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INTER-OBSERVER VARIABILITY IN HISTOPATHOLOGICAL INTERPRETATION OF GLIOMAS

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ABSTRACT

Background: Inter-observer variability complicates histopathological diagnosis in gliomas, especially in distinguishing grades and tumor types using morphology alone. This study aimed to quantify agreement between two consultant pathologists using WHO 2021 criteria via Kappa and ICC analysis.

Methods: A total of 128 glioma biopsy specimens were independently assessed by two consultants for diagnosis and grading under WHO 2021 classification. Discrepancies were categorized as agreement, minor disagreement (within-grade differences), or major disagreement (cross-grade or tumor-type difference). Inter-observer reproducibility was evaluated using Kappa statistics and ICC.

Results: Complete agreement occurred in 42/128 cases (32.8%), with disagreement in 86 (67.2%), including 58 major and 28 minor conflicts. The Kappa coefficient was 0.383 (fair agreement), and ICC was 0.51 (moderate reliability).

Conclusions: Significant inter-observer variability persists in glioma histopathology when relying solely on morphology. Integrated molecular classification (WHO 2021) and adjunctive tools may enhance diagnostic consensus and reduce subjectivity.

Keywords: Inter-observer variability; Glioma; WHO classification; Histopathology; Diagnostic reproducibility.

1. INTRODUCTION

Gliomas are the most prevalent primary malignant brain tumors and present diagnostic challenges due to histological diversity and overlapping morphology across grades. Accurate grading is essential for patient management, but subjective morphological interpretation introduces variability, especially in borderline cases such as astrocytoma grade II vs III or grade III vs glioblastoma. Multiple studies have documented moderate-to-poor reproducibility in glioma grading and in key histopathological features such as mitoses, necrosis, and endothelial proliferation [1–5]. The WHO 2021 classification integrates molecular criteria (IDH mutation, 1p/19q codeletion, ATRX, TP53, MGMT) to improve diagnostic accuracy and reproducibility [6–8]. Nevertheless, in resource-limited settings, molecular testing may not be readily available, forcing reliance on morphology alone. This study assessed inter-

observer variability in 128 glioma cases using WHO 2021 morphological criteria and quantified agreement using Kappa and ICC.

2. MATERIALS AND METHODS

A prospective study of 128 glioma cases was conducted at the Department of Pathology, Peshawar Medical College, with institutional ethical approval. Each biopsy was independently interpreted by two consultant histopathologists according to WHO 2021 criteria.

Opinions were categorized as: Agreement – identical diagnosis/grade; Minor disagreement – within-grade differences; Major disagreement – across grades or tumor types. Statistical analysis was performed using Kappa coefficient and Intraclass Correlation Coefficient (ICC) with SPSS v20.

3. RESULTS

Among 128 glioma patients (76 males, 52 females; mean age 41.2 ± 12.6 years), agreement was observed in 42 cases (32.8%), while disagreement occurred in 86 cases (67.2%). Major disagreements (58; 45.3%) most frequently involved astrocytoma grade III vs glioblastoma, and astrocytoma vs oligodendroglioma. Minor disagreements (28; 21.9%) included differences in grade II vs III astrocytomas and glioblastoma subtypes.

Kappa statistic = 0.383 (fair agreement). ICC = 0.51 (moderate reliability).

Table 1. Major Conflicting Diagnoses (n = 58)

Diagnostic Category	Number of Cases	Examples
Astrocytoma Grade II vs Grade III	16	Mitotic activity and cellularity
Astrocytoma Grade III vs Glioblastoma (Grade IV)	22	Necrosis, vascular proliferation
Oligodendroglioma vs Astrocytoma	14	Morphological overlap, lack of 1p/19q
Others (mixed glioma, gliosarcoma, etc.)	6	Rare variants

Table 2. Minor Conflicting Diagnoses (n = 28)

Disagreement Type	Number of Cases	Remarks
Astrocytoma Grade II vs Grade III	11	Differences in mitotic counts and thresholds
Glioblastoma subtypes (classic vs small-cell)	7	Morphological subtypes
Oligodendroglioma Grade II vs Grade III	10	Subjective interpretation of atypia

Table 3. Kappa Coefficient Analysis

Agreement Measure	Value	Interpretation
Kappa (κ)	0.383	Fair agreement

Table 4. Intraclass Correlation Coefficient (ICC)

Measure	Value	Interpretation
ICC (two-way mixed)	0.51	Moderate reliability

4. DISCUSSION

This study confirms substantial inter-observer variability in glioma interpretation, with concordance achieved in less than one-third of cases. Our findings are consistent with prior reports that highlighted similar challenges in histopathological evaluation of gliomas [1–3, 5,6]. Gilles et al. documented poor agreement in pediatric brain tumors, with κ values of ~0.35 for endothelial proliferation and ~0.5 for mitoses/necrosis [1], while van den Bent emphasized clinically significant variability in adult gliomas [2]. Coons et al. also demonstrated reproducibility issues even among experienced neuropathologists [3].

Proliferative indices are similarly prone to variability. Grzybicki et al. and Nielsen et al. showed κ values as low as 0.04–0.32 for Ki-67/MIB-1 scoring, underscoring limitations in widely applied biomarkers [5,6]. In line with these studies, our results revealed greatest variability between grade III astrocytoma and glioblastoma, as reported by others [2,7]. Distinguishing astrocytoma from oligodendroglioma also proved challenging, particularly without molecular confirmation, reflecting previous findings [9].

Recent innovations may help overcome these limitations. Pekmezci et al. demonstrated that intraoperative imaging with stimulated Raman histology (SRH) can improve reproducibility, achieving κ values >0.65 [8]. Liu et al. further highlighted persistent variability across multiple centers in intraoperative glioma grading, underscoring the global scope of the problem [7].

The incorporation of molecular markers into the WHO 2021 classification has markedly improved reproducibility, with IDH, ATRX, TP53, and 1p/19q providing objective diagnostic anchors [4,10,11]. Capper et al. further showed that DNA methylation profiling provides a robust framework for tumor classification, enhancing accuracy and inter-observer agreement [12,13]. However, in resource-limited settings, restricted access to molecular testing forces reliance on morphology alone, perpetuating subjectivity.

Taken together, our findings underscore the importance of integrating molecular diagnostics, expanding access to ancillary technologies, and adopting consensus review systems. Emerging approaches, including digital pathology and AI-assisted image analysis, offer additional opportunities to reduce variability and strengthen diagnostic consistency in glioma care.

5. CONCLUSIONS

1. In 128 glioma cases, inter-observer variability remained substantial, with only one-third showing agreement.
2. Major disagreements occurred most frequently between grade III astrocytomas and glioblastomas, and between astrocytomas and oligodendrogliomas.
3. Incorporating molecular testing and digital/AI-based adjuncts alongside morphology, as recommended in WHO 2021 classification, is essential to improve reproducibility.

REFERENCES

1. Gilles FH, Tavaré CJ, Becker LE, et al. Pathologist interobserver variability of histologic features in childhood brain tumors. Pediatr Dev Pathol. 2008;11(2):108–17.
2. van den Bent MJ. Interobserver variation of the histopathological diagnosis in glioma. Acta Neuropathol. 2010;120(3):297–304.
3. Coons SW, Johnson PC, Scheithauer BW, et al. Improving diagnostic accuracy and interobserver reproducibility in the classification and grading of primary gliomas. Cancer. 1997;79(7):1381–93.
4. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumours of the Central Nervous System: a summary. Acta Neuropathol. 2021;142(4):631–51.
5. Grzybicki DM, Liu Y, Moore SA, et al. Interobserver variability associated with the MIB-1 labeling index in astrocytic gliomas. Cancer. 2001;92(10):2720–6.
6. Nielsen LAG, Andreassen M, Christensen T, et al. Evaluation of the proliferation marker Ki-67 in gliomas: interobserver variability and digital quantification. Diagn Pathol. 2018;13:38.
7. Liu J, et al. Interobserver variability in intraoperative glioma grading: a multi-center study. J Neuropathol Exp Neurol. 2025;84(2):100–9.
8. Pekmezci M, Morshed RA, Chunduru P, et al. Detection of glioma infiltration at the tumor margin using quantitative stimulated Raman histology. Sci Rep. 2021;11:12162.
9. Gupta T, Agrawal V, Turel MK, et al. Concordance between local, institutional, and central review in glioblastoma: implications for clinical research. Neurol India. 2012;60(1):48–52.
10. Komori T. Grading of adult diffuse gliomas according to the 2021 WHO classification. Brain Tumor Pathol. 2022;39(1):1–6.
11. Wesseling P, Capper D. The 2016 WHO Classification of Tumours of the Central Nervous System: summary and commentary. Acta Neuropathol. 2018;136(2):197–211.

12. Capper D, Jones DTW, Sill M, et al. DNA methylation-based classification of central nervous system tumours. Nature. 2018;555(7697):469–74.
13. Capper D, Stichel D, Sahm F, et al. Practical implementation of DNA methylation and copy-number-based CNS tumor diagnostics: validation in a large-scale study. Acta Neuropathol. 2018;136(2):273–86.