Child's Nervous System (2019) 35:63–72
https://doi.org/10.1007/s00381-018-3904-9

ORIGINAL PAPER

Monitoring optic chiasmatic-hypothalamic glioma volumetric changes by MRI in children under clinical surveillance or chemotherapy

Nathalia Cunha Calixto[1] · Gustavo Novelino Simão[1] · Antonio Carlos dos Santos[1] · Ricardo Santos de Oliveira[2] · Luiz Guilherme Darrigo Junior[3] · Elvis Terci Valera[3] · Murilo Bicudo Cintra[1] · Alessandro Spano Mello[1]

Received: 9 January 2018 / Accepted: 4 July 2018 / Published online: 4 August 2018

Abstract

Purpose Optic pathway gliomas represent 5% of pediatric brain tumors and are typically low-grade lesions. Because of their unpredictable clinical course, adequate treatment approaches have been controversial, involving surveillance, surgery, chemotherapy, and radiotherapy. In this study, we use volumetric imaging to compare evolution of optic chiasmatic-hypothalamic gliomas (OCHG) treated with and without chemotherapy, analyzing tumor volume variation during the overall period.

Methods A total of 45 brain MRI were retrospectively analyzed for 14 patients with OCHG. Volumetric assessment of the lesions was performed by a neuroradiologist, using software DISPLAY. OCHG patients were allocated into two groups: group 1 ($n = 8$) who underwent chemotherapy and group 2 ($n = 6$) who did not receive chemotherapy. Outcome analysis was performed comparing tumor volume evolution of these two groups.

Results The results showed a reduction of 4.4% of the volume of the lesions for group 1 after the end of chemotherapy, with an increase of 5.3% in volume in the late follow-up examination. For group 2, we found a slight reduction (5%) of the overall volume of the lesions, both with no statistical significance ($p > 0.05$).

Conclusions From the limited series analyzed in this study, no significant differences were observed in relation to the volume change of lesions treated or not treated with chemotherapy. Larger prospective clinical trials are needed to better evaluate the effect of chemotherapy and radiological response of OCHG.

Keywords Optic pathway gliomas (OPG) · Radiology · Pediatric neurosurgery · Chemotherapy

Introduction

Optic pathway gliomas (OPG) occur mainly during the first decade of life and account for approximately 5% of brain tumors in this population [1, 2]. These lesions can arise anywhere along the optic pathway, from just behind the globe to the occipital cortex [3].

OPG diagnosis is currently based on Magnetic Resonance Imaging (MRI), and biopsies are usually restricted to cases with unusual radiological findings. The majority of OPG are pathologically low-grade lesions [4]. Patients with symptomatic gliomas generally have ophthalmological abnormalities, including decreased visual acuity, optic nerve atrophy, or proptosis [5]. Lesions with chiasmatic and/or hypothalamic involvement, optic chiasmatic-hypothalamic gliomas (OCHG), can further cause endocrinological disturbance, such as precocious puberty and hydrocephalus [6] and some authors report a worse prognosis [3, 4, 7, 8].

Although OPG have been historically believed to be benign hamartomatous lesions [9], currently they are more accepted as true neoplasms with unpredictable course. To date there are no specific clinical or neuroimaging features to differentiate aggressive from indolent OPG lesions [3]. Because of this behavior, adequate treatment methods have been

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00381-018-3904-9) contains supplementary material, which is available to authorized users.

✉ Nathalia Cunha Calixto
nathaliacalixto28@gmail.com

[1] Division of Radiology, Department of Clinics, University Hospital of Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto 14049-900, Brazil

[2] Division of Pediatric Neurosurgery, Department of Surgery and Anatomy, University Hospital of Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto 14049-900, Brazil

[3] Division of Pediatric Neuroncology, Department of Pediatrics, University Hospital of Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto 14049-900, Brazil

controversial, ranging from clinical surveillance, surgical removal, chemotherapy, and radiation therapy [8, 10–13], with chemotherapy being advocated as the initial treatment approaches [12, 14–17].

The most used chemotherapy regimen stems from reports published by Packer et al. [12, 14], using the combination of carboplatin and vincristine (Carbo/VCR). Other treatment possibilities are indicated in case of allergy or failure of treatment [18, 19]. Long-term management of these patients is based upon frequent MRI studies, together with clinical and ophthalmological evaluations [20] and treatment is generally initiated when there is radiological progression or clinical deterioration, especially visual worsening [21].

Some recent studies [22, 23] have described a lack of correlation between visual and radiological outcomes, claiming for a more accurate radiological assessment. Although the literature on volumetric measurements of OPG is scarce and not yet routinely performed, it could provide a more accurate monitoring of OPG evolution [24].

In this study, we performed volumetric measurements of OCHG of 14 patients, comparing the evolution of tumors treated and non-treated with chemotherapy.

Methods

Study population

This study was approved by the institutional ethics committee at Ribeirão Preto Medical School, University of São Paulo (HCFMRP-USP), process number 46594015,1,0000,5440. All patients under follow-up care of the Institution over the years 2001–2015 were considered for this study. Inclusion criteria were presence of an expansive lesion with the epicenter in the optic chiasm and/or hypothalamus (Dodge II/III) [25], age at diagnosis under 18 years old, and at least three MRI studies, with at least one performed before initiating treatment. Patients with tumors epicentered outside of the hypothalamic/chiasmatic area, very infiltrative tumors with no reproducible measurement, tumors that underwent surgery during follow-up and patients with insufficient follow-up data were excluded. Twenty-two patients were initially selected. On review, eight patients met one or more of the described exclusion criteria, with a total of 14 cases entering the study.

Diagnosis and treatment modalities

The diagnosis of OCHG was based primarily on MRI findings. Ten patients had histopathologic confirmation. Histopathology revealed juvenile pilocytic astrocytoma (JPA) in seven, ganglioglioma in two, and pilomyxoid astrocytoma in one case. For all patients that underwent surgery or biopsy, the baseline MRI was considered after the procedures.

Among the 14 patients entering this study, eight patients were treated with chemotherapy (group 1), with Carbo/VCR as first-line regimen in seven [12, 14]. Six patients (group 2) were only clinically observed during the time interval.

Neuroimaging and volumetric measurements

Volumetric assessment of the lesions was manually performed by the same neuroradiologist (N.C.C.) for all patients, using the MNI-DISPLAY software (Montreal Neurological Institute). This software allows lesion visualization in three orthogonal planes simultaneously, and voxel-by-voxel identification. The tumor volume is calculated from the identification of each single voxel, and the labeled structures are saved in a file for further verification. Figure 1 shows an example of the volumetric measurement using Display.

All MRI protocols included T2-weighted images and/or FLAIR images (fluid-attenuation inversion recovery) and T1-weighted sequences before and after gadolinium injection, with preference for volumetric sequences when available. Follow-up measurements were obtained using the same imaging sequence as the initial.

Tumor responses were categorized as follows: partial response: a reduction of 50% or more in tumor volume; minor response: more than 25% but less than 50% reduction in size; stable disease: no change or a decrease of 25% or less in tumor size; and progressive disease, with a tumor volume increase of 25% or more [12, 26].

For patients treated with chemotherapy (Group 1) we analyze 3 MRI studies: the first chronological MRI acquired immediately before the treatment initiation (baseline/considered as Time 1), a second MRI study following the end of chemotherapy (0–3 months after/Time 2) and a third MRI study of late follow-up after chemotherapy (18 to 24 months after the end of treatment/Time 3). For patients that had cystic and solid components, tumor volume was calculated separately. For patients who did not undergo chemotherapy we analyzed all the MRI studies available in the time interval. In these patients, all lesions had solid components exclusively.

Statistical analysis

Statistical analysis was performed using the Mann-Whitney test for independent samples. For dependent samples, the Wilcoxon paired test was used. To determine the association between qualitative variables, data were evaluated by Fisher's exact test. The statistic data were analyzed with SAS e R software. All significance tests were two-sided; P values less than 0.05 were considered statistically significant.

Fig. 1 Example of volumetric assessment of a chiasmatic-hypothalamic lesion, using MRI (T1-weighted images after gadolinium) and display software

Results

A total of 14 patients were included (five male and nine female). Four of these also had NF-1. These patients were grouped into patients treated with chemotherapy (group 1; eight patients—57%), and those who did not receive chemotherapy (group 2; six patients—43%). All four patients with mixed solid-cystic lesions were allocated in Group 1. Among the patients of Group 1, seven (87.5%) were treated with Carbo/VCR as first-line agents [12, 14]. Five of these were also treated with vinblastine (62.5%). One patient was treated with cisplatin and etoposide regimen as first-line (12.5%). Table 1 summarizes data regarding treatment regimens and radiological outcomes for group 1.

For group 1, the mean age at diagnosis was 3.5 years (range 8 months–11 years). For group 2, the mean age was 7.4 years (range 2–11 years). A total of 45 MRI studies were included.

Effect of chemotherapy in OCHGs patients

Figures 2 and 3 summarize tumor changes for different time points (1, 2, and 3), grouping the patients according to the presence or absence of cystic components at presentation.

Table 1 Data regarding epidemiology, treatment regimens, and radiological outcomes for group 1

Case	Sex	Age at diagnosis	Surgery/year	Histopathology	First-line treatment	Second-line treatment	NF-1	Follow-up period (years)	Overall radiological changes
1	f	5 years	pe, 2008	jpa	Carbo/VCR	NA	No	2011–2015	mr
2	m	3 years	pe, 2008	jpa	Carbo/VCR	Vinblastine	No	2010–2015	Progression
3	f	1 year	pe, 1998	jpa	Carbo/VCR	Vinblastine	No	2001–2013	Stable
4	f	5 years	pe, 2011	jpa	Carbo/VCR	Vinblastine	No	2011–2015	pr
5	m	1 year	pe, 2010	jpa	Carbo/VCR	Vinblastine	No	2010–2013	mr
6	f	8 months	pe, 2013	pma, grade 2	Carbo/VCR	Vinblastine	No	2013–2015	Stable
7	f	11 years	pe, 2001	jpa	Cisplatin/toposide	NA	No	2007–2015	mr
8	f	2 years	na	na	Carbo/VCR	NA	Yes	2006–2015	Progression

m male, *f* female, *pe* partial excision, *jpa* juvenile pilocytic astrocytoma, *mr* minor response, *na* not available, *pma* pilomyxoid astrocytoma, *pr* partial response, *Carbo/VCR* carboplatine/vincristine, *nf-1* neurofibromatosis

For group 1, we found an average reduction of 4.4% of total tumor volume in time 2 and an increase 5.3% of tumor volume in time 3, with no significant difference ($p > 0.05$). By analyzing the results for exclusively solid tumors, we found a slight increase of tumor volume in time 2 (5%) for the entire group, followed by an increase in time 3 (30.4%), also with no significant difference ($p > 0.05$).

When comparing the solid and cystic components separately for mixed lesions, we found a decrease in both solid and cystic components for the entire group (19.4 and 9.6%, respectively, in overall analysis), again with no significant difference ($p > 0.05$). One interesting finding is that, for mixed solid/cystic lesions, the solid component of the tumor appears to have a better response to treatment than purely solid lesions (19.4% volume reduction compared to 30.4% of volume increasing for overall period), but without statistical significance.

When we analyze the individual response to treatment for group 1 we found that two patients had disease progression (25%), two remained stable (25%), and four patients (50%) experienced a measurable tumor response, three of them with a minor response and one with a partial response (patient 4). Although many lesions did not show significant changes in the radiological aspect during follow-up (Fig. 4), we found that three patients in group 1 had significant changes. Patient 2 had a 50% increase in the volume of the lesion, even during the chemotherapy period, that was stable in the follow-up period. Patient 8 had a 21% increase in tumor volume in time 2 and a 65% increase in time 3, but this patient only received induction treatment. Patient 4 showed an impressive 70% shrinkage in the volume of the lesion in time 2 with stability in the follow-up period (Fig. 5). Figure 6 shows individual changes in tumor volume for group 1.

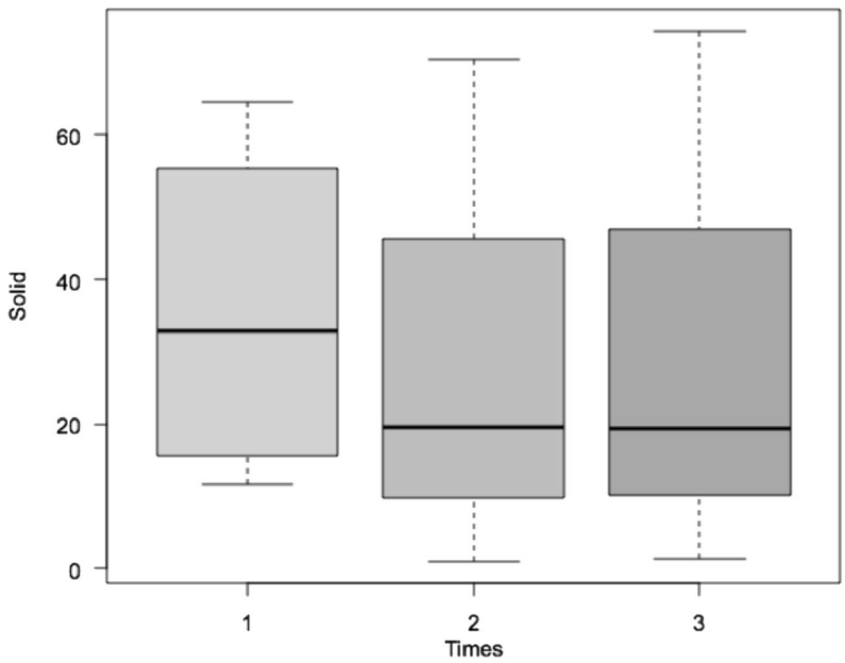

Fig. 2 Changes in solid component volume following time interval

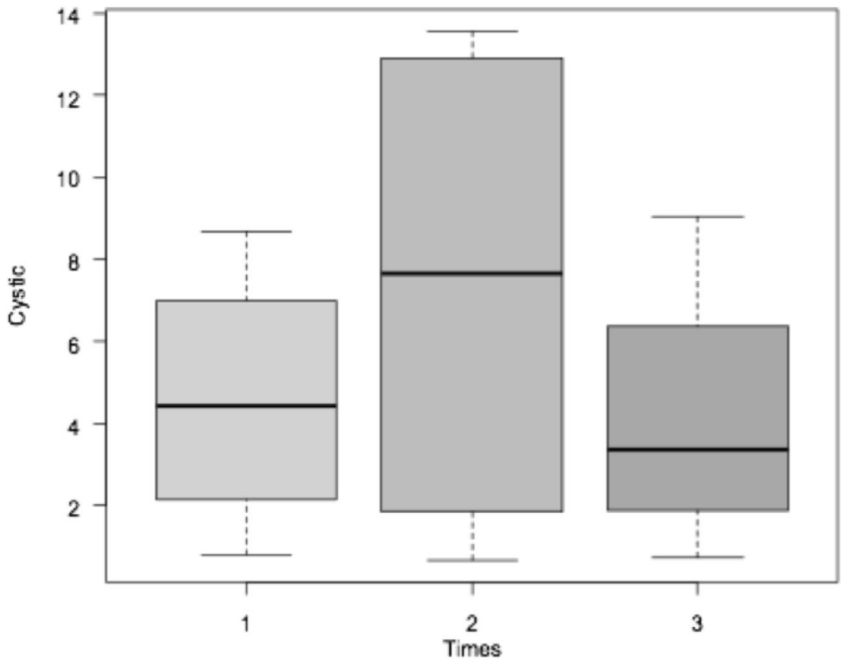

Fig. 3 Changes in cystic component volume following time interval

Evaluation of patients in surveillance

For the group that did not undergo chemotherapy, we found a light reduction of tumor volume for the entire group (17%), but without statistical significance ($p > 0.05$).

When we look at individual response, we found that one patient (16.6%) had a slight progression, two patients (33.3%) remained stable, and three (50%) showed a spontaneous reduction in tumor mass. Figure 7 shows the individual evolution of group 2 patients. Data regarding radiological findings in group 2 are presented in Table 2.

Discussion

OPG are rare pediatric tumors with variable clinical course, ranging from asymptomatic lesions to locally aggressive tumors. Despite this behavior, most lesions are low-grade neoplasms with excellent overall survival [27].

One of the most extensive reviews regarding OPG was published by Dutton [4], based on 2297 cases. The author found that mean estimated survival depends on tumor location. When confined to the optic nerve, overall mortality is about 5%; nevertheless, if the hypothalamus is involved, mortality rates rise sharply to over 50%.

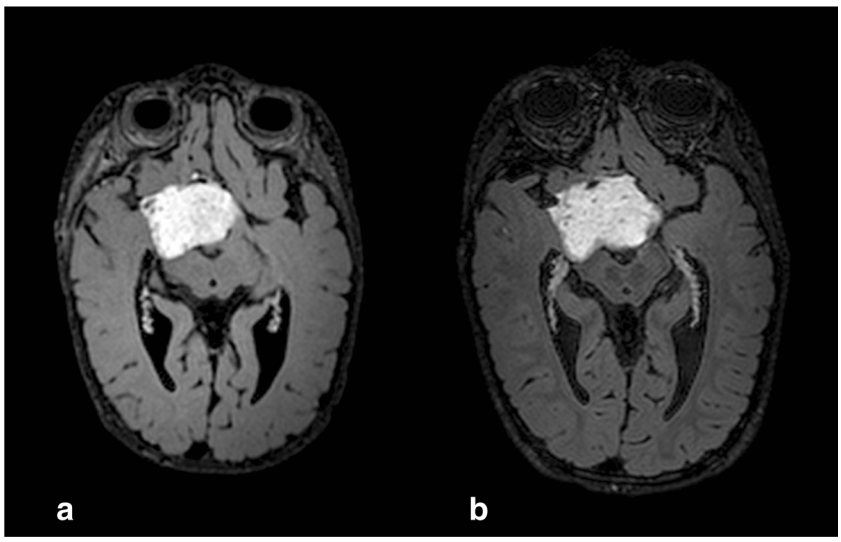

Fig. 4 Axial flair images of patient 6 (group 1) show expansive chiasmatic-hypothalamic lesion before chemotherapy (**a**) and at late follow-up after treatment (**b**), without significant change in volume and radiological appearance of the lesion

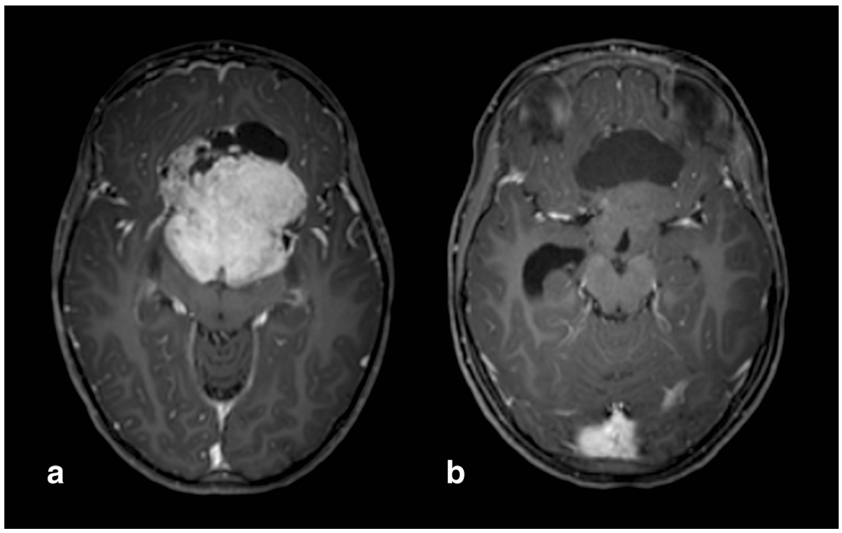

Fig. 5 Axial T1-weighted images after gadolinium administration of patient 4 (group 1) show extensive chiasmatic-hypothalamic lesion before chemotherapy (**a**) and at late follow-up after treatment (**b**), with an important shrinkage of tumor volume, reduction of enhancement areas, and increase of cystic component

Association between OPG and NF-1 has long been recognized, with variations in incidence and prevalence of gliomas in NF-1 population, ranging between 20 and 40% in most reports [1, 4, 8, 14, 18]. Compared with sporadic OPG, these patients tend to show a more indolent course and are more likely to remain stable or even undergo spontaneous reduction over time [3, 4, 28].

The use of imaging methods in the evaluation of OPG, especially MRI, is necessary for diagnosis and monitoring of these lesions, especially for assessment of disease progression and complications.

The standard imaging technique to evaluate OPG is the MRI of the brain and orbits with thin slices acquisition [5]. OPG lesions are characterized by diffuse enlargement of the optic nerves and/or the chiasm, with or without hypothalamic extension, sometimes with optic tract or optic radiation involvement. These lesions are usually isointense on T1-weighted and isointense/hyperintense on T2-weighted

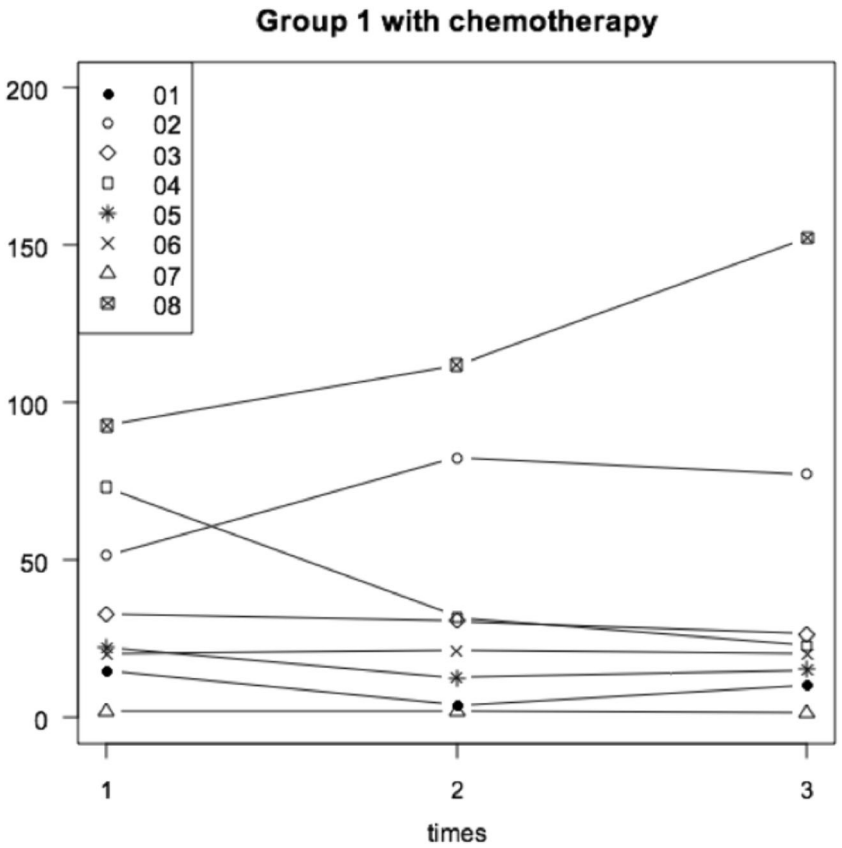

Fig. 6 Tumor volume changes in overall period for group 1

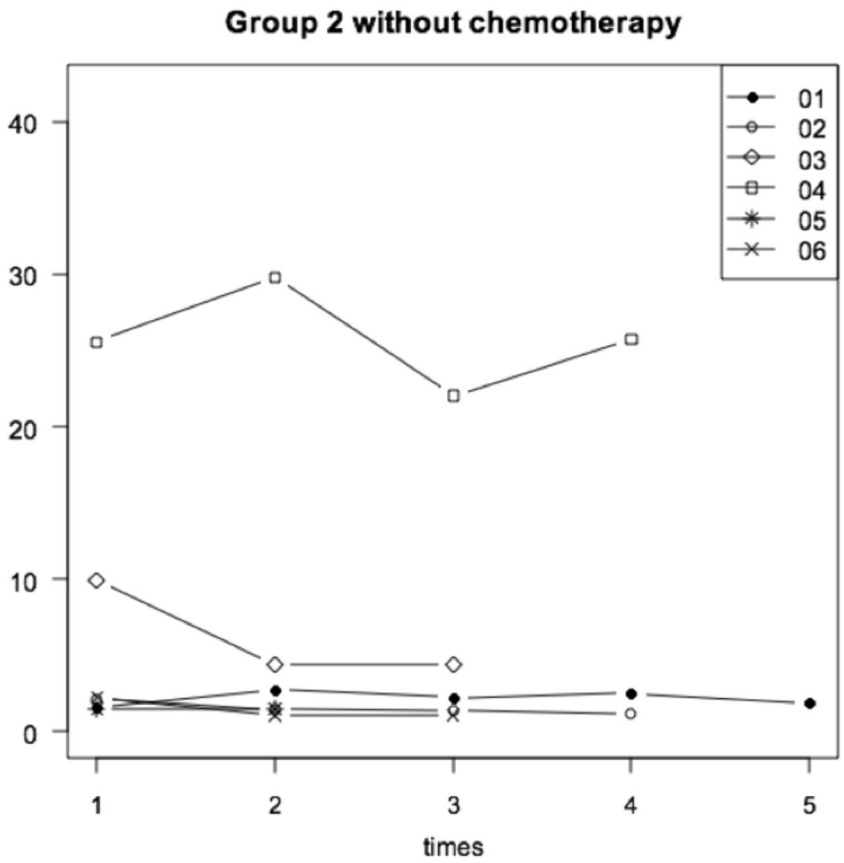

Fig. 7 Tumor volume changes in overall period for group 2

sequences, with variable enhancement after contrast administration. Sporadic OPG are more prone to depict cystic components or show gadolinium enhancement than what is observed in NF-1 gliomas and show higher proportion of tumors involving the chiasm and posterior optic pathway [5, 20, 28, 29].

On the other hand, bilateral optic nerve gliomas without chiasmal involvement are virtually diagnostic of NF-1.

Due to their erratic behavior, therapeutic management of OPG still is controversial. Currently, the most accepted recommendation is to start treatment in the presence of visual decline or radiological progression, with a trend to chemotherapy as first line [12, 17, 21, 23]. Despite being in force for over 20 years, some recent studies have questioned the effectiveness of chemotherapy in the treatment of OPG, especially in relation to the improvement of visual acuity, progression-free survival (PFS), and overall survival [22, 30, 31].

In their multicenter study, Fischer et al. [23] found only 34–38% of concordance for radiological and visual outcomes for NF-1 patients treated with chemotherapy, questioning the use of MRI response rates as the guiding information for treatment success for OPG.

In clinical routine, the most used methods for determining responses to treatment in brain tumors are the Macdonald and RANO criteria and less commonly the Response Criteria in Solid Tumors (RECIST). While Macdonald and RANO

Table 2 Data regarding epidemiology and radiological outcomes for group 2

Case	Sex	Age at diagnosis (years)	Surgery/year	Histopathology	Indications for treatment	Follow-up period (years)	NF-1	Overall radiological changes
1	m	7	pe, 1995/1999	jpa	Surveillance	2006–2014	No	Progression
2	m	7	na	na	Surveillance	2006–2015	Yes	mr
3	f	2	na	na	Surveillance	2011–2014	Yes	pr
4	f	11	Biopsy, 2012	Gangliogioma	Surveillance	2011–2014	No	Stable
5	m	11	na	na	Surveillance	2011–2015	Yes	Stable
6	f	6	pe, 1998	Gangliogioma	Surveillance	2001–2015	No	pr

m male, *f* female, *pe* partial excision, *jpa* juvenile pilocytic astrocytoma, *mr* minor response, *na* no available, *pr* partial response, *nf-1* neurofibromatosis

criteria incorporate two-dimensional (2D) measurements (measuring the longest single diameter and the longest diameter perpendicular to that), RECIST criteria evaluate tumor response based on measurement of the longest one-dimensional (1D) diameter [32]. These methods, although fast and easy to perform, are highly user dependent, with low accuracy and reproducibility, limiting the comparison between sequential studies.

On the other hand, 3D volumetric evaluation of lesions of the CNS intuitively seems to be a more accurate method to monitor the actual changes in tumor size, and has emerged as a promising tool in the evolution of the therapeutic response of these tumors, especially with respect to subtle changes in volume that may or may not impact on treatment. Among the available volumetric methods, the technique called Manual Region of Interest (ROI) is used for lesion contours segmentation manually carried out by radiologist experts, being considered as the gold standard of evaluation of these lesions [33].

Corroborating this claim, Dempsey et al. [34] compared tumor size of high-grade gliomas with patient survival using 1D, 2D, and 3D manual volumetric methods and found that only volumetric measurements were predictive of survival. They also found that 1D and 2D methods had a tendency to overestimate tumor size compared to 3D method. In another paper, Kanaly et al., [35] showed stronger agreement regarding radiological response with a semiautomated volumetric approach compared to traditional linear methods for 57 MRI of 13 GBM patients. Warren et al., [36] have found somewhat discordant results, with high concordance among 1D, 2D, and 3D methods in detecting partial response, but with lower concordance in classifying tumors in the minor response or tumor progression.

Despite the potential advantages of volumetric evaluation, this technique requires manual delineation of the edges of the lesion, which is technically challenging, tedious, expensive, and time consuming, precluding its use in clinical practice.

In order to approximate the volumetric in the radiological routine, several softwares are already available for automated and semiautomated analysis, aiming to reduce the processing time in relation to manual volumetric, with promising but still controversial results. Joe et al., [37] compared the reliability of two approaches to measuring brain tumor volume, using the standard manual tracing and a semiautomated computer method (threshold-based) and found that the tumor measurements were comparable in interoperator reliability for both methods, noting that the semiautomated method was faster. Chow et al., [38] found similar results comparing 1D, 2D and manual and semiautomated methods for measurements of postsurgical GBMs.

Although some studies have found promising results, it is worth noting that most of these were based exclusively on the enhancement area of the lesion in postcontrast T1 imaging, limiting its application in case of alterations in blood-brain barrier properties, gliomas under treatment with anti-angiogenic drugs, and also in the evaluation of low-grade gliomas, since most of these lesions have little or no contrast enhancement. Furthermore, the area of T2 signal abnormality in MRI usually indicates infiltrating tumor cells and/or edema and should be considered in response assessment. An important study was performed by Gallanis et al. [39] comparing 565 MRI of 67 gliomas with respect to tumor measurements in 1D, 2D, and 3D volumetric methods, using both T1 postcontrast and T2-weighted images. They found comparable results using 1D and 2D methods in determining time to response, duration of response, and time to progression both in T1 postcontrast and T2 images. Related to volumetric measurements, there was good agreement between volumetric and 1D and 2D methods for T1 postcontrast images, but with a weaker agreement for T2 images. They also found that using time to progression as the primary outcome, results may vary considerably depending on the imaging methodology, noticing a shorter time to progression of nonenhancing tumors when assessment is performed by 1D or 2D T2 images as compared to volumetric T2 images. This emphasizes significant methodological problems in relation to the evaluation of treatment response of nonenhancing tumors, and the need to prospectively validate imaging methods that can better predict their outcome.

In the only study available in our knowledge related to advanced volumetric techniques in patients with OPG treated with chemotherapy [30], a co-registration was performed between the T1- and T2-weighted sequences, which would allow a more accurate correlation between these sequences and borders of the lesion. In our study, the co-registration of sequences was not available, and it was decided to measure the lesion in the sequence with more precise delimitation of its borders (in a radiologist's opinion) and that same sequence was used for the follow-up images.

We believe from our own experience with the manual volumetric processing of these lesions and the data available in the literature to date that it is still not possible to standardize an MRI sequence or a specific method (1D, 2D, 3D) for OPG measurement. This is an interesting point, which can and should be better elucidated in future studies.

It is important to highlight the many limitations of our study. A lack of randomization is a bias for the majority OPG studies comparing the use of chemotherapy, radiotherapy, or clinical observation alone. The most accepted policy is to advise chemotherapy for very symptomatic patients or in cases of clinical worsening following the "watch and wait" approach. Asymptomatic children or with minor symptoms and stable lesions at brain MRI are treated with close clinical observation alone in most institutions, including ours. This was a retrospective study where treatment was based on these standard treatment indications. Our results regarding volumetric MRI findings for a non-randomized retrospective group

must be considered with caution in view of this possible confounding factor. Since this is a study focusing on the radiological aspects of OPG, we are also aware of the lack of uniformity between the MRI sequences used, as well as the lack of correlation of clinical and visual data, limiting tumor evaluation to radiological aspects.

In spite of being described for over 200 years, OPG are still challenging neoplasms, with controversial management. More accurate and reproducible radiological measurements can be valuable to evaluate treatment changes and to improve the correlation between visual and radiological outcomes, as well as help in defining the most appropriate therapeutic approach. This may be particularly important in the entering era of new targeted therapies to cancer, where radiological assessment is crucial to substantiate new treatment approaches.

Conclusion

Due to an unpredictable clinical course, optimal therapeutic management of OPG remains controversial. In our limited series, no significant differences were observed in relation to tumor volume changes for children treated or not with chemotherapy for OPG. Most lesions from both study groups remained stable or experienced minor partial responses during the follow-up, probably reflecting the indolent course of these lesions.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Shamji MF, Benoit BG (2007) Syndromic and sporadic pediatric optic pathway gliomas: review of clinical and histopathological differences and treatment implications. Neurosurg Focus 23:E3
2. Binning MJ, Liu JK, Kestle JR, Brockmeyer DL, Walker ML (2007) Optic pathway gliomas: a review. Neurosurg Focus 23:E2
3. Kornreich L et al (2001) Optic pathway glioma: correlation of imaging findings with the presence of neurofibromatosis. Am J Neuroradiol 22(10):1963–1969
4. Dutton JJ (1994) Gliomas of the anterior visual pathway. Surv Ophthalmol 38(5):427–452
5. Avery RA, Fisher MJ, Liu GT (2011) Optic pathway gliomas. J Neuroophthalmol 31(3):269–278
6. Danoff BF, Kramer S, Thompson N (1980) The radiotherapeutic management of optic nerve gliomas in children. Int J Radiat Oncol Biol Phys 6(1):45–50
7. Tao ML, Barnes PD, Billett AL, Leong T, Shrieve DC, Scott RM, Tarbell NJ (1997) Childhood optic chiasm gliomas: radiographic response following radiotherapy and long-term clinical outcome. Int J Radiat Oncol Biol Phys 39:579–587
8. Wisoff JH (1992) Management of optic pathway tumors of childhood. Neurosurg Clin N Am 3:791–802
9. Alvord EC Jr, Lofton S (1988) Gliomas of the optic nerve or chiasm. Outcome by patients' age, tumor site and treatment. J Neurosurg 68:85–98
10. Horwich A, Bloom HJG (1985) Optic gliomas: radiation therapy and prognosis. Int J Radiat Oncol Biol Phys 11:1067–1079
11. Jenkin D, Angyalfi S, Becker L et al (1993) Optic glioma in children: Surveillance, resection, or irradiation? Int J Radiat Oncol Biol Phys 25:215–225
12. Packer RJ et al (1997) Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive low-grade gliomas. J Neurosurg 86(5):747–754
13. Erkal HŞ, Serin M, Çakmak A (1997) Management of optic pathway and chiasmatic-hypothalamic gliomas in children with radiation therapy. Radiother Oncol 45(1):11–15
14. Packer RJ, Sutton LN, Bilaniuk LT, Radcliffe J, Rosenstock JG, Siegel KR, Bunin GR, Savino PJ, Bruce DA, Schut L (1988) Treatment of chiasmatic/hypothalamic gliomas of childhood with chemotherapy: an update. Ann Neurol 23:79–85
15. Grabenbauer GG et al (2000) Radiation therapy of optico–hypothalamic gliomas (OHG)–radiographic response, vision and late toxicity. Radiother Oncol 54(3):239–245
16. Grill J, Couanet D, Cappelli C, Habrand JL, Rodriguez D, Sainte-Rose C, Kalifa C (1999) Radiation-induced cerebral vasculopathy in children with neurofibromatosis and optic pathway glioma. Ann Neurol 45(3):393–396
17. Jahraus CD, Tarbell NJ (2006) Optic pathway gliomas. Pediatr Blood Cancer 46(5):586–596
18. Lafay-Cousin L, Holm S, Qaddoumi I, Nicolin G, Bartels U, Tabori U, Huang A, Bouffet E (2005) Weekly vinblastine in pediatric low-grade glioma patients with carboplatin allergic reaction. Cancer 103:2636–2642
19. Lancaster DL, Hoddes JA, Michalski A (2003) Tolerance of nitrosurea-based multiagent chemotherapy regime for low-grade pediatric gliomas. J Neuro-Oncol 63:289–294
20. Listernick R, Ferner RE, Liu GT, Gutmann DH (2007) Optic pathway gliomas in neurofibromatosis-1: controversies and recommendations. Ann Neurol 61:189–198
21. Grill J, Laithier V, Rodriguez D, Raquin MA, Pierre-Kahn A, Kalifa C (2000) When do children with optic pathway tumours need treatment? An oncological perspective in 106 patients treated in a single centre. Eur J Pediatr 159:692–696
22. Shofty B et al (2011) Visual outcome following chemotherapy for progressive optic pathway gliomas. Pediatr Blood Cancer 57(3): 481–485
23. Fisher MJ, et al. (2012) Visual outcomes in children with neurofibromatosis type 1–associated optic pathway glioma following chemotherapy: a multicenter retrospective analysis. Neuro-oncology nos076
24. Shofty B et al (2011) MRI internal segmentation of optic pathway gliomas: clinical implementation of a novel algorithm. Childs Nerv Syst 27(8):1265–1272
25. Taylor T, et al (2014) Radiological classification of optic pathway gliomas: experience of a modified functional classification system. Br J Radiol
26. Gnekow AK (1995) Recommendations of the brain tumor subcommittee for the reporting of trials. Med Pediatr Oncol 24(2):104–108
27. Opocher E et al (2006) Prognostic factors for progression of childhood optic pathway glioma: a systematic review. Eur J Cancer 42(12):1807–1816
28. Czyzyk E et al (2003) Optic pathway gliomas in children with and without neurofibromatosis 1. J Child Neurol 18(7):471–478
29. Chateil JF, Soussotte C, Pedespan JM, Brun M, Le Manh C, Diard F (2001) MRI and clinical differences between optic pathway tumours in children with and without neurofibromatosis. Br J Radiol 74:24–31

30. Shofty B et al (2015) The effect of chemotherapy on optic pathway gliomas and their sub-components: A volumetric MR analysis study. Pediatr Blood Cancer 62(8):1353–1359
31. Moreno L et al (2010) Does chemotherapy affect the visual outcome in children with optic pathway glioma? A systematic review of the evidence. Eur J Cancer 46(12):2253–2259
32. Gaonkar B, Macyszyn L, Bilello M, Sadaghiani MS, Akbari H, Attiah MA, Ali ZS, da X, Zhan Y, Rourke DO', Grady SM, Davatzikos C (2015) Automated tumor volumetry using computer-aided image segmentation. Acad Radiol 22(5):653–661
33. Clarke LP, Velthuizen RP, Clark M, Gaviria J, Hall L, Goldgof D, Murtagh R, Phuphanich S, Brem S (1998) MRI measurement of brain tumor response: comparison of visual metric and automatic segmentation. Magn Reson Imaging 16(3):271–279
34. Dempsey MF, Condon BR, Hadley DM (2005) Measurement of tumor "size" in recurrent malignant Glioma: 1D, 2D, or 3D? AJNR Am J Neuroradiol 26:770–776
35. Kanaly CW, Mehta AI, Ding D, Hoang JK, Kranz PG, Herndon JE II, Coan A, Crocker I, Waller AF, Friedman AH, Reardon DA, Sampson JH (2014) A novel, reproducible, and objective method for volumetric magnetic resonance imaging assessment of enhancing glioblastoma. J Neurosurg 121(3):536–542
36. Warren KE, Patronas N, Aikin AA, Albert PS, Balis FM (2001) Comparison of one-, two-, and three-dimensional measurements of childhood brain tumors. J Natl Cancer Inst 93(18):1401–1405
37. Joe BN, Fukui MB, Meltzer CC, Huang Q-s, Day RS, Greer PJ, Bozik ME (1999) Brain tumor volume measurement: comparison of manual and semiautomated methods. Radiology 212(3):811–816
38. Chow DS, Qi J, Guo X, Miloushev VZ, Iwamoto FM, Bruce JN, Lassman AB, Schwartz LH, Lignelli A, Zhao B, Filippi CG (2014) Semiautomated volumetric measurement on postcontrast MR imaging for analysis of recurrent and residual disease in glioblastoma multiforme. Am J Neuroradiol 35(3):498–503
39. Galanis E et al (2006) Validation of neuroradiologic response assessment in gliomas: measurement by RECIST, two-dimensional, computer-assisted tumor area, and computer-assisted tumor volume methods. Neuro-oncology 8(2):156–165