### Title

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### Journal

Ophthalmology Science, 4(6)



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### Publication Date

2024

### DOI

10.1016/j.xops.2024.100577

Peer reviewed

AMERICAN ACADEMY OF OPHTHALMOLOGY®

# Retinal Microstructural Changes Reflecting Treatment-Associated Cognitive Dysfunction in Patients with Lower-Grade Gliomas

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***Purpose:*** To determine whether microstructural retinal changes, tumor features, and *apolipoprotein E (APOE) ε4* polymorphism are correlated with clinically detectable treatment-associated cognitive dysfunction (TACD) in patients with lower-grade gliomas.

***Design:*** Cohort study.

***Participants and Controls:*** Sixteen patients with lower-grade glioma at a United States academic ophthalmology department between January 2021 and November 2023. Normal controls were recruited from convenient sampling.

***Methods:*** Montreal Cognitive Assessment (MoCA) scores and retinal changes were assessed in 6-month intervals. *Apolipoprotein E* genotyping was performed, and tumor details were recorded. Partial least-squares discriminant (PLSD) model was established to evaluate the association between TACD with *APOE* genotype, ophthalmic, and tumor features.

***Main Outcome Measures:*** The main outcome measure was cognitive status as measured by the MoCA score and analyzed in relation to ophthalmic measurements, tumor features, and *APOE* genotype.

***Results:*** Median time to first eye examination was 34 months (2−266) from tumor diagnosis and 23 months (0−246) from radiation. Nine patients (56%) had abnormal cognition (MoCA <26/30). Montreal Cognitive Assessment scores were significantly worse in patients with temporal (22 ± 7.2) than frontal lobe tumors (26 ± 3.1, $P = 0.02$) and those with oligodendrogliomas (22 ± 4.1) than astrocytomas (26 ± 3.6, = 0.02). Patients with TACD had significant radial peripapillary capillary density loss (45% ± 4.6) compared with those with normal cognition (49% ± 2.6, $P = 0.02$). A PLSD model correlated MoCA scores with retinal nerve fiber thickness, intraocular pressure, foveal avascular zone, best-corrected visual acuity, months since first diagnosis, and tumor pathology (oligodendroglioma or not). Using these features, the model identified patients with TACD with 77% accuracy. *Apolipoprotein E* genotyping showed: 2 *ε2/ε3* (13%), 10 *ε3/ε3* (63%), and 1 *ε3/ε4* (6%).

***Conclusions:*** Retinal microstructural changes may serve as biomarkers for TACD in patients with lower-grade gliomas. Temporal lobe tumors and oligodendrogliomas may increase susceptibility to TACD. Utilization of retinal markers may enhance TACD diagnosis, progression monitoring, and inform management of lower-grade patients with glioma. A larger study with serial eye examinations is warranted to evaluate the role of *APOE* ε4 and develop a predictive model.

***Financial Disclosures:*** Proprietary or commercial disclosure may be found in the Footnotes and Disclosures at the end of this article. *Ophthalmology Science 2024;4:100577* 

*Supplemental material available at www.ophthalmologyscience.org.*

World Health Organization grade 2 and 3 gliomas, or "lower-glade gliomas,"[1] include low and intermediate-grade central nervous system (CNS) neoplasms.[2] They primarily affect middle-aged adults.[3,4] Survival rates vary from 1 to 15 years, depending on the tumor histology and molecular features.[3] Early and aggressive treatment can increase progression-free survival.[5,6] Treatment strategies include surgery and concurrent chemoradiation followed by observation or adjuvant chemotherapy.[7] The most common long-term sequela from brain tumor treatment is cognitive dysfunction.[8–10] Radiotherapy is the most common cause of treatment-associated cognitive dysfunction (TACD) in patients undergoing cranial radiation for cancer.[11,12] The timing of postoperative radiotherapy is not standardized and remains controversial in neuro-oncology.[13,14] Early postresection radiotherapy prolongs



https://doi.org/10.1016/j.xops.2024.100577
ISSN 2666-9145/24

progression-free survival by approximately 2 years[14] but does not change overall survival[15] and leads to premature cognitive decline.[16] A *wait-and-see* approach may be adopted to preserve quality of life and neurologic function[17] in younger adults without significant neurological impairment and favorable prognostic factors.[18]

Treatment-associated cognitive dysfunction predominantly manifests as impairment in executive functioning, memory, and attention[19] and may share similar pathophysiology with neurodegenerative conditions, such as Alzheimer's disease (AD).[20] There are currently no reliable markers of TACD. Genetic polymorphisms in the apolipoprotein E (APOE) and catechol-O-methyltransferase genes, anemia, and increased proinflammatory cytokine levels have been proposed as potential predictors of TACD.[21,22] Several common pathways, including genetic predisposition,[23,24] inflammation,[23] senescence,[25] and DNA and vascular alterations,[20] are thought to be involved. Retinal microvasculature has been used as a proxy for cerebrovascular changes due to physiological and morphological homology between cerebral and retinal vasculatures.[26,27] Emerging evidence suggests that cerebrovascular dysfunction may precede neurodegeneration in AD[28] and can manifest as disruption of retinal microvasculature.[29] Autopsy data of 86 patients with mild cognitive impairment (MCI) and AD showed increased amyloid-β protein retinal deposits,[30] and retinal tau protein accumulation has been shown to precede behavioral changes and cerebral tau aggregation in mice.[31] Therefore, multimodal retinal imaging may be utilized to detect microstructural and microvascular retinal changes to detect early onset cognitive dysfunction in brain tumor patients.

*Apolipoprotein E ε4* allele is the strongest genetic risk factor for late-onset AD[32] and has been linked to cognitive dysfunction in patients with brain tumors.[22,33] The *APOE* gene encodes a vital lipid transport protein and has 3 major allelic variants located on chromosome 19q.13.31 with the following prevalences: *ε2* (8%), *ε3* (78%), and *ε4* (14%).[34] *Apolipoprotein E ε4* polymorphism may offset a cascade of aberrant processes[35] that contribute to AD pathogenesis by facilitating amyloid-β plaque deposition in neuritic and cerebrovascular tissue,[36–38] inducing neuronal hyperactivity,[39] neuroinflammation,[35] cerebral hypoperfusion, and blood–brain barrier dysfunction.[40,41]

We hypothesize that by combining the retinal and genetic risk factor evaluations, we can estimate cognitive risk in patients with lower-grade glioma and help guide provider and patient decisions of chemoradiation after surgical resection.

## Methods

This is a preliminary cohort study that included patients with World Health Organization grade 2 and 3 gliomas. The study was conducted in accordance with the Declaration of Helsinki. The Institutional Review Board approved the study protocol at the University of California, Davis. All participants signed an informed consent before enrollment. Subjects were recruited at any time during their glioma treatment course and reevaluated in 6-month intervals. Each patient examination was treated as an individual time point for analysis.

### Study Population

Between January 2021 and November 2023, we screened 44 consecutive patients with a lower-grade glioma diagnosis who received neuro-ophthalmic care at the University of California, Davis and were treated with surgical resection plus radiotherapy or chemotherapy (Table 1). Sixteen eligible patients consented and were enrolled in the study. The enrollment criteria included patients >18 years of age with a lower-grade glioma diagnosis confirmed by pathology. The exclusion criteria included patients with (1) history of psychiatric or other neurologic disorders unrelated to the brain tumor or its prior therapy, (2) known or discovered history of ophthalmic conditions, and (3) presence of a significant refractive error. Seven nonage-matched healthy controls were recruited through convenience sampling to evaluate the ophthalmic changes in patients with glioma in comparison to normal controls. The control patients did not have Montreal Cognitive Assessment (MoCA) scores and OCT data available.

### APOE Genotyping

At the initial visit, patients completed a blood test for *APOE* genotyping, which was processed by Athena Diagnostics (Worcester, MA).

Table 1. Patient Demographics and Tumor Characteristics (n = 16)

| | |
|---|---|
| Mean age at first diagnosis (yrs, standard deviation) | 34 (11.5) |
| Sex | |
| Female | 5 (31%) |
| Male | 11 (69%) |
| Treatment regimen | |
| Surgical resection + concurrent radiotherapy and temozolomide | 6 (38%) |
| Surgical resection + radiotherapy | 8 (50%) |
| Surgical resection only | 1 (6%) |
| Tumor recurrence | |
| Once | 3 (29%) |
| Twice | 1 (6%) |
| Tumor type | |
| Astrocytoma | 8 (50%) |
| Oligodendroglioma | 7 (44%) |
| Ependymoma | 1 (6%) |
| Tumor location | |
| Frontal lobe | 10 (63%) |
| Temporal lobe | 2 (13%) |
| Brainstem | 2 (13%) |
| Cerebellum | 1 (6%) |
| Sella turcica | 1 (6%) |
| Tumor laterality | |
| Right | 5 (31%) |
| Left | 8 (50%) |
| Tumor World Health Organization classification | |
| Grade 2 | 12 (75%) |
| Grade 3 | 4 (25%) |
| Tumor molecular features | |
| *IDH 1* mutant | 13 (81%) |
| *IDH 2* mutant | 2 (13%) |
| α thalassemia retardation X-linked loss | 5 (31%) |
| O6-Methylguanine-DNA-Methyltransferase methylated | 6 (38%) |
| 1p19q codeletion | 7 (44%) |
| P53 positive | 9 (56%) |
| Olig2 positive | 5 (31%) |
| Phosphatase and tensin homolog deletion | 1 (6%) |
| Glial gibrillary acidic protein positive | 4 (25%) |

IDH 1 = isocitrate dehydrogenase 1; IDH 2 = isocitrate dehydrogenase 2.

### MoCA Testing Protocol

Patients completed a MoCA test in their primary spoken language at each study visit. Montreal Cognitive Assessment is a validated and sensitive tool for detecting MCI that has shown superiority in diagnosing cognitive impairment compared with the Mini Mental State Examination in several pathologies, including TACD.[42–44] A score of ≥26 (out of 30) signifies normal cognitive function, 18 to 25 suggests MCI, 10 to 17 suggests moderate impairment, and ≤10 indicates severe cognitive impairment.[45]

### Ophthalmic Imaging

Each participant completed a neuro-ophthalmic examination at each visit, which included Snellen best-corrected visual acuity (BCVA), intraocular pressure (IOP), color perception test, pupil examination, ocular motility, slit lamp examination, and a dilated fundus examination. We also obtained office-based ophthalmic tests, including Humphrey visual field (Carl Zeiss Meditec, Inc); peripapillary retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) thicknesses (μm) using Cirrus HD5000 OCT (Carl Zeiss Meditec, Inc); and radial peripapillary capillary (RPC) density (%) at the optic disc, superficial vascular plexus (SVP) and deep vascular plexus densities, and foveal avascular zone (FAZ) area ($mm^2$) at the macula using Avanti (Optovue Inc).

### Statistical Analysis

The main outcome measure was cognitive status, as measured by MoCA. Independent variables included ophthalmic measurements, tumor features, and *APOE* genotype. Ophthalmic metrics were averaged between 2 eyes for analysis of change in markers elapsed since diagnosis. We used GraphPad Prism 10 (version 9.5.0, Dotmatics) and Microsoft Excel (version 16.68, Microsoft Corp) to analyze the data and generate descriptive statistics. The data are reported as the mean ± standard deviation, median and range, number, and percentage, as appropriate. The differences in the ophthalmic data were evaluated using the *t* test or analysis of variance and Pearson correlation test. The findings were considered significant if the *P* value was <0.05. Visual acuities were converted to the logarithm of minimal angle of resolution for analysis.

### Machine Learning Analysis

Initial analysis of the features was conducted using cross-correlation and a random forest classifier trained to predict instances where the MoCA score was ≥26. In our analysis, feature importance was calculated using the built-in feature importance attribute in the random forest classifier. The resulting feature importance was plotted, and the top 6 features were selected based on their high feature importance scores, indicating significant influence. The most descriptive features associated with MoCA included the RNFL thickness, IOP, FAZ, BCVA, months since first diagnosis, and a binary feature indicating whether the tumor was an oligodendroglioma or not. For stability and generalization, feature importance was examined across each patient. Consistently, it was found that the top features played carried the most correlation with cognitive outcomes across patients, highlighting the robustness and reliability of the selected features in the model.

Next, a partial least-squares discriminant (PLSD) model was built using the strongest features identified using the random forest classifier. A leave-1-patient-out cross-validation approach was used, where all samples (2 eyes and multiple visits) of 1 patient were excluded from training and used as the test samples. The mean accuracy, precision, recall, and feature loadings of the models were analyzed.

## Results

### Patient and Tumor Characteristics

Forty-four patients were screened prior to enrollment. Sixteen patients were eligible and included in the study cohort. All patients underwent surgical resection of the tumor. One patient (6%) was treated with surgical resection only, 8 (50%) patients were treated with surgery and concurrent radiotherapy, and 6 (38%) patients underwent surgical resection and concurrent radiotherapy and temozolomide (Table 1). Twenty-eight patients were excluded because of a history of prior ophthalmic conditions or declining to participate. Treatment regimens and patient and tumor characteristics are summarized in Table 1. The median time from diagnosis to the first eye examination was 34 months (2–266). The median time from the last day of radiation to the first examination was 23 months (0–246).

The median age at first diagnosis and surgical resection was 35.5 years (range 16–54). The median age at the time of radiotherapy was 39 years (range 21–55). Patients were enrolled from 2 to 266 months since diagnosis and 0 to 246 months since radiation therapy. The eye data were standardized to unit time based on the timing of the study visit since the first diagnosis and the last day of radiotherapy and subsequently stratified into tertiles based on the interquartile ranges of standardized time of eye examination (Table 2). The data were divided into 3 groups from the time of first diagnosis to the eye examination as follows: 0 to 1 year (6 patients, 12 eyes), 1 to 3 years (7 patients, 14 eyes), and >3 years (8 patients, 16 eyes). The ophthalmic metrics were averaged between the right and left eyes for comparison of changes since time from diagnosis. For patients with frontotemporal tumors who received radiotherapy, the data were divided into 3 groups from the time of radiotherapy to the eye examination as follows: 0 to 1.5 years (4 patients, 8 eyes), 1.5 to 3 years (5 patients, 10 eyes), and >3 years (5 patients, 10 eyes). The ophthalmic metrics were compared between eyes ipsilateral and contralateral to the radiation field.

### MoCA Scores Distribution

Eight patients had MCI (50%), and 1 (6%) had severe cognitive impairment. Among patients with abnormal MoCA scores (n = 9), the most prevalent areas of cognitive impairment were memory (average domain score ± standard deviation: 2.2 ± 1.8 out of 5), language (1.3 ± 1.4 out of 3), and abstraction (1.2 ± 0.9 out of 2). Montreal Cognitive Assessment performances were not significantly different between groups but were lower, on average, >1 year after diagnosis and treatment (Fig 1A, B). Montreal Cognitive Assessment scores were significantly lower in patients with oligodendrogliomas than astrocytomas (22 ± 4.1 vs. 26 ± 3.6, $P = 0.02$). Patients with temporal lobe tumors had significantly lower MoCA scores ($P = 0.02$) compared with those with frontal lobe tumors (22 ± 7.2 vs. 26 ± 3.1, respectively). There was no significant difference ($P = 0.16$) in MoCA scores based on tumor laterality, although cognitive scores were, on average, lower in right (26 ± 2.7) compared with left lobe tumors (24 ± 4.7).

Table 2. Ophthalmic Data Based on the Time from Diagnosis or the Last Day of Radiotherapy to the Eye Examination

| | | MoCA Performance | RNFL (μm) | GCC (μm) | HVF (MD) | FAZ ($mm^2$) | RPC density (%) | SVP density (%) | DVP density (%) |
|---|---|---|---|---|---|---|---|---|---|
| **Control Eyes** | | — | — | — | — | 0.247 ± 0.1 | 56 ± 2.1 | 52 ± 5.5 | 50 ± 6 |
| ***Time Since Diagnosis*** | | | | | | | | | |
| **0 to 1 years** | | 26 ± 4 | 105 ± 8 | 87 ± 5 | -3.5 ± 5.9 | 0.251 ± 0.1 | 52 ± 3 | 49 ± 3.4 | 47 ± 8.1 |
| **1 to 3 years** | | 23.5 ± 5 | 92 ± 6 | 77 ± 8 | -1.9 ± 3.9 | 0.269 ± 0.1 | 51 ± 2.7 | 50 ± 2.9 | 51 ± 8.5 |
| **3+ years** | | 24 ± 4 | 85 ± 19 | 70 ± 20 | -3.6 ± 4.3 | 0.205 ± 0.1 | 46 ± 4.9 | 47 ± 4.4 | 50 ± 5 |
| ***Time Since Radiotherapy*** | | | | | | | | | |
| **0 to 1.5 years** | Ipsilateral Eye | 25 ± 4 | 102 ± 5 | 86 ± 4 | -4.7 ± 5.9 | 0.263 ± 0.1 | 52 ± 4.5 | 52 ± 2.1 | 51 ± 9.8 |
| | Contralateral Eye | 25 ± 4 | 104 ± 8 | 85 ± 5 | -2.5 ± 7.1 | 0.242 ± 0.1 | 52 ± 3 | 48 ± 3.3 | 48 ± 9.6 |
| **1.5 to 3 years** | Ipsilateral Eye | 23 ± 6 | 93 ± 6 | 74 ± 9 | -2.5 ± 5.3 | 0.263 ± 0.1 | 50 ± 4.3 | 47 ± 2.6 | 49 ± 8.2 |
| | Contralateral Eye | 23 ± 6 | 92 ± 10 | 75 ± 8 | -2.4 ± 4 | 0.225 ± 0.03 | 49 ± 1.4 | 49 ± 2.2 | 46 ± 11.7 |
| **3+ years** | Ipsilateral Eye | 23 ± 4 | 91 ± 6 | 73 ± 22 | -2.5 ± 3.2 | 0.230 ± 0.09 | 48 ± 2.6 | 47 ± 4.3 | 48 ± 5.3 |
| | Contralateral Eye | 23 ± 4 | 90 ± 7 | 73 ± 22 | -1.4 ± 3.1 | 0.186 ± 0.04 | 48 ± 2.4 | 50 ± 2.5 | 52 ± 6.2 |
| ***Ophthalmic Data by MoCA Performance: Low (<26) vs. Normal (≥ 26)*** | | | | | | | | | |
| **0 to 1 years** | Low MoCA | 22 ± 7.9 | 91 ± 28 | 78 ± 25 | -1.8 ± 3.5 | 0.252 ± 0.08 | 47 ± 15 | 43 ± 13.5 | 43 ± 13.5 |
| | Normal MoCA | 28 ± 0.8 | 107 ± 8.3 | 86 ± 5.7 | -1 ± 4.3 | 0.241 ± 0.1 | 51 ± 3 | 50 ± 3 | 48 ± 10.4 |
| **1 to 3 years** | Low MoCA | 19 ± 4 | 89 ± 19 | 77 ± 17 | -3.1 ± 5 | 0.242 ± 0.07 | 48 ± 10.9 | 47 ± 11 | 48 ± 12.7 |
| | Normal MoCA | 25 ± 8.6 | 84 ± 31.7 | 71 ± 27 | -0.6 ± 1.5 | 0.281 ± 0.1 | 45 ± 15.1 | 44 ± 14.6 | 46 ± 14.1 |
| **3+ years** | Low MoCA | 22 ± 3.3 | 81 ± 18 | 65 ± 21.9 | -4 ± 4.6 | 0.185 ± 0 | 45 ± 4.6 | 47 ± 4.9 | 51 ± 5.8 |
| | Normal MoCA | 27 ± 0.9 | 99 ± 7.7 | 84 ± 2.8 | -1.2 ± 1.2 | 0.260 ± 0.07 | 49 ± 2.6 | 48 ± 4 | 49 ± 4.2 |

Abbreviations and Definitions: Contralateral eye = eye contralateral to the radiation field, DVP= deep vascular plexus, GCC = ganglion cell complex, FAZ = fovea avascular zone area, HVF, Ipsilateral eye = eye ipsilateral to the radiation field, MoCA = Montreal Cognitive Assessment, , RNFL = retinal nerve fiber layer, RPC = radial peripapillary capillary, SVP = superficial vascular plexus.

## APOE Genotyping

One patient was an *APOE ε4* carrier (*ε3/ε4,* 6%), 2 patients were heterozygous for *ε2/ε3* (13%), and 10 were homozygous for *ε3/ε3* (63%, Fig 1C). Three patients (18%) did not complete genetic testing.

The *APOE ε4* carrier in our study was a 47-year-old female college graduate recruited within 3 years since first diagnosis and radiotherapy. Her MoCA performance indicated severe cognitive impairment at 2 consecutive visits (16 and 15) and was comparatively lower than patients with a *ε2/ε3* (27 ± 2.4) and *ε3/ε3* profile (25 ± 3.4, MCI).

## MoCA Performance vs. Ophthalmic Data

We also compared ophthalmic data between patients with normal (≥26) and low (<26) MoCA scores (Fig 2). Within 1 year from diagnosis, 2 patients had abnormal cognition. Within 1 to 3 years, 3 patients had abnormal cognition, and 6 patients had low MoCA score >3 years after diagnosis. Patients with low MoCA scores 3 years after diagnosis had significantly lower RNFL thickness ($P = 0.002$), GCC thickness ($P = 0.002$), and RPC density ($P = 0.02$) than those with normal MoCA scores, respectively (Figure 2A, B, D). Among patients with low MoCA scores, the average GCC thickness and RPC and SVP densities (Figure 2B, D, E) were significantly lower 3 years after diagnosis than within the first or 1 to 3 years ($P < 0.05$).

## Radiation Dosing Mean/Standard Deviation of Ipsilateral Eye vs. Contralateral Eyes

In patients with frontal or temporal gliomas treated with radiotherapy (n = 12, 75%), we compared the ophthalmic metrics between the eyes ipsilateral and contralateral to the radiation field (Fig S3, available at www.ophthalmologyscience.org). The average radiation dose received by the ipsilateral eye (1748 ± 1185 cGy) was significantly greater than the contralateral eye (1249 ± 735 cGy, $P = 0.02$). The maximal dose to the ipsilateral eye was also significantly greater to the ipsilateral (2801 ± 1666 cGy) than the contralateral eye (2086 ± 1225 cGy, $P = 0.005$). The Pearson correlation test showed a significant negative correlation between GCC thickness and average radiation dose ($r = -0.8$, $P < 0.001$) and the maximum radiation dose received ($r = -0.76$, $P < 0.001$).

The average RNFL thickness in eyes contralateral to radiation field treated within 1.5 years was significantly greater ($P < 0.05$) compared with contralateral eyes of patients treated

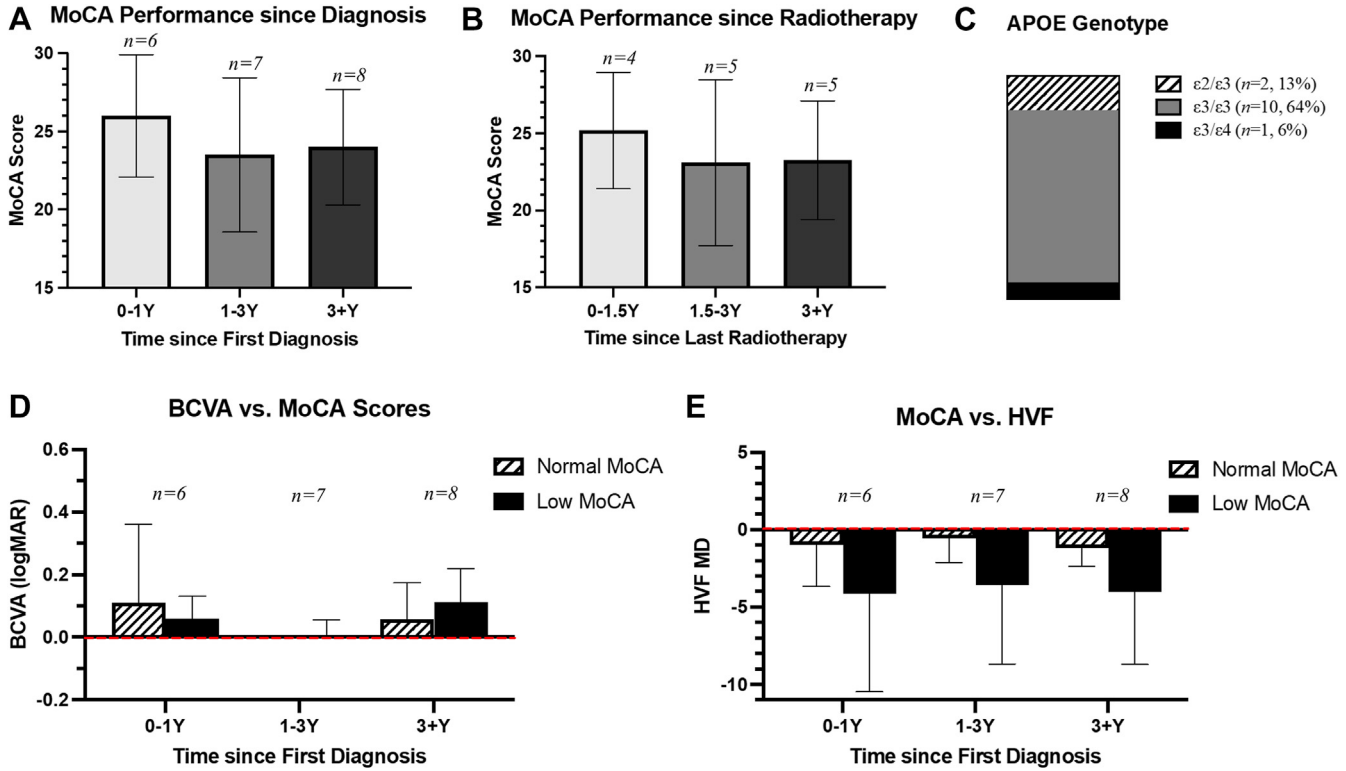


**Figure 1.** Comparison of MoCA performance since diagnosis and radiotherapy (**A** and **B**), *APOE E* genotyping (**C**), and Snellen BCVA measured in logMAR (**D**) and HVF defect (**E**) between patients with normal (MoCA score ≥26/30) and impaired (<26/30) cognition. APOE = apolipoprotein E; BCVA = best-corrected visual activity; HVF MD = Humphrey visual field mean deviation; logMAR = logarithm of minimal angle of resolution; MoCA = Montreal Cognitive Assessment.

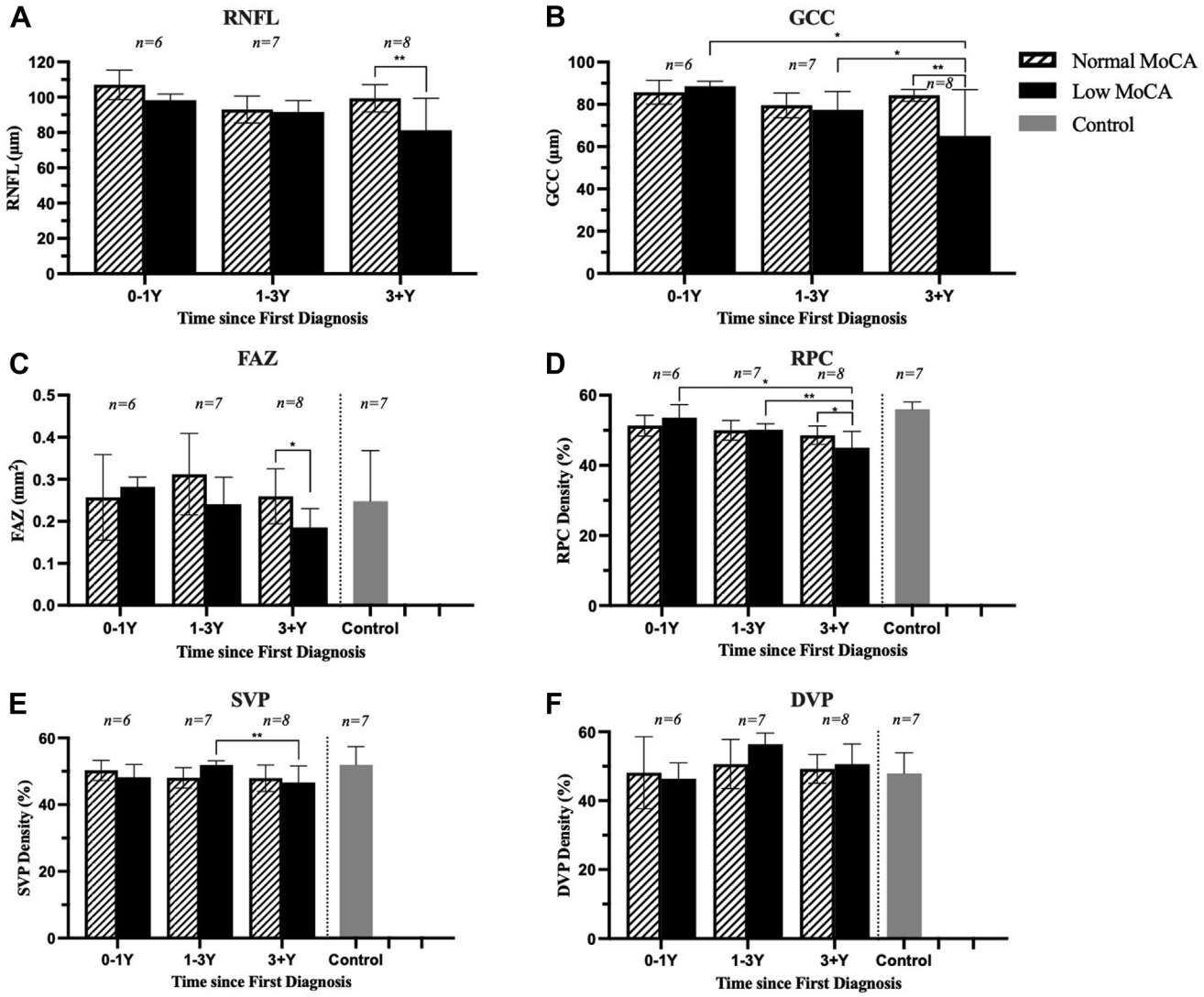


**Figure 2.** Comparison of retinal thickness and microvasculature densities between patients with normal and impaired cognition stratified by time from the first diagnosis to the first eye examination: within 1 year (0−1Y), within 1 to 3 years (1−3Y), and >3 years (3+ Y), including RNFL thickness (**A**), GCC thickness (**B**), FAZ area (**C**), as well as RPC density (**D**), SVP density (**E**), and DVP density (**F**). DVP = deep vascular plexus; FAZ = foveal avascular zone; GCC = ganglion cell complex; MoCA = Montreal Cognitive Assessment; RNFL = retinal nerve fiber layer; RPC = radial peripapillary capillary; SVP = superficial vascular plexus.

within 1.5 to 3 years or after 3 years (Table 2, Fig S3A, available at www.ophthalmologyscience.org). OCT angiography data showed significantly enlarged FAZ in ipsilateral compared with contralateral eyes 3 years after radiotherapy (Table 2, Fig S3C). Radial peripapillary capillary density was significantly reduced in lower-grade glioma eyes, both ipsilateral and contralateral to the radiation field, compared with controls ($P < 0.001$, Table 2, Fig S3D, available at www.ophthalmologyscience.org). Superficial vascular plexus densities were significantly different ($P < 0.001$) between ipsilateral and contralateral eyes (Table 2, Fig S3E, available at www.ophthalmologyscience.org). Among ipsilateral eyes, the SVP density was significantly lower 3 years after radiotherapy than before 3 years ($P < 0.05$). Superficial vascular plexus densities were significantly lower in ipsilateral eyes treated within 1.5 years or after 3 years compared with controls ($P < 0.05$). The deep vascular plexus density was significantly lower ($P = 0.01$) in ipsilateral than contralateral eyes 3 years after radiotherapy (Table 2, Fig S3F, available at www.ophthalmologyscience.org).

### Ophthalmic Changes since Diagnosis

The average logarithm of minimal angle of resolution BCVA (Fig 1D) was $0.06 \pm 0.1$ (equivalent to Snellen acuity 20/23). One patient had abnormal color vision (2/14 using the Ishihara color vision test) due to congenital color blindness. No patients had increased IOP or afferent pupillary defect. The Pearson correlation test showed a significant correlation between RPC density and RNFL ($r = 0.79$, $P < 0.001$) and GCC ($r = 0.66$, $P < 0.0001$) thicknesses.

Since there were no major differences between eyes ipsilateral and contralateral to the radiation field, ophthalmic metrics were averaged between the right and left eyes of each patient for evaluation of ophthalmic changes since diagnosis. OCT data showed abnormal RNFL in 1 patient (7%). The RNFL thickness was significantly greater in the first year of diagnosis compared with 1 to 3 years ($P = 0.02$) and >3 years ($P < 0.001$) after diagnosis (Table 2). Six (38%) patients had GCC thinning. Ganglion cell complex was significantly thinner 3 years after diagnosis than within 1 year ($P < 0.001$). The RPC density was significantly reduced 3 years after diagnosis than within the first year ($P < 0.001$) or 1 to 3 years since diagnosis ($P < 0.001$). Patients with lower-grade glioma also had significantly lower RPC densities compared with control patients at any timepoint since diagnosis (Table 2): within 1 year ($P = 0.04$), 1 to 3 years ($P < 0.001$), and >3 years ($P < 0.001$). The SVP density was significantly lower in lower-grade glioma eyes 3 years after diagnosis compared with controls ($P = 0.003$, Table 2).

### Machine Learning Model Analysis

The mean accuracy of the PLSD models was 77%. The model identified patients with moderate to severe cognitive decline with a precision of 80% and a recall of 73%, while patients with normal MoCA scores (≥26) were identified with a precision of 74% and a recall of 81%.

In terms of feature loadings in the PLSD model, the first component placed higher weight on the BCVA and months since the first diagnosis, indicating that these features significantly contribute to the model's predictive capacity (Fig S4A and B, available at www.ophthalmologyscience.org). The second component emphasized the influence of oligodendrogliomas, FAZ, and minimally on RNFL.

## Discussion

In this preliminary study, we conducted a comprehensive evaluation of cognitive performance in relation to ophthalmic changes, genetics, diagnosis, and treatment in patients with lower-grade glioma and brought to light evidence of radiation-associated retinopathy. We identified retinal microstructural and microvascular changes in patients with lower-grade gliomas after treatment and identified markers associated with TACD. Additionally, a machine learning algorithm highlighted several ophthalmic metrics associated with cognitive status in these patients.

Our study sheds light on the sequelae of lower-grade glioma treatment on ophthalmic and neurocognitive changes. Radiotherapy is thought to be the main contributor to neurocognitive decline in patients with lower-grade glioma,[16,46–48] especially with whole brain irradiation[49] or higher fractional doses of radiation.[47] The pathophysiology of radiotherapy-induced CNS changes is not entirely understood but is hypothesized to involve multiple mechanisms, including white matter demyelination, free-radical oxidative injury,[50] vascular injury,[51,52] and ischemia[53] leading to impaired neuronal function and neurogenesis.[51,54] Concurrent chemotherapy may further act as a radiosensitizer and synergistically induce CNS damage.[55]

We suggest that patients with temporal lobe tumors may have greater susceptibility to developing TACD. The proximity of the tumor and treatment to the language centers likely explains the widespread dysfunction in the language domain.[56] The disruption of hippocampal neurogenesis following radiation and chemotherapy[57–59] may explain extensive short-term memory impairment and significantly lower cognitive performance in patients with temporal compared with frontal lobe tumors. In this small cohort, patients with oligodendrogliomas had significantly worse cognitive function. Patients with oligodendroglioma pathology may benefit from the newly available molecularly targeted therapies. Vorasidenib, an isocitrate dehydrogenase 1 and 2 inhibitor, showed a significantly improved progression-free survival[60] and can be evaluated as an alternative to radiotherapy, especially in younger patients or those with greater baseline TACD risk to preserve cognitive function and quality of life.

The PLSD model identified patient with low versus normal MoCA performance with a 77% accuracy. Random Forest identified a conjuncture of importance features, including pathology (oligodendroglioma), RNFL thickness, time since diagnosis, IOP, FAZ area, and BCVA (Fig S4A, S2B, available at www.ophthalmologyscience.org). Clearly, the visual

function parameters were more influential in classifying the MoCA scores. The weights from PLSD indicate the contribution of each feature in explaining the maximal covariance between the dependent variable (MoCA score) and the independent variables (eye or tumor markers). While these individual markers alone were not well correlated with MoCA performance, the model reflects the combined contribution of these features and could better explain the variability in MoCA better than a single eye marker alone (Fig S4C, available at www.ophthalmologyscience.org).

Our observations also highlight the importance of comprehensive neuro-ophthalmologic screening for patients with lower-grade gliomas. Several OCT angiography studies demonstrated early microvascular changes after radiotherapy[61–63] that become more apparent several years after treatment.[16,55] Patients with low MoCA performance exhibited significant retinal changes, particularly 3 years after radiotherapy. Patients had significant RPC density loss compared with control eyes, which preceded changes in our retinal structures. Radial peripapillary capillary density was proposed as a possible biomarker of MCI;[64] however, we did not find it a standalone marker to serve as a proxy of TACD. Early detection of RPC changes may be due to the capillaries running in parallel with RNFL axons[63] and primarily supplying the RNFL.[65] This may explain the significant positive association between RPC density with RNFL and GCC thicknesses seen in our cohort and other studies.[66,67] Sequential RPC loss followed by RNFL thinning likely occurs secondary to radiation-induced ischemia of RPC plexus.[68] Notably, these changes were present in both eyes, regardless of the maximum radiation exposure to the eye. These findings suggest that the RPC network may be more sensitive to radiation-induced damage. Additionally, the disruption in retinal architecture may be more profound in patients with TACD. Our patients had normal visual acuity despite retinal abnormalities. These findings may have been missed without close follow-up. Thus, we recommend early serial neuro-ophthalmic evaluations in future studies to establish an accurate baseline for comparison of the progression of ophthalmic changes to detect early signs of retinal disruption.

*Apolipoprotein ε4* polymorphism emerged as a potential risk factor for TACD in patients with brain tumor.[22] Montreal Cognitive Assessment scores of the *APOE ε4* carrier indicated severe cognitive impairment; however, we were unable to evaluate the association between TACD and *APOE* genotype due to only one patient being an *APOE ε4* carrier in our study. Anecdotally, her MOCA scores indicated severe cognitive impairment 3 years after treatment. Her frontal oligodendroglioma was treated with concurrent radiotherapy and adjuvant chemotherapy; therefore, radio-sensitization could have further exacerbated TACD. A larger study is warranted to further explore this potential association.

The limitations of our study include a small cohort, rendering regression analysis unsuitable. Our findings regarding TACD susceptibility in patients with frontal versus temporal tumors and oligodendrogliomas versus astrocytomas should be interpreted with caution due to the small number of patients and heterogeneity of the cohort. Only 1 patient was a carrier of *APOE ε4* polymorphism, rendering comparison of cognitive outcomes in relation to the *APOE* genotype unsuitable. A long median time from diagnosis/radiation to the first examination (>30 months) restricted our capacity to measure the baseline ophthalmic and cognitive function and detect early retinal changes that could potentially be early signs of TACD. Patients also had different treatment regimens, which may account for some variability in our findings. The next steps entail data collection in a larger cohort over a 5-year follow-up span and conducting time-related regression analysis. Additionally, a larger study with early and serial neuro-ophthalmic examinations and a consistent treatment regimen is recommended in future investigations.

In conclusion, this study demonstrates that patients with lower-grade gliomas, particularly those with temporal tumors and oligodendrogliomas, undergoing early aggressive chemoradiation may be at greater risk of developing TACD, assessable by bedside MoCA screening. Retinal structural and microvascular density changes may serve as potential surrogate markers for cognitive changes and aid in diagnosing TACD. The feature importance of several ophthalmic and clinical metrics warrants exploration of predictive modeling for TACD in patients with glioma in larger cohorts. A larger study is warranted to further examine the role of *APOE* ε4 in TACD and inform the management of patients with lower-grade glioma, especially those with gross total resection.

## Acknowledgments

The authors would like to thank Dr Robert O'Donnell and Dr Jui-Kai Wang for their critical review of this manuscript.

## Footnotes and Disclosures

Originally received: May 8, 2024.
Final revision: July 10, 2024.
Accepted: July 10, 2024.
Available online: July 25, 2024. Manuscript no. XOPS-D-24-00145.

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Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The authors have made the following disclosures:

M.E.D.: Consultant – AstraZeneca Pharmaceuticals LP, Novocure Inc. Genentech, Inc.

G.Y.: Consultant − Abbvie, Adverum, Alimera, Bausch & Lomb, Clearside, Endogena, Genentech, Gyroscope, Intergalactic, Iridex, Janssen, Myro, NGM Bio, Novartis, Regeneron, Thea, Topcon, Zeiss.

Y.A.L.: Consultant − Myrobalan, Argenx

Y.A.L. was supported in part by a UC Davis Cancer Research Career Development Award Dean's Scholarship. The sponsor or funding organization had no role in the design or conduct of this research.

O. Aboud, Merck Sharp & Dohme LLC, Exelixis Inc.

HUMAN SUBJECTS: Human subjects were included in this study. The study was conducted in accordance with the Declaration of Helsinki. The Institutional Review Board approved the study protocol at the University of California, Davis. All participants signed an informed consent before enrollment.

No animal subjects were included in this study.

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Obtained funding: Liu

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Abbreviations and Acronyms:
**AD** = Alzheimer's disease; **APOE** = apolipoprotein E; **BCVA** = best-corrected visual acuity; **CNS** = central nervous system; **FAZ** = fovea avascular zone area; **GCC** = ganglion cell complex; **IOP** = intraocular pressure; **MCI** = mild cognitive impairment; **MoCA** = Montreal Cognitive Assessment; **PLSD** = Partial least-squares discriminant; **RNFL** = retinal nerve fiber layer; **RPC** = radial peripapillary capillary; **SVP** = superficial vascular plexus; **TACD** = treatment-associated cognitive dysfunction.

Keywords:
Apolipoprotein E, Lower-grade glioma, Ophthalmic markers, Retinal changes, Treatment-associated cognitive dysfunction.

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