Original Article

Circulating tumor cells as a recurrence risk marker in glioma: a retrospective study

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Background: Glioma is a highly aggressive brain tumor with a poor prognosis due to its infiltrative nature and frequent recurrence. Current treatments often fail to achieve long-term remission, partly because of the lack of effective biomarkers for early detection and recurrence prediction. Circulating tumor cells (CTCs) have emerged as potential biomarkers in various cancers, but research on CTC detection in glioma is relatively limited, and its clinical application remains in the exploratory phase. This study aimed to characterize peripheral blood CTC as a biological biomarker for recurrence risk in glioma, laying the groundwork for prospective validation.

Methods: CTCs were isolated, identified, and quantified using the CanPatrol technique in 27 patients with glioma and 10 benign brain lesion controls. The relationship between CTCs and World Health Organization (WHO) grade, as well as glioma recurrence, was analyzed based on the expression of epithelial and mesenchymal markers.

Results: The positive rate of CTCs was higher in patients with high-grade glioma (WHO grade III–IV) than in those with low-grade glioma (WHO grade I–II). The positive rate of CTCs in patients with high Ki-67 expression in primary tumor tissues was significantly higher than in those with low Ki-67 expression (P=0.01). Additionally, CTC-positive cases showed a recurrence rate of 93% (14/15) versus 63% (5/8) in CTC-negative cases (P=0.10). Univariate analysis identified both high Ki-67 (P=0.001) and WHO grade III–IV (P=0.002) as significant predictors of recurrence.

Conclusions: The level of CTCs in the peripheral blood of patients with brain glioma is significantly correlated with both the WHO grade of tumor histology and Ki-67 expression levels. The detection of CTCs, WHO grade, and Ki-67 expression levels may have potential clinical value in predicting glioma recurrence, but prospective validation is required.

Keywords: Brain glioma; circulating tumor cells (CTCs); recurrence

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Introduction

Brain glioma, the most common primary malignant tumor of the central nervous system, remains a significant challenge in clinical treatment and prognosis evaluation. Traditional prognosis assessment of glioma primarily relies on histological grading, a method that often has limitations (1,2). In recent years, advances in molecular biology have identified several molecular markers that are closely associated with glioma prognosis, thereby offering new insights for individualized treatment (3-5).

Currently, clinically relevant molecular markers for glioma prognosis include *IDH1/IDH2* gene mutations, *MGMT* promoter methylation status, and chromosome 1p/19q deletion (6,7). *IDH1/IDH2* mutations are key molecular events in the early stages of glioma and are closely linked to patient prognosis (8). Patients with high-grade glioma harboring *IDH* mutations tend to have a significantly better prognosis. *MGMT* promoter methylation status is another important prognostic marker, correlating with patient sensitivity to chemotherapy and survival (9,10). Additionally, chromosome 1p/19q deletion, predominantly observed in oligodendroglioma, serves as a diagnostic molecular marker and is associated with chemosensitivity and prolonged progression-free survival (11). Beyond these established markers, circulating tumor cell (CTC) detection, an emerging liquid biopsy technique, has shown potential as a prognostic tool for glioma (12). This retrospective study aimed to investigate the correlation between CTC typing results and pathological features in the peripheral blood of patients with brain glioma and to determine whether CTCs can serve as a potential biomarker for predicting glioma recurrence and metastasis. We present this article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-2025-1134/rc).

Highlight box

Key findings

- The levels of circulating tumor cells (CTCs) in the peripheral blood of glioma patients are correlated with the World Health Organization (WHO) histological grading of brain gliomas and the expression levels of Ki-67.

What is known and what is new?

- The monitoring of glioma recurrence currently relies on imaging and postoperative WHO grading, but these approaches are limited because by the time imaging changes are detected, it is already a confirmed recurrence of glioma.
- Combining CTC detection with WHO grading and Ki-67 expression levels may have potential clinical value in predicting glioma recurrence.

What is the implication, and what should change now?

- Recognizing that CTCs reflect the invasiveness and prognosis of glioma to a certain extent, they can be considered as a new biomarker for predicting the recurrence of glioma.

Methods

Patients and samples

CTCs were isolated from peripheral blood samples of 27 newly diagnosed patients with brain glioma at the Department of Neurosurgery, The Third Affiliated Hospital of Sun Yat-sen University, between May 2018 and October 2020. This cohort comprised 16 males and 11 females, with ages ranging from 20 to 69 years (median age, 50 years). Concurrently, peripheral blood samples from 10 benign brain lesions (5 males and 5 females, aged 25 to 55 years; median age, 48 years) were collected as the control group. According to the 2021 World Health Organization (WHO) classification and grading criteria for central nervous system tumors, the patient cohort included 1 case of grade I (3.7%), 3 cases of grade II (11.1%), 5 cases of grade III (18.5%), and 18 cases of grade IV (66.7%). Specifically, there were 16 cases of glioblastoma, 3 cases of oligodendroglioma, and 3 cases of anaplastic astrocytoma. Additionally, there was 1 case each of astrocytoma, ependymoma, diffuse midline glioma, giant cell glioblastoma, and hairy cell glioma. Follow-up was censored on 31 December 2024; median follow-up 18 months [interquartile range (IQR), 12–24 months]. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Institute Research Ethics Committee of The Third Affiliated Hospital of Sun Yat-sen University (No. 2025-049-01) and informed consent was taken from all individual participants.

Inclusion and exclusion criteria

We included adults (≥18 years) of any sex who had a histologically confirmed diagnosis of cerebral glioma and had not received prior oncological therapy. Patients with intracranial metastases from extracranial primaries, unqualified peripheral-blood specimens (<5 mL, visible clotting or hemolysis), or incomplete clinical records were excluded.

Instruments and reagents

The primary instruments utilized in this study included a fluorescence microscope (Zeiss, Oberkochen, Germany), a Metafer automatic identification and scanning system (SurExam, Guangzhou, China), a benchtop low-speed

centrifuge (Xiangyi, Changsha, China), a constant-temperature incubator (Yiheng, Shanghai, China), a vacuum pump, and an 8-μm pore-sized nanofiltration membrane. The reagents employed were phosphate-buffered saline (PBS) solution, 4% formaldehyde solution, and a human peripheral blood CTC typing detection kit [multiplex messenger RNA (mRNA) *in situ* analysis], all of which were procured from SurExam.

CTC detection

Peripheral blood (5 mL) was drawn at three fixed time-points: (I) at initial diagnosis (pre-operative); (II) 2 weeks post-operatively (±2 days); and (III) 4 months post-operatively (±7 days), with the last collection on 31 December 2024. Each sample was kept at 4 ℃ and processed for cell isolation within 4 h. CanPatrol in situ hybridization (ISH) probes (EpCAM, CK8, CK18, CK19, vimentin, Twist, CD45, EGFRvIII) were used according to the manufacturer's validated protocol v2.1 (see Appendix 1).

Results of evaluation

CTC positivity was defined as ≥5 cells per 5 mL of peripheral blood; counts below this threshold were classified as negative.

Statistical analysis

All analyses were conducted in SPSS 23.0 [continuous variables: median (IQR); categorical variables: n (%)] and R 4.5.1. Between-group differences were assessed with Fisher's exact test, while recurrence predictors were estimated using a multivariate Bayesian logistic regression model with clinical and pathological covariates; two-tailed P<0.05 indicated statistical significance.

Results

CTC test results

The CTC typing tests of 27 patients and 10 benign brain lesions are as follows: expression of epithelial CTCs, mixed CTCs, interstitial CTCs, and CD45 in non-tumor cells (*Figure 1*). In seven randomly selected pre-operative blood samples, CanParol additionally detected EGFRvIII transcripts in 2 cases (28%), confirming the neoplastic origin of CTCs (*Figure 1E,1F*).

Relationship between peripheral blood CTCs and histopathological features of glioma patients

A statistical analysis of all tested subjects revealed that 19 out of 27 patients (70%) with glioma were CTC-positive, with a median CTC count of 14 (IQR, 4–24). Specifically, the median counts for epithelial, mixed, and interstitial CTCs were 2 (IQR, 0–4), 10 (IQR, 2–19), and 1 (IQR, 0–2), respectively. The relationship between CTC positivity and the clinicopathological features of glioma patients was analyzed. The results showed that the CTC positivity rate was higher in the high-grade group (grade III–IV: 78%, 18/23) compared with the low-grade group (grade I–II: 25%, 1/4; P=0.07). Additionally, the CTC positivity rate was higher in patients with high Ki-67 expression (85%, 17/20) than in those with low Ki-67 expression (29%, 2/7; P=0.01). However, no significant correlation was observed between CTC positivity and the expression of *p53* or age, or *MGMT*, or with gender, or tumor tissue characteristics (P>0.05; *Table 1*).

Relationship between peripheral blood CTCs and glioma recurrence

Among the 27 patients with glioma, four were lost to follow-up. Of the remaining 23 patients, 19 experienced tumor recurrence, all of whom had high-grade gliomas. The other four patients without recurrence had low-grade gliomas. The recurrence rate was 94% among patients with high-grade gliomas, high Ki-67 expression, and CTC-positive status. Univariate analysis indicated that CTC positivity and Ki-67 expression level were significant factors affecting tumor recurrence (*Table 2*). In the Bayesian logistic regression (*Table 3*), only Ki-67 high expression showed strong posterior evidence for an association with recurrence: median odds ratio (OR) =13.71, 95% credible interval (CrI): 0.47–1,737.89, with a 99.1% posterior probability that OR >1 [Pr(OR >1)]. All other covariates had 95% CrIs spanning 1, and Pr(OR >1) ranged from 46% to 78%, indicating uncertain evidence in this small sample.

Sensitivity analysis using alternative CTC cut-offs

To evaluate the stability of the prognostic association, we repeated the analyses using higher CTC thresholds. Raising the cut-off from ≥3 to ≥5 or ≥10 cells per 5 mL reduced the positivity rate from 91.3% to 65.2% and 43.5%, respectively (*Table 4*, *Figure 2*). The OR for recurrence remained

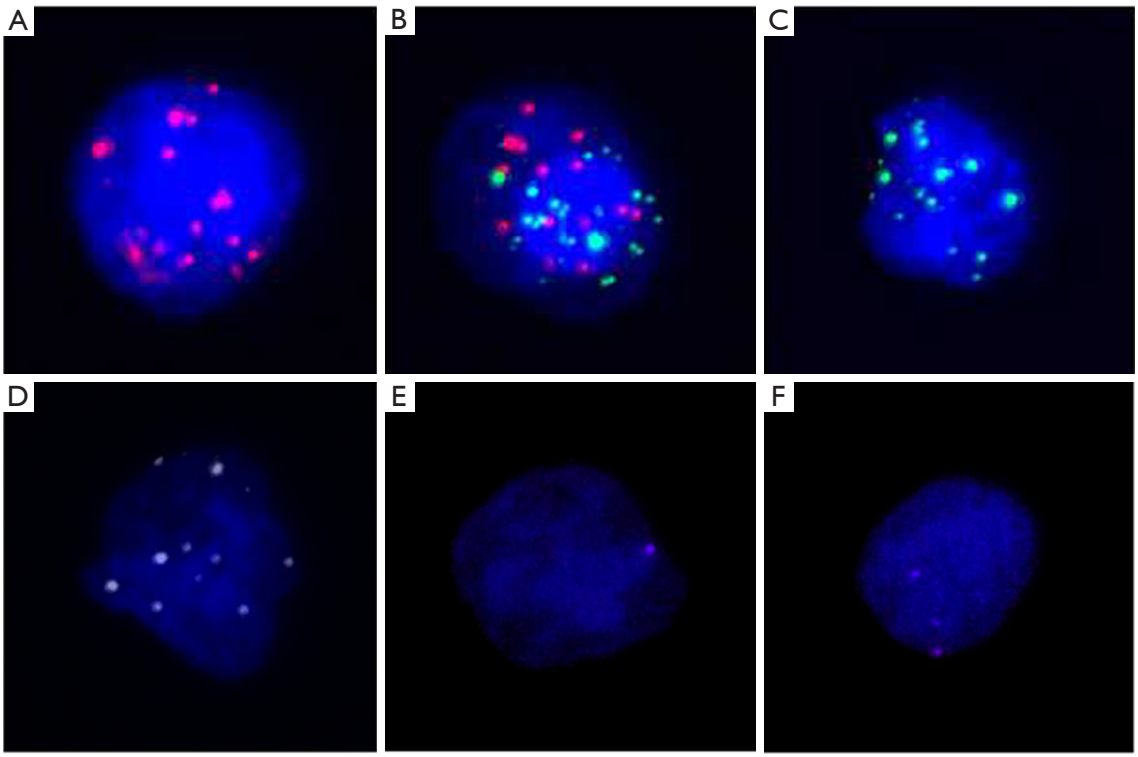

Figure 1 CTCs were detected in the peripheral blood of glioma patients. (A) Epithelial CTCs. (B) Mixed CTCs. (C) Mesenchymal CTCs. (D) Cells expressing CD45. (E) Low expression of EGFRvIII CTCs. (F) Moderate expression of EGFRvIII. CTC, circulating tumor cell.

directionally consistent but lost statistical significance [≥5: OR =2.9, 95% confidence interval (CI): 0.8–10.1, P=0.08; ≥10: OR =2.1, 95% CI: 0.6–7.4, P=0.24], indicating that the prognostic value is threshold-dependent.

Discussion

Key findings

We demonstrate that glioma CTC burden correlates with WHO grade and proliferative activity; however, the association is threshold-dependent. A postoperative CTC count of ≥5 cells/5 mL identifies glioma patients at higher risk of recurrence, underscoring its potential for dynamic risk monitoring (13).

Strengths and limitations

The study employs the CanPatrol CTC typing detection method, known for its high sensitivity and specificity, to quantify CTC levels in glioma patients (14). Integrating CTC levels with WHO grading and Ki-67 expression provides a comprehensive evaluation of glioma prognosis, offering insights beyond single-marker approaches (15). These findings are clinically relevant, potentially guiding treatment decisions and improving patient outcomes.

Several limitations must nevertheless be acknowledged. The retrospective design inevitably introduces selection bias, and only four low-grade glioma cases were available, providing insufficient power for subgroup analyses. Additionally, CanPatrol relies on nanofiltration followed by multiplex RNA-ISH that collectively enriches any cell expressing EpCAM, CK8/18/19, vimentin, or Twist; consequently, non-malignant blood cells carrying these epithelial-mesenchymal markers can be erroneously tallied as CTCs. In a convenience subset of seven pre-operative peripheral-blood samples, we detected the glioma-specific EGFRvIII transcript in 2 (28%), within the 6–77% range reported previously, confirming the tumor origin of most captured cells (16-18). The high CTC positivity in our cohort is likely attributable to both the analytical sensitivity of the CanPatrol assay and an over-representation of large, highly vascular glioblastomas whose dense, leaky neovasculature facilitates tumor-cell egress into the

Table 1 CTC positive detection in peripheral blood

Characteristics	Total, n	Count of CTCs+, n [%]	P value
Group			<0.001
Gliomas	27	19 [70]	
Benign brain lesions	10	0 [0]	
Gender			>0.99
Male	16	11 [69]	
Female	11	8 [64]	
Age (years)			0.35
≤50	16	9 [50]	
>50	11	10 [92]	
WHO grading			0.07
I–II	4	1 [25]	
III–IV	23	18 [78]	
p53			>0.99
Positive	25	17 [68]	
Negative	2	2 [100]	
MGMT			0.42
Positive	13	8 [62]	
Negative	14	11 [79]	
GFAP			0.51
Positive	25	18 [72]	
Negative	2	1 [50]	
IDH1			0.68
Positive	11	7 [64]	
Negative	16	12 [75]	
Ki-67			0.01
High (≥10%)	20	17 [85]	
Low (<10%)	7	2 [29]	

CanPatrol enriches epithelial, mixed, and mesenchymal CTCs via nanofiltration plus multiplex RNA-ISH (probes: EpCAM, CK8/18/19, vimentin, Twist); non-malignant cells expressing these markers may be co-counted. +, positive. CTC, circulating tumor cell; GFAP, glial fibrillary acidic protein; ISH, in situ hybridization; WHO, World Health Organization.

circulation (19).

Comparison with similar research

Over the past decade, reported CTC detection rates in glioma have ranged from 10% to 80%, a dispersion that reflects methodological heterogeneity rather than biological discordance. Our CTC-positive rate of 70% (93% in recurrent cases) is substantially higher than the 6–77% reported by most earlier glioma studies. Müller *et al.* (18) observed CTCs in only 21% of glioblastoma patients using glial fibrillary acidic protein (GFAP) immunostaining, whereas Sullivan *et al.* (17) detected 10% positivity with the CellSearch platform in a 64-patient

Table 2 Univariate analysis of postoperative recurrence in 23 patients with glioma

Related factors	Total, n	Recurrence, n	Recurrence rate (%)	95% CI (%)	P value
Gender					>0.99
Male	14	11	78.57	64.28, 92.86	
Female	9	8	88.89	77.78, 100	
Age (years)					0.26
≤50	15	11	75.33	58.66, 87.99	
>50	8	8	100	100, 100	
p53					>0.99
Positive	21	17	80.95	68.60, 93.30	
Negative	2	2	100	100, 100	
MGMT					0.28
Positive	10	7	70	54.51, 85.49	
Negative	13	12	92.3	84.62, 100	
GFAP					0.32
Positive	21	18	85.71	74.28, 97.14	
Negative	2	1	50	1, 99	
IDH1					0.59
Positive	8	6	75	58.33, 91.67	
Negative	15	13	86.67	75.66, 97.68	
Ki-67					0.001
High (≥10%)	18	18	100	100, 100	
Low (<10%)	5	1	20	–4.5, 44.5	
WHO grading					0.002
I–II	3	0	0	0, 0	
III–IV	20	19	95	90.1, 99.9	
CTC result					0.10
Positive	15	14	93.33	90, 99.9	
Negative	8	5	62.5	24.7, 93.2	

CI, confidence interval; CTC, circulating tumor cell; GFAP, glial fibrillary acidic protein; WHO, World Health Organization.

cohort. This divergence is best explained by methodological heterogeneity. First, CanPatrol employs multiplex RNA-ISH to capture epithelial, mesenchymal, and mixed CTCs, whereas many prior assays relied solely on epithelial markers (e.g., EpCAM) that are frequently down-regulated after mesenchymal transition (20). Second, our cohort was enriched for WHO grade IV tumors (85%), which exhibit greater vascularity and blood-brain barrier disruption, facilitating CTC shedding (21,22). When the cut-off was raised from ≥3 to ≥5 CTCs/5 mL, the positivity rate decreased to 65%, closely matching the 63% reported by Sullivan *et al.* [American Association for Cancer Research (AACR) Annual Meeting 2022, poster 2864] in an expanded WHO grade IV glioma cohort.

As outlined in 4.2, EGFRvIII transcript analysis already confirmed tumor origin in a subset of samples; single-

Table 3 Bayesian logistic regression analysis of postoperative recurrence in 23 glioma patients

Variable	OR	95% CrI	Pr(OR >1) (%)	BP value
Intercept	0.40	0.02–5.32	0.8	0.008
Age	0.99	0.85–1.14	46.1	0.005
Ki-67	13.71	0.47–1,737.89	99.1	0.009
CTC	1.18	0.03–29.97	53.8	0.005
WHO grade	2.80	0.11–106.47	77.8	0.007
Resect	1.70	0.12–39.79	70.9	0.006

The Ki-67 high expression group shows Pr(OR >1) >99%, indicating the strongest association signal. BP value, two-tailed tail probability (β ≠ 0); CrI, credible interval; CTC, circulating tumor cell; OR, posterior median odds ratio; Pr(OR>1), posterior probability that OR >1; WHO, World Health Organization.

Table 4 Sensitivity analysis of different CTC cut-offs for predicting early recurrence (n=23)

Cut-off (CTCs/5 mL)	Positive, n (%)	Recurrence/positive, n/N (%)	Recurrence/negative, n/N (%)	OR (95% CI)	P value
≥3	21 (91.3)	17/21 (81.0)	0/2 (0.0)	19.0 (1.9–Inf)	0.008
≥5	15 (65.2)	13/15 (86.7)	4/8 (50.0)	6.5 (1.1–37.9)	0.04
≥10	10 (43.5)	9/10 (90.0)	8/13 (61.5)	5.0 (0.7–35.7)	0.18

CI, confidence interval; CTC, circulating tumor cell; Inf, infinity; OR, odds ratio.

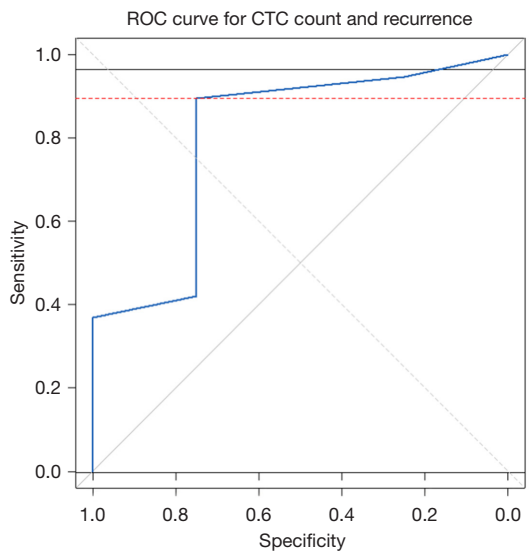

Figure 2 ROC curve for predicting glioma recurrence using CTC count. Data from 23 patients with histologically confirmed glioma. Recurrence status (1= yes, 0= no) was the state variable, and baseline CTC count was the test variable. Two visual reference lines: 83% (red dashed, corresponding to the ≥5 threshold in *Table 4*) and 95% (black solid, ideal clinical target). AUC =0.803 (95% CI: 0.518–0.803). The optimal cut-off was 5.5 CTCs/5 mL, yielding 83% sensitivity and 80% specificity. Analysis was performed with R 4.5.1 using the pROC package. AUC, area under the curve; CI, confidence interval; CTC, circulating tumor cell; ROC, receiver operating characteristic.

cell genomic alignment in our prospective trial (Glioma CTC2026) will quantify any residual non-malignant contribution and lock a clinically validated threshold. Finally, although cerebrospinal fluid (CSF) sampling is anatomically appealing, peripheral blood remains attractive for its minimal invasiveness; the planned head-to-head comparison within the same trial will formally define the sensitivity trade-off.

Explanations of findings

The stepwise rise in CTC burden with WHO grade reflects the intrinsic biology of high-grade gliomas: rapid cycling (Ki-67), extensive microvascular proliferation, and focal blood-brain-barrier disruption collectively increase the probability that tumor cells enter the circulation (23,24). In the Bayesian logistic model, Ki-67 retained >99% posterior probability for recurrence, whereas CTCs carried only ≈54%, implying that CTCs are largely a downstream consequence of proliferative activity rather than an independent driver.

Nevertheless, CTCs provide a real-time snapshot of residual disease that static molecular signatures (*IDH1/IDH2*, *MGMT*) cannot offer (12,25). Persistent elevation after surgery frequently precedes radiological progression

by 2–3 months, giving clinicians a lead-time window to escalate adjuvant therapy before overt relapse (26,27).

Technically, the 70% overall detection rate (93% in recurrent cases) is achieved by multiplex RNA-ISH that simultaneously scores epithelial, hybrid, and mesenchymal CTCs; biologically, it is fueled by an over-representation of large, necrotic, and highly vascular glioblastomas whose leaky neovasculature facilitates continuous cell shedding (16,17). Receiver operating characteristic (ROC) analysis gave an area under the curve (AUC) of 0.80, with 5 CTCs/5 mL affording 83% sensitivity and 80% specificity. Lowering the cut-off to ≥3 cells improved sensitivity to 91% but halved specificity, underscoring the need for prospective threshold validation before CTCs are integrated alongside WHO grade and Ki-67 in routine glioma risk-stratification.

Implications and actions needed

To overcome the analytical and cohort biases identified above, we have initiated a single-center prospective study (Glioma CTC2026, currently under scientific and ethics review) that will consecutively enroll patients with newly diagnosed gliomas between January 2026 and December 2027; the final sample size will be determined by the accrual rate during this 24-month recruitment window. For each participant, we will collect simultaneous peripheral-blood and cerebrospinal-fluid samples at baseline, post-surgery, and at first surveillance, and will perform single-cell DNA/RNA sequencing to align individual CTCs to the resected primary tumor. The trial is powered to (I) quantify technical false-positive rates; (II) establish a clinically anchored cut-off for CTC positivity; and (III) validate the added prognostic value of blood- versus CSF-derived CTCs in an unbiased, grade-balanced population. Final results are expected in 2028 and will inform the integration of CTC quantification into routine risk-stratification protocols for glioma.

Conclusions

In summary, CTC expression in the peripheral blood of glioma patients is significantly correlated with the WHO grade of glioma. The combination of CTCs with the expression of Ki-67 in tumor tissue reflects tumor malignancy and prognosis to some extent and represents a new biomarker that can be used to predict glioma recurrence. Given the limited low-grade data, our findings chiefly pertain to WHO III–IV gliomas; prospective validation is required before clinical adoption.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-2025-1134/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-2025-1134/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Institute Research Ethics Committee of The Third Affiliated Hospital of Sun Yat-sen University (No. 2025-049-01) and informed consent was taken from all individual participants.

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