• Clinical Research •

Clinicopathological analysis of 719 pediatric and adolescents' ocular tumors and tumor-like lesions: a retrospective study from 2000 to 2018 in China

Xi-Zhe Dai[1], Lin-Yan Wang[1], Yi Shan[1], Jiang Qian[2], Kang Xue[2], Juan Ye[1]

[1]Department of Ophthalmology, the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310009, Zhejiang Province, China
[2]Department of Ophthalmology, Eye & ENT Hospital of Fudan University, Shanghai 200031, China
Correspondence to: Juan Ye. Department of Ophthalmology, the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310009, Zhejiang Province, China. yejuan@zju.edu.cn
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Abstract

● **AIM:** To describe the clinicopathologic features and classification of pediatric and adolescent ocular tumors and tumor-like lesions

● **METHODS:** A total of 719 cases of pathologically confirmed ocular tumors and tumor-like lesions in a pediatric population from two academic institutions over an 18-year period were retrospectively analyzed. The main outcome measures were the clinical and pathological features of the cases.

● **RESULTS:** Benign tumors accounted for 92.1% of all cases while malignant tumors accounted for 7.9%. The most common ocular benign tumors were (epi-)dermoid cysts (19.8%), nevi (15.2%), corneal dermoid tumors (9.8%), and calcified epitheliomas (8.8%). The most common ocular malignant tumors were retinoblastoma (80.8%), and rhabdomyosarcoma (3.9%). Eyelid and ocular surface tumors comprised 73.3% of benign tumors while intraocular and orbital cavity comprised 94.2% of malignant tumors. For tumor site, the upper eyelid was up to 1.79 times more than lower eyelid (P<0.05). Age at surgery and sex also had an association with different lesions (P=0.006, P=0.035, respectively).

● **CONCLUSION:** Most ocular tumors and tumor-like lesions in children and adolescents are benign. Pediatric ocular tumors are distinct from those in adults in terms of histological origin. (Epi-)dermoid cysts are the most common benign tumors while retinoblastomas the most common malignant tumors.

● **KEYWORDS:** ocular tumors; dermoid cyst; retinoblastoma; rhabdomyosarcoma; children
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INTRODUCTION

A variety of tumors can occur in the ocular area due to the complexity of the embryogenic origins. The eyeball and orbit develop from different germinal layers[1]. Compared with adults, orbital tumors are relatively rare among children and adolescents, but the diversity and variety do not decrease greatly.

Most tumors affecting children and adolescents are benign. Malignancies such as retinoblastoma (RB) and rhabdomyosarcoma, however, can be both life and vision threatening[2-4]. For benign tumors, because of the overlapping features like dilatational orbital mass or exophthalmos and the inconspicuous signs at the early stages, there is difficulty with differential diagnosis in clinics[5]. For malignant ocular tumors, any misdiagnosis or missed diagnosis could potentially be detrimental to a patient's vision as well as life. Thus, understanding the clinicopathological characteristics of these lesions in children would be beneficial to visual and/or life preservation.

Children have their own specificities in both clinical and socioeconomic aspects[5-7]. Relatively speaking, young people have poorer communication with doctors, either due to the linguistic immaturity or their fears of doctors. It might cause many important symptoms and signs cannot be effectively detected by doctors, which could then interfere with their judgments. Furthermore, the global burden of eye tumor disease also imposes greater economic costs on society[8].

The purpose of our study is to make a detailed and large-scale clinicopathological analysis of ocular tumors among children and adolescents in east China.

Table 1 Characteristics of study population

Parameters	Male		Female		Total		
	n (%)	Age (y)	*n* (%)	Age (y)	*n* (%)	Age (y)	Ratio (M/F)
Benign	298 (45.2)	13.43±4.84	309 (46.9)	12.19±4.89	607 (92.1)	12.91±4.88	0.96:1
Malignant	33 (5.0)	10.73±5.1	19 (2.9)	15.29±3.53	52 (7.9)	12.96±4.65	1.74:1
Total	331 (50.2)	13.23±4.91	328 (49.8)	12.32±4.88	659 (100)	12.91±4.86	1.01:1

Table 2 Age distribution of all tumors *n* (%)

Parameters	0-5y	6-10y	11-15y	16-20y	Total
Benign	57 (9.4)	134 (22.1)	200 (32.9)	216 (35.6)	607 (100)
Malignant	4 (7.7)	13 (25.0)	16 (30.8)	19 (36.5)	52 (100)
Total	61 (9.3)	147 (22.3)	216 (32.8)	235 (35.7)	659 (100)

SUBJECTS AND METHODS

Ethical Approval Ethical approval for the study was obtained and the study adhered to the declaration of Helsinki. Informed consent was waived due to the retrospective nature of the study.

The medical records of all patients (<20 years old) with eye neoplasms or lesions at Department of Ophthalmology, the Second Affiliated Hospital, Zhejiang University School of Medicine (ZJU) from January 2000 to December 2018 were retrospectively reviewed by three board-certificated pathologists using the 4th edition of the World Health Organization Classification of Tumors of the Eye. When there was dissent between three pathologists, department discussion or remote diagnosis from the University of California Los Angeles Medical Center (UCLA) was taken to ensure accuracy. Patients who had one of the following were excluded: eyeball atrophy caused by trauma or congenital factor, and those who did not have a clear diagnosis. A total of 659 cases from ZJU were included in this study.

Considering the referral system of malignant tumors, retinoblastoma patients were recommended to the Eye and ENT Hospital of Fudan University (FU) for salvage treatment. The records of 60 patients with retinoblastoma were displayed as an independent cohort from 2017 to 2018.

Following ocular tissue excision biopsy or eyeball removal, all specimens were fixed at 4% paraformaldehyde solution, embedded in paraffin and then stained with Hematoxylin and Eosin. When necessary, immunohistochemical staining and another special staining was used. Data analyzed included age at diagnosis, sex of patient, location and size of the tumor, preoperative diagnosis, and clinical description of the tumor. Each patient was independently reviewed by at least three pathologists.

Statistical Analysis Statistical analysis was performed using SPSS 23.0 Statistical Software (SPSS Inc., Chicago 2015, USA). Continuous variables were reported as the mean±standard deviation (SD). The Chi-square test was used for analysis. A *P*-value<0.05 was considered statistically significant.

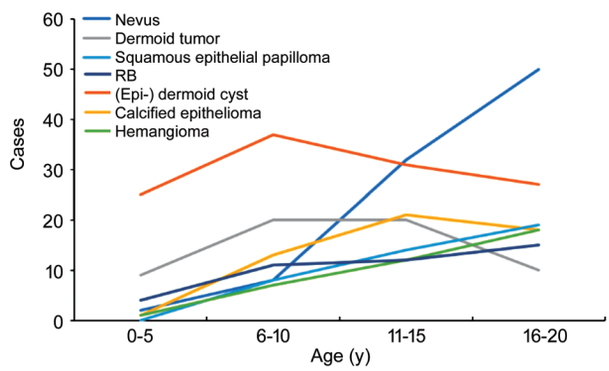

Figure 1 Age distribution of common ocular tumors.

RESULTS

A total of 659 cases were included in the Eye Center of the Second Affiliated Hospital of ZJU (Table 1). Of these tumors, benign lesions accounted for 92.1%. Of the patients, 331 were males and 328 were females, and the male-to-female ratio was 0.96:1 (298/309) for benign tumors, and 1.74:1 (33/19) for malignant tumors. There is a weak association between properties of the tumor and sex of the patient (*P*=0.047). The overall mean age of patients at diagnosis was 12.91±4.86y; 12.91±4.88 and 12.96±4.65y in the benign and malignant groups respectively.

All collected cases were divided into four groups according to age with an interval of five years (Table 2). In both benign and malignant tumors, patients over 10y accounted for nearly 67% of cases.

The top six benign tumors and the top malignant tumors are listed in the Figure 1. These are nevus, (epi-)dermoid cyst, dermoid tumor, calcified epithelioma, squamous epithelial papilloma and hemangioma for benign tumors, and retinoblastoma for malignant. As the age group increases, there are similar increasing trends in squamous epithelial papilloma, hemangioma and retinoblastoma. Pigmented nevus increased significantly in the 11-15 and 16-20 age groups. The other tumor subtypes, (epi-)dermoid cyst (37 cases) and dermoid tumor (20 cases) both peaked in the 6-10 age group then went down quickly, while the number of calcified epithelioma continuous to grow in the first three groups and fell in the last.

All cases were divided into four anatomical categories: eyelid, ocular surface, orbital cavity and intraocular (Table 3). Regarding the 607 cases of benign tumors, the eyelid was the most frequently occurring site (*n*=265, 43.7%) followed by the ocular surface (*n*=177, 29.2%), orbital cavity (*n*=151, 24.9%), and finally the intraocular site (*n*=14, 2.3%). Of the malignant tumors, 44 (84.6%) were intraocular tumors, 5 (9.6%) were orbital tumors, 2 (3.9%) were ocular surface tumors and 1 (1.9%) was an eyelid tumor. In eyelid tumors, the upper eyelid was affected significantly up to 1.79 times more often than lower the eyelid. However, no difference was observed in ocular surface or orbital cavity (*P*=0.826) for laterality. A higher proportion of females presented with orbital tumors while intraocular tumors were more prevalent among males.

Table 4 shows the frequency of clinicopathological subtypes and demographic statistics (age, sex ratio) of patients, and the anatomical position of the benign tumors are more specifically described. Among benign tumors, nevus (*n*=48, 18.1%), calcified epithelioma (*n*=41, 15.5%), squamous papilloma (*n*=25, 9.4%), (epi-)dermoid cyst (*n*=25, 9.4%) and hemangioma (*n*=19, 7.2%) are the most frequent and accounted together for 59.6% of all eyelid cases. In benign ocular surface tumors prevalence is different: dermoid tumor (*n*=57, 32.2%), nevus (*n*=43, 24.3%) and hemangioma (*n*=16, 9.0%) form two thirds of total ocular surface tumors. There are 90 (59.6%) (epi-)dermoid cysts in the orbit and 12 (8.0%) of both calcified epithelioma and hemangioma. Only six cases of benign intraocular tumors: two iris cysts, one hemangioma, two posterior scleral staphyloma and one inflammation. The malignant tumors constituent ratio has retinoblastoma as the highest (*n*=42, 80.8%), followed by rhabdomyosarcoma (*n*=2, 3.9%). The remaining eight subtypes (melanoma, meibomian adenocarcinoma, schwannoma, optic neuroblastoma, meningioma, T-lymphoblastic lymphoma, marginal zone lymphoma of mucosa-associated lymphoid tissue, primary acquired melanosis of the conjunctiva) have one case each. Focusing on the whole eye, Table 4 also indicated the most common ocular benign tumors were (epi-)dermoid cysts (19.8%), nevi (15.2%), corneal dermoid tumors (9.8%), and calcified epitheliomas (8.8%).

Dermoid tumors and (epi-)dermoid cysts located in orbital were more prevalent in younger age groups, the mean age of each is 10.42±4.61 and 9.42±4.67y respectively. The mean age for nevus is 15.77±4.25y (eyelid) and 14.98±3.54y (ocular surface), 14.16±4.28y (eyelid) and 13.5±3.73y (orbital) for calcified epithelioma, and 15.48±3.30y (eyelid) and 13.63±4.46y (ocular surface) for squamous papilloma.

The male-to-female ratio for calcified epithelioma (0.52:1) and squamous papilloma (0.45:1) show females account for more cases than males. For hemangioma (2.17:1), retinoblastoma (1.63:1) the male-to-female ratio showed predominance of males. There is a significant association between tumors and sites (*P*<0.001) and statistical analysis showed age at surgery and sex had an association with different lesions (*P*=0.006, 0.035, respectively).

Table 5 shows the different histological origin compositions of benign tumors, malignant tumors in ZJU. For benign lesions, the most common origin is cystic (*n*=149, 24.5%), followed by epidermal (*n*=117, 19.3%), melanocytic (*n*=92, 15.2%), skin

Table 3 Anatomical classification of benign and malignant ocular tumors

Classification	Benign	Malignant	Total
Eyelid, *n* (%)	265 (43.7)	1 (1.9)	266 (40.4)
Male/female	139/126	0/1	139/127
Laterality (right/left/bilateral)	147/114/1	0/1/0	147/115/1
Location (up/low/bilateral)	135/75/55	1/0/0	136/75/55
Ocular surface, *n* (%)	177 (29.2)	2 (3.9)	179 (27.2)
Male/female	87/90	1/1	88/91
Laterality (right/left/bilateral)	85/92/0	1/1/0	86/93/0
Orbital cavity, *n* (%)	151 (24.9)	5 (9.6)	156 (23.7)
Male/female	62/89	4/1	66/90
Laterality (right/left/bilateral)	75/76/0	1/4/0	76/80/0
Intraocular, *n* (%)	14 (2.3)	44 (84.6)	58 (8.8)
Male/female	10/4	28/16	38/20
Laterality (right/left/bilateral)	8/6/0	32/12/0	40/18/0
Total, *n* (%)	607 (100)	52 (100)	659 (100)
Male/female	298/309	33/19	331/328
Laterality (right/left/bilateral)	288/315/1	18/34	349/306/1

Table 4 Pathological classification of common benign and malignant ocular tumors

Pathological type	*n* (%)	Mean age, y	Sex ratio (M/F)
Benign eyelid tumors	265 (100)	14.45±4.45	1.10 (139/126)
Nevus	48 (18.1)	15.77±4.25	1.29 (27/21)
Calcified epithelioma	41 (15.5)	14.16±4.28	0.52 (14/27)
Squamous papilloma	25 (9.4)	15.48±3.30	0.92 (12/13)
(Epi-)dermoid cyst	25 (9.4)	16.24±3.79	1.08 (13/12)
Hemangioma	19 (7.2)	14.95±3.91	2.17 (13/6)
Benign ocular surface tumors	177 (100)	12.56±4.71	0.97 (87/90)
Dermoid tumor	57 (32.2)	10.42±4.61	0.78 (25/32)
Nevus	43 (24.3)	14.98±3.54	1.87 (28/15)
Squamous papilloma	16 (9.0)	13.63±4.46	0.45 (5/11)
Dermoid cyst	5 (2.8)	12.57±4.66	0.67 (2/3)
Hemangioma	5 (2.8)	12.77±4.68	4 (4/1)
Benign orbital cavity tumors	151 (100)	10.73±4.93	0.7 (62/89)
(Epi-)dermoid cyst	90 (59.6)	9.42±4.67	0.7 (37/53)
Calcified epithelioma	12 (8.0)	13.5±3.73	0.2 (2/10)
Hemangioma	12 (8.0)	13.75±4.6	0.71 (5/7)
Benign intraocular tumors	14 (100)	12.54±5.12	2.5 (10/4)
Malignant tumors	52 (100)	12.96±4.65	1.74 (33/19)
Retinoblastoma	42 (80.8)	12.71±4.68	1.63 (26/16)
Rhabdomyosarcoma	2 (3.9)	6.00±0.00	- (2/0)

Table 5 Histological origin classification of benign and malignant tumors in ZJU

Histologic origin	Benign	*n* (%)	Malignant	*n* (%)	Total, *n* (%)
Epithelial		117 (19.3)			117 (17.8)
	Dermoid tumor	59			
	Squamous epithelial papilloma	41			
	Wart	11			
	Basal cell papilloma	5			
	Keratoacanthoma	1			
Cystic		149 (24.5)			149 (22.6)
	Epidermoid cyst	66			
	Dermoid cyst	54			
	Sebaceous cyst	15			
	Conjunctival cyst	9			
	Other cysts	5			
Melanocytic		92 (15.2)		2 (3.8)	94 (14.3)
	Nevus	92	Melanoma	1	
			Conjunctival melanosis	1	
Skin adnexal		63 (10.4)		1 (1.9)	64 (9.7)
	Pilomatrixoma	53	Meibomian adenocarcinoma	1	
	Chalazion	4			
	Hidradenoma	4			
	Pleomorphic adenoma	1			
	Trichofolliculoma	1			
Mesenchymal		55 (9.1)		2 (3.8)	57 (8.6)
	Hemangioma	38	Rhabdomyosarcoma	2	
	Lipoma	9			
	Fibro-epithelial polyp	2			
	Xanthoma	2			
	Fibroma	2			
	Hamartoma	2			
Neural		5 (0.8)		45 (86.5)	50 (7.6)
	Neurofibroma	2	Retinoblastoma	42	
	Schwannoma	2	Neuroblastoma	1	
	Glioma	1	Meningioma	1	
			Schwannoma	1	
Lymphoid				2 (3.8)	2 (3.0)
			T-cell lymphomas	1	
			B-cell lymphomas	1	
Others	Proliferation and inflammation	126 (20.8)			126 (19.1)
Total		607 (100)		52 (100)	659 (100)

adnexal (*n*=63, 10.4%), mesenchymal (*n*=55, 9.1%) and neural (*n*=5, 0.8%). Furthermore, every specific tumor diagnosis was classified as subtype of histologic origin. For example, in tumors of melanocytic origin, benign tumors consist of 38 hemangiomas, 9 lipomas, and malignant tumors consist of two rhabdomyosarcomas. While neural origin tumors account for 86% in malignant tumors, it only reaches 8% overall. The distribution proportion of overall tumors compared to benign tumors is similar, with the biggest difference being tumors of neural origin having a larger overall percentage of cases.

Retinoblastoma Analysis from two Center At the Eye and ENT Hospital of FU, the first-time parents and their child went to the doctors' offices was recorded. The age range of the 60 cases was 2 to 100mo, and the average age was 22.89±20.04mo. The laterality at presentation was also recorded, with 21 cases in the right eye, 17 cases in left eye and 22 cases both eyes. The first symptoms noticed by parents were recorded including leukocoria, squint, proptosis and others, with is 42, 6, 5, 7 cases respectively. The gender ratio was 1:1.

In the Second Affiliated Hospital of ZJU, only patients who underwent enucleation operation were recorded. The age distribution of retinoblastoma cases showed a trend of decrease age from 2000 to 2018, with the age dropping below 4y from 2014 onwards (Figure 2). The age at surgery of 42 cases was from 4 to 20 years old, and the average age was 12.71±4.68y. Due to the relatively late stage of this disease, involvement of the optic nerve constituted 28.57% (n=12) of all cases.

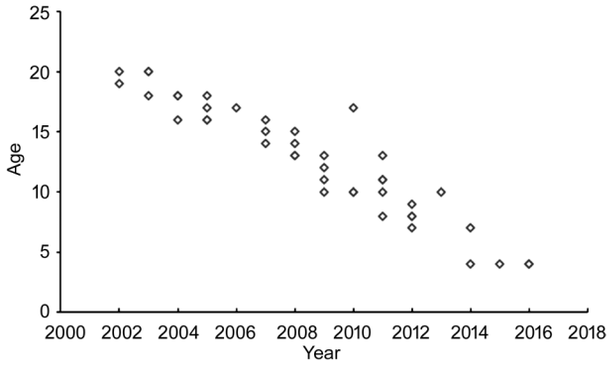

Figure 2 Age distribution (in years) of retinoblastoma from 2000 to 2018.

DISCUSSION

There is little in the literature about the clinical spectrum of childhood eye neoplasms and no comprehensive classification has been proposed[9]. The majority of information regarding the frequency and spectrum of eye tumors is restricted to adults or only one part of the eyes, such as orbital, or eyelid[10-11]. Due to the complexity and diversity of ocular tumors, the spectrum of tumor diseases at different ages often differs. Each type of lesion has rather characteristic, but not pathognomonic, clinical features. Moreover, because of different knowledge levels among people, the tumor may be missed or misdiagnosed, causing the tumor burden and treatment burden could to be unbearable for children and their caregivers[12]. Therefore, a relatively comprehensive eye cancer study in children provides strong support for clinicians in diagnosis and treatment.

In our study, benign tumors make up the majority of ocular neoplasms, accounting for 92.11% of all cases. In all benign cases, the number of cases increases with age group. The 16-20y group (35.48%) had the majority of cases, and most of them were nevi (Figure 1). A possible reason may be that adolescents can pay more attention to their appearance. What is worth noting is (epi-)dermoid cysts are shown to have a high rate in the 6-10y group. This range is consistent with a retrospective review in Switzerland, which reported the median age of (epi-)dermoid cyst at surgery time was 7y[13].

For all malignant tumors, the median age is 12.96±4.65y. Retinoblastoma was the most frequent lesion. According to FU resources, the average diagnosis age was 22.89±20.04mo. Based on a worldwide population-based registry study, retinoblastoma was most frequent in children aged 0-4y[14]. As mentioned in previous articles, retinoblastoma is usually diagnosed at an average age of 18mo with 95% of children diagnosed by 5 years of age[4,15-17]. Gao *et al*[18] reported that in South Western China, the median age at diagnosis is less than 2y.

The median age of enucleation was 12.71±4.68y in ZJU from 2000-2018. This relatively older age may be caused by avoiding seeing a doctor. Figure 2 reflects that the age of treatment decreased with time and was under 4y after 2014, which is consistent with previous observations. With the development of economic and sanitary conditions in the last decade in China, it has become easier to seek medical treatment and childhood diseases can be discovered earlier.

Ophthalmic tumors can be anatomically divided into eyelid, ocular surface, orbit and intraocular. In a study by Zhao *et al*[9], 99.2% of benign tumors occurred in the eyelid and ocular surface while 91.6% of malignant tumors in the intraocular and orbital cavity, our results are similar with 73.3% of benign tumors occurring in the eyelid and ocular surface, and 94.2% of malignant lesions occurring in the intraocular and orbit. In contrast, eyelid and ocular surface were also the most common location for benign lesions in adults (83.1%). However, for adult malignant tumors, orbital cavity and intraocular tumors only accounted for 18.2%[19].

Furthermore, the eyelid can be described in more detail as upper or lower eyelid. Calcified epithelioma, also termed as pilomatrixoma, is an uncommon benign skin neoplasm, with up to 40% of cases 40% originated from head[20]. Based on the discoveries of large masses of shadow cells, combined with basophilic cells, inflammation, foreign body giant cells, calcification, and ossification, diagnosis can be made[21]. In this study, eyelid and orbital cavity were the most frequent location of calcified epithelioma, 41 and 12 cases respectively. And 30 (73.17%) cases occurred at the upper eyelid and nine at the lower eyelid. Levy *et al*[21] noted that the upper lid and brow are involved most frequently, as observed in their series in which 69% of cases developed in the upper eyelid or eyebrow.

Dermoid cysts and epidermoid cysts are lesions that have overlapping features. Epidermoid cysts are derived from ectoderm with the cysts lined solely by squamous epithelium, while dermoid cysts are also ectodermal inclusion cysts but are more complex, neither of them is strictly eye neoplasms[22]. Considering the similarity, cases were counted together in this study. They can be found in any subcutaneous location but more than 80% located in the region of the head, with the majority in the eyelid and orbital area, usually near the zygomaticofrontal suture[23]. Epidermal cysts were the most common eyelid tumors (23.1%) found in the Hsu and Lin's[24] study. In the Wills Eye Hospital pathology series, dermoid cysts accounted for 46% of childhood orbital lesions and for

89% of all cystic lesions[25]. In addition, excision operations are safe procedures for ophthalmologists dealing with this disease, even in young patients, and early resection is recommended due to the potential adverse effects that may occur if these cysts are left untreated[13,26].

Retinoblastoma is the most common intraocular malignancy representing 3% of all childhood cancers[16]. The retinoblastoma referral system might explain why only two cases a year were reported at the Second Affiliated Hospital of ZJU. Usmanova and Kivelä[27] stated that about 1100 retinoblastomas are predicted to occur in the entire Chinese population. MacCarthy *et al*[28] analyzed 1601 children with retinoblastoma diagnosed in England (1963-2002) and estimated an annual incidence rate of 3.5 per million children under 15 years of age. Darwich *et al*[29] found it was 11.58 cases per 1 million in children younger than 5y between 1992 and 2010 in Canada. Based on 40 years of data from the USA, Fernandes *et al*[30] arrived at the rate of 12.14 per million children below 4 years old in 2018. Further analyses indicated that mortality is about 70% in countries of low and middle income[31]. Risk factors for metastasis are multiple recurrences, aggressive histopathological appearance, and orbital/sinus invasion. The main cause of metastasis is delay in diagnosis and treatment. Therefore, it seems that the management of retinoblastoma is not a common scientific research topic. In orbital tumors, reports that include only childhood cases had a greater incidence of rhabdomyosarcoma whereas reviews confined to older patients were more likely to have a higher incidence of lymphoma[17,32-33]. Maheshwari and Finger[17] states that epithelial origin was the most common origin for malignant lesions of all age groups, however in our study the majority of malignant tumors were of neurogenic origin.

This study was affected by a number of limitations, including those inherent to a retrospective analysis. Due to the uncommon nature of recurrence after surgical excision, the long-term follow-up was not scheduled but left to the discretion of patients' parents and ophthalmologists. Furthermore, single center data were collected in this study, upon which a relative composition ratio was calculated, but the incidence rate and mortality rate could not be calculated. Multicenter clinical data will be collected in further studies. Finally, the category of other malignant tumors other than retinoblastoma was not abundant enough, otherwise the spectrum of childhood eye tumors could be better described.

In summary, this study presents an 18-year, comprehensive description of eye tumors and lesions in east China. The significance of providing up-to-date epidemiological data about child and adolescent eye lesions cannot be ignored. With deeper understanding of children and adolescent eye tumors, combining the clinical, radiologic, and histopathologic features, doctor diagnosis can be compared with the classification in order to better evaluate a child with an eye lesion. Based on the improvement of diagnosis and children eye health service, the prospects of early detection, early treatment even multidisciplinary treatment strategies will be brilliant.

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