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Handheld Optical Coherence Tomography During Sedation in Young Children With Optic Pathway Gliomas

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IMPORTANCE Monitoring young children with optic pathway gliomas (OPGs) for visual deterioration can be difficult owing to age-related noncompliance. Optical coherence tomography (OCT) measures of retinal nerve fiber layer (RNFL) thickness have been proposed as a surrogate marker of vision but this technique is also limited by patient cooperation.

OBJECTIVE To determine whether measures of circumpapillary RNFL thickness, acquired with handheld OCT (HH-OCT) during sedation, can differentiate between young children with and without vision loss from OPGs.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional analysis of a prospective observational study was conducted at a tertiary-care children's hospital. Children with an OPG (sporadic or secondary to neurofibromatosis type 1) who were cooperative for visual acuity testing, but required sedation to complete magnetic resonance imaging, underwent HH-OCT imaging of the circumpapillary RNFL while sedated.

MAIN OUTCOMES AND MEASURES Area under the curve of the receiver operating characteristic, sensitivity, specificity, positive predictive value, and negative predictive value of the average and quadrant-specific RNFL thicknesses.

RESULTS Thirty-three children (64 eyes) met inclusion criteria (median age, 4.8 years; range, 1.8-12.6 years). In children with vision loss (abnormal visual acuity and/or visual field), RNFL thickness was decreased in all quadrants compared with the normal-vision group ($P < .001$ for all comparisons). Using abnormal criteria of less than 5% and less than 1%, the area under the curve was highest for the average RNFL thickness (0.96 and 0.97, respectively) compared with specific anatomic quadrants. The highest discrimination and predictive values were demonstrated for participants with 2 or more quadrants meeting less than 5% (sensitivity = 93.3; specificity = 97.9; positive predictive value = 93.3; and negative predictive value = 97.9) and less than 1% (sensitivity = 93.3; specificity = 100; positive predictive value = 100; and negative predictive value = 98.0) criteria.

CONCLUSIONS AND RELEVANCE Measures of RNFL thickness acquired with HH-OCT during sedation can differentiate between young children with and without vision loss from OPGs. For young children who do not cooperate with vision testing, HH-OCT measures may be a surrogate marker of vision. Longitudinal studies are needed to delineate the temporal relationship between RNFL decline and vision loss.

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Low-grade gliomas are the most common central nervous system tumor in children.[1] Low-grade gliomas that involve the pregeniculate afferent visual pathway are labeled as optic pathway gliomas (OPGs) and histologically are grade 1 pilocytic or, less commonly, grade 2 fibrillary astrocytomas. Optic pathway gliomas are intrinsic to the axons of the visual pathway and not amenable to surgical resection.[2] They are often sporadic but may arise in as many as 20% of children with neurofibromatosis type 1 (NF1), a multisystem genetic disorder occurring in approximately 1:4000 births.[3] Although children with OPGs have a low mortality rate, with a 5-year survivorship of greater than 75%,[1] they have frequent visual morbidity with permanent visual acuity (VA) loss ranging from mild (ie, 20/40) to complete blindness.[2,4]

The management of young children with OPGs can be complex. Vision loss takes place in many, but not all, of those with sporadic OPGs and in roughly half of children with NF1-related OPGs.[5] Therefore, in an attempt to avoid unnecessary chemotherapy, treatment of OPGs is often only initiated once new or progressive VA loss has been detected. Most OPGs cause VA and/or visual field (VF) loss between 1 and 8 years of age.[6] Accurately measuring VA/VF in these young children is highly dependent on their cooperation; this can be especially difficult in those with NF1 due to associated cognitive and behavioral problems.[7,8] Unfortunately, functional tests, such as visual evoked potentials,[9-13] or changes in imaging features (ie, tumor size or contrast enhancement) have no temporal relationship to VA/VF loss.[4,6,14] The inability to assess young children for visual deterioration puts them at greater risk to experience significant and permanent visual loss before treatment is initiated. To better guide therapy, a reliable quantitative biomarker of vision that does not rely on patient cooperation is needed in young children with OPGs.[6]

For more than a decade, the relationship between VF loss and circumpapillary retinal nerve fiber layer (RNFL) thickness, as measured by optical coherence tomography (OCT), has been firmly established in adults with glaucoma.[15-17] However, the mechanism of axonal degeneration causing RNFL thinning in glaucoma is clearly different from that implicated in OPGs.

Two studies have used time-domain OCT to examine circumpapillary RNFL thickness in older children with OPGs.[18,19] Most participants in both studies were older than 8 years of age, when NF1-related OPGs typically are no longer symptomatic. Even in some of these older children, accurate and reliable OCT acquisition could not be accomplished owing to poor cooperation.[19] Recently, a number of investigators have used a spectral-domain handheld OCT (HH-OCT; Bioptigen) device to image the retina and optic nerve of infants and young children with a variety of conditions.[20-25]

The aim of this study was to determine whether measures of circumpapillary RNFL thickness, acquired with HH-OCT during sedation, can differentiate between young children with and without vision loss from OPGs.

Methods

Patients

Children with OPGs and control participants were identified during their routine clinical visits to the neuro-ophthalmology or ophthalmology clinics at Children's National Medical Center. Written informed consent from the parent/guardian and written assent from the child, when applicable, were obtained before study enrollment. The study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board of the Children's National Medical Center. All data collected were Health Insurance Portability and Accountability Act compliant.

Patients with OPGs had to be diagnosed as having an NF1-related OPG using established National Institutes of Health criteria or biopsy-proven sporadic OPG. Patients with OPGs and control participants meeting the following inclusion criteria were enrolled: (1) ability to perform age-appropriate VA testing; (2) undergoing magnetic resonance image (MRI) under sedation as part of their routine clinical care; (3) absence of ophthalmologic or neurologic disease that could possibly affect optic nerve function or VA independently of OPG status (eg, history of suppression or pattern distortion amblyopia, glaucoma, elevated intracranial pressure, ventriculoperitoneal shunting, cataracts, or retinopathy of prematurity); and (4) willingness to receive mydriatic eye drops prior to MRI. Control participants received a comprehensive neuro-ophthalmologic examination, were required to have normal VA for age, and could forgo sedated MRI. Children with NF1 whose brain MRI exhibited a normal visual pathway (ie, no OPG) were included in the control group because their RNFL measures were not different than those of healthy control participants without NF1.[19]

All participants received a $10 gift card for their participation. Participants who were unable to cooperate with VA testing were not included in the study because we would not be able to assess the relationship between RNFL thickness and VA. Children with ophthalmologic or neurologic disease that could possibly affect optic nerve function or VA also were excluded to minimize the impact of non-OPG–related vision loss on RNFL. For instance, children with vision loss from amblyopia or optic atrophy secondary to hydrocephalus could confound our interpretation of the relationship between RNFL thickness and OPG-related vision loss.

Vision Testing

All participants underwent a complete ophthalmologic examination within 2 weeks before or after their MRI. Best-corrected VA testing was performed using age-appropriate methods (eg, Teller grating acuity cards using an established protocol[26] or recognition acuity testing with computer-based HOTV optotypes). Visual acuity loss was calculated using age-based norms and considered abnormal when the result was greater than or equal to 0.2 logMAR below normal for age. Children who were unable to reliably complete grating or recognition VA testing were not included in the analysis. Visual field testing was performed by confrontation or Goldmann kinetic

perimetry. When VF defects were reliably detected in any quadrant (ie, single or multiple quadrants), the participant's VF was defined as abnormal. Our participants' young age and frequency of associated behavioral problems prevented reliable completion of automated perimetry and thus limited our ability to quantify VF deficits; therefore, VF abnormalities were categorized as either present or absent.

Clinical Characteristics

Clinical characteristics were collected at study enrollment using a standardized form that included age, sex, race, ethnicity, diagnosis of NF1, history of chemotherapy, and location of OPG on MRI (determined by a pediatric neuroradiologist). The location of OPGs was classified as (1) absent; (2) isolated optic nerve; (3) optic chiasm with or without optic nerve involvement; or (4) optic tracts with or without involvement of the chiasm or optic nerves. Both patient eyes were classified as having OPG when the OPG was present in the optic chiasm and/or optic tracts. For participants with a unilateral optic nerve glioma, the unaffected contralateral optic nerve was classified as having no OPG. When available, both participant eyes contributed to the analysis because each eye can be affected differently by the OPG.

Image Acquisition With Handheld OCT

One hour before undergoing MRI, all participants received mydriatic eye drops (1% tropicamide and 2.5% phenylephrine hydrochloride). All participants with OPGs underwent sedation induction by inhaled nitrous oxide followed by inhaled sevoflurane. Once adequately sedated and intravenous access had been achieved, all children were given a continuous infusion of propofol to maintain sedation. No patient required mechanical ventilation using this sedation protocol. Once the propofol infusion began, HH-OCT imaging commenced using a high-resolution HH device acquiring 36 000 A-scans per second with a 3.5-µm tissue resolution and a 2.17-mm scan depth (Bioptigen). The operator was positioned at the head of the bed, and eyelids were moved away from the pupil by the operator's fingers. The HH-OCT was placed over the patient's eye and positioned until optimal image quality was achieved. The working distance between the HH-OCT probe and the cornea was based on the child's axial length and adjusted according to previous recommendations.[20] If the working distance was suboptimal, producing clipping or vignetting of images, the working distance could be adjusted manually during the imaging session by altering the reference arm length.[20] Movement of the HH-OCT probe was minimized by the operator gently bracing his or her hand on the patient's forehead. To optimize image quality, the horizontal and vertical B-scan images were displayed in real time and were adjusted to achieve optimal alignment to position the optic nerve head in the center of the acquisition. For children with refractive error, the focus of the HH-OCT bore was instantly adjusted while viewing the live horizontal and vertical B-scan images. Once correct alignment and focus were achieved, the imaging was initiated by pressing a foot pedal that acquired a 6 mm × 6 mm rectangular scan centered on the optic nerve head using 1000 A-scans across 100 B-scans. Each acquisition was completed in 3 seconds. Given the relatively small differences in axial length among our participants, the scan dimensions and acquisition parameters were not adjusted for individual patients. Owing to an evolving imaging protocol, 1 participant was imaged using a 6 mm × 6 mm 300 A-scans per 300 B-scans protocol. Once image acquisition was complete, a horizontal B-scan and an en face volume intensity projection image were displayed so the operator could assess the quality and alignment of the image. Poor image quality from decreased image signal, image clipping, increased speckle noise, and motion artifact were qualitatively assessed by the operator during the imaging session. If the image quality was unacceptable, the acquisition could be restarted using the foot pedal. In many cases, the entire imaging session of both optic nerves could be completed in less than 60 seconds. When the operator was unsure whether the image quality was sufficient, he or she acquired additional images, potentially extending the imaging session an additional 1 to 2 minutes.

Handheld OCT Analysis

Raw OCT data were exported and analyzed using custom-made software designed to measure circumpapillary RNFL thickness using a segmentation algorithm modified from a previously reported algorithm.[27] The optic nerve head margin was detected automatically or drawn manually if the automatic disc margin detection failed. A 3.45-mm circle was then placed over the geometric center of the optic nerve head. The RNFL thickness measurements were sampled from 1024 A-scans around the 3.45-mm circle. The 1024 samples were equally divided into 4 quadrants (ie, 256 samples per quadrant).

Statistical Analysis

Demographic and clinical characteristics were summarized by standard descriptive statistics (eg, means and standard deviations for continuous variables, such as age, and percentages for categorical variables such as sex). The Shapiro-Wilk test was used to determine the normality of the mean global RNFL thickness (microns). Between-group *t* tests were used to compare average and quadrant-specific RNFL thicknesses between participants with OPG with normal and abnormal vision, as well as between participants with OPG with normal vision and control participants.

Receiver operating characteristic analysis, sensitivity, specificity, positive predictive value, and negative predictive value were determined by comparing the participants with OPG with normal vision with those with abnormal vision. The criterion for abnormal RNFL thickness was determined as the lower fifth and first percentile in the normal-vision OPG group.

To examine the relationship between the magnitude of VA loss (logMAR) and RNFL thickness, while considering the influence of other clinical variables, we used a generalized estimating equation approach to variance estimation to account for the correlation between eyes of patients. This linear regression model determined the unadjusted and adjusted associations of RNFL thickness, age, diagnosis (NF1 or sporadic OPG), location of the OPG, and history of chemotherapy treat-

Table 1. RNFL Thickness Measures in Young Children With and Without Vision Loss

	Optic Pathway Gliomas, Mean (SD)		
	Normal Vision (n = 49)	Abnormal Vision (n = 15)	Control (n = 31)
RNFL thickness, mean (SD), μm			
Average	125.1 (13.9)	75.8 (16.8)[a]	128.1 (11.0)[b]
Superior	153.1 (22.1)	94.8 (18.6)[a]	153.2 (23.4)[b]
Nasal	104.3 (21.0)	68.3 (25.1)[a]	103.3 (14.6)[b]
Inferior	151.5 (20.3)	91.7 (29.3)[a]	150.8 (20.1)[b]
Temporal	98.6 (23.5)	48.4 (19.7)[a]	105.5 (14.0)[b]

Abbreviation: RNFL, retinal nerve fiber layer.

[a] $P < .001$ for comparison between patients with optic pathway glioma with and without vision loss.

[b] $P > .05$ for comparison between patients with optic pathway glioma with normal vision and control participants with normal vision.

Table 2. Discriminating Ability of Retinal Nerve Fiber Layer Thickness to Detect Vision Loss in Young Children With Optic Pathway Gliomas

Location	AUC	Sensitivity	Specificity	PPV	NPV
All quadrants					
<5%	0.96	93.3	81.6	60.8	97.5
<1%	0.97	93.3	95.9	87.5	97.9
Superior					
<5%	0.91	86.7	95.9	86.7	95.9
<1%	0.85	73.3	97.9	91.6	92.3
Nasal					
<5%	0.81	66.7	95.9	83.3	90.3
<1%	0.79	60	100	100	90.7
Inferior					
<5%	0.90	86.7	93.8	81.2	95.8
<1%	0.92	86.7	97.9	92.9	96.0
Temporal					
<5%	0.83	73.3	93.8	78.5	92.0
<1%	0.86	73.3	100	100	92.4

Abbreviations: AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value.

ment with VA (logMAR below normal for age). Data were analyzed using commercially available software (Stata version 11; StataCorp).

Results

Thirty-three children with OPGs (n = 25 NF1 related and n = 8 sporadic) were included for a total of 64 study eyes. Two patients contributed only 1 study eye owing to severe vision loss and optic atrophy in their contralateral eye with failure of image acquisition or segmentation. Participants were equally distributed across sex (n = 18 female) but were primarily white (n = 26) compared with Asian (n = 3) and African American (n = 3). The median age was 4.8 years (range, 1.8-12.6 years), with 28 of 33 children (84.8%) being 6 years of age and younger. Fifteen OPG participant eyes had abnormal vision; 1 eye had abnormal VA only, 7 eyes had abnormal VF only, and 7 eyes had both abnormal VA and VF. Forty-nine OPG participant eyes had normal VA and VF. Optic pathway gliomas were isolated to the optic nerve (n = 15 eyes), involved the optic chiasm (n = 25 eyes), or involved the optic tracts (n = 17 eyes). Fifteen participants received treatment with chemotherapy before or during the study. No participant experienced worsening of vision 3 months before or after their HH-OCT acquisition. Twenty control participants contributed 31 study eyes. Nine control participant eyes were not included owing to amblyopia of the contralateral eye, inadequate mydriasis resulting in failure of HH-OCT acquisition, or the inability to cooperate with testing. The median age among control participants was 8.7 years (range, 1.7-16.7 years) with 7 of 20 (35%) children being female.

Participants with OPG with normal vision demonstrated greater RNFL thickness measures in each of the 4 anatomic quadrants compared with those with vision loss ($P < .001$ for all comparisons, **Table 1**). There was no statistical difference in RNFL thickness between patients with OPG with normal vision and control participants ($P > .05$ for all comparisons, Table 1).

Table 2 lists the receiver operating characteristic and detection analysis for patients with OPG with 1 or more quadrants below the fifth or first percentiles. Analyzing the overall mean RNFL thickness yielded the highest area under the curve at both the fifth and first percentiles compared with individual quadrants. Using the inferior quadrant as the gold standard, there was no statistical difference in the area under the curve among the other 3 quadrants at both the less than 5% and less than 1% cutoff ($P > .05$). **Table 3** lists the sensitivity, specificity, positive predictive value, and negative predictive value using the criteria of 1 or more and 2 or more abnormal quadrants.

The linear regression model using the generalized estimating equation approach demonstrated that mean RNFL

Table 3. Detection of Patients With Abnormal Vision Based on the Number of Abnormal Quadrants

Criteria	Sensitivity	Specificity	PPV	NPV
≥1 Abnormal quadrant				
<5% cutoff	93.3	81.6	60.8	97.5
<1% cutoff	93.3	95.9	87.5	97.9
≥2 Abnormal quadrant				
<5% cutoff	93.3	97.9	93.3	97.9
<1% cutoff	93.3	100	100	98

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

Table 4. Unadjusted and Adjusted Analysis of Factors Associated With Visual Acuity in Patients With Optic Pathway Gliomas

Variable	Unadjusted Coefficient	Adjusted Coefficient	95% CI	*P* Value
Mean RNFL	−0.011[a]	−0.001	−0.013 to −0.008	<.001
Age	−0.022	−0.027	−0.059 to 0.005	.10
Diagnosis				
NF1	Reference	Reference		
Sporadic	0.505[a]	0.064	−0.027 to 0.156	.17
Glioma location				
Absent	Reference	Reference		
Optic nerve	0.126	0.053	−0.171 to 0.276	.64
Optic chiasm[b]	0.209	−0.160	−0.394 to 0.074	.18
Optic tracts[b]	0.228	−0.078	−0.316 to 0.160	.52
Treatment status				
No treatment	Reference	Reference		
Chemotherapy	0.284[a]	0.084	−0.083 to 0.252	.32

Abbreviations:
NF1, neurofibromatosis type 1;
RNFL, retinal nerve fiber layer.

[a] Denotes *P* < .01 in unadjusted analysis.

[b] Includes structures anterior to this location.

thickness, diagnosis of a sporadic OPG, and treatment with chemotherapy were significantly associated with VA in the unadjusted analysis (**Table 4**).[28] However, when accounting for these other variables in the adjusted multivariable analysis, only RNFL thickness remained significantly associated with VA.

Discussion

An accurate assessment of VA and VF is imperative when monitoring young children with OPGs because treatment decisions are based on identifying new or progressive vision loss. Unfortunately, many young children with OPGs have trouble completing quantitative VA and VF testing.[5,29] Our study demonstrates that HH-OCT measures of RNFL thickness can accurately differentiate between young children with and without vision loss secondary to OPGs. The area under the curve, sensitivity, specificity, and predictive values were greatest when examining the cumulative number of abnormal quadrants, although the superior and inferior quadrants performed well. The ability to discriminate between those with and without vision loss improved when using a criterion of 2 or more abnormal quadrants. The linear regression model also found a strong relationship between the magnitude of VA loss and decline in RNFL thickness, suggesting the latter holds the potential to be a surrogate marker of vision.

Using HH-OCT during sedation in this medically vulnerable patient population is beneficial for a number of reasons. It is likely that young children who cannot cooperate with VA testing are unable to cooperate with conventional OCT devices, whereas HH-OCT permits longitudinal acquisitions from infancy through adulthood. The portability and speed of HH-OCT obviate the need for additional sedation during clinically mandated procedures (eg, MRI). The ability to acquire high-resolution spectral-domain OCT in young children is particularly relevant to those with OPGs because most become symptomatic and are treated during early childhood.

The current study extended the findings of the prior time-domain OCT studies[13,14] in 2 important ways. First, most of the participants in the current study were younger than 6 years old—the age when most OPGs become symptomatic—compared with the time-domain OCT studies[13,14] whose participants with NF1 were enrolled well beyond an age when NF1-related OPGs become symptomatic. Next, by performing receiver operating characteristic and discrimination analyses, the clinical usefulness of HH-OCT is justified. The negative predictive values of greater than 97% confirm that those children with normal RNFL thickness indeed had normal vision. This finding is relevant to a child who cannot cooperate with VA testing but whose normal HH-OCT RNFL measures could provide reassurance that the vision is indeed normal.

The RNFL values in the current study using HH-OCT were greater in patients with OPG with vision loss when compared with our prior study using time-domain OCT.[14] In our study using HH-OCT, young children with normal vision had a higher average RNFL (mean = 125 µm) than older children imaged with time-domain OCT (mean = 101 µm). Additionally, those patients with isolated vision loss had an average RNFL thickness of 75 µm using HH-OCT compared with the older patients with the same type of vision loss whose time-domain

OCT RNFL thickness measures were approximately 65 µm.[14] There are multiple factors that could account for the discrepancy between RNFL thickness measures in these 2 studies. The HH-OCT is a much higher resolution device (3.5 µm) compared with the time-domain OCT (12 µm). In addition, each device uses a different computer software algorithm to segment the images and measure the RNFL. Lastly, the children in the previously published study underwent OCT imaging many years after their OPG caused vision loss.[14] If the RNFL thickness measures between devices were near equivalent, this discrepancy suggests that axonal degeneration could continue well beyond the time when OPGs are believed to be symptomatic (ie, after 8 years of age).

A number of important limitations should be considered when interpreting the data from our study. Although typical for this patient population, the percentage of participants with VA/VF loss was relatively low and likely weakened our statistical power despite our robust results. We used a cross-sectional design, thereby limiting our ability to establish a causal relationship between RNFL thickness and visual function. Ultimately, a multicenter longitudinal study is needed to determine the temporal relationship between a decline in RNFL thickness and vision loss. Next, we only enrolled individuals who were able to complete VA testing. Although those who were unable to complete VA testing may benefit most from HH-OCT, this inclusion criterion was necessary for the current study to establish the relationship between RNFL thickness and vision loss.

We imaged children across an age range over which axial lengths vary considerably, thereby influencing the HH-OCT sampling. Although we adhered to the recommendations of Maldonado et al[20] to adjust the reference arm and working distance based on patient age, there is a possibility that children with different axial lengths had different image sampling rates. We specifically chose the 6 mm × 6 mm image dimension for all patients to ensure the acquisitions, even when not exactly centered, would be sufficient to analyze the data from the 3.45-mm circle positioned around the optic nerve head. Given the paucity of data quantifying RNFL thickness in young children using HH-OCT, it is difficult to determine the magnitude that sampling difference may have had on our results. Fortunately, the difference in RNFL thickness between participants with normal and abnormal vision is quite robust, likely decreasing the influence of under or over sampling.

At this time, we do not recommend using HH-OCT measures of RNFL thickness to influence clinical care decisions in children with OPGs. For research purposes, acquiring these measures at the same frequency as their clinically indicated MRI will likely provide the most insight into the structure-function relationship between RNFL thickness and vision. If future research demonstrates that longitudinal changes in RNFL thickness are closely coupled to functional changes, it is conceivable that HH-OCT could reduce the need and/or frequency of MRIs. Performing HH-OCT instead of MRI would be beneficial in significantly reducing the length of sedation, visit duration, and total cost. Outside of the risks of sedation, repeated HH-OCT imaging sessions are safe and fall well within standard recommendations.[30,31] Despite the potential benefits of HH-OCT, it should never replace a thorough ophthalmologic examination by a clinician experienced in caring for children with OPGs.

Conclusions

In conclusion, this study demonstrated the ability of RNFL thickness measures, acquired with high-resolution HH-OCT in sedated children, to differentiate between young children with and without vision loss secondary to OPGs. The ability to acquire high-resolution spectral-domain OCT images using an HH device in sedated children ultimately may be helpful in young children who cannot cooperate with vision testing or traditional OCT imaging. Until longitudinal multicenter studies can better delineate the temporal relationship between RNFL decline and vision loss, OCT results should not be used to make clinical decisions. It is our hope that RNFL thickness eventually may serve as a reliable and objective surrogate marker of vision that may allow for early detection and treatment of young children with OPGs.

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Author Contributions: Dr Avery had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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