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IDH-mutant gliomas. State of the art

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ABSTRACT
The article is focused on current state of diagnosis of *IDH*-mutant gliomas in Russia: potential of predictive neuroimaging, intraoperative mass spectrometry, traditional immunohistochemistry and molecular analysis of paraffin-embedded glioma tissue and targeted therapy with FDA-approved *IDH* inhibitors.

Keywords: *IDH, gliomas, targeted inhibitors.*

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Introduction

To date, molecular pathologists debate the distinction between "IDH-wildtype glioblastoma" and "H3- and IDH-wildtype diffuse glioma" and advocate for mandatory time-consuming and costly diagnostic methods such as DNA methylation analysis and next-generation sequencing (NGS) of DNA and RNA [1]. In these circumstances, IDH-mutant gliomas can be considered fortunate. About 80-90% of these tumors can be diagnosed quickly and inexpensively via immunohistochemistry [2]. Along with identification of new methylation classes and subclasses of CNS tumors (from 91 in 2021 to 184 in 2026) [3, 4], only a few tumor types including IDH-mutant gliomas retain diagnostic, histological, molecular, clinical and neuroimaging-related commonality. They demonstrate predictable treatment responses and prognoses, reminding us of general oncological principles (albeit while acknowledging the need for individualized patient care).

Diagnosis of IDH-mutant gliomas in the Russian Federation

In the Russian Federation, diagnosis of IDH-mutant gliomas in adults—as with any other CNS tumor—is based on modern guidelines (primary CNS tumors, 2025) [5]. These guidelines incorporate the 5th edition of the WHO classification of CNS tumors (2021) [2]. Even five years after release, this book continues to spark debate among morphologists and clinicians. After all, fully meeting the diagnostic criteria recommended by classification requires one to be not merely morphologist but molecular pathologist capable of interpreting DNA methylation and next-generation sequencing of DNA/RNA. Furthermore, not all diagnostic decisions in this edition appear clear or well-conceived. Many diagnoses require refinement and clarification. Unfortunately, many pathologists, particularly in Russian regions, perceive the current version of the classification as excessively complex and still prefer the 2016 edition. In reality, for all emphasis on molecular data, the classification or rather its authors-neuropathologists acknowledge disparities in diagnostic capabilities among pathologists worldwide. Consequently, they still allow for a so-called "descriptive" histological diagnosis accompanied by recommendations for further testing at specialized centers in Russia.

New articles (cIMPACT-NOW) in 2025 indicate preparing a new edition of the WHO classification of CNS tumors [1, 6—8]. Recognizing the "gray zones" of the current classification, the cIMPACT-NOW working group provides recommendations on grading of meningiomas, DNA methylation in CNS tumor diagnosis, newly identified CNS tumors not yet included in classification and diagnostic criteria for IDH-wildtype and H3-wildtype gliomas.

Current guidelines classify glial tumors into adult-type diffuse gliomas (either IDH-mutant or IDH-wildtype; **Table)**, pediatric-type high-grade diffuse gliomas and circumscribed astrocytic gliomas [5]. Importantly, the term "glioblastoma WHO Grade IV" is now reserved for adults with malignant glial tumors and no IDH mutation. For children with malignant gliomas, one should

Classification of diffuse gliomas in adults (2021) [2, 5]

Gliomas	WHO 2021 malignancy grade	Molecular features
Adult-type diffuse gliomas		
IDH-mutant astrocytoma	II—IV	Mutations in *IDH1* and *IDH2* genes (rare; more typical for oligodendroglioma than astrocytoma), mutations in *ATRX* and *TP53* genes; homozygous deletion of *CDKN2A/B*
IDH-mutant oligodendroglioma with 1p/19q-codeletion	II, III	Mutations in *IDH1* and *IDH2* genes (rare; more typical for oligodendroglioma than astrocytoma), *TERT* mutation; 1p/19q co-deletion
IDH-wildtype glioblastoma	IV	No mutations and *IDH* wild-type; *TERT* mutation; *EGFR* amplification; gain of chromosome 7 and loss of chromosome 10

use the term "diffuse pediatric-type high-grade glioma WHO Grade I", even though histological appearance of tumors is identical. Moreover, IDH-mutant glioblastoma WHO Grade IV belongs to previous 2016 classification. Such tumors should now be designated as IDH-mutant astrocytoma WHO Grade IV".

Park J.W. et al. [9] found peritumoral cells with low IDH1 mutation in approximately 40% of patients with IDH-mutant glioma (baseline driver mutation) and no any additional mutations were found. This suggests that IDH gene mutation initiating glioma occurs in distant progenitor cells. Glial and oligodendrocyte progenitor cells remain histologically normal, and tumor itself is formed by cells with additional mutations. In mouse models of IDH-mutant glioma, IDH-mutant oligodendrocyte progenitor cells underwent clonal expansion, sequentially acquired additional driver mutations, and progressed into IDH-mutant gliomas. The resulting tumors faithfully recapitulated histological structure and single-cell transcriptomic profiles of their human counterparts. These findings provide experimental evidence that glial and oligodendrocyte progenitor cells in peritumoral cortex can serve as origin of IDH-mutant gliomas. At the same time, IDH-wildtype glioblastomas likely arise from stem cells in periventricular zone [10].

IDH status, neuroimaging and extent of resection

IDH mutation in gliomas was discovered almost 20 years ago [11]. Today, we can predict IDH mutation status of glioma at the neuroimaging stage. When preparing for surgery, neurosurgeons may be aware not only of suspected nature of tumor but also of its mutation status. Theoretically, this information could influence decisions regarding optimal extent of resection and improve the prognosis [12]. This aligns with the 2026 EANS-EANO guidelines on extent of glioma resection. These guidelines recommend the most aggressive resection for IDH-mutant tumors while preserving functional status. This is essential for better survival and epilepsy control (evidence level B) [13].

However, neurosurgeons always aim for the greatest possible extent of resection considering potential functional and other consequences. Indeed, knowledge of IDH gene status may not actually influence decision-making. Furthermore, extent of resection is less important in certain tumors, such as oligodendrogliomas due to high sensitivity to chemotherapy.

Safe redo resection is feasible in patients with recurrent IDH-mutant gliomas [13].

According to the principles of radiomics [14] and radiogenomics [15], there are models for non-invasive prediction of IDH mutation status in gliomas. These models include a redefined T2-FLAIR mismatch sign, subcortical FLAIR signal drop (scFLAIR-D) and *in vivo* MR spectroscopy to detect neurochemical differences between gliomas with IDH mutations and 1p/19q codeletion versus those without codeletion [16—20]. Clinical accuracy and significance of these models are currently analyzed.

Detection of IDH mutations: traditional and emerging methods

One can determine IDH mutation status using intraoperative mass spectrometry. Such researches were conducted at Heidelberg University Hospital (Germany), Purdue University (USA), Tsinghua University (China), Huashan Hospital at Fudan University (China), and Mayo Clinic (USA). Tandem mass spectrometry was used to analyze concentration of 2-hydroxyglutarate relative to endogenous glutamate in intraoperative small tissue samples. Researchers harvested tumor core samples to assess IDH status, whereas margins of postoperative cavity were analyzed regarding IDH status in infiltration zone. The authors emphasize the need to compare results of intraoperative mass spectrometry with those of Sanger sequencing on frozen or paraffin-embedded material [21—24].

Now-standard analysis of IDH gene mutation status in formalin-fixed paraffin-embedded tumor tissue in a stepwise manner is a cost-effective measure. In patients younger 55 years with supratentorial gliomas, there is no need for polymerase chain reaction (PCR) and se-

quencing if mutant IDH protein is detected via immunohistochemistry. Conversely, sequencing is recommended in case of negative result of immunohistochemistry or infratentorial tumor [2].

IDH-mutant brainstem gliomas

One should bear in mind possible IDH-mutant brainstem gliomas. These are undoubtedly rare tumors, and there are only case reports in the literature [25, 26]. Nevertheless, we tend to focus on IDH mutations in supratentorial tumors, often overlooking the fact that tumors harboring such mutations (albeit with different amino acid substitutions) can also affect infratentorial structures. This approach needs to change. The IDH mutation status of gliomas in any location should be investigated more extensively. We observed only 2 cases of IDH-mutant brainstem gliomas, as morphological study of brainstem gliomas in our hospital began recently. Researches are ongoing.

Returning to supratentorial gliomas in adults, certain factors may lead pathologists to suspect IDH mutation: young age, temporal or frontal location, gemistocytic tumor subtype and heterogeneous focal differentiation within the same tumor.

Immunohistochemistry, polymerase chain reaction and Sanger sequencing are the simplest and cost-effective methods for assessing IDH mutation status [2, 27, 28].

No IDH mutation in a diffuse histologically benign glioma in adult patient warrants further investigation using high-resolution molecular methods, such as DNA methylation analysis and DNA/RNA next-generation sequencing. In our practice, the so-called "pediatric-type" gliomas in adults are not uncommon.

Does a key recurrent mutation offer an opportunity for targeted therapy?

Currently, targeted therapy for CNS tumors is primarily used in pediatric neuro-oncology for tumors harboring alterations in BRAF, FGFR, NF or NTRK. Researchers encountered and overcame challenges related to resistance, secondary mutations and tolerability. In some cases, they shifted from monotherapy to combined regimens. In pediatric oncology, they are now primarily debating optimal timing for targeted agents (first-line treatment or, as traditionally practiced, upon disease progression).

Following the FDA approval of IDH inhibitors, the landscape for adult CNS tumors may also change. Certainly, further study is necessary [29—32].

Conclusion

IDH-mutant gliomas in adults are the most extensively studied tumors and accurately diagnosed in most cases. The suspected diagnosis becomes apparent after assessment of clinical and neuroimaging data. Histological and molecular diagnosis in the Russian Federation does not present significant challenges. Diagnostic measures are governed by current guidelines as well as capabilities of pathology departments, bureaus, and molecular laboratories. Major Russian cities have specialized and general laboratories available for molecular analysis of complex cases. Antibodies for immunohistochemistry and real-time PCR kits may be available locally for rapid and cost-effective diagnosis. Such "rapid" methods cover the majority of amino acid substitutions associated with IDH mutations (not all, but many of them). PCR kits and instruments hold necessary registration certificates in the Russian Federation. Sanger sequencing and next-generation sequencing are available to detect rare substitutions. However, diagnosis of diffuse histologically benign IDH-wildtype glioma in adults necessitates additional complex molecular analyses, such as DNA methylation profiling and next-generation sequencing of DNA and RNA.

However, as we investigate CNS tumors more extensively, our perspective and understanding of these tumors broaden. We are gradually gaining further insight into IDH-mutant gliomas. Some of these can develop in the brainstem, while very rare cases may arise in context of hereditary syndromes associated with mutations in TP53 gene (Li-Fraumeni syndrome) and genes responsible for DNA repair.

We are currently re-evaluating our approach to surgery and considering appropriateness of neurosurgical intervention although extent of resection remains a key prognostic factor for glial tumors. Moreover, new IDH inhibitors appear promising, though their efficacy requires further study and validation.

No conflict of interests to declare

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Comment

This article presents a timely analytical review of a comprehensive approach to diagnosis and management of IDH-mutant gliomas. Addressing the requirements of modern neuro-oncology and neurosurgery, the study covers critical aspects determining treatment strategies and prognoses for this population. The manuscript combines molecular-biological data with practical recommendations focused on actual operating conditions of Russian medical institutions, including regional hospitals.

A distinct advantage of this report is clear practical focus. The author goes beyond description of "gold-standard" international protocols and analyzes the gap between requirements of the 2021 WHO classification and cIMPACT-NOW recommendations, on the one hand, and actual capabilities of pathology services in Russian regions, on the other. Analysis of availability of diagnostic methods (such as immunohistochemistry and polymerase chain reaction) registered in the Russian Federation is of particular value, as this influences the choice of diagnostic strategy in routine clinical practice.

An important methodological contribution of the article is clear explanation of terminological changes, specifically the well-founded move away from the term "IDH-mutant glioblastoma" in favor of correct designation "IDH-mutant astrocytoma WHO Grade IV". This is of fundamental importance for neurosurgeons and pathologists. Indeed, this prevents errors in formulation of diagnosis and, consequently, subsequent management.

The author demonstrates a systematic approach to diagnosis, sequentially outlining the capabilities of various methods: from non-invasive neuroimaging (radiomic markers, such as T2-FLAIR mismatch sign) to intraoperative technologies (mass spectrometry) and standard morphological examination. This integration of various data provides the reader with comprehensive understanding of diagnostic algorithm. Attention to diagnostic "gray zones" (rare tumor locations (brainstem gliomas) and necessary extended molecular profiling) enhances clinical significance of this report.

The novelty of this article lies in adaptation of modern international standards to the Russian context, as well as in systematization of diagnostic approaches depending on their availability. Theoretical significance of the article lies in updating of terminology and classification. Practical value lies in formulation of a realistic algorithm for various physicians (particularly neurosurgeons) who must make decisions under limited resources and necessary rapid intraoperative verification.

Bekyashev A.Kh. (Moscow)