edition was published, now under recognition of the WHO [3]. The last edition (2007) was not only edited by 2 neuropathologists (Drs Louis and Wiestler) but also by 2 molecular biologists (Drs Ohgaki and Cavenee), reflecting the gradual shifts in modern pathology [1]. The chapters were written by various groups of authors while the final version of the text was centrally edited. The result is a compact catalogue on brain tumour prototypes based on the consensus of a large group of experts. The book is meant to present the most recent consensus view of diagnosing intracranial tumours in the context of their radiologic presentation and to provide an update on their genetic background. Although the information on the entities mentioned is helpful for differential diagnosis, the book first of all provides tumour prototypes and their diagnostic delineations. The definitions are crucial for protocols in clinical management and translational research.

## ■ Definitions

In the WHO edition, the gold standard used for the definition and diagnosis of brain tumours is the microscopic aspect of the tumour [1]. In addition, immunohistochemical profiles are provided, while in few tumours also the characteristic (or definitional) genotypes are included. For some tumours data from electron microscopy is also available. In only few centres, ultrastructural investigations for tracing lineage-specific cellular structures or extracellular components are still carried out on a daily basis. Because of advances in site-specific proteomics it may well be that in the future ultrastructural aspects of tumours will return to

the diagnostic armamentarium. In the 1970s, immunohistochemistry was introduced into the diagnostic setting as an important addition for making diagnoses. In the WHO fascicle for each entity the complete immunohistochemical profile is summarized, irrespective of its discriminative value in differential diagnostics. For particular diagnoses, however, a specific immunoreactive profile is required. For instance, when diagnosing a central neurocytoma, a tumour type closely resembling oligodendroglioma, neuronal differentiation of the tumour cells should be proven by immunohistochemistry [4]. Immunohistochemical verification is also helpful in the differential diagnosis of certain glioblastomas with resemblance to metastatic tumours (or vice versa), lymphomas which should be delineated from non-tumour infiltrates and the differentiation of meningeal tumours from other primary brain tumours or metastatic tumours. Immunohistochemistry to the Ki-67 protein (Mib-1 antibody) is an important aid to estimate the proliferation of tumours, particularly in small specimens in which counting mitoses is not easily accomplished [5, 6].

In the WHO editions published in 2000 and 2007, respectively, and the IARC precursor edition of 1997, available data on molecular changes in the genome of tumours were carefully referenced and updated. Among the many genetic aberrations there are several associated with a particular histopathology or clinical/radiological presentation. In the 2007 edition, the WHO incorporated characteristic genotypical changes into the definition of some particular entities. For instance, in the definition of oligodendroglioma the phrase “*often harbouring deletions of chromosomal arms 1p and 19q*” was added, and for the entity of AT/RT “*associated with inactivation of the INI1/hSNF5 gene in virtually all cases*”. These additions herald the incorporation of molecular data in definitions of entities and reflect the need for prognostic and predictive parameters in clinical neuro-oncology.

## ■ Gliomas

The recent WHO fascicles conceptually divided glial tumours into those with diffuse infiltration in cerebral tissue and those that grow relatively circumscribed [1–3]. The diffusely infiltrating glioma group includes astrocytomas and oligodendrogliomas and their mixed forms as well as their various malignancy

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grades up to glioblastomas. The circumscribed glial neoplasms are mainly represented by pilocytic astrocytomas and gliomas with ganglion cells, with some rare tumours such as pleomorphic xanthoastrocytomas belonging to this category as well.

In the WHO fascicle, the low-grade and anaplastic stages of diffusely infiltrating gliomas are presented in distinct chapters as if they represented different entities. However, a large part of diffusely infiltrating gliomas will invariably progress from low to high grade, eventually meeting the criteria of glioblastoma (so-called “secondary glioblastomas”). While these secondary glioblastomas have risen from a lower-grade (astrocytic) precursor, so-called “primary glioblastomas” appear to have followed another oncogenic pathway. A particular low-grade precursor lesion for this subset has not been identified [7, 8]. Within the group of glioblastomas, some more subtypes are distinguished. Giant-cell glioblastoma and gliosarcoma are microscopically recognizable entities, both deviating in clinical course from other glioblastomas: the former progressing more slowly and the latter faster. The morphological criteria for the delineation of mixed oligoastrocytomas are unclear and for most tumours with mixed morphology the genotypical characteristics of either oligodendroglioma or astrocytoma exist.

Attributing malignancy grades to the tumours of the diffusely infiltrating group has proven to be of clinical relevance. Based on the available literature, the WHO provides some provisional criteria for grading gliomas into low and high grade (anaplastic) without issuing strict schemes for scoring. Data on prognostic histological parameters for oligodendrogliomas and astrocytomas is mostly based on retrospective studies [9]. The various histological parameters mentioned by the WHO are still being scrutinized in prospective settings [10]. Since the histopathological definition of mixed oligoastrocytomas is subject to large interindividual variability, it is obvious that grading criteria are not really available since one cannot grade a tumour type which has not been clearly defined. Since the main representatives of this ill-defined group are molecularly divided into either oligodendroglioma or astrocytoma, grading should be done according to the best schemes for these glioma subtypes.

The circumscribed tumours are generally associated with young age and also a characteristic location as well as scan appearance. The delineation between “diffuse” and “circumscribed” should not be taken too literally – diffuse gliomas may well have parts that are sharply demarcated from surrounding brain tissue while circumscribed tumours usually display invasive behaviour as well but progress more slowly. Circumscribed gliomas are usually rather stationary but in the long run some may show malignant behaviour. In gangliogliomas, the glial component may eventually undergo anaplastic change, as seen in diffusely infiltrating gliomas. The histological features of anaplastic change of pilocytic astrocytoma may be difficult to appreciate with the exception of the mitotic index (or Mib-1 labelling index) [11].

### ■ Guides for Clinical Management: Prognostic and Predictive Factors

Some tumour entities listed in the WHO fascicle occur far more frequently than others. Clearly, the reliability of data

concerning clinical courses and effective therapies is larger for the more frequently occurring tumours. Only for the more common tumours data obtained in prospective studies are available. There are several ongoing trials on therapies for the commonly diffusely infiltrating gliomas (anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic mixed oligoastrocytoma, glioblastoma) and it is of paramount importance that pathologists take part in these studies in order to test their definitions and grading schemes of entities for consistency and validate their criteria for prognostication or prediction of therapy success [12]. It is difficult to gather evidence-based data for relatively uncommon tumours. International collaborations and trial initiatives are needed to identify prognostic and predictive factors for these tumour groups.

The molecular characteristics of tumours may be associated with particular morphological subtypes and therefore provide lineage specificity. An example is the loss of 1p and 19q for oligodendroglial lineage [13]. Molecular findings may also correlate roughly with the tumour grade. For instance, EGFR amplification/over-expression, LOH 10q, or mutation of PTEN are relatively late events in the development of diffusely infiltrating gliomas and thus associated with a higher malignancy grade [14–16]. Furthermore, molecular aberrations may carry prognostic information or may be predictive of the success of particular therapeutic interventions. The putative prognostic or predictive value of particular genetic changes has been tested in the context of clinical trials [17–26]. Loss of 1p/19q is mutually exclusive with EGFR amplification and appears not only to be predictive of the response to alkylating chemotherapy but also emerged as a prognostic factor [27, 28]. Since the location and extent of the losses on 1p correlate with the clinical aggressiveness of the tumour [24], relevant techniques are necessary to detail the 1p losses. Interestingly, loss of 1p/19q was found to correlate with immunoreactivity to  $\alpha$ -internexin (INA) [29, 30]. The  $\alpha$ -internexin gene encodes for a neurofilament-interacting protein which, just like 1p/19q loss, correlates with oligodendroglial morphology. Whether immunohistochemistry for INA would offer an alternative method to replace testing for 1p/19q should be assessed in a prospective setting.

Methylation of the promoter gene of O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT) leads to loss of expression of MGMT and causes vulnerability to alkylating agents. Testing the methylation status of the CpG islands therefore would be a direct test predictive for the success of therapy. In a prospective setting, it was found that patients with glioblastomas with MGMT promoter methylation who received treatment with temozolomide survived longer [20]. In oligodendrogliomas the effect of MGMT promoter hypermethylation appeared to be prognostic rather than predictive [31]. However, thresholds for reading out methylation tests are still subject to debate [32, 33]. At this point, the status of methylation assays in the prognostication or therapy effect prediction requires additional study. Recently, heterozygous point mutations in codon 132 of the IDH1 gene coding for NADP<sup>+</sup>-dependent isocitrate dehydrogenases were found in large numbers of diffusely infiltrating gliomas, among them astrocytomas but also oligodendrogliomas [34]. In the retro-

spective series studied, IDH1 mutation (more specifically, the R132H mutation) appeared to positively influence survival when controlled for tumour grade and this prognostic effect was confirmed in trials on anaplastic astrocytomas [35], oligodendrogliomas, and glioblastomas [36–38]. IDH1 immunohistochemistry may serve as a diagnostic tool in certain situations. Its contribution as prognosticator in the context of other prognostic parameters should be further explored. In retrospective surveys of large numbers of gliomas, characteristic tandem duplication leading to fusion of BRAF with KIAA1549 was found in > 70 % of pilocytic astrocytomas, particularly in those with cerebellar location [39]. Another recent finding is the presence of the specific BRAF V600E mutation occurring in 2/3 of pleomorphic xanthoastrocytomas and 18 % of gangliogliomas [40]. The mutation was also specifically observed in extra-cerebellar pilocytic astrocytomas [40]. Both the BRAF-KIAA tandem duplication and the V600E mutation are useful genetic signatures for making diagnoses. Importantly, the activating effect of BRAF mutations in the RAS/RAF/MEK/ERK kinase pathway opens possibilities for therapeutic intervention and candidate inhibitors should be explored in clinical trials. The strategies of incorporating testing for certain molecular markers in trials against the background of a limited repertoire of available drugs remain a matter of ongoing dispute [18, 41, 42]. The search for evidence-based prognostic and predictive parameters will continue and will gradually confine laboratory investigations meant to provide relevant information for therapeutic intervention. Future WHO editions will certainly be updated on the developments in improving diagnostic criteria as well as listing molecular parameters to be incorporated in a prognostic or predictive relevant diagnosis.

Over the past 10 years, high-throughput investigations on the expression of genes have been carried out in order to find genes and pathways which are important for tumour genesis or progression and thus would be candidate targets for therapy. The results of studies in gene expression arrays can be divided into those in which supervised analyses were carried out and those in which unsupervised clustering was performed. Supervised analyses included analyses in which the pathology diagnosis or particular prognostic categories were leading [43–45]. In general, for those lesions with better defined morphological characteristics (like low-grade astrocytomas) more specific and consistent expression profiles were obtained, while the entities with more variable morphologies (like glioblastomas) exhibit a much larger variation of expression patterns [43]. In some studies, unsupervised analyses of expression data showed intrinsic prognostic and predictive relevance of the molecular clusters without correlation with the histological diagnosis [45, 46]. Molecular classification within particular diagnostic categories like glioblastomas was shown to add prognostic information, and was therefore considered – to some degree – to be superior to conventional histology [47]. Classifying molecular signatures including proneural, proliferative, or mesenchymal profiles have been identified in expression array studies [43, 47]. The genes and their protein products underlying the clusters of tumours are rather variable, although specific genetic changes such as EGFR amplification, IDH1 mutation, and 1p/19q loss relate to particular tumour clusters.

It remains to be established what more genes are relevant for prognostication and which expressional patterns are important predictors for the success of therapies aiming at components of particular pathways. Issues like genetic or expressional heterogeneity of tumours, changing expression patterns as a result of the administration of certain therapies [17, 48], have as yet hardly been addressed. Molecular investigations searching for clinically relevant parameters can only be carried out successfully in the context of clinical trials. By now, there are still many difficulties to overcome in carrying out translational studies in trials. On the clinical side, there are many difficulties in accrual and passing ethical committees [49, 50]. Problems of property and transferring materials, especially in international studies, are the main barriers to be overcome by pathology and translational research. Nevertheless, significant steps are being made at a rather quick pace and it is to be expected that future WHO fascicles will require faster updates than ever before in order to keep up with developments.

### ■ Conflict of Interest

JMK has no conflict of interest to declare.

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In reminiscence of Dr Robert Charles Janzer, neopathologist and fine colleague in the EORTC Neuropathology Panel.

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