Original Article

The Impact of Eye Size in Retinoblastoma

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Background: The typical imaged findings of retinoblastoma are an intraocular tumor with intratumoral calcification. Normal eye size is a supported finding of retinoblastoma. In practice, more than just a few cases had an altered eye size.

Objective: To evaluate the effect of eye size in retinoblastoma.

Materials and Methods: The present study included 47 patients with 54 diseased eyes. Twenty-seven patients underwent enucleation with histopathological results. The axial lengths (AL) and equatorial diameters (ED) were measured in both diseased and normal eyes. The imaging characteristics, tumor volume, and histopathological findings were recorded and analyzed.

Results: The results showed no statistically significant differences between AL, ED, and calculated eye volumes (EV) between diseased and normal eyes. Anterior chamber depths were statistically shallower in retinoblastoma eyes ($p<0.001$). EV was weakly associated with tumor volumes. Large eye size was significantly related to choroidal invasion, massive choroidal invasion, scleral invasion, and optic nerve invasion in pathology ($p=0.04$, 0.03, 0.02, and 0.04, respectively).

Conclusion: There were no statistically significant differences of eye size parameters in the eyes with retinoblastoma when compared to the normal eyes. Large eye size and large tumor volume are significantly related to invasive histopathological results.

Keywords: Retinoblastoma, Intraocular tumor, Eye size, Tumor volume, Histopathology, Neoplasm invasion

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Retinoblastoma is the most common intraocular neoplasm in children with an incidence of one in 17,000 births[1,2]. Retinoblastoma typically presents in the first 2 to 3 years of life. With early diagnosis and prompt treatment, the cure rate can be as high as 95%[3].

Retinoblastoma is usually diagnosed by the clinical manifestation and fundoscopic findings. A diagnostic biopsy is contraindicated due to the risk of extraocular spread. In some cases, similar clinical manifestation and fundoscopic findings of other benign conditions such as persistent hyperplastic primary vitreous (PHPV), or Coats disease were found[4,5]. The treatments of these benign conditions are different from retinoblastoma, hence imaging plays an important role in diagnosis. Several imaging modalities are used to evaluate retinoblastoma such as ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI). MRI is the modality of choice in diagnosis, staging, and follow up for retinoblastoma. The typical imaging characteristics of retinoblastoma are an intraocular tumor, intratumoral calcification with normal eye size[2,6]. The diagnosis could be confirmed with histopathological results if surgery was performed. The histopathological risk factors include post-laminar optic nerve invasion, massive choroidal invasion, and an extraocular extension, which could predict the dissemination of the disease[1,7].

The eye size is an additional radiological finding, which supports the approach of the pediatric intraocular lesion. The eye size of retinoblastoma is accepted as normal size[8]. In contrast, PHPV usually

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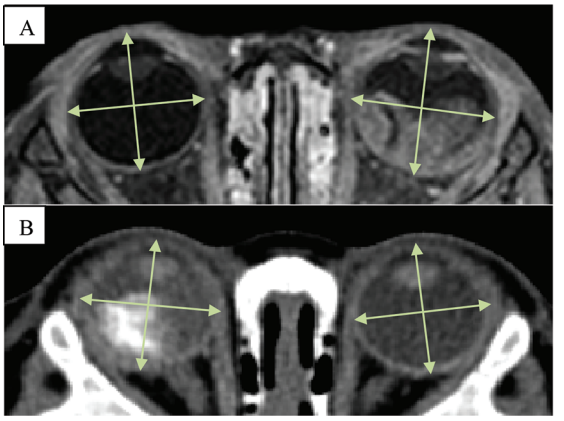

Figure 1. Axial contrast-enhanced T1-weight fat suppression MRI (A) and axial post-contrast phase CT image (B) showing left and right eyes in unilateral retinoblastoma. The vertical arrows represent AL which was defined as the distance through the visual axis from anterior corneal surface to posterior wall of the choroid. The horizontal arrows represent ED which was defined as maximum transverse distance between the temporal and nasal end of the choroid perpendicular to the AL.

has a smaller eye size and Coats disease has a normal or smaller eye size. Nevertheless, there were more than just a few cases with retinoblastoma who had an unequal size between the affected eye and normal eye seen in daily practice. Only a few studies mention eye size and its effect on retinoblastoma[4,5]. The objectives of the present study were to compare the eye sizes of retinoblastoma to normal eyes in axial length (AL), equatorial diameter (ED), calculated eye volume (EV) on CT or MRI, and to evaluate the effects of eye size in retinoblastoma.

Materials and Methods

Patient population

The present study was approved by the local institutional review board for ethical issues with a waiver of informed consent. Patients enrolled were diagnosed with retinoblastoma between January 2008 and August 2015 with pretreatment evaluation by CT or MRI of the orbits. Patients with inadequate imaging, coexisting intraocular infections, or congenital eye anomalies were excluded from the study.

Imaging protocols

CT scans were performed on 31 patients by either a 128-detector row helical scanner (Brilliance ICT-SP128, Phillips) or a dual source 64-detector row helical scanner (Somatom Definition Flash, Siemens) with axial, coronal, sagittal orbital plane reconstruction. Images were obtained with parameters as follows: 80 to 100 kVp, section thickness intervals of 1 to 3 mm, iodinated contrast 1 ml/kg, 40 to 50 seconds delayed scan after contrast injection. MRI was performed in 16 patients by either a 3T MR scanner (Phillips Achieva; Philips, Best, the Netherlands) or a 1.5T MR scanner (MAGNETOM Aera; Siemens, Erlangen, Germany). The routine protocol for orbit includes: axial and coronal pre-contrast T1-weighted imaging (T1WI), axial, coronal, sagittal oblique T2-weighted imaging (T2WI) with fat saturation, axial and sagittal T1WI fat-suppressed gradient echo sequences after administration of a gadolinium-based contrast agent (0.1 mmol/kg).

Measurement and imaging evaluation

The CT and MRI images were evaluated by two radiologists, one with 30 years' experience in pediatric imaging and the other with 2.5 years' experience in neuroradiology, who were both blinded to the clinical data and histopathological findings. The eye size parameters were measured by a third-year resident and a radiologist. All collected data were recorded independently. Any discordance was solved by consensus. The eye size parameters in the present study included AL, ED, and calculated EV. The AL and ED were evaluated in post-contrast CT images or post-contrast T1-weighted fat suppression MRIs on axial orbital planes. The AL was defined as the distance from the anterior corneal surface to posterior wall of the choroid in the axial view at the level of the lens, and it included the anterior chamber depth, lens thickness, and vitreous length (Figure 1). The ED was determined as the maximum transverse distance between the temporal and nasal end of the choroid in the axial view which was perpendicular to the AL. Each observer measured each AL and ED of affected eyes and normal eyes three times. The EV is calculated from means of the AL and ED by the following formula[9]: $[((AL+ED)/2)/2]^3 \times (4/3\pi)$. The EV is then converted from mm^3 to cm^3. Anterior chamber depth was defined as the distance from posterior vertex of the cornea to the anterior surface of lens along visual axis. All eyes with unilateral retinoblastoma were categorized into three groups, including small, normal, and large eye sizes in comparison to the patient's contralateral normal eye. Small eye size was defined as an eye with both AL and ED less than 1SD below the mean of their normal eye, large eye size was defined as an eye having both AL and ED more than 1SD, and normal eye size was defined an eye that did not meet the criteria of

Table 1. Ocular size parameters (n=47)

	Normal eye (n=40)	Affected eye (n=54)	p-value
AL (mm)			0.47
Mean±SD	23.76±1.42	23.64±1.77	
Range	20.40 to 28.24	20.39 to 27.87	
ED (mm)			0.60
Mean±SD	23.93±1.44	23.67±1.69	
Range	20.23 to 27.09	20.70 to 27.32	
EV (cm^3)			0.42
Mean±SD	7.17±1.25	7.03±1.52	
Range	4.39 to 11.09	4.54 to 10.89	
Anterior chamber depth			<0.001*
Mean±SD	2.32±0.44	1.89±0.60	
Range	1.18 to 3.25	0.9 to 3.3	

AL=axial length; ED=equatorial diameter; EV=eye volume; SD=standard deviation

* Significant difference between normal and affected eyes

either small or large eye size. Different size groups were compared, regarding imaging characteristics and histopathological results, to find the effect of eye size in retinoblastoma. Tumor volume (cm^3) was calculated by multiplication of summation of regions of interest (ROIs) drawn around the tumor and slice thickness. For CT scan, ROIs were drawn on post-contrast image. For MRI, ROIs were drawn on T2-weighted image and intersection gap was also added in volume calculation. Tumor volume was categorized into less than 1.5 cm^3, or more than or equal to 1.5 cm^3.

Imaging characteristics including the presence or absence of calcification, anterior chamber enhancement, and optic nerve abutment, pattern of enhancement, location of the tumor, and tumor growth pattern were recorded by the senior radiologist. Pattern of enhancement was classified as none, homogeneous, and heterogeneous. Tumor locations were anterior chamber, posterior chamber, or combined. Tumor growth pattern was classified as endophytic, exophytic, infiltrative, or combined[10].

Histopathological interpretation

Twenty-seven patients underwent enucleation and had available histological slides or specimens. All of the histopathological findings were reviewed by a pathologist with more than 20 years' experience, who was blinded to the clinical data, imaging findings, and previous pathological reports. All pathology reports included the presence or absence of vitreous seeding, choroidal invasion, scleral invasion, optic nerve invasion, anterior chamber invasion, and extraocular extension. Massive choroidal invasion was defined as choroidal invasion more than 3 mm in depth.

Statistical analysis

All data were analyzed with the Stata, version 10 (StataCorp LP, College Station, TX, USA). The inter-observer agreement of AL and ED measurements was assessed by the interclass correlation coefficient (ICC). Demographic data, imaging, and pathological findings of the tumor were interpreted by descriptive analysis and were compared by using Fisher's exact or chi-square test. The continuous variables of ocular parameters were reported as mean and standard deviation. The mixed-effect regression model was used to compare ocular parameters of the eyes with retinoblastoma and the normal eyes when the sex and age of patients were adjusted. The eye size parameters of unilateral retinoblastomas were also compared with their normal eyes by using a paired t-test. Pearson's correlation was used to find the relationship between EV and tumor volume coefficients. The p-values of less than 0.05 indicated statistical significance of all statistic tests, and 95% confidence intervals (CIs) were analyzed by the logistic regression model.

Results

Forty-seven patients with fifty-four retinoblastomas were included. There were seven patients with bilateral retinoblastoma. Of these, 28 (59.6%) patients were boys and nineteen (40.4%) were girls. The mean age was 26.4 (±18) months (2.8 to 68.1 months). Right eyes were affected in 23 patients (42.6%) and left eyes in 31 patients (57.4%). Thirty-one patients (66%) underwent preoperative CT scan while sixteen (34%) had preoperative MRI. For imaging characteristics, 52 retinoblastomas (96.3%) showed intratumoral calcification. Eleven retinoblastomas (21.2%) demonstrated no enhancement, seven retinoblastomas (13.5%) were homogeneously enhanced, and 34 retinoblastomas (65.3%) were heterogeneously enhanced. Two retinoblastomas did not have post contrast image. All retinoblastomas were located within the posterior chamber. Fifty retinoblastomas (92.6%) had optic nerve head abutment. For growth pattern, forty-seven retinoblastomas (87%) were endophytic, four (7.4%) were exophytic, three (3.6%) were combined, and none was infiltrative.

The results showed no statistically significant

Table 2. Imaging characteristics of unilateral retinoblastoma classified with eye size group

Eye size	Large (n=6) n (%)	Normal (n=32) n (%)	Small (n=2) n (%)	p-value
Sex				0.05
Male	6 (100)	17 (53.1)	2 (100)	
Female	0 (0.0)	15 (46.9)	0 (0.0)	
Age (months); mean±SD	29.7 (13.3)	31.5 (18.6)	50.8 (24.5)	0.80
Affected eye side				0.69
Right	2 (33.3)	14 (43.8)	0 (0.0)	
Left	4 (66.7)	18 (56.3)	2 (100)	
Calcification	6 (100)	32 (100)	1 (50.0)	0.05
Enhancement pattern				0.68
None	2 (33.3)	7 (23.3)	0 (0.0)	
Homogeneous	0 (0.0)	7 (23.3)	0 (0.0)	
Heterogeneous	4 (66.7)	16 (53.4)	2 (100)	
Anterior chamber enhancement	1 (16.7)	0 (0.0)	0 (0.0)	0.20
Optic nerve contact by the tumor	6 (100)	31 (96.9)	2 (100)	1.00
Growth pattern				0.50
Endophytic	5 (83.3)	28 (87.5)	2 (100)	
Exophytic	0 (0.0)	3 (9.4)	0 (0.0)	
Combined	1 (16.7)	1 (3.1)	0 (0.0)	
Infiltrative	0 (0.0)	0 (0.0)	0 (0.0)	

SD=standard deviation

differences of AL, ED, and calculated EV between the eyes with retinoblastoma compared to the normal eyes (Table 1). These eye size parameters of unilateral retinoblastoma were analyzed separately by the paired t-test compared to their normal eyes. The results also showed no statistical differences in all eye size parameters. The anterior chamber depth was significantly shallower in the eyes with retinoblastoma ($p<0.001$). Between the two observers, the ICC of AL and ED measurements were 0.958 (95% CI 0.936, 0.973) and 0.902 (95% CI 0.818, 0.944), which indicated a strong agreement.

The unilateral retinoblastoma patients were divided into three groups as small (two retinoblastomas, 5%), normal (32 retinoblastomas, 80%), and large (six retinoblastomas, 15%) eye size groups. There were no statistically significant differences of imaging characteristics among these three size groups (Table 2). Twenty-seven patients with unilateral retinoblastoma underwent enucleation. None of the bilateral retinoblastomas underwent surgery. The mean duration from the day of imaging and the day of enucleation was 21.78 days, a range of 1 to 100 days. Of the 27 patients with unilateral retinoblastoma that underwent enucleation, seven were in the large eye size group and 23 were in the normal group. Several significant pathologic findings including choroidal invasion, massive choroidal invasion, scleral invasion, and optic nerve invasion were found to be related to the large eye size ($p=0.04$, 0.03, 0.02, and 0.04, respectively). Tumor volume was significantly related to vitreous seeding, choroidal invasion, and massive choroidal invasion ($p=0.03$, 0.03, and 0.03, respectively) (Figure 2, Table 3). Pearson's correlation coefficient of the linear relationship of EV (mm^3) and tumor volume (mm^3) was 0.378, which indicated a weak positive association (Figure 3).

Discussion

An accurate imaging diagnosis of retinoblastoma is essential because this tumor should not be biopsied, and treatment is different from other benign pediatric ocular lesions. Eye size is one of the parameters that could help the radiologist differentiate retinoblastoma from other conditions. Retinoblastoma is considered to have a normal eye size[2,5]. In the present study, there were no statistically significant differences of all eye size parameters (AL, ED, and EV) between the eyes

Table 3. Histopathological results of unilateral retinoblastoma classified with eye size and tumor volume

	Eye size; n (%)		p-value	Tumor volume; n (%)		p-value
	Normal	Large		<1.5 cm^3	≥1.5 cm^3	
Vitreous seeding	20 (87.0)	4 (100)	0.444	8 (72.7)	16 (100)	0.027**
Choroidal invasion	10 (43.5)	4 (100)	0.037*	3 (27.3)	11 (68.8)	0.034**
Massive choroidal invasion	8 (34.8)	3 (100)	0.032*	2 (18.2)	9 (60.0)	0.033**
Scleral invasion	0 (0.0)	1 (25.0)	0.015*	0 (0.0)	1 (6.3)	0.398
Optic nerve invasion	10 (43.5)	4 (100)	0.037*	4 (36.4)	10 (62.5)	0.182
Postlaminar optic nerve invasion	3 (13.0)	2 (50.0)	0.079	3 (27.3)	2 (12.5)	0.332
Anterior chamber invasion	5 (21.7)	0 (0.0)	0.302	2 (18.2)	3 (18.8)	0.970
Extraocular extension	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA

NA=not applicable

* Statistically significant for chi-square test comparing between large and normal eye size

** Statistically significant for chi-square test comparing between tumor size

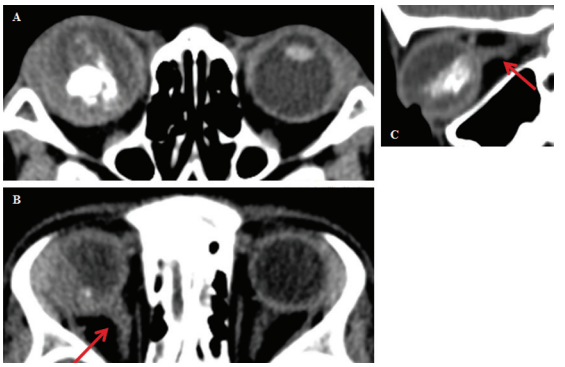

Figure 2. Post-contrast CT scans in axial (A, B) and sagittal (C) planes show enlarged right eye globe with intraocular calcified tumor. Enlarged size with enhanced right optic nerve (arrow) is noted with pathological-finding proven retinoblastoma with massive choroidal and post-laminar optic nerve invasion.

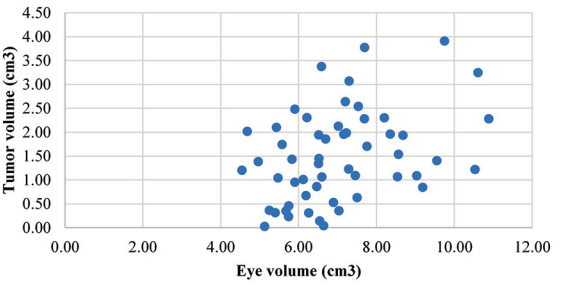

Figure 3. The scatter-plot graph shows correlation of EV (cm^3) and tumor volume (cm^3). The Pearson's correlation coefficient was 0.378 indicating a weak positive association.

with retinoblastoma and the normal eyes. These results were in the same direction with previous studies and hypotheses[8,11]. On the other hand, de Graaf et al retrospectively reviewed eye sizes of retinoblastomas and found a significantly smaller size as reported in their study[12]. The different measurement methods may be the cause of inconsistent results. In the current study, choroid thickness was included in the measurement. The effects of the choroid and scleral thickness in retinoblastoma should be further studied.

The anterior chamber depth in the present study was significantly shallower in retinoblastoma ($p<0.001$), which could be explained by an effect of increased intraocular pressure due to the presence of the intraocular mass. The relationship between anterior chamber findings and prognosis or disease extension of retinoblastoma was stated in previous studies[13-15]. The present study is one of the first study that reported a significant finding of the anterior chamber depth in the role of diagnosis of the disease. A study comparing anterior chamber depths of other pediatric ocular disorders such as PHPV, or Coats disease would be of benefit in the future.

Large eye size was significantly related to several invasive pathology including massive and non-massive choroidal invasion, scleral invasion, and optic nerve invasion ($p=0.03$, 0.04, 0.02, and 0.04, respectively). The EV and the tumor volumes showed a weak positive association. Still, the authors found that larger tumor volume (larger than 1.5 cm^3) was significantly related to vitreous seeding, choroidal invasion, and massive choroidal invasion ($p=0.03$, 0.03, and 0.03, respectively). Several studies reported that large tumor size or volume is related to invasive pathology[16-19]. To the best of the authors' knowledge, no previous study has reported the relationship between affected eye size and the invasiveness in

pathology. Clinical data such as increased intraocular pressure or the presence of secondary from glaucoma, which are known to relate to retinoblastoma, can also be a potential cause of increase eye size, but those data were not included in the present study[20,21]. The affected eye size can be assessed easily with excellent agreement. The authors believe that this simple parameter can be helpful in pre-operative evaluation.

There were some limitations of the present study. First, it was a retrospective study. Second, to collect larger populations, the cases with both CT or MRI in which CT might not evaluate eye structure as accurately as MRI were included. Third, the numbers of bilateral retinoblastoma cases in the present study were small, so further research of eye size of bilateral retinoblastoma compared to normal eyes in a standard population and unilateral retinoblastoma is recommended. Finally, the numbers of histopathologically proven cases of unilateral retinoblastoma were relatively small. Even though, the authors found significant relationship between the eye size and the pathology, multicenter collaboration should be pursued for larger population. The collaboration would be feasible because most centers would have preoperative imaging, with either CT or MRI, and histopathological result as their routine practice in retinoblastomas.

Conclusion

There were no statistically significant differences of eye size parameters in the eyes with retinoblastoma compared to the normal eyes. Anterior chamber depths were significantly shallower in the affected eyes. Retinoblastomas with large eye size significantly related to choroidal, scleral, and optic nerve invasion in pathology.

What is already known on this topic?

The eye size is an additional radiological finding that supports the diagnosis of retinoblastoma in pediatric intraocular lesions and it is accepted as normal size. Nevertheless, there were more than just a few patients with retinoblastoma who had an unequal size between the affected eye and normal eye, as seen in daily practice.

What this study adds?

Overall, there is no significant difference in eye size between retinoblastoma and the normal eye. Fifteen percent of retinoblastoma in this study have large eye size, which significantly related to several invasive pathology including massive and non-massive choroidal invasion, scleral invasion, and optic nerve invasion. This finding may lead to different treatment approach in the future.

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Ethical approval and consent to participate

All procedures performed in the report involving human participants were in accordance with the ethical standards of the institutional or the national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of report, formal consent is not required.

Informed consent was not obtained. Office of The Khon Kaen University Ethics Committee in human research KKU EC approved the present study with trial number "HE581427".

Authors' contributions

Prasertcharoensuk S contributed to the conception or design of the work, and analysis. Srinakarin J contributed to the conception or design of the work and final approval. Boonrod A ensured that the study received all necessary IRB approvals, and contributed to the conception or design of the work, revising it critically for important intellectual content and final approval. Koonmee S contributed to the conception or design of the work. Wongwai P contributed to the conception or design of the work.

Conflicts of interest

The authors declare that they have no conflict of interest.

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