Diagnostic Approaches to Adult-Type Diffuse Glial Tumors

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Gliomas are the most frequent intrinsic central nervous system tumors. The new 2021 WHO Classification of Central Nervous System Tumors brought significant changes into the classification of gliomas, that underline the role of molecular diagnostics, with the adult-type diffuse glial tumors now identified primarily by their biomarkers rather than histology. The status of the isocitrate dehydrogenase (IDH) 1 or 2 describes tumors at their molecular level and together with the presence or absence of 1p/19q codeletion are the most important biomarkers used for the classification of adult-type diffuse glial tumors.

glial tumors | diagnostic approaches | central nervous system | tumor

1. Introduction

The expansion of knowledge in the central nervous system (CNS) tumor's molecular alterations has been massive in the last decade. Former tumors have been defined histologically. Molecular information only provided complementary data [1]. However, despite having equivalent histological patterns, treatment outcomes for IDH-wildtype and IDH-mutant diffuse gliomas were substantially different [2].

Molecular diagnostics in recent years have changed not only clinical outcomes but also the whole classification of glial tumors. The most recent alterations were made in 2021. The biggest changes include the distinctive features that are seen in adults and children. Gliomas and other neuronal tumors are divided into six finer groups, but adult-type diffuse gliomas are the most relevant in clinical practice. Adult-type diffuse gliomas now are identified primarily by their biomarkers rather than histology. This family includes three types of tumors: astrocytoma (IDH-mutant), oligodendroglioma (IDH-mutant, and 1p/19q-codeleted), and glioblastoma (IDH-wildtype). All diffuse adult-type astrocytomas, IDH-mutants, are considered a single type and are graded as 2, 3, or 4; oligodendroglioma, IDH-mutant, and 1p/19q-codeleted are graded as 2, 3; and glioblastomas comprise only IDH-wildtype tumors and are graded as 4. Therefore, being IDH-wildtype tumors, glioblastomas are now a separate diagnosis from astrocytomas, IDH-mutant tumors. However, for a astrocytic glioma to be able to qualify as glioblastoma the tumor should at least have microvascular proliferation, a site of necrosis, mutation of the TERT promoter, EGFR gene amplification, or changes in the copy number of +7/−10 chromosomes [3].

2. Biomolecular Diagnostics

2.1. Isocitrate Dehydrogenase (IDH)

IDH mutations are considered important in glioma genesis, determining a more favorable outcome and longer survival with mutated IDH, than patients with wild-type IDH; therefore, IDH-1 status can also be used as a clinical prognosis indicator [4][5][6][7]. The presence of IDH mutations excludes glioblastomas according to the 2021 Classification of CNS Tumors, as all glioblastomas are IDH-wildtype.

By combining radiological features with genetic signatures, a wider view of glial tumors can be achieved [8]. A study of 280 patients who were diagnosed with glioblastoma and underwent surgical treatment showed that tumor contrast enhancement [9], multifocality [10], tumor location [11][12], edema [10], and cysts [13] can be linked with genetic attributes and survival outcome in glioblastoma patients.

2.2. 1p19q Codeletion

1p19q codeletion together with IDH mutation decides the course of treatment for oligodendroglioma. It is an evident biomarker concerning long-term survival after aggressive multimodal treatment [14]. Such courses can be considered by combining surgical resection, followed by radiotherapy and chemotherapy with procarbazine, CCNU (lomustine), and vincristine (PCV) [15]. IDH-mutant and 1p/19q codeleted grade-3 oligodendrogliomas have a dramatically longer overall survival median when treated with radiotherapy and PCV in comparison to only radiotherapy treatment. In contrast, survival rates are significantly shorter for patients with 1p/19q intact grade-3 gliomas.

2.3. MGMT Promoter

O (6)-methylguanine-DNA methyltransferase (MGMT) is a DNA repair protein that can neutralize its alkylation when chemotherapy is administered. Hypermethylation of the *MGMT* promoter results in gene silencing [16][17]; therefore, gliomas with methylated MGMT promoters are more susceptible to the effects of alkylating agent therapy, such as temozolomide.

3. Imaging Techniques for the Guidance of Glioma Diagnostic

3.1. Computed Tomography

While most glial tumors can be diagnosed on computed tomography, it is a less comprehensive imaging modality when compared to MRI; therefore, it plays a secondary role in the diagnostic imaging of gliomas. CT imaging is sensitive enough for long-term posttreatment tracking. However, if tumor progression has been detected, the patient should be directed for MRI [18]. CT can also be used as the main imaging modality on rare occasions when MRI is contraindicated (ferromagnetic foreign bodies, pacemakers, and cochlear implants are most common).

3.2. MRI

By having intricate and subtle architectural changes in the brain, magnetic resonance imaging (MRI) is sensitive enough to suspect the radiographical characteristics of glioma. The usage is not instrumental in making a diagnosis but also in pre- and posttreatment [19].

In recent years more advanced imaging has entered oncological diagnostics; however, basic MRI sequences are still the foundation of the radiological workload. They show the location, size, margins, structure, and spread of the tumor, and the presence or absence of vasogenic edema [20][21][22]. T1 contrast-enhanced (T1CE) images with gadolinium-based contrast agents reveal disruption of the blood–brain barrier. Susceptibility-weighted images (SWI) are helpful for a better depiction of tumoral hemorrhages and calcifications. Diffusion-weighted images can show areas of increased diffusion, while automatically calculated apparent diffusion coefficient (ADC) may have a role in predicting the tumor grade for gliomas and evaluating posttreatment response.

3.3. Perfusion-Based Imaging

Perfusion-weighted imaging provides spatial blood flow through tissue. Due to signal changes in glial tumor blood flow circulation, a more profound conclusion can be made. A healthy tissue can maintain metabolism, remove byproducts, and keep a stable temperature; however, pathological tissue cannot sustain these processes. Mainly two approaches are used for MR perfusion. Dynamic susceptibility contrast (DSC), which heavily depends on contrast uptake (mostly gadolinium-chelate) and dynamic contrast enhancement (DCE), is another contrast-related sequence that depends on the imaging approach when perfusion defects and hyperdense regions of the lesion are seen. The last one (arterial spin labeling (ASL) does not require contrast media; instead, advanced rapid pulse sequences and blood flow “act” as a contrast [23].

3.3.1. Dynamic Susceptibility Contrast

DSC is more useful when discussing cerebral tissue. Due to having a large vessel network and, thus, by contrast remaining in the blood flow system. The paramagnetic nature of the contrast agent increases local tissue susceptibility, causing increased T2∗ dephasing of nearby tissues. Gradient echo and well-perfused tissue exhibit a reduction in the signal relative to the precontrast images or the poorly perfused tissues. This criterion is a substitute marker for capillary density or neoangiogenesis and often is relative to the contralesion brain tissue. The duration and reliability of DSC are the main advantages. However, calculations of absolute parameter measures and sensitivity to susceptibility-related artifacts depend on the user. Artifacts are commonly observed at the base of the skull or the site of postoperative hemosiderin deposition [24]. Tumor growth leads to neovascularity in high-grade gliomas; therefore, microvascular density is increased which leads to elevated relative cerebral blood volume (rCBV). For such patients, DSC may be helpful in the preoperative diagnosis or followup of malignant lesions [25].

3.3.2. Dynamic Contrast Enhancement

DCE is a T1-weighted sequence that usually uses the spoiled gradient echo technique; therefore, longer effectuation (fulfilment) time is required compared with DSC [26]. When imaging is obscure due to microvascular permeability or the blood–brain barrier, DCE gains an advantage against other perfusion-related techniques. Also,

compared with DSC, reduction in susceptibility-related artifacts has been reported [27]. Disadvantages include the longer scan time, decreased temporal resolution, and disagreements about the best suitable contrast substance. Even though DCE has a decreased temporal imaging capability, when a lesion with mixed pathology is discovered it is still the preferred method due to improved spatial resolution [23].

3.3.3. Arterial Spin Labelling

Lastly, when discussing perfusion adaption for glial tumors arterial spin labelling (ASL) uses different sets of images than DSC or DCE. Mainly, two technique alterations are being used for ASL [28]. Signals for both methods are primarily being made due to moving spins of blood and no statistical difference for diagnostics has been seen [29]. However, ASL has some setbacks. The main one is that long scanning times are needed, and motion artefacts cannot be evaded.

3.4. Advanced MR Imaging

3.4.1. Spectroscopy

In most cases, MRI provides all the needed information about the tumor size and its tissue extension. However, sometimes the information can be inconclusive for pseudoresponse or pseudoprogression evaluation [30]. Even though functional and molecular imaging can provide more accurate information and lately these methods attracted a lot of attention, getting data about lesions metabolism is sometimes also needed. Magnetic resonance spectroscopy imaging (MRS) is a technique that provides metabolomic information despite overlayed anatomical structures [31].

A high percentage of brain tumors have decayed signals for N-acetyl aspartate (NAA). The changes in neuronal tissue: temperature, metabolism, and byproducts exchange lead also to increased levels of Choline (Cho). It is observed that glioblastomas are linked with peaked Cho levels in the lesion. Knowing that glioblastomas often have the site of necrosis in which anaerobic oxidation overtakes the energy production, leading to increased levels of lactate explaining Cho [32].

3.4.2. fMRI

For decades physicians struggled with neurological assessment concerning various senses. In some cases, for example, a glial tumor can interfere with motor and sensory functions of a patient, and functional MRI (fMRI) and a better understanding. This modality is based on the basic principles of MRI physics. Endogenous oxygenated hemoglobin is diamagnetic and has increased signal waves in comparison to deoxygenated hemoglobin, which has a shorter relaxation time on T2* resulting in a decreased signal. By applying these assumptions brain activation can be monitored. Stimulated cortex areas will have increased blood flow with higher levels of oxygenated blood.

3.4.3. Diffusion Tensor Imaging

DTI is a method that reconstructs a model of subcortical connectivity. Doing so can help more accurately plan the resection site based on the tract's invasion level. It is also more likely to reduce the functional impairments postsurgically, helping neurosurgeons to be aware of the location of white matter tracts. Glioma's heterogenic nature makes it difficult to differentiate from normal tissue and, thus, DTI would be helpful to segregate the two. Recent studies suggest that DTI is more efficacious when combined with other modalities. Combined with a tumor-isolating "fence-post" catheter (insertion of catheters around the border of tumor margins) technique, motor-evoked potentials from cortical areas can facilitate the resection of high-grade glioma up to 1 cm from the corticospinal tract [33].

3.5. Nuclear Medicine Imaging

3.5.1. Positron Emission Tomography

Positron emission tomography (PET) is paving the way in understanding complex heterogenous tumors such as gliomas. The glioma genesis is still not understood completely; however, including PET gives a better understanding of the tumor's genesis. One of the hardest aspects of posttreatment diagnostics is the complexity and ability to remodel. It is one of the main reasons why it is hard to discern TP from PsP or radiation necrosis. By having a better comprehension of the tumor's ecosystem, a better prognosis and treatment plan could be possible [34]. One of the most promising trackers that has been seen is 18F-FDG. Utilizing it for a recurrent glioma could have a better treatment prognosis.

3.5.2. SPECT

When comparing nuclear medicine imaging SPECT is not only more widely accessible but also cheaper than PET; however, due to the attribution of nuclear decay, gamma rays used (two for PET, one for SPECT) makes the spatial resolution inferior compared to PET. However, isotopes used for SPECT are sensitive enough to observe various process regarding glial tumors. Technetium-99m-labelled compounds have been one of the main tracers used for differentiation between glioma progression and radiation necrosis. When 99mTc-sestamibi and 99mTc-tetrofosmin enter the blood flow no signs of conversion in a healthy brain have been registered. If uptake is seen, tumors recurrence or necrosis induced by radiation can be expected. Hence, the assimilation of radioactive tracer can be a differentiative tool.

3.6. Posttreatment Imaging

3.6.1. True Progression

Criteria defining progression was first introduced in 2010. The RANO (Response Assessment in Neuro-oncology) guidelines depict true progression concerning imaging features also reflecting on chemoradiation time of completion (<12 weeks and >12 weeks). Enhancement outside of the radiation field, enlargement of perpendicular diameter by 25% or greater between the first and twelves week postradiotherapy scan, or clinical deterioration were progression-determining factors. The guidelines additionally considered the influence made on the imaging of

antiangiogenic drugs. Increased FLAIR signal for nonenhancing lesions in such patients could indicate disease progression [35].

3.6.2. Pseudoprogression

Post-treatment radiographic changes can be challenging for a clinician on excluding tumor progression (TP) from pseudoprogression (PsP). In a study of 208 patients, PsP is observed relatively commonly. A correlation was observed between MGMT-methylated tumors and PsP. Converting to numbers, 31% of the sample group was diagnosed with PsP. A more sophisticated treatment planning should be carried out dealing with methylated tumors if a preferable outcome is to be expected. Hence, PsP patients can endure a more robust treatment, achieving longer progression-free survival compared to TP patients [36]. Although, radiologic assessment in neuro-oncology has come a long way since McDonald's criteria, which only had four basic features and relied solely on MRI. It is still frequently a tough decision to pass in the clinical field when it comes to distinguishing TP/PsP [37]. In situations such as radiation-induced treatment basic MRI imaging cannot always segregate the differences between PsP and TP. At first imitation of progression in the early stages of healing can occur, relying only on conventional imaging can be troublesome. In the application of chemoradiation, a common appearance of glioblastoma can be present on FLAIR, impeding diagnostics. Hence, advanced imaging is indispensable in contemporary glial tumor assessment.

3.6.3. Pseudoresponse

Another significant post-treatment highlight worth discussing is a pseudoresponse. The main difference from PsP is that pseudoresponse is observed in the setting of antiangiogenic therapy. VEGF, hepatocyte growth factor, fibroblast growth factor, platelet-derived growth factor, angiopoietins, and IL-8 are the proangiogenic agents known for glioblastoma's angiogenic growth upregulation. Brain tumors express the VEGF-A factor in a considerable huge amount. Bevacizumab is a humanized monoclonal antibody that normalizes tumor vascularization by decreasing vessel size and permeability [38]. Therefore, tumor exposure to chemotherapy and/or radiation therapy is improved significantly. Response rates differ between 25% and 60% [39]. Changes in radiological features are followed as early as one day after initiation of anti-VEGF therapy [39]. Imaging findings show decreased contrast enhancement, edema, and vessel permeability. Sadly, even having this kind of impact, no correlation between bevacizumab and prolonged survival has been proven [40]. However, patients show a longer timeframe for progression-free survival and the need for steroid treatment. Nevertheless, patients who show a response radiographically develop a rapid worsening of the disease. The changes are best seen in no-enhancing T2 signal hyperintensity on T2 FLAIR sequences [41].

3.6.4. Radiation Necrosis

Even though radiation necrosis is the opposite extreme of pseudoprogression, several studies refer to it as a single collective entity. However, pseudoprogression and radiation necrosis are diverse from each other in timing, pathological mechanisms, histopathology, and prognosis [42][43]. Pseudoprogression typically occurs up until a few months after treatment, whereas radiation necrosis can be seen after a prolonged time, typically between nine to

twelve months but there have been cases when it was observed even after several years. This peculiarity occurs because new areas of contrast enhancement are bounded by the initial radiation field [44]. When it comes to survival prognosis, pseudoprogression has a more favorable outcome compared with radiation necrosis. Life quality is also affected by radiation necrosis, as neurologic functions often decline [45]. Patients with a 1p/19q codeletion can expect a much higher risk of developing radiation necrosis compared with other genetic markers [46].

3.6.5. Imaging after Immunotherapy

Immunotherapy has come a long way since it was introduced. In 2018 Nobel Prize in Medicine was awarded to James Allison and Tasuku Honjo for their breakthrough research in immunotherapy. Today, it is mostly used as an adjuvant treatment; however, it is believed that immunotherapy is the future of cancer treatment [47]. In the setting of treatment, an increase in lesions can reflect a localized inflammatory response despite immunotherapy. A new, enhancing lesion may be the response of the immune system in previously nonenhancing, infiltrative disease. “Flare phenomenon” or overdue response can occur [48].

4. Conclusions

Glial tumors are among the most malignant brain tumors. New research in the biomolecular field helps to differentiate and better foresee the glioma’s outcome, which is reflected in a new 2021 WHO Classification of CNS Tumors. While standard diagnostic imaging usually provides necessary information for identifying and characterizing adult-type diffuse brain gliomas, advanced imaging techniques such as fMRI and DTI may be required for treatment planning. However, differentiation between true progression, pseudoprogression, and radiation necrosis on posttreatment followup imaging can be challenging and usually additionally requires perfusion MRI as part of a routine protocol on followup examination. When tumor progression is suspected, MR spectroscopy and SPECT or PET imaging can be of value when the result of the routine examination remains ambiguous. For the best glial tumor treatment results, a multimodal approach is needed. Combining various imaging techniques, and considering the strengths and limitations, the radiologist can develop a more evidence-based assessment.

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