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RESEARCH ARTICLE

# Treatment of isolated pediatric optic nerve glioma: A nationwide retrospective cohort study and systematic literature review on visual and radiological outcome

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## Abstract

**Background:** Progressive isolated optic nerve glioma (ONG) in children is a rare disease, treated with various modalities. A global treatment consensus is not available.

**Methods:** We conducted a national retrospective multicenter cohort study (1995–2020) to investigate how different treatment strategies impact outcome for ONG in children, by assessing treatment responses to systemic anticancer therapy (SAT), surgery, and radiotherapy for ONG. The primary endpoints included changes in best-corrected visual acuity (BCVA) and tumor volume (TV) on MRI, both evaluated at the start and end of therapy and at long-term follow up.

**Results:** A total of 21 ONGs (20 patients) received SAT ($n = 14$ (66.7%)), surgery ($n = 4$ (19.0%)), and radiotherapy ($n = 3$ (14.3%)). After SAT BCVA stabilized or improved in 66.6% ($n = 4$) and the TV decreased by a median of 45.1% (range: −88.6% to

**Abbreviations:** BCVA, best-corrected visual acuity; DCOG, Dutch Childhood Oncology Group; JBI, Johanna Briggs Institute; LogMAR, logarithm of the minimum angle of resolution; MDC, modified dodge classification; NF1, neurofibromatosis type 1; ONG, isolated optic nerve glioma; OPG, optic pathway glioma; RT, radiotherapy; SAT, systemic anticancer therapy; TV, tumor volume; VF, visual field; VI, visual impairment.

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+31.5%) ($n = 13$). Before resection two eyes were already blind. After resection BCVA decreased to blindness in one eye. In total all four eyes were blind after resection. After first-line RT BCVA decreased in 66.7% of ONG to counting fingers or less, TV increased <3 months after RT by a median of 47.3% (range: −42.8% to +245.1%) ($n = 3$), followed by a long-term decrease of 94.4 and 13.8% ($n = 2$), respectively.

**Conclusion:** SAT appears to be the preferred modality for progressive ONG in case of potential rescue of visual functions. Complete resection of ONG appears effective to reduce proptosis in case of preexisting blindness. The use of radiotherapy requires careful consideration due to the risk of severe visual impairment and secondary disease.

**KEYWORDS**
children, low grade glioma, MRI, optic nerve glioma, response assessment, visual function

## 1 | INTRODUCTION

Pediatric isolated optic nerve glioma (ONG) is a subset of low grade glioma (mostly pilocytic astrocytoma, World Health Organization criteria grade 1[1,2]) confined solely to the optic nerve with no involvement of the chiasm or optic tract. This tumor is considered a rare disease, accounting for nearly 3% of orbital tumors.[3] Isolated ONG represents approximately 20–25% of the total spectrum of optic pathway glioma (OPG).[4,5] In cases associated with neurofibromatosis type 1 (NF1), the majority of ONGs remain clinically and radiologically stable and do not require treatment.[6] Patients, both with NF1 associated ONG and sporadic ONG, commonly present with symptoms like proptosis, visual decline, and/or strabismus. Unlike the posterior located OPG, ONGs are not associated with endocrine and systemic neurologic disorders.

Prior to the introduction of chemotherapy (hereafter represented by: systemic anticancer therapy (SAT)) for OPG,[7] progressive ONG was typically managed through resection or radiotherapy. Complete resection of ONG has been considered effective to alleviate painful proptosis only in eyes with no remaining visual function[4] as the risk of blindness is significant following resection or even after biopsy alone.[8] Numerous studies conducted before 1990 have explored the effects of surgery and radiotherapy on ONG. Nevertheless, these studies are often biased due to the inclusion of chiasmal OPGs and are limited in their ability to provide detailed analyses of visual outcome and tumor volume (TV) dynamics due to the lack of MRI availability.[4] Currently, there is no global consensus regarding the optimal therapeutic strategy for ONG.

Currently, SAT, represented by chemotherapy, is considered the initial treatment choice for progressive OPG with no neurological progression. Approximately, 45–66% of OPG require successive therapy due to progression[9,10] and a decrease of monocular best-corrected visual acuity (BCVA) of 6–21% and binocular BCVA of 9–31%[11] is reported after first-line SAT.

In this study, we conducted both a systematic literature review and a national retrospective cohort study to assess treatment response of pediatric ONG, including short and long-term evaluation of visual function and radiological response.

## 2 | MATERIALS AND METHODS

### 2.1 | Literature search

A literature search was conducted in OVID MEDLINE by use of PubMed interface (January 1970–August 2024). The primary outcomes of interest in treatment of pediatric ONG were: (1) change in monocular visual function and/or (2) change in TV as assessed by MRI. Treatment response was evaluated for first-line SAT, surgery, and radiotherapy. Assessment of the risk of bias was performed using the critical appraisal tool "Checklist for Case Series" of the Johanna Briggs Institute (JBI).[12]

### 2.2 | Study design of the cohort study

This nationwide retrospective study was conducted across all eight university medical centers in the Netherlands. The study selected all patients (0–18 years) with an isolated ONG, diagnosed between January 1995 and December 2018, with a follow up until December 2020. Patients that had received treatment following clinical or radiological progression of the ONG were included in this study.

The study received approval from the Dutch Childhood Oncology Group (DCOG). Ethical committees of all participating centers granted permission for the collection of coded data. Informed consent was obtained from patients and/or parents or legal guardians registered with the DCOG and/or at the Princess Máxima Center.

## 2.3 | Data collection

Clinical data were extracted from medical records, including age at diagnosis, gender, NF1 status, clinical presentation, type of treatment, BCVA, and pathology results. ONG was defined as a progressive ONG, when treatment was initiated because of clinical or radiological progression. Treatment indication and the choice of therapy was determined by the local responsible treatment team. The ONGs that required additional treatment after initial therapy were excluded from analysis of visual function and TV at the end of follow up. However, the course of TV and BCVA after successive therapy is available (Supporting Information, File S3).

## 2.4 | Objectives

The primary objectives of this study were: (1) to evaluate the response of monocular visual function and (2) to evaluate the course of TV following various first-line treatment strategies (surgery, SAT, and radiotherapy). Changes in both parameters were evaluated between the start and end of first-line therapy, as well as between the end of therapy and end of follow up.

## 2.5 | Visual function

Monocular BCVA and visual field (VF) tests were collected when performed within 3 months prior to the start of therapy, within 3 months after the end of therapy and at the end of follow up. BCVA was registered from age-appropriate testing methods (Teller Acuity Cards, Cardiff Acuity Test, Kays Pictures, and Snellen charts)[2] and subsequently converted to the logarithm of the minimum angle of resolution (LogMAR) for statistical purposes. Visual acuity values representing *counting fingers*, *hand motion*, *light perception*, and *no light perception* were converted to 2.0, 2.4, 2.7, and 3.0 LogMAR.[13] Changes in BCVA were categorized as improved (decrease of ≥0.2 LogMAR), stable (change within 0.2 LogMAR), or decreased (increase of ≥0.2 LogMAR).[11] The prevalence of severe monocular visual impairment (VI) and blindness was scored at the end of follow up using the WHO[14] (BCVA < 0.1 decimal or >1.0 LogMAR). VF data were evaluated by two experienced ophthalmologists (C. A. B. and G. L. P.) following a predefined protocol.[15]

## 2.6 | Radiological evaluation

Radiological analysis was independently conducted by two experienced neuroradiologists (E. A. B. and P. d. G.). The anatomic location of the ONG was classified according to the modified Dodge classification (MDC), which includes stage 1A (a single optic nerve), stage 1B (bilateral optic nerve), and/or 1C (cisternal segment optic nerve).[16] Response assessment was performed by calculation of the product of the largest three perpendicular measurements on T2-weighted, STIR, or contrast-enhanced fat-suppressed T1-weighted MR images, represented by TV in this article. This product was multiplied by a corrective factor of 0.52[17] to correct for the tubular shape of the ONG within the orbit.

## 2.7 | Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (v.28.0.1.1). Descriptive statistics were used to analyze the data. Categorical data were presented as count and percentage. The distribution of the continuous data was tested for normality. Continuous data were presented as either mean and standard deviation or median and range. The Mann–Whitney *U* test was applied for comparison of continuous non-normally distributed data of two subgroups. The chi-squared test was used for categorical data. A $p$ value of <.05 was considered statistically significant.

To quantify the interrater reliability of the TV, an intraclass correlation coefficient (ICC) was calculated by use of a two-way mixed-effects model with absolute agreement: ICC scores below 0.5 were indicative of a poor reliability, scores ranging from 0.5 to 0.75 indicated moderate reliability, scores from 0.75 to 0.90 indicated good reliability, and scores above 0.9 indicated excellent reliability.[18]

# 3 | RESULTS

## 3.1 | Literature review

The literature search resulted in 332 articles. After evaluation of abstracts and full texts, two articles met the inclusion criteria.[2,19] The complete literature search is provided in Supporting Information, File S1.

These two included studies contained a total of 17 ONG that received a single treatment modality with available data on the trajectory of visual function represented by BCVA at the start, after the end of treatment for ONG or at the end of follow up. Data on TV response evaluation were available in one study[2] according to the response assessment in neuro-oncology criteria.[20] An overview of the characteristics of the studies and patient is presented in Table 1. Based on the JBI critical appraisal the study was considered to have a low risk of bias,[2] while the other study had an uncertain risk of bias.[19]

## 3.2 | Cohort study

Within the period of inclusion 61 patients were diagnosed with an ONG, 41 patients (67.2%) did not receive treatment (NF1 ($n = 36$)/sporadic ($n = 5$)). In total, 21 ONGs of 20 patients met the inclusion criteria. One ONG was excluded from analysis: this ONG (left orbit) was part of a bilateral ONG, that progressed after 1st line SAT. Radiological

**TABLE 1** Study and patient characteristics of the literature review.

| Authors (year) | Tow et al. (2002)[19] | | | Hamideh et al. (2018)[2] | |
|---|---|---|---|---|---|
| Country | USA | | | USA | |
| Period data collection | NA | | | 1985–2015 | |
| Study design | Retrospective, monocenter | | | Retrospective, monocenter | |
| Pt: NF1/sporadic OPG: *n* | 2/6 | | | 5/4 | |
| Histology: *n* (%) | Grade 1 astrocytoma: 7 (36.8)[a] | | | Pilocytic astrocytoma: 3 (100.0) | |
| ONG (*n*): BCVA available | 10 | | | 11 | |
| Age at diagnosis (years): median (range) | 8.5 (3.0–20.0)[b] | | | 4.0 (1.0–16.0) | |
| Follow up (years): median (range) | 14.0 (10.0–24.0) | | | 6.0 (2.0–17.0) | |
| **Type of TX: *n* (ONG)** | **SX: 5** | **RT: 4[c,d]** | **SX →RT: 1** | **SAT: 8** | **SAT +/− RT → SX: 3** |
| Radiological response analysis | NA | NA | NA | SD: 6<br>RD: 2 | NED: 2 |
| BCVA start of therapy (LogMAR): median (range) | 1.0 (0.1–2.4) | 1.3 (1.0–1.5) | 1.0 | 0.8 (0.1–2.7) | 0.7 |
| BCVA end of FU (LogMAR): median (range) | 3.0 (3.0–3.0) | 3.0 (0.1–3.0) | 3.0 | 0.0 (−0.1 to 3.0) | 3.0 |
| BCVA improved (≥0.2 LogMAR): *n* (%) | 0 (0) | 1 (25.0) | 0 (0) | 5 (62.5) | 0 (0) |
| BCVA stable (<> 0.2 LogMAR): *n* (%) | 0 (0) | 0 (0) | 0 (0) | 1 (12.5) | 0 (0) |
| BCVA decreased (≥ 0.2 LogMAR): *n* (%) | 5 (100.0) | 3 (75.0) | 1 (100.0) | 2 (25.0) | 2 (100.0) |
| Severe VI/blindness end of FU: *n* (%) | 5 (100.0) | 4 (100.0) | 1 (100.0) | 2 (25.0) | 3 (100.0) |
| Progression: *n* (%) | 1 (20) | – | – | 2 (25.0) | 2 (100.0) |

Abbreviations: BCVA, best-corrected visual acuity; FU, follow up; LogMAR, logarithm of the minimum angle of resolution; NA, not available; NED, no evidence of disease; NF1, neurofibromatosis type 1; ONG, optic nerve glioma; Pt, patients; RD, regressive disease; RT, radiotherapy; SAT, systemic anticancer treatment; SD, stable disease; SX, surgery; VI, visual impairment; →, successive treatment after progression.

[a]Data were obtained from seven of 19 ONG (total study cohort); no data were available on the subgroup that received treatment ($n = 10$).

[b]One patient was >18 years old.

[c]One patient had a bilateral ONG, both sites received RT. Monocular analysis of BCVA at diagnosis showed 1.5 LogMAR and 3.0 LogMAR in each eye at the last follow up.

[d]The range of cumulative doses of RT: 45.0–54.0 Gray.

data were lacking at the start of SAT2. The ONG in the right orbit was included in the cohort analysis (Supporting Information, File S2: pt 12).

## 3.3 | Baseline characteristics

Ten patients (50.0%) had NF1. One patient (5.0%) (NF1) presented with a bilateral ONG. None of the patients experienced endocrine dysfunction. The baseline characteristics of the study cohort are summarized in Table 2.

The indication for the start of treatment, as defined in individual patient files, was: a progressive decrease of BCVA compared with age-based norms in 28.6%, isolated proptosis in 23.8%, a combined decrease of BCVA and proptosis in 28.6%, a combined decrease of BCVA and radiological progression 14.3% and isolated radiological progression in 4.8% of ONGs.

Patients started therapy at a median age of 7.2 years (range: 1.9–17.9 years). Patients with NF1 started treatment at a younger age than patients with a sporadic ONG (4.6 years [range: 1.9–13.0 years] and 10.9 years [range: 3.5–17.9 years]); Mann–Whitney *U*: $p = .020$). No significant differences were observed in clinical presentation and ocular examination between NF1 and sporadic ONGs.

## 3.4 | Treatment

Fourteen ONGs (66.7%) received first-line SAT (vincristine and carboplatin) for a median period of 15.5 months (range: 2.0–22.1 months).

**TABLE 2** Baseline characteristics of 20 patients with 21 isolated optic nerve gliomas.

| | All ONG[a] | SAT | SX | RT |
|---|---|---|---|---|
| Number of ONGs: *n* (%) | 21 (100.0) | 14 (66.7) | 4 (19.0) | 3 (14.3) |
| Male: *n* (%) | 8 (40.0) | 5 (37.5) | 3 (62.5) | 0 (0) |
| NF1: *n* (%) | 11 (52.4) | 9 (64.3) | 2 (50.0) | 0 (0) |
| Eye examination at diagnosis (per ONG): *n* (%) | | | | |
| Strabismus | 8 (38.1) | 4 (28.6) | 3 (75.0) | 1 (33.3) |
| Optic nerve atrophy | 5 (23.8) | 3 (21.4) | 1 (25.0) | 1 (33.3) |
| Papilledema/infiltration | 10 (47.6) | 7 (50.0) | 1 (25.0) | 2 (66.7) |
| Anatomic location (MDC stage): *n* (%) | | | | |
| MDC: 1a | 12 (57.1) | 6 (42.9) | 3 (75.0) | 3 (100) |
| MDC: 1a + 1c | 9 (42.9) | 8 (57.1) | 1 (25.0) | 0 (0) |
| Right optic nerve involved | 12 (57.1) | 10 (71.4) | 2 (50.0) | 0 (0) |
| MRI features at start of TX ($n = 19$): *n* (%) | | | | |
| T1-CE: | | | | |
| Homogenous | 11 (57.9) | | | |
| Heterogeneous | 8 (42.1) | | | |
| T2-FLAIR: | | | | |
| Hyperintensity | 19 (100.0) | | | |
| Pathology: *n* (%) | | | | |
| Pilocytic astrocytoma | 6 (28.6) | 1 (7.1) | 4 (100) | 1 (33.3) |
| Therapy: median (range) | | | | |
| Age at start of therapy (years) | 7.2 (1.9–17.9) | 6.2 (1.9–14.2) | 6.0 (3.5–13.0) | 11.1 (7.7–17.9) |
| Interval diagnosis–start therapy (months) | 2.9 (0.0–39.0) | 2.0 (0.0–39.0) | 4.0 (2.0–7.0) | 4.0 (2.9–9.0) |
| Time of follow up (years) | 10.7 (2.3–18.4) | 10.2 (2.3–18.4) | 12.0 (5.0–18.4) | 15.8 (8.0–16.2) |
| Deceased | 1 (4.8) | 1 (7.1) | 0 (0) | 0 (0) |

Abbreviations: BCVA, best-corrected visual acuity; CE, contrast enhancement; MDC, modified Dodge classification (stage 1A (a single optic nerve), stage 1B (bilateral optic nerve), and/or 1C (cisternal segment optic nerve)); NF1, neurofibromatosis type 1; ONG, optic nerve glioma; RT, radiotherapy; SAT, systemic anticancer therapy; SX, surgery; TX, therapy.

[a]One patient had a bilateral ONG. At diagnosis, the patient presented with left side blindness and proptosis, the left ONG was resected. The right ONG was present at diagnosis; the age-appropriate BCVA was normal. After 2.9 years, the right ONG showed radiological progression with no clinical abnormalities: SAT was initiated.

Three ONGs (21.4%) progressed at median 2.1 years (range: 1.3–2.8 years) after cessation of SAT. One patient (with NF1) died 3 months after the start of 3rd line SAT as a result of gliomatosis cerebri. Four ONGs (19.0%) underwent first-line surgery achieving complete resection, no subsequent progression appeared. Three sporadic ONGs (14.2%) received first-line radiotherapy at the age of 13.4 years (range (8.1–17.9 years) with a cumulative dose of 52.2 Gray (range 52.2–54.0 Gray); one ONG progressed 9.5 years after the start of RT. In all cases of progression, the chiasm was not involved. The flowchart of all therapy sequences is presented in Figure 1.

## 3.5 | Radiological response analysis: interrater reliability

In total, the calculation of TV was performed in 53 MRI scans. The median volumes calculated per radiologist were 962.5 $mm^3$ (range: 4.9–19,008.0 $mm^3$) and 949.1 $mm^3$ (range: 59.6–17,037.8 $mm^3$). The interrater reliability analysis yielded an excellent ICC of 0.96 (95% CI: 0.94–0.98) for TV measurements.[18]

## 3.6 | Visual function and TV: early treatment evaluation and long-term follow up

Data of VF was available in only five patients at the end of follow up (no abnormalities [$n = 2$], cecocentral scotoma [$n = 1$], quadrant anopia [$n = 1$], and temporal remnant (60 × 30 degrees) [$n = 1$]). Data on color vision, contrast sensitivity, VEP and OCT were absent in >85%. Therefore, hereafter we report solely on (change of) BCVA as representative of visual function. Two ONGs were excluded from radiological response assessment due to the lack of available MRI data. At the start of therapy, none of the ONGs showed any cystic component within or attached to the solid tumor mass. Cumulative data on the course of

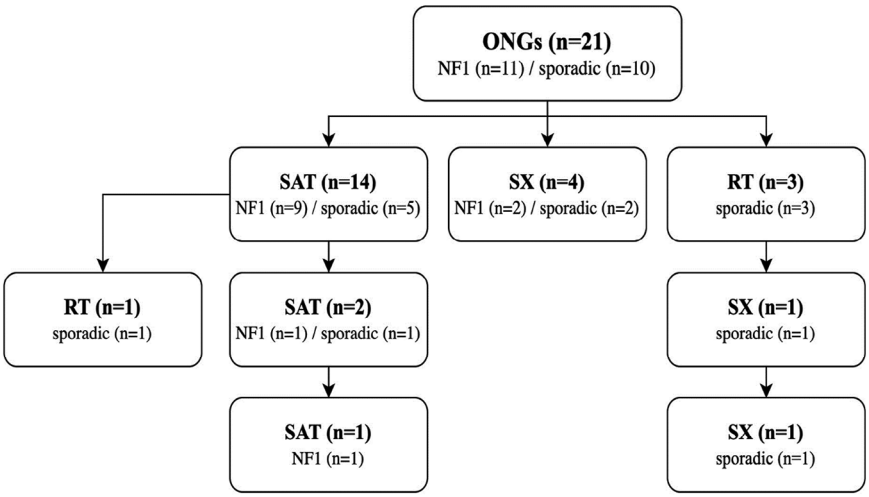


**FIGURE 1** Flowchart of the variety in treatment lines of 21 isolated pediatric optic nerve gliomas. NF1, neurofibromatosis type 1; ONG, isolated optic nerve glioma; RT, radiotherapy; SAT, systemic anticancer therapy; SX, surgery.

BCVA and TV is presented in Table 3. Individual data on BCVA, VF, and TV after first line therapy are available in Supporting Information, File S2. Individual data of the ONGs that received successive therapy are available in Supporting Information, File S3. A comparison of NF1 associated and sporadic ONG is available in Supporting Information, File S4. Supporting Information, File S5 contains MRI images illustrating the course of TV following SAT and RT in two patients.

At the start of all therapy BCVA ranged from 0.0 to 3.0 LogMAR ($n = 14$). Four affected eyes (28.6%) had severe VI or were blind.[14] At the start of therapy BCVA did not differ between NF1 ($n = 6$) and sporadic ONG ($n = 8$) ($p = .36$), nor did TV (NF1: $n = 9$/sporadic: $n = 10$, $p = .12$). At the end of follow up severe VI or blindness was present in 82.4% ($n = 14$) of ONGs that received first-line therapy only and in 71.4% of the total cohort.

After SAT, BCVA improved or stabilized in four ONGs (66.6%). The TV exhibited a median decrease of 45.1% (range: −88.6% to +31.5%) after SAT ($n = 13$), representing a partial response in 46.1%, a minor response in 23.1%, stable disease in 23.1%, and progressive disease in 7.7% according to the current radiological response assessment criteria for low grade glioma (RAPNO).[21] Between the end of SAT and the end of follow up, TV decreased further by a median of 21.5% (range: −58.9%/+120.9%) ($n = 10$). No significant differences in change of TV were observed between NF1 and sporadic ONGs within the period from start to end of SAT (Mann–Whitney $U$: $p = .35$). Analysis on correlation between the change of TV and change of BCVA could not be performed due to the low number of ONG with available data ($n = 6$). The course of the TV of ONGs that received SAT or RT is presented in Figure 2.

Before resection was performed, two of the four affected eyes (75.0%) were already blind, one eye (25.0%) ended blind after complete resection. All ONGs were completely resected. No information was available of the surgical approach of the ONG. The median TV of the ONGs that were resected, was larger compared with the ONG that received SAT (7537.2 $mm^3$ [range: 4370.7–18,022.9 $mm^3$) and 1465.6 $mm^3$ (range: 153.2–8345.9 $mm^3$) ($p = .03$).

The ONGs that received RT had a median BCVA of 0.3 LogMAR (range: 0.0–3.0 LogMAR) ($n = 3$) at the start of RT. After RT, BCVA deteriorated to median 1.0 LogMAR (range: 0.0–3.0 LogMAR). By the end of FU, BCVA had further deteriorated to 2.4 and 2.7 LogMAR in the ONGs that had not progressed ($n = 2$). The medical records did not reveal specific information on the cause of this decline. After the end of therapy, TV increased with median 47.3% (range: −42.8% to +245.1%) ($n = 3$). Two ONGs did not progress ($n = 2$) after RT, they showed an additional decrease of volume of 94.4 and 13.8% at the end of follow up. No secondary tumors developed.

## 4 | DISCUSSION

This nationwide retrospective cohort study revealed that, within the population of children with an isolated pediatric ONG, one in three patients ($n = 21$ ONGs) had received various treatments. At the start of treatment severe VI or blindness was present in more than one in three ONGs and in four out of five of ONGs at long-term follow up. Only after the use of SAT, represented by chemotherapy, BCVA resulted in stabilization or improvement in two out of three ONGs, combined with a median decrease of TV of more than 40%. After complete resection BCVA decreased to blindness in one of three ONG. After RT BCVA reduced to a severely visual impaired level of BCVA in all eyes, TV showed a temporary vast increase after RT, followed by a long-term decrease.

Previously, Hamideh et al.[2] reported stabilization or improvement of BCVA after cessation SAT in 75.0% of ONG ($n = 6$), the TV remained stable (within ±25% of change, $n = 6$) or regressed (>25% [$n = 2$]). Three eyes had light perception at the start of therapy, two eyes were blind at long term follow up, one eye improved to 20/400 (a nonquantitative representation of visual acuity measurements). Fisher et al.[22] reported improvement or stability of BCVA in 78.6% ($n = 11$) of patients within 3 months after cessation of SAT. Falzon et al.[23] reported long-term improvement or stability of BCVA after SAT in 55.6% of patients ($n = 5$). In both studies, no data were available on change in BCVA solely of the affected eye. In all studies, SAT was represented by chemotherapy.

In our cohort, BCVA remained stable or improved in four ONGs (66.7%). The report on the individual course of BCVA and TV (Sup-

**TABLE 3** Course of monocular BCVA and tumor volume after first-line treatment for 21 isolated optic nerve glioma.

| | All treated ONG | SAT | SX | RT |
|---|---|---|---|---|
| ONG (*N*) | 21 | 14 | 4 | 3 |
| BCVA: start 1th line TX: *n* | 14 | 8 | 3 | 3 |
| Median (range) | 0.5 (0.0–3.0) | 0.3 (0.0–3.0) | 3.0 (0.6–3.0) | 0.3 (0.0–1.7) |
| BCVA: end 1th line TX: *n* | 13 | 9 | 1 | 3 |
| Median (range) | 1.3 (0.0–3.0) | 1.0 (0.0–3.0) | 3.0 (–) | 1.7 (1.3–3.0) |
| BCVA: end FU: *n*[a] | 17 | 11 | 4 | 2 |
| Median (range) | 2.7 (0.0–3.0) | 1.7 (0.0–3.0) | 3.0 (3.0–3.0) | 2.6 (2.4–2.7) |
| Change of BCVA: start TX-end 1th line TX: *n* | 10 | 6 | 1 | 3 |
| Improved (≤0.2 LogMAR): *n* (%) | 2 (20.0) | 2 (33.3) | – | 0 (0.0) |
| Stable (within 0.2 LogMAR): *n* (%) | 4 (40.0) | 2 (33.3) | 1 | 1 (33.3) |
| Decreased (≥0.2 LogMAR): *n* (%) | 4 (40.0) | 2 (33.3) | – | 2 (66.7) |
| Change of BCVA: end 1th line TX-end FU: *n*[a] | 9 | 6 | 1 | 2 |
| Median (range) | 0.0 (0.0–1.1) | 0.0 (0.0–0.3) | 0.0 (–) | 1.9 (1.1–2.7) |
| Improved (≤0.2 LogMAR): *n* (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Stable (within 0.2 LogMAR): *n* (%) | 7 (77.8) | 5 (83.3) | 1 (100.0) | 1 (50.0) |
| Decreased (≥0.2 LogMAR): *n* (%) | 2 (22.2) | 1 (16.7) | 0 (0.0) | 1 (50.0) |
| VI (WHO categories) end FU: *n*[a] | 17 | 11 | 4 | 2 |
| No- mild VI (≤0.5 LogMAR): *n* (%) | 3 (17.6) | 3 (27.3) | – | – |
| Moderate VI (>0.5 ≤ 1.0 LogMAR) | – | – | – | – |
| Severe visual impairment (>1.0 ≤ 1.3 LogMAR): *n* (%) | 1 (5.9) | 1 (9.1) | – | – |
| Blindness (>1.3 LogMAR): *n* (%) | 13 (76.5) | 7 (63.6) | 4 (100.0) | 2 (100.0) |
| TV: start TX: $cm^3$: *n* | 19[b] | 13 | 3 | 3 |
| Median (range) | 1.48 (0.15–1.80) | 1.47 (0.15–8.35) | 7.54 (4.37–1.80) | 1.05 (0.63–2.07) |
| TV: end TX: $cm^3$: *n* | 19 | 13 | 3 | 3 |
| Median (range) | 0.47 (0.0–8.86) | 0.65 (0.07–8.86) | 0.0 | 1.55 (0.36–7.14) |
| TV: end FU: $cm^3$: *n*[a] | 15 | 10 | 3 | 2 |
| Median (range) | 0.31 (0.0–5.82) | 0.43 (0.03–5.82) | 0.0 | 0.20 (0.09–0.31) |
| Change TV: start- end TX: %; *n* | 19 | 13 | 3 | 3 |
| Median (range) | −45.1 (−100.0/+245.1) | −45.1 (−88.6/+31.5) | −100.0 | 47.3 (−42.8/+245.1) |
| Change TV: end TX-end FU: %; *n*[a] | 15 | 10 | 3 | 2 |
| Median (range) | −13.8 (−94.4/+120.9) | −21.4 (−58.9/+120.9) | 0.0 | −54.0 (−94.4/−13.8) |

Abbreviations: BCVA, best-corrected visual acuity (presented in LogMAR); CR, complete resection; FU, follow up; LogMAR, logarithm of the minimum angle of resolution; NA, not available; SAT, systemic anticancer therapy; SX, surgery; RT, radiotherapy; TV, tumor volume; TX, therapy; VI, visual impairment; WHO, world health organization.

[a]ONGs that progressed after first-line treatment were excluded.

[b]At the start of therapy none of the ONGs showed any cystic component within the solid tumor mass.

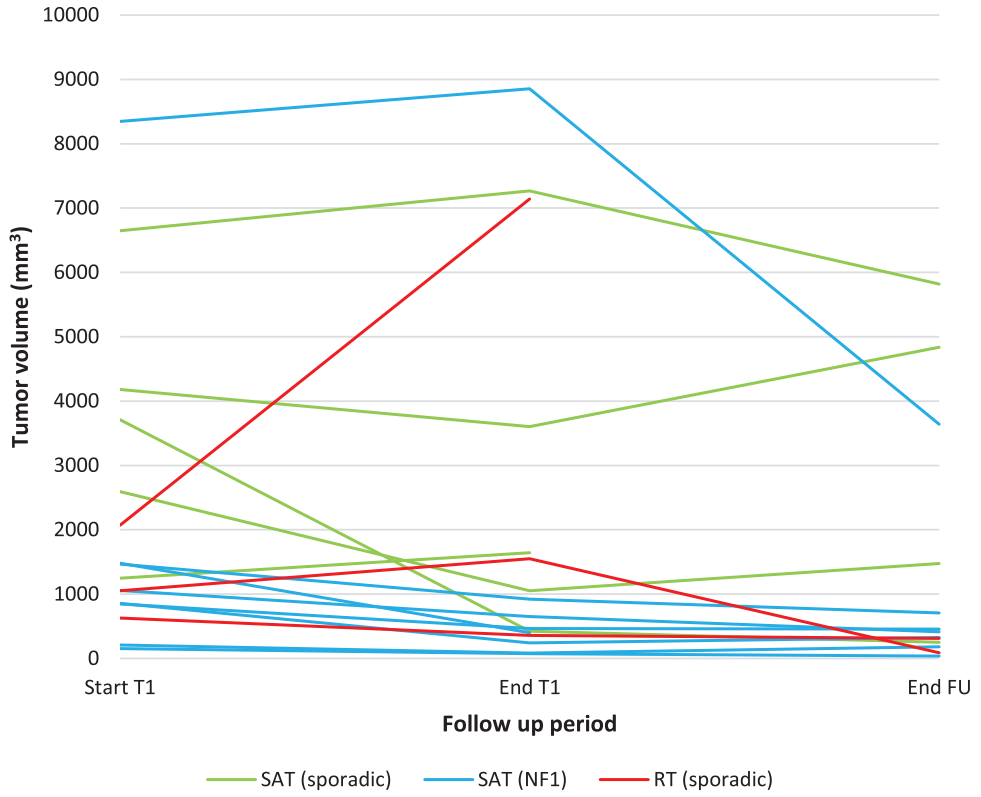


**FIGURE 2** Individual course of the tumor volume on MRI of ONG that received first line SAT ($n = 13$) versus first line RT ($n = 3$). FU, follow up; NF1, neurofibromatosis type 1; RT, radiotherapy; SAT, systemic anticancer therapy; T1, first-line therapy.

porting Information, File S2) requires specific attention, because of the large variety in TV and BCVA at the start of therapy: for example, BCVA was considered normal for an age-appropriate norm in four eyes (LogMAR < 0.3),[24] but SAT had been started because of a decrease of visual functions. Data reporting other visual functions were not available. Likewise, six ONGs (42.9%) exhibited severe VI or blindness at the end of follow up after receiving first-line SAT, but BCVA data at the start of SAT were missing in three patients; therefore, discussion remains on the course of BCVA preceding severe VI or blindness.

The above mentioned studies are highly limited in number and include a wide variety in outcome parameters in studies. However so far, their results contribute to the suggestion that SAT could be the preferred treatment approach for progressive ONG to enhance or preserve BCVA.

The rarity of the diagnosis of pediatric progressive ONG and the limited knowledge on the treatment effects of SAT require prospective international studies examining the longitudinal effect of various SAT strategies, including targeted therapy, on the course of TV and its relation to changes of visual functions (supported by VF and OCT). These studies are also essential to: (1) select those patients that may have limited VI, but require SAT because of the risk of severe progression, and (2) determine whether SAT can assist in improvement or stabilization of BCVA in ONG with severe VI and therefore justify the use of the relatively long-term course of SAT, including its risk for systemic side effects,

Complete surgical resection of ONG has proven to be effective for the management of blind, cosmetically disabling, or painful eyes with proptosis,[6,25] preventing the need for SAT or mitigating secondary sequalae after RT. Our results support to reserve resection exclusively for eyes devoid of any remaining visual function, as BCVA further decreased to blindness in all eyes with prior residual BCVA in both the literature review ($n = 5$) and cohort study ($n = 1$). Complete resection of ONG, not invading the chiasm on MRI, is advocated to prevent recurrent growth,[4,25] which also was supported by our results.

The impact of RT on visual function of progressive ONG, has been a subject of debate for several decades. Despite a low rate of progression after RT, changes of BCVA are reported from complete loss to stabilization or significant improvement. Studies contain various confounding factors such as the inclusion of nonisolated ONG with chiasmal spreading.[4,26] In our literature review Tow et al.[18] reported a decrease of BCVA in 75% ($n = 3$), VI or blindness was present at long-term follow up after RT in all eyes ($n = 4$). In our cohort, a profound loss of BCVA was observed to the extent of counting fingers or less (≥2.0 LogMAR) between the end of RT and the end of follow up. Our small cohort study on the course of TV after RT suggests a temporary increase (pseudo-progression), followed by a long-term decrease, as has been described before in low grade glioma in the brain.[27] However, in ONG the transient increase of volume may induce extensive axonal damage, especially in ONGs with a posterior orbital extension into the bony optic nerve canal resulting in successive loss of BCVA.

Additionally, radiotherapy can induce secondary ophthalmological risks including secondary cataract, dry eye syndrome, radiation optic neuropathy, or retinopathy,[28] which can further decrease visual function. In our study we were unable to evaluate the long-term ophthalmological side effects of RT; nevertheless, no secondary tumors were observed. Despite the limited number of ONG studied, we believe that the combinations of a high risk of severe loss of visual function and the risk of secondary complication renders the use of RT as a first-line treatment modality for pediatric ONG less appropriate.

This study is subject to limitations inherent to its retrospective design, including missing data on BCVA and VF at the start of therapy, which, for example, limited the exploration of possible correlations between changes in TV and BCVA after therapy. We were unable to integrate detailed analysis of visual functions, such as color vision, contrast sensitivity, VEP, and ganglion cell layer analysis using OCT, due to the high rate of missing data. Analysis on a relatively low number of ONGs revealed no significant difference in TV of NF1 and sporadic ONGs at the start and no difference in change of TV after completing SAT. However, Figure 2 suggests a tendency for a smaller TV for NF1-associated ONG, requiring a future upgrade in study volume to contribute to the future approach in personalized use of SAT for ONG. One patient (Supporting Information, Files S2 and S3 [including subscript 1]: pt 12) had a bilateral ONG. The right ONG was included in our analysis, the left ONG was excluded: this ONG was small and had no clinical progression at the start of SAT1. MRI data were lacking within 1 year before up to the start of 2nd line SAT, but the MRI after the start of 2nd line SAT showed drastic progression. The patient died due to gliomatosis cerebri, of which the first lesion appeared 4.1 year after start of SAT1. We are aware that the tumor biology, which was not available, may be responsible for a more aggressive tumor behavior, which may skew the outcome of the total ONG population. Nevertheless this case illustrates the concurrent decrease of TV after SAT1 in case of bilateral ONGs.

The strength of this study lies in the comprehensive analysis of a nationwide population of pediatric ONG, including a detailed long-term analysis of both BCVA and TV. To mitigate debate on diverse outcome parameters, we have clearly presented the applied definitions for change in BCVA, VI, and double rating of TV evaluation.

## 5 | CONCLUSION

Despite the infrequency of progressive pediatric ONG necessitating treatment and the limited availability of literature regarding the effects of various treatments, SAT could be considered the preferred treatment approach in case of potential preservation or improvement of visual function, regardless of progression of one out of five ONG after SAT. Resection of ONG appears effective to alleviate (painful) proptosis in case of preexisting blindness. Radiotherapy should be considered less appropriate due to the high risk of severe VI or blindness and the potential for secondary complications. Comprehensive studies with larger sample size in multicenter international cooperation are needed to investigate the treatment effects on both visual function and TV to establish a robust basis for treatment guidance.

### AUTHOR CONTRIBUTIONS

*Conceptualization*, *funding acquisition*, *methodology*, *project administration*, *resources*, *supervision*, *validation*, *writing*, *original draft preparation*: Carlien A. Bennebroek. *Project administration*, *resources*, *writing*, *original draft preparation*: Maartje C. Montauban van Swijndregt. *Resources*, *writing—review and editing*: Judith van Zwol. *Formal analysis*, *investigation*, *writing—review and editing*: Sanjhana Bhusal. *Resources*, *writing—review and editing*: Anne T. Dittrich. *Resources*, *writing—review and editing*: Rianne Oostenbrink. *Resources*, *writing—review and editing*: Jan W. R. Pott. *Investigation*, *normal analysis*, *writing—review and editing*: Erik A. Buijs. *Funding acquisition*, *resources*, *writing—review and editing*: Antoinette Y. Schouten-van Meeteren. *Normal analysis*, *resources*, *writing—review and editing*: Giorgio L. Porro. *Conceptualization*, *methodology*, *investigation*, *resources*, *supervision*, *funding acquisition*, *writing—review and editing*: Pim de Graaf. *Conceptualization*, *methodology*, *funding*, *supervision*, *writing—review and editing*: Peerooz Saeed.

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### CONFLICT OF INTEREST STATEMENT

Author R. Oostenbrink provides advisory consultations for Alexion, with incidental honoraria and is a full member of Genturis ERN.

### DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

### ETHICS STATEMENT

This is a retrospective study. The Research Ethics Committee of the Amsterdam UMC, Erasmus MC, Radboud UMC and UMC Groningen have confirmed that no ethical approval is required. Approval according to the principles of the Declaration of Helsinki was granted by the Ethics Committee of University of the UMC Utrecht and Princess Máxima Center.

### CONSENT OF PARTICIPATE

Written informed consent for the use of patient data was obtained from parents, legal guardian(s), or children depending on the age of the patients by the UMC Utrecht and Princess Máxima Center.

An Opt Out procedure was applied for the patients, parents, or legal guardian(s) by the Amsterdam UMC.

Data of patients from the Erasmus MC, Radboud UMC, and UMC Groningen were collected anonymously, and patients were not asked for consent before or after collection of data with approval of the research ethics committees.

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## REFERENCES


1. Bø HK, Solheim O, Jakola AS, Kvistad KA, Reinertsen I, Berntsen EM. Intra-rater variability in low-grade glioma segmentation. *J Neurooncol*. 2017;131(2):393-402.
2. Hamideh D, Hoehn ME, Harreld JH, Klimo PD, Gajjar A, Qaddoumi I. Isolated optic nerve glioma in children with and without neurofibromatosis: retrospective characterization and analysis of outcomes. *J Child Neurol*. 2018;33(6):375-382.
3. Shields JA, Bakewell B, Augsburger JJ, Flanagan JC. Classification and incidence of space-occupying lesions of the orbit. A survey of 645 biopsies. *Arch Ophthalmol*. 1984;102(11):1606-1611.
4. Dutton JJ. Gliomas of the anterior visual pathway. *Surv Ophthalmol*. 1994;38(5):427-452.
5. Nicolin G, Parkin P, Mabbott D, et al. Natural history and outcome of optic pathway gliomas in children. *Pediatr Blood Cancer*. 2009;53(7):1231-1237.
6. Shofty B, Ben-Sira L, Kesler A, et al. Isolated optic nerve gliomas: a multicenter historical cohort study. *J Neurosurg Pediatr*. 2017;20(6):549-555.
7. Packer RJ, Lange B, Ater J, et al. Carboplatin and vincristine for recurrent and newly diagnosed low-grade gliomas of childhood. *J Clin Oncol*. 1993;11(5):850-856.
8. Revere KE, Katowitz WR, Katowitz JA, Rorke-Adams L, Fisher MJ, Liu GT. Childhood optic nerve glioma: vision loss due to biopsy. *Ophthal Plast Reconstr Surg*. 2017;33(3S):S107-S109. Suppl 1.
9. Laithier V, Grill J, Le Deley MC, et al. Progression-free survival in children with optic pathway tumors: dependence on age and the quality of the response to chemotherapy–results of the first French prospective study for the French Society of Pediatric Oncology. *J Clin Oncol*. 2003;21(24):4572-4578.
10. Gnekow AK, Walker DA, Kandels D, et al. A European randomised controlled trial of the addition of etoposide to standard vincristine and carboplatin induction as part of an 18-month treatment programme for childhood (≤16 years) low grade glioma—a final report. *Eur J Cancer*. 2017;81:206-225.
11. Bennebroek CAM, Wijninga LE, Limpens J, Schouten-van Meeteren AYN, Saeed P. Impact of systemic anticancer therapy in pediatric optic pathway glioma on visual function: a systematic review. *PLoS One*. 2021;16(10):e0258548.
12. Institute JB, Joanna Briggs Institute Critical Appraisal (JBI-CA) tool for case series. 2017. Accessed 30 November 2023. https://jbiglobal/sites/default/files/2019-05/JBI_Critical_Appraisal-Checklist_for_Case_Series2017_0pdf
13. Moussa G, Bassilious K, Mathews N. A novel excel sheet conversion tool from Snellen fraction to LogMAR including 'counting fingers', 'hand movement', 'light perception' and 'no light perception' and focused review of literature of low visual acuity reference values. *Acta Ophthalmol*. 2021;99(6):e963-e965.
14. World Health Organization. International Statistical Classification of Diseases and Related Health Problems: 10th Revision. ICD-10 Version 2019. Accessed 30 November 2023. https://icd.who.int/browse10/2019/en#/H54.9
15. Bennebroek CAM, van Zwol J, Porro GL, et al. Impact of bevacizumab on visual function, tumor size, and toxicity in pediatric progressive optic pathway glioma: a retrospective nationwide multicentre study. *Cancers*. 2022;14(24):6087.
16. Taylor T, Jaspan T, Milano G, et al. Radiological classification of optic pathway gliomas: experience of a modified functional classification system. *Br J Radiol*. 2008;81(970):761-766.
17. Gnekow AK, Kandels D, Tilburg CV, et al. SIOP-E-BTG and GPOH guidelines for diagnosis and treatment of children and adolescents with low grade glioma. *Klin Padiatr*. 2019;233(3):107-122.
18. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med*. 2016;15(2):155-163.
19. Tow SL, Chandela S, Miller NR, Avellino AM. Long-term outcome in children with gliomas of the anterior visual pathway. *Pediatr Neurol*. 2003;28(4):262-270.
20. Chukwueke UN, Wen PY. Use of the Response Assessment in Neuro-Oncology (RANO) criteria in clinical trials and clinical practice. *CNS Oncol*. 2019;8(1):Cns28.
21. Fangusaro J, Witt O, Hernáiz Driever P, et al. Response assessment in paediatric low-grade glioma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group. *Lancet Oncol*. 2020;21(6):e305-e316.
22. Fisher MJ, Loguidice M, Gutmann DH, et al. Visual outcomes in children with neurofibromatosis type 1-associated optic pathway glioma following chemotherapy: a multicenter retrospective analysis. *Neuro Oncol*. 2012;14(6):790-797.
23. Falzon K, Drimtzias E, Picton S, Simmons I. Visual outcomes after chemotherapy for optic pathway glioma in children with and without neurofibromatosis type 1: results of the International Society of Paediatric Oncology (SIOP) Low-Grade Glioma 2004 trial UK cohort. *Br J Ophthalmol*. 2018;102(10):1367-1371.
24. Leone JF, Mitchell P, Kifley A, Rose KA. Normative visual acuity in infants and preschool-aged children in Sydney. *Acta Ophthalmol*. 2014;92(7):e521-e529.
25. Zipfel J, Tellermann J, Besch D, et al. Surgical management of prechiasmatic intraorbital optic nerve gliomas in children after loss of visual function-resection from bulbus to chiasm. *Children (Basel)*. 2022;9(4):459.
26. Zagirov RI, Trunin YY, Serova NK, Pronin IN, Antipina NA, Golanov AV. Hypofractionated stereotactic irradiation for optic nerve glioma. *Zh Vopr Neirokhir Im N N Burdenko*. 2022;86(5):74-80.
27. Lu VM, Welby JP, Laack NN, Mahajan A, Daniels DJ. Pseudoprogression after radiation therapies for low grade glioma in children and adults: a systematic review and meta-analysis. *Radiother Oncol*. 2020;142:36-42.
28. Nuzzi R, Trossarello M, Bartoncini S, et al. Ocular complications after radiation therapy: an observational study. *Clin Ophthalmol*. 2020;14:3153-3166.


## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.


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