TREATMENT EVALUATION AND DETERMINATION OF PROGNOSTIC FACTORS IN PEDIATRIC OPTIC PATHWAY GLIOMA

Carlien A.M. Bennebroek

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Copromotores:	dr. A.Y.N. Schouten-van Meeteren	Prinses Máxima Centrum
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To my everlasting supporters,
my dear parents

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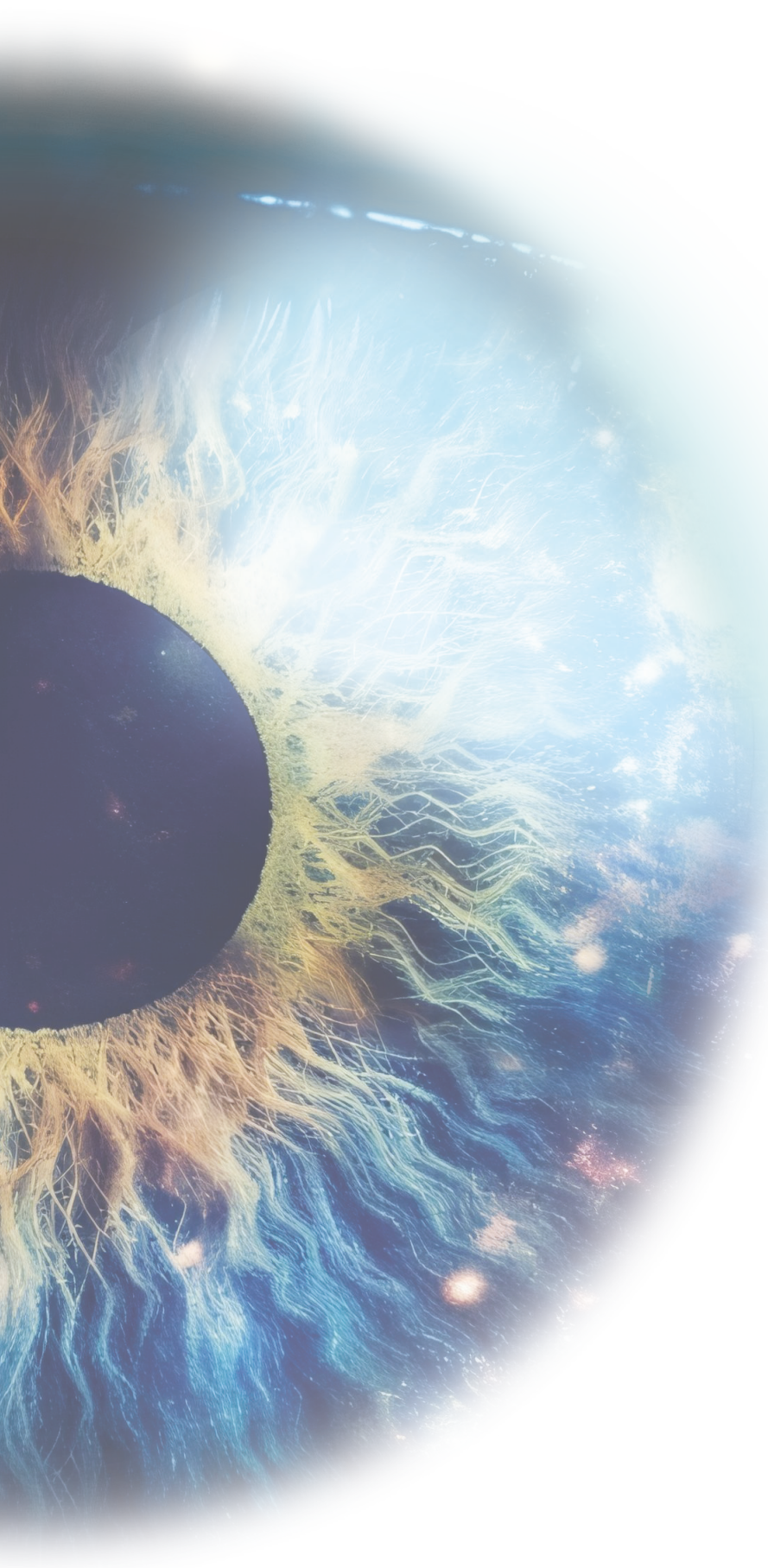

CHAPTER 1

General introduction and aims of this thesis

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Optic pathway Gliomas in children

Optic pathway glioma (OPG) is a rare kind of tumor located in and around the optic nerve, chiasm, and optic tract. The tumor is classified as a low-grade glioma (LGG), which develops from glial cells, astrocytes, within the central nervous system (CNS). Glial cells are star-shaped cells that surround and support neuronal cells in both the central and peripheral nervous system, ensuring their proper functioning. OPGs are identified as pilocytic astrocytomas in 85-95% of patients. According to the World Health Organization (WHO) tumor grading system (1), OPGs are classified as grade I or II tumors, and are considered benign, slow-growing tumors. However, despite their slow growth, OPGs can cause significant morbidity, mostly represented by visual impairment.

The earliest reports date back to 1833, when Wishart documented on intradural tumors affecting the optic nerve (2), followed by the histological identification of glioma in 1912 (3).

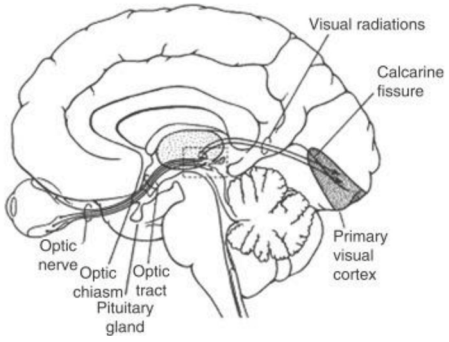

Fig. 1.1. Anatomic representation of optic pathways
(www.sciencedirect.com/topics/medicine)

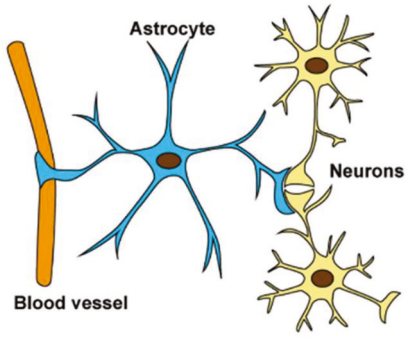

Fig. 1.2. Anatomical connection of astrocytes
(www.researchgate.net/figure/Astrocytes-have-close-morphological-and-functional-associations-with-microvasculature-and_fig1_290479871)

Low-grade gliomas account for approximately 25-45% of pediatric brain tumors (4-6), with OPGs representing approximately 15-30% of these LGGs (7, 8). In the Netherlands, among the 3.3 million children under the age of 18 years, annually 7 to 12 children are diagnosed with an OPG and 5 to 9 children require initiation of treatment (4). The tumor is diagnosed most around the age of 4-7 years, although it can present in the entire range of 0 to 17 years. While these tumors may develop

sporadically without association to other conditions, 25-50% of children with OPGs are diagnosed with Neurofibromatosis type 1 (NF1) (9, 10), a tumor predisposition syndrome that affects approximately 1 in 3000 individuals globally and affects multiple organ systems, with the nervous system primarily being involved (11). About half of NF1 cases result from a pathogenic germline mutation inherited from one or both parents, while the other half arise due to a sporadic (de novo) mutation (11).

In children with NF1, OPGs occur in approximately 15-20% of cases (12, 13). Unlike sporadic OPGs, NF1-associated OPGs follow a more indolent course, often growing slowly and presenting with less aggressive symptoms. Children with NF1 are periodically screened by the ophthalmologist for the potential presence of an OPG or its progression (14). In case of tumor growth, its central location may lead to compression of surrounding anatomic structures, resulting in a range of symptoms, including a decline of visual functions, endocrinological and neurological abnormalities, as well as developmental delays.

Pathophysiology

The development of OPG in NF1 is driven by mutations in the NF1 gene located on chromosome 17. Approximately half of patients with NF1 inherit a pathogenic germline mutation from a parent, while in the other half occur due to a spontaneous (*de novo*) mutation.

The NF1 gene encodes for the protein neurofibromin. Under normal conditions, neurofibromin suppresses the RAS/ MAPK **(**Mitogen-Activated Protein Kinase) signaling pathway**.** Inactivation of the NF1 gene results in the loss of neurofibromin, which upregulates the RAS/ MAPK pathway. Likewise, sporadic OPGs are also associated with genetic alterations, such as mutations (e.g BRAF-V600E) or fusions (e.g KIAA1549-BRAF), which similarly dysregulate the RAS/ MAPK pathway (15, 16).

The MAPK-pathway is triggered by the binding of extracellular signaling molecules, which initiate a cascade of intracellular events. A central component is RAS, a small GTPase protein. RAS activation occurs, when GDP exchanges GDP for GTP, transitioning from an inactive to an active state. In its active form, RAS activates a group of proteins, called MAPKs. Once activated, MAPKs translocate to the cell nucleus where they support the activity of various transcription factors. These transcription factors regulate the expression of genes involved critical cellular processes such as division, differentiation, survival, and apoptosis. Dysregulation of the MAPK-pathway leads to tumor development and progression (17, 18).

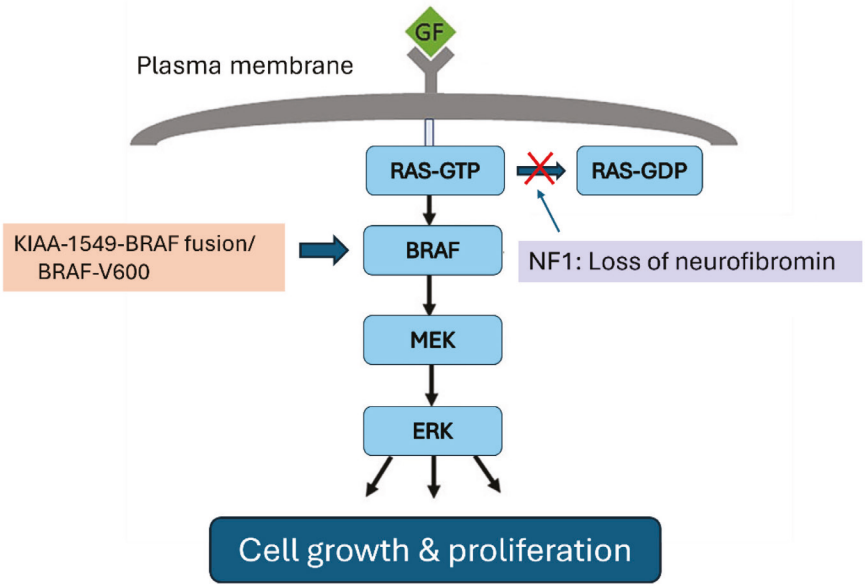

Fig. 1.3. RAS/ MAPK signaling pathway

Clinical Presentation

The clinical presentation of OPGs in children is highly variable and is dependent on the tumor size, location within the optic pathways, and its growth rate. One of the primary symptoms is progressive loss of visual functions, which may manifest as a decrease in visual acuity (74-89%) (19) or visual field defects (55-78%) (20, 21), nystagmus (11-22%) (9), strabismus (12-22%) or proptosis in case of optic nerve involvement (9-26%) (22-24). The decline in visual acuity is caused by (direct or retrograde) optic neuropathy, expressed as swelling or atrophy of the optic nerve heads. Visual field defects are mostly represented by homonymous or heteronymous hemianopia due to compression of the optic chiasm or optic tract.

In the NF1 population, up to 70% of patients with an OPG may be asymptomatic at diagnosis (23), when the OPG is discovered during routine ophthalmological screening. Several factors may contribute to a delay in diagnosis: 1) young children may not be aware of or do not communicate their visual loss; 2) parents may not recognize visual loss; or 3) examination may be difficult due to limited cooperation during clinical assessment, delaying MRI evaluation to detect OPG (25).

In addition to visual symptoms, children with a suprasellar OPG may exhibit endocrine abnormalities (28%) (26), such as growth hormone deficiency, precocious puberty or hypothalamic dysfunction. Nonspecific neurological symptoms such as headache, nausea, vomiting, or developmental delays, may occur (11-23%) (19),

particularly if the tumor causes increased intracranial pressure or affects adjacent brain structures.

Treatment and prognostic factors for progression

As OPGs may remain stable over time or even regress spontaneously (27), treatment is indicated only in case of significant deterioration of visual or neurological functions or when the tumor volume increases by more than 25%, including the risk of future neurologic or visual dysfunction (28). Besides diencephalic syndrome, endocrine dysfunction is no indication for treatment, as hormonal imbalances are treated with hormonal suppletion. The most common observed indication for initiating treatment is loss of visual functions, which is observed in both NF1-associated (61-74%) (19, 29) and sporadic OPGs (89%) (19). Despite a high rate of overall survival of 90-100% after treatment, severe long-term visual impairment (VI) or blindness according to the World Health Organization appears in 16-63% (21, 30-33) and remains the main limiting outcome factor contributing to a reduced quality of life (34).

Before the introduction of systemic anticancer therapy (SAT) in 1988, represented by chemotherapy (35), treatment of OPGs consisted of surgical resection and/or radiotherapy, of which the first available reports date back to 1922 (36)**.** Due to the complex anatomical location of these tumors, complete resection is often considered impossible, leading to recurrent progression within five years in more than one in two children (37, 38). Additionally, patients may face the risk of severe neurological damage and deterioration of visual functions (39). Radiotherapy has been considered relatively effective in controlling tumor growth, but its use is associated with long-term side effects like cerebral vasculopathy (40, 41), and an increased risk of secondary nerve system tumors and/or cognitive impairment in children with NF1 (42). As a result, radiotherapy (preferably proton therapy) is currently reserved for older children, who exhibit tumor progression despite attempts of successive SAT.

Over the past four decades, first-line treatment protocols for OPGs have typically involved a combination of vincristine and carboplatin (7), followed by vinblastine monotherapy in first- or second-line settings (8), or regimens like thioguanine, procarbazine, lomustine, and vincristine (9), and bevacizumab (and irinothecan) since 2009 (10-12). However, a global consensus on the use of selected adjuvant therapies (SAT) remains lacking (13), as randomized comparative trials are exceedingly rare. These SAT strategies are typically characterized by recurrent progression after first-line and subsequent treatment (8, 10, 43), imposing a long-term burden on both children and their families. Progression occurs within five

years in 44-61% of cases after the start of first-line SAT, necessitating subsequent treatment and increasing the risk of visual impairment.

Identifying risk factors for progression after SAT for OPG is crucial, to work towards individualized treatment strategies for children at risk for a more aggressive course. Earlier studies on prognostic factors for progression after first-line SAT have identified several risk factors for progression after starting SAT, including children requiring start of SAT below the age of one year, the sporadic appearance of OPGs and non-pilocytic astrocytoma as independent risk factors for progression (10, 44). The limited number of studies on these risk factors are supported by studies on LGGs that include various anatomical locations or studies on diverse LGG locations including separate analyses on OPGs (45). These studies do not provide a fair representation of OPGs, as the progression rate is lower for OPG than other cerebral locations (46-48).

Targeted therapies, particularly those targeting the Ras/Raf/MAPK signaling pathways, have demonstrated promising results for OPG in effectively reducing tumor volume and minimizing progression, potentially influencing the approach to subsequent SAT strategies (49). International trials evaluating outcome are currently running (50).

Treatment evaluation by outcome in visual functions

Treatment monitoring of OPGs requires a multidisciplinary approach to assess treatment response, involving ophthalmologic examination to evaluate clinical outcomes and MRI analysis for radiological response. Reporting on visual functions in pediatric OPG for clinical research purpose include several challenges: first, children undergo significant visual development, primarily during the first eight years of life across all areas of visual functioning. Concurrent growth of OPGs affects the visual pathways within the brain, which, due to their central location, impacts both eyes symmetrically of asymmetrically. A reduction in visual function can further impair or stagnate visual development. Second, the development of amblyopia can occur during or after treatment, posing a confounding factor when assessing treatment outcome.

The majority of studies evaluating treatment outcome of SAT for OPG, have primarily reported on change in best-corrected visual acuity (BCVA) as outcome parameter (32, 51), while studies addressing changes in visual fields or visual evoked potentials (VEP) as outcome parameter remain limited (52).

In 2013, the REiNS collaboration established criteria for monitoring treatment by visual testing in children with NF1, using BCVA as the only outcome measure (53). This approach included a standardized method employing Teller acuity cards or HOTV for older children. The last years, the definition of change in monocular best-corrected visual acuity (BCVA) ($\geq$ or $\leq$ 0.2 LogMAR) is internationally accepted as a standard classification in reporting outcome, nevertheless reporting of the binocular or monocular state varies, making cross-study comparison difficult.

Reporting on long-term outcome of the rate of visual impairment after treatment of OPG is essential, to evaluate its correlation with the quality of life and ability of economic contribution to society. Severe visual impairment is reported in 16-63% of children (21, 32, 54) and remains the main limiting outcome factor contributing to a reduced quality of life (34). So far, studies applied two different approaches for the classifications of visual impairment (55, 56), which vary in the definitions among categories of visual impairment and focus on monocular/ binocular outcome and used only BCVA as an outcome measure for visual impairment.

Treatment evaluation by radiological response assessment

Imaging of OPGs has been performed using MRI since the 1990s, following earlier use of X-ray and CT imaging. A standardized classification of the anatomical location is used worldwide: the Dodge classification (57), which was modified in 2007 to the modified Dodge classification (58). This classification categorizes the presence of the OPG into anatomical sublocations, including the optic nerve, chiasm, anterior and posterior parts of the optic tract, hypothalamic involvement, and leptomeningeal dissemination.

Modified Dodge classification:

1 a-b	Uni-/ bilateral optic nerve
1 c	Cisternal segment optic nerve
2 a	Central chiasmatic
2 b	Asymmetric chiasmatic
3	Optic tracts
3 b	Asymmetric tracts
4	Posterior optic tract
4 b	Asymmetric posterior tracts
H +/-	Hypothalamic involvement
LM+/-	Leptomeningeal involvement

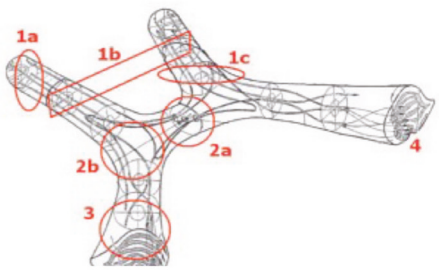

Fig. 1.4. Modified Dodge classification: anatomic classification of OPG (Taylor et al, 2008)

The current approach to clinical and scientific radiological response evaluation for OPG treatment is typically based on the calculation of tumor volume by the measurement of the maximal tumor diameters (TDM) in two or three directions (59). While this method is practical and suitable for routine use in daily practice, it is considered inaccurate for assessing volumetric changes, as OPGs are highly irregular and asymmetrical in shape. Furthermore, so far, studies have not found a correlation between change in tumor volume, as measured by two of three TDM, and change in visual functions (51, 60). An increasing number of studies on (semi-) automated segmentation for LGG but also OPG, overcome these issues by outlining tumor segments slice by slice and calculating tumor (segment) volumes based on the number of voxels representing the tumor (61). This technique provides a more refined response evaluation for treatment, as well facilitating longitudinal intra-tumor evaluation (62-64) and evaluating the role of contrast in longitudinal MRI evaluation (65).

Aims and outlines of this thesis

This thesis consists of retrospective multicenter cohort studies and a systematic review, which were performed by the Dutch Optic Pathway Glioma (OPG-NL) study group. This study group was a collaboration between all eight university medical centers in the Netherlands, the national pediatric oncology center (Princess Máxima Center) and the two Dutch visual rehabilitation centers. Data on children diagnosed with an OPG were collected between January 1995 and December 2018. The search rendered data on 258 children, of whom, after exclusion of two cases, 156 children received treatment due to progression of the OPG. Various aspects of (successive) treatment courses were studied to enhance understanding of treatment outcome and address risk factors for progression.

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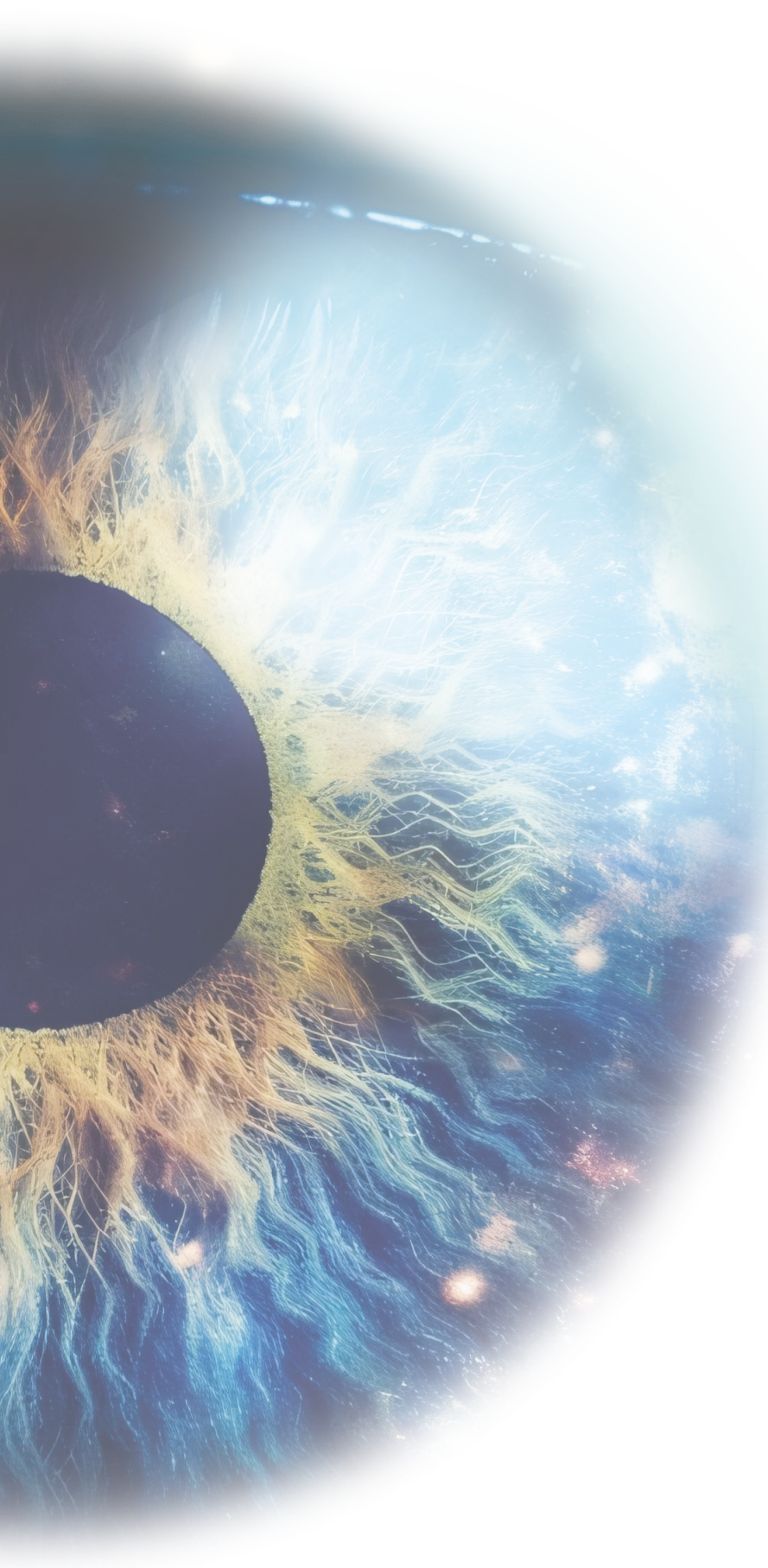

CHAPTER 2

Impact of systemic anticancer therapy in pediatric optic pathway glioma on visual function: a systematic review

C.A.M. Bennebroek*, L.E. Wijninga*, J. Limpens, A.Y.N. Schouten-van Meeteren, P. Saeed

*both authors contributed equally to this work.

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Abstract

Introduction:

Pediatric optic pathway glioma (OPG) can seriously decrease visual function in the case of progression. Systemic anticancer therapy (SAT) is considered the treatment of first choice for unresectable OPG. New SAT modalities for the treatment of progressive OPG have been introduced in the last decade, including VEGF and MAPK pathway inhibition. This systematic review evaluated the effect of SAT on change in visual acuity and visual field in OPG.

Methods:

A systematic review was performed on SAT for OPG (January 1990 to August 2020). MEDLINE and EMBASE (Ovid) were searched for studies reporting on change in visual acuity and visual field after treatment with SAT for OPG.

Results:

Overall, 11 series, including 358 patients, fulfilled the eligibility criteria. After follow-up of median 3.7 years (range: cessation of SAT – 8.2 years), improvement in binocular VA was found in 0–45% of studies, stability in 18–77% and a decrease in 0–82%. Two studies reported on change in visual field (improvement in 19% and 71% of patients), although either the change was not defined or the testing strategy was lacking.

Considerable heterogeneity was present among the included studies, such as variety in the combinations of SAT administered, status of neurofibromatosis type 1, definition regarding change in visual acuity, 1- or 2-eye analysis, diversity in anatomic location, and extent of follow-up, all of which made meta-analysis inappropriate.

Conclusion:

This systematic review suggests that the impact of SAT in OPG on visual function is still unclear. The wide ranges reported on the efficacy of SAT and the observed heterogeneity highlight the need for prospective studies with uniform definitions of outcome parameters.

Introduction

Optic pathway glioma (OPG) is considered a rare subtype of pediatric low-grade glioma (LGG) located in the optic pathway from the optic nerve to the optic tract. OPG presents on average at the age of 3–9 years (range 0–7 years), either in association with neurofibromatosis type 1 (NF1) (incidence: 10–60%) or without NF1 (nNF1) [1, 2, 3]. Most frequently, OPG is a pilocytic astrocytoma followed by a pilomyxoid astrocytoma. Treatment is indicated in the case of radiologic or clinical progression, including significant visual deterioration or neurological symptoms, as OPG may remain stable in volume (presumed to be mostly NF1) or, rarely, regresses spontaneously in the case of NF1 OPG [4].
Regardless of the high rate of 5-year overall survival (OS) after treatment (89–95%) [1, 5-7], loss of visual function can be extensive and may have a significant impact on the quality of life [8]. Long-term analysis of visual outcome after diverse treatment strategies for OPG presents binocular BCVA $\leq$ 20/200 in 16–26% [9, 10] or < 20/100 in 58% of patients [11].

Systemic anticancer treatment (SAT), mostly chemotherapy, is considered the treatment of first choice for OPG because the possibility of surgery is often limited or not feasible due to the risk of damaging visual, neurologic or endocrine function [12]. As 45–66% of OPG progresses during or after first-line SAT [1, 6], successive systemic treatment is often necessary. In non-surgical cases, second-line up to fifth-line SAT can be applied when there is progression. Maximum delay in the application of radiotherapy is highly preferred because of its long-term side effects, considering endocrine deficiencies, vasculopathy, and neurocognitive impairment [13-15]. Many different first-line or next-line SAT regimens have been introduced since the first results were published in 1976 [1, 16-19], with increased frequency of introduction from 1990 onwards. Initial therapy is frequently carboplatin-based. In Europe, treatment with carboplatin and vincristine over a period of 18 months represents the current first-line strategy proposed by the Societé Internationale d'Oncologie Pédiatrique (SIOP) [1]. The anti-vascular endothelial growth factor (anti-VEGF) agent bevacizumab was introduced in 2009 as the next-line treatment for progressive OPG [20], as angiogenesis plays a vital role in the growth of LGG. Results on treatment outcome show a rapid radiological response [20, 21] with anecdotally profound visual improvement [22, 23]. Internationally, bevacizumab is not part of the standard of care for progressive pediatric OPG, as recurrence of progression after discontinuation of bevacizumab is frequent (15–93% within 6 months after cessation) [21, 23-25] and toxicity profiles are still being studied. Recently, the effect of targeted inhibition of the MAPK pathways on low-grade glioma is being

increasingly studied regarding dose, treatment duration, effectiveness and toxicity [26-28].

A decrease of visual function is mostly more prominent than neurologic dysfunction and is one of the leading clinical indicators for starting treatment for OPG [29]. After treatment, decreased visual function is also considered the main invalidating outcome parameter. Currently, treatment evaluation is based on a combination of radiological response and clinical evaluation. Regarding the latter, to date, visual acuity (VA) is the only visual outcome parameter that can represent change in function after treatment [30]. Visual field is assumed to mirror VA function [30], but there is insufficient evidence to substantiate this assumption.
So far no correlation has been found between (the current 2-dimensional) radiological response after SAT and change in visual function (analyzed mainly with NF1 patients) [29-31]; hence the focus on the clinical effect of therapy on visual function is essential.
In 2010, Moreno et al. [32] published a systematic review to evaluate the effect of SAT on VA, which suggested several trends: 14% improvement in VA, 47% improvement of stability of VA and a decrease in VA of 39% of patients after chemotherapy. The way in which change in VA was defined was not evaluated. No statistical analysis could be performed due to the heterogeneity of the included studies. The authors concluded by urging for standardization of treatment indications and evaluation.

In 1997 the NF1 OPG Task Force consensus statement provided rational guidelines for the diagnosis and treatment of OPG in NF1 [33]. Updates in 2007 and 2017 added a focus on visual function represented by VA measurement, which included the proposed usage of validated test modalities to measure the VA suitable per age category, and definitions of an age-based norm for normal VA [34-36]. In 2020 the RAPNO working group suggested defining change in VA by change in <> 0.2 LogMAR [37], substantiated by the application of this definition in prior studies [29, 30]. In view of the fact that recommendations have been developed and new treatment modalities have become available, we performed a systematic review to evaluate the effect of SAT on visual function (VA and VF), including VEGF and MAPK inhibition.

Materials and Methods

Search Strategy

This study was conducted in accordance with the PRISMA guidelines (PRISMA checklist October 2015) and registered in the PROSPERO international prospective register of systematic reviews (Reg. no. CRD42020125576, see Supplement 2.1).

A medical information specialist (JL) performed a comprehensive search of OVID MEDLINE (using the PubMed interface) and OVID EMBASE from January 1990 until August 5, 2020. Empirically we found that we would miss relevant studies which did not mention specific drugs or mentioned only OPG treatment. Therefore we constructed a search consisting of three parts combined with a pediatric search filter: (1) OPG + chemotherapy, (2) OPG + other anticancer agents, and (3) cohort studies on managing pediatric OPG (major topic). Conference abstracts were excluded from EMBASE. Detailed searches for both databases are available (see Supplement 2.2 and 2.3). Reference lists and articles cited in the included papers, as well as relevant reviews, were crosschecked for additional relevant studies.
Titles, abstracts and full-text articles were screened independently by two authors (CB and LW). Differences in opinion were resolved through discussion; if necessary, a third author (PS) was consulted.

Eligibility Criteria

The primary endpoint of this review was the percentage and range of OPG patients with change in VA after SAT, divided into 3 categories: improvement, stability, or decrease of VA. The secondary endpoint was change in VF.
Studies were included when or if they (1) reported on change of visual acuity in children (≤ 18 years) after receiving SAT for OPG; (2) included a minimum of 10 patients per study; (3) were written in any language, as long as the original authors were willing to translate their manuscript into English; and (4) reported on patients with or without surgical treatment (biopsy/ventricular drainage (VD)/tumor resection) prior to SAT. Studies containing the results of patients who required additional therapy after SAT were also included.
Studies reporting on radiotherapy prior to SAT were excluded. When the results of the studies appeared to overlap, the study with the most recent data was included.

Data Collection

The following data were extracted: study characteristics, patient characteristics, variables regarding visual function, and prognostic factors for a decrease in VA and/or VF (Tables 2.1 and 2.2).

Critical Appraisal

Assessment of methodological quality was performed in parallel by two authors (CB, PS). Study quality was weighed using the Oxford Centre for Evidence-Based Medicine (CEBM) evidence rating system. If studies were case series, the Joanna Briggs Institute Critical Appraisal (JBI-CA) tool for case series "Checklist for Case Series" [38] was used, in which bias is evaluated by means of 10 questions answered by Yes, No or Unsure. As several of the included studies did not focus

primarily on the effect of SAT, we performed a critical appraisal pertinent to the primary endpoint of this review. If no statistical analysis was performed, question 10 was evaluated as Unsure. We considered a low risk of bias if the Yes answers were ≥ 50%, a high risk of bias if the No answers were ≥ 50%, and uncertain risk of bias if the Unclear answers were ≥ 50%.

Statistical Analysis

Study characteristics, patient characteristics and definition of change in VA and VF between the start of and after treatment with SAT were reported descriptively. Data regarding change in VA were reported as range (percentage) and cumulative proportion (number and percentage of change) (see Discussion) or are calculated data.

Results

Search

The search strategy identified a total of 818 studies. After evaluation of the abstracts and full texts, 11 studies were included. One study was excluded due to suggested overlap [39]. The PRISMA selection flowchart is presented in Figure 2.1.

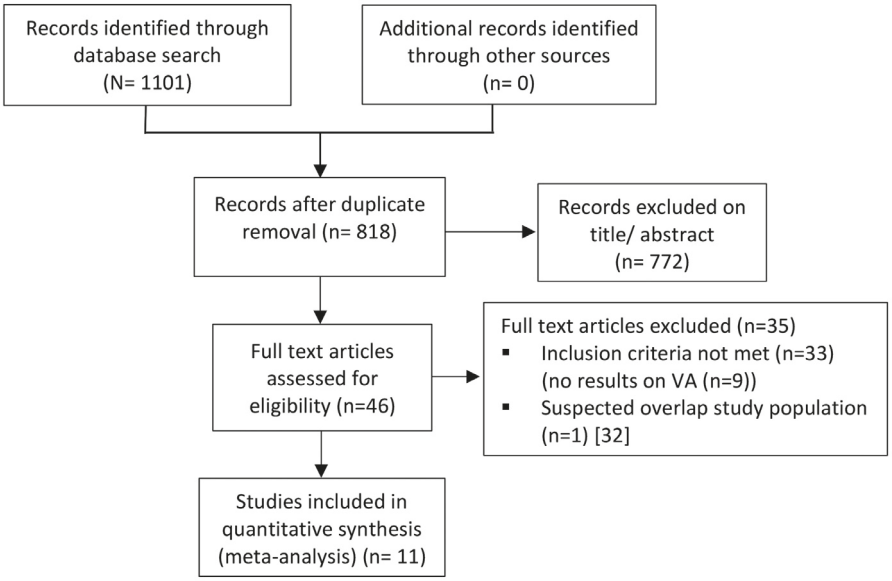

Figure 2.1. PRISMA flowchart for identification and selection of studies

Study, Patient and Treatment Characteristics

All 11 included studies were case studies. The studies presented the results of 1,336 patients, of whom 427 had received SAT. Data for the analysis of change in VA were available for 358 patients. Patient characteristics are presented in Table 2.1. The type of SAT, type of visual test and prognostic factors are shown in Table 2.2. The cumulative gender distribution among the patients analyzed could be extracted for 178 (of 358) patients from 2 studies [29, 40] (male (N=88)/female (N=117)). In 6 studies NF1 status (77%) could only be extracted from the total study population (see Table 2.1), which also included patients not treated with SAT. The median or mean age at the start of SAT varied from 3.2 to 8 years (range 0.3–17.2 years).

All studies reported on the start of treatment with first-line SAT. They applied various combinations of SAT (see Table 2.3). SAT regimes were carboplatin-based in 326 of 427 patients (76%). Studies on VEGF or MAPK signaling inhibition did not match the inclusion criteria due to the study volume being < 10 patients or the outcome parameters not matching the focus of this systematic review.

Table 2.1. Study & patient characteristics

Author (year)	Country	Study design	Change in VA analyzed (total population)	NF1/ nNF1, registration (total study population)	Age start CT: mean/median (SD/range) (years)	Time interval (median/range) VA started CT–final VA (years)	(M)DC stage	Definition of change VA	VA ↑ binoc: n (%)	VA ↔: binoc: n (%)	VA ↓: binoc: n(%)
Massimino et al. (2002) [17]	Italy	Prospective, multicenter	22 (34)	8/ 26a	3.2 (0.3–15.6)	3.7 (0.8–10)	2	No definition	10 (45)	7 (32)	5 (23)
Dalla Via et al. (2007) [42]	Italy	Prospective, monocenter	11 (20)	20 NF1	2.2 (1.1–4.2)b	6.3 (0.4–18)c	1, 2, 3	No definition	0 (0)	2 (18)	9 (82)
Massimino et al (2010) [43]	Italy	Prospective, center: NEP	17 (37)	7/ 30a	6.0 (0.5–16.5)a	End of CT cycle	1, 3	No definition	7 (41)	10 (59)	0 (0)
Shofty et al. (2011) [45]	Israel	Retrospective, multicenter	19 (19)	11/ 8	5.2 (1–9.4)	4.2 (0.3–11)	2 ,3, 4	No definition	1 (5)	4 (21)	14 (74)
Fisher et al. (2012) [40]	USA, UK, Australia, Canada	Retrospective, multicenter	88 (115)	88 NF1	4.0 (0.5–16.2)	3 months after completion of CT cycle	1, 2, 3, 4	≤ = ≥ 0.2 Snellen lines	28 (32)	35 (40)	25 (28)
Kalin-Hadju et al. (2014) [31]	Canada	Retrospective, monocenter	14 (17)	10/ 7a	3.4 (3.2–6.6)	8.2 (3.5–12.9)	1, 2, 3, 4	Change per (WHO) category of CVI scale	1 (7)	7 (50)	6 (43)
Dodgshun et al. (2015) [9]	Australia	Retrospective, monocenter	35 (104)	33/ 71a	4.6 (0.4–12)	At cessation of CT/ (6.5 (ND)D	1, 2, 3, 4	Change in ICO category (13)	5 (14)	27 (77)	3 (9)
Prada et al. (2015) [44]	USA	Retrospective, monocenter	22 (826)	22 NF1	4 (1.8–12)	Not registered	1, 2, 3, 4	No definition	4 (17)	6 (27)	12 (56)
Doganis et al. (2016) [36]	Greece	Retrospective, monocenter	16 (20)	15/5a	5.3 (1.5–11.4)	End of CT cycle/ 5.2 (2.8–9.4)d	1, 2, 3	No definition	7 (44)	7 (44)	2 (12)
Lassaletta et al. (2016) [18]	Canada	Prospective, multicenter	24 (54)	13/ 41a	8 (0.7–17.2)	5 yr (ND)	2, 3, 4	No definition	5 (21)	15 (62)	4 (17)
Falzon et al. (2018) [29]	UK	Prospective, multicenter	90 (90)	46/ 44	3.8 (0.8–14) NF1, 3.2 (0.4–15) nNF1	6.5 (2.0–10.2)	1, 2, 3	≤ = ≥ 0.2 LogMAR	19 (21)	35 (39)	36 (40)
Total			358 (1336)	178/52							

Abbreviations: CVI: Childhood Visual Impairment; CT: chemotherapy; FU: follow-up; ND: no data; NEP: no extraction possible; NF1 neurofibromatosis type 1; nNF1: no systemic association with neurofibromatosis type 1; (M)DC: (Modified) Dodge Classification; SD: standard deviation; TX: treatment; VA: visual acuity.
*: monocular
a: results only available from total population of study, b: age at diagnosis, age at start of tx not available, c: interval age at diagnosis – final VA,
d: long-term data available, change in VA not registered in this table. See Table 2.3.

Table 2.2. SAT combinations, prior surgical intervention, VA test, VF test and prognostic factors on decrease of VA.

Author (year)	SAT (N)	Previous TX (N)	VA: type of test	VF: type of test	Change in VF after SAT	Prognostic factors decrease of VA
Massimino et al. (2002)[17]	Cispl - ETO (34)b	ND	ND	-	ND	ND
Dalla Via et al. (2007) [41]	CB-VC	No	TAC, LH, Snellen	ND	ND	ND
Massimino et al. (2010) [42]	Cispl- ETO (37)A	Prior CT/ RT: no, SX: ND	ND	-	ND	ND
Shofty et al. (2011) [43]	CB- VC (19)	No	Snellen, self-made grading system	-	ND	ND
Fisher et al. (2012) [30]	CB-VC (105), CB (9), VB (1)	Biopsy + (ND), SX: ND, prior CT/RT: excluded	TAC, Lea, HOTV, Snellen	ND	Total population: 5 (19%) improved, 10 (38%) remained stable, 11 (42%) decreased. No definition of change	Location in optic tracts/ radiation: (OR 3.0; 95% CI: 1.1–8.3; P=0.032)
Kalin-Hadju et al. (2014) [31]	CB-VC (7), CB (4), CB-VB (2), CP (2), TPCV (1), VC-AC (1)	3/17 VD, prior CT/RT: ND	BFP, TAC, Allen card, Snellen	-	ND	ND

Table 2.2. continued

Author (year)	SAT (N)	Previous TX (N)	VA: type of test	VF: type of test	Change in VF after SAT	Prognostic factors decrease of VA
Dodgshun et al. (2015) [9]	CB (38), CB-VC (4)B	Biopsy + (ND), SX/ RT: ND	Snellen, Kay Pictures	ND	7/35 (20%) abnormalities at diagnosis: 2/ 7 (29%) improved, 5/7 (71%) stable (no definition of change)	ND
Prada et al. (2015) [44]	CB/VC (21), VC/DC (1)B	ND	ND	-	ND	ND
Doganis et al. (2016) [45]	CB-VC (16), of which switch to VB (5) due to allergy	ND	Snellen, Kay Pictures	-	ND	ND
Lassaletta et al. (2016)[18]	VB (24)	Previous sx/ biopsy + (ND)	ND	-	ND	ND
Falzon et al. (2018) [29]	CB-VC (46), CB & VC or ETO (44)	Biopsy + (ND), S: ND, prior CT/RT: excluded	TAC, Snellen	-	ND	-NF1: Age ≤ 5 years (OR 5.3; 95% CI: 1.0–26.7; P=0.04) and (M)DC stage 3 (OR 7.1; 95% CI: 1.8–33.3; P=0.006) -nNF1: No prognostic factor found

Abbreviations: AC; actinomycin, BFP: binocular fixation preference; CB: carboplatin; CI: confidence interval; Cispl: cisplatin; DC: dactinomycin; ETO: etoposide; HOTV: HOTV eye test chart; (M)DC: (Modified) Dodge Classification; ND: no data; NF1: neurofibromatosis type 1; nNF1 No systemic association with neurofibromatosis type 1; P: P-value; PCZ: procarbazine; OR: odds ratio; RT: radiotherapy; SAT: Systemic Antitumor Therapy; SX: surgery; TAC: Teller Acuity Cards; TPCV: thioguanine, procarbazine, lomustine and vincristine; TX: treatment; VA: visual acuity; VB: vinblastine; VC: vincristine; VD: ventricular drain; VF: visual field

A : Results only available for total population that received SAT.

B : Subpopulation that received SAT.

Table 2.3. Binocular and/ or monocular change in VA after chemotherapy for OPG

Change in VA/ Author (year)	VA ↑ binoc, N (%)1	VA ↔ binoc, N (%)1	VA ↓ binoc, N (%)1	VA ↑ binoc, N (%)2	VA ↔ binoc, N (%)2	VA ↓ binoc, N (%)2	VA ↑ monoc, N (%)1	VA ↔ monoc, N (%)1	VA ↓ monoc, N (%)1	VA ↑ monoc, N (%)2	VA ↔ monoc, N (%)2	VA ↓ monoc, N (%)2
Massimino et al. (2002) [17]				10 (45)	7 (32)	5 (23)						
Dalla Via et al. (2007) [41]				0 (0)	2 (18)	9 (82)				2 (9)	5 (23)	15 (68)
Massimino et al. (2010) [42]	7 (41)	10 (59)	0 (0)									
Shofty et al. (2011) [43]				1 (5)	4 (21)	14 (74)						
Fisher et al. (2012) [30]	28 (32)	35 (40)	25 (28)				37 (22)	96 (57)	35 (21)			
Kalin-Hadju et al. (2014) [31]	0 (0)	11 (69)	5 (31)	1 (7)	7 (50	6 (43)	0 (0)	27 (79)	7 (21)	1 (3)	24 (71)	9 (26)
Dodgshun et al. (2015) [9]	5 (14)	27 (77)	3 (9)	4 (11)	20 (57)	11 (31)	7 (10)	59 (84)	4 (6)			
Prada et al. (2015) [44]				4 (17)	6 (27)*	12 (56)*						
Doganis et al. (2016) [45]	7 (44)	7 (44)	2 (13)	4 (25)	9 (56)	3 (19)						
Lassaletta et al. (2016) [18]				5 (21)	15 (62)	4 (17)						
Falzon et al. (2018) [29]				19 (21)	35 (39)	35 (39)						

Abbreviations; binoc: binocular, mono: monocular, VA: visual acuity

*: the interval between initiation or cessation of treatment and measurement of VA was not presented

1: time of measurement < 3 months after completion of chemotherapy cycle

2: time of measurement > 3,5 years after start of chemotherapy

Critical Appraisal

All studies were judged as grade 4 evidence according to the CEBM [46]. Critical JBI-CA appraisal of all case series revealed 6 studies with a low risk of bias (see Supplement 2.4). The focus on change in VA as an outcome parameter was variable among the studies. Four studies presented change in VA as the primary or secondary outcome parameter [9, 29-31]. In other studies change in VA was classed as a higher-order outcome parameter, accompanied mainly by a lack of information on the definition of change in VA.

Outcome, Definition and Prognostic Factors on Change in Visual Function

After treatment with SAT, 11 included studies (N=358) showed binocular improvement in VA within the range of 0–45 %, stability in the range of 18–77%, and a decrease in VA in the range of 0–82%. Cumulative outcome proportions of the total population are presented in the Discussion section. As the studies presented a high variability in the definition of change in VA, we considered these calculations unreliable. This diversity within variables is discussed below.

Change in VF was evaluated in 2 studies [9, 30]. Fisher et al. reported on the outcome of VF in 26 patients: 19% improved, 38% remained stable and 42% decreased. Dodgshun et al. reported 7/35 (20%) abnormalities at diagnosis, of which 2/7 (29%) improved after SAT and in 5/7 (71%) of which VF defects persisted. Neither study reported on the extent of VF loss, the age of the tested population, the type of VF test and the definition of change in VF.

The variability in the definitions of change in VA resulted from the various components used. First, different definitions of change in VA were used in each of 4 studies (see Table 2.1). Fisher et al. applied change $\leq = \geq 0.2$ Snellen lines [30] and second, Falzon et al. $\leq = \geq 0.2$ LogMAR [29]. We consider these definitions as equal, as mostly similar VA cards were used in both studies, which are (partially) validated for conversion to the linear representation of VA: logarithmic minimum angle of resolution (LogMAR), and $\leq = \geq 0.2$ in Snellen lines is considered equal to $\leq = \geq 0.2$ LogMAR. In these 2 studies the time interval between starting point and evaluation varied greatly (3 months after cessation of SAT [30] – median 6.5 years [29]). Dodgshun et al. defined change in VA according to the ICO (International Council of Ophthalmology: reporting visual loss in research) categories, i.e., a change of 0.3 LogMAR per category [9]. Kalin et al. defined change in VA per category according to the WHO Childhood Visual Impairment Scale: a change of 0.4 LogMAR per category [31]. Seven studies gave no definition of change in VA, nonetheless reporting on such change.

A second variable regarding change in VA is monocular/binocular evaluation. All studies presented results on binocular change in VA. Four studies presented both binocular and monocular change [9, 30, 31, 41] (see Table 2.3).
A third variable is term of follow-up. Five studies reported on change in binocular VA from start to within 3 months after the end of SAT [9, 30, 31, 42, 45], 3 of which also provided long-term data [9, 31, 45]. Nine studies published long-term results (range of median follow up was 2.2–8 years after the start of SAT (see Table 2.1)).
Finally, stratification for anatomic location is essential in evaluating change in VA. Only Falzon et al. [29] and Fisher et al. [30] evaluated change in VA per anatomic location; these results are discussed below.

In 6 of these 9 studies tumor progression after first-line SAT was recorded, presenting progression in 86 out of 159 patients (54%). Only in 2 studies was information on change in VA available for between-group analysis on progressed vs. non-progressed OPG, on which we did not perform cumulative analysis as the volumes were too small (18 of 30 progressed) and the studies were not comparable [41, 43].

Prognostic factors for a decrease in VA could not be determined due to the diversity in outcome parameters of the included studies, and therefore they were registered when available per study. Both Falzon et al. [29] and Fisher et al. [30] performed multivariate analyses on prognostic factors for a decrease in VA after CT (see Table 2.2). Multivariate analysis per subject (with NF1) showed that OPG located posterior to the chiasm ((M)DC stage 3) appears to be a negative risk factor for a decrease in VA [29, 30], but not in nNF1 OPG [29]. Patients under the age of 5 years had a similar negative risk factor for a decrease in VA for NF1 OPG, but not for nNF1 OPG [29].

Discussion

This systematic review evaluated the impact of SAT for pediatric OPG on VA and VF. Improvement in binocular VA was found in 0–45%, stability in 18–77%, and a decrease in 0–82% of studies after a median follow-up after the start of SAT of 3.7 years (range: cessation of SAT – 8.2 years).

SAT is currently widely applied for progressive pediatric OPG. More than a decade ago, Moreno et al. performed a systematic review on the effect of SAT on visual outcome (1990–2008) [32]. However, all their included studies were of low methodologic quality and were highly heterogeneous. A cumulative decrease in VA after SAT was found in 38% of 174 patients. No analysis was performed on the definitions applied to assess change in VA or VF. Stratification for anatomic location or NF1 status was impossible due to insufficient information. Among the different studies, the following arguments hold true: (1) contamination of treatment results with surgery/radiotherapy and no SAT [47]; (2) a small population of those completing SAT (< 10 patients) [48]; (3) incomplete data on stability of or decrease in VA [49]; and (4) no report available on change in VA [6, 50]. One study was retracted from publication [51].

Our systematic review (search 1990–2020) shows a significant increase in the cumulative population (N=358) and an increase in studies focusing on change in VA as the primary outcome parameter. The urgency to upgrade future study protocols persists to enable the effect of SAT treatment on visual function to be evaluated, and to enable stratified analysis of NF1 status, age, and anatomic location.

At present in pediatric OPG studies, VA is accepted as the overarching parameter representing visual function [37, 40]. This review showed that no uniform definition of change in VA was applied in existing studies, as 4 different definitions were used in 4 studies, and in 5 studies no definition was provided. The Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group recommends using the definition of change in VA of $\leq$ or $\geq$0.2 LogMAR in future studies on pediatric OPG [37]; this definition is already being applied in the protocols of ongoing studies [52].

At the start of this review, we intended to perform cumulative analysis on the effect of SAT on VA. However, in our opinion, this was not feasible after we had systematically reviewed the 11 included articles, as diverse variables concerning change in VA, such as monocular/binocular evaluation, anatomic location, definition of change in VA/VF and term of follow-up, differed greatly. In working towards an

international consensus, we suggest that agreement should first be reached on the definition of change in VA.

A first variable contributing to the definition of in change in VA, is the term of follow –up.. Cumulative analysis on 5 studies on change in VA within 3 months after cessation of SAT shows 27% improvement in VA (n=47), 52% stability (n=90) and a 20% decrease (n=20) in VA. Evaluation of 9 long-term studies (follow-up range of 2.2–8 years) shows improvement in 19% (n=48), stability in 42% (n=105) and a decrease in 39% (n=99). We believe these percentages should be interpreted with caution as definitions of change in VA among the studies differ or are not available.

A second variable contributing to the definition of change in VA is the distinction between monocular or binocular analyses of VA. Clinical experience suggests that the analysis of 1 or both eyes may differ in the course of OPG, as the anatomic location may result in an asymmetric burden on VA per eye. For example, in the case of a unilateral optic nerve glioma (stage 1 (M)DC), monocular VA may decrease considerably due to the progression of OPG, but as visual function of the other eye is not affected, binocular change in VA can remain unaffected. In this review, the studies defined monocular change in various ways, and therefore this outcome was not comparable. Future assessment of both the monocular and binocular status should evaluate the effect of therapy through per-eye analysis, and should evaluate functional visual disability through 2–eye analysis.

A third variable contributing to the definition of change in VA is anatomic location of OPG. This requires stratified analysis as the location of (NF1) OPG posterior to the chiasm appears to be a prognostic factor for a decrease in VA after SAT [29, 30], and there appears to be diversity in progression-free survival (PFS) among different anatomic locations [53].

The fourth variable contributing to the definition on change in VA is age at start of treatment. The combination of ongoing natural development of childhood visual function and known risk factors for the progression of OPG (age (<1 year [53]) or a decrease in VA after SAT (age < 5 year [29, 30]) requires stratification for different age categories. In this review, age at the start of treatment (median 3.2–8 years (range 0.4–17.2 years)) and duration of follow-up after SAT (median 3,7 years (range 0–8,2 years)) varied widely varied among the included studies. Stratification according to age categories was not possible as categorical or individual data were lacking in the majority of the studies.

Optic pathway glioma located in the chiasm and optic tract mostly results in a combination of defects in central (VA) and peripheral vision (VF). In the literature, both VA and VF are considered to mirror each other's function [30]. This assumption could not be substantiated in this review, as only 2 studies (on 33 patients) reported on these parameters. No association between VA and VF could be determined. In addition, a definition of change in VF was lacking. Performing VF tests at a young age (< 7 years) or on children with limited cooperation is highly challenging with a high risk for bias, which could explain the discrepancy between wide integration of VF examination in study protocols and the low level of presentation of results [30].

As, currently, 2D volume changes on MRI are poorly predictive for change in VA [29, 30], other forms of (more objective) examination like optical coherence tomography (OCT) have gained increased attention. OCT has proved to be a potent biomarker for visual loss in the case of screening for (NF1) OPG [54]. Regarding the monitoring of treatment effect, retinal nerve fiber layers (RNFL) appear to be associated with change in visual function. However, larger volume studies on the correlation between change in VA and RNFL or ganglion cell layer–inner plexiform layer are required [54].

Since 2008 treatment options for recurrent pediatric OPG have expanded with VEGF and MAPK pathway inhibitors. In this systematic review of studies on the effect of SAT on change in VA, these treatment modalities were not included as either their outcome parameters had no focus on the effect of visual function (8 studies), or the series were still very small (< 5 patients per series) [22, 55]. Nonetheless, the results on improvement/recovery of VA and/or VF after bevacizumab are considerable and impressive, necessitating future studies of larger volume and quality. Although a thorough and definitive effect analysis of MAPK inhibition on visual function is currently unavailable, several ongoing studies do include such an analysis [52, 56].

The findings of this review should be interpreted in the light of several limitations. First, the included studies presenting an outcome on change in VA are all non-comparable cohort studies with a high level of variability in outcome parameters among them. The rarity of the diagnosis as well as the diversity of location and tumor behavior of OPG make it difficult to perform high-quality prospective studies in this field.

Secondly, we included studies with surgical intervention prior to SAT, which may bias the effect on change in VA. Tumor resection or reducing intracranial pressure by VD can affect visual function and some days to several months may be required to evaluate this effect. In 5 studies, prior to the start of treatment, OPG had

been resected or biopsied, or VD had been placed (see Table 2.2 [9, 18, 29-31]). No information was available on the time interval after surgery, the extension of resection or the surgical effect on VA before the start of SAT. Three studies presented no data on prior surgical therapy [17, 44, 45]. Only Shofty et al. [45] excluded surgery. Surgical intervention frequently needs to be followed promptly by the start of SAT, limiting separate evaluation of the effect of surgery on VA and creating bias regarding the effect of SAT on change in VA.

Thirdly, in this review 6 out of 9 studies covered long-term follow–up, including results on subsequent progression: 54% of OPG cases progressed, of which the majority received sequential therapy, but no cumulative proportion could be calculated due to missing data. Within this time interval different parameters may affect visual function, either positively (e.g., individual potential for visual maturation), or negatively (e.g., a further decrease in VA at progression and during subsequent treatment of OPG).

Fourthly, in our series the incidence of NF1 patients is high (77%), which we consider an unreliable representation. In 6 studies the NF1 status was derived from the total study population, including OPG that had received no SAT or other, non-SAT treatment. Several multicenter studies on various treatments for OPG report a lower incidence of NF1 association of between 6 and 27% [6, 57, 58]. One study stated that treatment with SAT renders a higher PFS for NF1-associated OPG compared to nNF1 OPG [2], but this was contradicted in other studies.
In this review stratified analysis on the outcome for NF1/nNF1 was not performed due to the lack of individual data on VA outcome as per NF1 status. The only comparative results on NF1 status were available from Falzon et al.: NF1 is associated with a decrease in VA after SAT when the child is diagnosed with OPG at age $\leq$ 5 years and the anatomic location is posterior to the chiasm [29].

Conclusion

This systematic review on the treatment effect of SAT on visual function for pediatric OPG found an improvement in binocular VA in 0–45%, stability in 18–77% and a decrease in 0–82% in 11 studies, including 358 eligible patients. Although in the last decade studies have increased their focus on the effect of SAT on visual function, the quality of the studies persists on level 4 (CEBM) and the high diversity in outcome variables on the definition of change in VA limits meta-analysis. Reports on the effect of treatment on VF were scarce and outcome parameters were not defined. Treatment was carboplatin-based in 76% of OPG. No studies reporting on change in visual function after VEGF or MAPK signaling inhibition met the eligibility criteria due to low study volume (N=< 5). Future studies on the effect of SAT for pediatric OPG, including uniform VA monitoring protocols, are needed to evaluate treatment outcomes and to determine prognostic factors for the effect of SAT on visual function.

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Conflict of interest:

The authors have declared that no competing interests exist.

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Supplement 2.1.
Systematic research protocol

NIHR, National Institute for Health research
International prospective register of systemic reviews

Supplement 2.2.
Search strategy Ovid MEDLINE(R) and Epub Ahead of Print

In-Process & Other Non-Indexed Citations and Daily 1946 to August 04, 2020. Date search: 2020-08-06

#	Searches	Results
1	optic nerve glioma/	**457**
2	(glioma/ or astrocytoma/) and (optic tract/ or optic nerve/ or optic chiasm/ or optic nerve neoplasms/)	**817**
3	*optic nerve neoplasms/dt	**29**
4	((((optic or visual) adj2 (pathway* or tract*)) or (optic adj2 (thalam* or hypothala* or prechias*)) or postchias* or chias*) and (gliom* or astrocytom*)).tw,kf.	**1295**
5	(ONG or ONGs or OPG or OPGs or OPHG or OPHGs or OCHG* or OHPA or OHPAs).tw,kf. and (gliom* or astrocytom* or ((nerve or optic) adj3 tum*)).mp.	**205**
6	(optic nerve adj (gliom* or astrocytom*)).tw,kf.	**368**
7	optic glioma*.tw,kf.	**479**
8	(((low-grade adj3 (glioma or gliomas or astrocytom*)) or pilocytic astrocytom*).tw,kf. or ((LGG or LGGs or PLGG or PLGGs).tw,kf. and gliom*.mp.)) and (vision or hypovision* or visual or visually or optic or VA or blind* or ((partial* or impair*) adj2 sight*) or op?thalmologic*).mp.	**709**
9	(((((optic or visual) adj2 (pathway or tract* or chias* or prechias* or postchias* or hypothal* or thalam*)) or (chiasm* adj1 (hypothal* or thalam*))) adj3 (tumo?r* or neoplasm*)) or optic nerve tumo?rs*).ti.	**102**
10	or/1-9 [OPGs / OPT as major topic]	**2648**
11	antineoplastic combined chemotherapy protocols/	**140355**
12	carboplatin/ or cisplatin/ or procarbazine/ or antineoplastic agents, phytogenic/ or etoposide/ or vinblastine/ or vincristine/ or antibiotics, antineoplastic/ or doxorubicin/ or antimetabolites, antineoplastic/ or fluorouracil/ or thioguanine/ or antineoplastic agents, alkylating/ or cyclophosphamide/ or dacarbazine/ or mitolactol/ or nitrosourea compounds/ or carmustine/ or lomustine/ or hydroxyurea/	**268552**
13	(cystostat* or chemother* or chemo-ther* or polychemother* or multichemother*).tw,kf.	**415714**
14	(carboplatin* or cisplatin* or cis-platin* or cis-diamminedichloroplat* or CDDP or CisPt or Cis-Pt or procarbazin* or etoposi* or eposid* or VP-16 or VP16 or vinca alkaloid* or vinblastin* or vincristin* or vinorelbin* or doxorubicin* or antimetabolit* or anti-metabolit* or fluorouracil* or 5FU or 5-FU or t?ioguanin* or alkylating drug* or cyclophos* or CY or d#carbazin* or DTIC or ICDT or mitolactol* or dibromodulcitol* or NSC-104800 or NSC104800 or nitroso* or carmustin* or BCNU or BiCNU or lomustin* or CCNU or CeeNU or hydroxyurea* or hydrea hydroxycarbamid* or oncocarbamid*).tw,kf.	**268044**
15	(SFOP or BBSFOP or TPDCV).tw,kf.	**91**
16	or/11-15 [chemotherapy]	**703973**
17	10 and 16 [I OPG + chemotherapy]	**382**
18	*antineoplastic agents/ or molecular targeted therapy/	**221049**
19	angiogenesis inhibitors/ or antibodies, monoclonal, humanized/ or "antineoplastic agents, immunological"/ or bevacizumab/	**65656**
20	protein kinase inhibitors/ or exp *protein kinases/ai or exp proto-oncogene proteins/ai or benzimidazoles/	**100026**
21	(trametinib or AZD 6244 or dabrafenib).rn.	**1229**

22	((antineoplast* or anti-neoplast* or anticancer or anti-cancer or antitumo?r or anti-tumo?r) adj3 (agent* or drug* or therap* or treatment* or biological*)).tw,kf.	**117216**
23	(molec* adj1 target* adj2 (therap* or treat* or drug* or agent* or medicin*)).tw,kf.	**10840**
24	(((angiogene* or vascular endothelial growth factor* or VEGF*) adj3 (inhibit* or anti or block* or antagonist* or targeting or targeted)) or antiangiogene* or antiVEGF or (humanized adj2 (Ab or Abs or Moab* or monoclonal* or antibod*)) or bevacizumab or BVZ or Avastin or Mvasi).tw,kf.	**54297**
25	(((protein kinas* or BRAF* or MEK* or MAPK* or MAP-kinase) adj3 (inhibit* or anti or antagonist* or block* or targeting or targeted)) or trametinib or mekinist or JTP74057 or JTP-74057 or GSK1120212 or GSK-1120212 or selumetinib or ZD6244 or ZD-6244 or AZD6244 or AZD-6244 or ARRY142886 or ARRY-142886 or dabrafenib or GSK2118436 or GSK-2118436).tw,kf.	**52358**
26	or/18-25 [antineoplastic agents, VEGF- & protein kinase inhibitors]	**499911**
27	10 and 26 [II OPG and neoplastic agents, VEGF & protein kinase inhibitors]	**78**
28	((optic pathway gliom* or optic nerve gliom*).ti. or *optic nerve glioma/) and (child* or infant* or p?ediatric).ti. and (vision or hypovision* or visual or visually or VA or blind* or ((partial* or impair*) adj2 sight*) or op?thalmologic*).mp. and (management.ti. or (treatment or therapy).tw. or dt.fs.) and ((exp case-control studies/ or exp cohort studies/ or cross-sectional studies/ or registries/ or (cohort or prospectiv* or cross*ection* or cross-section* or retrospect* or registry* or registries).tw,kf.) not (editorial/ or review/ or (review or cochrane).ti.)) [III cohort studies on management pediatric OPG (major topic)]	**33**
29	17 or 27 or 28 [I II III chemotherapy/other antineoplastic agents/ management OPG]	**427**
30	(exp child/ or exp infant/ or (p?ediatric* or child or children* or childhood or infant* or infanc* or neonat* or neo-nat* or newborn* or new-born* or baby or babies or toddler* or prekindergarten* or kindergarten* or preschool* or school-age* or schoolage* or puber* or teens or teenager* or youth or juvenile* or boys or girls).tw,kf.) not (exp animals/ not humans/) [pediatric filter]	**3143257**
31	29 and 30 [I II human pediatric OPG + chemotherapy / management]	**347**
32	limit 31 to yr="1990 -Current" [I II III pediatric OPG therapy >1990]	**336**
33	remove duplicates from 32 [I II III human pediatric OPG + chemotherapy / management >1990 - deduplicated]	**336**

Supplement 2.3.
Search Strategy Embase Classic+Embase 1947 to 2020 August 05. Date of search: 2020-08-06

#	Searches	Results
1	optic nerve glioma/ or pilocytic astrocytoma/ or (optic pathway adj2 glioma*).dq.	4515
2	(glioma/ or astrocytoma/) and (optic tract/ or optic nerve/ or optic chiasm/ or optic nerve neoplasms/)	1229
3	*optic nerve neoplasms/dt or (*glioma/dt and cancer grading/ and preschool child/)	72
4	((((optic or visual) adj2 (pathway* or tract*)) or (optic adj2 (thalam* or hypothala* or prechias*)) or postchias* or chias*) and (gliom* or astrocytom*)).tw,kw.	2173
5	(ONG or ONGs or OPG or OPGs or OPHG or OPHGs or OCHG* or OHPA or OHPAs).tw,kw. and (gliom* or astrocytom* or ((nerve or optic) adj3 tum*)).mp.	402
6	(optic nerve adj (gliom* or astrocytom*)).tw,kw.	590
7	optic glioma*.tw,kw.	774
8	(((low-grade adj3 (glioma or gliomas or astrocytom*)) or pilocytic astrocytom*).tw,kw. or ((LGG or LGGs or PLGG or PLGGs).tw,kw. and gliom*.mp.)) and (vision or hypovision* or visual or visually or optic or VA or blind* or ((partial* or impair*) adj2 sight*) or op?thalmologic*).mp.	1448
9	(((((optic or visual) adj2 (pathway or tract* or chias* or prechias* or postchias* or hypothal* or thalam*)) or (chiasm* adj1 (hypothal* or thalam*))) adj3 (tumo?r* or neoplasm*)) or optic nerve tumo?rs*).ti.	131
10	or/1-9 [OPGs / OPT as major topic]	7234
11	cancer chemotherapy/ or chemotherapy/ or combination chemotherapy/ or cancer combination chemotherapy/ or multimodal chemotherapy/ or chemosensitivity/	542725
12	*alkylating agent/ or carboplatin/ or cisplatin/ or dacarbazine/ or nitrosourea derivative/ or carmustine/ or lomustine/ or procarbazine/ or cyclophosphamide/ or mitolactol/ or *antineoplastic alkaloid/ or etoposide/ or vinblastine/ or vincristine/ or *anthracycline antibiotic agent/ or doxorubicin/ or *antineoplastic antimetabolite/ or fluorouracil/ or tioguanine/ or hydroxyurea/	648522
13	(cystostat* or chemother* or chemo-ther* or polychemother* or multichemother*).tw,kw.	673278
14	(carboplatin* or cisplatin* or cis-platin* or cis-diamminedichloroplat* or CDDP or CisPt or Cis-Pt or procarbazin* or etoposi* or eposid* or VP-16 or VP16 or vinca alkaloid* or vinblastin* or vincristin* or vinorelbin* or doxorubicin* or antimetabolit* or anti-metabolit* or fluorouracil* or 5FU or 5-FU or t?ioguanin* or alkylating drug* or cyclophos* or CY or d#carbazin* or DTIC or ICDT or mitolactol* or dibromodulcitol* or NSC-104800 or NSC104800 or nitroso* or carmustin* or BCNU or BiCNU or lomustin* or CCNU or CeeNU or hydroxyurea* or hydrea hydroxycarbamid* or oncocarbamid*).tw,kw.	388155
15	(SFOP or BBSFOP or TPDCV).tw,kw.	123
16	or/11-15 [chemotherapy]	1269706
17	10 and 16 [I OPG + chemotherapy]	1549
18	*antineoplastic agents/	117642
19	*molecularly targeted therapy/ or (molecularly targeted therapy/ and (mapk signaling/ or vegf signaling/ or exp protein serine threonine kinase/))	15785
20	exp *angiogenesis inhibitor/ or immunological antineoplastic agent/ or antineoplastic monoclonal antibody/ or bevacizumab/	145946
21	exp *protein serine threonine kinase inhibitor/ae, ad, cb, cm, ct, dt, iv, po or exp *protein tyrosine kinase inhibitor/ae, ad, cb, cm, ct, dt, iv, po or b raf kinase inhibitor/ or *dabrafenib/ or exp mitogen activated protein kinase kinase inhibitor/ [incl. trametinib & selumetinib]	109293

22	((antineoplast* or anti-neoplast* or anticancer or anti-cancer or antitumo?r or anti-tumo?r) adj3 (agent* or drug* or therap* or treatment* or biological*)).tw,kw.	**154326**
23	(molec* adj1 target* adj2 (therap* or treat* or drug* or agent* or medicin*)).tw,kw.	**16647**
24	(((angiogene* or vascular endothelial growth factor* or VEGF*) adj3 (inhibit* or anti or block* or antagonist* or targeting or targeted)) or antiangiogene* or antiVEGF or (humanized adj2 (Ab or Abs or Moab* or monoclonal* or antibod*)) or bevacizumab or BVZ or Avastin or Mvasi).tw,kw.	**88233**
25	(((protein kinas* or BRAF* or MEK* or MAPK* or MAP-kinase) adj3 (inhibit* or anti or antagonist* or block* or targeting or targeted)) or trametinib or mekinist or JTP74057 or JTP-74057 or GSK1120212 or GSK-1120212 or selumetinib or ZD6244 or ZD-6244 or AZD6244 or AZD-6244 or ARRY142886 or ARRY-142886 or dabrafenib or GSK2118436 or GSK-2118436).tw,kw.	**67930**
26	or/18-25 [antineoplastic agents, VEGF- & protein kinase inhibitors]	**571352**
27	10 and 26 [II OPG and antineoplastic agents, VEGF- & protein kinase inhibitors]	**453**
28	((optic pathway gliom* or optic nerve gliom*).ti. or *optic nerve glioma/ or *pilocytic astrocytoma/) and (child* or infant* or p?ediatric).ti. and (vision or hypovision* or visual or visually or VA or blind* or ((partial* or impair*) adj2 sight*) or op?thalmologic*).mp. and (management.ti. or (treatment or therapy).tw. or dt.fs.) and ((exp case control study/ or cohort analysis/ or follow up/ or longitudinal study/ or prospective study/ or retrospective study/ or cross-sectional study/ or register/ or (cohort or prospectiv* or cross*ection* or cross-section* or retrospect* or registry* or registries).tw,kw.) not (review.pt. or review.ti.)) [III cohort studies on management pediatric OPG (major topic)]	**114**
29	17 or 27 or 28 [I II III chemotherapy/other antineoplastic agents/ management OPG]	**1768**
30	(child/ or preschool child/ or school child/ or toddler/ or childhood cancer/ or (p?ediatric* or child or children* or childhood or infant* or infanc* or neonat* or neo-nat* or newborn* or new-born* or baby or babies or toddler* or prekindergarten* or kindergarten* or preschool* or school-age* or schoolage* or puber* or teens or teenager* or youth or juvenile* or boys or girls).tw,kw.) not (exp animal/ not human/)	**3623988**
31	29 and 30 [I II III human pediatric OPG + chemotherapy / management]	**1356**
32	editorial/ or (editorial or note or conference abstract or conference review).pt.	**5366106**
33	31 not 32 [I II human pediatric OPG + chemotherapy / management - not conference abstracts, editorials, notes]	**828**
34	limit 33 to yr="1990 -Current" [I II III pediatric OPG therapy >1990]	**806**
35	34 not medline.cr. [I II III pediatric OPG therapy >1990, embase records only]	**769**
36	remove duplicates from 35 [I II III pediatric OPG therapy >1990, embase records only - deduplicated]	**765**

Supplement 2.4. JBI-Critical appraisal of included case series

Author/ JBI-CA assessment	1: Clear criteria for inclusion?	2: Condition measured in standard, reliable way?	3: Valid methods for identification of condition?	4: Consecutive inclusion participants?	5: Complete inclusion participants?	6: Clear reporting demographics participants?	7: Clear reporting clinical information participants?	8: Outcome follow up results clearly reported?	9: Clear reporting presenting site/ demographics?	10: Statistical analysis appropriate?	Cumulative response per study		
											Yes	No	Unsure
Massimino et al. (2002) [9]	Y	U	Y	U	U	Y	N	N	N	U	3	3	4
Dalla Via et al. (2007) [36]	Y	Y	Y	Y	Y	Y	Y	N	Y	U	8	1	1
Massimino et al. (2010) [37]	Y	U	Y	U	U	Y	N	N	N	U	3	4	3
Shofty et al. (2011) [39]	Y	Y	Y	Y	Y	Y	N	N	N	Y	7	3	0
Fisher et al. (2012) [23]	Y	Y	Y	U	U	Y	Y	Y	U	U	6	0	4
Kalin-Hadju et al.(2014) [24]	Y	N	N	U	U	Y	Y	Y	Y	U	5	2	3
Dodgshun et al. (2015) [35]	Y	N	Y	U	Y	Y	Y	U	Y	Y	7	1	2
Prada et al (2015) [45]	Y	U	U	Y	Y	Y	N	N	N	U	4	3	3
Doganis et al.(2016) [38]	U	Y	U	Y	Y	U	N	Y	N	U	4	2	4
Lassaletta et al. (2016) [11]	Y	U	Y	U	Y	Y	N	N	N	U	4	3	3
Falzon et al. (2018) [22]	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	9	0	1

Light grey rows: low risk of bias

Supplement 2.5.
PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	9
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	9-10
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9-10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	10
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	11

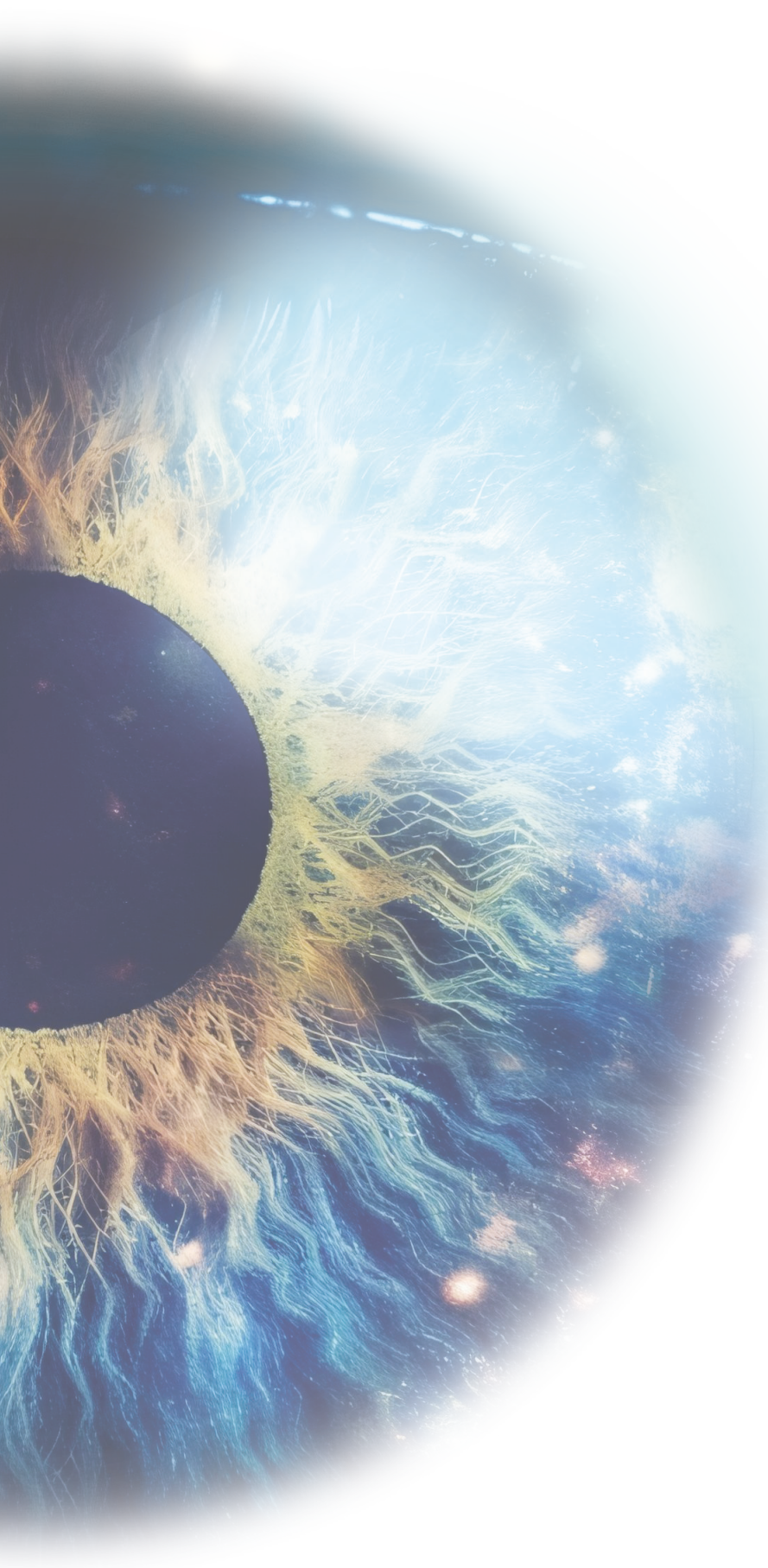
Supplement 2.5.
PRISMA 2009 checklist continued

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	11
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12-16
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	17-22
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	21-22 24-25
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	26
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	29-30
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	31
FUNDING			

Supplement 2.5.
PRISMA 2009 checklist continued

Section/topic	#	Checklist item	Reported on page #
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	In financial disclosure section of submission system: NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097



CHAPTER 3

A retrospective, nationwide, multicenter study on diagnosis and treatment outcome of pediatric chiasmatic-hypothalamic gliomas including analysis on risk factors for progression after systemic anticancer therapy

C.A.M. Bennebroek, J. van Zwol, M.C. Montauban van Swijndregt, G.L. Porro, MD, R. Oostenbrink, A.T.M. Dittrich, J.W. Pott, L. Meijer, E.J.M. Janssen, S. Klinkenberg, N.J. Bauer, I.C. Notting, M.M. van Genderen, M.W. Tanck, P. de Graaf, P. Saeed and A.Y.N. Schouten- van Meeteren

Cancers.2025 Feb 20;17(5):716

Abstract:

Introduction:
The current standard therapy for pediatric chiasmatic-hypothalamic optic pathway glioma (OPG) is systemic anticancer therapy (SAT) over surgery and radiotherapy. Nevertheless, recurrent radiological or clinical tumor progression after SAT forms a considerable challenge. Sporadic OPGs are considered to have a higher tendency for progression after first-line systemic anticancer therapy (SAT) compared to Neurofibromatosis type 1-associated (NF1) OPGs.

Methods:
The objective of this study was to conduct a national retrospective cohort analysis of children who received various treatments for progressive OPG between 1995 and 2020. The study aimed to examine the differences in clinical course and the range of treatment modalities applied to both sporadic and NF1-associated OPGs. Additionally, we sought to identify risk factors for 3- and 5-year progression following first- and second-order SAT.

Results:
In total, 136 children received treatment, of whom 49 of 136 (36.0%) had NF1. Within median 7.5 years (range: 0.1-23.8 years) of follow-up, sporadic OPG received more treatments compared to NF1-associated OPG (median 2 (range: 1-8) vs. median 1 (range: 1-7) ($p<0.01$)). Nine children with a sporadic OPG (6.6%) died. Of 112 children (82.4%) receiving SAT, 92% received combined first-line vincristine and carboplatin. These children had a 3- and 5-year progression-free survival of 61.8% (95% CI: 51.0–72.6%) and 48.4% (95% CI: 38.0–58.8%), respectively. Sporadic OPGs had a higher rate of second progression ($p<0.01$). Starting first-line vincristine and carboplatin at the age below one year was the only independent risk factor for progression.

Conclusion:
In this national historic cohort of pediatric OPG four out of five children received SAT. Sporadic OPGs received a higher number of various SATs compared to NF1-associated OPGs, but were no independent risk factor for progression after combined vincristine and carboplatin, as only starting SAT before the age of one year was.

Introduction

Pediatric chiasmatic-hypothalamic glioma involving the optic pathways (OPG) is a subset of low-grade glioma (LGG), primarily localized in the chiasm, optic tract with or without optic nerve involvement. OPGs represent approximately 2–5% of all pediatric intracranial tumors and are histologically classified as pilocytic astrocytomas (PA) in 85-90% (1, 2). These tumors are associated with Neurofibromatosis type 1 (NF1) in 30-50% of children. While OPGs are generally slow-growing, their progression can lead to significant morbidity, including the loss of visual functions, neurological deficits, and, in some cases, death.

Progressive OPGs requiring intervention are generally treated with systemic anticancer therapy (SAT), represented by various chemotherapy strategies, anti-VEGF and MAP-kinase directed therapy, because surgery poses a high risk of damaging adjacent critical brain structures. Also, both surgery and radiotherapy can lead to severe cognitive, visual and endocrine impairment (3, 4). Additionally, radiotherapy can result in cerebral vasculopathy (5, 6) (7) or secondary tumors in patients with NF1 (9), which emphasizes the importance of maximally delaying radiotherapy in young children.

Considering a high overall survival (OS) rate of 90-100% (10), the use of SAT requires ongoing balancing between effectiveness and toxicity to minimize long-term sequelae resulting from both disease and therapy. Over the last four decades, combined vincristine and carboplatin have become the most frequently applied standard of care for first-line SAT (11) (12), while in some countries vinblastine is considered the first-line standard of SAT (13). However, no global consensus exists on the use of successive SAT (14). The current experience with available SAT strategies is characterized by progression after both first-line and successive treatment lines, which places a long-term burden on both children and their parents (11, 13, 15). Recently, targeted therapy in the Ras/Raf/4 signaling pathways has revealed promising outcomes in effectively reducing tumor volume and minimizing the rate of progression (16, 17), leading to changes in subsequent SAT strategies.

Studies investigating risk factors for progression following initial SAT for OPG have concluded that children starting treatment below the age of one year are at an increased risk of recurrent progression (11, 15). Additionally, sporadic OPGs (not associated with NF1) are suggested to have a more aggressive disease course compared to NF1-associated OPGs, leading to earlier progression after SAT (15) (13). This evidence is supported by studies on LGGs that include various anatomical locations (18) or studies on diverse LGG locations including separate analyses on

OPGs (19). The former do not provide a fair representation of treatment outcomes specifically for OPGs, which is reflected in studies comparing outcome for diverse anatomic locations of LGGs, as 5- and 10-year progression-free survival (PFS) is significantly lower for OPGs compared to LGGs in other cerebral locations (2, 18, 20). Consequently, there is an ongoing need for more comprehensive data to assess treatment outcome based on NF1 status and to work towards individualized treatment strategies for children at risk for a more aggressive course.

In this retrospective national cohort study, we present an overview of diagnosed and treated OPGs, including focus on comparing progression, survival outcomes and risk factors for progression between NF1-associated and sporadic OPGs across various treatments.

Material and Methods

Study Population

Data were retrospectively obtained from children aged 0-17 years who were diagnosed with an OPG between January 1995 and December 2018 and from children who were treated for progressive OPGs between January 1995 and December 2020. Data were collected from children who were registered in the national database of the Dutch Childhood Oncology Group (DCOG) between January 2003 and December 2018. Additionally, existing local databases in the pediatric oncology, ophthalmology and neurology departments of all participating centers were reviewed to include patients from January 1995 to December 2018. Patients with an isolated optic nerve glioma, both uni- and bilateral, were excluded, as these were published separately (21). Patients were treated in one of the eight university medical centers in the Netherlands or at the national pediatric oncology center (Princess Máxima Center). The study included both OPGs associated with NF1 and sporadic OPGs. Data were included from all children who received various treatments for a progressive OPG located within the chiasm and/or optic tract and/or involvement of the optic nerve(s), with or without hypothalamic involvement. To represent the complete national cohort of diagnosed pediatric OPGs, baseline data were collected for patients who did not receive treatment.

The study received approval from the DCOG and the ethics committees of all university medical centers, the Princess Máxima Center and two visual rehabilitation centers. Informed consent was obtained from patients (or their parents/ guardians) registered with the DCOG and UMC Utrecht. An opt-out procedure was offered to patients registered in the local databases of the Amsterdam UMC. Other centers granted permission to use anonymized patient data.

Data Collection

Demographic information, tumor-related characteristics and the sequence of treatment modalities were extracted from medical records and compared between NF1-associated and sporadic OPGs. The diagnosis of OPG was based on biopsy or, in case of unequivocal neuroradiological findings on orbital (T2-weighted, STIR or contrast-enhanced fat-suppressed T1-weighted) or brain (T2, FLAIR or contrast-enhanced T1-weighted) MRI**.** The NF1 status was assessed by clinical criteria substantiated by DNA analysis, when available.

In the Netherlands, until 2017, the individual indication and choice of treatment for progressive OPG were determined by local academic treatment teams. This process was subsequently centralized with the establishment of the national pediatric oncology center from 2018 on. We defined 'progression' as the start of first-line or successive treatment or as significant clinical deterioration (visual and/or neurological but no endocrinological functions) or radiological progression defined by the local multidisciplinary team, but in the absence of further treatment. First-line SAT, mostly represented by combine vincristine and carboplatin, was generally administered according to the SIOPe LGG study protocol (22), represented by a standard induction regimen involving ten weekly administrations of vincristine at a dose of 1.5 mg/m^2 via intravenous bolus, along with four single doses of carboplatin at 550 mg/m^2 as a 1-hour intravenous infusion, administered at 3-week intervals. This was followed by three cycles of concurrent VC treatment at 4-week intervals; doses were adjusted by weight for children below the age of 1 year and/or 10 kg). Total chemotherapy treatment lasted 18 months (23).

In case of a preterm change of SAT due to side effects, this switch was not considered as successive SAT. The anatomic location of the OPG was evaluated according to the Modified Dodge Classification (MDC) (24) by a 14-year experienced neuroradiologist (PG).

Three- and five-year progression-free survival (PFS) and OS analyses were performed following the start of first-line vincristine and carboplatin, as this combination accounted for more than 90% of first-line SAT, and all second-line SAT. Risk factors for progression after the start of SAT were assessed at three and five years after the start of first-line vincristine and carboplatin and as well as all second-line SAT.

Statistical Analysis

Continuous data were presented by mean and standard deviation (normal distribution) or median and range (non-normal distribution) and categorical data by

frequency and percentage. Regarding the NF1 status, between-group differences were examined using the Student's t-test for normally distributed continuous data, the Mann–Whitney U test for non-normally distributed continuous data, and the χ^2 test or Fisher's exact test for categorical data. The three- and five-year PFS and OS were calculated using the Kaplan–Meier method, defining progression as the date of start of successive therapy or the date of defined progression with no subsequent treatment. Patients were censored in case of death or loss to follow-up. Stratified comparison of the PFS distribution was performed using log-rank analysis ($p<0.05$).

Cox proportional hazards regression was used for both univariable ($p<0.05$) and multivariable analysis ($p<0.2$ in the univariable analysis) to identify prognostic factors for 3- and 5-year PFS ($p<0.05$). The analyzed variables were: NF1 status, age at the start of treatment and the anatomic location (MDC) of OPGs. Statistical analyses was conducted using SPSS software for Windows (version 26.0.0.1, SPSS Inc., Chicago, IL, USA).

Results

Between 1995 and 2018, 197 children were diagnosed with an OPG (see Table 3.1). Two patients were excluded because their parents refused data collection. Fifty-nine (29.9%) patients did not receive treatment, 91.5% of them had NF1. They were diagnosed at a median age of 5.8 years (range: 0.2-16.7 years) and followed for a median of 9.1 years (range: 0.1-23.8 years). Within the NF1 population, no significant differences were observed in sex, age at diagnosis or anatomic location of the OPG between patients who received various treatments and those who did not ($p=0.27$, $p= 0.10$, $p= 0.09$). Within the population of untreated patients, one child with NF1 was diagnosed at the age of four months and did not receive treatment before dying.

Table 3.1. The annual and 5-year number of children who were diagnosed with an OPG and number of children who received various treatments.

	Diagnosis : n	Diagnosis / yr	Start TX: n	Start various TX/ yr: n (%)
Total	195		136 (69.7)	
1995-1999	12	2.4	5	1 (41.7)
2000-2004	34	6.8	23	4.6 (67.6)
2005-2009	38	7.6	26	5.2 (68.4)
2010-2014	62	12.4	46	9.2 (74.2)
2015-2018	49	9.8	36	7.2 (73.5)

Abbreviations: TX: therapy, Yr: years.

Baseline Characteristics

A total of 136 children (69.7%) who received treatment, was included in this study. Among them, 36.0% had NF1 and 45.6% were male. Children were diagnosed at a median age of 4.6 years (range 0.3- 16.5 years). Sporadic OPGs were diagnosed at a younger age (median 3.8 years) compared to NF1-associated OPGs (median 5.4 years) ($p<0.01$). Treatment was initiated at a median age of 5.4 years (range: 0.3-16.5 years) and was started at a younger age for sporadic OPGs (median: 4.2 years) compared to NF1-associated OPGs (median: 7.3 years) ($p<0.01$). Treatment for sporadic OPGs started at a shorter interval after diagnosis compared to NF1-associated OPGs ($p<0.01$). Ninety-two children (67.7%) started with therapy shortly after diagnosis. The median follow-up period was 7.5 years (range: 0.1-23.8 years), with no difference based on the NF1 status. Diffuse OPGs, extending along the optic tract (MDC stage (1-)2-3-(4)), were present in 64.0% of cases, hypothalamic involvement was present in 62.5%. Both features were more common in sporadic OPGs ($p<0.01$). Initial treatment was started based on abnormalities in visual function in 76.0%, while neurological and/or endocrine symptoms were present in 42.1%. Histopathological analysis was available in 75 OPGs (55.1%), of which 84.0% were pilocytic astrocytomas. The baseline characteristics of the study cohort are summarized in Table 3.2.

Table 3.2. Baseline characteristics of pediatric patients treated for a progressive OPG: a comparison of NF1-associated and sporadic OPGs.

	Total population	NF1 ass. OPGs	Sporadic OPGs
Study cohort: n (%)	136 (100.0)	49 (36.0)	87 (64.0)
Male	62 (45.6)	23 (46.9)	39 (44.8)
NF1: Clinical diagnosis	-	22 (44.9)	-
DNA diagnosis	-	27 (55.1)	-
Indication start of treatment: n (%)			
Clinical abnormalities	121 (89.0)	35 (71.4)	86 (98.9)
Ophthalmological [1]	92 (76.0)	25 (71.4)	67 (77.0)
Neurological/ endocrinological [2]	51 (42.1)	15 (42.9)	36 (41.9)
Radiological progression [3]	9 (6.8)	8 (18.6)	1 (1.1)
No data	6 (4.4)	6 (12.2)	0 (0.0)
Anatomic location: MDC			
MDC 2	13 (9.6)	2 (4.1)	11 (12.6)
MDC 1-2	36 (26.5)	14 (28.6)	22 (25.3)
MDC **(1-)2-3-(4)** [4]	87 (64.0)	33 (67.3)	54 (62.1)
Hypothalamic involvement	85 (62.5)	27 (55.1)	58 (66.7)
LM metastases	11 (8.1)	0 (0.0)	11 (100.0)
Histopathology (73)			
Biopsy/ resection	75 (55.1)	10 (20.4)	65 (74.7)
Pilocytic astrocytoma	63 (84.0)	7 (70.0)	56 (86.2)
Pilomyxoid astrocytoma	7 (9.3)	0 (0.0)	7 (10.8)
Astrocytoma gr. 1	2 (2.7)	1 (10.0)	1 (1.8)
Astrocytoma gr. 2	1 (1.3)	0 (0.0)	1 (1.8)
Inconclusive	2 (2.7)	2 (20.0)	0 (0.0)
Treatment: m (r)			
Age at diagnosis (yr): m (r)	4.6 (0.3-16.5)	5.4 (1.5-13.9)	3.8 (0.3-16.5)
Age at start TX (yr): m (r)	5.4 (0.3- 16.5)	7.3 (2.3-16.3)	4.2 (0.3-16.5)
Diagnosis - start TX (yr): m (r)	0.1 (0.0-13.5)	0.6 (0.0-13.5)	0.1 (0.0-7.3)
Start TX – end FU (yr): m (r)	7.5 (0.1-23.8)	7.1 (0.1-22.3)	7.6 (0.17-23.8)
Nr. of TX: m (r)	2 (1-8)	1 (1-7)	2 (1-8)
1st line SAT (pts): n (%)	112 (82.4)	45 (91.8)	67 (77.0)
VCR/ CBDCA	103 (92.0)	39 (86.7)	64 (96.5)
VCR/ CBDCA/ ETP	3 (2.7)	0 (0.0)	3 (4.5)
Vinblastine	4 (3.6)	4 (8.2)	0 (0.0)
BVZ/ irinotecan	1 (0.9)	1 (20)	0 (0.0)
Temozolomide	1 (0.9)	1 (2.0)	0 (0.0)

1st line TX only (pts): n (%)	51 (37.5)	30 (61.2)	21 (24.1)
SAT	36 (70.6)	27 (90.0)	9 (42.9)
SX 5	10 (21.6)	1 (3.7))	9 (42.9)
RT	5 (3.6)	2 (7.4)	3 (14.3))
SX 4: 1st line or succ.: n (%)	66 (48.5)	8 (16.3)	58 (66.7)
RT: 1st line or succ.: n (%)	24 (17.6)	5 (10.2)	19 (21.8)
> 3 TXs: n (%)	30 (22.1)	5 (10.2)	25 (28.7)

Abbreviations: ass: associated, BVZ: bevacizumab, CBDCA.: carboplatin, ETP.: etoposide, FU: follow-up, LM: lepto-meningeal, MDC: Modified Dodge classification (stage 1: optic nerve involvement; stage 2: chiasm; stage 3; anterior optic tract/ stage 4; posterior optic tract), M (r): median (range), NF1: Neurofibromatosis type 1, Pts: patients, Sporadic: no association to NF1, RT: radiotherapy, SAT: systemic anticancer therapy, Succ.: successive, SX: surgery, TX: therapy, VCR: vincristine, Yr: years.

1: Ophthalmological symptoms include: a decrease in best-corrected visual acuity or visual field and/or proptosis. 2: Neurological or endocrinological symptoms, with or without ophthalmological symptoms. 3: Radiological progression on MRI, no clinical data available or no clinical abnormalities. 4: The MDC (1-)2-3-(4) stage includes: chiasmatic and anterior optic tract involvement with possible involvement of the optic nerve(s) and/or posterior tract. 5: Surgery was represented by partial or complete surgical resection, but not by biopsy only.

Treatment

The population received a median of two various treatments (range: 1-8). Sporadic OPGs received a median of two treatments, compared to one in NF1-associated OPGs ($p<0.01$). A flowchart representing the sequence of the various treatments is presented in Figure 1. In total, 37.5% received a single episode of first-line treatment only, which was more common in NF1-associated OPGs (58.8%) compared to sporadic OPGs (41.2%) ($p<0.01$). Thirty children (22.1%) received more than three different treatments, among whom 83.3% had a sporadic OPG. Initial resection was performed in 49 children (36.0%), followed by successive therapy in 37 children (75.5%) within a median of 0.3 years (range: 0.0-7.2 years). In total, nine children (6.6%) who received treatment died, seven of them due to progression of the OPG. One patient died due to infectious meningitis and one died by suicide. All patients had a sporadic OPG. One patient died within one month after diagnosis at the age of four months due to progression of the OPG. Treatment was not initiated at the request of the parents, due to rapid progression, discomfort and the absence of visual functions of the child. The NF1 status was not determined, but no clinical signs fitting NF1 were present.

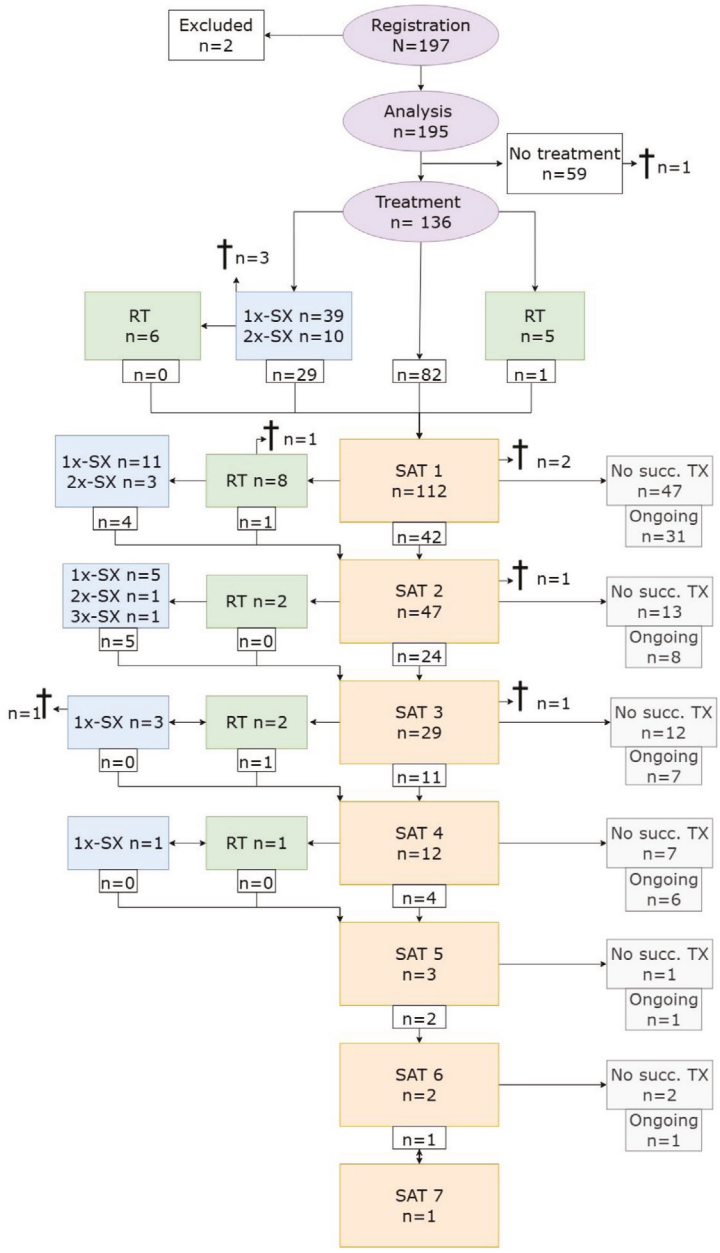


Figure 3.1. flowchart of various (successive) treatments for progressive pediatric OPGs.

Abbreviations: RT: radiotherapy, SAT: systemic anticancer therapy, Succ.: successive, SX: surgery, TX: therapy.

†: number of patients that died. Subscript: In case of preterm change of SAT due to side effects, a switch of SAT was not considered as successive SAT.

Systemic Anticancer Therapy

First-line SAT was administered to 112 patients (82.4%). Seventy-five children (67.0%) started within three months after the diagnosis of OP. Thirteen children (11.6%) started SAT within three months after surgical resection. Combined vincristine and carboplatin was administered in 103 children (92.0%), of whom 46 children (44.7%) developed an allergic reaction to carboplatin, resulting in 23 children (50%) switching SAT. Second-line SAT was administered to 47 children (42.0%), consisting of vinblastine monotherapy in 59.6% and a combination of bevacizumab and irinotecan in 19.1%. Children with sporadic OPGs received a greater number of SAT lines compared to children with NF1-associated OPGs ($p<0.01$) (see Figure 3.2). An overview of the different types and combinations of successive SAT lines is provided in Table 3.3.

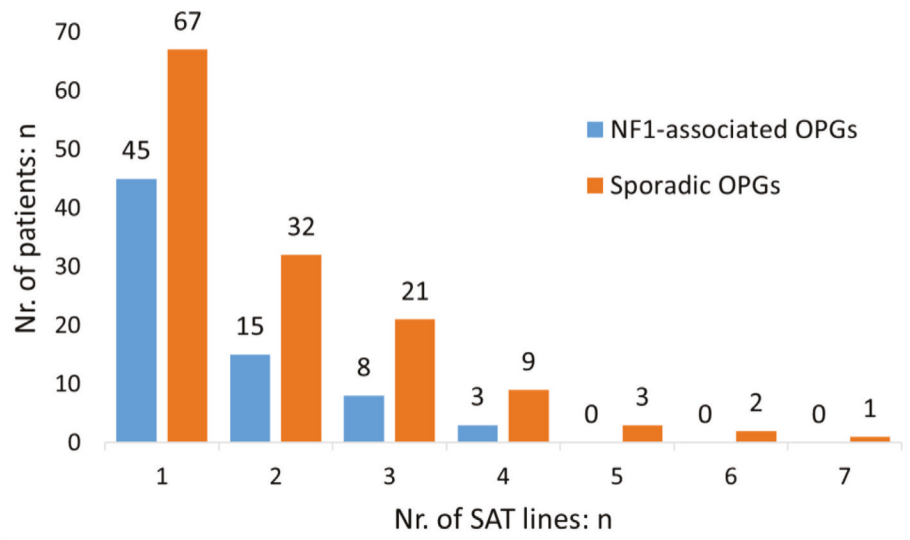


Figure 3.2. Successive number of treatment lines of systemic anticancer therapy (SAT) (n=112): a comparison of sporadic and NF1-associated OPGs.

Abbreviations: NF1: Neurofibromatosis type 1, Nr: number, SAT: systemic anticancer therapy , Sporadic: OPG not associated to NF1.

The 3- and 5-year PFS rates following first-line treatment with vincristine and carboplatin were 61.8% (95% CI: 51.0–72.6%) and 48.4% (95% CI: 38.0–58.8%). The progression rate was higher for sporadic OPGs compared to NF1-associated OPGs (Log-rank test: $p<0.01$) and varied across the four different age categories (Log-rank test: $p<0.01$). The 3- and 5-year OS were 95.5% (95% CI: 91.9-99.1%) and 93.5% (95% CI: 88.9-98.1%). Regarding second-line SAT (n=47), the 3- and 5-year PFS rates were

28.6% (95% CI: 13.8- 43.4%) and 13.1% (95% CI: 1.5- 24.7%). The rate of progression did not differ between sporadic and NF1-associated OPGs (Log-rank test: p= 0.22). Additionally, the rate of progression did not differ between second-line vinblastine and other second-line SAT combinations (p= 0.10). The Kaplan-Meier curves of PFS and OS for both first-line vincristine and carboplatin and second-line SAT are presented in Figure 3.3.

Table 3.3. Types of SAT of 112 children that received SAT for a progressive optic pathway glioma.

	SAT 1	Course: m (r) (mnths)	SAT 2	Course: m (r) (mnths)	SAT 3	Course: m (r) (mnths)	SAT 4	Course: m (r) (mnths)	SAT 5	Course: m (r) (mnths)	SAT 6	Course: m (r) (mnths)	SAT 7	Course m (r) (mnths)
Total pts	**112**		**47**		**29**		**12**		**3**		**2**		**1**	
VCR / CBDCA														
NF1	39	18 (1-32)	1	16										
sporadic	64	18 (1-24)	5	12 (10-20)										
VCR / CBDCA/ ETP														
NF1	0													
sporadic	3	18 (7-19)			1									
VCR														
NF1			1	2.0										
sporadic														
Vinblastin														
NF1	4	11 (11-14)	8	12 (2-12)	2	4 (2-5)	1	7						
sporadic	0		20	11 (2-21)	9	7 (2-12)								
BVZ/ IRI														
NF1	1	2	4	12 (4-24)	5	13 (8-22)	1	12						
sporadic	0		5	11 (6-14)	6	11 (6-15)	7	12 (6-36)	1	13				
BVZ														
NF1														
sporadic					1	6			1	18	1	55	1	22
BVZ/ vinbl.														
NF1														
sporadic			2	10 (8-12)	1	3	1	9						
Trametinib														

Table 3.3. Continued.

	SAT 1	Course: m (r) (mnths)	SAT 2	Course: m (r) (mnths)	SAT 3	Course: m (r) (mnths)	SAT 4	Course: m (r) (mnths)	SAT 5	Course: m (r) (mnths)	SAT 6	Course: m (r) (mnths)	SAT 7	Course m (r) (mnths)
NF1							1	8						
sporadic					2	19 (13-24)	1	4	1	18	1	4		
Temozolamide														
NF1	1	5	1	4										
sporadic					2	9 (6-11)								

Abbreviations: BVZ: bevacizumab, CBDCA: carboplatin, ETP: etoposide, IRI: irinotecan, Mnths: months, M (r): median (range), NF1: OPG associated to Neurofibromatosis type 1, pts: patients, SAT: systemic anticancer therapy, Sporadic: OPG with no association to NF1, VCR: vincristine, Vinbl: vinblastin

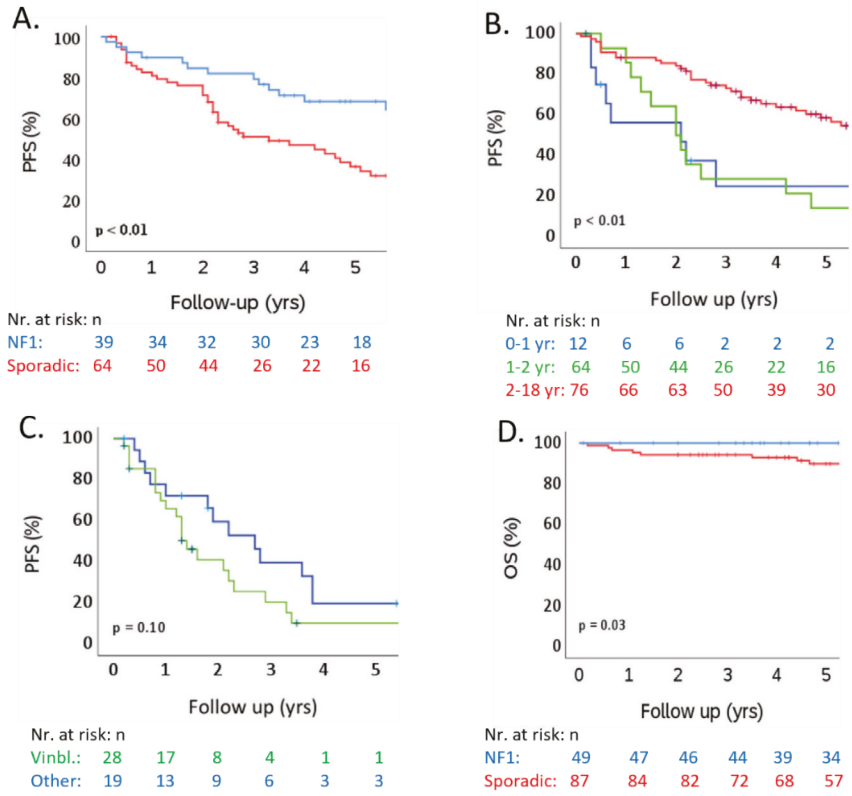


Figure 3.3. Kaplan Meier curves of PFS since the start of first-line vincristine/ carboplatin and various second-line SAT (n=103), and OS of the whole cohort that received various treatment.

A: PFS after first-line vincristine/ carboplatin: a comparison of NF1-associated and sporadic OPGs. B: PFS after first-line vincristine/ carboplatin (n=103): a comparison of age categories: 0- < 1yr vs. 1 to < 2 yr vs. 2- < 18 yr. C. PFS after second-line SAT (n=47: a comparison of vinblastin and other various second-line SAT (see Table 3.3). D: OS of the total cohort (N=136) after various treatments: a comparison of NF1-associated and sporadic OPGs (N=136).

Abbreviations: NF1: neurofibromatosis type 1, Nr: number, OS: overall survival, PFS: Progression-free survival, SAT: systemic anti-cancer therapy, Sporadic: no association to NF1, VCR/ CBDCA: vincristine/ carboplatin, Vinbl.: vinblastine, Yr(s): year(s).

Predictive Factors for Progression After First-Line SAT

Uni- and multivariate analyses of risk factors for progression identified age younger than 1 year at the start of vincristine and carboplatin as an independent predictive factor for both 3- and 5-year PFS (hazard ratio (HR): 2.8, 95% CI: 1.3–6.1, p<0.01))/ (HR: 2.4, 95% CI: 1.2-4.8, p= 0.02). Sporadic OPGs (3-yr PFS: HR: 2.3, 95% CI: 1.3-4.1, p<0.01)/ (5-year PFS: HR: 1.6, 95% CI: 1.2- 4.8, p<0.01) and age >1 - ≤ 2 yr at the start of therapy (3-year PFS: HR: 2.5, 95% CI: 1.3-4.9, p<0.01)/ (5-year PFS: HR: 2.3,

95% CI: 1.2-4.2, p= 0.01) were identified as dependent risk factors for progression in univariable analysis (see Table 3.4). As no patient within the groups of children aged under two years at the start of therapy (0 to < 1 and 1 to < 2 years) had NF1, a sensitivity analysis was performed within the population of children aged 2 to < 18 years using the variables of the NF1 status and MDC location of the OPGs. No (in) dependent prognostic factor was identified for the population of this age category.

Analysis of second-line SAT, including second-line vinblastine monotherapy, did not identify any (in)dependent prognostic factors for 3- or 5-year PFS.

Table 3.4. Uni- and multivariate analysis by Cox-regression: Prognostic factors for 3- and 5-year progression-free survival after start of 1st line vincristine and carboplatin.

PFS		Univariate: 3-year			Multivariate 3-year			Univariate: 5-year			Multivariate 5-year		
Variables	**n**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
NF1-associated OPGs	39	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-
Sporadic OPGs	64	2.3	1.3-4.1	<0.01	1.6	0.8-3.1	0.17	1.879	1.2-4.8	0.01	1.4	0.8-2.4	0.24
Age: 0-≤ 1 yr	12	3.4	1.7-6.9	<0.01	2.8	1.3-6.1	0.01	2.8	1.5-5.4	<0.01	2.3	1.2-4.8	0.02
Age: >1-≤ 2 yr	15	2.5	1.3-4.9	<0.01	1.9	0.9-4.2	0.09	2.3	1.2-4.2	0.01	1.8	0.9-3.5	0.10
Age: >2-≤ 18 yr	76	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-
MDC 2	10	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-
MDC 1+ 2	30	0.5	0.2-1.1	0.08	0.8	0.3-2.1	0.68	0.5	0.2-1.0	0.04	0.7	0.3-1.6	0.37
MDC (1-2)-3-(4)	63	0.5	0.2-1.1	0.08	0.7	0.3-1.6	0.38	0.4	0.3-1.1	0.09	0.7	0.3-1.4	0.32

Abbreviations: CI: confidence interval, HR: hazard ratio, MDC: modified Dodge classification (stage 1: optic nerve involvement; stage 2: chiasm; stage 3; anterior optic tract/ stage 4; posterior optic tract),, NF1: Neurofibromatosis type 1, PFS: progression-free survival, SAT: systemic anticancer therapy, Sporadic: OPGs not associated to Neurofibromatosis type 1, Yr: year.

Radiotherapy

Twenty-four children (17.6%) received RT at a median age of 10.0 years (range: 4.7-18.3 years). Five children (20.8%) received RT as initial treatment, two of whom had NF1; all five were treated between 2002 and 2004. Nineteen children received RT as successive treatment, three of whom had NF1. In 87.5% of children, radiotherapy was initiated before 2014.

The patients received a median dose of 54.0 Gray (range: 45.0- 57.6 Gray) and were followed for a median of 15.3 years (range 3.8- 23.4 years). The 3- and 5-year PFS rates were both 86.5% (95% CI: 72.1- 100.0%), the 10-year PFS was 80.0% (95% CI: 63.6%- 98.2%). No difference in PFS was observed between NF1-associated and sporadic OPGs. No patient died during follow-up.

Discussion

This national cohort study provides a historical overview of the number and diversity of treatments applied to children with progressive OPGs. NF1-associated OPGs accounted for 36.0% of cases. These OPGs were diagnosed and started treatment at an older age than sporadic OPG and received a lower total number of treatments. Among the population that received first-line vincristine and carboplatin, children with a sporadic OPG who started this treatment below the age of one year, had an increased risk of progression.

To our knowledge, no nationwide historic cohort study has been published on pediatric OPGs so far. One study presented monocenter data on the natural history of both sporadic and NF1-associated OPGs (25) and two on NF1-associated OPGs only (26) (27). All studies included both isolated optic nerve gliomas (ONGs) (8.5-48.1%) and other OPGs in the overall analysis. We have published a separate report on these entities as progression rates differ among ONGs and OPGs (21). Nicolin et al. (25) reported on NF1-association in 58.6% of the diagnosed OPGs including treatment in 23.1% of NF1-associated and 92.7% of the sporadic OPGs. NF1-associated OPGs were diagnosed at a younger age compared to sporadic OPG ($p<0.01$), no data was available on the age at the start of treatment. Data extraction for purely OPGs (excluding ONGs) could not be performed (25).

Trevisson et al. (27) and Listernick et al. (26) reported an incidence of NF1-associated OPGs, including ONGs at screening of 12.6% and 18.8%, respectively, compared to 7.1% and 11.2% without ONGs. MR imaging was performed in 44.7% and 100.0%. Treatment was initiated in 15.3% (OPG & ONG) and 6.1% (OPG only). In our study 47.6% of the NF1-associated OPGs and 94.6% of sporadic OPGs received treatment. Comparing the treatment rates for NF1-associated OPGs across these studies, we suspect that the high treatment rate in the present study, may be caused by underreporting of NF1-associated OPGs that were discovered at screening and did not require treatment, as these patients may have been registered incompletely in the Netherlands. Likewise, MRI examination is performed only in case of a clinically suspected OPGs. Both factors may have contributed to selection bias.

Similar to previous studies, in the present study no clinical differences (sex/ age at diagnosis/ MDC status) were observed between the OPGs that received treatment or did not (both NF1-associated and sporadic OPGs). Table 3.1 shows the 5-year incidence of the number of children that were diagnosed and started treatment, suggesting an increase of in the number of OPGs receiving treatment since 2010. This can be explained by inclusion bias in the years prior to the start of the national registration by the DCOG and, potentially, by a true increase of the treatment rate due to heightened awareness of clinical treatment indications and growing confidence in the effects of SAT. To provide insight into differences in local treatment approaches, we investigated the rate of initial radiotherapy or surgery per institute, but no clear differences in the initial local approach could be identified. We did not perform analysis on a possible shift in SAT strategy due to the small number of patients receiving alternative treatments next to the predominance of vincristine and carboplatin as first-line therapies.

With the increasing use of new SAT modalities in the recent decades, prolonged treatment with successive SAT strategies for recurrent progressive disease has postponed the use of radiotherapy as is shown in our cohort with a maximum of seven successive SAT modalities. In this study, targeted therapy was administered in only seven patients as successive treatment. This modality has become a promising strategy as successive but as well as first-line SAT (17), as radiological response and progression rates appears to be superior to conventional SAT strategies. The changing landscape of prioritizing of targeted therapy requires comparison with the current first-line SAT modalities in the subgroup solely consisting of OPGs (not LGGs at diverse anatomic locations). The two largest studies evaluating combined first-line vincristine and carboplatin (and etoposide in 1 treatment arm) (23), showed a 5-year PFS of 43.5% (n=169) (23) and 60.5% (n=123) (11). In the first study, NF1-association was present in 29.3% and the median age at the start of SAT was 4.3 years in the total population (N=497 LGG). In the second study, the NF1 incidence could not be extracted, the median age at the start of SAT was 2.9 years. Kotch et al. reported on 103 patients with NF1 who received vincristine and carboplatin in 75.9%, 26% had an ONG. Children started treatment at the age of 3.3 years (29). Forty percent of the total cohort showed progression within five years. In our study, the 5-year PFS was 48.4% (n=103), 37.9% had NF1 and the median age at the start of SAT was 5.4 years.

First-line treatment with vinblastin for LGGs (N=55) showed a 5-year PFS of 53.2%. In 54.4% LGGs were represented by OPGs, but no separate analysis on PFS was available for OPGs (13). The French BBSFOP trial showed a 5-year PFS of 34.0%, NF1 was present in 27%, the median age at the start of SAT was 1.4 years (15).

Identifying factors that increase the risk of progression after first-line or successive therapy is essential given the rarity of pediatric OPG, the rate of progression and the risk of impaired vision. Earlier studies on prognostic factors for progression after first-line SAT, which focused solely on pediatric OPG, including both NF1-associated and sporadic OPGs, have identified several risk factors. These include children starting therapy before one year of age (11, 15), non-pilocytic astrocytoma (11), the sporadic appearance of OPGs (15) and/or failure of early response after first-line of SAT (15) as independent risk factors for progression. The presence of diencephalic syndrome was considered a dependent prognostic factor for progression (11). A multicenter study on NF1-associated OPGs by Kotch et al. showed that children starting SAT below the age of two years and a posterior tumor location of the OPG, including the optic tract, were both risk factors for progression at two and five year after the start of SAT (29). This was the only available study in which children with NF1 started treatment under two years of age. Also, treatment failure with decreased survival in infants below one year is shown by Mirow et al (30). In the present study, children who started first-line vincristine/ carboplatin treatment below the age of one were at increased risk of progression. However, in addition to the infants below one year of age, the initiation of SAT at the age of **>**1- $\leq$ 2 yr years was found to be a dependent risk factor ($p<0.01$), and nearly significant independent risk factor ($p=0.09$/ 0.10) for progression after 3- and 5-year. Further studies with larger cohorts are needed to determine whether the younger population of >1- $\leq$ 2 yr years, or possibly older age, have an increased risk of progression. The sporadic appearance of OPGs was identified as a dependent risk factor for progression; however, all children below the age of two years in this treated cohort had a sporadic OPG, which was similar to the studies by Gnekow (11) and Laithier (15) et al.

Children requiring treatment at such an early age are known to be at risk for long-term severe visual impairment or blindness (31), which was also observed in our study (results to be published in the near future). These children require intensified monitoring and more effective treatment modalities.

The studies discussed include the largest available analyses on first-line progression and risk factors for progression. However, they all vary in baseline characteristics and the type of SAT used, making effective comparison challenging. None of these studies included molecular profiles or examined their subsequent effect on tumor growth and treatment response OPGs. Such information is crucial for optimizing treatment for children at increased risk of progression and worse functional outcome, as currently implemented in the LOGGIC/ Firefly-2 study (17).

The use of RT in the treatment of OPGs requires careful consideration. Despite high rates of long-term tumor control (10-yr PFS: 66-89%) and survival (10-yr OS: 83-100%) (3, 4, 32, 33), patients remain at risk for long-term morbidity (6) The role of NF1 status as a risk factor remains controversial in the literature, as RT in children with NF1, when applied below the age of ten years, increases the risk of death due to cerebrovascular accidents and secondary malignant tumors (6) Children with sporadic OPGs are suggested to have a lower risk long-term progression five years after RT (6) compared to those with NF1-associated OPGs, although this is contradicted by another study (33). In our study, the 10-year PFS was 80.0%, which did not differ between NF1-associated (n=5) or sporadic OPGs (n=19). First-line RT was applied in five patients between 2002 and 2004, indicating that treatment teams developed a learning curve and began to avoid early RT in subsequent years. The majority of irradiated children (87.5%) received RT between 1995 and 2013, suggesting that the need for RT decreased with he increasing availability of various SAT modalities, like bevacizumab and emerging MAPK-targeted therapy. In future studies, these modalities do necessitate a thorough discussion, particularly in regard to their toxicity profiles. For instance, combinations of bevacizumab with irinotecan are associated with an increased incidence of gastrointestinal toxicities (34). In cases of poor tolerance, transitioning from combination therapy to single-agent bevacizumab may be necessary, although alternative drug options in third- or fourth-line treatments are increasingly limited. This cohort specifically has long time survivors where future questions on long term safety can be addressed. Regarding RT, the current treatment guidelines recommend RT only in limited cases, preferably using high-precision techniques (35).

Strengths and Limitations

A key strength of this study is its nationwide inclusion of children who received various treatments for progressive OPG. Selection bias was minimized by searching local databases in addition to obtaining data via the national registry (DCOG). This comprehensive approach helped ensure a broad representation of cases diagnosed with OPG. However, the retrospective design of the study should be interpreted in the context of several limitations.

First, the data for this study were collected from medical records and evaluations over a 25-year period, which may have led to inconsistencies in data affecting the results. Regarding missing data, details on the clinical presentation at the start of therapy were incomplete, including ophthalmological examination and the presence of diencephalic syndrome, as well as information on the decision on the initiation of treatment, treatment evaluation including toxicity rates after SAT and long-term systemic effects after RT. Data on tumor biology, which is currently

considered essential in treatment considerations (36), was lacking for more than 80% of biopsies, therefore this outcome was not presented in this study.

Second, treatment approaches may have varied locally as knowledge of treatment effects and available SAT modalities evolved, leading to changes in the choice of treatment strategy. Nevertheless, we were unable to recognize a trend in differences of approach.

Third, the Kaplan Meijer-analysis of second-line SAT contained a variety of six different SAT strategies, represented by vinblastin in the majority. As PFS did not differ between vinblastin and the other five SAT strategies (Figure 3.C), we have not extended on a comparison of the baseline characteristics of patients or tumors, which may have varied in NF1 status, age and MDC location.

Fourth, treatment evaluation lacked structured radiological response assessment (37) and reporting on outcome on long-term visual functions. Therefore, data on visual functions will be published separately in the near future.

Conclusion

This study provided a national overview of 25 years of diagnoses and treatment of pediatric OPGs. Seven out of ten children required treatment. Sporadic OPGs received a higher number of treatments and exhibited a higher rate of progression compared to NF1-associated OPGs. Children below the age of one year who were treated with first-line vincristine and carboplatin were at risk of progression after three and five years. These findings highlight the need for stratified treatment strategies based on OPG subtype and patient age.

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Conflicts of Interest statement:

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

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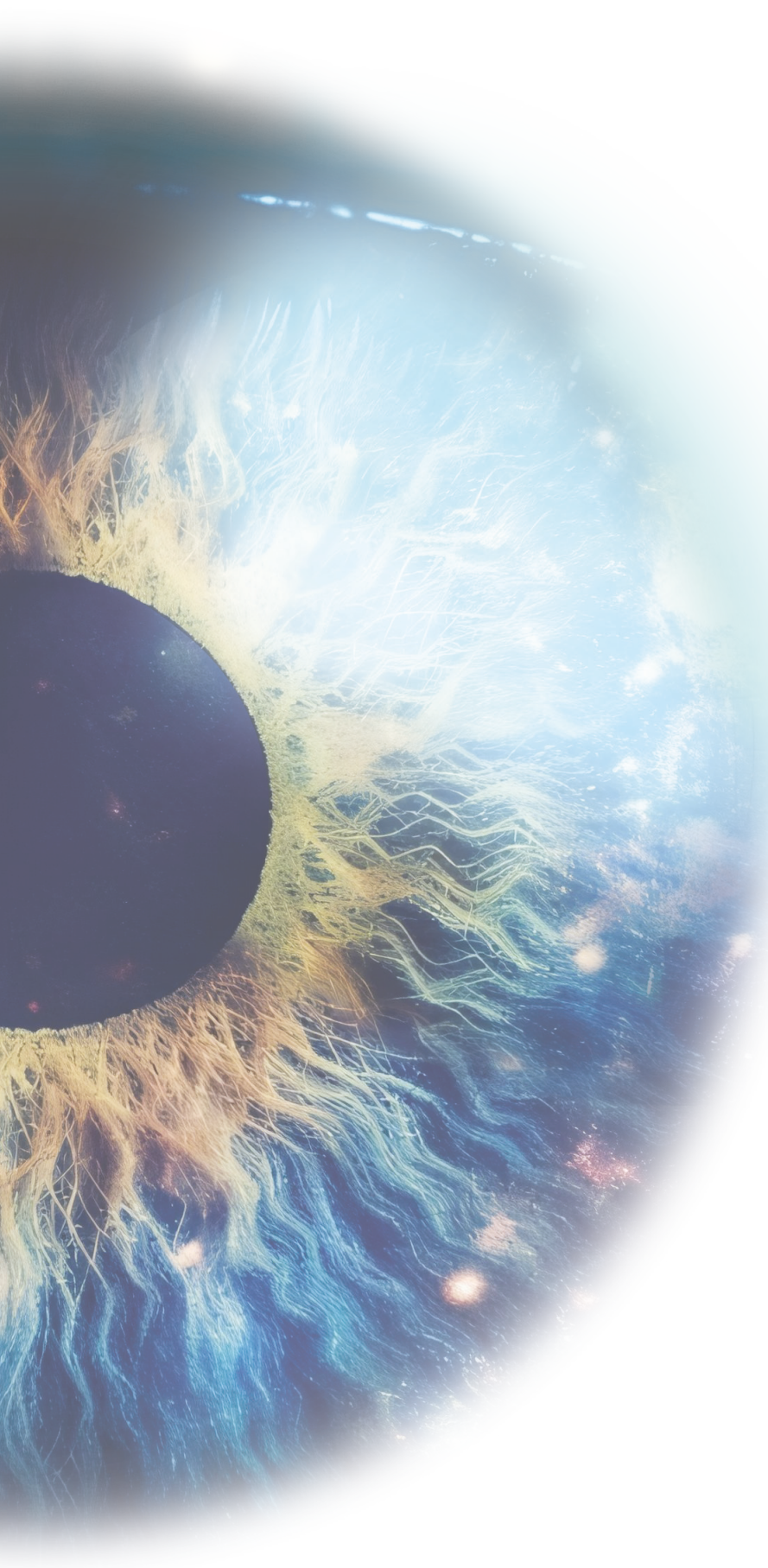

CHAPTER 4

Visual outcome including visual field defects after treatment of pediatric optic pathway glioma: a nationwide cohort study

C.A.M. Bennebroek, J. van Zwol, MDM.C. Montauban van Swijndregt, S.E. Loudon, A.L.W. Groot, N.J.C. Bauer, J.W. Pott, I.C Notting, A.J. van Sorge, M.M. van Genderen, P. de Graaf, A.Y.N. Schouten- van Meeteren, P. Saeed, G.L. Porro

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Abstract

Purpose:
To examine long-term visual impairment and visual field examination (VF) after diverse treatment for pediatric optic pathway glioma (OPG), and to determine prognostic factors for long-term severe visual impairment or blindness.

Methods:
A nationwide retrospective cohort study (1995-2018) was performed on pediatric OPGs that received various (successive) therapies. The analysis of severe VI or blindness was represented by the outcome of both BCVA and VF testing. Prognostic factors for long-term severe VI or blindness were identified.

Results:
Data on BCVA and VF was available in 117 of 136 children (86.0%) who received treatment. After a median follow-up of 8.3 years (range: 0.1-23.8 years) after the start of treatment, severe VI or blindness (> 1.0 LogMAR) was observed in both eyes in 18.8% of 117 patients and in 34.6% of 234 included eyes. This impairment was more common in sporadic OPGs. Monocular VF defects were present in 80.0% in a subgroup of 110 eyes (47.0%), predominantly represented by hemianopia in 69.3% and various scotoma in 28.4%. Independent prognostic factors on severe VI or blindness included starting therapy under the age of two years and hypothalamic involvement of the OPG.

Conclusion:
In this study, long-term binocular severe VI or blindness appeared in almost one in five patients and in one in three eyes after diverse treatment for pediatric OPG. Visual field data were available in only one in two children, VF defects were present in four out of five eyes. Children starting therapy under the age of 2 years were particularly at risk for long-term severe VI or blindness. Future prospective studies need to include VF analysis as an outcome parameter and should analyse treatment effects on both monocular and binocular BCVA.

Introduction:

Optic pathway glioma (OPG) is considered a subgroup of low-grade glioma, which constitutes approximately 5% of all pediatric brain tumors [1]. In 30-59% of children, OPGs are associated with neurofibromatosis type 1 (NF1) (1). The biological behaviour of OPGs is highly variable, ranging from stability to unpredictable progression, but also spontaneous regression may occur (2). Therapeutic options exist of systemic anticancer therapy (SAT), mostly represented by chemotherapy, surgery and radiotherapy.

Since the introduction of SAT for OPGs (3), this modality has been prioritized over both surgery and radiotherapy, to mitigate the risk of serious loss of visual functions and prevent the risk of endocrine, vascular or cognitive impairment. Nevertheless, approximately 45–66% of OPGs progress after first-line SAT and require successive therapy (4, 5). The decline of visual functions is the paramount concern of progression, often driving (successive) treatment initiation. Despite a high rate of overall survival of 90-100%, severe long-term visual impairment (VI) or blindness according to the World Health Organization (WHO) (6) represented by BCVA > 1.0 and/or a concentric restriction < 20 degrees in a radius around central fixation, appears in 16-63% (7-11) and remains the main limiting outcome factor contributing to a reduced quality of life (12).

In 2013 the international collaborative initiative of the Response Evaluation in Neurofibromatosis and Schwannomatosis Visual Outcomes Committee developed standardized criteria to evaluate treatment response by use of visual functions in patients with NF1-associated OPGs (13). Best-corrected **visual acuity** (BCVA), using Teller acuity cards and HOTV, was advised as primary outcome measurement for the design of future clinical trials (14). Adding other functional measurements, which represent visual functions, including visual field examination (VF) and Optical Coherence Tomography (OCT), was not recommended, as more evidence was required before implementing these parameters as outcome measures.

So far, studies on the long-term outcome of visual functions mostly report on outcome of BCVA. Long-term results on VF outcome are presented in two studies (n=15 and 32 patients) (7, 8). Studies on long-term outcome in contrast sensitivity and color vision are not available.

Studies evaluating prognostic factors for long-term severe VI or blindness following first-line SAT revealed the sporadic appearance of OPGs, starting treatment at the age under one year, and hypothalamic involvement of OPGs to be predictive

for this impairment (9-11). However, the variety in clinical characteristics in these cohorts, including variety in treatment approach, the rate of NF1 association, length of follow-up, and the applied criteria to categorize VI, limits generalizability of the results.

In this study, we evaluated long-term outcome of visual functions represented by both BCVA and VF examination in a national cohort of pediatric OPGs (both NF1-associated and sporadic) that received various (successive) treatments. Prognostic factors for severe VI or blindness were determined to assist future selection of those patients who are at increased risk of developing severe VI or blindness and therefore may benefit from earlier start of therapy and rehabilitation.

Methods:

Retrospective data were collected from a cohort of 197 children, aged 0-17 years, diagnosed with an OPG (chiasmatic and optic tract and/or optic nerve) in the Netherlands between 1995-2018 and selection of those children, who had received treatment because of progression between January 1995 and December 2020. Patients diagnosed between 1995-2002 were identified via local databases of the University Medical Centers (UMC) and from 2003 onwards via the Dutch Childhood Oncology Group registry (DCOG).

All UMCs, the national tertiary pediatric oncology center (Princess Máxima Center (PMC)) and the two visual rehabilitation centers of the Netherlands (Bartiméus and Royal Dutch Visio) participated. Ethical approval was obtained from the DCOG and all UMCs. Informed consent was obtained from patients or their guardians (DCOG, PMC and UMC Utrecht) and an opt-out procedure was offered to patients treated in the Amsterdam UMC. Other UMCs granted permission for anonymized use of patient data. The study was performed in accordance with the tenets of the Declaration of Helsinki.

Patients with an isolated optic nerve glioma were not included as these data were published separately (15), likewise patients with an OPG (or their parents or caretakers) who refused the collection of data.

Data collection:

Clinical and pathological data were collected, including age at diagnosis, sex, medical (including ophthalmological) history, NF1 status, tumor histology and the type and number of treatment modalities applied. The diagnosis of OPG was confirmed by the appearance on MRI histopathology and molecular data in case

a biopsy or neurosurgical resection was performed. The anatomic location of the OPG was classified by an experienced neuroradiologist (PG) using the Modified Dodge Classification (MDC) (including stage 1: optic nerve involvement/ stage 2: chiasm/ stage 3: anterior optic tract/ stage 4: posterior optic tract) (16). In the Netherlands, the individual indication and choice of treatment for progressive OPGs were determined by local academic treatment teams until 2017, which was followed by centralization in the national tertiary pediatric oncology center from 2018 on. Treatment was initiated in case of profound deterioration of visual functions or of neurological status, or progression identified on MRI, as defined in the HIT-LGG 1996 study (17) and following SIOPe LGG 2004 study protocol(18). Data were anonymized and entered into electronic case report forms (Castor EDC).

Data on BCVA and VF was collected within a three-month window before the start of all therapy and at the most recent ophthalmological examination. Therapy existed of a variety of SAT strategies, surgical resection or radiotherapy. Data on BCVA measurements were obtained from age-appropriate testing methods (Teller Acuity Cards, Cardiff Acuity Test, Kays Pictures and Snellen charts) and were converted to the Logarithm of the Minimum Angle of Resolution (LogMAR). Visual acuity values represented by counting fingers, hand motion, light perception and no light perception were converted to 2.0, 2.4, 2.7, and 3.0 LogMAR (19). Binocular BCVA and the level of binocular VI or blindness were determined based on the BCVA of the best-seeing eye. The change in monocular BCVA was categorized as improved (a decrease of $\geq$ 0.2 LogMAR), stable (change within 0.2 LogMAR) or decreased (an increase of $\geq$ 0.2 LogMAR) (20). The degree of visual impairment was determined according to the definitions of binocular visual impairment (VI) and blindness provided by the International Statistical Classification of Diseases and Related Health Problems (tenth revision) (6) (Revision.) (ICD-10 Visual Disturbances and blindness) (ICD-10 Visual Disturbances and blindness) (ICD-10 Visual Disturbances and blindness); no- mild VI: BCVA $\leq$ 0.5 logMAR ($\geq$ 0.3 decimal); moderate VI: BCVA > 0.5 to $\leq$ 1.0 logMAR (< 0.3 and $\geq$ 0.1 decimal); severe VI: BCVA > 1.0 to $\leq$ 1.3 logMAR (< 0.1 to $\geq$ 0.05 decimal) or a binocular VF no greater than 20° in radius around central fixation; and blindness: BCVA > 1.3 logMAR (< 0.05 decimal) or a binocular VF no greater than 10° in radius around central fixation (6).

Visual fields were obtained from tests performed on the Behavioral Visual Field Screening Test (BEFIE) (21), the semiautomatic-static Peritest (22), Goldmann kinetic perimetry (23) or the Humphrey Visual Field Analyzer. Two experienced ophthalmologists (CB, GP) assessed the VF data for the presence of defects based on predefined protocols (21, 24, 25). Discrepancies between raters were resolved through discussion. Unreliable VF tests were excluded from analysis. Combined

monocular abnormalities, like the simultaneous presence of temporal hemianopia and nasal quadrantanopia, were scored separately as overarching defect in both eyes. Binocular VF abnormalities were registered in case of the presence of homonymous or heteronymous hemianopia or quadrantanopia, or in case of aa concentric restriction in a radius around central fixation < 20 degrees (categorized as severe VI) or < 10 degrees (categorized as blindness) as defined by the WHO. Hemianopia or quadrantanopia was defined as the presence of an absolute defect in ≥ 65% of the involved field, therefore including partial or complete hemianopia or quadrantanopia. The presence of scotoma was represented by (ceco)central, paracentral, pericentral and Bjerrum scotoma, which could also include a combination of diverse scotoma.

(ICD-10 Visual Disturbances and blindness); no- mild VI: BCVA ≤ 0.5 logMAR (≥ 0.3 decimal); moderate VI: BCVA > 0.5 to ≤ 1.0 logMAR (< 0.3 and ≥ 0.1 decimal); severe VI: BCVA > 1.0 to ≤ 1.3 logMAR (< 0.1 to ≥ 0.05 decimal) or a binocular VF no greater than 20° in radius around central fixation, and blindness: BCVA > 1.3 logMAR (< 0.05 decimal) or a binocular VF no greater than 10° in radius around central fixation.

Statistical Analysis:

Continuous data was presented as median and range as all data had a non-normal distribution, while categorical data was expressed as numbers and percentages. Between-group differences of the continuous data were assessed using the Mann–Whitney U test and chi-square test or Fisher's exact test for categorical data. A p-value < 0.05 was considered statistically significant. To identify prognostic variables for severe VI or blindness, univariate analysis followed by successive multivariate analysis (in case p < 0.2 in univariate analysis) was performed using a stepwise logistic regression to estimate the adjusted odds ratios and 95% confidence intervals for each potential prognostic factor. Statistical analysis was conducted using SPSS software for Windows (version 26.0.0.1, SPSS Inc., Chicago, IL, USA).

Results

In 117 of 136 patients (234 eyes) who had received treatment for progressive OPGs, data was available for ophthalmological assessment. Forty-five patients (38.5%) had NF1. The median age at the start of therapy was 5.9 years (0.3-16.5 years). The median period of follow-up between the start of treatment and most recent ophthalmological assessment was 8.3 years (range: 0.1-23.8 years). The total cohort received a median number of two various treatments (range: 1-8). Seventy-two patients (61.5%) received SAT as first-line modality, which was composed of a combination of vincristine and carboplatin in 88.9%. Forty-four patients (37.6%) received no successive therapy after first-line treatment. Twenty-seven patients (23.1%) received > 3 treatments. Baseline data are presented in Table 4.1. Figure 1 shows an overview of the variety of applied (successive) treatment modalities. Four patients died at a median age of 11.1 years (range: 3.8- 16.4 years), all had a sporadic OPG.

Data on visual functions were lacking in 19 children who had received treatment. This group started treatment at a younger age (median 2.0 years (range: 0.4-11.7 years) compared to the population included in this study (p<0.01). Also, their last examination occurred at a younger age (median 7.8 years (range: 2-8-36.8 years), p<0.01). The NF1 status and the anatomic location of the OPGs did not differ between both groups (p=0.14 and p=0.51).

Table 4.1. Baseline characteristics of children that received treatment for a progressive OPG

Study cohort	
Patients (eyes): n (n)	117 (234)
Male: n (%)	55 (47.0)
NF1: n (%)	45 (38.5)
Age at start TX (yrs): m (r)	5.9 (0.3-16.5)
Age categories at start TX:	
0- <1 yr	13 (11.1)
≥1- <2 yr	11 (12.8)
≥2- 8 yr	53 (45.3)
>8-18 yr	40 (34.2)
Interval start-end FU (yrs): m (r)	8.3 (0.1-23.8)
Age end FU (yrs): m (r)	14.7 (2.5-36.8)
Anatomic location:	
MDC: 2	10 (8.5)
MDC: 3 or 4	2 (1.7)
MDC: 1-2	33 (28.2)
MDC (1)-2-3-(4)	72 (61.5)

Table 4.1. Continued.

Study cohort	
Hypothalamic involvement	70 (59.8)
Lepto-meningeal metastases	9 (7.7)
Treatment: n (%)	**117 (100.0)**
Nr of TX: m (r)1	2 (1-8)
First-line SAT	72 (61.5)
Vincr./ carbopl.	64 (88.9)
Vincr./ carbopl./ etop.	2 (2.8)
Vincr. only	1 (1.4)
Vinblastine	4 (5.6)
BVZ/ irinotecan	1 (1.4)
First-line TX only	44 (37.6)
SX: first line or successive	56 (47.9)
RT: first line or successive	24 (20.5)
> 3 TX modalities	27 (22.2)
Deceased: n (%)	**4 (3.4)**
Cause: Progression OPG	2 (1.7)
Meningitis	1 (0.9)
Suicide	1 (0.9)

Abbreviations: BVZ: bevacizumab, Carbopl.: carboplatin, Etop.: etoposide, FU: follow up, MDC: Modified Dodge classification (stage 1: optic nerve/ stage 2: chiasm/ stage 3: anterior optic tract/ stage 4: posterior optic tract), M (r): median (range), NF1: Neurofibromatosis type 1, RT: radiotherapy, SAT: systemic anticancer therapy, SX: surgery, TX: therapy, Vincr.: vincristine, Yrs: years
1: this overview concerned the whole spectrum of diverse treatment, including SAT, SX and RT

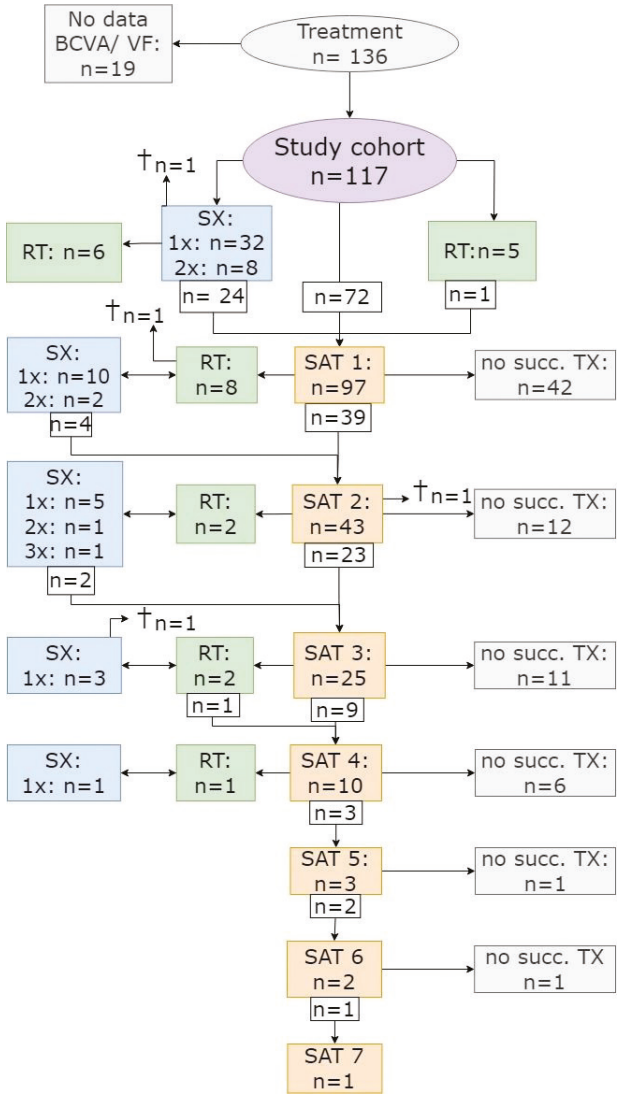

Figure 4.1. Flowchart of various treatment lines for progressive pediatric OPG which the study population received

Abbreviations: BCVA: best-corrected visual acuity, VF: visual field, RT: radiotherapy, SAT: systemic anticancer therapy, SX: surgery, no succ. TX: no successive therapy.

†: number of patients that have died.

At the end of follow-up, twenty-two patients (18.8%) had severe VI or were blind in both eyes (BCVA > 1.0 LogMAR), which appeared more common in children with sporadic OPGs ($p< 0.01$). Likewise, the rate of severe VI or blindness was higher for children that started treatment under the age of two year (58.3%) compared to older age ($p< 0.01$). Monocular severe VI or blindness was present in 81 eyes (34.6%), which was also more common in the eyes of patients with sporadic OPGs ($p<0.01$). Two of the four patients who died, had no or mild VI at their last ophthalmological examination, one had moderate VI and one was blind. Data on BCVA and the level of VI at the end of follow-up are available in Table 4.2, including a comparison of outome in NF1 and sporadic OPGs.

Data on BCVA both at the start of therapy and at the end of follow-up was available for a subgroup of 59 patients (50.4%). During follow-up, monocular BCVA improved in 13.4%, remained stable in 62.5% and decreased in 24.1% of eyes. Six eyes, which had no light perception at the start of therapy, did not show improvement over time. No difference in BCVA or rate of VI was present among NF1 and sporadic OPGs at the start of treatment ($p=0.97$, $p=0.66$), but during follow-up, monocular BCVA decreased at a higher rate in the NF1 population (37.0 vs. 10.9%). In the population of sporadic OPGs monocular BCVA remained stable at a higher rate of eyes (73.4 vs. 53.7%). At the start of therapy, severe VI or blindness was present in 5.1% of patients and 15.2% of eyes, which reduced to 3.4% of patients but increased to 15.2% of eyes at the end of follow-up. This subgroup (group 1) was not representative for the total population, as we compared this group with the group with no available pre-treatment BCVA assessment, but only available data at the end of follow-up (group 2). The children in group 1 were older at the start of therapy, they received a lower number of treatment lines, had a higher level of BCVA and a lower rate of severe VI or blindness at the end of follow-up (all factors: $p< 0.001$, Mann-Whitney U test). The results are available in Supplement 4.1.

Table 4.2. Long-term binocular and monocular BCVA and representation of grading of visual impairment or blindness at median 8.3 years after start of treatment for pediatric OPG; a comparison between children with a NF1 associated and sporadic OPG

VI analysis: end FU	Total cohort	NF1-ass OPG	Sporadic OPG
Binocular BCVA end of FU: n	117	45	72
Binocular (LogMAR): m (r)	0.1 (-0.2-3.0)	0.1 (-0.2-3.0)	0.1 (-0.2-2.7)
VI/ B * end of FU: n (%)			
No- mild VI	81 (69.2)	37 (82.2)	44 (61.1)
Moderate VI	14 (12.0)	5 (11.1)	9 (12.5)
Severe VI	7 (6.0)	1 (2.2)	6 (8.3)
Blindness	15 (12.8)	2 (4.4)	13 (18.1)
Monocular BCVA end of FU: n	234	90	144
All eyes (LogMAR): m (r)	0.3 (-0.2-3.0)	0.2 (-0.2-3.0)	0.8 (-0.2-3.0)
Best eye (LogMAR): m (r)	0.1 (-0.2-3.0)	0.1 (-0.2-3.0)	0.1 (-0.2-2.7)
Worst eye (LogMAR): m (r)	1.1 (-0.1-3.0)	0.7 (-0.1-3.0)	2.7 (-0.1-3.0)
VI/ B* categories (all eyes): n (%)			
No- mild VI	123 (52.6)	58 (64.4)	65 (45.1)
Moderate VI	30 (12.8)	13 (14.4)	17 (11.8)
Severe VI	12 (5.1)	5 (5.6)	7 (4.9)
Blindness	69 (29.5)	14 (15.6)	55 (38.2)
Binocular BCVA available at start TX: pts	59	27	32
Age at start therapy (yrs): m (r)	7.4 (0.6-16.5)	7.3 (2.9-14.3)	7.8 (0.6-16.5)
Binocular BCVA at start TX (LogMAR): m (r)	0.1 (-0.1-3.0)	0.0 (-0.1-1.2)	0.1 (-0.1-3.0)
Binocular VI/ B * start TX: n (%)			
No- mild VI	53 (89.8)	26 (96.3)	27 (84.4)
Moderate VI	3 (5.1)	0 (0)	3 (9.4)
Severe VI	1 (1.7)	1 (3.7)	0 (0)
Blindness	2 (3.4)	0 (0)	2 (6.3)
Monocular BCVA at start TX: n	118	54	64
Best eye (LogMAR): m (r)	0.1 (-0.1-3.0)	0.1 (-0.1-1.2)	0.1 (-0.1-3.0)
Worst eye (LogMAR): m (r)	0.5 (-0.1-3.0)	0.5 (0.0-2.7)	0.5 (-0.1-3.0)
Monocular VI/ B* start TX: all eyes: n (%)			
No- mild VI	84 (71.2)	40 (74.1)	44 (68.8)
Moderate VI	16 (13.6)	7 (13.0)	9 (14.1)
Severe VI	3 (2.5)	2 (3.7)	1 (1.6)
Blindness	15 (12.7)	5 (9.3)	10 (15.6)
Change of BCVA: start TX – end FU: n (%)			
Improved: ≥ 0.2 LogMAR	15 (12.7)	5 (9.3)	10 (15.6)
Stable: ≤ 0.2 LogMAR	76 (64.4)	29 (53.7)	47 (73.4)
Decreased: ≥ 0.2 LogMAR	27 (22.9)	20 (37.0)	7 (10.9)

Abbreviations: BCVA: best-corrected visual acuity, FU: follow up, LogMAR: Logarithm of the Minimum Angle of Resolution, M (r): median (range), Pts: patients, VI: visual impairment, VI/ B: categories of binocular visual impairment or blindness

*: Categories of VI/ B according to the International Statistical Classification of Diseases and Related Health Problems (tenth revision): No- mild VI: BCVA ≤0.5 logMAR (≥0.3 decimal); moderate VI: BCVA >0.5 to ≤1.0 logMAR (<0.3 and ≥ 0.1 decimal); severe VI: BCVA >1.0 to ≤1.3 logMAR (<0.1 to ≥0.05 decimal) and blindness: BCVA >1.3 logMAR (<0.05 decimal)

Visual field examination

In total, VF examinations were available at the end of follow-up in 67 of 117 patients (110 eyes), 26 patients (38.8%) had NF1. Normal or mild VI appeared in 85.1% of these patients. In 43 patients (64.2%) monocular VF examinations were available for both eyes. Visual field examination was absent in the second eye in 24 patients (35.8%): one eye (4.2%) had severe VI and 15 eyes (62.5%) were blind. Homonymous or heteronymous (bitemporal) hemianopia was present in 22 patients (51.1%). Binocular VF abnormalities were more common in children with a sporadic OPG (55.6% vs. 37.5% in NF1 OPG, p<0.01), specifically bitemporal hemianopia (51.9 vs. 0.0%). No binocular restriction < 20 degrees in a radius around central fixation was present. Monocular VF abnormalities were present in 88 of 110 examined eyes (80.0%), predominately represented by hemianopia (69.3%) (temporal or nasal) and variable scotoma in 28.4%. Hemianopia was relatively more common in eyes of children with a sporadic OPG (84.9 vs. 45.7%), but in total the rate of VF defects was similar (79.1 vs. 81.4%) among eyes representing both sporadic and NF1-associated OPGs. A VF restriction $\leq 10°$ **in radius around central fixation**, representing blindness according to the WHO appeared in one eye of one patient (1.5%) (the second eye had no light perception).

Longitudinal data on VFs performed both at the start of therapy and end of follow-up was available in 18 patients (26.9%) and 32 eyes (29.1%): At the start of therapy, VF defects were present in 71.9% of eyes. Between the start of therapy and the end of follow-up, monocular VFs improved in 15.6%, remained stable in 37.5% and deteriorated in 46.9%. Data on VF examination at the start of therapy and at the end of follow-up are available in Table 4.3. A comparison of VF abnormalities between children with NF1-associated and with sporadic OPGs is available in Supplement 4.2.

Risk factors for severe VI or blindness

Multivariable analysis by stepwise logistic regression on risk factors for long-term severe VI or blindness showed that starting therapy under the age of two years (OR: 5.5, 95% CI: 1.1- 26.4, p= 0.04) and hypothalamic involvement of OPGs (OR: 3.5, 95% CI: 1.0- 11.8, p=0.04) were both independent prognostic factors. A sensitivity analysis showed that both age < 1 year and age $\geq$ 1 to < 2 years were independent prognostic factors for severe VI or blindness (p < 0.01 and p= 0.01). Therefore, both categories were combined into one category, age below 2 years, to limit bias due to the low number of patients per category. Backward elimination by the exclusion of the factors of > 3 treatments and hypothalamic involvement, revealed no independent prognostic value for sporadic or NF1-associated OPG (p= 0.55). Sporadic OPG and receiving >3 treatment modalities, were dependent prognostic factors for severe VI or blindness. Results are available in Table 4.4. The rate of VI or blindness per prognostic factor is available in Supplement 4.3.

Table 4.3. Visual field tests abnormalities at the end of follow-up at median 14,5 years after the start of first treatment for progressive pediatric OPG

VF analysis	VF available at end FU	VF available at start TX and end FU
Available VF (pts): n (%)	67 (57.3)	18 (15.4)
Age at start TX (yr): m (r)	6.4 (0.5-16.5)	10.3 (3.0-16.2)
Age end FU (yr): m (r)	15.6 (4.8-29.5)	17.9 (6.7-28.5)
Type of test performed (per eye): n (%)	**67 (100.0)**	**32 (100.0)**
BEFIE	3 (4.8)	2 (6.3)
Goldmann	31 (46.3))	12 (37.5)
Peritest	17 (25.4)	12 (37.5)
HFA	16 (23.9)	6 (18.8)
Category binocular VI/ B: n (%)	**67 (100.0)**	**18 (100.0)**
No- mild VI	57 (85.1)	16 (88.9)
Moderate VI	6 (9.0)	-
Severe VI	2 (3.0)	-
Blindness	2 (3.0)	-
Missing data on BCVA	-	2 (11.1)
Bilateral VF performed (pts): n (%)	**43 (64.2)**	**18 (26.8)**
Bilateral VF defects: n (%)	21 (48.8)	5 (27.7)
Bitemporal hemianopia [1]	14 (32.5))	1 (20.0)
Homonymous hemianopia [1]	7 (16.3)	3 (60.0)
Homonymous quadrantanopia [1]	1 (2.3)	1 (20.0)
Restriction ≤ 10 degrees [2]	0 (0.0)	0 (0.0)
Monocular VF performed (eyes): n	**110**	**32**
BVCA of eyes with VF: (LogMAR): m (r)	0.1 (-0.2-1.3)	0.1 (-0.1-3.0)
Monocular VF data not available: n	24	0
BVCA: VF data absent (LogMAR): m (r)	2.3 (0.0-3.0)	-
Monocular VF defects (eyes): n (%)	88 (80.0)	23 (71.9)
Hemianopia1	61 (69.3)	13 (50.0)
Quadrantanopia [1]	15 (17.0)	10 (38.5)
Various scotoma	25 (28.4)	3 (11.5)
Restriction ≤ 10 degrees [2]	1 (1.1)3	0 (0.0)
Change VF: start TX – end of FU (eyes): n (%)	**nd**	**32 (100.0)**
Improvement	nd	5 (15.6)
Stable	nd	12 (37.5)
Deterioration	nd	15 (46.9)

Abbreviations: BEFIE: Behavioral Visual Field Screening Test, BCVA: best-corrected visual acuity, FU: follow up, HFA: Humphrey visual field analyzer, LogMAR: Logarithm of the Minimum Angle of Resolution, M (r): median (range), Nd: no data, VF: visual field test, VI: visual impairment, TX: therapy, VI/ B: categories of binocular visual impairment and blindness based on the definitions of the WHO (https://icd.who.int/browse10/2019/en#/H54.9, classification), yr: year
1: Hemianopia or quadrantanopia was defined as presence of the defect in ≥ 60% of the involved field, including incomplete or complete hemianopia or quadrantanopia.
2: a concentric restriction ≤ 10 degrees in a radius around central fixation (representing blindness according to the WHO). 3: This eye was considered blind due to a combination of light perception only (LogMAR 2.7) and a restricted VF ≤ 10 gr degrees in a radius around central fixation

Table 4.4. Uni- and multivariable logistic regression analysis for predictors of long term visual impairment or blindness after diverse treatment for pediatric optic pathway glioma

			Univariable			Multivariable		
Variables	**n**	**VI & B: n (%)**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
NF1 association	45	3 (6.7)	ref	-	-	-	-	-
Sporadic OPG	72	18 (25.0)	5.0	1.4-18.1	0.01	1.6	0.4-7.4	0.55
Age 0 - <2 yr	24	14 (58.3)	12.6	3.4-46.9	<0.01	5.5	1.1-26.4	0.04
Age ≥ 2 - 8 yr	53	4 (7.5)	0.7	0.2-3.1	0.68	0.7	0.2-3.0	0.59
Age > 8 - 18 yr	40	4 (10.0)	ref	-	-	-	-	-
MDC (1-) 2	43	6 (14.0)	ref	-	-	-	-	-
MDC (1-2-) 3 (-4)	74	16 (21.6)	1.7	0.6-4.7	0.31	-	-	-
Hypothalamus +	70	17 (24.3)	2.7	0.9-7.9	0.07	3.5	1.0-11.8	0.04
> 3 treatments	27	13 (48.1)	8.4	3.0-23.2	<0.01	1.8	0.5-6.4	0.34

Abbreviations: CI: confidence interval, Hypothalamus+: involvement of the OPG within the hypothalamus, MDC: modified Dodge classification (stage 1: optic nerve involvement/ stage 2: chiasm/ stage 3: anterior optic tract/ stage 4: posterior optic tract), NF1: Neurofibromatosis type 1, nNF1: no association to NF1, pts: patients, OPG: optic pathway glioma, OR; odds ratio, Ref; reference, TX: treatment, VI & B: visual impairment and / or blindness, Yr: year

Discussion

In this nationwide long-term cohort study on pediatric OPG following various treatment modalities, data on outcome in BCVA and VF was available in 117 (86.0%) of 136 children. We identified severe VI or blindness in both eyes in 18.8% of 117 patients and 34.6% of 234 eyes after a median of 8.3 years from the start of treatment. Both severe VI and blindness were more common in children with sporadic OPGs. Visual field defects were present in 80.0% of the 110 examined eyes, predominantly represented by hemianopia (69.3%) and various scotoma (29.8%). Homonymous or heteronymous (bitemporal) hemianopia was present in 48.8% of patients and was more common in children with a sporadic OPG. Starting treatment under two years of age and hypothalamic involvement of the OPG were both independent predictors for long-term severe VI or blindness.

Visual impairment or blindness after treatment

In daily practice, severe VI or blindness requires early initiation of visual rehabilitation to prevent or catch up on developmental delays, as severe visual impairment can lead to reduced physical activity and inadequate motor skills, which can negatively impact the quality of life (12, 26, 27). Previously, five studies reported data on long-term VI according to the WHO criteria after various treatments for pediatric OPG. These studies were relatively small (range: 15-42 patients), retrospective, and all but one monocenter studies. They also varied in the reporting of monocular and binocular VI or blindness, NF1 status and definitions of VI. Binocular severe VI or blindness according to the WHO criteria was reported in median 33.7% (range: 16.1- 63.6%) (7, 8, 10, 11) or blindness (LogMAR > 1.3) in 26.5% (9) compared to 18.8% (LogMAR > 1.0) and 12.6% (LogMAR > 1.3) in the present study. Falzon et al. (n=90 patients) (28) reported on monocular long-term data of VI defined by BCVA $\geq$ 0.7 LogMAR (29) in 28% of NF1-associated eyes and 57% of eyes of sporadic OPG. Combined long-term binocular and monocular analysis of severe VI or blindness was present in 31.4% (N=42) (10) and 63.6% (N=15) of patients (8) and in 47.1% and 68.1% of eyes. In our study, binocular and monocular severe VI or blindness was present in 18.8% and 34.5% and was more common in children with a sporadic OPG. The difference in mono- and binocular VI may be explained by the asymmetric distribution of OPGs within the optic tract resulting in asymmetric damage of visual functions. Nevertheless, the difference in outcome substantiates the need to include both monocular and binocular BCVA as outcome parameters in future studies.

Visual field abnormalities

In OPGs, damage to the nerve tissue involving the chiasm and optic tract is typically represented by VF defects. These defects may occur independently of a decrease in BCVA, they may mirror the change of BCVA (30) or may precede a decrease of BCVA. So far, long-term outcome of VF abnormalities after various treatments for progressive OPG has been reported by four studies (7, 8, 10, 31). A detailed description is provided by two retrospective monocenter studies (n=32/ n=37) (7, 31), revealing VF abnormalities in 55-78% of patients at the start of therapy and 46-87% after a median follow-up of 6.0 and 6.8 years. Within this interval VFs showed improvement in 24.3%, stabilization in 56.8% and deterioration in 18.9% of patients (31). The current study confirmed the high rate of abnormalities in a larger population (n=67), presenting VF abnormalities in 80.0% of the involved eyes and bilateral defects in 48.8% of patients after a median of 8.5 years from the start of treatment.

All other studies reporting VF outcome after various combinations of SAT, consist of analysis within three months after cessation of a single line of SAT. Two of these studies (n=16 and 26) (30, 32) showed improvement of VF defects in 19-38%, stability in 38-44% and a deterioration in 38-42% of patients with NF1. The effect of bevacizumab on change in VFs was presented in two nationwide studies (33, 34).

Abnormalities were present in 42% of patients (n=24): VF defects improved in 4% and worsened in 13% (33). Abnormal VFs were present at the start in 92.3% of eyes (n=26): defects improved in 73.1% and worsened in 7.7% (34). Regardless of a high rate of 80.0% of monocular VF defects in a subgroup in the present study, this rate may be an underestimate of the VF defects in the total cohort, as the group with available VF tests (n=67 (57.3%)) demonstrated a relatively high rate (85.1%) of normal to mild VI compared to the total study cohort (69.2%). We suspect that eyes with a higher lever of VI may include a higher rate of VF defects. The high rate of VF abnormalities reported in the current and previous studies and the relative absence of VF defects fitting the WHO criteria for VI, implicate the need for future collaborative studies to reevaluate the role of VF abnormalities as an outcome parameter for visual functions and determine their effect on functioning in daily life.

In the current study, the rate of severe VI or blindness according to the definitions of the WHO, was based on the results of decrease of BCVA (>1.0 LogMAR) in both eyes (n=22), but was not substantiated by VF abnormalities which were consistent with the definition of severe VI (simultaneous constriction of the VF < 20 degrees in a radius around central fixation) in any patient. As the WHO categories 'normal to

mild VI' and 'moderate VI' do not contain a representation of VF defects, we suggest this classification of VI may not be suitable to represent outcome in children with an OPG.

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Visual field examination at young age

Visual field examination in young children can be challenging due to a limited attention span or fear of examination, especially in NF1-associated OPGs, as these children can also suffer from behavioral problems and neuro-cognitive impairment (35). In our study, VF examination was performed by Goldmann examination in the majority. During the collection of data, we observed large differences in the relative available numbers of VF examinations among the centers, as well as differences in the various types of tests used. For example, the BEFIE test, available since 1998 (36), was available in two out of eight centers and was used for 4.8% of the children. Considering the age representation of the population that had performed a VF test at the start of treatment, no child was under the age of three years, suggesting poor cooperation under that age or unfamiliarity with test availability in the past decennia. As examination at a young age remains a challenge, a potential role for handheld optical coherence tomography (OCT) should be addressed for these children, which may require sedation (37). OCT has proven to be a useful tool, as cross-sectional studies have shown that a declined thickness of the ganglion cell-inner plexiform layer (GC-IPL) and retinal nerve fiber layer (RNFL) correlates with the decrease in BCVA or VF in both NF1 and sporadic OPGs (38-41), including a higher success rate of performing OCT compared to VF examination. Limited longitudinal studies have suggested that the decline of RNFL thickness can serve as a surrogate for deterioration of BCVA of VF (38, 42). Children participating in these studies on non-handheld OCT, were older than four years in the majority, which leads to a continuing search for the optimal protocol for ophthalmological follow-up of young children requiring treatment.

Prognostic factors for severe visual impairment or blindness

Independent prognostic indicators for long-term VI or blindness after various treatments have previously been reported by two studies. First, starting treatment under the age of one year, receiving successive treatment following initial chemotherapy and the presence of raised intracranial pressure requiring one or more surgical interventions, have been identified as prognostic factors for blindness (LogMAR > 1.3) (N=132) (9). Second, starting treatment at the age of five years or younger and involvement of OPGs within the optic tract (MDC stage 3) have been identified as prognostic factors for VI (BCVA $\geq$ 0.7 LogMAR) for NF1-associated OPG (N=90) (28). Two studies reported a higher rate of severe VI (11) and blindness (10) in hypothalamic OPG compared to OPG with no hypothalamic involvement. The present study identified two independent prognostic indicators for severe VI or blindness ($\geq$ 1.0 LogMAR): starting treatment under the age of two years and hypothalamic involvement of the OPG. When comparing the studies that identified young age as a risk factor, the authors assessed different age cut-offs (<1 vs. <5 years). Studies evaluating treatment response after first-line chemotherapy, identified starting treatment at the age of under one year as a risk factor for recurrent progression (4, 43). Combining the risk of progression and risk of long-term severe VI, children at very young age require maximum effort in obtaining information about their visual functions to guide treatment and start early rehabilitation.

To value hypothalamic involvement of OPG as a risk factor, we believe a comparison of tumor volume between OPGs with and without hypothalamic involvement is required to substantiate its role in damaging visual functions, which was not performed in this study.

Strengths and limitations

The results of this study should be interpreted considering several limitations. First, there are limitations inherent to the retrospective study design, including selection bias and missing data on: 1) ophthalmological (optic nerve) and orthoptic examination, 2) missing data on BCVA and VF at the start of treatment and the end of follow-up, and 3) missing data on the clinical or radiological indication for the start of treatment. The high rate of absence of data on BCVA, but mostly VF examination requires prospective evaluation on the feasibility of these testing methods in children with progressive OPGs. The use of OCT should be included as an objective measurement, to extend insight into its longitudinal correlation with both BCVA and VF outcome and correlation to radiological response assessment. Information bias was evident in the subgroup of patients with available data on BCVA at the start of treatment: the high rate of normal to mild VI at the end of

follow-up in this group did not represent the distribution of VI among the total population. Due to a high rate of lacking data on molecular analyses and a lack of available tissue to analyze in retrospect, information on the molecular biomarkers, like BRAF V600 mutation or KIAA1549 BRAF fusion, and their association with the rate of VI is not reported. Data could not be obtained from two patients as parents refused consent.

Second, to maximize collection of data, we needed to use data on BCVA which were obtained by the use of four different BCVA charts differing in grading acuity and optotype acuity. Likewise, BCVA measurements have not been made in comparison to age based norms due to a limited availability of these norms in literature (14) and a lack of insight in variety in cognitive functioning and cooperation during the tests (in NF1).

Third, the VF examinations were performed by four different tests, including both manual and automated, static and dynamic perimetry with varying target size and luminance, limiting uniform comparison and lacking the opportunity of (retrospective) assessment of the quality of three of the four tests (44). All included tests have different limitations: HFA, which nowadays is considered the state-of-the-art VF test in children, is only considered to be executable from eight years on (45). Simple conventional perimetry methods, such as Goldmann perimetry, are often of limited quality under the age of six years (46). The BEFIE test is suitable from the age of four months and can detect absolute peripheral VF defects, but no relative peripheral defects or central scotoma (21). Also, this test is susceptible to variability in outcome due to limited cooperation, psychomotor or attention impairment.

The strengths of this study include the long-term analysis of a large cohort of children with progressive OPG who received various treatments. The data on visual outcome are specified as detailed as possible for both outcome in monocular and binocular BCVA and VF. Visual field defects were scored independently by 2 experienced raters.

Conclusion

This study demonstrated that severe VI or blindness was present in nearly one in five children and one in three eyes after various treatments for progressive OPG. Visual field defects were present in four out of five eyes and were more common in children with a sporadic OPG. Severe VI or blindness occurred more common in children with sporadic OPGs. Predictors for long-term severe VI or blindness include initiating treatment at the age of under two years and hypothalamic involvement of the OPG. These findings underscore the importance of future studies focusing on the assessment of baseline visual functions from the start of therapy and integrating measurement of both BCVA and VF in study protocols. Future treatment protocols should consider intensified monitoring (by MRI and ophthalmologist) of young children under the age of 2 years and those with hypothalamic involvement to facilitate early intervention to maximize preservation of visual functions.

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E. Kraal, MD. Department of Ophthalmology, Amsterdam UMC, location Vrije Universiteit Amsterdam , Amsterdam, The Netherlands
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M. Tanck, PhD. Department of Epidemiology and Data Science, Amsterdam UMC: location University of Amsterdam, Amsterdam, The Netherlands

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Conflict of interest statement

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Supplement 4.1.
A comparison of baseline parameters, BCVA and rate of VI or blindness in 2 subgroups with available data at both the start and end of follow up (group 1) and available data only at the end of follow up (group 2)

	Sub group 1: analysis at start TX and end FU	Sub group 2: analysis end FU only	p-value
Patients/ eyes: n	59/ 118	58/ 116	
Male: n (%)	26 (44.1)	29 (50.0)	0.52
NF1: n (%)	27 (45.8)	18 (31.0)	0.10
Age at start therapy (yrs): m (r)	7.4 (0.6-16.5)	3.4 (0.3-16.3)	<0.01
Interval start TX- end FU: m (r)	7.2 (0.0-20.3)	8.7 (2.2-23.8)	0.04
Anatomic location (MDC): n (%)			
MDC: 2	3 (5.1)	7 (12.1)	0.12
MDC: 1-2	22 (37.3)	11 (19.0)	
MDC: 3 or 4	1 (1.7)	1 (1.7)	
MDC (1)-2-3(-4)	33 (55.9)	39 (67.2)	
Hypothalamic involvement	32 (54.2)	38 (65.5)	0.21
Nr of treatment lines: m (r)	2 (1-5)	3 (1-8)	<0.01
Binoc BCVA start TX (LogMAR): m (r)	0.1 (-0.1-3.0)		
Binocular VI/ B * start TX			
No- mild VI	53 (89.8)		
Moderate VI	3 (5.1)		
Severe VI	1 (1.7)		
Blindness	2 (3.4)		
Monocular BCVA at start TX: n	118		
Best eye (LogMAR): m (r)	0.1 (-0.1-3.0)		
Worst eye (LogMAR): m (r)	0.5 (-0.1-3.0)		
Monocular VI/ B* start TX: all eyes	118		
No- mild VI	84 (71.2)		
Moderate VI	16 (13.6)		
Severe VI	3 (2.5)		
Blindness	15 (12.7)		
Change of BCVA: start TX – end FU: n (%) @			
Improved: $\geq$ 0.2 LogMAR	15 (13.4)		
Stable: $\leq$ 0.2 LogMAR	70 (62.5)		
Decreased: $\geq$ 0.2 LogMAR	27 (24.1)		
Binocular BCVA at end FU (LogMAR): m (r)	0.0 (-0.2-3.0)	0.4 (-0.2-3.0)	<0.01

Table Continued

	Sub group 1: analysis at start TX and end FU	Sub group 2: analysis end FU only	p-value
Binocular VI/ B* end FU: n (%)			
No- mild VI	50 (84.7)	31 (53.4)	<0.01
Moderate VI	7 (11.9)	7 (12.1)	
Severe VI	0 (0.0)	7 (12.1)	
Blindness	2 (3.4)	13 (22.4)	
Monocular BCVA at end FU: n	118	116	
Best eye (LogMAR): m (r)	0.0 (-0.2-3.0)	0.4 (-0.2-3.0)	<0.01
Worst eye (LogMAR): m (r)	0.7 (-0.1-3.0)	2.7 (-0.1-3.0)	<0.01
Monocular VI/ B* end FU: all eyes: n (%)			
No- mild VI	75 (63.6)	48 (41.4)	<0.01
Moderate VI	19 (16.1)	11 (9.5)	
Severe VI	4 (3.4)	8 (6.9)	
Blindness	20 (16.9)	49 (42.2)	

Abbreviations: BCVA: best-corrected visual acuity, FU: follow up, LogMAR: Logarithm of the Minimum Angle of Resolution, MDC: modified Dodge classification (stage 1: optic nerve involvement/ stage 2: chiasm/ stage 3: anterior optic tract/ stage 4: posterior optic tract), M (r): median (range), NF1: neurofibromatosis type 1, TX; therapy, VI/ B: visual impairment/ blindness, Yrs: years

*: Categories of VI/ B according to the International Statistical Classification of Diseases and Related Health Problems, World Health Organization.: 10th Revision. ICD-10 (Version 2019 :Available from: https://icd.who.int/browse10/2019/en#/H54.9): no- mild VI : BCVA ≤0.5 logMAR (≥0.3 decimal); moderate VI: BCVA >0.5 to ≤1.0 logMAR (<0.3 and ≥ 0.1 decimal); severe VI: BCVA >1.0 to ≤1.3 logMAR (<0.1 to ≥0.05 decimal) or a binocular VF no greater than 20° in radius around central fixation and blindness: BCVA >1.3 logMAR (<0.05 decimal) or a binocular VF no greater than 10° in radius around central fixation.

@: six eyes had no light perception (LogMAR 3.0) at the start of therapy, they were excluded from this analysis. BCVA did not improve in any of these eyes.

Supplement 4.2.
Long-term binocular and monocular visual field abnormalities at median 8.3 years after start of treatment for pediatric OPG; a comparison between children with a NF1 associated and sporadic OPG

VF analysis: end FU	Total cohort	NF1 OPG	Sporadic OPG
Available VF (pts): n (%)	67	27	40
Type of test performed (per pt): n (%)	67	27	40
BEFIE	3 (4.8)	1 (3.7)	2 (5.0)
Goldmann	31 (46.3))	14 (51.9)	17 (42.5)
Peritest	17 (25.4)	7 (25.9)	10 (25.0)
HFA	16 (23.9)	5 (18.5)	11 (27.5)
Bilateral VF performed (pts): n (%)	43 (64.2)	16 (59.3)	27 (67.5)
Bilateral VF defects present: n (%)	21 (48.8)	6 (37.5)	15 (55.6)
Bitemporal hemianopia [1]	14 (32.5)	0 (0.0)	14 (51.9)
Homonymous hemianopia [1]	7 (16.3)	4 (25.0)	3 (11.1)
Homonymous quadrantanopia [1]	1 (2.3)	1 (6.3)	0 (0.0)
Restriction $\leq$ 10 degrees [2]	0 (0.0)	0 (0.0)	(0.0)
Monocular VF performed (eyes): n	110	43	67
Monocular VF defects (eyes): n (%)	88 (80.0)	35 (81.4)	53 (79.1)
Hemianopia [1]	61 (69.3)	16 (45.7)	45 (84.9)
Quadrantanopia [1]	15 (17.0)	8 (22.9)	7 (13.2)
Various scotoma	25 (28.4)	10 (28.6)	15 (28.3)
Restriction $\leq$ 10 degrees [2]	1 (1.1)	1 (2.9)	0 (0.0)

Abbreviations:
BEFIE: Behavioral Visual Field Screening Test, FU: follow up, HFA: Humphrey visual field analyzer, Pts: patients, VF: visual field
1: Hemianopia or quadrantanopia was defined as presence of the defect in $\geq$ 60% of the involved field, including incomplete or complete hemianopia or quadrantanopia.
2: a concentric restriction $\leq$ 10 degrees in a radius around central fixation (representing blindness according to the WHO).

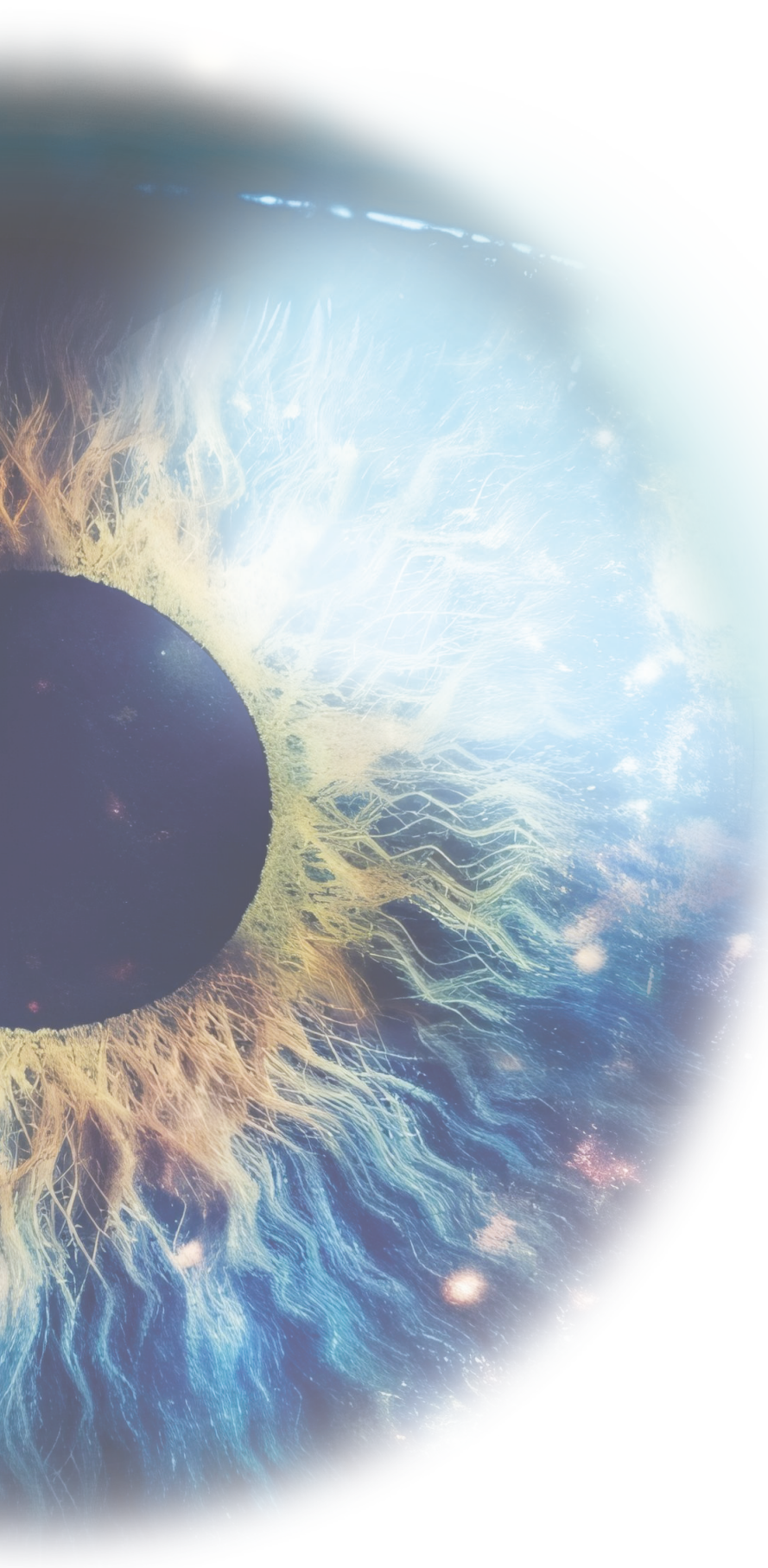
Supplement 4.3.
Rate of binocular visual impairment or blindness at the end of follow up of patients with an OPG per anatomic location (MDC), NF1 association and age at start of therapy.

Patients: n (%)	No- mild VI*	Moderate VI*	Severe VI*	Blindness*	Severe VI&B
NF1: n (%)	37 (82.2)	5 (11.1)	1 (2.2)	2 (4.4)	3 (6.7)
Sporadic: n (%)	44 (61.1)	9 (12.5)	6 (8.3)	13 (18.0)	19 (26.4)
Age start TX (yrs): n (%)					
0- <1	3 (23.1)	1 (7.7)	1 (7.7)	8 (61.5)	9 (69.2)
>1- <2	2 (18.2)	4 (36.4)	2 (18.2)	3 (27.3)	5 (45.5)
≥2- <8	45 (84.9)	4 (7.5)	2 (3.8)	2 (3.8)	4 (7.5)
≥8-18	31 (77.5)	5 (12.5)	2 (5.0)	2 (5.0)	4 (10.0)
MDC: n (%)					
2	6 (60.0)	1 (10.0)	0 (0.0)	3 (30.0)	3 (30)
1-2	27 (81.8)	3 (9.1)	2 (6.1)	1 (3.0)	3 (9.1))
(1)-2-3-(4)	47 (65.3)	10 (13.9)	4 (5.6%)	11 (15.3)	15 (20.8)
3 or 4	1 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)	1 (50)
Hypothalamus +	43 (61.4)	10 (14.3)	4 (5.7)	13 (18.6)	17 (24.3)

Abbreviations: MDC: Modified Dodge classification (stage 1: optic nerve involvement/ stage 2: chiasm/ stage 3: anterior optic tract/ stage 4: posterior optic tract), NF1: Neurofibromatosis type 1, nNF1: no NF1, TX: therapy, VI: visual impairment, VI & B: visual impairment and blindness, yrs: years

*: Categories of VI/ B according to the International Statistical Classification of Diseases and Related Health Problems, World Health Organization.: 10th Revision. ICD-10 (Version 2019 :Available from: https://icd.who.int/browse10/2019/en#/H54.9):

no- mild VI : BCVA ≤0.5 logMAR (≥0.3 decimal); moderate VI: BCVA >0.5 to ≤1.0 logMAR (<0.3 and ≥ 0.1 decimal); severe VI: BCVA >1.0 to ≤1.3 logMAR (<0.1 to ≥0.05 decimal) and blindness: BCVA >1.3 logMAR (<0.05 decimal).



CHAPTER 5

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

C.A.M. Bennebroek*, M.C. Montauban van Swijndregt*; J. van Zwol, S. Bhusal, A.T. Dittrich, R. Oostenbrink, J.W.R. Pott, E.A. Buijs, A. Y.N. Schouten- van Meeteren, G.L. Porro, P. de Graaf and P. Saeed

*Both authors contributed equally.

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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 +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:
Systemic anticancer therapy 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 pre-existing blindness. The use of radiotherapy requires careful consideration due to the risk of severe visual impairment and secondary disease.

Introduction

Pediatric isolated optic nerve glioma (ONG) is a subset of low grade glioma (mostly pilocytic astrocytoma, WHO 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, represent 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 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 to 21% and binocular BCVA of 9 to 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.

Materials and methods

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 tumor volume (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).

Study design of the cohort study

This nationwide retrospective study was conducted across all 8 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.

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. Optic nerve glioma 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 (Online Resource 3).

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.

Visual function

Monocular BCVA and visual field (VF) tests were collected when performed within three months prior to the start of therapy, within three 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 $\geq$ 0.2 LogMAR), stable (change within 0.2 LogMAR) or decreased (increase of $\geq$ 0.2 LogMAR) (11). The prevalence of severe monocular visual impairment (VI) and blindness was scored at the end of follow up using the World Health Organization criteria (WHO) (14) (BCVA < 0.1 decimal or > 1.0 LogMAR). Visual field data were evaluated by two experienced ophthalmologists (CB and GP) following a predefined protocol (15) .

Radiological evaluation

Radiological analysis was independently conducted by two experienced neuroradiologists (EB and PG). 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 tumor volume (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.

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 was presented as count and percentage. The distribution of the continuous data was tested for normality. Continuous data was 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 <0.05 was considered statistically significant.

To quantify the interrater reliability of the TV, an intra-class 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).

Results

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 Supplement 5.1.

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 RANO criteria (Response assessment in neuro-oncology) (20). An overview of the characteristics of the studies and patient is presented in Table 5.1. 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).

Table 5.1. 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) [1]			Pilocytic astrocytoma: 3 (100.0)	
ONG (n): BCVA available	10			11	
Age at diagnosis (years): m (r)	8.5 (3.0-20.0) [2]			4.0 (1.0-16.0)	
Follow up (years): m (r)	14.0 (10.0-24.0)			6.0 (2.0-17.0)	
Type of TX: n (ONG)	SX: 5	RT: 4 [3,4]	SX →RT: 1	SAT: 8	SAT +/- RT → SX: 3
Radiological response analysis	NA	NA	NA	SD: 6 RD: 2	NED: 2

Table 5.1. Continued.

Authors (year)		**Tow et al. (2002) (19)**		**Hamideh et al. (2018) (2)**	
BCVA start of therapy (LogMAR): m (r)	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): m (r)	3.0 (3.0-3.0)	3.0 (0.1-3.0)	3.0	0.0 (-0.1-3.0)	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, M (r): median (range), 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

[1] Data was obtained from 7 of 19 ONG (total study cohort), no data were available on the sub group that received treatment (n=10)

2 One patient was >18 years old.

3 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.

4 The range of cumulative doses of RT: 45.0-54.0 Gray

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 data were lacking at the start of SAT2. The ONG in the right orbit was included in the cohort analysis (Supplement 5.2: pt 12).

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 5.2.

The indication for the start of treatment, as defined in individual patient files, was: a progressive decrease of BCVA compared to 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=0.020). No significant differences were observed in clinical presentation and ocular examination between NF1 and sporadic ONGs.

Table 5.2. Baseline characteristics of 20 patients with 21 isolated optic nerve gliomas

	All ONG	1th line SAT	1th line SX	1th line 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)

Table 5.2. Continued.

	All ONG	1th line SAT	1th line SX	1th line RT
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 anti-cancer therapy, SX: surgery, TX: therapy

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). 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 5.1.

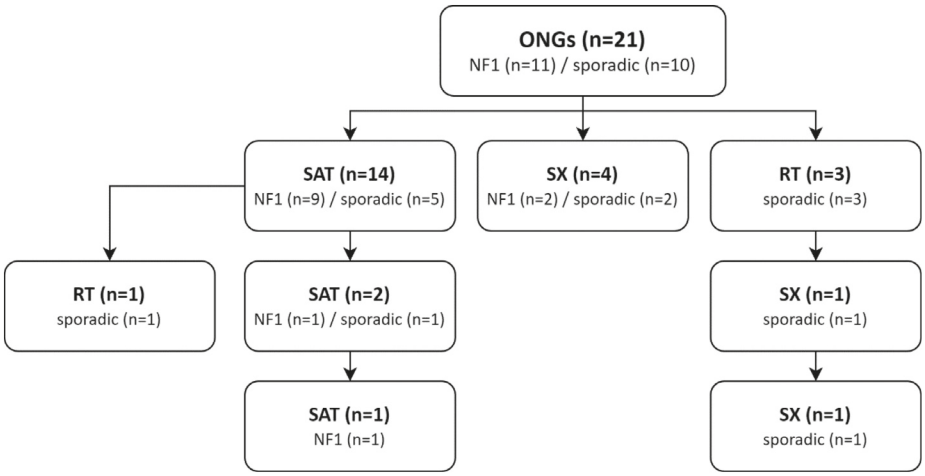

Figure 5.1: Flowchart of the variety in treatment lines of 21 isolated pediatric optic nerve gliomas

Abbreviations: NF1: neurofibromatosis type 1, ONG: isolated optic nerve glioma, RT: radiotherapy, SAT: systemic anticancer therapy, SX: surgery

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 mm3 (range: 4.9 - 19008.0 mm3) and 949.1 mm3 (range: 59.6 - 17037.8 mm3). The interrater reliability analysis yielded an excellent ICC of 0.96 (95% CI: 0.94-0.98) for TV measurements (18).

Visual function and tumor volume: 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 (60x 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 BCVA and TV is presented in Table 5.3. Individual data of the ONGs that received successive therapy are available in Supplementary Table 5.4. Individual data on BCVA, VF and TV after first line therapy are available in Supplement 5.5. A comparison of NF1 associated and sporadic ONG is available in Supplement 5.6. Supplement 5.5 contains MRI images illustrating the course of TV following SAT and RT in two patients.

Table 5.3. 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 [1]	17	11	4	2
Median (range)	2.7 (0.0-3.0)	1.7 (0.0-3.0)	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 [1]	9	6	1	2

Table 5.3. Continued.

	All treated ONG	SAT	SX	RT
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*	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 VI (>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: cm3: n	191	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: cm3: 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: cm3: n [1]	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 [2]	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 [1]	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 antican-cer therapy, SX: surgery, RT: radiotherapy, TV: tumor volume, TX: therapy, VI: visual impairment, WHO: world health organization.

[1]: ONGs that progressed after first-line treatment were excluded

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

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=0.36), nor did TV (NF1: n=9/

sporadic: n=10, p=0.12). 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=0.35). 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 5.2.

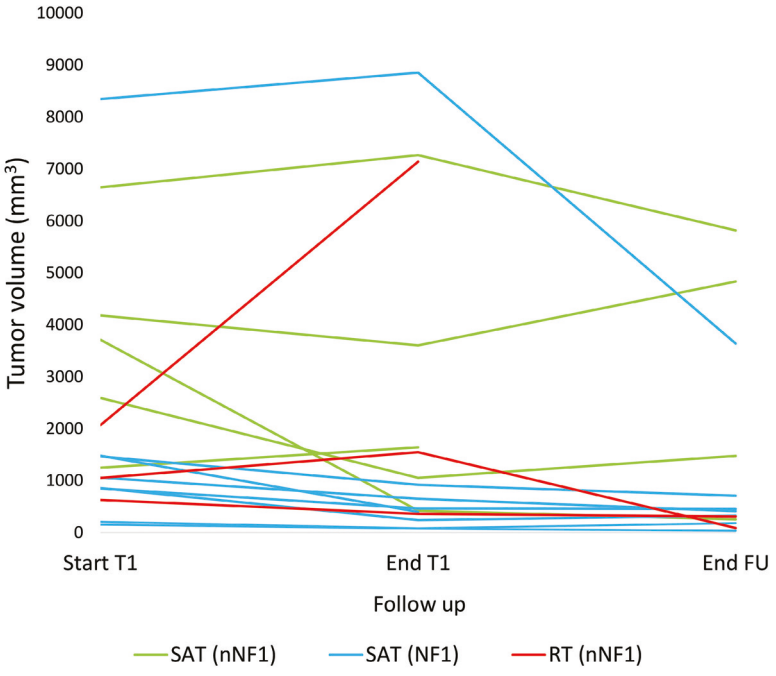

Figure 5.2. Individual course of the tumor volume on MRI of ONG that received first line SAT (n=13) versus first line RT (n=3)

Abbreviations: FU: follow up, NF1: neurofibromatosis type 1: radiotherapy, SAT: systemic anticancer therapy, T1: first-line therapy

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 to the ONG that received SAT (7537.2 mm3 (range: 4370.7-18022.9 mm3) and 1465.6 mm3 (range: 153.2-8345.9 mm3) (p=0.03).

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.

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, 1 eye improved to 20/400 (a non-quantitative representation of visual acuity measurements). Fisher et al. (22) reported improvement or stability of BCVA in 78.6% (n=11) of patients within three 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 (Online Resource 2) 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 visual impairment, 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 non-isolated 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 5.2 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 (Online Resource 2 and 3 (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 one 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, visual impairment and double rating of TV evaluation.

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 1 out of 5 ONG after SAT. Resection of ONG appears effective to alleviate (painful) proptosis in case of pre-existing 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.

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Conflict of interest:

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

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Supplement 5.1.
Search strategy literature review and critical appraisal of case series.

Literature search

A literature search was conducted in PubMed (1) on the 18th of August 2023 to identify articles regarding treated patients with an ONG.w

The following search was applied: "Optic Nerve Glioma"[Mesh] OR "optic nerve glioma"[tiab] OR "optic pathway glioma"[tiab]) AND ("Drug Therapy"[Mesh] OR "chemotherapy"[tiab] OR "SAT"[tiab] OR "systemic anticancer therapy"[tiab] OR "General Surgery"[Mesh] OR "surgery"[tiab] OR "debulking"[tiab] OR "resection"[tiab] OR "Radiotherapy"[Mesh] OR "radiotherapy"[tiab] OR "radiation therapy"[tiab]).

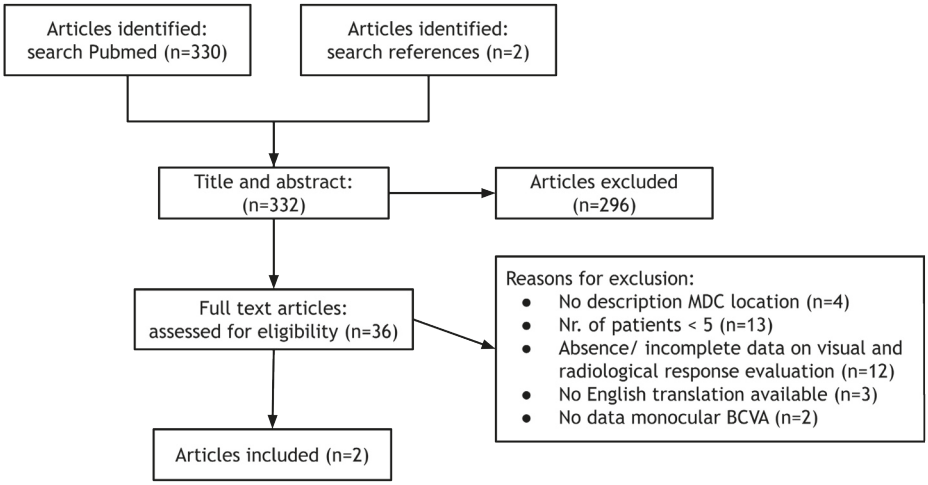
The titles and abstracts of the identified articles were screened. Relevant articles were selected for a full text assessment and evaluated according to the following pre-specified inclusion criteria:

- isolated OPG in the optic nerve (MDC-1)
- age 0-18 years at diagnosis
- five or more patients with an ONG
- treatment with SAT, surgery or radiotherapy because of a progressive ONG
- analysis on visual and/or radiological outcome
- publication between 1970 and present

Data extraction

The following data were collected: study characteristics, characteristics of the study population, type of therapy, visual and/or radiological outcomes after therapy. In case of missing data authors were contacted by e-mail (n=2) to receive additional data.

Supplement 5.2.
Flowchart literature search



Supplement 5.3. JBI critical appraisal of included case series (2)

Article (year publication)	Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Were valid methods used for identification of the condition for all participants included in the case series?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting of the demographics of the participants in this study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow up results of cases clearly reported?	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?
Tow et al. (2002) (3)	No	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear
Hamideh et al. (2018) (4)	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	Unclear

Subscript: A study is considered to have a low risk of bias if ≥ 50% is answered with 'yes' , a high risk of bias if ≥ 50 % is answered with 'no', an uncertain risk if ≥ 50% is answered with 'unclear'.

Supplement 5.4. Individual patient characteristics, BCVA and tumor volume measurements.

Pt	NF1: +/-	Reason start therapy@	Type Tx	BCVA start TX (LogMAR)	BCVA after TX (LogMAR)	BCVA end FU (LogMAR)	TV: start TX (mm3)	TV end TX (mm3)	Change TV; start - end TX: %	TV End FU (mm3)	TV Change; end TX – end FU: %	Time to progress (yr)	TX2	Time to progress. (yr)	TX3	FU (yr)
1	-	1, 3	SAT	1.0	3.0	3.0	2592.3	1053.7	-59.4	1475.7	+40.05	1.3	SAT	-	-	9.7
2	+	1, 2	SAT	0.3	0.0	0.0	848.9	466.3	-45.1	454.4	-2.55	-	-	-	-	9.3
3	+	1, 2	SAT	0.3	0.0	0.3	856.8	239.3	-72.1	324.3	+35.51	-	-	-	-	8.8
4	-	1	SAT	3.0	-	3.0	3712.3	422.1	-88.6	252.9	-40.09	-	-	-	-	11.5
5	+	1, 3	SAT	1.0	-	3.0	1465.6	919.3	-37.3	708.8	-22.90	-	-	-	-	11.6
6	-	1, 3	SAT	-	2.7	2.7	6648.5	7267.7	+9.3	5817.9	-19.95	-	-	-	-	2.3
7	+	1	SAT	-	-	1.7	8345.9	8856.1	+6.1	3639.4	-58.91	-	-	-	-	10.7
8	+	3	SAT	-	-	0.0	153.2	74.7	-51.2	34.3	-54.09	-	-	-	-	18.0
9	+	1, 3	SAT	-	3.0	3.0	-	-	-	-	-	-	-	-	-	13.1
10	-	1, 3	SAT	0.2	0.0	0.9	1248.3	1641.5	+31.5	1102.7	-32.82	2.8	RT	-	-	4.8
11	-	3	SAT	0.7	1.3	1.3	4180.3	3604.5	-13.8	4834.9	+34.14	-	-	-	-	13.8
12	+	3	SAT	-	1.0	1.7	1479.9	398.5	-73.1	633.0	+58.83	2.1	SAT	2.0	SAT	8.6
13	+	1	SAT	-	-	-0.1	207.0	81.9	-60.5	180.8	+120.87	-	-	-	-	8.7
14*	+	2	SAT	0.0	0.0	0.0	1058.1	650.2	-38.5	412.5	-36.56	-	-	-	-	18.4
	+	3	SX	3.0	3.0	3.0	-	-	-	-	-	-	-	-	-	18.4
15	-	3	SX	3.0	-	3.0	18022.9	0	-100.0	0	0	-	-	-	-	9.4
16	-	1	SX	-	-	3.0	7537.2	0	-100.0	0	0	-	-	-	-	5.0
17	+	1, 3	SX	0.6	-	3.0	4370.7	0	-100.0	0	0	-	-	-	-	14.5
18	-	1	RT	0.3	1.3	2.4	1051.0	1547.6	47.3	87.3	-94.36	-	-	-	-	8.0
19	-	1, 2	RT	0.0	3.0	3.0	2069.5	7140.9	245.1	748.8	-89.51	0.7	SX	8.3	SX	16.2

Individual patient characteristics, BCVA and tumor volume measurements. (Continued)

Pt	NF1: +/-	Reason start therapy@	Type Tx	BCVA start TX (LogMAR)	BCVA after TX (LogMAR)	BCVA end FU (LogMAR)	TV: start TX (mm3)	TV end TX (mm3)	Change TV; start - end TX: %	TV End FU (mm3)	TV Change; end TX – end FU: %	Time to progress (yr)	TX2	Time to progress. (yr)	TX3	FU (yr)
20	-	1	RT	1.7	1.7	2.7	627.5	358.7	-42.8	309.4	-13.75	-	-	-	-	15.8

@1= a decrease of age-appropriate visual functions, 2: progression shown on MRI, 3: proptosis

*Patient with a bilateral ONG. At first, OS received surgery, later OD was treated with SAT.

Abbreviations: BCVA: Best corrected visual acuity, FU; follow up, LogMAR; Logarithm of the Minimum Angle of Resolution, NA; no abnormalities, pt; patient, RT; radiotherapy, SX; surgery, SAT; systemic anticancer therapy, TV; tumor volume, TX; therapy, yr; year, VF; visual field

Supplement 5.5. Individual data on the course of BCVA and tumor volume in four patients that received successive therapy.

Pt+	Site ONG	TX 1	TV start TX1 (mm3)	TV after TX1 (mm3)	Change TV (%)	BCVA start TX1*	BCVA after TX1*	Time to TX2 (yr)	TX 2	TV start TX2 (mm3)	TV after TX2 (mm3)	Change TV (%)	BCVA start TX2*	BCVA after TX2*	Time to TX3 (yr)	TX3	TV start TX3 (mm3)	TV | after TX3 (mm3)	Change TV (%)	BCVA start TX3*	BCVA after TX3*	Interval end TX to last FU (yr)
1	OD	SAT1: VCR/ CP	2592.3	1053.7	-59.4	1.0	3.0	1.3	SAT2: Vinbl.	3140.3	3289.4	+4.7	3.0	3.0	-	-	-	-	-	-	-	4.3
10	OS	SAT: VCR/ CP	1248.3	1641.5	+31.5	0.2	0.0	2.8	RT	ND	ND	ND	0.92	0.92	-	-	-	-	-	-	-	0.1
12[1]	OD	SAT1: VCR/ CP	1479.9	398.5	-73.1	ND	1.0	2.1	SAT2: Vinbl.	ND	1026.4	ND	0.5	ND	2.0	SAT3: Vinbl.	3176.4	2249.6	-29.2	>1.0	2.0	0.8
	(OS)	SAT1: VCR/ CP	508.8	170.5	-66.5	ND	0.0	2.1		ND	2378.6	ND	0.25	ND	2.0		2110.7	1560.9	-26.0	0.3	0.5	0.8
19	OS	RT	2069.5	7140.9	+245.1	0.0	3.0	2.1	SX	12973.8	4975.5	-61.6	ND	ND	8.3	SX	15184.6	1438.6	-90.5	3.0	3.0	5.7

Abbreviations: BCVA: best corrected visual acuity, FU: follow up, ND: no data, Pt: patient, OD: oculus dexter (right eye), OS: oculus sinister (left eye), RT: radiotherapy, SX: surgery, SAT: systemic anticancer therapy (SAT1-3: successive line of SAT), TV: tumor volume, TX: therapy, yr: year, Vinbl: vinblastin, VCR/ CP: combined vincristine and carboplatin

+: the number of de patients relate to the numbers of the patients presented in Online Resource 2.

*: BCVA is registered in LogMAR: Logarithm of the Minimum Angle of Resolution

1: Pt 12 (with Neurofibromatosis type 1): 1st and 2nd line SAT was initiated because of progression of an ONG in the right orbit, all clinical and radiological information of the choice for start of 2nd line treatment of the left ONG was not available, therefore the left sided ONG was not included in this study. No biopsy was performed in both ONGs. Vinblastin was restarted (SAT3) because of radiological progression and visual deterioration of the right ONG. At the start of SAT3 a minor thalamic asymmetry was present at, which showed a drastic volume expansion after cessation of SAT 3. A biopsy of the thalamic lesion showed a pilocytic astrocytoma. The patient did not receive successive treatment and died six months later due to gliomatosis cerebri. No analysis on tumor biology was available in this patient.

Supplement 5.6.

Comparison of clinical features of NF1 and sporadic associated ONG that received various treatments.

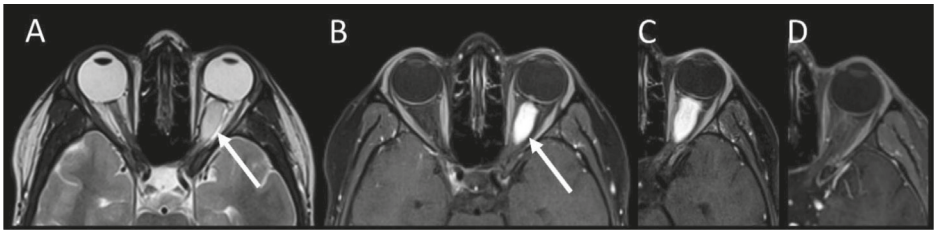
	Total population	NF1	Sporadic	p-value
ONG: n	21	11	10	
Unilateral ONG (pt): n	19	9	10	
Bilateral ONG (pt): n	1	1	0	
Male: n (%)	8 (38.1)	4 (36.4)	4 (40.0)	0.86
Age at diagnosis (years): m (r)	6.6 (1.7-17.6)	3.8 (1.7-12.8)	9.7 (2.9-17.6)	0.01
Clinical presentation diagnosis: n (%)				
Decrease of visual function	14 (66.7)	6 (54.5)	8 (80.0)	0.22
Proptosis	13 (61.9)	7 (63.6)	6 (60.0)	0.86
MRI finding, no clinical abnormalities	2 (9.5)	2 (100)	0 (0)	0.16
Eye examination at diagnosis: n (%)				
Strabismus	8 (38.1)	4 (36.4)	4 (40.0)	0.86
Optic nerve atrophy	5 (23.8)	3 (27.3)	2 (20.0)	0.70
Papiledema	10 (47.6)	5 (45.5)	5 (50.0)	0.84
Pathology: n (%)				
Pilocytic astrocytoma	6 (100)	2 (33.3)	4 (66.7)	0.39
1st line TX				
Age start TX (years): m (r)	7.2 (1.9-17.9)	4.6 (1.9-13.0)	9.9 (3.5-17.9)	0.02
Interval diagnosis - start therapy (months): m (r)	2.9 (0.0-39.0)	3.0 (0.9-39.0)	2.5 (0.0-9.0)	0.40

A/ C/ E: Axial T2 weighted MRI image at the start of SAT (A), two months after the end of the 21-month SAT (C) and after 11.7 years of follow up (E). The tumor volume (TV) at the start of SAT (1465.6 mm3) (A), decreased with 37.3% to 919.3 mm3 after SAT (C) and further decreased with 22.9% to 708.8 mm3 at the end of follow up (E).

B/ D/ F: Axial fat-suppressed contrast-enhanced T1- weighted MRI image at the start of SAT (A), two months after the end of the 21-month SAT (C) and after 11.7 years of follow up (E). At the start of SAT (B), the ONG showed diffuse complete enhancement, which fully disappeared at the end of SAT (D). White arrow: Optic nerve glioma.

Supplement 5.7.1.

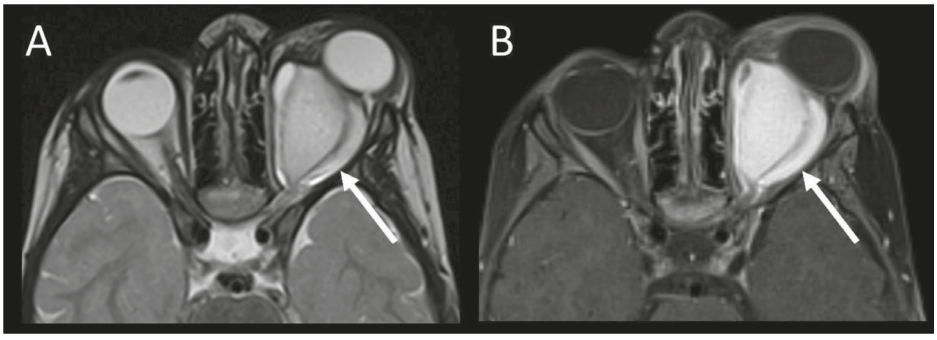
Axial T2 (A) and fat-suppressed contrast-enhanced T1-weighted (B-D) MRI of a child with an isolated optic nerve glioma that received radiotherapy (RT) at the start of therapy (A, B), end of therapy (C), and at the end of follow up (D)



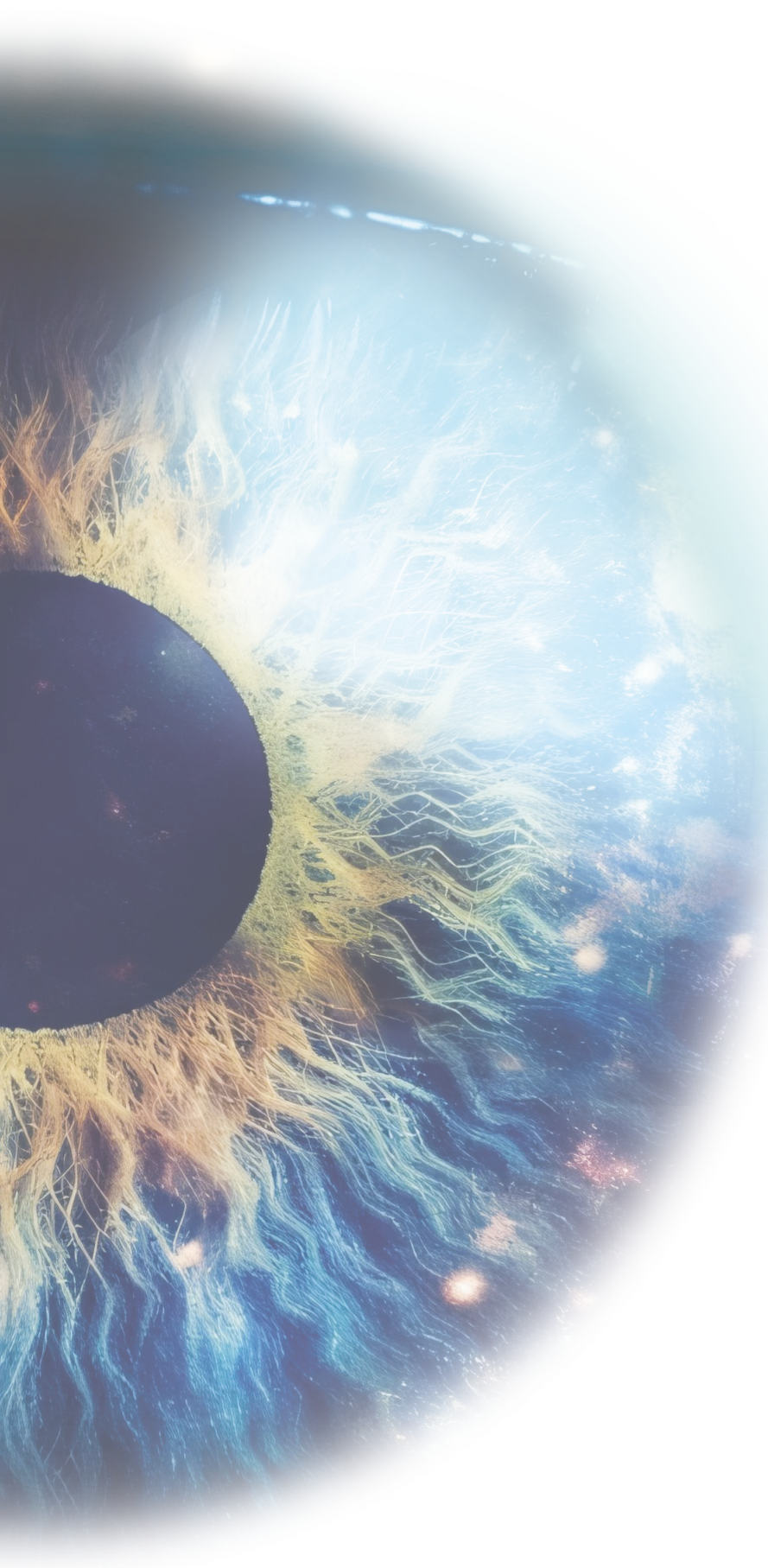
The TV at the start of radiotherapy (1051.0 mm3) (A) increased with 47.3% to 1547.6 mm3 after cessation(C) and further decreased with 94.36% to 87.3 mm3 at the end of follow up (D). The diffuse enhancement fully disappeared at the end of follow up (D versus C).
White arrow: Optic nerve glioma.

Supplement 5.7.2.

Axial T2 (A) and fat-suppressed contrast enhanced T1-weighted (B) MRI of a child with proptosis and blindness of the left eye due to a progressive ONG before surgical resection



A/ B: The tumor volume was 18022.9 mm3 before complete resection.
White arrow: Optic nerve glioma.



CHAPTER 6

Impact of bevacizumab on visual function, tumor size, and toxicity in pediatric progressive optic pathway glioma: a retrospective nationwide multicenter study

C.A.M. Bennebroek, J. van Zwol, G.L. Porro, R. Oostenbrink, A. T.M. Dittrich, A.L.W. Groot, J.W. Pott, E. Janssen, N.J. Bauer, M.M. van Genderen, P. Saeed, M.H. Lequin, P. de Graaf, A.Y.N. Schouten- van Meeteren

Cancers: 2022 Dec 10;14(24):6087

Abstract:

Background:
Bevacizumab (BVZ) is used as subsequent line of treatment for pediatric optic pathway glioma (OPG) in case of progression. Data on the treatment effect concerning tumor progression and visual function are scarce and nationwide studies are lacking.

Methods:
We performed a retrospective, nationwide, multicenter cohort study including all pediatric patients with OPG treated with BVZ in the Netherlands (2009-2021). Progression free survival, change in visual acuity and visual field, MRI-based radiologic response and toxicity were evaluated.

Results:
In total, 33 pediatric patients with OPG were treated with BVZ (median 12 months).

Visual acuity improved in 20.5%, remained stable in 74.4%, and decreased in 5.1% of 39 of all analysed eyes. Monocular visual field improved in 73.1%, remained stable in 15.4%, and decreased in 7.7% of 25analysed eyes. Radiologic response at the end of therapy showed a partial response in seven patients (21.9%), minor response in seven (21.9%), stable disease in 15 (46.9%) and progressive disease in three (9.3%). Progression free survival at 18 and 36 months after start of BVZ reduced from 70.9% to 38.0%. Toxicity ($\geq$ grade 3 CTCAE) during treatment was observed in six patients (18.2%).

Conclusion:
Treatment of BVZ in pediatric patients with OPG revealed stabilisation in the majority of patients, but was followed by progression at a later time point in more than 60% of patients. This profile seems relatively acceptable with the benefits of visual field improvement in more than 70% of analysed eyes and visual acuity improvement in more than 20% of eyes.

Introduction

Pediatric optic pathway glioma (OPG) concerns a low grade glioma (LGG) (WHO grade 1) confined to the optic pathway, histologically represented by pilocytic astrocytoma (PA) in 90% of cases. In case of tumor growth and/or clinical deterioration, systemic anticancer treatment (SAT), mostly chemotherapy, is often preferred over radiotherapy to avoid endocrine, vascular and/or cognitive damage (1).

Initial systemic therapy is mostly represented by carboplatin and vincristine, followed by vinblastine in case of progression (2). Bevacizumab (BVZ) combined with irinotecan (IRI) was introduced in 2009 as the next-line of treatment for progressive LGG (3). As humanized monoclonal antibody, BVZ is a potent vascular endothelial growth factor (VEGF) inhibitor due to its highly specific binding capacity to VEGF isoforms (4). Histological studies on PA substantiate the antiangiogenic effect of BVZ by presence of vascular endothelial growth factor receptor 2 (VEGFR-2) on PA endothelium (5). So far, the majority of studies on pediatric LGG at diverse anatomic locations have evaluated treatment outcome after the combination of BVZ and IRI (3, 6-9), diverse combined strategies (10) or BVZ monotherapy (11, 12). All studies reveal a small sample size (N=7-35).

Treatment of LGG with BVZ tends to stabilize tumor volume, but progression frequently occurs after discontinuation of BVZ (14-93% within median 5-12 months after cessation of BVZ (7-11)). Studies on toxicity profile are reported and show an acceptable profile of grade 3 toxicity according to CTCAE criteria (Common Terminology Criteria for Adverse Events) (8, 10, 11), which is reversible after cessation (8, 10). So far reports on treatment outcome of BVZ specifically for OPG concern low patient numbers (N=2-12) (7-9, 11).

Evaluation of the treatment effect on OPG requires twofold analyses, containing evaluation of visual function and radiologic response (according to the RAPNO criteria (Response Assessment in Pediatric Neuro-Oncology)) (13). Currently, no correlation among both outcome parameters is shown (14, 15). Bevacizumab has shown promising effect on visual function in a small sample study (N=4) (16), but larger studies with predefined outcome parameters on visual function are lacking.

In the past era drugs targeting the molecular biologic changes in the MAP-kinase pathway became successful for LGG treatment (17, 18). The activation of this pathway is caused by activation of the BRAF-oncogene, in pediatric OPG frequently represented by the KIAA1549-BRAF fusion, which can be identified in 50-60% of

OPG (19, 20). The 5-year progression free survival (PFS)of OPG with KIAA1549-BRAF fusion is superior to non-fusion OPG after first line SAT (19), so far knowledge of OPG progression after SAT with or without KIAA1549-BRAF fusion is lacking.

We evaluated the efficacy and safety of BVZ for OPG in a nationwide cohort of patients by analysing visual functions (best corrected visual acuity (BCVA) and visual field (VF), tumor size, toxicity profile and progression free survival.

Materials and methods

Study design and data collection

This is a retrospective nationwide multicentre study. All consecutive children (0-17 year) in the Netherlands diagnosed with an OPG (Modified Dodge Classification (MDC) stage 1-4) (21) and treated with BVZ during at least one month, with or without other chemotherapy, were eligible for this study. The diagnosis of OPG with or without neurofibromatosis type 1 (NF1) was confirmed by its appearance on MRI and/or tissue analysis obtained via surgery or biopsy.

The study was approved by the Dutch Childhood Oncology Group (DCOG). Ethical committees of participating centers (Princess Máxima Center (the national tertiary pediatric oncology center), Amsterdam UMC, Erasmus MC, University Medical Center Utrecht (UMCU), Radboud university medical center, UMC Groningen, Maastricht University Medical Center) and visual rehabilitation centers in the Netherlands (Stichting Bartiméus and Visio) gave approval for collection of coded data. Patients were retrieved by the registry of national database of the DCOG (diagnosed with OPG from January 2003 until December 2018) and all patients from the Princess Máxima Center (diagnosed with OPG from January 2019 until December 2021). In addition, pediatric ophthalmologists and oncologists from all Dutch university hospitals have been consulted to identify potentially non-registered patients since 2003. For 32 patients follow-up was continued until June 18th 2022, for one patient until December 31st 2020.

Informed consent was given by patients and/or parents or legal guardians registered at the DCOG and was additionally required at two participating centers: UMCU and Princess Máxima Center. An opt-out procedure was offered to patients registered in local databases in the Amsterdam UMC. Other centers provided permission to use coded patient data by waiver of consent.

Clinical data collection

Data were collected by reviewing medical records on patient characteristics including sex, NF1 status, age at diagnosis, age at start of initial treatment and start of BVZ, previous treatment, indication for start of BVZ (ophthalmological / radiological), number of treatment cycles and dosage of BVZ and concurrent systemic anticancer therapy (SAT). If tumor biopsy was performed, histology and BRAF V600E mutation and KIAA1549-BRAF fusion were registered.

Response Evaluation:
Outcomes

The primary endpoint existed of a combination outcome parameters analysing the treatment effect of BVZ. These parameters were: change in best corrected visual acuity (BCVA), visual field (VF), radiologic response and progression free survival. A secondary endpoint was toxicity of BVZ.

Visual Function

Visual functions were extracted from medical records by collecting BCVA and VF performed within 2 months before start of BVZ and within 3 months after cessation of BVZ. Monocular BCVA was registered from age-appropriate testing methods (Teller Acuity Cards, Cardiff Acuity Test, Kays Pictures, Snellen charts) and converted into the logarithm of minimal angle of resolution scale (LogMAR) for statistical purposes. Binocular visual impairment was categorized according to the definitions of visual impairment and blindness as described by the World Health Organization: mild or no visual impairment (BCVA $\leq$ 0.5 LogMAR), moderate visual impairment (BCVA > 0.5 - $\leq$ 1.0 LogMAR), severe visual impairment (BCVA >1.0 - $\leq$ 1.3 LogMAR), and blindness (BCVA > 1.3 LogMAR) (22). Change in BCVA was defined as a change of $\geq$ or $\leq$ 0.2 LogMAR. Visual acuity values corresponding to counting fingers, hand motion, light perception, and no light perception were converted to 2.0, 2.4, 2.7, and 3.0 LogMAR, respectively (23).

Available age-adapted VF testing methods included the Behavioral Visual Field (BEFIE) Screening test (24), the semiautomatic-static Peritest (25), Goldmann kinetic perimetry or the automatic Humphrey Visual Field Analyzer (HFA). Visual fields were blinded and evaluated by two independent experienced (pediatric (CB) & neuro- (GP)) ophthalmologists for abnormalities and change. Discrepancies between graders were resolved by discussion and mutual agreement. In case of HFA, low reliability, defined by test-specific cut-off values (i.e. HFA 30-2: false-positive errors, false-negative errors or fixation losses greater or equal to 20%) were excluded from further analyses. The following items were scored: scotoma (central/ paracentral/ cecocentral), quadrant- or hemianopia (partial/ absolute) and

location of defects: nasal/ temporal/ central. The change in VF defects was scored as: any change in visual field according to the clinical judgement of both assessors (BEFIE and Goldmann kinetic perimetry), change of ≥ 3 consecutive significant defects (P< 0.05) (HFA and Peritest).

Radiologic response

Radiologic analyses were independently performed by two experienced neuroradiologists (ML and PG). The anatomic location of OPG was classified following the MDC (21) (stage 1: optic nerve(s),stage 2: chiasm, stage 3: optic tract, stage 4: posterior optic tract, presence of hypothalamic involvement and leptomeningeal dissemination).

Radiologic tumor size and response evaluation, according to the RAPNO criteria (13), was performed on the MRI obtained previous to start and MRI most recent after cessation of BVZ. Response assessment was performed by calculation of the product of 3 perpendicular measurements on T1 with contrast enhancement and/ or T2-FLAIR. Both cystic and solid compartments were included in the measurements. Diffuse OPG were divided in two subcategories: involvement versus non-involvement of the optic tract. The response categories applied in this study are defined as: complete response: complete disappearance of the OPG; partial response: ≥ 50% decrease, minor response: 25–49% decrease, stable disease: 24% decrease to 25% increase; progressive disease: > 25% increase of OPG [13].

Toxicity

The toxicity profile of BVZ, from grade 2 onwards, was scored based on documentation in patients records during the treatment period according to the pediatric-specific criteria of the Common Terminology Criteria for Adverse Events (CTCAE v5.0) (26)

Progression

Progression, as defined by the local medical team, was scored as progression due to increase of tumor size, decrease of BCVA and/ or VF or new dissemination. In case of progression, successive therapy was scored. Time to progression was measured by comparison between start of BVZ to the earliest date of progression. Progression free survival was determined at 18 and 36 months after start of BVZ, which can be translated to 6 and 24 months after the intended completion of 12 months of BVZ).

Comparison of PFS was made among the NF1 and KIAA1549-BRAF fusion population, the four age categories (0-2 yr/ 3-5 yr/6-9 yr/ 10-18 yr) and diverse treatment combinations.

Data analysis

Data were collected by creating electronic case report forms in Castor (Castoredc.com) and exported to SPSS software for Windows (version 26.0.0.1, SPSS Inc., Chicago IL) for statistical analyses. Data analysis was performed using descriptive statistics. Continuous variables were presented by mean and standard deviation (in case of normal distribution) or median, range and interquartile range and categorical data by frequency and percentage. For continuous variables, differences between groups were tested with Student's t test for normally distributed data or Mann-Whitney U test for non-normally distributed data.

The 18 & 36 month PFS with 95% confidence interval (CI) after start of BVZ were calculated with the Kaplan–Meier method for the total population. Stratified comparison of the PFS was performed by applying log rank analysis.

Results

This nationwide study cohort consisted of 33 patients, who started BVZ between December 2009 and December 2021. Initially, 35 patients with OPG treated with BVZ were identified. One patient was excluded due to lacking data on treatment schedule, toxicity of BVZ and visual function, another single patient received one dosage of BVZ and immediately stopped treatment because of suspected severe allergy.

Baseline characteristics

The study cohort contained 20 males (60.6%) and 13 females (39.4%). Thirteen patients had NF1 (39.4%). The baseline characteristics are presented in table 6.1. Five OPGs were located solely in the chiasm. Twenty eight (84.8%) OPGs presented with diffuse spreading along the optic pathway along diverse stages (stage 1-4 MDC) (Supplement 6.1), of which 24 involved spreading in the posterior pathway (≥ MDC stage 3). In 17 (51.5%) patients (three with NF1, 14 without NF1) a biopsy was performed, of which 13 (76.5%) revealed a pilocytic astrocytoma (PA). Twenty eight OPG (84.8%) showed hypothalamic involvement and in six patients (18%) leptomeningeal metastases were present. BRAF V600E evaluation was available in 12 biopsies and revealed no mutations. KIAA1549-BRAF fusion was present in nine of 15 samples analysed for this fusion: eight samples were a PA and one a pilomyxoid astrocytoma.

Patients were diagnosed with OPG at median age of 2.4 years (range: 0.3 – 10.2 years) and started BVZ therapy at median age of 7.2 years (range: 0.3-10.2 years). The median number of prior episodes of SAT was two (range: 0-4 episodes). The diverse types of (prior) therapy applied per treatment phase are presented in Supplement 6.2. Treatment was initiated due to radiologic progression in 19 patients (57.6%), decrease of visual function in 12 (36.4%), a combined deterioration in one patients (3.0%) and presence of metastases in one patient (3.0%). Thirty-three patients received a median of 26 (range 4-89) doses of BVZ (10mg/ kg, started every 2 weeks) combined with IRI in 27 patients (81.8%) (IRI: median of 16 doses (range 4-54)) (125mg/m2, started every 2 weeks) and combined with vinblastine (VBL) in five patients (15.2%) (VBL: median 3mg/ m2, weekly) (median of 32 doses (range 9-66)). All individual treatment schedules are presented in Supplement 6.3. As treatment cycles show a variability in the combination of BVZ with or without IRI or VBL, further communication is this article is represented by 'BVZ'. Ten patients had prolonged BVZ treatment after the intended protocol of 26 doses in 12 months (median doses: 36.5 (range 30-89) . The median follow-up after start of BVZ was 40 months (range 6-150 months).

One patient was still on BVZ treatment at the end of follow-up (total of 13 doses BVZ (Supplement 6.3: patient 4). Treatment was terminated prematurely in eight patients; in five due to radiologic progression of OPG (median 6 months after start (range 2-8 months) and in three due to severe side effects.

Table 6.1. Baseline characteristics of pediatric patients with OPG at start of treatment with BVZ.

	Nr of patients (%)
Total population	33
Male	20 (60.6)
NF1	13 (39.4)
Diagnosis by: clinical signs	6
DNA analysis	7
Anatomic location: stage MDC	
MDC 2	5 (15.2)
MDC 1&2	4 (12.2)
MDC 2&3	14 (42.4)
MDC ≥ 3 stages	10 (30.3)
Hypothalamic involvement	28 (84.8)
Lepto-meningeal metastases	6 (18.2)
Biopsy performed (NF1/ nNF1)	17 (3/ 14)
Obtained during surgery	9 (1/ 8)
Biopsy only	8 (2/6)
Pathology	17 (51.2)
Pilocytic astrocytoma	13
Fibrillary astrocytoma	2
Pilomyxoid astrocytoma	2
Tumor biology (NF1 / nNF1)	13 (3/ 10)
BRAF V600E mutation (analyzed in 12 samples)	0
KIAA1549-BRAF fusion (analyzed in 15 samples)	9 (0/ 9) (8 of 9: PA)
Age at diagnosis of OPG	
Median (yr) (NF1/ nNF1)	2.4 (5.2/ 1.1)
Range (yr)	0.3 – 10.2
NF1	2.4-10.2
nNF1	0.3-5.1
IQR (yr)	0.8 - 5.0
Age at start of all therapy	
Median (yr) (NF1/ nNF1)	2.4 (5.6- 1.2)
Range (yr)	0.3-16.0
NF1	2.4-16.0
nNF1	0.3- 5.4
IQR (yr)	1.1-5.3

Table 6.1. Continued.

	Nr of patients (%)
Age at start of BVZ	
Median (yr) (NF1/nNF1)	7.2 (11.0/ 4.2)
Range (yr)	0.7 – 17.7
NF1	4.7-17.7
nNF1	0.7-15.1
IQR (yr)	3.4 – 11.0
Indication start BVZ	
Radiologic progression	19 (57.6)
Radiologic progression and visual deterioration	1 (3.0)
Visual deterioration	12 (36.4)
New metastases	1 (3.0)
BVZ initiation in SAT episode	
1st	1 (3.0)
2nd	12 (36.3)
3rd	8 (24.2)
4th	2 (6.0)

Abbreviations: BRAF: the human gene which encodes the B-Raf protein, BVZ: bevacizumab, , IQR: interquartile range, KIAA1549: human gene which encodes the KIAA1549 protein, MDC: Modified Dodge classification (stage 1: optic nerve(s),stage 2: chiasm, stage 3: optic tract, stage 4: posterior optic tract), NF1: Neurofibromatosis type 1, nNF1: no Neurofibromatosis type 1 , PA: pilocytic astrocytoma, SAT: systemic anticancer therapy, yr: year.

Visual function

At start of therapy three children (11.5%) had binocular moderate visual impairment ((BCVA > 0.5 - ≤ 1.0 LogMAR), two (7.7%) had severe impairment (BCVA >1.0 - ≤ 1.3 LogMAR), and seven (26.9%) were considered blind (BCVA > 1.3 LogMAR) according WHO criteria of visual impairment and blindness (22)). Three children were blind in both eyes (LogMAR 3.0) at start of treatment, seven other patients were blind in one eye (see table 6.3), BCVA did not improve in time in any blind eye at follow up. Monocular data of BCVA and VF were absent in seven patients (21.2%) with a median age of 1.2 year (range 1.1—3.3 years). A cause for absence of registration was a frequently found item: Limited cooperation at young age.

Monocular evaluation of the treatment effect of BVZ on BCVA (≥ or ≤ 0.2 LogMAR) was performed in 39 eyes of 23 patients (eyes with LogMAR 3.0 excluded). The median BCVA at start was 0.2 LogMAR (range -0.10 to 1.8 LogMAR). Eight of the 39 eyes (20.5%) showed improvement of BCVA after the end of treatment, 29

eyes (74.4%) remained stable and two eyes (5.1%) deteriorated. After cessation the median BCVA was 0.32 LogMAR (range: -0.08-3.0 LogMAR).

Visual fields at start and after cessation of BVZ were obtained from 15 children: VF of one eye in five patients and of both eyes in 10 patients. The BEFIE test was performed in two patients (13.3%), Peritest in eight (53.3%), Goldmann in two (13.3%) and HFA in three (20.0%). The median age at start of therapy of patients of whom a visual field was available was 9.9 year (range 2.3-17.7 years), compared to median 3.8 year (range 1.1-12.0 years) of patients with no available VF (exclusion of patients with BCVA of LogMAR $\geq$2.7). No VF met the criteria of visual impairment (constriction $\leq$ 30 degrees) or blindness (constriction $\leq$ 10 degrees) according to the WHO.

Monocular change of VF was evaluated in 26 eyes. Nineteen of 26 eyes (73.1%) eyes showed improvement, four eyes (15.4%) remained stable, two eyes (7.7%) showed deterioration and in one eye (3.8%) the VF defect shifted from one quadrant to another.
Baseline data and effects in change of BCVA and VF are presented in table 6.2. Simultaneous evaluation of BCVA and VF could be performed in 20 eyes of 14 patients: Combined improvement of BCVA and VF appeared in five eyes, stable BCVA and improved VF in 11 eyes, BCVA decrease and VF improvement in one eye, both stable BCVA and VF in one eye, stable BCVA and decrease VF in two eyes.
All individual data on BCVA and VF are reported for each case separately in Supplement 6.2.

Table 6.2. Baseline data on visual acuity and visual field and change in function after treatment with BVZ.

BCVA at start of BVZ (N=eyes)	**52**
Bilateral blindness (N=patients)	3
Blind eyes	13
No data (N=per eye)	14
BCVA per eye [1] (N=eyes)	39
Median (LogMAR)	0.4
Range	-0.1 - 2.7
IQR	0.1 - 1.3
Binocular BCVA [1] at start BVZ (n=pts)	23
Median (LogMAR)	0.2
Range	-0.1 - 1.8
IQR	0.0 -1.0
BCVA after end BVZ (N=eyes)	52
Bilateral blindness (N=patients)	3
Monocular blindness (N=eyes)	13
No data (N=per eye)	10

Table 6.2. Continued

BCVA per eye [1] (N=eyes)	39
Median (LogMAR)	0.3
Range	-0.1 – 3.0
IQR	0.0 - 1.3
Change in BCVA [1] (N=eyes)	39
Median (LogMAR)	0
Range	-0.7 - 1.2
IQR	-0.1 - 0.02
Improvement (≤ 0.2 LogMAR)	8 (20.5%)
Stable (change within 0.2 LogMAR)	29 (74.4%)
Decrease (≥ 0.2 LogMAR)	2 (5.1%)
Change in VF (N=eyes)	26
Improvement	19 (73.1%)
Stable	4 (15.4%)
Decrease	2 (7.7%)
Shift[3]	1 (3.8%)

Abbreviations: BCVA: Best Corrected Visual Acuity, IQR: interquartile range, VF: visual field.
BCVA is scored in LogMAR
Ad 1: After exclusion of blind eyes at start of BVZ
Ad 2: According to WHO classification of low vision (22)
Ad 3: VF shift: VF loss in one quadrant, which on subsequent VF evaluation changes to VF loss in a different quadrant.

Radiologic evaluation

MRI data for radiologic response assessment (RAPNO) within three months after cessation of treatment were available in 32 patients (97.0%). Seven patients with OPG (21.9%) showed a partial response, seven (21.9%) showed a minor response, 15 (46.9%) OPG remained stable, three OPG showed progressive disease (9.3%). In more than 50% of diffuse OPG (involvement > 1 MDC stage) manual measurements of tumor dimension in 3 perpendicular lines could not be performed due to the irregular pattern of OPG in the individual MDC sub location. No separate measurements were performed on the diverse MDC sub locations, but 3 perpendicular measurements at the level of the chiasm were performed instead.

Toxicity profile

Toxicity grade 2 or 3 (CTCAE) occurred in 12 of 33 patients (36.4%) during BVZ therapy: grade 2 toxicity occurred in six patients (18.2%) and ≥ grade 3 in six patients (18.2%) (see table 6.3). In five patients (15.5%) 2 different side effects of ≥ grade 2 were observed simultaneously. Side effects (≥grade 2) appeared after median 6.9 months after start of treatment (range 0-46) (median 15 doses (range 2-84)), which required cessation of BVZ in 83.4%. Grade 3-4 toxicity appeared after median nine weeks (range 4-24 weeks) of treatment. Four patients stopped treatment prematurely after median 6.5 doses (range 4-9 doses) of BVZ due to

side effects (lower intestinal haemorrhage grade 4 CTCAE (N=1), hypertension grade 3 CTCAE (N=3) and concurrent proteinuria grade 3 CTCAE (N=1)).
All adverse events recovered after appropriate treatment or after discontinuation of BVZ.

Table 6.3. Side effects during treatment with bevacizumab

Side effect	CTCAE: grade	n (%)
Nausea	Grade 2	4 (12.1)
Hypertension	Grade 2	1 (3.0)
	Grade 3	3 (9.1)
Proteinuria	Grade 2	2 (6.1)
	Grade 3	1 (3.0)
Fatigue	Grade 2	2 (6.1)
Abdominal pain	Grade 3	1 (3.0)
Lower intestinal hemorrhage	Grade 4	1 (3.0)
Gastric hemorrhage	Grade 3	1 (3.0)
Pneumonia	Grade 3	1 (3.0)

Subscript: Side effects during treatment occurred in 12 patients: grade 2 and 3 according to CTCAE criteria (Common Terminology Criteria for Adverse Events)(version 5.0) (26).
All side effects recovered.

Progression

Progression occurred in 21 patients (63.6%) after a median of 24.5 months (range 2-98 months) after start of BVZ. The increase of tumor volume in 18 patients (85.7%) and decrease of visual function in three patients (14,3%) were considered as progression by the local oncology team. The PFS curve is presented in figure 1A (Kaplan-Meier plot). At 18 and 36 months after start of BVZ (6 and 24 months after intended cessation) PFS reduced from 70.9% (CI 54.8-87.0) to 38.0% (CI 20.3-55.7).

Progression occurred in eight of nine children with KIAA1549-BRAF fusion positive OPG, all were nNF1. In seven of 13 NF1 patients OPG progressed. The PFS curve of the 13 NF1 patients and 9 patients with KIAA1549-BRAF fusion are shown in figure 1B. Comparison of PFS between both groups group showed a significant difference in PFS (log rank $p< 0.01$).

The various treatment combinations (BVZ only/ BVZ and IRI/ BVZ and VBL) showed no difference among groups in PFS (log rank: $p=0.591$). A trend towards a difference in PFS was observed among the diverse age categories (log rank: $p=0.083$), however group volumes were too small to reach significance.

Five out of 21 patients were on treatment when progression was observed and sequential treatment was initiated. The median age at start of this group was 1.2 years (range 0.9-8.2 year) and contained 1 patient with NF1 (20%). One patient switched therapy prematurely as visual function did not improve and OPG tumor size did not reduce. Of the total population that progressed (N=21), sequential therapy consisted of surgery (N=2 (9.5%)), vinblastine (N=2 (9.5%)), trametinib (N=4 (19%) and BVZ restart (N=12 (57.1%)) after an interval of median 8.5 months (range 4 – 75 months). One infant (nNF1), diagnosed at five months old, died at age of 2.7 years at 6 months after start of BVZ (third line SAT) due to progression.

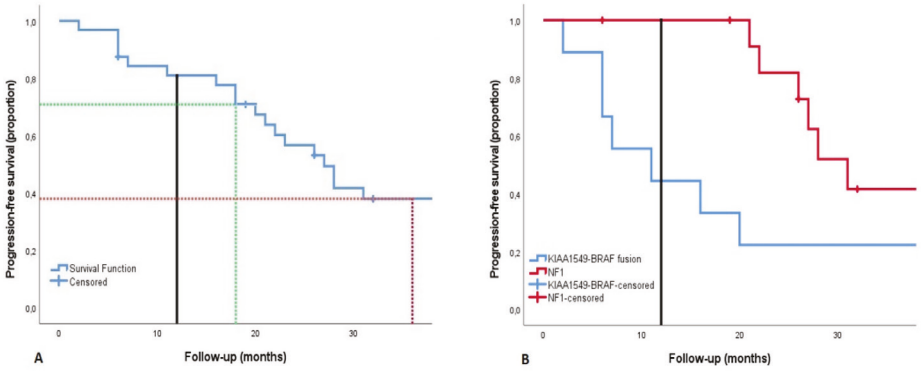


Figure 6.1. Kaplan-Meijer plot of progression free survival for OPG treatment with BVZ.

Abbreviations: BVZ; bevacizumab, PFS: progression free survival.

1A: Cumulative PFS overall population after start of treatment with BVZ for OPG: PFS reduces from 70.9% to 38.0% from 18 (green reference line) to 36 months (red reference line) after start (presumed 6 and 24 months after intended cessation of therapy).

1B: Cumulative PFS of NF1(N=13) and KIAA1549-BRAF fusion positive population (N=9) (log rank: $p < 0.01$). Black line: reference line at 12 months (median completion of therapy cycles).

Discussion

In this nationwide retrospective study on treatment for pediatric patients with OPG with BVZ outcome was relatively effective as treatment resulted in temporary stabilisation of tumor volume and improvement of visual function in the majority of children. Radiological or clinical progression occurred in 21 patients (63.6%) after a median of 20 months after start of therapy. On the other hand, visual function, represented by BCVA, remained stable in 74.4% of analysed eyes, and VF improved in 73.1.0%. Serious side effects occurred in almost one in five patients, but recovered after cessation of BVZ.

Multiple treatment episodes with SAT are a well-known necessity in subgroups of children with progressive OPG (27). Since the publication of the first results on BVZ / IRI for LGG in 2009 (3), a total of eight studies (in English language) have reported on successive treatment with BVZ for progressive LGG in children. These studies included low numbers of patients with LGG (range 7-35 patients), containing 2-12 OPG per cohort (3, 6-12) and mainly focussed on radiologic response and toxicity profile. The median follow-up was short with 5-12 months after cessation of treatment. The current study exclusively evaluates progressive OPG treated with BVZ and mostly IRI, evaluating visual outcome in addition to PFS, radiologic tumor response and toxicity.

In this study, OPG progression occurred during the intended 12 months of BVZ treatment in 15.1% of patients, but accumulated to 63.6% during follow-up after cessation of BVZ. The PFS at 18 and 36 months after start of treatment reduced from 70.9 to 38.0%. Only Zhukova et al (10) have reported a longer term of PFS after cessation of BVZ for LGG of 71.5% ± 13.9% at 11 months and 44.7% ± 17.6% at 15 months. Previous reports on the rate of progression as an outcome parameter for treatment with BVZ for patients with LGG (in different cerebral locations), rendered median 45% (range 14-93% after 5-12 months of follow-up (6-11). Our data support the moderate, but relatively temporary effectiveness of BVZ.

The relevance of tumor biology is evaluated via the KIAA1549-BRAF fusion status for progressive OPG, which showed a reduced PFS compared to NF1 OPG. Analyses on treatment of larger volumes of KIAA1549-BRAF fusion positive OPG would allow fusion subtype analyses (28), possibly revealing individual risk factors for choice of optimal treatment. Nonetheless, as often biopsy is not performed due to the risk of further deterioration of visual functions, BVZ should currently be considered a feasible non-targeted alternative treatment.

Visual functions can be seriously impaired in OPG. Therefore testing is an essential component of therapy evaluation of OPG. Visual acuity is currently considered as the main parameter of visual function evaluation in OPG.

Studies on BCVA, preferably monocular, as outcome parameter for treatment evaluation require evaluation within a short time interval after cessation. So far studies evaluating SAT show variability in terms of type of evaluation and definitions of change in VA (29). Previous studies show that carboplatin based first order SAT results in monocular improvement of BCVA in 10-22%, stabilization in 57-84% and decrease in 6-21% (15, 30). In our study BCVA stabilized or improved in 95% of analyzed eyes.

Chiasmal and optic tract glioma mostly cause a combined decrease of BCVA and VF, but studies on VF as outcome parameter for treatment of OPG are limited. Fisher et al. presented VF evaluation in 30 eyes after first order SAT with stabilisation or improvement in 63% (31) and Fangusaro et al. reported on 19 patients, treated with selumetinib, which 26% showed improvement and 74% stabilisation of binocular VF (32). In our study monocular VF improved in 73.1% and stabilized in 15.4%. VF was obtained from analyses on 25 eyes of 16 patients only. VF testing was lacking in 17 patients (due to blindness (N=3) and lacking data (N=14). Performing VF tests at a young age (< 6 years) or in children with limited cooperation can be challenging with a high risk of bias. Limited cooperation on young age, low vision or cognitive impairment in NF1 children could account for this low frequency of VF reporting.
However, so far the relatively high level of improvement of VF justifies analysis in future trials. As BCVA and VF parameters did not fully change function similarly (improvement/ stability/ decrease) (Supplement 6.2), combined analysis of BCVA and VF is warranted.

Previous studies on toxicity in BVZ treatment (CTCAE $\geq$ grade 3) report a median incidence of 12% (range 0-29%) during a treatment period of median 16 doses BVZ (10m/kg every 2 weeks) (range 10-24 doses) (6-12). In our study side effects (18.2% of CTCAE $\geq$ grade 3) occurred after early after start of BVZ (and IRI/ VBL) (median 9 weeks), which required cessation of BVZ (and IRI/ VBL) in 83.4%. No side effect rendered long term morbidity or mortality, since all functions recovered after appropriate treatment or cessation of BVZ and IRI. These results suggest an acceptable toxicity profile in relation to the clinical and radiologic stabilizing effect of BVZ.

Strengths and limitations

The strength of this study is the analysis of a nationwide group of children treated with BVZ for progressive OPG without selection bias. To minimalize debate on diverse outcome parameters we have clearly presented applied definitions of visual functions based on international consensus on published best available criteria in children with a brain tumor (22, 26). Although BCVA and VF were not obtained by a standard validated protocol, the data were carefully reviewed for outliers.

The limitation is found in the retrospective design of the study which leads to missing data on the visual function, possible underreporting of side effects, irregularities in follow-up intervals and diversity in applied MRI protocols.

At young age visual functions are part of continuing visual maturation. As currently change in VA function and radiologic response effect are not correlated (15), improvement of VA after treatment should be considered a combination of treatment effect and maturation of VA.

As well, the learning curve for performing a VF with HFA, Goldmann or Peritest is considerable for children. The high percentage of improvement of VF in this study could have a confounding effect of the individual learning process among patients as VF test variability has not been tested at start of treatment with BVZ.

Radiologic response measurement in OPG encounters many challenges on volumetric evaluation. Although the RAPNO-criteria on radiologic response assessment (13) are designed for pediatric LGG evaluation, manual 3 directional measurements of diffuse OPG do not provide a reliable representation for response evaluation of this tumor with posterior offshoots and highly irregular contours. This inevitable problem necessitated solely chiasmal response evaluation in > 50% of diffuse OPG. The 25% volumetric change does not seem appropriate for OPG, as volumetric change $\geq$ 25% will be preceded by loss of visual function. Possibly, future semi-automated segmentation with extraction of tumor volume could assist in more detailed response assessment in OPG.

Conclusion

The treatment of BVZ for progressive OPG can be considered a relatively safe strategy, with temporary stabilization in a majority of patients. As visual function shows a high rate of improvement (in VF) and stabilisation (in BCVA), BVZ treatment is suggested to be a useful successive SAT. Since the incidence of progressive OPG is low, its tissue analysis is scarce and treatment with BVZ is rare, international retrospective and prospective collaboration is highly recommended to refine analysis of treatment effect of BVZ in relation to NF1 status, anatomic location and individual differences in tumor biology.

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Conflicts of interest

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

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Supplement 6.1. Individual characteristics of anatomic location, volumetric response and change in visual acuity/ visual field

Pt	MDC	Volume respons (RAPNO)	BCVA OD Start1	VF start OD	BCVA OS start1	VF start OS	Change BCVA OD1	Change VF OD	Change BCVA OS1	Change VF OS
1	2A-3	PD	NDA	NDA	NDA	NDA	NDA	NDA	NDA	NDA
2	2B-3(L>R)	MR	0,4	Relative partial superior arcuate defect & absolute inferior altitudinal defect	0,2	Absolute complete temporal hemianopia and partial quadrantanopia inferior nasal	-0,13	↑	-0,15	↑
3	2-3R	SD	3,0	NDA	0,2	Absolute complete temporal hemianopia and partial quadrantanopia inferior nasal	0	NDA	0,17	↓
4	2A	PR	0,1	Central scotoma	0	Central scotoma	-0.06	↑	0	↑
5	2-3L	MR	0,4	Absolute complete temporal hemianopia & absolute partial nasal inferior quadrantanopia	1,8	NDA	-0,36	↑	0	NDA
6	1A-2B(L)	SD	0	No defect	1,5	NDA	0	↓	1,2	NDA
7	1C-2A	SD	0	Combined absolute/ relative concentric defects	0,1	Combined absolute/ relative concentric defects	0,1	↑	NDA	↑
8	2a-3(R+L)	PD	NDA	NDA	NDA	NDA	NDA	NDA	NDA	NDA
9	1B(L>R)-2A-3(L>R)-4B (L)	PR	NDA	NDA	NDA	NDA	NDA	NDA	NDA	NDA
10	2A	PR	1,8	NDA	3,0	NDA	0	NDA	0	NDA
11	1C(R> L, 2A	SD	3,0	NDA	3,0	NDA	0	NDA	0	NDA
12	2A3B	SD	NDA	NDA	NDA	NDA	NDA	NDA	NDA	NDA
13	1B(L>R)-2A-3	SD	0,3	NDA	3,0	NDA	-0,25	NDA	0	NDA
14	2A-3B(R)	PR	2,8	NDA	1,1	Absolute concentric contraction	0	NDA	0	↑
15	1A-1C(L), 2(A>R)	SD	-0.08	NDA	3,0	NDA	0	NDA	NDA	NDA
16	1C-2A-3A	MR	3,0	NDA	3,0	NDA	0	NDA	0	NDA
17	2A-3B	MR	1,6	Concentric contraction	2,7	Concentric contraction	-0,3	↑	-0,7	Stable

Table continued

Pt	MDC	Volume respons (RAPNO)	BCVA OD Start1	VF start OD	BCVA OS start1	VF start OS	Change BCVA OD1	Change VF OD	Change BCVA OS1	Change VF OS
18	2A	SD	1	Absolute complete temporal hemianopia, partial nasal quadrantanopia	2,7	NDA	0,3	↑	0,1	NDA
19	2A-3-4B (L)	SD	1,3	Absolute partial quadrantanopia	2	Temporal rest <20 degrees	-0,6	↑	-0,3	↑
20	1B-2A-3-4	No data	0,2	NDA	0,3	NDA	0,12	NDA	0,02	NDA
21	1A(L)-2B(R)-3B (L>R)	SD	0	Enlarged blind spot	0,5	No abnormalities	0,03	Stable	0	Stable
22	1B-2A-3 (L>R)	MR	0,9	NDA	3,0	NDA	-0.22	NDA	0	NDA
23	2A-3B	SD	0,8	NDA	1,3	NDA	-0,01	NDA	0	NDA
24	2A	PR	3,0	NDA	3,0	NDA	0	NDA	0	NDA
25	2A	PR	NDA	Absolute complete temporal hemianopia	NDA	NDA	NDA	Stable	NDA	NDA
26	1A(R)-2A	SD	0,2	Incomplete absolute temporal hemianopia	0	Partial relative superior bow scotoma	0,01	↑	-0,04	Shift 3
27	2A-3A(L)	SD	NDA	NDA	NDA	NDA	NDA	NDA	NDA	NDA
28	2A-3(L>R)	SD	3,0	NDA	1	NDA	0	NDA	0,04	NDA
29	2A-3B	MR	0,4	Absolute incomplete temporal hemianopia	0,2	Absolute incomplete temporal hemianopia	-0,4	↑	-0,19	↑
30	2A-3B	PD	0,1	Absolute incomplete temporal hemianopia	0,4	Absolute incomplete nasal hemianopia	0	↑	-0,04	↑
31	2A-3B(R)	SD	NDA	NDA	NDA	NDA	NDA	NDA	NDA	NDA
32	1B 2A 3 4(R>L)	PR	2,7	NDA	3,0	NDA	0,1	NDA	0	NDA

Table continued

Pt	MDC	Volume respons (RAPNO)	BCVA OD Start1	VF start OD	BCVA OS start1	VF start OS	Change BCVA OD1	Change VF OD	Change BCVA OS1	Change VF OS
332	1B L>R 2A R>L 3A-4	MR	0.02	Absolute cecocentral scotoma	0.05	Absolute cecocentral scotoma	-0.09	↑	-0.12	↑

Abbreviations: BCVA: Best Corrected Visual Acuity, L: left, MDC: Modified Dodge classification (stage 1: optic nerve(s),stage 2: chiasm, stage 3: optic tract, stage 4: posterior optic tract), MNP: measurements not possible due to diffuse location of OPG with minor chiasmal involvement, MR: minor response, NDA: no data available, OD: Oculus Dexter = right eye, OS: Oculus Sinister= left eye, PD: progressive disease, R: right, SD: stable disease, VF: Visual Field, ↑: improvement, ↓: decrease
Ad 1: BCVA in LogMAR
Ad 2: Ongoing BVZ treatment, evaluation 6 months after start BVZ
Ad 3: VF shift: VF loss in one quadrant, which on subsequent VF evaluation changes to VF loss in a different quadrant

Supplement 6.2.
Type of therapy applied per treatment phase for OPG.

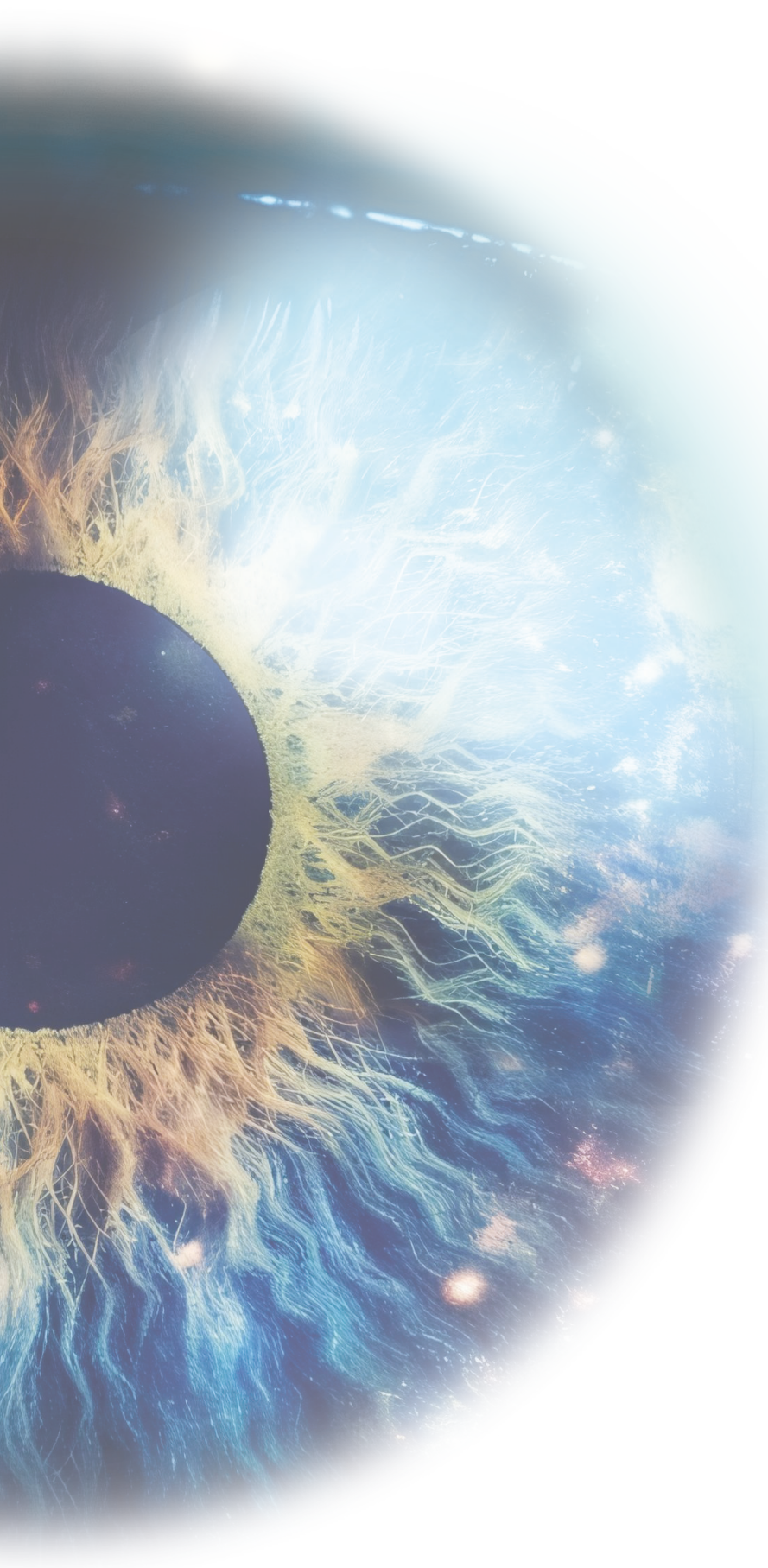
Type of therapy per phase	Nr of patients (%)
SAT in episode 1	33
Carboplatin/vincristin	30 (90.9)
Carboplatin/vincristin/etoposide	1 (3.0)
Vinblastine	1 (3.0)
Bevacizumab/irinotecan	1 (3.0)
SAT in episode 2	32
Vinblastine	18 (56.2)
Vinblastine/carboplatin	2 (6.2)
Bevacizumab/irinotecan	12 (37.5)
SAT in phase 3	22
Temodal	3 (13.6)
Vinblastine	2 (9.1)
Bevacizumab/irinotecan	17 (77.3)
SAT in phase 4	1
Bevacizumab/irinotecan	1 (3.0)
Previous resection prior to BVZ	9
1x resection	8 (24.4)
4x resection	1 (3.0)
Previous radiotherapy	1
1x	1 (3.0)

Abbreviation: SAT: systemic antitumor therapy.

Supplement 6.3.
Individual dosage and treatment schedule of bevacizumab, irinotecan and vinblastine.

Pt	Nr of doses: BVZ	Nr of doses: IRI	Nr of doses: VBL	Interval BVZ/ IRI	Interval VBL	Dosage BVZ	Dosage IRI	Dosage VBL
1	26	26	-	1x 2 weeks		10 mg/kg	125mg/m2	-
2	45	26	-	1x 2 weeks		10 mg/kg	125mg/m2	-
3	9	9	-	1x 2 weeks		10 mg/kg	125mg/m2	-
4	26	12	-	1x 2 weeks		10 mg/kg	125mg/m2	-
5	11	-	11	1x 2 weeks	weekly	10 mg/kg	-	1.5 mg/m2
6	25	25	-	1x 2 weeks		10 mg/kg	125mg/m2	-
7	9	9	-	1x 2 weeks		10 mg/kg	125mg/m2	-
8	12	12	-	1x 2 weeks		10 mg/kg	125mg/m2	-
9	52	52	-	1x 2 weeks		10 mg/kg	125mg/m2	-
10	24	14	-	1x 2 weeks		10 mg/kg	125mg/m2	-
11	12	6	-	1x 2 weeks	weekly	10 mg/kg	-	3 mg/m2
12	16	16	-	1x 2 weeks		10 mg/kg	125mg/m2	-
13	19	19	-	1x 2 weeks		10 mg/kg	125mg/m2	-
14	26	-	-	1x 2 weeks		10 mg/kg	-	-
15	30	14	-	1x 2 weeks		10 mg/kg	125mg/m2	-
16	65	50	-	41 doses 1x/ 2 weeks, 15 doses 1x/ 3 weeks, 9 doses, 1x/ 4 weeks		41x at 10 mg/kg 24 at 9 mg/kg	125mg/m2	-
17	26	14	-	1x 2 weeks		10 mg/kg	125mg/m2	-
18	15	15	-	1x 2 weeks		10 mg/kg	125mg/m2	-
19	18	18	-	1x 2 weeks		10 mg/kg	125mg/m2	-
20	26	21	-	1x 2 weeks		10 mg/kg	125mg/m2	-
21	30	13	-	1x 2 weeks		10 mg/kg	125mg/m2	-
22	26	26	-	1x 2 weeks		10 mg/kg	125mg/m2	-
23	22	10	-	1x 2 weeks		10 mg/kg	125mg/m2	-
24	31	31	-	1x 2 weeks		10 mg/kg	125mg/m2	-
25	26	-	9	1x 2 weeks	weekly	10 mg/kg	-	3 mg/m2
26	21	21	-	1x 2 weeks		10 mg/kg	125mg/m2	-
27	19	-	38	1x 2 weeks	weekly	10 mg/kg	-	3 mg/m2
28	89	28	-	1x 2 weeks		10 mg/kg	125mg/m2	-
29	34	34	-	1x 2 weeks		10 mg/kg	125mg/m2	-
30	4	4	-	1x 2 weeks		10 mg/kg	125mg/m2	-
31	16	-	32	1x 2 weeks	weekly	10 mg/kg	-	3 mg/m2
32	33	-	66	1x 2 weeks	weekly	10 mg/kg	-	3 mg/m2
33	39	13	-	1x 2 weeks		10 mg/kg	125mg/m2	-

Abbreviations: BVZ: bevacizumab, IRI: irinotecan, VBL: vinblastine



CHAPTER 7

Treatment evaluation by volumetric segmentation in pediatric optic pathway glioma: evaluation of the effect of bevacizumab on intra-tumor components

C.A.M Bennebroek, C.R. Schouten, M.C. Montauban van Swijndregt, P. Saeed, G.L. Porro, J.W.R. Pott, A.T.M. Dittrich, R. Oostenbrink, A.Y.N. Schouten- van Meeteren, M.C. de Jong, P. de Graaf

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Abstract

Introduction:
Progressive pediatric optic pathway gliomas (OPGs) are treated by diverse systemic antitumor modalities. Refined insights on the course of intra-tumoral components are limited.

Methods:
We performed an exploratory study on the longitudinal volumetric course of different (intra-)tumor components by manual segmentation of MRI at the start and after 3, 6 and 12 months of bevacizumab (BVZ) treatment.

Results:
Thirty-one patients were treated with BVZ (median 12 months, range 2-39 months). During treatment the total tumor volume decreased with median 19.9% (range: -62.3 to +29.7%; n=30) within the first three months, decreased 19.0% (range: - 68.8 to +96.1%; n=28) between start and six months and 27.2% (range: -73.4 to +36.0%; n=21) between start and 12 months. Intra-tumoral cysts were present in 12 OPGs, all showed a decrease of volume during treatment. The relative contrast enhanced volume of NF1 associated OPG (n=11) showed an significant reduction compared to OPG with a KIAA1549-BRAF fusion ($p < 0.01$). Three OPGs progressed during treatment, but were not preceded by an increase of relative contrast enhancement.

Conclusion:
Treatment with BVZ of progressive pediatric OPGs leads to a decrease of both total tumor volume and cystic volume for the majority of OPGs with emphasis on the first three months. NF1 and KIAA1549-BRAF fusion related OPGs showed a different (early) treatment effect regarding the tumor enhancing component on MRI, which did not correlate with tumor volume changes. Future research is necessary to further evaluate these findings and its relevance to clinical outcome parameters.

Introduction

Pediatric optic pathway gliomas (OPGs), a subgroup of low grade gliomas (LGG), are primarily located within the optic pathway. Regardless of their relatively slow growth rate, progression of OPGs can lead to significant visual impairment (1) and endocrine (2, 3) dysfunction in case of hypothalamic involvement. To mitigate the risk of damage to the visual functions by surgery or radiotherapy, systemic antitumor treatment (SAT) is considered the first therapeutic choice. The heterogeneous background of OPGs, including variations in tumor biology, association with neurofibromatosis type 1 (NF1) and/or anatomic sub-location, may contribute to a variety in SAT response (4, 5).

Current clinical radiological analysis of treatment response of OPG is performed by assessment of a product of 2- or 3-directional tumor diameter measurements (TDM) (6). A practical method, which is applicable for busy daily practice, however for representation of volumetric response it should be considered imprecise and currently is unable to reveal any correlation between changes in tumor volume and change in visual functions (7, 8). Conventional TDM will not recognize potential clinically significant intra-tumoral changes, which could influence preservation or recovery of visual functions. The first two case series on semi-automated segmentation presented detailed longitudinal intra-tumoral responses, including a variability in the course of cystic volumes and changes in contrast enhancement (9, 10). Both studies warranted future studies of larger volume and analysis on various SAT.

So far, no global consensus exists on the successive choice of SAT in case of progression (11). Bevacizumab (BVZ) combined with irinotecan (IRI), introduced in 2009, has generally demonstrated stabilization of tumor volume and visual functions accompanied by an acceptable toxicity profile (12, 13). As BVZ is known for its strong antiangiogenic effect via inhibition of vascular endothelial growth factor in LGG (14), we performed an exploratory study on changes in tumor volume and intra-tumor components, such as cysts and contrast-enhancement in order to identify OPG profiles that may benefit from (early) intervention with BVZ.

Materials and Methods

Study design

Data were obtained from a nationwide retrospective cohort of patients (0-17 years) who were treated for progressive OPG with BVZ (2009-2022) in the Netherlands.

Ethical approval for the collection of coded patient data was provided by the involved ethical comities. Written informed consent for the use of patient data was obtained from parents, legal guardian(s) and/or children depending on the age of the patients.

Collection of data was approved by the Dutch Childhood Oncology Group (DCOG) and ethical committees of all participating centers (Princess Máxima Center (the national tertiary pediatric oncology center), Amsterdam UMC, Erasmus MC, UMC Utrecht, Radboud UMC and UMC Groningen).

Patients were eligible for inclusion when treated with BVZ for a minimum of two months and a minimum of two contrast-enhanced MRI scans were available (at least at the start and within two months after cessation of BVZ). Patients with MRI images of low imaging quality were excluded.

Outcome parameters

The primary outcome of this study concerned the presentation of the volumetric course of the total tumor volume (TTV), intra-tumoral solid and cystic component and relative contrast enhancement. The secondary outcome was a comparison of the effect of NF1 status and KIAA1549-BRAF fusion status on changes in volume and tumor enhancement of the OPGs.

Data collection

Patient characteristics were obtained from medical records, including sex, NF1 status (defined by clinical status and/or DNA analysis), histology obtained during prior surgery or biopsy and tumor biology (including KIAA1549-BRAF fusion and BRAF-V600 mutations), previous therapy, indication for the start of BVZ therapy, age at start of BVZ therapy, dosing schedules for BVZ and possible concurrent SAT.

Subsequent MRI scans were collected at the start of BVZ therapy and at 3, 6 and 12 months during treatment. All encoded imaging data were stored in the picture archiving and communication system of the Amsterdam UMC.

Radiological assessment

The anatomical location of the OPGs according to the Modified Dodge Classification (MDC) was evaluated by a 12-year experienced neuro-radiologist (PG) based on the involvement of the optic nerve(s) (MDC 1); optic chiasm (MDC 2); optic tract(s) (MDC 3) and diffuse posterior tracts(s) (MDC 4) (15).

Manual volumetric segmentation (hereinafter referred to as: segmentation) was performed by a single technical analyst (CS) checked by the neuro-radiologist (PG). Individual tumor volumes (solid component, cystic component and relative contrast enhanced component) were obtained by manually marking all voxels representing tumor tissue by use of 3D Slicer software (v4.10.2). The solid component was measured in the T2/ T2 FLAIR sequence. The cystic and relative enhanced volume were measured on contrast enhanced T1. The relative contrast enhanced tumor volume (T1 post contrast sequence) was calculated as the proportion of the entire solid tumor mass (measured on the T2/ T2-FLAIR sequence). T2 and pre-contrast T1-weighted images were used as a reference for definitions of segment borders. Intra-tumoral cysts were identified as a 'tumor cyst' according to the criteria of de RAPNO classification (6).

Analyses were longitudinally performed (with) at the start of BVZ therapy and during therapy with intervals from start of treatment to 3 months, from start to 6 months and from start to 12 months.

Statistical analysis

Statistical analysis was performed using IBM SPSS statistics (v28.0.1.1). Data was analyzed by use of descriptive statistics. Continuous variables were presented by mean and standard deviation when normally distributed or otherwise presented as median and range. Categorical data was presented by frequency and percentage. Student's t-test was used to compare groups with normally distributed continuous variables, whereas the Mann-Whitney U test was used in case of non-normally distributed continues variables. A p-value ≤ 0.05 was considered statistically significant.

Results

The study cohort consisted of 31 patients. Thirty-three OPG patients were eligible for inclusion: one patient was excluded because of refusal of informed consent and one patient was excluded because tumor borders were ill-defined on a poor quality MRI scan.

Patient characteristics

Eleven patients (35.5%) had NF1. A diffuse OPG (including $\geq$ 2 MDC stages) was present in 27 patients (87.1%), four patients (12.9%) had an OPG solely located within the optic chiasm (MDC stage 2). Baseline patient characteristics are shown in table 7.1. A tumor biopsy was performed in 16 patients (two with NF1, 14 nNF1). A KIAA1549-BRAF fusion was present in 9 out of 14 analyzed biopsies (no concurrence with NF1), none showed a BRAF V600E mutation (analyzed in 11 samples).

The median duration of BVZ treatment was 12.0 months (range 2.0-39.0 months) with a median of 26 doses of BVZ (range: 4-65 doses, dosage at start: 10mg/kg every 2 weeks) in 31 patients. One patient (3.2%) received BVZ monotherapy (26 doses). BVZ treatment was combined with irinotecan (IRI) in 24 patients (77.4%) (median 16 doses, range: 4-52 , dosage at start: 125mg/m2, every 2 weeks) and combined with vinblastine (VBL) in 6 patients (19.4%) (median 22 doses, range: 9-32, dosage at start: 3mg/m2 every week). Treatment was discontinued prior to 12 months in eleven patients (35.5%) due to radiological progression (n=6), side effects (n=3) and at parents request (n=2). In total, 110 MRI scans were available for analysis including 31 scans at the start of BVZ therapy and 30 (96.8%), 28 (90.3%) and 21 (67.7%) scans at 3, 6 and 12 months during BVZ treatment respectively. As one patient stopped therapy after 11 months, the MRI at 12 months after start of treatment was included for evaluation. Individual baseline characteristics and MRI scan parameters are presented in Supplement 7.1 and 7.2.

Table 7.1. Baseline characteristics of pediatric patients with an OPG that received treatment with bevacizumab

Characteristics	Nr of patients (%)
Total population	31
Male/ female	19/ 12 (61.3/ 38.7)
NF1/ nNF1	11/ 20 (35.5/ 64.5)
Age at start of BVZ (years)	
Median (NF1/ nNF1)	7.2
Range	0.7-17.7
Tumor location	
MDC 2	4 (12.9)
Diffuse OPG (≥ 2 MDC stages)	27 (87.1)
MDC 1&2	4 (12.9)
MDC 2&3	15 (48.4)
≥ 3 MDC stages	8 (25.8)
Biopsy (NF1/ nNF1)	16 (2/12)
Histology	
Pilocytic astrocytoma	12 (75.0)
Pilomyxoid astrocytoma	3 (18.8)
Inconclusive	1 (6.2)
Tumor biology	
KIAA1549-BRAF fusion (analysis in n=14)	9 (NF1: 0/ nNF: 9)
BRAF V600E mutation (analysis in n=11)	0
Therapy prior to BVZ treatment	
Surgery	11 (35.5)
Radiotherapy	1 (3.2)
Number of prior SAT	
0	1 (3.2)
1	11 (35.5)
2	17 (54.8)
3	2 (6.5)
BVZ treatment (months)	
Median duration (range)	12.0 (2.0-39.0)
Treatment	
BVZ	31 (100)
Median nr. doses (range)	26 (4 - 65)
IRI	24 (77.4)
Median nr. doses (range)	16 (4 - 52)
VBL	6 (19.4)
Median nr. doses (range)	22 (9 - 32)

Abbreviations: BVZ: Bevacizumab; IRI: irinotecan; KIAA1549-BRAF: fusion of the human gene that encodes the KIAA1549 protein and the B-raf (proto-)oncogene; MDC: Modified Dodge Classification (1: optic nerve(s); 2: optic chiasm; 3: optic tract(s); 4: posterior optic tract(s)); NF1: Neurofibromatosis type 1; nNF1: no Neurofibromatosis type 1; SAT: systemic anticancer therapy; VBL: Vinblastin

Tumor volumes at baseline

The median TTV and solid tumor volume at the start of BVZ treatment was 18.9 cm^3 (range: 0.5- 179.4cm^3) and 18.9cm^3 (range: 0.5-144.4cm^3) respectively. Twelve OPGs (38.7%) had one or more tumor cysts at baseline, with a median total volume of 2.1cm^3 (range: 0.7 - 35.0cm^3), of which seven patients had a KIAA1549-BRAF fusion and one patient had NF1. At start of BVZ therapy 27 OPGs (87.1%) showed (partially or complete) contrast enhancement, with a median volume of 13.0cm^3 (range: 0.1 - 144.4cm^3) and a median relative contrast enhanced volume of 67.8% (range: 0.4-100.0%). All use of contrast was gadolinium-based.

Change in tumor volumes during BVZ therapy

Between start and 3 months of use of BVZ the TTV decreased with a median of 19.9% (range: -62.3 to +29.7%) (n=30), likewise the TTV decreased 19.0% (range: -68.8 to +96.1%) (n=28) between start and 6 months and 27.2% (range: -73.4 to +36.0%) (n=21) between start and 12 months. The solid tumor volume was reduced with a median of 19.9% (range: -66.1 to +16.7%) (n=30), 16.7% (range: -66.1 to +117.0%) (n=28) and 27.2% (range: -71.2 to +37.3%) (n=21) between the start and 3, 6 and 12 months of BVZ therapy respectively. Two OPGs progressed >20% within the first three months: one OPG was a pilocytic astrocytoma associated with NF1, of which its treatment was continued as the treatment team evaluated the MRI as stable disease. One OPG further progressed to 196.0% of its original TTV, therefore treatment was discontinued. Biopsy revealed a pilomyxoid astrocytoma (PMA). In both OPGs the increase of TTV did not relate to change in relative enhancement. Two other OPGs were also PMA, both showed a decrease of both TTV (-32.7 and -38.0% within the interval of 0-12 months) and relative contrast enhancement. Long term evaluation of the course of TTV during a period of 24 months of dosage of BVZ was performed in three patients who received treatment with BVZ for a period of median 24 months (range 24-39 months). The individual change in TTV for these 3 patients was -25,3%; -53,3% and -26,6% for the treatment period of 0-12 months and was -36,4%; -54,2% and -32,3% respectively for the interval of 0-24 months.

Four intra-tumoral cysts, of the 12 OPGs with cysts, fully resolved within 3 months after the start of BVZ (volume at start of BVZ: median 2.0cm^3 (range: 0.67-14.46cm^3)) (KIAA1549-BRAF fusion: n=2, NF1: n=0). At the end of therapy 8 cysts remained with a median volume of 1.77cm^3 (range 0.25-33.90cm^3) The median tumor cyst volumes decreased with 66.9% (range: -100.0 to +21.9%) (n=12), 78.5% (range: -100.0 to +25.4%) (n=12) and 65.8% (range: -100.0 to +19.5%) (n=8) between start and 3, 6 and 12 months. Supplement 7.3 shows an example of the reduction of both cystic and solid tumor volume. One cyst in one OPG increased in volume from 2.1 to 3.1cm^3 within 12 months of treatment. The TTV of this OPG changed from

33.1 to 43.0cm^3 within the first three months. No patients developed new cysts during BVZ treatment.

The relative contrast enhanced volumes decreased with a median of 47.5 percent point (pp) (range: -100.0 to +18.7pp) (n=27), 64.9pp (range: -100.0 to +12.7pp) (n=24) and 95.1pp (range: -100.0 to 0.1pp) (n=18) between start and 3, 6 and 12 months. The four OPGs without contrast enhancement at baseline (NF1: n=3, KIAA1549-BRAF fusion absent: n=3/ unknown: n=1), showed a median decrease of 15.0% of TTV (range: -4.0 to -27.0%) within 0-3 months after start of BVZ, with no progression of TTV within 12 months. Three OPGs progressed with $\geq$ 25% of TTV increase at six months after an initial decrease of TTV (median: -24.0% (range: -14.6 to -30.4%) at three months, of which all patients carried a KIAA1549-BRAF fusion. This progression was preceded by a relative median reduction of contrast enhancement of 8.0pp (range: 0.0 to -9.8pp) (baseline relative enhancement: median: 100.0% (range: 97.5-100.0%)). The volumetric changes of the diverse tumor components during BVZ treatment within the three analysed time intervals are illustrated in Figure 7.1 The individual changes in tumor component are shown in figure 7.2a-d.

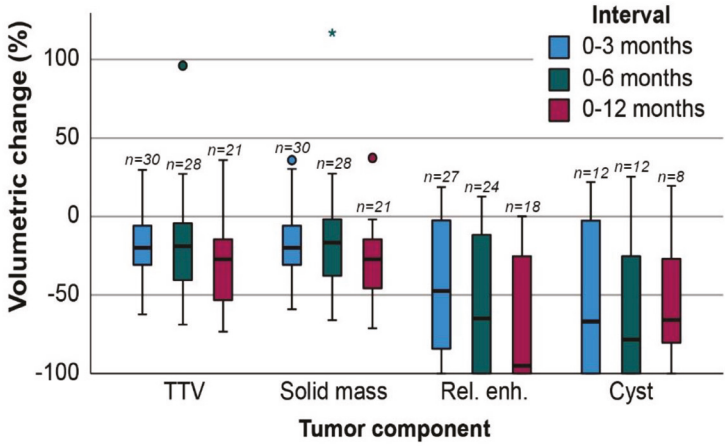

Figure 7.1. Boxplot of relative volumetric change in total tumor volume, solid tumor volume, relative contrast enhancement and cystic volumes of OPG during treatment with BVZ

Abbreviations: TTV: total tumor volume; Solid: solid tumor volume; Rel. enh: relative contrast enhanced solid tumor volume; Cyst: intra-tumoral cystic volume.

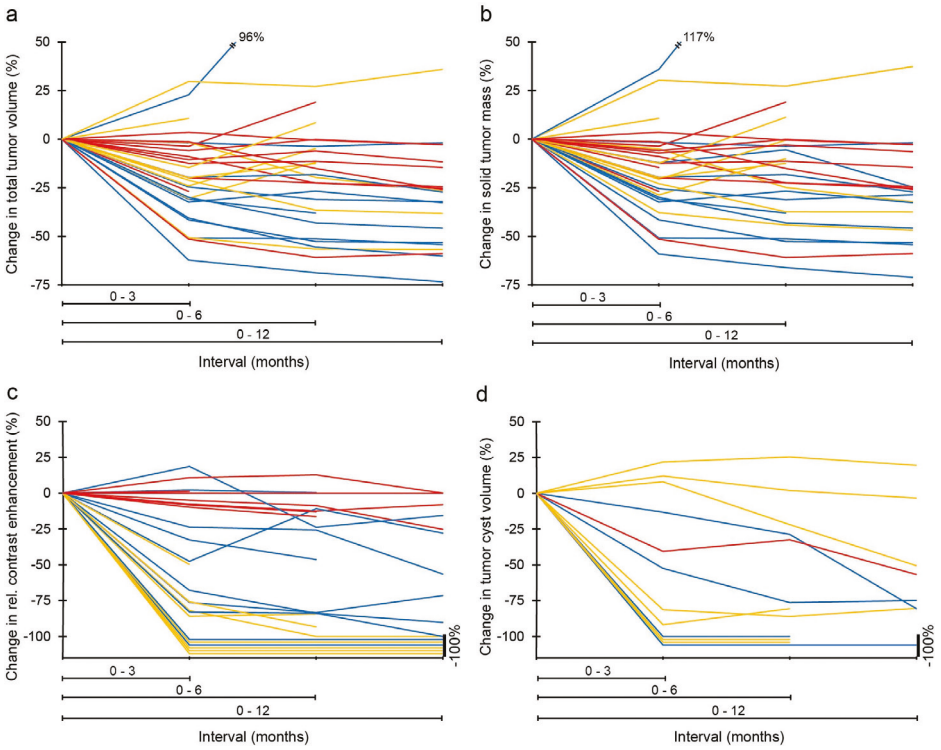

Figure 7.2. Individual change of tumor volume during bevacizumab (BVZ) treatment represented in 3 time intervals: 0-3, 0-6, 0-12 months after start of BVZ

Subscript a: change of total tumor volume (n=31). b: change in solid tumor volume (n=31). c: change in relative contrast enhanced tumor volume (n=27). d: change in intra-tumor cystic volume (n=12).
Yellow line: Neurofibromatosis type 1; Red line: KIAA-BRAF1549 fusion, Blue line: no neurofibromatosis type 1 and no KIAA-BRAF1549 fusion.

NF1 versus KIAA1549-BRAF fusion

A comparison of the changes in (intra-)tumor volumes between the NF1 (n=11) and KIAA1549-BRAF population (n=9), showed a difference in total tumor and solid tumor volume at the start of treatment ($p < 0.01$), but not in change of volume during treatment.

The median relative contrast enhanced tumor volume at baseline was higher in the KIAA1549-BRAF group (99.9%) compared to the NF1 group (14.5%) (Mann Whitney U test: $p < 0.01$). The median decrease in relative contrast enhanced tumor volume during treatment was higher in the NF1 group compared to the KIAA1549-BRAF group ($p < 0.01$ at time interval 0-3, 0-6 and 0-12 months).

The difference in volumes among both populations are presented in Figure 7.3 and Table 7.2.

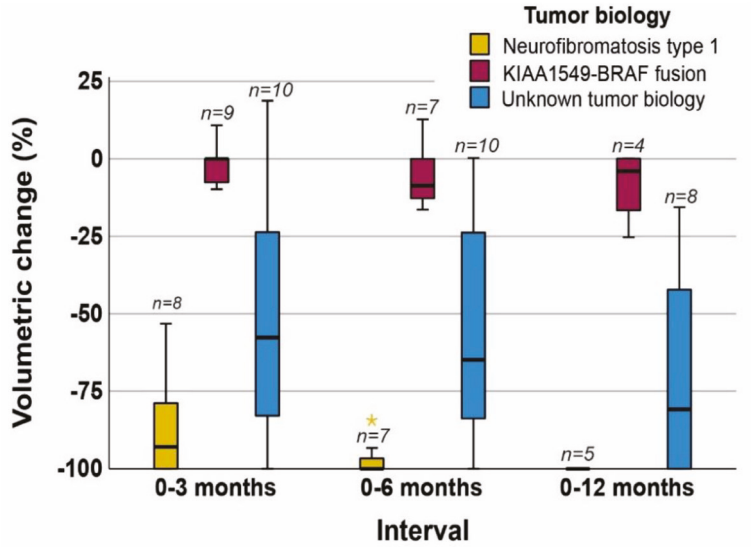

Figure 7.3. Boxplot of change in relative contrast enhanced solid tumor volume at 3, 6, and 12 months of treatment with BVZ compared to baseline: stratification on NF1 and KIAA1549-BRAF status

Abbreviations: NF1: neurofibromatosis type 1 population (n=11) (negative for /unknown KIAA1549-BRAF fusion), KIAA-BRAF fusion: KIAA1549-BRAF population (negative for NF1); Unknown tumor biology: patients negative for NF1 and negative/unknown KIAA1548-FRAF mutation status

Table 7.2. Comparison of change in (intra-)tumor volumes between OPG with NF1 association and OPG with KIAA1549-BRAF fusion

	NF1			KIAA1549-BRAF fusion			
	Median	Range	n	Median	Range	n	p-value
Start of BVZ							
TTV (cm3)	12.5	4.2-30.6	11	34.3	15.2-179.4	9	< 0.01
Solid TV (cm3)	12.5	4.2-30.6	11	34.3	14.4-144.4	9	< 0.01
Cyst. vol. (cm3)	1.1	-	1	1.7	0.7-35.0	7	0.51
Rel. enh. (%)	14.5	0.4-44.0	8	99.9	59.2-100	9	< 0.01
Interval start - 3 months							
Change TTV (%)	-10.5	-51.5/ +3.5	11	-19.8	-50.7/ +29.7	9	0.65
Change solid TV (%)	-8.9	-51.5/ +3.5	11	-19.8	-37.8/ +30.3	9	0.65
Change cyst. vol. (%)	-40.5	-	1	-81.3	-100/ +21.9	7	0.87
Change rel. enh. (%)	-92.9	-100/ -53.2	8	0	-9.8/ +10.8	9	< 0.01
Interval start - 6 months							
Change TTV (%)	-11.4	-60.9/ +19	9	-12.2	-56.6/ +27.1	8	1.00
Change solid TV (%)	-11.4	-60.9/ +19	9	-11.3	-44.2/ +27.3	8	0.92
Change cyst. vol. (%)	-32.4	-	1	-80.6	-100/ +25.4	7	0.83
Change rel. enh. (%)	-100.0	-100/ -84.4	7	-8.7	-16.4/ +12.7	7	< 0.01
Interval start - 12 months							
Change TTV (%)	-19.5	-58.9/ -2.8	8	-32.4	-56.8/ +36.0	4	0.40
Change solid TV (%)	-19.5	-58.9/ -.28	8	-34.9	-46.9/ +37.3	4	0.40
Change cyst. vol. (%)	-56.8	-	1	-27.0	-80.3/ +19.5	4	0.48
Change rel. enh. (%)	-100.0	-100/ -100	6	-4	-25.3/ +0.1	4	< 0.01

Abbreviations: BVZ: bevacizumab; cyst. vol: cystic volume; rel. enh.: relative enhancement of solid tumor volume; NF1: neurofibromatosis type 1; TV: tumor volume; TTV: total tumor volume

Discussion

This longitudinal retrospective study on manual volumetric segmentation of OPGs contains a detailed analysis of volumetric response during BVZ treatment. The results show that the largest change in total, solid and cystic tumor volume appears in the first 3 months of treatment in the majority of the OPGs. During treatment, contrast enhancement decreased significantly in NF1 patients compared to the population with KIAA1549-BRAF fusion. On-treatment progression of TTV was not preceded by an increase of relative contrast enhancement.

Radiological response assessment in daily practice is currently performed by two or three directional tumor diameter measurements (6), but is not suitable for reliable tracking of internal tumor components. Manual segmentation concerns an essential step in the process of development of (deep learning) automatic segmentation models. Despite the fact that this measurement technique is clinically impractical due to its time consuming nature and interrater variability (16), so far its outcomes are essential to obtain a more comprehensive understanding of volumetric responses on SAT treatment for progressive OPG. Larger sample studies in the growing field of (semi-)automated segmentation of pediatric OPG are still lacking. Semi-automated segmentation of first line SAT (n=15 OPG) represented by vincristine and carboplatin, showed an increase of intra-tumoral cystic volume (n=8 OPG) but a decrease of TTV and contrast enhanced volume at the end of SAT (10). The non-responsiveness of cystic components to SAT has been topic of discussion earlier, nevertheless in our cohort, all intra-tumoral cysts reduced in volume and four cysts fully resolved.

This study on segmentation at fixed intervals of 3, 6 and 12 months from start of BVZ treatment showed a median decrease of volume of all tumor segments (solid tumor mass, tumor cyst and contrast enhanced tumor mass) across all time points when compared to the baseline volumes. Remarkably, in these patients a large proportion of the total decrease in volumetric tumor component was achieved within the first three months of BVZ therapy, with a more stable course after this time point. Currently in the Netherlands BVZ therapy is regarded as a second or third line SAT for OPG, however, with the results of our study suggesting a relatively early effect (within 3 months of initiation) of BVZ on the different intra-tumor components, BVZ might be considered as a viable therapeutic option earlier in the treatment course in case of fast radiological progression combined with decrease of visual function.

Treatment of pediatric OPG with SAT requires long term follow up substantiated by multiple serial MR images. The use of contrast in LGG is part of an ongoing clinical debate in treatment of OPG, concerning the risk of long term potential toxic effects at young age (17) and the lack of prove for association between changes in contrast enhancement and TTV (18). Contrast sequences are considered useful in distinguishing NF1 associated focal areas of signal intensity and in evaluation of spinal lesions and leptomeningeal disease (6). Our results show an early median reduction of contrast enhancement for the overall population, with a significant decrease for NF1 associated OPG compared to KIAA1549-BRAF fused OPG. The mechanism of the difference in change of contrast enhancement in both populations, for example impairment or restoration of the blood brain-barrier due to bevacizumab (19), is unknown.

In our limited sample the increase of relative enhancing tumor volume did not precede on-treatment progression (n=3) and was of no use in defining tumor borders during manual segmentation. As these results solely studied the intra-tumoral course during BVZ treatment evaluation, other SAT modalities require (larger) equivalent studies to determine the value of use of contrast on and off SAT treatment.

Strengths and limitations

So far, this explorative study is the largest available series on intra-tumoral response assessment of OPG with fixed time intervals, showing promising insights on the (early) effect of BVZ on tumor components. The limitations relate to the rarity of the diagnosis of OPG, including a limited number of participants and number of patients per subgroup (NF1 status and KIAA1549-BRAf fusion). As this study focussed on intra-tumoral response assessment and manual segmentation is a time-consuming activity, manual segmentation has only been conducted by one rater, hindering the analysis of inter-rater variability (16, 20).

The analysis was solely restricted to BVZ as treatment strategy regardless of concurrent SAT. Repeated measurement analysis could not be performed due to the number of 11 patients who terminated before the intended use of 12 months of BVZ, however we have adjusted response analysis to time intervals from start of therapy to provide a maximum of insight on intra-tumoral behaviour.

From a clinical perspective the visual function is considered the most important outcome parameter for treatment evaluation of OPG. In this study we were unable to correlate change of TTV to change in visual function due to a high

number of lacking data (> 80%) on visual acuity or visual fields on the three studied time intervals.

Conclusion

Longitudinal volumetric intra-tumor study on the effect of BVZ treatment for pediatric OPG revealed an early decrease in total tumor volume and volume of intra-tumor cysts in the majority of patients. This early effect could support the purpose of maximal preservation of visual and endocrine functions, which should be validated in future studies on comparative SAT modalities. OPG in NF1 patients showed an early and substantially greater decrease of contrast enhancement compared to OPG in patient with a KIAA1549-BRAF fusion without any correlation to changes in tumor volume. Future studies are necessary to evaluate the value of using contrast material during the on- and off-treatment follow-up of OPGs with MRI.

Funding

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Conflicts of interest

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

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Supplement 7.1.
MRI scanning parameters

MRI Sequence	2D T1 (+ gd) (n=61)	3D T1 (+ gd) (n=172)	2D T2 (n=73)	3D T2 (n=50)	2D FLAIR (n=35)	3D FLAIR (n=78)
Echo time (ms): m (r)	9.1 (7.8-15.0)	3.8 (1.9-4.2)	96.0 (80.0-120.0)	287 (96-305)	120 (87-140)	319 (300-356)
Repetition time (ms): m (r)	550 (439-1900)	8.3 (6.3-2100)	5207 (2367-12244)	2800 (2000-3000)	9000 (8000-11000)	4800 (4800-5000)
Inversion time (ms): m (r)	-	-	-	-	2500 (2000-2800)	1660 (1650-1800)
Pixel size (mm): m (r)	0.7 (0.4-0.9)	0.5 (0.4-1.0)	0.4 (0.4-0.7)	0.5 (0.3-0.5)	0.5 (0.4-0.9)	0.6 (0.2-1.0)
Slice thickness (mm): m (r)	5.0 (3.0-5.0)	1.0 (0.9-2.0)	3.0 (3.0-5.0)	1.0 (0.5-1.0)	4 (3.0-5.0)	1.1 (0.6-1.2)
Rows (n): m (r)	320 (256-512)	480 (230-640)	512 (320-512)	480 (480-512)	512 (256-512)	384 (230-1024)
Columns MRI (n): m (r)	308 (256-512)	480 (230-640)	512 (280-512)	480 (480-512)	512 (256-512)	384 (216-1024)
Fat suppression: yes/ no	1/ 60	26/ 146	3/ 70	0/ 50	0/ 35	0/ 78
Magnetic field strength: 1.0T/ 1.5T/ 3.0T	4/ 50/ 7	0/ 104/ 68	2/ 43/ 28	0/ 34/ 16	2/ 31/ 2	0/ 42/ 36

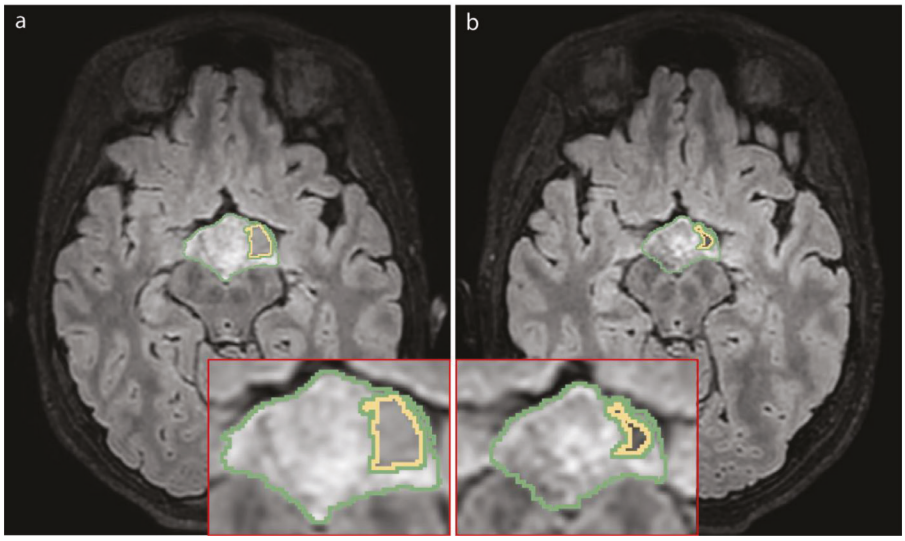
Abbreviations: D: dimensional; gd: gadolinium; ms: millisecond; mm: millimeter; T: Tesla

Supplement 7.2.
Baseline characteristics: patients with a progressive OPG treated with bevacizumab

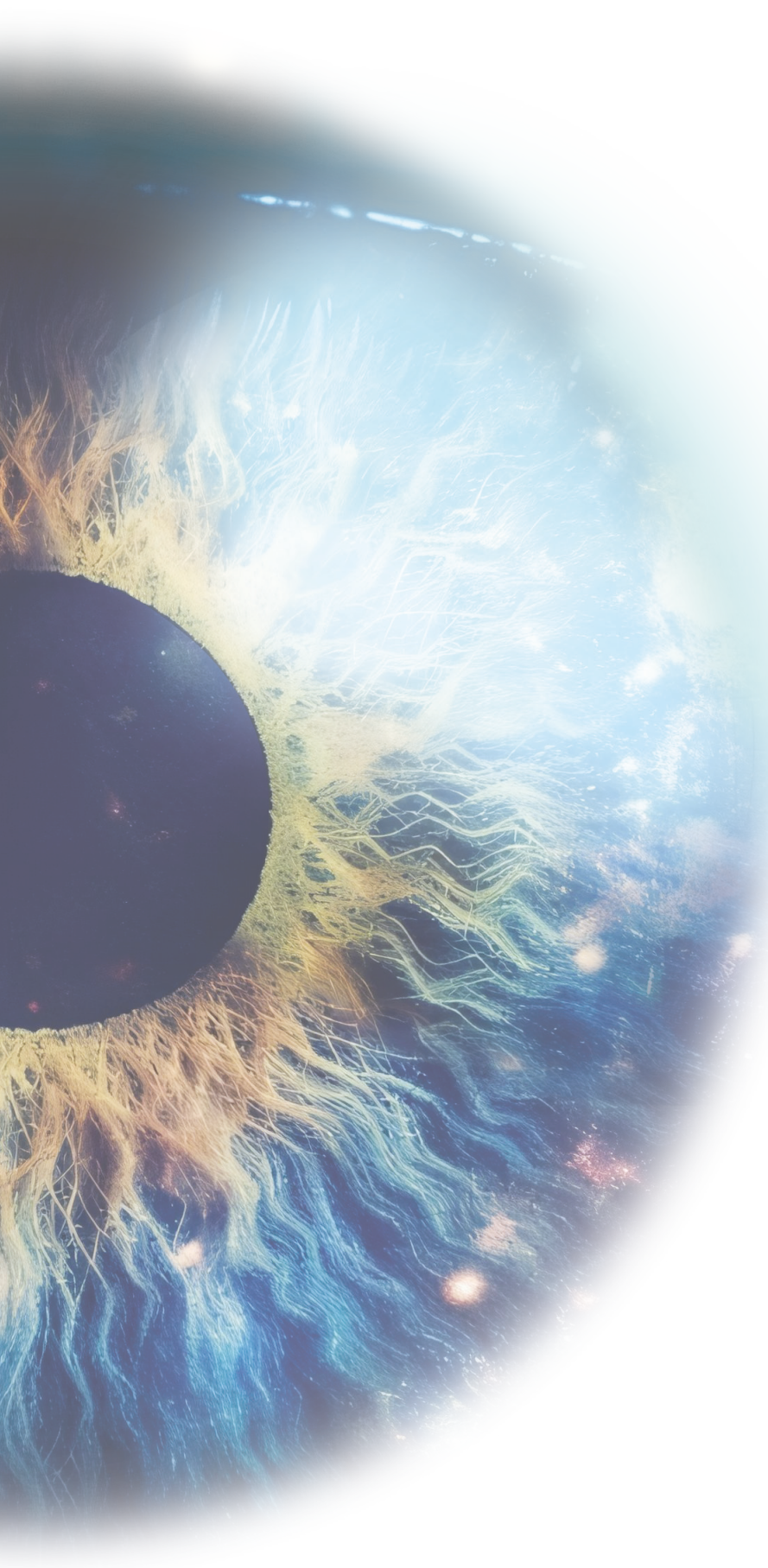
Patient nr.	MDC	NF1	KIAA1549-BRAF	Tumor pathology	Previous SAT (n)	Prior debulking	Indication start BVZ	BVZ doses (n)	Interval BVZ (weeks)	Dosage BVZ (mg/ kg)	IRI doses (n)	Dosage IRI mg/ m2)	VBL doses (n)	Dosage VBL mg/ m2	Premature cessation BVZ
1	2/3	Y	N	PA	2	Y	RPD	9	2	10	9	125			Y
2	2/3	N	Y	PA	2	Y	RPD	26	2	10	26	125			N
3	2	N	N	PA	1	Y	RPD	26	2	10			9	3	N
4	1/2	N			2	N	VF↓	30	2	10	14	125			N
5	1/2 /3	Y	N		2	N	RPD	30	2	10	13	125			N
6	1/ 2/3	Y	N	INC	2	N	RPD	26	2	10	26	125			N
7	1/2	N	Y	PA	1	Y	RPD	6	2	10			12	3	Y
8	2/3	N	N	PA	2	N	RPD	26	2	10	14	125			N
9	1/2 /3/4	Y	N		1	N	RPD	33	2	10			66	3	N
10	2/3	N	Y	PA	1	Y	RPD	16	2	10			32	3	Y
11	2/3	N	Y	PA	1	N	RPD	19	2	10			38	3	Y
12	2/3	N			1	N	RPD	31	2	10	31	125			N
13	2	N	Y	PA	2	Y	RPD	24	2	10	14	125			N
14	1/2 /3/4	N			2	N	RPD	52	2	10	52	125			N
15	2	N			2	N	RPD	26	2	10	12	125			N
16	2/3	N	Y	PA	2	N	RPD	16	2	10	16	125			Y
17	2/3	N	Y	PMA	3	N	VF↓	34	2	10	34	125			N
18	2/3	N		PMA	2	N	RPD	12	2	10	12	125			Y
19	2/3	N	N	PA	2	Y	VF↓	11	2	10			11	15	Y
20	2/3	N	N	PMA	2	Y	RPD	34	2	10	28	125			N
21	1/2	N			1	N	VF↓	25	2	10	25	125			N
22	1/2 /3	N	Y	PA	2	Y	mets	65	41x2 15x3 9x4	41x 10 24x 9	50	125			N
23	2/3	Y	N		1	N	VF↓	45	2	10	26	125			N
24	2/3	Y	N		0	N	VF↓	22	2	10	10	125			Y
25	2/3	N			3	N	VF↓	26	2	10					N
26	2/3 /4	Y	N		2	N	VF↓	18	2	10	18	125			N
27	1/2	Y	N		1	N	VF↓	21	2	10	21	125			N
28	1/2 /3/4	Y	N		2	N	RPD & VF↓	39	2	10	13	125			N
29	2	N	Y	PA	1	Y	RPD	15	2	10	15	125			Y
30	1/2/3	Y	N		1	N	VF↓	9	2	10	9	125			Y
31	2/3	Y	N		2	N	VF↓	4	2	10	4	125			Y

Abbreviations: BVZ: Bevacizumab, HT: hypertension, IRI: irinotecan, KIAA1549-BRAF: fusion of human gene that encode the KIAA1549 protein and the B-raf (proto-)oncogene, MDC: Modified Dodge classification, mets: metastases, N: no, NF1: Neurofibromatosis type 1, PA: pilocytic astrocytoma, PMA: pilomyxoid astrocytoma, RPD: radiologic progressive disease, PU: proteinuria, SAT: systemic antitumor therapy, SD: stable disease radiological evaluation, VBL: vinblastine, VF↓: deterioration of visual function, Y: yes.

Supplement 7.3.
Axial T2-FLAIR-weigthed image of a child with a chiasmal optic pathway glioma at the start (a) and at 12 months of bevacizumab therapy (b)



a: The total tumor volume (TTV) (solid + cystic volume) was 18,7cm3, the solid tumor volume (green encircled area) 17,5 cm3 and the cystic volume (yellow encircled area) 1,3 cm3.
b: The TTV after 12 months of BVZ treatment reduced to 12,7 cm3 (-32,2%), the solid tumor volume reduced to 12,5 cm3 (-28,6%) and the cystic volume to 0,3 cm3 (-80,6%).



CHAPTER 8

Volumetric tumor segmentation on MRI in pediatric optic pathway glioma: variety in outcome of radiologic response assessment

C.A.M. Bennebroek, C.R. Schouten, M.C. Montauban van Swijndregt, M.C. de Jong, A.Y.N. Schouten- van Meeteren, P. de Graaf

Submitted for publication

Abstract

Introduction:
Radiologic response assessment of pediatric optic pathway glioma (OPG) is currently performed according to the RAPNO-recommendations by calculation of the change of the product of two or three directional tumor diameters on MRI. The highly irregular contour and asymmetric shape of this tumor may lead to an inaccurate response assessment.

Methods:
In this study we compared change in tumor volume by both manual segmentation and three directional tumor diameter measurements (3TDM) in 31 OPGs that were treated with bevacizumab.

Results:
Volumetric response assessment performed by segmentation yielded an absolute difference of 7.9 percent point compared to 3TMD ($p < 0.001$), which lead to a change in the conventional radiologic RAPNO category in 12.9% of patients.

Conclusion:
Before entering refined future response assessment assisted by segmentation by artificial intelligence, these results support the awareness of the level of variety in the current practice of 2/ 3TDM radiologic response assessment of treatment for OPG.

Introduction

Pediatric optic pathway gliomas (OPG) are a subgroup of low grade gliomas that occur exclusively in the visual pathways, specifically the optic nerve(s), chiasm and / or optic tract. Systemic antitumor therapy is considered the primary treatment approach for OPG in case of radiologic progression or clinical deterioration.

Accurate and reproducible quantification of tumor volume is crucial in evaluating treatment response in clinical studies for OPG. The current strategy in radiological response assessment is based on the RAPNO recommendations (1), suggesting the use of the product of two or three perpendicular maximal tumor diameters (3TDM) for measurement of tumor size, which represents analysis of a cuboid structure. However, as OPGs are highly irregular and asymmetrical in shape, conventional tumor diameter measurements result in a relatively high intra- and interrater disagreement, which under- or overestimates the response to treatment (2). Automatic tumor segmentation by deep-learning methods has the useful potential for detailed reproducible response assessment of longitudinal intra-tumor components in OPG (3), but is currently not available in daily practice.

The purpose of this compact study was to highlight the differences in tumor volume obtained by manual segmentation and conventional 3 directional tumor diameter measurements on MRI in OPG following treatment with bevacizumab (BVZ). Additionally, the variances between segmentation and 3TDM in radiologic response categories of RAPNO were assessed.

Material and methods

Data were obtained from a nationwide retrospective cohort of Dutch patients (0-17 years) who were treated for progressive OPG with BVZ (2009-2022).

Ethical approval for the collection of coded patient data was provided by the involved ethical comities. Written informed consent for the use of clinical and MRI data was obtained from parents, legal guardian(s) and / or children depending on the age of the patients.

The location of the OPG was scored according to the modified Dodge classification (4). The total tumor volume (TTV) was determined at two time points: within two months before start and after cessation of BVZ. Intratumoral cysts were included in the measurements, as all where matching the definition of *true tumor cysts* according to the RAPNO recommendations (1).

Calculation of the product of 3TDM, used as a reference value, was performed by a neuro-radiologist (PG) with 12 years of experience in pediatric neuroradiology. Manual volumetric segmentation (hereinafter referred to as: segmentation) was performed by a single technical analyst (CS) checked by the neuro-radiologist (PG). Individual tumor volumes were obtained by manually marking all voxels representing tumor tissue with use of 3D Slicer (v4.10.2), a free open source software including segmentation of 2D/ 3D images. Both measurements were performed on T2-FLAIR-weighted MR images (with T2, T1- pre- and post-contrast T1-weighted images as second reference to define tumor borders). Differences in outcome in the radiologic response categories, defined according to the RAPNO recommendations (see subscript of Table 8.1) were identified.

Statistical analysis was conducted using IBM SPSS statistics (v28.0.1.1). Data was analyzed using descriptive statistics. For continuous variables with normal distribution, mean and standard deviation were used; for non-normally distributed continuous variables, median and range were used. Categorical data are presented as frequency and percentage. Student's t-test was used to compare normally distributed continuous variables, the Mann-Whitney U test was used for non-normally distribution.

Results

Thirty-one patients were included; one patient was excluded due to ill-defined tumor borders and morphology of the OPG. Four patients had an OPG located solely within the optic chiasm (12.9%), the majority of patients (n=27; 87.1%) had an OPG with diffuse optic tract localization ((optic nerve), chiasm and optic tract). The median duration of BVZ treatment was 12 months (range 2-39 months) during which a median of 26 doses of BVZ were administered (range: 4–65 doses).

Before the start of treatment, the median tumor size obtained by segmentation was 18.9 cm^3 (range: 0.5 – 179.4 $cm^{3)}$. Twelve OPGs (38.7%) had one or more tumor cysts, with a median total volume of 2.1 cm^3 (range: 0.7 – 35.0 cm^3). At the end of BVZ treatment the cysts of 8 OPG resolved completely, four reduced in size to median 2.1cm^3 (range 0.4- 31.3cm^3).

Comparison of the relative change in TTV by segmentation and 3TDM showed a median decrease of 19.8% (range -87.8% to + 95.0%) and 24.4% (range: - 80.9 to + 96.1%), respectively. An example of the difference of 3TDM and segmentation on MRI is shown in Supplementary Figure S8.1. The median absolute difference in change of TTV between the two techniques was 7.9 percent point (range: 0.7 - 38.8 percent point: $p< 0.001$). The mean relative difference of change in TTV was -3.7 percent point ($p = .092$, 95%, CI -8.0 - 0.6 percent point). In OPGs restricted to the optic chiasm (n=4), the difference in change of tumor size ranged from -11.7 to 17.2 percent point (see: light grey bars in Figure 8.1). The individual differences in relative change of TTV between 3 TDM and segmentation are shown in Figure 8.1.

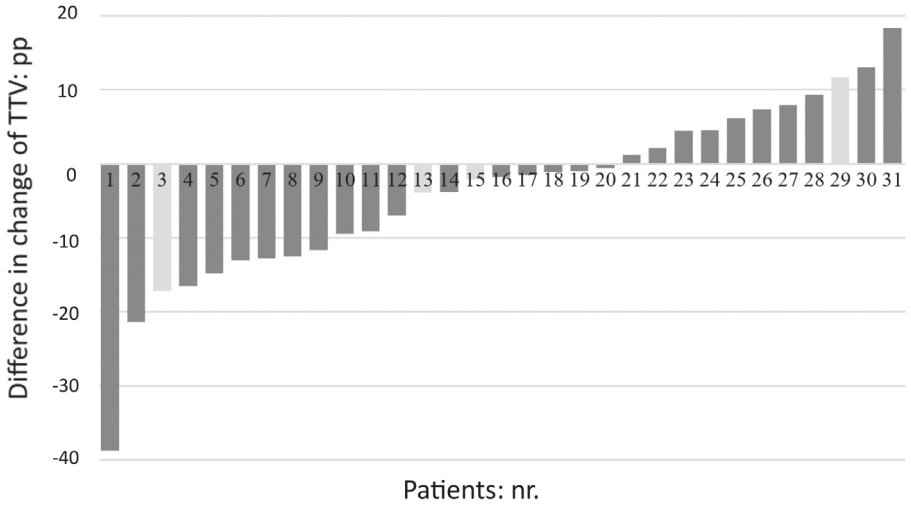


Figure 8.1. Individual variance in change of total tumor volume (TTV) during BVZ treatment for OPG: manual volumetric segmentation compared to three directional tumor diameter measurements (3TDM)

Abbreviation: pp: percent point, TTV: total tumor volume

Dark grey bar: diffuse OPG: extension of the OPG into two or more locations within the optic pathway (optic nerve/ chiasm/ optic tract). Light grey bar: chiasmal glioma: location of the OPG solely within the chiasm.

Radiologic response assessment according to the RAPNO criteria by 3TDM showed a major response in 3.2% (n=1), partial response in 19.4% (n=6), minor response in 22.6% (n=7), stable disease in 48.4% (n=15) and progressive disease in 6.5% (n=2). Segmentation showed a major response in 3.2% (n=1), partial response in 16.1% (n=5), minor response in 29.0% (n=9), stable disease in 45.2% (n=14) and progressive disease in 6.5% (n=2). The comparison of outcome of radiological response categories based on segmentation and 3TDM, showed a different category in 12.9% (n=4) (see Table 8.1).

Table 8.1. Comparison of RAPNO response categories to bevacizumab treatment using conventional 3 directional tumor diameter measurements (3TDM) vs. manual volumetric segmentation.

		Manual Segmentation					Total
		PR	**MinR**	**SD**	**PR**	**MajR**	
3TDM	MajR	1	0	0	0	0	1
	PR	0	5	1[a]	0	0	6
	MinR	0	0	6	1[a]	0	7
	SD	0	0	2[a]	13	0	15
	PR	0	0	0	0	2	2
	Total	1	5	9	14	2	31

Abbreviations: MajR: major response (≥ 75% decrease in TTV); PR: partial response (≥ 50% and < 75% decrease); MinR: minor response (≥ 25% and < 50% decrease); SD: stable disease (≤ 25% increase and < 25% decrease); PD: progressive disease (> 25% increase)

[a]: Difference in response category between segmentation and 3TDM

Discussion

The results of this exploratory MRI study on radiologic response assessment in pediatric OPG show a variance in outcome in radiological response categories of 12.9% between manual volumetric segmentation and 3TDM.

As interobserver variety is a long term recognized point of debate in radiologic response assessment of therapy in different anatomic locations of the brain (5), stabilization or improvement of visual function is a priority in the treatment of OPG. So far, 2 or 3TDM response evaluation (RAPNO) has not shown to correlate with changes in visual function after systemic antitumor treatment (6, 7). The upgrade to segmentation strategies promises an opportunity of detection a correlation between change in visual function and tumor volume

The strength of this pilot study is the analysis on low grade glioma (LGG) only confined to the optic pathways, represented by a higher complexity in shape and borders compared to LGG confined to other anatomical structures. The limitations of this study are a small sample size and variety within the diverse anatomic locations in the optic pathway and evaluation restricted to BVZ as main treatment strategy. Due to the time consuming activity of manual segmentation (median 30 minutes per MRI in this study), only single rating has been performed, preventing analysis on inter-rater variability. These limitations may limit the generalizability of the results.

Manual segmentation concerns a time consuming task and requires experienced staff, what makes its use inappropriate for current daily practice. In order to refine radiological response evaluation and develop a prediction model for visual function, prior (small sample) studies using (semi-)automated and artificial intelligence for segmentation have shown promising results for detailed longitudinal response analysis (8, 9).

In conclusion, our small study shows that radiologic MRI response assessment by segmentation and conventional 3TDM for OPG leads to a difference in RAPNO response category in approximately one in eight patients. Current treatment teams should be aware of this variability in response assessment. Future development of automated imaging analysis techniques is required to optimize radiological treatment monitoring of treatment of OPG.

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R. Oostenbrink, MD, PhD. ENCORE-NF1 center, department of general Pediatrics, Rotterdam, Erasmus MC, The Netherlands

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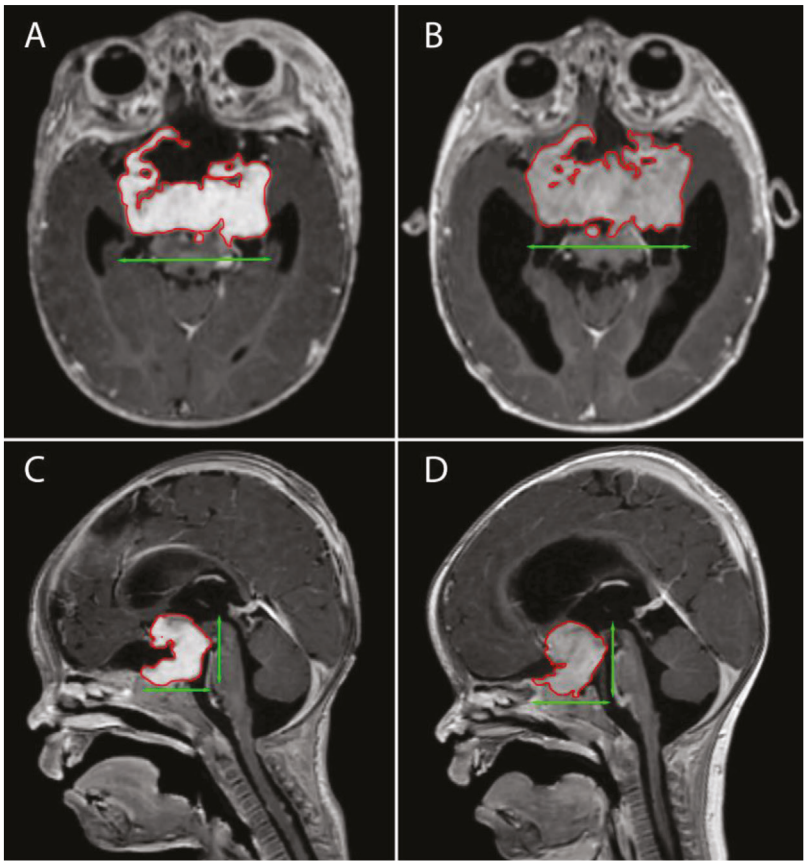
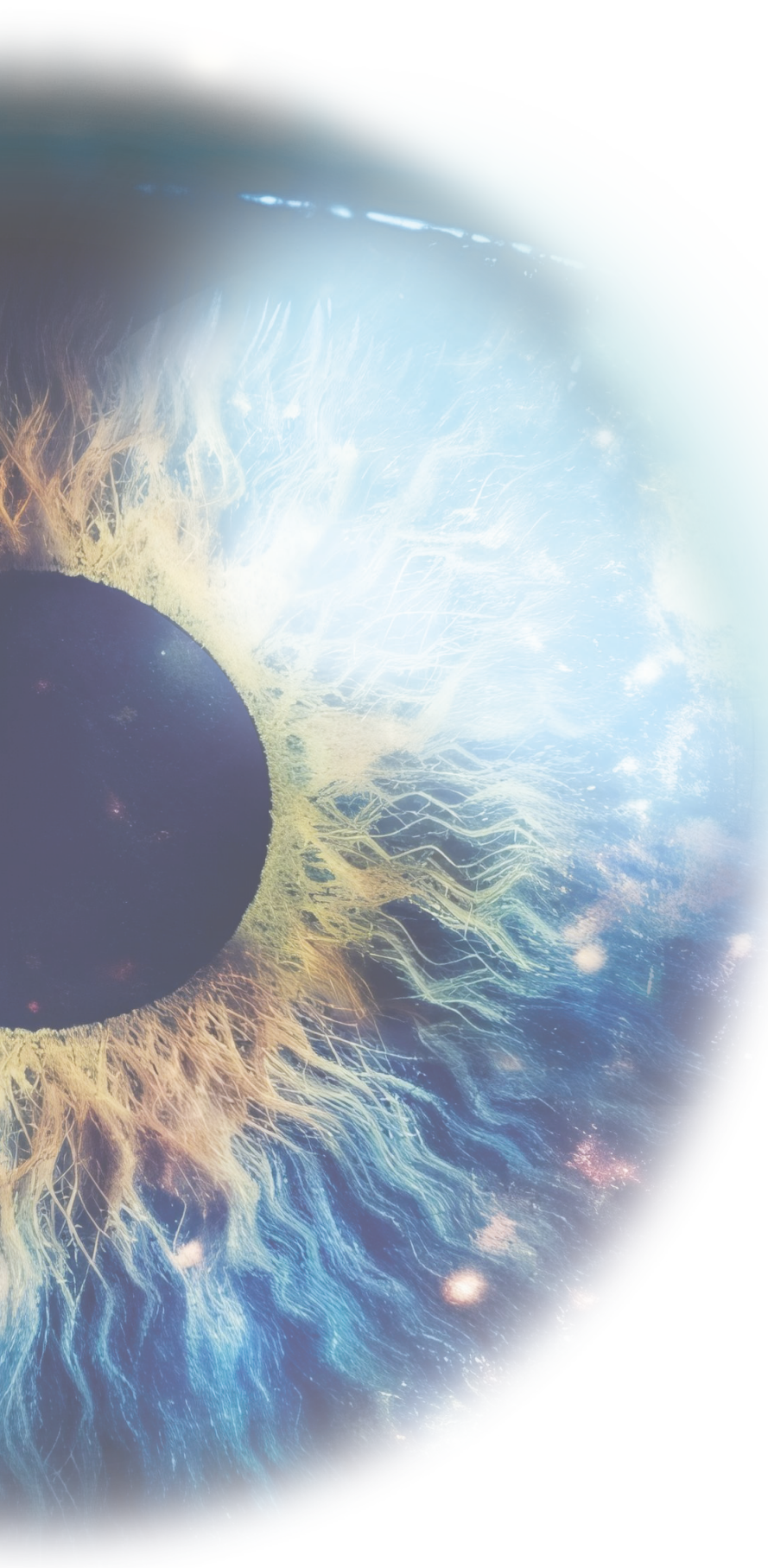
Supplement 8.1.
Example of 2 MR images of a child with a chiasmal optic pathway glioma: comparison of manual segmentation (red line) and 3 directional tumor diameter measurements (3TDM) (green line)



A+B: Axial contrast-enhanced T1-weigthed image at start (A) and at the end of bevacizumab (B).
C+D: Sagittal contrast-enhanced T1-weigthed image at start (C) and after cessation of bevacizumab (D).
The percentage of change in tumor volume measured by 3TDM showed a decrease of 2.1%. The percentage of change in tumor volume measured by manual segmentation showed an increase of 10.70%. The absolute difference in change of tumor size between the two techniques was 12.8 percent point.



CHAPTER 9

General discussion and future perspectives

General discussion and future perspectives

This thesis presents the outcome of a national study on children who received treatment for progressive optic pathway glioma (OPG) and isolated optic nerve glioma (ONG). Various outcome parameters following a range of (successive) treatments have been analyzed from the ophthalmological, radiological, medical oncological, and microbiological perspective.

The rarity of the diagnosis of OPG, combined with the global variability in treatment approaches and the challenges in optimizing treatment monitoring, leaves many aspects of the treatment course currently unexplored. Nonetheless, there is a increasing emphasis on improving treatment strategies and preventing irreversible damage to visual functions in these patients. In the creation of a comprehensive dataset from a long-term national cohort of OPGs and ONGs in the OPG-NL study, extensive data are collected to study and assess the progression of treatment and disease. This opportunity warrants the development of future objectives and strategies, including structured international collaboration. This discussion will explore some future directions of OPG treatment and monitoring.

Data collection and bias

When conducting a retrospective national study over a period of 25 years, bias is inevitable as a consequence of missing data. This is a common phenomenon in the existing literature discussing outcome in SAT treatment for OPG: a considerable number of studies, with which the results of our studies are compared, are retrospective and of small sample size. Nevertheless, in case of rare diseases, many lessons can be learned from retrospective studies, provided they include clear reporting of applied definitions, to establish a foundation for subsequent prospective studies.

Since 2018, all children diagnosed with a brain tumor in the Netherlands have been treated and monitored at the Princess Máxima Center or at one of the shared care centers. This centralization of care has led to a concentration of expertise in the treatment of OPG and an increase in the number of children willing to participate in scientific research. However, the rarity of the (subsequent) treatment indication for OPG makes international collaboration for scientific studies essential. Future pooling of international data sets will be highly valuable to ensue sufficient sample size for studies on OPG subtypes or specific treatment evaluation, as formalized in the SIOP LGG-bevacizumab subgroup.

Raising Awareness for Early Identification to Prevent Permanent Visual Loss

A critical aspect of OPG management is its early detection and diagnosis, as this indirectly influences long-term treatment outcome. Early visual dysfunction occurs due to compression of the chiasm, optic tract and/ or optic nerve by the OPG. Visual impairment does not improve for the majority, leading to life-long disability.

Children at a young age are often unaware of diminished functions, such as symptoms of slowly progressive visual or endocrine decline, and may not communicate these abnormalities. Parents, caregivers, but as well doctors, often only recognize problems after a prolonged period, due to the slow progression or nonspecific presentation of the dysfunction. The rarity of OPG and the wide variability in clinical symptoms necessitates continuous and ongoing efforts to prevent diagnostic delays and ensure early referral to a specialized pediatric neuro-oncology center. Establishing a national multidisciplinary collaboration on education about the topic of diagnosis of pediatric brain tumors, including OPG, could provide a structured and recurring service for residents and doctors in specialties adjacent to the diagnosis, promoting consistent awareness of the risk of a pediatric brain tumor.

Screening for OPG in NF1

In the ophthalmological field, regular screening of children with NF1 by an experienced pediatric ophthalmic team, as defined according to international consensus guidelines (1), can assist in early identification. When ONGs and OPGs are detected, significant uncertainty arises for parents, as no predictive profile for the risk of progression is available and, as treatment is only indicated in case of clinical or radiological progression, the risk of need to treatment remains unclear. In our study, nearly 30% of children with NF1 did not receive treatment for their OPG and nearly 70% of ONG in children with NF1 did not receive treatment. Future studies on ONG should evaluate whether biomarkers within the genetic profile of the child, tumor biology, or radiological profile in NF1-associated patients can assist to identify ONGs and OPGs at risk for progression and requiring treatment. These children could benefit from an intensified screening protocol and early initiation of treatment, with a focus on maximizing the retention of visual function.

The role of the ophthalmologist during and after treatment

Treatment and monitoring of OPG requires a collaborative approach involving pediatric oncologists, neurologists, endocrinologists, ophthalmologists, and neuroradiologists. These children undergo prolonged monitoring during and after (successive) treatment, often requiring numerous hospital visits from a young age

on. Cooperation during examination is often limited at young age, due to fear or behavioral challenges, which can result in incomplete data, hindering effective monitoring and guiding treatment. A supportive and child-friendly environment, particularly one that reduces anxiety, will enhance both the patient's comfort and cooperation, improving the likelihood of successful monitoring of visual functions. One of the key factors in optimizing ophthalmological examination is conducting the examination without time pressure, guided by a consistent team of orthoptist and pediatric ophthalmologist.

In recent years, scientific reporting on the treatment outcomes of pediatric OPGs, as represented by visual functions, has increased. BCVA is considered the primary outcome factor and the definition of change in BCVA ($\geq$ or $\leq$ 0.2 LogMAR) is uniformly applied. Nevertheless, further discussion is needed as no uniform definition exists for evaluating treatment outcomes when monocular BCVA change in BCVA is opposite between eyes (e.g. improvement in one eye while deterioration occurs in the other), making cross-study comparisons difficult. Likewise, evaluation of change in BCVA in single-line SAT evaluation requires stratification by age groups or comparison with age-matched normative BCVA data and BCVA tests (2-4) as an ongoing natural development of childhood BCVA confounds the evaluation of treatment effect for OPG.

Earlier studies and treatment guidelines did not report visual field (VF) examination as an outcome parameter of visual functions (5-7). This approach has changed last years and VF is increasingly added as an outcome parameter, which is highly justified, as we reported VF abnormalities in 80% of eyes in chapter 4. A uniform consensus should be defined on the definition of change in visual field (VF) examination in OPG management in children, to integrate VF examination as outcome parameter in future studies.

Successful testing of monocular VFs remains a challenge in children under the age of three, as it is highly dependent on the cooperation and attention of the child. Ophthalmologist should be aware of available of peripheral VF testing methods, like the behavioral VF test (8). Future alternatives are awaited for more objective VF testing methods like pupil perimetry, which objectively measures pupil responses to map visual sensitivity across the visual field, (9).

Optimizing more objective testing methods requires the use of optical coherence tomography (OCT), which was not applied in the studies in this thesis as data were highly incomplete and scanning devices changed in time in the participating centers.

OCT represents an efficient, non-invasive and objective testing method, providing quantitative retinal layer thickness measurements which correlate with change in BCVA or VF abnormalities (10-12). Age-based normal values for individual layer thickness in children are available for different OCT devices (13). A hand-held version can provide analysis under anesthesia in non-cooperative children, but requires future automatic retinal layer segmentation and development of the application to perform longitudinal measurements at identical anatomic locations. Future analysis should include assessment of longitudinal correlation between OCT measurements with both BCVA and VF outcome and correlation to radiological response assessment provided by automated segmentation.

Long-term visual impairment or blindness are one of the leading disabilities resulting from OPG treatment and will affect patients' quality of life (QOL) (14, 15). In chapter 4, we reported a long-term rate of severe visual impairment or blindness in nearly one in five children, by applying the classification of visual impairment defined by the World Health Organization (16). Nevertheless, in our study, grading visual impairment was not supported by VF abnormalities, as these abnormalities did not align with the definitions stated by the WHO. Future studies should focus on the impact of visual field abnormalities as part of visual impairment on QOL, which could help substantiate the development of an appropriate classification for visual impairment in the field of OPG.

Radiological response evaluation in OPG

Radiological response evaluation is currently performed using 2- or 3-directional tumor diameter (according to the RAPNO criteria) (17). In chapter 8, we demonstrated in a small series that the conventional measurement method is easy to apply in daily practice, but results in an inconsistent radiological response criterion in 13% of children compared to manual segmentation. This method of response evaluation is highly time-consuming and not suitable for routine clinical use. Development of automated segmentation strategies has proven to lead to a more refined response evaluation (18). Future studies including automated segmentation should focus on identifying differences in (early) longitudinal volumetric change between SAT strategies, which may support prioritizing SAT strategies that could support visual improvement following rapid (cystic) tumor progression.

To date, studies have failed to show a correlation between conventional 2- or 3-directional radiological response evaluation and changes in visual functions, represented by change in BCVA, during SAT (19, 20). The introduction of automatic segmentation requires re-evaluation of the association between changes in tumor

volume and changes in BCVA, VF and OCT examination. Future studies should address if detailed radiological follow-up by MRI can serve as a surrogate for changes in VF in the population aged under four years, as reliable VF testing remains challenging. Likewise, the use of Diffusion Tensor Imaging should be explored as representative of longitudinal vision functions (21).

Similarly, the benefit of the use of contrast agents needs to be reevaluated, as its clinical application remains under discussion to evaluate SAT effects in OPG, but requires more detailed intratumor component analysis (22) in order to decrease the systemic burden of repetitive use of contract during MRI examination.

Isolated optic nerve glioma

Isolated optic nerve gliomas (ONGs) form a distinct cohort within optic pathway gliomas (OPGs) due to their isolated location within the orbit. In the case of progression, they rarely grow into the chiasm, therefore, central neurological or endocrine abnormalities are absent. Due to the bony boundaries of the orbit, growth of ONG result in a more severe loss of monocular visual functions because of compression of invasion of the optic nerve compared to OPG. The swelling of the tumor leads to anterior displacement of the eyeball, causing disfiguring and painful proptosis. The latter requires surgical debulking, which concerns a specific task for ophthalmologists specialized in the orbit, but this treatment leads to blindness in all affected eyes.

Most studies that have evaluated the effects after SAT have included ONGs within the cohort of optic pathway gliomas in general, and only a few reports have identified isolated optic nerve glioma as a distinct entity (23, 24). In chapter 5, we demonstrated in a small retrospective series and literature review, that treatment of progressive ONGs with SAT is the most effective strategy for preserving or improving visual acuity. Recurrence of progression was also less common in ONGs compared to OPGs after first-line SAT. This limited evidence justifies analysis of treatment effects of ONG separate from OPG in future comparative prospective trials, requiring international collaboration to create sufficient sample size in this rare disease.

Factors needing to be addressed in future studies are the impact of different SAT strategies, regarding their effect on (early) changes in visual functions in relation to changes in tumor volume. As a result, those patients with ONG could be identified who achieve maximal benefit with visual preservation, which outweighs the use of (a minimum of 12-month schedule of) SAT and its side effects

Comparison of new medication strategies with current treatment approaches

Newer medication strategies, including targeted therapies as BRAF- or MEK-inhibitors, have emerged as potential alternatives for conventional SAT strategies (25). These approaches aim to limit toxicity while maintaining or improving therapeutic efficacy.The long-term safety and efficacy of these new treatments need to be studied in comparison to traditional therapies. Comparative studies on side effects and the effects of treatment on visual functions are needed in determining whether these new treatments should become first-line for OPG patients.

Prognostic factors guiding treatment strategies

The OPG-NL study demonstrated, consistent with previous studies (6, 26), that children who start SAT before the age of one year have an increased risk of progression and requirement of repeated treatments. All these children had sporadic OPGs. Additionally, it was found that children under the age of 2 are at higher risk for severe long-term visual impairment or blindness. These children should be closely monitored in future studies. Comparative therapeutic studies should assess whether targeted therapy is more effective than conventional SAT. Further study of tumor biology is needed to identify the molecular relationship between the tumor's anatomical location, the child's age, and its response to new SAT strategies.

Conclusion by the author

It may not come as a surprise to the reader that the results of the OPG-NL study only provide a small piece of the puzzle to the broader field of clinical research of OPG treatment. The author of this thesis sincerely believes that these contributions can assist in merging into larger sample size collaborative studies, which will enhance the understanding of this rare disease of OPG and ultimately improve treatment outcomes with the goal of preservation of visual functions and increasing the quality of life of children with OPG.

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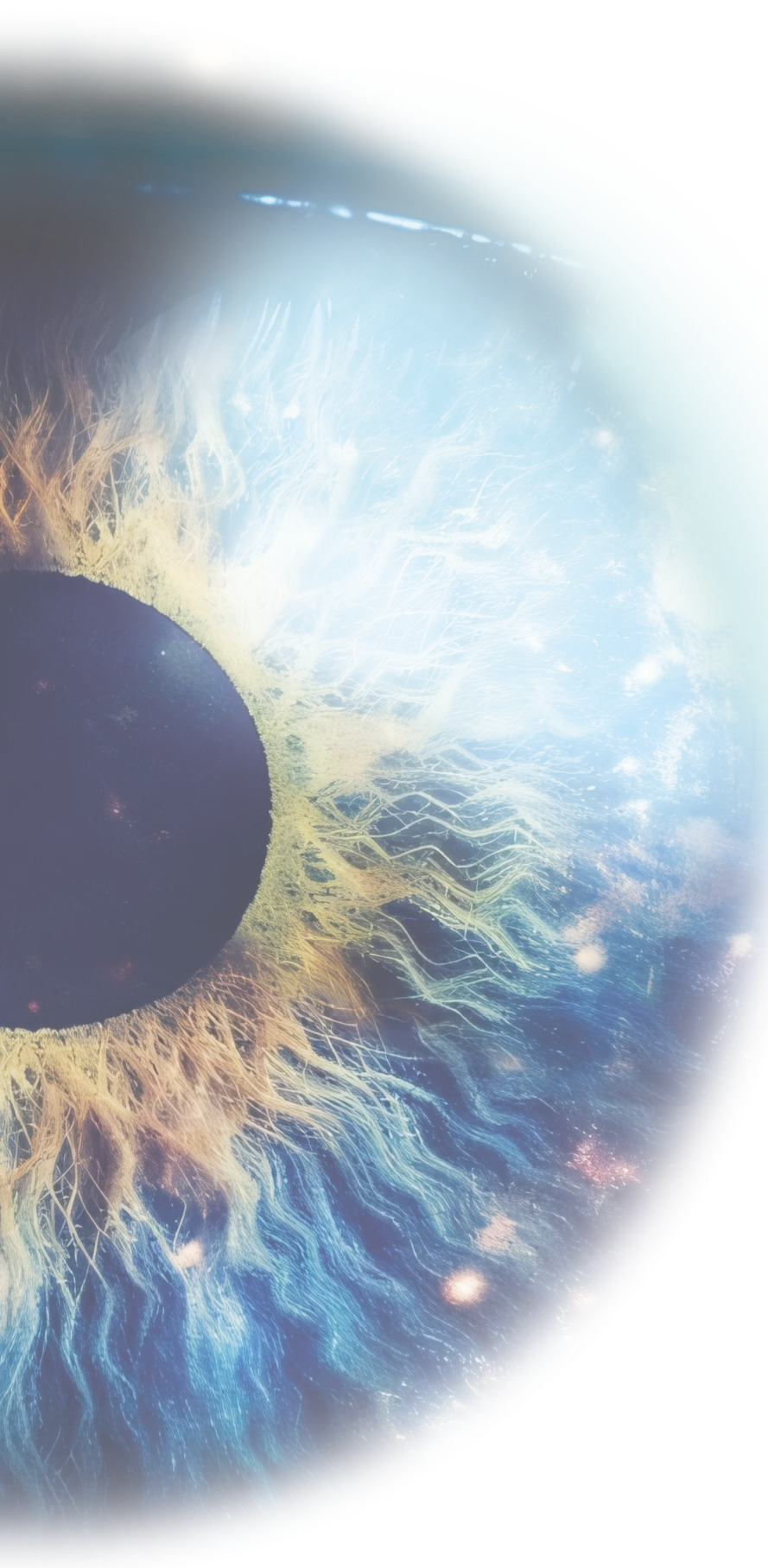


APPENDICES

ABBREVIATIONS

BCVA	Best-corrected visual acuity
BEFIE	Behavioral Visual Field Screening test
BVZ	Bevacizumab
CEBM	Centre for Evidence-Based Medicine
CI	Confidence interval
CR	Complete response
CT	Chemotherapy
CTCAE	Common Terminology Criteria for Adverse Events
DCOG	Dutch Childhood Oncology Group
HFA	Humphrey Field Analyzer
ICO	International Council of Ophthalmology
IRI	Irinotecan
JBI-CA	Joanna Briggs Institute – Critical Appraisal
KIAA1549-BRAF	Fusion of the human gene that encodes the KIAA1549 protein and the B-raf (proto-)oncogene
LGG	Low-grade glioma
LogMAR	Logarithm of the minimum angle of resolution
MR	Minor response
MRI	Magnetic resonance imaging
MAPK	Mitogen-Activated Protein Kinase
MDC	Modified Dodge Classification
NF1	Neurofibromatosis type 1
nNF1	No association with neurofibromatosis type 1
OCT	Optical coherence tomography
ONG	Isolated optic nerve glioma
OPG	Optic pathway glioma
OS	Overall survival
PA	Pilocytic astrocytoma
PD	Progressive disease

PFS	Progression-free survival
PMA	Pilomyxoid astrocytoma
PMC	Princess Máxima Center
PP	Percent point
Rano	Response assessment in neuro-oncology
RAPNO	Response Assessment in Pediatric Neuro-Oncology
RNFL	Retinal nerve fiber layers
RT	Radiotherapy
SAT	Systemic anticancer therapy
SD	Stable disease
Segmentation	Manual volumetric segmentation
SX	Surgery
(3)TDM	(Three directional) tumor diameter measurements
TTV	Total tumor volume
UMC	University Medical Center
UMCU	University Medical Center Utrecht
VA	Visual acuity
VBL	Vinblastine
VEGF	Vascular endothelial growth factor
VF	Visual field
VD	Ventricular drainage
VI	Visual impairment
WHO	World Health Organization

ENGLISH SUMMARY

Annually, approximately 120 children are diagnosed with a brain tumor in the Netherlands. Optic pathway glioma (OPG), a low-grade glioma affecting the eye-brain pathway, are present in 3-7% of these children. The survival rate for OPGs is relatively favorable compared to other types of childhood brain tumors, ranging from 91 to 100%.

These tumors are located in and around the optic nerve, optic chiasm and optic tract. Within this pathway, information from various visual functions is transmitted from the eyeball to the posterior brain regions (the occipital lobes). The tumor is commonly diagnosed in children aged 2 to 5 years, although earlier or later can occur with a range from 0 to 17 years of age.

OPG occurs in 30 to 60 percent of children with Neurofibromatosis type 1 (NF1) as well as in otherwise healthy children, where OPG is considered a sporadic lesion. Due to the tumor location, the quality of various visual functions is often (severely) impaired at the time of diagnosis. Not all OPGs necessitate therapy. Treatment of low-grade glioma (LGG) is only initiated when: 1) visual functions deteriorate significantly, 2) MRI images show significant tumor growth, and 3) the patient's neurological condition worsens.

During the past 35 years, treatment of OPG has shifted to treatment with various types of medication (systemic anticancer treatment (SAT)), most commonly chemotherapy. Treatment with SAT is preferred over tumor resection via surgery or radiation, as both are associated to the risk of severe damage to visual and/or neurological or hormonal functions. Children with and without NF1 have been treated using similar SAT strategies; particularly sporadic OPGs carry a higher risk of recurrent growth during or after treatment cessation.

Prior to 2018, treatment was administered across all eight academic hospitals in the Netherlands. Since then, treatment indications and choices for the type of treatment have been guided by the tumor board neuro-oncology at the Princess Máxima Center.

Globally, OPG diagnosis is a rare entity in children and treatment is provided to a smaller proportion of patients. Between countries differences exist in treatment choices and the discussion remains about the most optimal treatment approach.

The objective of this thesis was to provide insight in the incidence of OPG and its treatment in children in the Netherlands, to identify prognostic factors for recurrent progression of OPG, to determine the long-term effects of various treatments on different visual functions and to assess detailed radiological response evaluation by manual segmentation of MRI scans.

Chapter 1 provides a general introduction of the incidence, pathophysiology, treatment options and evaluation of treatment for OPGs in children in the Netherlands. The objectives and structure of this dissertation are also outlined.

Chapter 2 presents a systematic literature review of all published literature prior to August 2020, focusing on changes in best-corrected visual acuity (BCVA) and visual fields following the first start of SAT for OPGs in children. Eleven studies, with 358 patients, met the inclusion criteria. All studies were cohort studies, with five being prospective studies. Two studies reported on changes in the visual field. After a median follow-up of 3.7 years, BCVA improved in 0–45% of children, stabilized in 18–77%, and deteriorated in 0–82%. There was considerable variation between the studies in terms of study population characteristics or therapy-related parameters, which made a meta-analysis unfeasible. We concluded that the available literature on the impact of SAT treatment on change in BCVA is limited and inconclusive. To further evaluate this effect, prospective multinational longitudinal multicenter studies with use of uniform definitions of visual outcome are needed to evaluate both short- and long-term effects of SAT on visual functions.

In **chapter 3** we describe a nationwide retrospective cohort study examining the clinical aspects of 195 children diagnosed (1995-2018) and treated (136 children: 1995-2020, 36% had NF1) in the Netherlands for a progressive OPG. The study analyzed differences in characteristics between children with sporadic and NF1-associated OPGs. Prognostic factors were identified for the risk of progression following treatment with SAT (first-line vincristine/ carboplatin).
The first-line treatment was initiated at a median age of 5.4 years. Overall, 112 children received SAT. One in five children received three or more treatments due to recurrent tumor growth. Children with a sporadic OPG were diagnosed and started treatment at a younger age than children with a NF1-associated OPG. Additionally, children with a sporadic OPG needed a greater number of different treatments than those with a NF1-associated OPG and had a higher rate of recurrent tumor growth after first-line SAT treatment.
Children who started first-line SAT before the age of one year had an increased risk of recurrent tumor growth, necessitating successive treatment. These findings

emphasize the need for more effective treatment strategies, particularly for young children with a sporadic OPG.

In **chapter 4** we describe the results of a national study on long-term visual functions of 117 children (with 234 eyes) who received various treatments for a progressive OPG. After a median period of more than eight years after the start of first treatment, 19% of the children and 35% of the affected eyes were severely visually impaired or blind, which was more common in children with a sporadic OPG than in those with an NF1-associated OPG.
In a sub analysis of 110 eyes, visual field defects were present in 80%, primarily represented by hemianopia (69.3%) and various scotomas (28.4%).
Both children who started treatment before the age of two years and those with an OPG involving the hypothalamus had an increased risk of severe visual impairment or blindness. These results suggest that future treatment protocols should not only include BCVA analysis but also visual field testing for the comprehensive monitoring of visual functions as treatment outcome measures.

In **chapter 5** we compare the effects of three different treatment modalities (chemotherapy, surgery, and radiotherapy) for 21 gliomas that appeared isolated in the optic nerve. In addition, a literature review was performed, which revealed only two previous studies which, partially incomplete, described these outcome parameters.
This analysis existed of measurement based on changes in BCVA and tumor volume (3-directional) on MRI imaging. Chemotherapy was found to be the most effective treatment for those eyes that were not yet severely visually impaired or blind; BCVA improved in 67% of the eyes, and tumor volume decreased by a median of 45%. Gliomas that were surgically removed, were relatively large; prior to surgery 50% of eyes were already blind which increased to 100% following surgery.
Radiotherapy also resulted in a long-term severe decline in BCVA in 67% of the affected eyes. A possible explanation for this further impairment is the temporary edema in the tumor tissue and optic nerve due to treatment with radiotherapy.
The results of this retrospective series provide a foundation for decision-making in the treatment of gliomas isolated to the optic nerve. The combination of both outcome in visual functions and change in tumor volume forms an essential combination for therapy evaluation in future studies.

Chapter 6 provides an overview of the effects of treatment of 33 children with an OPG with bevacizumab, a type of anti-angiogenic therapy that inhibits blood vessel growth within the tumor. This treatment has been used for progressive

OPGs in children since 2009. Treatment led to stabilization or improvement of BCVA in 88% of the examined eyes. Moderate to severe side effects occurred in 15% of the children, which resolved after discontinuation of treatment.
At the end of treatment, tumor volume had decreased or stabilized in 90% of the OPGs. However, recurrent growth within three years after the start of treatment was observed in 62% of the children. These results indicate that bevacizumab is effective in stabilizing or reducing OPG tumor size. However, once treatment is stopped, there is a significant risk of tumor regrowth.

In **chapter 7**, the results of a longitudinal MRI analysis of 31 OPGs treated with bevacizumab are presented. Volumetric analysis of different intra-tumor components was performed at 3, 6, and 12 months after the start of treatment using manual segmentation. Cysts were present in 39% of the OPGs, all of which showed a reduction in volume during treatment. The total tumor volume decreased by a median of 20%. The largest reduction occurred within the first three months after the start of treatment. This relatively rapid decrease in tumor volume may be particularly beneficial for children who experience worsening of visual functions due to recent tumor growth; tumor or cysts shrinkage could potentially lead to improvement of vision.
In addition, analysis showed that the relative contrast-enhanced volume did not follow a similar pattern as the rate of the decrease of total tumor volume, although it did show a significant decrease in sporadic OPGs with a KIAA1549-BRAF fusion compared to NF1-associated OPGs. The clinical significance of this difference in relative decrease of contrast enhancement remains currently unclear.

In **chapter 8**, two different methods are compared to evaluate changes in tumor volume of OPGs on MRI after bevacizumab treatment: the widely accepted international radiological response classification, using 2- or 3-directional tumor diameters (the RAPNO classification) compared to manual segmentation of the tumor. An absolute difference of a median of 8% of change in tumor volume was found between the two methods. This discrepancy resulted in a change in RAPNO radiological response category for 13% of patients. These findings support the assumption that the conventional RAPNO measurement method is not reliable for radiological response evaluation in the treatment of OPGs.
Manual tumor delineation is time-consuming and not feasible for daily clinical use. Until artificial intelligence-based segmentation methods for future radiological response assessment are refined and clinically applied, our results highlight to be aware of the variability in current radiological response assessment practices.

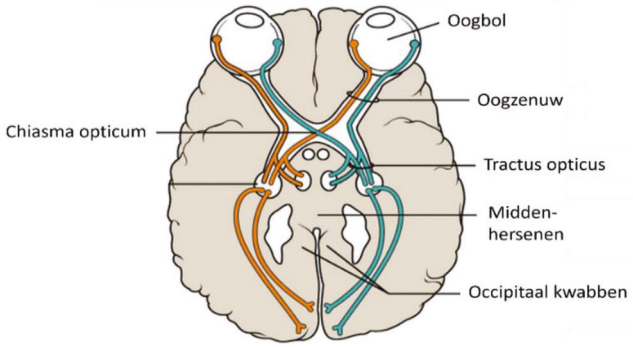
In **chapter 9**, the results of this thesis are discussed within a broader perspective. Suggestions for future research in children with OPGs are provided. Some topics that are being discussed include:

- The value of retrospective data collection in the rare disease OPG and ONG and need for future pooling of international datasets
- Raising awareness for the early detection of OPG
- Future focus on the identification of biomarkers for OPG and ONG in children at risk for progression
- Future expansion of outcome measures for visual functions in treatment protocols

NEDERLANDSE SAMENVATTING

Jaarlijks wordt in Nederland bij ongeveer 120 kinderen een hersentumor ontdekt. In 3-7% zijn dit optic pathway glioma (OPG), ofwel laaggradige gliomen van het oog-hersen-traject. De kans op overleving van deze tumor is relatief gunstig in vergelijking met andere soorten hersentumoren en bedraagt 91-100%.

Deze OPG tumoren bevinden zich in en rond het traject van de oogzenuw, chiasma en tractus opticus (zie fig. 1). Binnen dit traject wordt informatie van diverse functies van het zicht getransporteerd van oogbol naar de achterste hersenkwabben (occipitaal kwabben). De tumor wordt met name ontdekt rond de leeftijd van 2 tot 5 jaar, maar de diagnose kan ook eerder of later worden gesteld (spreiding: 0-17 jaar).



Figuur 1. Schematisch overzicht van het oog-hersen traject
(https://radiopaedia.org)

Optic pathway gliomen komen voor bij 30 tot 60 procent van de kinderen met het syndroom Neurofibromatose type 1 (NF1), maar ook bij gezonde kinderen, bij wie het OPG dan wordt gedefinieerd als een sporadische afwijking. Vanwege de locatie waar de tumor zich bevindt, is de kwaliteit van verschillende visuele functies vaak (ernstig) beschadigd wanneer de diagnose wordt gesteld. Niet voor alle OPG's is behandeling noodzakelijk. Behandeling van een laaggradig glioom (LGG) vindt alleen plaats, wanneer: 1) het zicht ernstig achteruit gaat, en/of 2) MRI beelden significante groei van de tumor laten zien, en 3) de patiënt op neurologisch gebied verslechtert (met name op basis van groei van de tumor).

De afgelopen 35 jaar is keuze in de behandeling van OPG verschoven naar behandeling met verschillende soorten medicijnen (systemic anticancer treatment (SAT)), meestal bestaand uit chemotherapie. Behandeling met SAT heeft de

voorkeur boven het verkleinen van de tumor via een operatie of bestraling, omdat beide type behandelingen het risico hebben op ernstige schade aan de visuele en/of neurologische of hormonale functies. Kinderen met NF1 en met sporadisch OPG's werden tot voor kort behandeld met dezelfde SAT combinaties: vooral sporadische OPG's hebben een verhoogd risico opnieuw te gaan groeien tijdens of na afloop van de behandeling.

Tot 2018 werd behandeling gegeven verspreid over alle 8 academische ziekenhuizen in Nederland. Sindsdien vindt het besluit tot en de keuze van het soort behandeling plaats binnen de tumor board neuro-oncologie van het Prinses Maximá Centrum.

Wereldwijd wordt de diagnose OPG bij kinderen zelden gesteld en vindt behandeling slechts bij een deel van de patiënten plaats. Onderling verschillen de landen in de keuze qua behandelstrategie en is er discussie over de meest optimale (vervolg)behandeling.

Dit proefschrift is geschreven met doel de incidentie van behandeling van OPG bij kinderen in Nederland in beeld te brengen, voorspellende factoren voor herhaaldelijke groei van de OPG's te identificeren, de lange termijn effecten van de diverse behandelingen op verschillende visuele functies te bepalen en gedetailleerde radiologische behandeleffecten te analyseren via handmatige segmentatie van MRI scans.

Hoofdstuk 1 geeft een algemene inleiding over de incidentie, pathofysiologie, de keuze voor en evaluatie van behandeling van OPG bij kinderen. De doelstelling en opzet van dit proefschrift worden beschreven.

Hoofdstuk 2 levert een systematisch literatuuroverzicht over alle gepubliceerde literatuur tot augustus 2020, gericht op verandering van het scherpzien (best-corrected visual acuity (BCVA)) en het gezichtsveld na de eerste start van behandeling met SAT voor OPG's bij kinderen. Elf studies, met in totaal 358 patiënten, voldeden aan de inclusiecriteria. Alle studies waren cohort studies, waarvan er 5 prospectief waren. Twee studies rapporteerden over veranderingen in het gezichtsveld. Na een mediane follow-up van 3.7 jaar, verbeterde BCVA in 0–45% van de kinderen, was de BCVA stabiel in 18–77% en verslechterde deze in

0–82%. Er was relatief veel variatie tussen de studies wat betreft kenmerken van de studiepopulatie of therapie-gerelateerde parameters, waardoor een meta-analyse niet mogelijk was. Wij concludeerden dat de beschikbare literatuur over de invloed van behandeling met SAT op verandering van het scherpzien beperkt is en geen

uniform effect beschrijft. Om het effect van SAT op OPG nader te evalueren, zijn prospectieve multinationale longitudinale multicenter studies met gebruik van uniforme definities nodig, die de korte en lange termijn effecten van de visuele functies evalueren.

In **hoofdstuk 3** beschrijven we in een landelijke retrospectieve cohort studie de klinische aspecten van 195 kinderen die in Nederland zijn gediagnosticeerd (1995-2018) en behandeld (136 kinderen: 1995-2020,) vanwege een OPG. De studie analyseerde verschillen in karakteristieken tussen kinderen met sporadisch en NF1 geassocieerd OPG's. Prognostische factoren werden geïdentificeerd voor het risico op progressie na behandeling met SAT (1e lijns vincristine/ carboplatin).
De 1e lijns behandeling werd gestart op een mediane leeftijd van 5.4 jaar. In totaal werden 112 kinderen behandeld met SAT. Een op de vijf kinderen onderging 3 of meer behandelingen vanwege herhaaldelijke groei van de tumor. Kinderen met een sporadische OPG werden op een jongere leeftijd gediagnostiseerd en startten behandeling op een jongere leeftijd dan kinderen met een NF1 geassocieerd OPG. Ook hadden kinderen met een sporadisch OPG een groter aantal behandelingen ondergaan vergeleken met kinderen met een NF1 geassocieerde OPG en hadden ze een hogere mate van hernieuwde groei na de start van 1e lijns SAT. Kinderen die waren gestart met SAT onder de leeftijd van het 1e jaar hadden een verhoogd risico op herhaaldelijke groei van het OPG met noodzaak tot aanvullende behandeling. Deze bevindingen ondersteunen de noodzaak om meer effectieve therapie te ontwikkelen, vooral voor jonge kinderen met een sporadisch OPG.

In **hoofdstuk 4** beschrijven we de resultaten van een nationale studie waarin de lange-termijn visuele functies van 117 kinderen (met 234 ogen) met een OPG na verschillende behandelingen worden gerapporteerd. Gemiddeld ruim 8 jaar na de start van de eerste behandeling waren 19% van de kinderen en 35% van de betrokken ogen ernstig slechtziend of blind; dit slechte zicht betrof vaker kinderen met een sporadisch OPG dan een NF1 geassocieerd OPG.
In een sub-analyse van 110 ogen waren gezichtsveld defecten aanwezig bij 80%, met name vertegenwoordigd door hemianopsie (69,3%) en diverse scotomen (28,4%).
Zowel kinderen die waren gestart met behandeling onder de leeftijd van 2 jaar en kinderen waarbij de tumor zich ook in de hypothalamus bevond, hadden een verhoogd risico op ernstige slechtziendheid of blindheid. Deze resultaten suggereren onder andere dat toekomstige behandelprotocollen niet alleen analyse van het scherpzien, maar ook van gezichtsveldonderzoek dienen te bevatten als uitkomstmaten van de visuele functies.

In **hoofdstuk 5** vergelijken we de effecten van drie soorten behandelingen, chemotherapie, chirurgie en radiotherapie, voor 21 gliomen die geïsoleerd in de oogzenuw voorkwamen. Daarnaast werd een literatuurstudie verricht, die slechts twee eerdere studies identificeerde, die deze, deels incomplete, effect analyse hadden beschreven. Deze analyse bestond uit metingen gebaseerd op de verandering van het scherpzien en de verandering van het tumorvolume (3-directioneel) op MRI beelden. De toepassing van chemotherapie bleek het meest effectief, wanneer de betrokken ogen nog niet ernstig slechtziend of blind waren; BCVA verbeterde in 67% van de ogen en het tumorvolume nam af met mediaan 45%. De gliomen die operatief werden verwijderd, waren relatief groot. Voor de operatie was 50% van de betrokken ogen al blind, wat toenam tot 100% na de operatie. Behandeling met radiotherapie leidde ook tot een sterke afname van het scherpzien op lange termijn in 67% van de aangedane ogen. Een mogelijke verklaring hiervoor is de tijdelijke zwelling van het tumorweefsel en druk op de oogzenuw als gevolg van de behandeling met radiotherapie.
De resultaten uit deze kleine retrospectieve serie leveren een basis voor de beslisvorming voor behandeling van de gliomen geïsoleerd voorkomend in de oogzenuw. De combinatie van zowel de uitkomst van visuele functies als verandering in tumorvolume vormen een essentiële combinatie voor evaluatie van behandeling in toekomstige studies.

Hoofdstuk 6 bevat een overzicht naar de effecten van behandeling van 33 kinderen met een OPG met bevacizumab, een soort SAT dat de groei van bloedvaatjes binnen in de tumor remt. Deze behandeling wordt sinds 2009 toegepast bij OPG bij kinderen. De behandeling leidde tot stabilisatie of verbetering van BCVA in 88% van de onderzochte ogen. Matig tot ernstige bijwerkingen kwamen voor bij 15% van de kinderen, die zich herstelden na het staken van de behandeling. Aan het einde van de behandeling was het tumorvolume van 90% van de OPG's afgenomen of gestabiliseerd. Echter, hernieuwde groei binnen drie jaar na de start van de behandeling was bij 62% van de kinderen aanwezig. Hieruit blijkt dat bevacizumab een effectief middel is om OPG qua grootte te stabiliseren of te verkleinen. Echter, wanneer het middel wordt gestopt, is er een grote kans dat de tumor weer doorgroeit.

In **hoofdstuk 7** worden de resultaten gepresenteerd van een longitudinale MRI analyse van 31 OPG's die behandeld zijn met bevacizumab. Volumetrische analyse van solide en cysteuze componenten van de tumor werd 3, 6 en 12 maanden na de start van bevacizumab uitgevoerd met gebruik van manuele segmentatie. In 39% van de OPG's waren cysten aanwezig, die allemaal afnamen in volume tijdens de behandeling. Het totale volume van de tumor nam af met

mediaan 20%. De grootste afname werd binnen de 1e drie maanden na de start van de behandeling gezien. Deze relatief vlotte afname van het tumorvolume kan nuttig zijn bij kinderen die recente verslechtering van de visuele functies ervaren ten gevolge van vlotte groei van de tumor. Snelle reductie van de tumor en/of van cysten met deze behandeling kan dan mogelijk leiden tot verbetering van de visuele functies.
Aanvullend bleek uit analyse dat het de afname van het relatieve contrast versterkte volume niet synchroon liep met de afname van het totale tumorvolume. De afname van dit contract versterkt volume nam wel sterker af bij sporadische OPG's met een KIAA1549-BRAF fusie vergeleken met NF1 geassocieerde OPG's. De klinische waarde van dit verschil is momenteel niet duidelijk.

In **hoofdstuk 8** worden twee verschillende meetmethoden vergeleken ter evaluatie van de verandering van het volume van OPG's op MRI na behandeling met bevacizumab: de gangbare internationaal geaccepteerde radiologische respons classificatie volgens meting via 2- of 3- directionele tumordiameter, de RAPNO-classificatie, vergeleken met het handmatig segmenteren van de tumor. Er bleek een absoluut verschil in de verandering van het tumorvolume tussen beide soorten metingen van mediaan 8% te zijn. Dit verschil leidde tot een verandering in de RAPNO radiologische respons categorie bij 13% van de patiënten. Deze resultaten onderbouwen de aanname, dat de conventionele RAPNO-meetmethode niet betrouwbaar is voor radiologische respons evaluatie van behandeling van OPG's. Echter, het handmatig segmenteren en uittekenen van een tumor is tijdsintensief en niet geschikt voor dagelijks klinische toepassing. Segmentatie via kunstmatige intelligentie kan hopelijk in de toekomst worden toegepast in radiologische respons beoordeling. Tot die tijd verhogen onze segmentatie-resultaten het inzicht in de variatie van huidige radiologische respons beoordeling.

In **hoofdstuk 9** worden de resultaten van dit proefschrift bediscussieerd in een breder perspectief. Suggesties voor toekomstig onderzoek bij kinderen met een OPG of ONG worden beschreven. Enkele onderdelen die worden bediscussieerd, zijn:

- De waarde van retrospectieve gegevensverzameling in het zeldzame ziektebeeld van OPG en de noodzaak voor toekomstige samenvoeging van internationale datasets
- Het bevorderen van vroege detectie van OPG
- De toekomstige focus op de identificatie van biomarkers voor OPG en ONG bij kinderen die het risico lopen op groei van de tumor
- De toekomstige uitbreiding van uitkomstmaten in visuele functies in behandelprotocollen

CONTRIBUTING AUTHORS AND AFFILIATIONS (in alphabetical order)

N.J. Bauer, ophthalmologist, Maastricht UMC
S. Bhusal, student medical physical science, former affiliated to Amsterdam UMC
E.A. Buijs, radiologist, Amsterdam UMC
A.T.M. Dittrich, pediatrician, Radboud MC
M.M. van Genderen, ophthalmologist, Bartiméus & UMC Utrecht
P. de Graaf, radiologist, Amsterdam UMC
A.L.W. Groot, ophthalmologist, Radboud MC
E.J.M. Janssen, pediatrician, Maastricht UMC
M.C. de Jong, radiologist, Amsterdam UMC
S. Klinkenberg, neurologist, Maastricht UMC
M.H. Lequin, radiologist, former affiliated to UMC Utrecht
J. Limpens, former information specialist, Amsterdam UMC
S.E. Loudon, ophthalmologist, Erasmus MC
L. Meijer, pediatric oncologist, Princes Máxima Center
M.C. Montauban van Swijndregt, medical student, Amsterdam UMC
I.C. Notting, ophthalmologist, Leiden UMC
R. Oostenbrink, pediatrician, Erasmus MC
G.L. Porro, ophthalmologist, UMC Utrecht
J.W.R. Pott, ophthalmologist, UMC Groningen
P. Saeed, ophthalmologist, Amsterdam UMC
C.R. Schouten, former medical student, Amsterdam UMC
A.Y.N. Schouten- van Meeteren, pediatric oncologist, Princes Máxima Center
A.J. van Sorge, ophthalmologist, Royal Dutch Visio
M.W. Tanck, Assistant professor in biostatistics and genetic epidemiology, Amsterdam UMC
L.E. Wijninga, former medical student, Amsterdam UMC
J. van Zwol, former medical student, Amsterdam UMC

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PORTFOLIO

1. PhD training	Year	Workload
Courses		
Practical Biostatistics	2020	1.4
Scientific writing course	2020	1.5
Basis legislation in Science (eBROK)	2019/ 2023	2.0
Presentations		
ESOPRS - oral presentation	2024	0.5
EUNOS - oral presentation	2024	0.5
NOG - oral presentation	2024	0.5
PNOC/ CBTN imaging meeting - oral presentation	2023	0.5
KIZZ symposium - oral presentation	2023	0.5
EPOS - - oral presentation	2023	0.5
ORCA - oral presentation	2023	0.5
LWS - oral presentation	2020	0.5
NENOS - oral presentation	2018	0.5
National/ international conferences		
NOG	2019-2024	7.5
EPOS	2023	1.5
ORCA	2023	1.0
EUNOS	2024	1.5
ESOPRS	2024	1.5
Other		
Writing study protocol	2018	4.0
Retrospective data collection	2019-2022	4.0
2. Teaching:		
Lecturing		
Ophthalmology Amsterdam UMC	2021-2024	3.0

Tutoring/ mentoring		
Research internship (M. Montauban-van Swijndregt)	2023	2.0
Bachelor student (F. de Jong)	2023	1.0
Research internship (C. Schouten)	2022	2.0
Bachelor student (L. Wijninga)	2020	1.0
ECTS PhD period 2018-2025	**Total**	**39.4**

3. Other activities:

Grands and funds	
ODAS Stichting (grant number: 2019-01)	2019
Stichting Kinderoncologisch Centrum Amsterdam	2021
Board memberships	
Landelijke werkgroep strabismuschirurgie	2017- 2025
Member of SIOP LGG-bevacizumab subgroup	2024- ongoing

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Wetenschappelijk onderzoek, een PhD-traject, was naar mijn idee eerder niet haalbaar. De combinatie van de grote wens naar het leveren van antwoorden voor onze patiënten en mijn wens om persoonlijke twijfel aan te gaan, waren sterk genoeg om de uitdaging aan te gaan. De periode van dit traject liep parallel met mijn zoektocht naar de succesformule van persoonlijk geluk en balans. Een fantastische combinatie van ontwikkeling die op beide fronten succes hebben geleverd en garant staan voor verdere groei en bloei in mijn leven.

Retrospectieve data verzameling in alle acht academische centra en twee revalidatiecentra in Nederland was niet de makkelijkste route naar het schrijven van dit boekje. Vele hobbels zijn genomen, zoals lokale discussie om data te verkrijgen en het maken van keuzes tot het juist opbouwen van de artikelen. Toch bracht dit avontuur vooral plezier en geluk in samenwerken en sámen werken, samen zoeken naar de oplossing bij tegenslag en het vieren van successen. Ik wil graag vele mensen bedanken voor alle hulp, het bieden van een luisterend oor en het samen vieren van het leven buiten al het werk om.

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ABOUT THE AUTHOR

Carlien Bennebroek was born in Alphen aan den Rijn, the Netherlands, on June 17, 1976.
She grew up as the youngest of two siblings.

In 1994, she graduated from secondary school (Gymnasium) at the Christelijk Lyceum in Alphen aan den Rijn. From 1994 to 1995, she studied Medical Biology at the University of Utrecht. In 1995, she started the study Medicine at Utrecht University. During her studies, she was an active member and treasurer of the board of the Erasmus Student Network.

After obtaining her Master's degree in Medicine in 2002, she started her residency in Ophthalmology at University Medical Center Utrecht, which lasted from 2005 to 2011. During her residency, she developed a passion for working with children, alongside a strong interest in eye pathology in childhood and performing strabismus surgery. In 2011, she completed a fellowship in pediatric ophthalmology and strabismus at the Department of Ophthalmology, Southampton University Hospital in the United Kingdom. Since 2014, Carlien has been a staff member of the Department of Ophthalmology at Amsterdam UMC, location AMC, specializing in complicated strabismus surgery and pediatric ophthalmology.

Carlien has been married to Marc Besselink since 2015. Together with their children, Joris (16) and Elin (14), and their dog Guusje, they live in Weesp. She greatly enjoys spending time with friends and family, walking and cycling in nature, swimming in the river the Vecht and exploring many adventures of life.