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# Role of Pathologist in Driver of Treatment of CNS Tumors

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Additional information is available at the end of the chapter

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## Abstract

The incidence of Central Nervous System (CNS) tumors is gradually increasing. Furthermore, metastatic neoplasms are frequently seen in neuropathology practice as a major cause of mortality and morbidity. Pathologists try to reach a more accurate diagnosis by mentally filtering a synthesis, comprising age, radiological characteristics and microscopic findings in the sample sent, starting already from the intraoperative diagnosis process. By displaying their skills, they unveil whether a lesion in the brain parenchyma is a normal or reactive tumor and if this is a tumor, is it primary or metastatic, and if it is primary, what is the tumor type or if it is metastatic, which organ could it be associated with. Pathologists use diagnostic, prognostic and predictive markers in order to enable the patient receive the most effective and sufficient treatment. They ensure that an individualized treatment is provided via these tools, by making a histological diagnosis of the lesion according to the WHO classification, identifying the course of the disease and preventing undesired and dangerous complications. This chapter will focus on answering these questions and share the value of a multidisciplinary approach in the management of brain tumors in neurosciences, which is gradually increasing in importance, and how pathologists execute this art.

**Keywords:** pathology, central nervous system, primary or metastatic tumor, neuropathology, oncologic treatment

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## 1. Introduction

Brain tumors could be classified according to the histogenesis and microscopic similarities of the tumors in the previous decades, and their degree of differentiation was identified. This

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characterization was a simulation effort of pathologists via the utilization of light microscopy, immunohistochemical markers and ultrastructural methods [1–3].

There were two major concepts accepted as basis in the WHO classification: the histological type and histological degree of the tumor.

**Histological typing of the tumor:** Histological typing in the WHO system was performed by defining the entity, variant and tissue pattern characteristics. The tumor group, which constituted clinicopathological integrity, where the cellular origin or the cell type from which they derived was accepted as common and formed the subtitles of the relevant section in the WHO booklet, was named entity; the tumor group, which belonged to an entity, was a tumor type of an original character from a clinical, morphological and/or molecular aspect and formed the subtitles of the relevant section in the WHO booklet, which was named a variant; and the tumor group, which had an original morphological character, did not differ from the other tumors of the entity from a clinical, molecular and/or prognostic sense and generally formed the paragraph titles of the section on entity, which was named tissue pattern.

WHO	Features of Grading
<b>Grade I</b>	have low proliferative potential and able to cure with surgical resection
<b>Grade II</b>	usually have diffuse infiltrative and low proliferative potential, but probability of low recurrence rate, some of them have risk of progression to high grade
<b>Grade III</b>	mostly known as anaplastic tumors and have malign histologic features, have high recurrence rate, usually need chemotherapy and radiotherapy
<b>Grade IV</b>	obviously malign tumors, which are necrotic and have capability of fast recurrence, most of them show diffuse spreading in CNS

**Table 1.** Characterization of CNS tumors according to the WHO grading.

**Tumor grading:** Grade IV was assigned for CNS tumors in relation to the cytological and histological criteria of WHO (WHO Grade I–IV) (**Table 1**). These grades were based on histopathological criteria fundamentally characterizing malignancies and also comprised the prediction of the clinical course of the patient [4].

The classification and grading system was a universally accepted and mostly easily repeatable system. However, there were some points which were not substantiated with sufficient data and posed problems in terms of repeatability within this system; 2007 classification was prepared by more than 70 specialists, in light of the literature data obtained until that time. The studies conducted on brain tumors in the last two decades unveiled the genetic basis of

tumorogenesis and demonstrated that it is possible to contribute to the classification of these tumors [5–11]. In fact, the Haarlem meeting held in 2014 paved the way for a major revision in the 2007 CNS classification of incompatible molecular findings in the diagnosis of brain tumors [12]; 2016 CNS WHO classification was prepared with the contribution of 117 participants from 20 countries and 35 neuropathologists and neuro-oncologists from 10 countries who elaborated on topics of debate [13].

This chapter will focus on active immunohistochemical evaluation in the diagnostic approach toward primary tumors and tumors with unknown primary, how to conduct differential diagnostics on metastatic tumors and the major changes in the current CNS tumor classification and will briefly describe the role undertaken by pathologists in guiding the treatment of CNS tumors.

## 2. Incidence of brain tumors and overview

The annual incidences of central nervous system tumors correspond to 10–17 in 100 thousand persons for intracranial tumors and 1–2 in 100 thousand persons for intraspinal tumors. Approximately half or three-fourth of these are primary tumors, while the rest are metastatic [14–16].

Central Brain Tumor Registry of the United States (CBRTUS), a professional research organization in the United States, which provides high-quality statistical data, recently published its report covering the years 2008–2012 [17]. Hence, malignant brain and CNS tumors constitute the 11th most prevalent types of cancer and the 3rd most frequent cause of mortality due to cancer in adolescents and young adults (AYAs). The most frequently diagnosed histologies in the AYA group are variable both in children (0–14 years) and in older adults (40+ years). While 53,083 adolescents and young adults (aged 15–39 years) in the United States were diagnosed with primary brain and CNS tumor between 2008 and 2012, the annual incidence rate was lowest in New England (9.42 per a population of 100,000) and the Pacific region (9.47 per a population of 100,000), and it was highest in the Middle Atlantic region (11.66 per a population of 100,000) and the Mountain region (11.14 per a population of 100,000). Knowing the age-specific histology of brain tumors and providing accurate statistical data enable clinicians to treat patients and provide reference to investigators for investigating new therapeutic agents.

Tumors in the central nervous system hold a larger share among childhood cancers and constitute almost 20% of all tumors. Childhood central nervous system tumors differ from the tumors in adults in terms of both their histological subtypes and location. Childhood tumors mostly tend to develop in the posterior fossa, while adult tumors are mostly seen in the supratentorial region [14–18].

The tumors in the nervous system bear specific characteristics which distinguish them from the neoplastic processes localized in the other regions of the body.

- A premalignant or in situ period is not identified in these tumors as in carcinomas.

- While even the most malignant gliomas rarely spread outside the CNS, the subarachnoid space allows tumor diffusion to distant regions along the neural axis, in addition to local infiltration [9, 14].

## 2.1. Practical use of immunohistochemistry in the diagnosis of CNS tumors

IHC has been undergoing a revolutionary process with an increasing use in diagnostic pathology in the last 50 years [19, 20]. While pathologists would say “insufficient biopsy for diagnosis” when they saw notably marked artifact areas in tiny biopsies in the past, today carcinoma diagnosis can be easily made with the cytokeratin (CK) stain [21]. If used wisely and combined with morphological interpretation skills, pathologists may achieve a more accurate diagnosis than “suspicion of malignancy.” Thus, IHC markers may be divided into three as those used for diagnostic purposes, those used for prognostic purposes and the other IHC markers (**Table 2**).

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### IHC markers used for diagnostic purpose

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Markers for glial tumors

GFAP

S-100

Markers for neuronal tumors

Synaptophysin

NSE

Beta-tubulin

Neurofilament

MAP-2

GFAP +/-

Markers for meningeal tumors

EMA

Vimentin

S-100

CK

Markers for choroid plexus tumors

CK

S-100

Transthyretin

Markers for lymphoma

LCA

T cell and B cell markers

Markers for Schwann cell tumors

S-100

Leu 7

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**IHC markers used for diagnostic purpose**

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Markers for germ cell tumors

AFP  
HCG  
PLAP  
HPL

Markers for melanocytic tumors

HMB-45  
S-100  
MART-1 (Melan-A)  
Microphthalmia transcription factor

Markers for vascular origin tumors

CD34  
Factor VIII  
VEGF  
*Ulex europaeus*

Markers for pituitary tumors

PRL  
GH  
ACTH  
MSH  
LH  
FSH  
TSH

Markers for neuroendocrine tumor

Chromogranin  
Synaptophysin

Marker for ATRT

INI-1/SMARCB-1

IC markers used for prognostic purpose

Cell cycle/proliferation markers

MIB-1  
Ki-67  
PCNA  
BrdU

Tumor suppressor gene/oncogene protein

p53 tumor suppressor gene  
Retinoblastoma tumor suppressor gene (Rb)  
C-myc oncogene

Growth factors/receptors

**IHC markers used for diagnostic purpose**

EGFR

The IHC markers

IDH1 and IDH2

ATRX

BRAF

GFAP, glial fibrillary acidic protein; IHC, immunohistochemistry; CK, cytokeratin; NSE, neuron-specific enolase; MAP-2, microtubule-associated protein-2; EMA, epithelial membrane antigen; LCA, leukocyte common antigen; AFP, alpha fetoprotein; HCG, human chorionic gonadotropin; PLAP, placental alkaline phosphatase; HPL, human placental lactogen; HMB-45, human melanoma black-45; VEGF, vascular endothelial growth factor; PRL, prolactin; GH, growth hormone; ACTH, adrenocorticotrophic hormone; MSH, melanocyte-stimulating hormone; LH, luteinizing hormone; FSH, follicle stimulating hormone; TSH, thyroid stimulating hormone; ATRT, atypical teratoid/rhabdoid tumor; MIB-1, molecular immunology Borstel-1; Ki-67, Kiel antibody-67; PCNA, proliferating cell nuclear antigen; BrdU, bromodeoxyuridine; EGFR, epidermal growth factor receptor; IDH1 and IDH2, isocitrate dehydrogenase-1 and -2; ATRX, alpha-thalassemia/mental retardation syndrome X-linked.

**Table 2.** Immunohistochemistry markers for central nervous system tumors [21].

Despite being a highly beneficial diagnostic tool, the limitations of IHC should also be recognized. The amount of antigen in tumors is variable. As the antigenic phenotype of tumor cells is measured with IHC, its antibody immune activity is nonspecific. Furthermore, the high number of markers used for a tumor raises the cost. Therefore, pathologists should pay attention to the compliance with tumor morphology and the clinical-radiological correlation when interpreting the outcome of an IHC. Immunohistochemical markers may be used within the framework of differential diagnosis in surgical neuropathology.

Astrocytoma, oligodendroglioma or mixed tumors? Currently, there is still no agreement reached among specialists regarding this topic, and the most experienced specialists cannot reach an agreement on this topic. The following table reflects one of the approaches to this topic and was prepared in light of current data [22–24]. Glial, glioneural or reactive? Some of the cells seen in many tumors are the normal residual cells as residues of the tissue occupied by the tumor following tumor infiltration. Neuronal cells which may be seen inside diffuse astrocytoma constitute the most typical example. We should also add the question of whether the lesion is reactive or neoplastic to this differential diagnosis [24, 25]. Glial vs glioneural tumors: GFAP, Olig-2, synaptophysin, Neu-N, neurofilament protein, p53, isocitrate dehydrogenase 1 (IDH1), CD34, BRAF v600e antibodies. Glial tumors vs gliosis IDH1, Ki67, p53, WT-1, CD68, LCA, GFAP, EGFRvIII antibodies. Glial tumors vs demyelinating diseases: IDH1, p53, Olig-2, CD68, GFAP, JC virus, myelin basic protein and neurofilament antibodies. Mesenchymal tumor, but which one? The first series of findings to determine the panel to be selected in the differential diagnosis of mesenchymal tumors are clinical and radiological data. In particular, the localization of the tumor determines the tumor types included into the bounds of possibility. It is very difficult to establish a panel series comprising each possibility in this topic. The panels which may be used according to localization have been provided below only as recommendation [26–28].

Schwannoma vs meningioma: S100, neurofilament, Sox2, EMA, progesterone receptor, collagen type IV, CD34 antibodies. Meningioma vs solitary fibrous tumor: EMA, progesterone receptor, CD34, collagen type IV, bcl2, CD99 antibodies. Chordoma vs chondrosarcoma: Brachyury, S100, vimentin, cytokeratin cocktail and EMA antibodies.

## 2.2. Neuroradiological tips for pathologists in surgical neuropathology

The concepts associated with localization are among the major concepts in neuroradiology. Assessments from various planes are made: the sagittal (vertical) section analyzes the brain as right and left, the coronal plane analyzes it as frontal and back, and the axial (horizontal) plane assesses its upper and lower parts. Moreover, the main modalities in anatomic imaging are the contrast images obtained by administering T1, T2, FLAIR and gadolinium. In addition to these four modalities, also diffusion, perfusion and spectroscopic methods provide valuable insight into MR imaging [29].

MR imaging is composed of tones of gray between black and white, as in CT. The tissues which receive an energy signal equivalent to that of the brain tissue in the brain MRI and are thus seen as at the same tone of gray are defined as “isointense”; those which receive more signal and appear whiter are named “hyper-intense,” while those which receive less signal and appear darker gray are defined as “hypo-intense.” It is possible to obtain different sequences at different images by modifying some shooting parameters in the MRI imaging. Basically, we may list the MRI sequences as *T1-weighted*, *proton-intense* and *T2-weighted*. In T1-weighted images, the cerebrospinal fluid (CSF) appears black; in proton-intense images, it appears gray; and in T2-weighted images, it appears white. The lesions are generally “hyper-intense” in proton-intense and T2-weighted sequences, while they are “hypo-intense” in T1-weighted sequences. In addition to the basic sequences, there also other sequences which suppress the cerebrospinal fluid and enable fluids to appear hypo-intense (such as fluid attenuated inversion recovery – FLAIR) [29, 30].

Unlike CT, a paramagnetic contrast agent containing gadolinium is used in MRI. Gadolinium has a much lower risk to cause allergic reactions compared to iodine contrast agents. Gadolinium permeates to pathological tissues with a destroyed blood-brain barrier as in iodine contrast agents. Only T1-weighted sequences are applied after administering gadolinium. The lesions involving the contrast agent gain a hyper-intense appearance in T1-weighted MRI appearances. The tumor lesions other than low-degree glial tumors, metastatic tumors, infections (meningitis and encephalitis), demyelinating lesions during the acute period and infarcts during the subacute period demonstrate contrast agent involvement. When the lesion has a contrast agent involvement, it may be used in the differential diagnosis of the lesion and also in defining the degree of the lesion in primary brain tumors. Generally, the tumors with contrast agent involvement have a high-degree histopathology. (There are some exceptions to this generalization. For instance, although pilocytic astrocytoma is a low-grade glial tumor, it has a considerably high contrast agent uptake.)

It is possible to analyze the chemical content of tissues with the *MR spectroscopy (MRS)*, which is another MR imaging technique. *N-acetyl aspartate (NAA)*, *creatinine (Cr)*, *choline (Cho)* and *myo-inositol (mI)* are major neurometabolites which may be detected via MR spectroscopy. NAA is



accepted as a neuro-axonal marker in the MRS assessment. It is known that neuro-axonal function is directly proportional to the number and concentration of NAA. Myo-inositol is used as an astrocyte marker. Pathologies which lead to an increase in the number of astrocytes inside the tissue (such as astrocytoma, encephalitis and subacute-chronic demyelinating plaques) elevate the myo-inositol concentration at MRS. Choline is a neurometabolite present on the cellular membrane and the myelin structure. Therefore, pathologies which lead to cellular proliferation (neoplastic diseases) or myelin destruction (demyelinating diseases) give rise to a notable increase in the choline level [29–32].

Infrared (IR) spectroscopic image system, which is a new method, is promising in identifying the primary in brain metastases. As metastatic cells comprise molecular information on the primary tissue and the probes of IR spectroscopy are the fingerprint of cells, this method introduces a new approximation method to the origin of brain metastases [31, 32].

### 2.3. Molecular pathological assessment in glial tumors

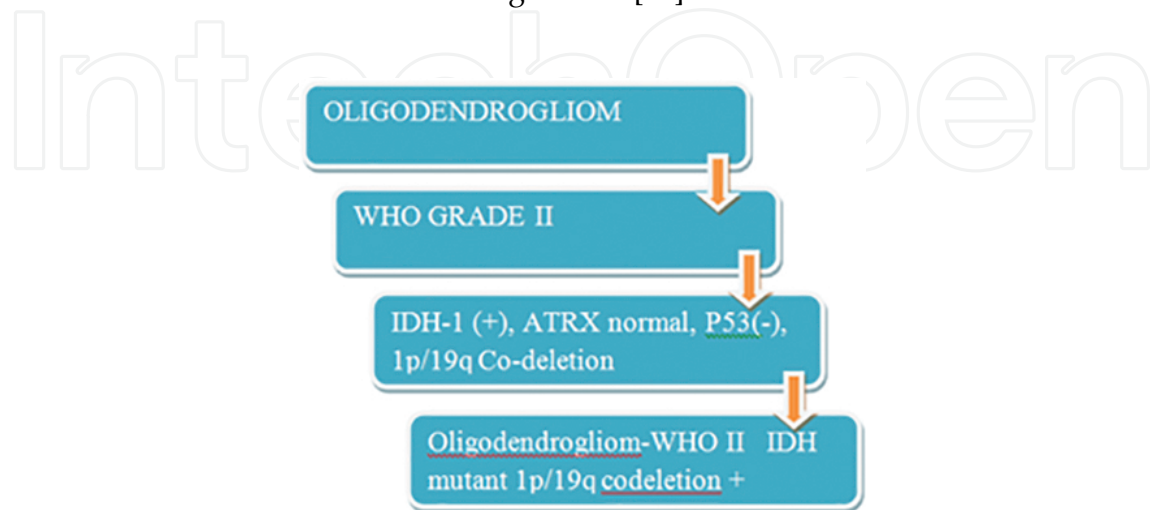
Molecular studies started with the identification of various clinical behaviors of oligodendroglial cells with 1p19q co-deletion. The detection of three major signal pathways [TRK/RAS/P1 (3) K (88%), P53 (87%) and Rb (78%)] initiated a new era in neuro-oncology [22, 33, 34].

The analysis of the number of DNA copies provided a new perspective in the evaluation of the gene expression profiles and the actual roles of the DNA methylation patterns and ERBB2, NF1 and TP53 genes. It unveiled the clinical and fundamental importance of the promotor methylation of MGMT genes. Today, it is accepted that treated glioblastoma (GBM) cases reveal the phenotype associated with the mismatch repair deficiency [35–37].

These developments demonstrated that the WHO 2007 CNS classification needs to be updated. It is necessary to include molecular data into the classification and to utilize the most appropriate, most widespread and convenient techniques in order to detect these. Thus, the Haarlem meeting was held in order to determine the usability of current diagnostic methods upon taking into account the clinical, experimental and etiological chance of correlation in the future and also considering the cost, without disrupting the current clinical and patient approach, and a consensus was reached. An integrated diagnosis comprises the histological diagnosis + WHO grading (histological grading) + molecular information or the Haarlem “layered diagnosis format” [12] (**Figure 1**).

Parsons et al. [37] published the (amplification and/or deletion) patterns of the protein coding 20.661 gene in human GBMs. New methodologies (aCGH, high-density oligonucleotide arrays, next-generation sequencing technologies, single nucleotide genomics, massively parallel DNA resequencing) confirmed the most unexpected results of the authors. The earliest genetic modification in most glial tumors impacts the gene which encodes the active area of the cytoplasmic form of a carbohydrate metabolizing enzyme (e.g., IDH, isocitrate dehydrogenase). Although there are many isoforms of this enzyme, the accepted IDH1 mutations are most prevalent in secondary GBMs occurring in relatively young patients with a better prognosis. These results were confirmed also by Balss et al. [38] and Yan et al. [39], and it was demonstrated that IDH mutations emerge in the systemic forms of rather specific and malig-

nant diseases of glial tumors. Zhao et al. [40] published their observations in 2009 and showed that the mutations (IDH1 R132 or IDH2 R172) reduce the affinity of the enzyme toward the substrate and, moreover, inactive heterodimers which dominantly block the WT-IDH1 activity. The rapid understanding of the molecular pathways of the pathogenesis of brain tumors especially in glial tumors led to the detection of reliable diagnostic, prognostic and predictive molecular markers and new molecular signatures [41].



**Figure 1.** An example of integrated diagnosis according to the Haarlem consensus.

Three molecular markers, namely 1p19q co-deletion, MGMT promoter methylation mutation and mutation in IDH1/2 genes, stand out in the management of disease course and surgical neuropathology routine at the basis of various clinical trials.

**Simultaneous loss of 1p/19q in glial tumors:** It was demonstrated that chromosomes 1p and 19q are characterized with combined allelic deletion in 80% of oligodendroglioma (Grade II), 60% of anaplastic oligodendroglioma (Grade III) and 50% of mixed glioma [42, 43]. Two clinical studies demonstrated that in case of combined 1p/19q loss in the tumor bed, anaplastic glioma patients benefit from combined radiotherapy + PCV chemotherapy [44, 45]

**MGMT promoter methylation:** As a DNA repair enzyme, O6-methylguanine DNA methyltransferase (MGMT) reuptakes the alkylation of the O6 position of guanine, thus leading to apoptosis. MGMT promoter methylation results in the silencing of the gene in relation to the increase in the insufficiency of the DNA damage repair and reduces DNA repair damage with alkali chemotherapeutic agents such as temozolamide. MGMT promoter methylation appears in 40% of primary glioblastomas (WHO Grade IV) and is associated with the increase in life expectancy following radiotherapy and temozolamide chemotherapy [46, 47].

**IDH1 and IDH2 mutations:** IDH (isocitrate dehydrogenase) and its mitochondrial isoform IDH2 encode the protein catalyzing isocitrate to  $\alpha$ -ketoglutarate and play an important role in the cellular control of this oxidative process. IDH1/2 mutations globally result in the functional changes of the tumor epigenome. The presence of somatic IDH1/2 point mutations is helpful in the differentiation of primary glioblastomas in most low-grade gliomas and secondary glioblastomas and the differentiation of pilocytic astrocytoma and the other brain tumors

characterized with this mutation. The presence of IDH1/2 mutations in anaplastic gliomas and glioblastomas also has a prognostic significance as IDH-mutant tumors have a longer overall survival compared to IDH wild-type neoplasms [48]. Certainly, continuous definition of new molecular markers widens the diagnostic molecular spectrum of brain tumors and strengthens the art of neuropathology.

#### 2.4. Problematic tumors in grading and major changes in 2016 CNS WHO

The major arrangement in WHO 2016 classification involved diffuse gliomas, medulloblastomas and other embryonal tumors. They were divided into three groups, namely glioblastoma, glioblastoma wild type, glioblastoma IDH-mutant, diffuse midline glioma and H3K27M-mutant, and the use of the NOS terminology was recommended when the molecular tests were not carried out or when there was no problem [13] (Table 3). Medulloblastomas were divided into widely accepted four genetic (molecular) groups, namely WNT-activated, SHH-activated and group 3 and group 4, which did not reveal either of these and were defined numerically.

*Glioblastom, IDH-wild type ( <b>entity</b> )	
Giant cell glioblastom	} <b>variant</b>
Gliosarcom	
Epithelioid glioblastom ( <b>new variant</b> )	
<i>Subtypes</i>	
Smal cell glioblastoma	} <b>patern</b>
Glioblastoma with primitive neuronal component	
Granuler cell glioblastoma	
Containing lipid or lipidise glioblastoma	
*Glioblastoma IDH mutant ( <b>entity</b> )	
*Diffuse midline glioma, H3 K27M-mutant ( <b>entity</b> )	
*Glioblastoma NOS	

**Table 3.** Classification of glioblastomas according to the WHO CNS 2016.

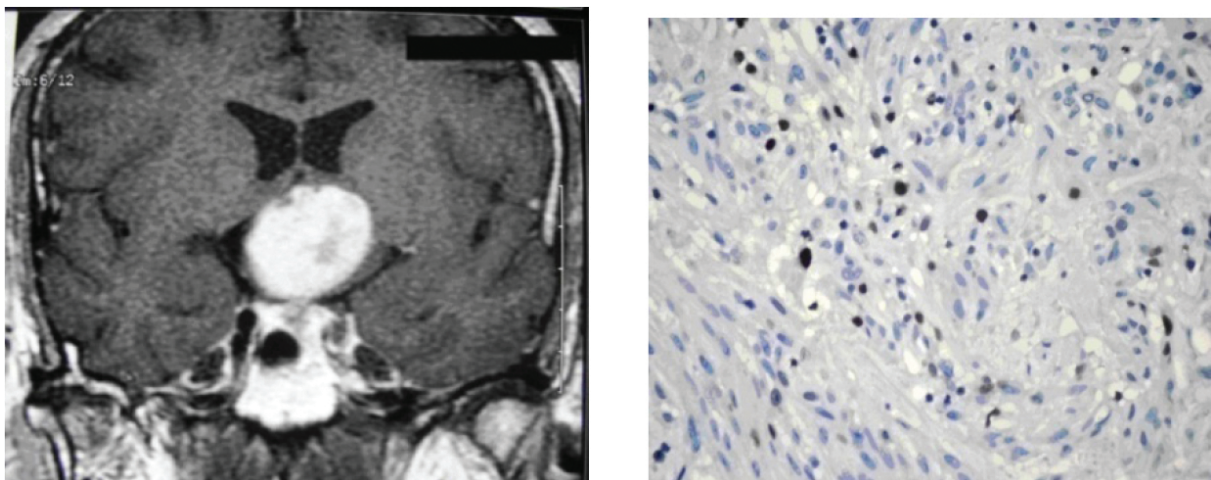
GBM with PNET components was a largely accepted subgroup and was designated as a pattern in 2016. Very distinct and small cell focal tumor nodules are present in the glioblastomas with PNET components. Neuronal differentiation differs compared to other fields. Furthermore, there is also the possibility to find MYC gene amplification in fields similar to PNET. However, the difference in prognosis, claimed to be present between variants and patterns, has not been proven yet. Although it is not certain whether there are differences between GBM with oligodendroglioma components and anaplastic oligodendrogliomas, some points which may be helpful for pathologists are summarized below.

Giant cell glioblastoma is a tumor with generally superficial localization, mostly composed of pleomorphic cells with scattered giant cells in between them. The most important point in differential diagnosis is that pleomorphic xanthoastrocytomas with anaplastic characteristics are not confused with this tumor.

Small cell glioblastoma is a monotonous tumor with a high number of mitosis, which may be confused with anaplastic oligodendrogliomas. Generally, it does not involve a 1p19q deletion and comprises EGFR gene amplification or mutant (EGFRvIII) forms [13, 37].

Glioblastomas with oligodendroglioma components constitute one of the most debated subtypes. This tumor may comprise fields in the typical oligodendroglial morphology, in addition to the classical glioblastomas and components including two different anomalies in some cases. The diagnosis is accepted as anaplastic oligodendroglioma in patients who previously have low-grade oligodendroglioma.

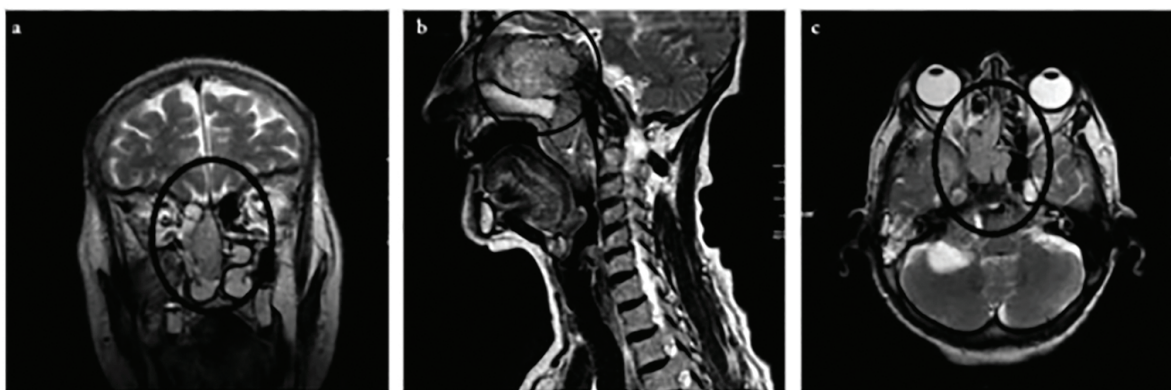
A chordoid glioma case of the third ventricle, which did not show such a high MIB-1 index (Figure 2) so far, was presented recently [49]. Interestingly, this patient had a long survival period. These cases will enter into the WHO CNS classification maybe as atypical chordoid glioma in the future.



**Figure 2.** (Left) Representative appearance of chordoid glioma on MR imaging. Note a suprasellar mass occupying the anterior portion of the third ventricle and compressing the anterior ventricular floor on coronal contrast-enhanced T1-weighted and note high Ki-67 LI in neoplastic cells (right).

## 2.5. Challenges in diagnosing brain tumors

Obtaining brain tissue by the surgeon does not always guarantee that a final diagnosis will be reached, because unfortunately sampling errors or misinterpretation of the findings may still occur. Stereotaxic biopsy provides merely a trivial amount of material, and only the normal tissue or nonspecific anomalies such as gliosis or necrosis may be seen in the histological assessment. The use of spectroscopy, PET and SPECT for guiding biopsy reduces the sampling challenge [50]. However, it should not be forgotten that the biopsy comes from different clinics. Pathologists should also remember that there may be extraneuroaxial meningioma (**Figure 3**) in a patient with the symptom of a mass at the nasopharynx [51]. Paraffin block analysis unveils major histological characteristics; however, the findings may not meet all diagnostic criteria for the suspected disease. At this point, the pathologist may be obliged to make a choice between a report without an outcome and the outcome report comprising the most probable diagnosis although it does not meet all diagnostic criteria. Rather than having the clinician focus only on the outcome, ensuring that he/she reads the whole pathology report is important for the treatment to be aware of the unconfirmed grade of the histological diagnosis made [52].



**Figure 3.** Coronal (a), sagittal (b) and axial (c) T2-sectional images of magnetic resonance imaging demonstrated a tumor beginning from the corner of the right cerebellopontine and extending along the nasopharynx-oro-pharynx-hypopharynx.

Accurate and timely diagnosis is the key principle in neuro-oncology [53]. Cancer treatment is often toxic; however, the risk of toxic effects is overlooked considering the potential gains in life expectancy when the appropriate treatment is administered to the right patient.

But, does the impact of each mass seen in the brain refer to a neoplasm? Diagnosing brain tumors is not crystal clear process. Many non-neoplastic neurological diseases may resemble brain neoplasms in the histological assessment or neuroimaging [54, 55]. In their review, Omura et al. [52] elaborated on differential diagnosis in these tumor-like lesions comprising multiple sclerosis, stroke, pyogenic abscess, toxoplasmosis, tuberculosis, cysticercosis, fungal infections, syphilis, sarcoidosis, Behçet's disease, radiation necrosis and venous thrombosis. They have detailed the elements supporting non-neoplastic diagnosis and helpful tips for differential diagnosis in brain lesions which uptake the contrast material. The findings which may support non-neoplastic diagnosis are as follows: sudden onset in young adults (AIDS),

traveling to endemic countries (cysticercosis, hydatidosis), sexual behavior and use of drugs in IV form (AIDS, syphilis), history of autoimmune or inflammatory disease (MS, Behçet's disease, sarcoidosis), chronic fever, dental procedures (brain abscesses) transient neurologic deficits and vision symptoms (MS), and skin rashes (Behçet's disease, sarcoidosis, AIDS).

The vital questions in guiding the treatment, to be raised by pathologists at each biopsy, gained a critical importance once again with what has been described here. Is biopsy sufficient for diagnosis? If the material is sufficient, is it neoplastic or non-neoplastic? If the histological findings comply with the tumor, is this tumor primary or metastatic?

## 2.6. Detection and importance of metastatic brain tumors

Many pathologists/neuropathologists must have experienced a case similar to the one described below during intraoperative diagnosis. The tissue sampled from the mass in the brain during the operation by the surgeon is sent to the pathology lab for a frozen procedure. The pathologist who realizes the atypical pigmented cells tells the clinician doctor to seek for a lesion in the pigment of the patient's skin and tells that the microscopic finding matches melanoma; the surgeon reviews his/her patient and reports that, yes, there is an irregular skin lesion at a diameter of 2 cm in the lumbar region. Certainly, the diagnosis of metastatic lesions cannot be made at the blink of an eye as described here.

Metastases constitute the most important cause of death from cancer, including the CNS tumors. Metastasis in the central nervous system (CNS) forms a major part of the routine in neuropathology. The annual prevalence in the United States is 170,000, which corresponds to 10 times more the prevalence of primary malignant brain tumors. It is known that a central nervous system metastasis occurs during this process in 20–40% of the patients with systemic cancer [13, 14, 54–56].

Metastatic lesions mostly carcinomas constitute 1/4–1/2 of intracranial tumors. The most frequent primary organs are the lungs, breasts, skin (melanoma), kidneys and the gastrointestinal canal tumors, and these account for 80% of metastatic tumors [56, 57].

Metastases form sharply circumscribed masses localized usually in the gray-white matter junction area inside the brain and are frequently surrounded by an edema belt. The border between the brain parenchyma and the tumor is markedly circumscribed microscopically by the reactive gliosis surrounding the tumor.

In addition to the direct and local effects of metastases, also paraneoplastic syndromes may affect the peripheral and central nervous system and may sometimes emerge as findings which enable malignant tumors to be noticed clinically [58]. There are antibodies developed against tumor antigens in most patients with paraneoplastic syndrome. Some of patterns seen more frequently are provided below:

- *subacute cerebellar degeneration* causing ataxia and involving destruction, gliosis and mild inflammatory infiltration in Purkinje cells
- *limbic encephalitis* causing subacute dementia, concentrated in the medial temporal lobe, involving perivascular inflammatory infiltration, microglial nodules and some neuronal loss

- *subacute sensorial neuropathy* causing change in the sensation of pain as a result of inflammation along with the loss in sensorial neurons in the dorsal stem ganglions
- *sudden onset psychosis, catatonia, epilepsy and coma syndrome* associated with the antibodies developing against ovarian teratoma and *N*-methyl-D aspartate (NMDA) receptor [14, 15].

CNS metastases typically emerge during the late phase of systemic malignancies [59]. In a large-series retrospective study of metastatic brain tumors, the average interval between the primary tumor and metastatic brain tumor was 8.5 months and this displayed a significant variation from 4 months in lung cancers up to 37 months in melanoma [60].

Systemic treatment models are not very effective in treating metastatic tumors in the brain. This is due to the fact that the blood-brain barrier prevents most chemotherapeutic agents from passing to the brain parenchyma. While surgical methods and the administration of excision or radiotherapy may be partially effective in solitary brain metastases, the disease may become fatal in multiple metastatic lesions and/or typically small cell carcinoma and melanoma, and even when there is leptomeningeal involvement associated with breast cancer [61, 62].

Most brain metastases occur with hematogenous diffusion. As most of the CNS blood flow occurs toward the cerebrum, 80% of metastatic tumors are seen in this region. Cerebrum is followed by the cerebellum with 15%, brain stem with 5% and deep structures. The lesions mostly emerge in the gray matter, and especially, the gray-white matter composition is impacted. A higher amount of involvement is seen in the areas fed by the mid-cerebral artery [63, 64]. The parietal lobe is the most affected lobe where arterial border zones and especially mid, anterior and posterior cerebral arteries display continuity. Frontal and occipital lobes are other regions where metastatic lesions are seen. The masses localized in the brain stem, corpus callosum and the deep white matter have a low chance of being metastatic [65]. Retrograde spread is possible in rare cases via cranial nerves, especially in the neoplasms of head-neck squamous carcinoma and malignant salivary gland [66, 67].

Radiologically, the metastases from the sharply circumscribed masses in the brain parenchyma are often surrounded by a belt of edema. Sometimes, necrotic areas with dark color at the center, as in glioblastomas (GBMs), require differentiation from high-grade gliomas, lymphomas, abscesses and even large demyelinating plaques [68].

## **2.7. Differential diagnosis of metastases from primary CNS tumors**

Pekmezci and Perry [69] presented the following detailed and significantly helpful information for pathologists in their comprehensive study published recently, entitled the *Neuropathology of Metastasis: Excluding a Primary CNS Tumor as a First Step in the Diagnosis of Metastatic Brain Lesion*. The information on malignancies, mostly hidden from pathologists by clinicians, is extremely beneficial especially in tissue diagnosis. However, even in patients with known cancer, 11% of these patients present with a solitary brain lesion and most of these are high-grade gliomas [70]. The microscopic characteristics of metastatic tumors usually resemble the primary tumor when the metastatic tumor is well differentiated and do not create problems in the diagnosis. However, poorly differentiated neoplasms in the brain parenchyma always

require that high-grade gliomas undergo differential diagnosis, as with glioblastomas, especially when they are solitary.

Epithelioid or rhabdoid glioblastomas may resemble metastatic tumors or melanomas. Negative staining specific to melanoma and carcinoma and additional glial markers such as GFAP, OLIG2 and SOX2 solve this dilemma almost in all cases [71].

As most metastatic lesions appear with fibrous stroma histologically, their borders with the surrounding brain parenchyma are marked. Generally, they may be easily differentiated from primary brain tumors. Differential diagnosis problems occur occasionally with diffuse infiltrative glioma, choroid plexus tumors and medulloblastoma and hemangioblastoma in the cerebellum. Small cell, epithelioid and adenoid type glioblastoma may sometimes be confused with undifferentiated carcinoma. Furthermore, the degenerative changes which may be seen in the metastatic tumor may mimic glioblastoma. It is necessary to differentiate papillary adenocarcinoma metastasis from choroid plexus carcinoma. In this case, it should not be forgotten that choroid plexus carcinoma occurs in the young age group. Although rare cases are reported in adults, newly defined choroid plexus markers such as Kin 7.1 and stanniocalcin-1 may provide additional help [72]. As diffuse immunohistochemicals, the EMA antibody, diffuse, strong staining pattern and Ber EP4 positivity indicate metastases. Considering the benign behavior of hemangioblastoma, the differential diagnosis of cerebellar hemangioblastoma and metastatic renal carcinoma is important. Moreover, both tumors may be seen in the von Hippel-Lindau disease. The use of inhibin alfa, aquaporin1 and epithelial markers may differentiate these two tumors [73–75]. It has been reported in recent studies that the antibody aquaporin1 is a very reliable marker for hemangioblastoma and that its use with the antibody AE1/AE3 (for RCC) is useful in differentiating the two tumors. The differentiation of small cell carcinoma of the lung and medulloblastoma may be challenging in the cerebellum. Although it is reported that some medulloblastomas may display positivity in EMA and cytokeratin, EMA and cytokeratin are still the most reliable markers in differential diagnosis [76, 77].

The number of metastatic foci varies between cases. In the retrospective surgical review, 45.6% of the patients had solitary brain metastasis (one CNS lesion, without other systemic metastases), 26.5% had single brain metastasis (one CNS lesion with other systemic metastases), while the rest had two or more brain metastases [77].

When they see an intracranial tumor, pathologists should not report the tumor as a metastatic tumor or metastatic carcinoma without the need for providing details after deciding whether it is primary brain tumor or not. Reporting the origin and typing of the primary tumor in brain biopsy are important due to the following reasons. First of all, the period spent by the clinician for investigating the localization of the primary tumor will lead to a loss of time and be costly for the patient. Secondly, unnecessary surgery will be avoided in cancers such as metastatic germ cell tumor and lymphoma in which medical treatment will be administered. Again, due to the same reason, it will be beneficial to diagnose breast, prostate, ovarian and small cell lung carcinomas where chemotherapy is effective, based on the metastatic tumor. Finally, in patients with metastatic brain tumor, the long-term prognosis is based on various factors such as the tumor type, the dimension and number of metastatic foci, degree of diffusion of the primary



tumor, the presence or absence of a metastatic tumor also in the other organs, the level of cognitive functions and the age of the patient. Thus, knowing the tumor type for the oncologist is critical in planning the treatment process [78]. It is aimed to make a diagnosis especially for metastatic tumors with unknown primary tumor with the introduction of immunohistochemical methods and a large variety of markers for routine use. Actually, considering the medical tests and procedures to be performed on the patient with a tumor in which the primary origin is unknown, the cost of immunohistochemical methods will be less. However, the most important topic to be discussed regarding this matter is the selection of suitable markers within this wide choice of antibodies and makes the most accurate diagnosis.

### **2.8. Immunohistochemical markers used in investigating the origin of brain tumors with unknown primary**

Often, it is possible to make a morphological distinction alone between carcinoma, lymphoma and melanoma. However, when morphology is not sufficient, additional supportive methods are applied. Usually, starting with the general markers such as cytokeratin (carcinoma), S100 (melanoma, glioma) and leukocyte common antigen (lymphoma) is the first widely accepted step [79, 80]. If there is no staining with any of these symptoms, then it may sarcoma, germ cell tumors or primary CNS tumor [81].

***Elevation of cytokeratin expression:*** The most frequently used cytokeratin in pathology practice is AE1/AE3. AE1 enters into reaction with CK10, CK15, CK16 and CK19, while AE3 enters into reaction with CK1, CK6 and CK8 [82]. Both display staining almost in all carcinomas. However, AE1 enters into reaction also with normal, reactive and neoplastic astrocytes at the same time. Therefore, it will be useful to start with the cocktail antibody CAM5.2 which comprises CK8 and CK18 that are known as small molecular weight keratins. Cytokeratin 7 and 20 antibodies are other antibodies which are beneficial in the investigation of the origin [77, 79–83] (**Table 4**).

***Melanocytic markers:*** Malignant melanoma is among the tumors most frequently metastasizing to the brain. In some cases, the presence of malignant melanoma may first be detected when there is a brain metastasis. Metastatic malignant melanoma displays positive staining with S100 protein. However, as the S100 protein may be expressed also in neurons, reactive astrocytes, glioma, neurophils and the Schwann cells, the use of these tumors in brain metastases is rather limited. As a nuclear transcription factor, SOX10 is expressed in the neural crest, melanocytes and the glial and Schwann cells. While there is limited expression in the CNS, it has a considerably high sensitivity also to melanoma [84]. Moreover, the use of the antibodies Melan-A, HMB-45, tyrosinase and MITF is also recommended [85, 86].

***Glial fibrillary acidic protein (GFAP):*** This antibody used very frequently in the neuropathology routine, normal, reactive and neoplastic astrocytes, normal ependymal cells, neoplastic ependymal cell processes and retinal Muller glial cells. Furthermore, it should not be forgotten that the Schwann cells, Kupffer cells, chondrocytes and myoepithelial cells may be GFAP positive [25, 87].

Rate of metastasis		CAM 5.2	CK7	CK20	TTF-1 (nuclear)	CK5/CK6	CD56	Melan-A, HMB-45, S100	GCDFP-15	CA125	CDX2 (nuclear)	Vimentin	CD10, RCCMa (nuclear)	Number of metastasis
50%	Lung non-small cell carcinoma	+	+	-	+	-	-	-	-	-	-	-	-	Multiple
	Lung small cell carcinoma	+/-	-	-	+	-	+	-	-	-	-	-	-	
	Squamous cell carcinoma	+	-	-	-	+	-	-	-	-	-	-	-	
11%	Melanoma	-	-	-	-	-	-	+	-	-	-	+	-	Multiple
15%	Breast carcinoma	+	+	-	-	-	-	-	+	-	-	-	-	Single
	Endometrial carcinoma	+	+	-	-	-	-	-	-	+	-	-	-	
10%	Renal cell carcinoma	+/-	-	-	-	-	-	-	-	-	-	+	+	Single
4%	Colorectal carcinoma	+	-	+	-	-	-	-	-	-	+	-	-	Single
	Gastric/gastroesophageal carcinoma	+	+/-	+/-	-	-	-	-	-	-	+/-	-	-	

+, positive; -, negative; +/-, can be positive or negative.

**Table 4.** Immunohistochemical signatures of common CNS metastatic neoplasms (adapted from Ref. [80]).

**Organ-specific markers:** The use of two well-known organ-specific markers, namely thyroglobulin and prostate-specific antigen (PSA) antibodies, is rather limited as the metastasis of thyroid and prostate cancer to the brain is very rare—thyroid transcription factor (TTF-1) is expressed by normal thyroid and lung epithelium. Therefore, other than squamous cell carcinoma, it is positive in most of adenocarcinoma, small cell carcinoma, poorly differentiated non-small cell carcinoma, neuroendocrine carcinoma and lung origin carcinoma [88]. However, TTF-1 expression was reported in a rare 3rd ventricle ependymoma [89]. Furthermore, its use with epithelial markers such as CK7 will be diagnostic, especially in the diagnosis of adenocarcinoma metastasis [25, 77, 79–83, 90]. CDX2 is a caudal-type gene encoding intestine-specific transcription factor expressed in the intestinal epithelium. Its use with cytokeratin 7 and 20 is beneficial in terms of differential diagnosis gastric, gastroesophageal, colorectal and mucinous ovarian adenocarcinoma metastases [25, 83, 91]. As an intermediate-sized basic cytokeratin, CK7 is positive in lung adenocarcinoma, breast, ovarian, pancreatic, biliary tract, endometrium, prostatic, thyroid, salivary gland and urinary bladder cancers. While the specificity of the gross cystic disease fluid protein 15 (GCDFFP-15)—used for the differential diagnosis of metastatic breast carcinoma—is 99%, its sensitivity level is rather low (50%). A strong HER2 amplification (immunohistochemical or FISH) may provide support at diagnosis [92, 93].

### 3. Concluding remarks

- If a poorly differentiated intracranial tumor is detected, the age, localization, and clinical and neurological findings should be questioned at first stage.
- Consequently, differential diagnosis should be made with these findings, and hematoxylin and eosin sections (primary tumor, metastatic carcinoma/melanoma/lymphoma/sarcoma) and immunohistochemical analysis should be performed.
- In order to make an immunohistochemical differential diagnosis for carcinoma, it is recommended to investigate the cytokeratin 7/20 profile and organ-specific markers upon ensuring that it is carcinoma by selecting a more specific marker such as CAM5.2 at first stage.

In conclusion, pathologists are aware of their responsibility in neurosciences which is increasing in importance, know the value of a multidisciplinary approach in the management of brain tumors together with oncologists, surgeons and radiologists and play an important role in the administration of individualized molecular treatment in metastatic cancers such as lung, breast and melanoma cancer by using skillfully immunohistochemical arguments not only in the accurate diagnosis of primary tumors but even in tumors where the primary source cannot be identified radiologically.

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