Original Article
Cent Asian J Med Sci. 2018 June;4(2):136-144. https://doi.org/10.24079/CAJMS.2018.06.005

Central Asian Journal of Medical Sciences
CAJMS

The Aspects of Diagnosis and Treatment of Retinoblastoma in Mongolia

Tsengelmaa Chuluunbat[1], Bayalag Munkhuu[1], Uranchimeg Bazarsad[3], Altankhuu Molom[1], Baasankhuu Jamiyanjav[2]

[1]Department of Ophthalmology, National Center for Maternal and Child Health, Ulaanbaatar, Mongolia, [2]Department of Ophthalmology, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia, [3]Department of Pathology, National Center for Maternal and Child Health, Ulaanbaatar, Mongolia

Submitted: April 15, 2018
Revised: May 12, 2018
Accepted: May 28, 2018

Corresponding Author
Tsengelmaa Chuluunbat, MD
Department of Ophthalmology, National Center for Maternal and Child Health, 16060 Khuvisglachdiin street, Bayangol district, Ulaanbaatar, Mongolia
Tel: +976-99123663
E-mail: chtsenge@gmail.com

Objectives: To describe the clinical characteristics and the treatment outcome of retinoblastoma in Mongolian children. **Methods:** Data of all children diagnosed with retinoblastoma at the National Center for Maternal and Child Health of Mongolia from 1987 to January 2017 were reviewed retrospectively. The ICRB classification was used. Survival characteristics of the cohort were analyzed. **Results:** Retinoblastoma was diagnosed in 100 eyes of 79 children during the study period. Median age of diagnosis was 23.2±5.8 months. There were no differences in sex ratio and 21 cases (27%) were bilateral. Fifty-two patients (66%) were from rural areas. The more frequent clinical presentations were leukocoria in 64 (81%) patients, unilateral mydriasis 35 (45%) and strabismus in 34 (44 %) patients. Sixty-nine (87.3%) patients were diagnosed with Classification D or worse when presented to us. Due to late diagnosis in the majority of cases, unilateral and bilateral enucleations were performed in 58 (58%) eyes and 26 (26%) eyes respectively; exenteration was done in 3 (3%) eyes, intravenous chemotherapy was done (11%) eyes and laser surgery was done (4%) eyes. After the mean follow up of 10 years, 67 (84.8%) patients were alive, 5 (6.3%) patients died and in 7 (8.8%) patients their vital status was unknown. The mean follow-up period was 144.1±16.3 (95% CI 122.6-165.5) months (range, 15-365months). In 5 cases in which immunohistochemistry analysis was performed, neuron-specific enolase (NSE), Ki-67 protein (Ki-67), B-cell lymphoma 2 (Bcl-2) positive cells were found in all of 5 (100%) cases and Rb protein was detected in 3 (60%) cases. **Conclusion:** The implementation of International Classification of Retinoblastoma, systemic intravenous chemotherapy and laser treatment for retinoblastoma, shows favorable outcome in the treatment of retinoblastoma and further prognosis.

Keywords: Retinoblastoma, Chemotherapy/adjuvant, Laser therapy, Mongolia

Introduction

Retinoblastoma (RB) is a cancer involving the retina of the very young; two-thirds are diagnosed before 2 years of age, and 95% before 5 years. For these reasons, therapeutic approaches need to consider not only the cure of the disease but also the need to preserve vision with minimal long-term side effects. The estimated incidence of RB is 1 in 16,000-18,000 births per year

worldwide [1-6].

Although retinoblastoma is very curable when diagnosed early and treated appropriately, the prognosis is poor when the basic methods of diagnosis and treatment are lacking. Survival rates in the developed world are very high but the rates are much lower in developing nations where it is detected at more advanced stages due to inadequately developed medical infrastructure, alertness of the parents as well as of pediatricians, and complex and deficient socioeconomic environments [7].

In Mongolia, only three to four new cases of retinoblastoma each year are estimated. However, retinoblastoma is an emerging health issue with problems of late diagnosis and poor visual outcome [8]. Although the Mongolia has good systems for tracking the occurrence of disease once it is diagnosed, there has been no system for collecting and collating important case data in the framework of a retinoblastoma study following new international classification and treatment protocols. Therefore, the purposes of this study were to review the current situation and to describe the clinical characteristics and the treatment outcome of retinoblastoma in Mongolian children.

Materials and Methods

Data of all children diagnosed with retinoblastoma from 1987 to 2017 at the National Center for Maternal and Child Health of Mongolia were reviewed retrospectively with approval from the Institutional Review Board of Mongolian National University of Medical Science (ID#18011). The National Center for Maternal and Child Health is only referral, tertiary care level hospital with a Pediatric Ophthalmology Department. The Department is responsible for pediatric eye care services for the entire country of Mongolia.

The data recorded included jurisdiction, sex, date of birth, age at diagnosis, and information on laterality of tumor, family history of RB, clinical presentations and mode of treatment. The diagnosis of RB was based on the results of slit lamp examination, indirect ophthalmoscope, echography, computerized tomography, or magnetic resonance imaging depending on the availability of the tools. The International Classification of Retinoblastoma (ICRB) was used (1).

Enucleation and exenteration combined with systemic chemotherapy were treatments used for these patients. No other treatment modalities such as, cryotherapy, selective ophthalmic arterial chemotherapy or intravitreal chemotherapy were available at our center.

The 1-year, 5-year, 10-year, 15-year and >25-year survival rate of the cohort were documented and analyzed.

With hematoxylin and eosin stain, the extent of tumor in optic nerve, choroid and anterior chamber were scored and confirmed by pathologists. The immunohistochemistry of retinoblastoma was performed at Beijing Tongren Hospital in China. The expressed protein checked in this study included RB protein, neuron-specific enolase, s-100 protein, *p53*, vimentin, bcl-2, ki67 and glial fibrillary acidic protein.

The data of retinoblastoma patients at our center from 1987 to 2017 were collected and analyzed. The data were presented as descriptive statistics. Patient survival were calculated and analyzed using the Kaplan-Meier method. Data were expressed as mean± sd.

Results

Patients

Seventy-nine eyes of 79 children were diagnosed with retinoblastoma at the Department of Pediatric Ophthalmology, National Center for Maternal and Child Health of Mongolia from January 1987 to March 2017. Since our hospital is the only hospital that treats and takes care of retinoblastoma patients in Mongolia, we determined the estimated the incidence of retinoblastoma was about 1 to 23,000-24,000 live births in the Mongolian population during that time period. The annual retinoblastoma incidence between 1987 and 2017 is varied from 0.14 to 0.9 per 10,000 livebirths (Figure 1). Among these 79 patients, 52 (66%) patients were from rural areas and 27 (34%) patients were from the capital city, Ulaanbaatar.

Gender and Laterality

There was equal gender distribution of our patients. Among the patients, 39 (49.4%) were boys and 40 (50.6%) were girls. In location, it was unilateral in 58 (73.4 %) patients and bilateral in 21 (27%) patients. The disease was familial in two (2.5%) patient and sporadic in 77 (97.5%) (Table 1).

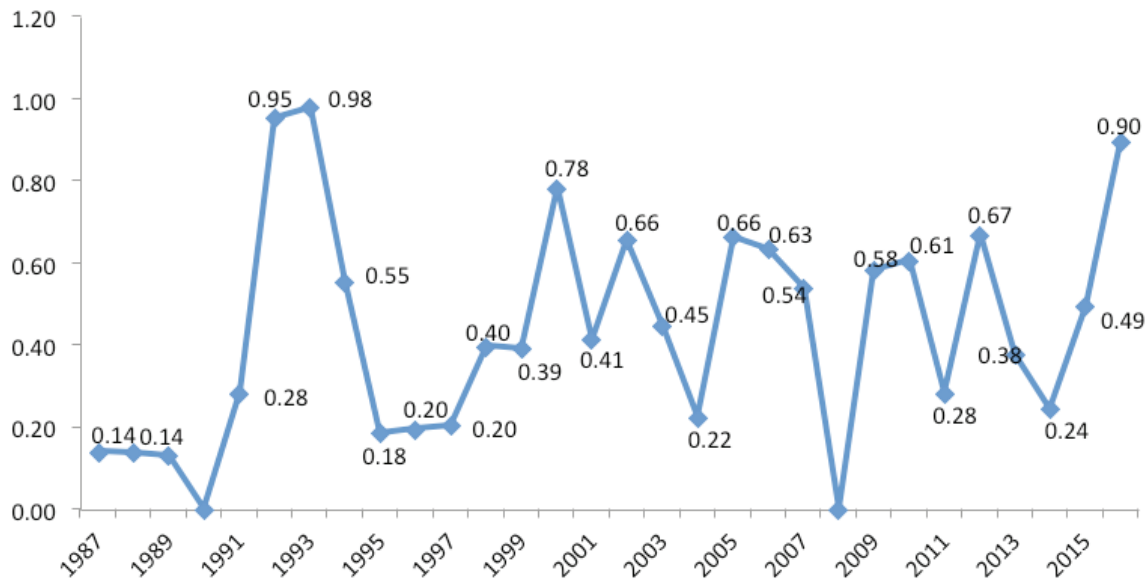

Figure 1. Estimation annual of incidence of retinoblastoma in Mongolia

Table 1. Characteristics of patients with retinoblastoma (1987-to January, 2017, Mongolia) (n=79 cases and 100 eyes)

Variable	No. of Cases (%)
Sex	
Male	39 (49.4%)
Female	40 (50.6%)
Laterality	
Unilateral	58 (73.4%)
Bilateral	21 (26.6%)
Family history	
Yes	2 (2.5%)
No	77 (97.5%)
Mode of treatment in Retinoblastoma cases (n=100 eyes)	
Unilateral enucleation	58 (58%)
Bilateral enucleation	26 (26%)
Unilateral exenteration	3 (3%)
Laser photocoagulation therapy with Systemic intravenous chemotherapy	2 (2%)
Systemic intravenous chemotherapy	9 (9%)
Laser treatment	2 (2%)
Histopathological findings in retinoblastoma (n=87 eyes)	
Undifferentiated type	46 (53%)
Optic nerve infiltration	5 (5.7%)
Rosettes	5 (5.7%)
Calcification	4(4.5%)
Necrosis	1(1.1%)
Hemorrhage	2(2.3%)

Age at Diagnosis

Age of diagnosis ranged from 1-72 months. Mean age of diagnosis was 24.5 ± 15.8 months. Fifty-three (83%) patients were diagnosed before the age of 3. The age at diagnosis was earlier in bilateral cases (mean age 13.9±2.4, months range 1-42) than in unilateral cases (mean age 26.6 ±1.9 months, range 1-72) ($p<0.001$).

Presenting Signs and Stage

The most prevalent clinical conditions were leukocoria (Figure 2) in 64 (81%) patients, unilateral mydriasis in 35 patients (44.3%), strabismus in 34 (43%) patients, secondary glaucoma in 26 (33%) patients, hyphemia in 9 (11%) patients and orbital cellulitis in 7 (11%) patients respectively.

Three (4.7%) patients presented as late, extraocular stage retinoblastoma (Figure 3). Sixty-nine (87.3%) patients were diagnosed of classification group D or worse when presented to us. In total, 83 (83%) eyes were diagnosed of Classification Group D and E, 10 (10%) eyes were group B and 7 (7%) eyes were group C.

Unilateral retinoblastoma (94.8%) was diagnosed Classfication group D or E which was higher classification compared to bilateral retinoblastoma (66.7%) which was diagnosed Classfication group D or E ($p=0.004$).

Disease Detection

Since there were no eye screening programs in Mongolia, all (100%) patients were referred to ophthalmologists for

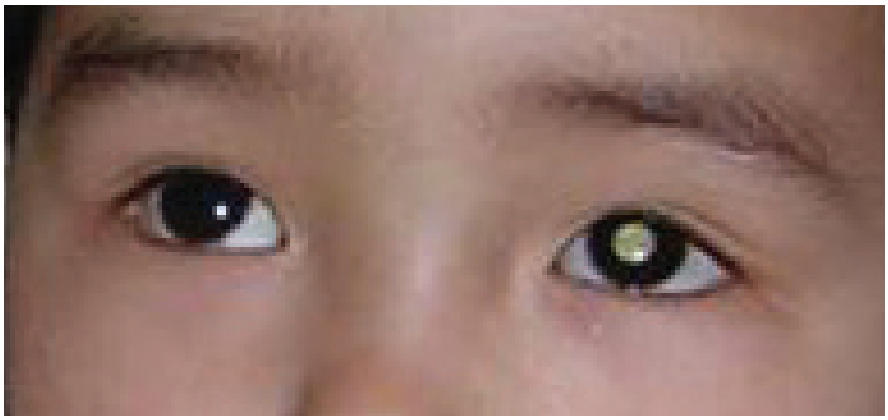

Figure 2. Leukocoria in a 3-year-old patient with retinoblastoma. Leukocoria is the abnormal white reflection from the retina in the pupil of the left eye

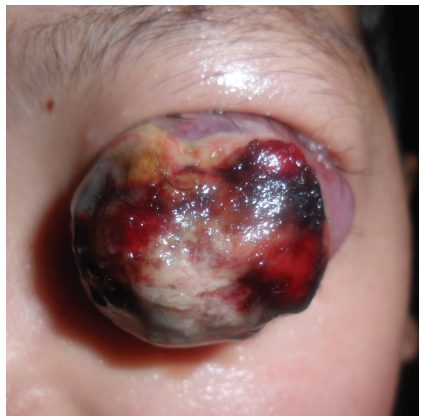

Figure 3. Retinoblastoma, extra ocular stage, left eye in a 4 year old girl

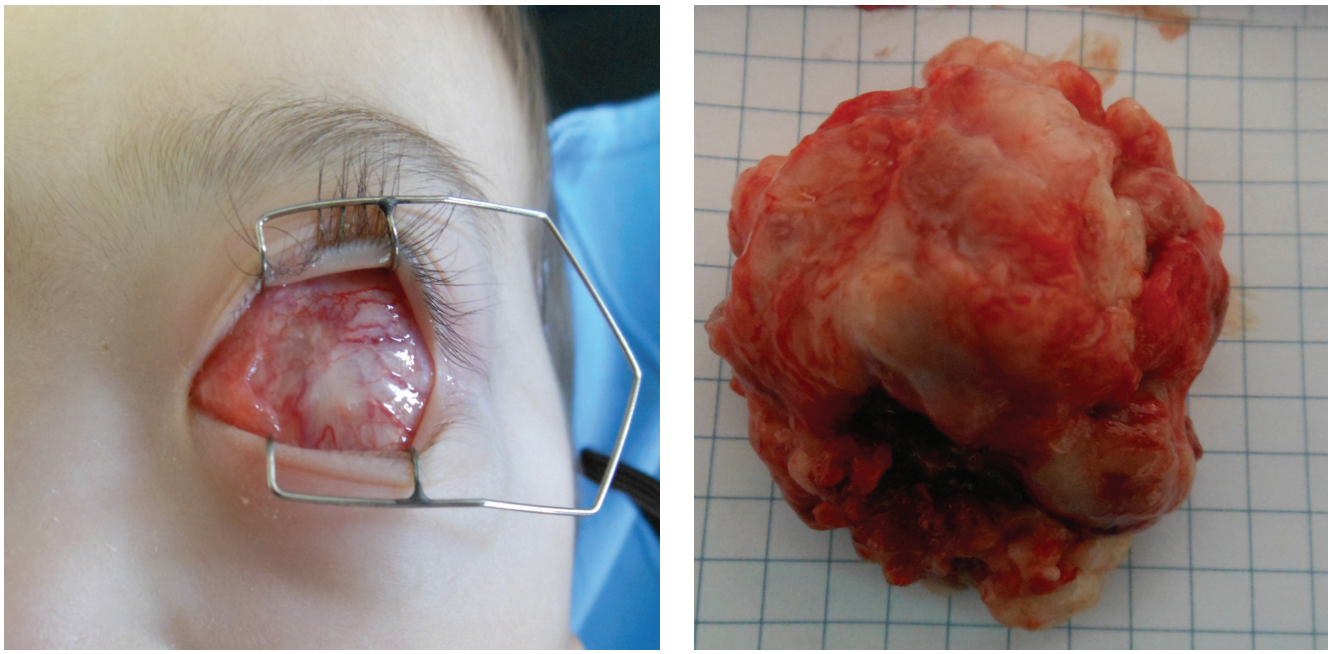

Figure 4. Recurrence of retinoblastoma in a 5 year old girl. A) Four years after the initial enucleation of left eye. B) After repeat exenteration. The specimen from the repeat exenteration measured 47 x 53 x 39 mm. The tumor had invaded the connective tissue and muscle and extended to the superior surgical margin and was not completely resected. Histopathological examination showed undifferentiated recurrent retinoblastoma. The patient died 5 months after the exenteration.

further evaluation due to various presenting signs mentioned above. Fifty-four (68.3 %) patients were examined with B scan ultrasound examination, 52 (66 %) patients with CT, and 45 (56 %) patients with MRI, 15(19%) patients underwent RetCam Portable (Clarity Medical Systems, Pleasanton, California) retinal examination under general anesthesia.

Spread of Tumor

One case (1.2%) had intracranial extension, three (3.8%) cases had extraocular extension and one (1.2%) case developed an orbital recurrence of RB four years after initial enucleation (Figure 4). The other 74 (93.6%) patients had intraocular retinoblastoma without any extraocular extension.

Secondary Tumor and metastasis

None of our cases developed a secondary malignant neoplasm before the cut-off date.

Mode of Treatment

Enucleation of one eye was performed in 58 eyes (58 %), bilateral enucleation in 26 eyes (26 %) and exenteration in 3 eyes (3%) in the early years of this study. Additional exenteration was done in one eye due to orbital of recurrence retinoblastoma four years after initial enucleation. Four eyes (3%) received the local laser treatment and eleven (11%) eyes received systemic intravenous chemotherapy only and the tumors were stable with partial regression (Table 1).

Histology

Histopathological examination was done in 87/100 (87%) eyes after enucleation and undifferentiated type was diagnosed in 46 (53%) eyes. Optic nerve infiltration was found in 5 (5.7%) eyes, rosettes (well-differentiated) in 5 (5.7%) eyes, calcification in 4 (4.5%) eyes, hemorrhage was in 2 (2.3%) eyes and necrosis was in one eye (1.1%) respectively. The histopathological analysis was unknown due to no information on the patient's chart in 24 eyes (27.6%) (Table 1).

Immunohistochemical analysis

Enucleated eyes of 5 children underwent histological and immunochemistry analysis. Regarding the histology, four tumors (80%) were classified as undifferentiated RB and one (20%) was well-differentiated RB on the basis of the presence of areas containing Flexner-Wintersteiner rosettes and fleurettes. In 5 cases with immunohistochemical analysis, neuron-specific enolase (NSE), Ki-67 protein (Ki-67), B-cell lymphoma 2 (Bcl-2) positive cells were found in all of 5 (100%) cases and Rb protein was detected in 3 (60%) cases. Vimentin was detected in two cases, glial fibrillary acidic protein (GFAP) in three cases, P-53 in two cases, and S-100 in three cases. The results are shown in (Table 2).

Regarding the adjacent structures, two in 5 (40%) cases demonstrated optic nerve involvement, three (60%) cases with retinal pigment epithelium (RPE) involvement, two (40%) cases choroid involvement, two (40%) cases had a calcification. The detailed information of the immunohistochemistry is shown in (Table 2).

Table 2. Histopathologic and Immunohistochemical result of five patients who has been done enucleation

Case/ID	Case1/0033	Case2/0034	Case3/0037	Case4/0042	Case5/0053
Code	X-1279	X-797	X-171	X-27	X-1345
Pathological type	Undifferentiated	Undifferentiated	Differentiated	Undifferentiated	Undifferentiated
Nerve involvement	NA	+	-	+	NA
RPE involvement	+	+	-	+	-
Choroid involvement	+	+	-	NA	-
Calcification	-	+	NA	-	+
Immunohistochemistry					
RB	+	+	-	+	+
Bcl-2	+	+	+	+	+
Ki-67	+	+	+	+	+
NSE	+	+	+	+	+
Vimentin	-/Stromal cells(+)	+	-/Stromal cells(+)	+	+
GFAP	+	+	-/Stromal cells(+)	-	+
P-53	+	-	+	-	+
S100	+	+	-	NA	+

RPE= retinal pigment epithelium; Rb=Retinoblastoma protein; Bcl-2=B-cell lymphoma 2; Ki-67= protein that in humans is encoded by the MKI67 gene (antigen identified by monoclonal antibody Ki-67); NSE=neuron-specific enolase; Vimentin=An immunohistochemical study of vimentin; GFAP=glial fibrillary acidic protein; P-53=Tumor protein *p53*; S-100=low-molecular-weight protein

Follow-up

At the time of last follow-up, 67 (85%) patients were alive, 5 (6.3 %) patients were dead and 7 (8.8%) patients had been lost to follow-up or unknown vital status. The mean follow-up was 144.1±16.1 months. (range 12–360 months) (Figure 5). The longest follow-up was a 32-year-old male with bilateral retinoblastoma, and his son was born with inherited bilateral retinoblastoma. The father enucleation underwent of his right eye and left eye at the age of 3 months and 44 months respectively. His son also received with bilateral enucleation at 2 months of age in right eye, and at 61 months of age in left eye. Five (6.3%) patients died due to delayed diagnosis of retinoblastoma with the presentation of extra ocular extension and intracranial spread.

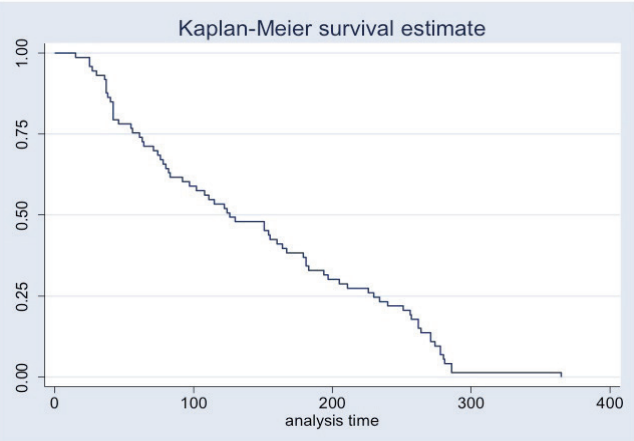

Figure 5. Kaplan-Meier survival estimate of patients with retinoblastoma. The horizontal axis is time since in diagnosis is months. The vertical axis is fraction of patients surviving.

The 1-year, 5-year and 10-year survival rates of the RB cases were 96.2% (76/79), 88.6% (70/79) and 84.8% (67/79) respectively (Table 3).

Discussion

Our study shows that the mean age of retinoblastoma patients at presentation was 23.2 months. The age at diagnosis was earlier in bilateral cases (13.9 months) than in unilateral cases (26.6 months). The common clinical presentations were leukocoria (81%), unilateral mydriasis (44.3%), strabismus (43 %). Sixty-nine (87.3%) patients were diagnosed with Classification D or worse when patients presented to us. Chemotherapy has achieved an important role in the management of intraocular retinoblastoma. We have used the standard intravenous chemotherapy (etopside, carboplatin, vincristine) for intraocular retinoblastoma since 2012 in Mongolia. Before 2012 a different guideline was used for the retinoblastoma treatment in Mongolia which included chemotherapy (cyclophosphamide) and external beam radiation therapy. There is a need to study on comparison of the clinical outcomes between patients diagnosed before 2012 and after 2012. Enucleation is still frequently used in advanced cases including large tumors, neovascular glaucoma, pars plana tumor seeding, anterior chamber involvement or choroid, optic nerve or orbital tumor extension, with no expectation for useful vision.

Late diagnosis is fairly common in our cases series; destructive procedures such as unilateral and bilateral enucleations and exenteration were performed in (87%) eyes. Globe salvage and preservation of vision were only 13%, much lower than the data reported from developed countries [3, 9-13]. Our data has shown that the retinoblastoma in Mongolia is frequently diagnosed at late stages and the vision outcomes are poor. These data show there are room to make improvement in the awareness of retinoblastoma and the early treatment of it in Mongolia.

In the worldwide studies there were no gender differences in retinoblastoma, and the average age at diagnosis is 18 months and the vast majority becomes clinically apparent before the age of 3 years [7, 9, 11, 14-16]. In most of the developed countries patients with bilateral tumors present earlier than those with unilateral involvement [1, 4]. The age at initial diagnosis is 23 months in China and 84% of them were diagnosed less than 3 years, 25 months in Brazil, 25 months in Turkey, 23.9 months in India, 28.5 months in Iran and 18 months in America [7, 9, 11, 14-16]. In our case series, median age of diagnosis was 23.2 months in Mongolia, similar to prior reports in other countries.

Table 3. Patient survival rates of Retinoblastoma in Mongolia

Variable	1 year	5 years	10 years
Patient survival (%)	96.2	88.6	84.8

Leukocoria is the most common presenting sign of retinoblastoma followed by strabismus all over the world. This could probably be due to geographical variation of the disease, awareness of the disease among the public, availability of medical facilities in that country and number of patients examined. The pattern of presentations in our study is consistent with many studies from different parts of the world. In addition to the above, Abramson et all reported many uncommon/rare presenting signs such as a inflammatory signs, proptosis, orbital cellulitis, hyphema, anisocoria, heterochromia iridis, vitreous hemorrhage and microphthalmos retinoblastoma [9]. However, proptosis as the presenting sign at the time of diagnosis was reported in high frequency from some of the developing countries like Nigeria (84.6%), Korea (80%), Pakistan (52.8%), Nepal (44.2%), Thailand (26.7%) and India (25.3%) [13,17-21]. In our studies, presenting signs of leukocoria, unilateral mydriasis and strabismus are more common and were seen in 81%, 44.3%, and 43% of our patients. Proptosis was a rare presenting sign with only 4.6% of our patients in our patients. Bilateral retinoblastoma was seen in 23.4% of patients in our case series which was lower than the figures reported from China (32%), Korea (31.4%), USA (41.5%), Australia (41%), India (37.2%), and Thailand (36.7%) [7, 9-10, 20-21].

Saving patients' life is the primary goal of the treatment in retinoblastoma. Enucleation and exenteration are effective methods to achieve that goal. But now with the introduction of local treatments, such as cryotherapy, intravitreal chemotherapy, chemoreduction, and selective ophthalmic artery infusion, ocular preservation rates are much higher. Some patients even enjoy good vision after treatment. Saving eyes and vision requires disease recognition before leukocoria, as demonstrated by better ocular salvage rates among patients who had a positive family history and received clinical surveillance via early, and routine dilated funduscopic examinations by an ophthalmologist [9].

Early diagnosis and prompt treatment are important factors in achieving high survival rates. In developing countries, late referral has been implicated as an important factor related to prognosis of RB patients [22]. In our analysis of 79 eyes with retinoblastoma, globe salvage and preservation of vision was 13 (13%) eyes, lower than for developed countries. As for survival, 67 (84.8%) patients lived, 7 (8.8%) had unknown vital status and (6.3%) patients died. In developing countries, poor education, lower socioeconomic conditions, and inefficient health care systems result in delayed diagnosis and suboptimal care. Furthermore, the complexity of multidisciplinary care required is seldom possible. While ocular salvage is a priority in the Western world, death from retinoblastoma is still a major problem in developing countries [23].

Worldwide, the incidence of retinoblastoma is recorded to be about 11 cases per million children younger than 5 years. A more commonly used estimate is 1 case of retinoblastoma per 18,000-30,000 live births, depending on the nation. An estimated 250-500 new cases of retinoblastoma occur in the United States yearly [9]. The average incidence of retinoblastoma varies by race or geographic location, but the average incidence is approximately one in 15 000 newborns [14, 17, 24-25]. In our studies, the estimated incidence of retinoblastoma was about 1 to 23,000-24,000 live births in Mongolia, which is a slightly similar incidence than internationally reported incidence. There may have been some patients who obtained medical care in other countries who were not registered in the National Center for Maternal Health, leading to an underestimation of the incidence. However, pediatric patients who sought for medical help in other countries usually first visited and registered at our medical center because of reimbursement mechanisms through insurance. Therefore, there is a little chance of being unregistered or not visiting our center.

The incidence of retinoblastoma is not distributed equally around the world. Whether these geographical variations are due to ethnic or socioeconomic factors is not well known. However, the fact that even in industrialized countries an increased incidence of retinoblastoma is associated with poverty and low levels of maternal education, suggests a role for the environment. In our study, 66% of retinoblastoma cases were diagnosed from rural areas where the socio-economic status is lower than urban population in Mongolia.

The retinoblastoma protein is a tumor suppressor protein that is inactivated and results in development of retinoblastoma cancer. In our series, three in 5 cases (60%) were detected to express retinoblastoma protein on immunohistochemical analysis. Sun, Yokoyama et al. found that neuron-specific enolase (NSE) is a substance that has been detected in patients with certain tumors and stained strongly positive in undifferentiated tumor cells and weakly positive in rosettes and fleurettes in most of the cases (21/27) [26]. In our study, NSE positive cells were found in all of 5 retinoblastoma cases and 4/5 (80%) cases were

classified undifferentiated retinoblastoma cells.

Karim et al. [27] revealed that S-100 protein, glial fibrillary acidic protein (GFAP), vimentin, neuron-specific enolase (NSE) were positive only for glial elements and NSE and bcl-2 for almost all tumor cells. These means that the majority of retinoblastoma are sporadic and those are composed of neuron-committed cells [27]. In our study, neuron-specific enolase (NSE), B-cell lymphoma 2 (Bcl-2) positive cells were found in all of 5 retinoblastoma (100%) cases.

In the current study, undifferentiated tumor cells was the most common type of histopathological finding and is positive in 53% of advanced enucleated cases. Kashyap et al identified poorly differentiated RB presented in 80.3% of cases and well-differentiated in 19.7% of 609 enucleated eyes for advanced intraocular retinoblastoma. Well- differentiated tumors were found to present earlier (median 1.2 years) than poorly differentiated tumors (median 2.5 years) and had better prognosis than the undifferentiated ones [28].

There are several limitations related to this study. The retrospective nature of the study, incomplete clinical data of some patients, and the immunohistochemical analysis data were available only in 5 patients could compromise the study outcome. Computed tomography scanning and magnetic resonance imaging were not introduced until 2001 in Mongolia. The laser or transpupillary thermal therapy was introduced and available in 2016 the whole nation. Selective ophthalmic arterial infusion has not yet been introduced at our center. Furthermore, retinoblastoma is a paramount example of of a condition requiring multidisciplinary care, which is difficult to achieve in a developing country like Mongolia [23].

In conclusion, patients with retinoblastoma from rural areas are more frequently diagnosed at late stages in Mongolia. This shows the importance of regular screening programs for early detection of tumors among in children aged less than 3. In addition, most Mongolian children with retinoblastoma usually present with leukocoria noted by parents, rather than routine pediatric screening via the red reflex test performed by an ophthalmologist. Further efforts are needed to detect early stages of retinoblastoma and render better treatments to increase survival, ocular preservation, and even functional vision for the patients in Mongolia. The implementation of International classification of RB, systemic intravenous chemotherapy and laser treatment for retinoblastoma, shows favorable outcome in the treatment of RB and further prognosis.

In addition, we need to improve the methods for early detection and diagnosis in Mongolia. This study emphasized the need to develop and implement following strategies that 1) improve and educate the pediatric eye health awareness among the public and 2) educate primary and secondary health care doctors to recognize retinoblastoma and refer to national center immediately and 3) establish the newborn and pediatric screening program for intraocular tumor retinoblastoma in nationwide. Multidisciplinary teams main goals are to save the patient's life, increase the ocular survival and preserve the vision.

References

1. Shields JA, Shields CL. Intraocular Tumors. Philadelphia, USA: Lippincott William& Wilkins; 2008. p 293-365.
2. Ramasubramanian A, Shields CL. Retinoblastoma. New Delhi, India: Jaypee Brothers; 2012. p 399-408
3. Shields CL, Shields JA. Retinoblastoma management: advances in enucleation, intravenous chemoreduction, and intra-arterial chemotherapy. Curr Opin Ophthalmol 2010; 21: 203-212.
4. Shields CL, Shields JA. Basic understanding of current classification and management of retinoblastoma. Curr Opin Ophthalmol 2006; 17: 228-234.
5. Ramasubramanian A, Shields CL. Retinoblastoma. New Delhi, India: Jaypee Brothers; 2012. p 70-78.
6. Dondey JC, Staffieri S, McKenzie J, Davie G, Elder J. Retinoblastoma in Victoria 1976-2000: Changing management trends and outcomes. Clin Experiment Ophthalmol 2004; 32: 354-359.
7. Zhao J, Li S, Shi J. Clinical presentation and group classification of newly diagnosed intraocular retinoblastoma in China. Br J Ophthalmol 2011; 95: 1372-1375.
8. Tsengelmaa C, Altankhuu M, Jamiyanjav B, Munkhuu B, Bazarsad U, Molom A, et al. Retinoblastoma in State Research Centre on Maternal & Children Health: Prevalence, Clinical and Survival Characteristics 1987-2005. Taiwan J Opthalmol 2016; 6: 79-84.
9. Abramson DH, Frank CM, Susman M, Whalen MP, Dunkel IJ, Boyd NW. Presenting signs of retinoblastoma. J Pediatr 1998; 132: 505-8.
10. Berman EL, Donaldson CE, Giblin M, Martin FJ. Outcomes

in retinoblastoma, 1974-2005: The Children's Hospital, Westmead. Clin Experiment Ophthalmol 2007; 35: 5-12.
11. Bonanomi MT, Almedia MT, Cristofani LM, Odone FV. Retinoblastoma: a three-year-study at a Brazilian medical school hospital. Clinics (Sao Paulo) 2009; 64: 427-434.
12. Chang CY, Chiou TJ, Hwang B, Bai LY, Hsu WM, Hsieh YL. Retinoblastoma in Taiwan: survival rate and prognostic factors. Jpn J Ophthalmol 2006; 50: 242-249.
13. Chung SE, Sa HS, Koo HH, Yoo KH, Sung KW, Ham DI. Clinical manifestations and treatment of retinoblastoma in Korea. Br J Ophthalmol 2008; 92: 1180-1184.
14. Ozkan A, Pazari H, Celkan T, Karaman S, Apak H, Yildiz I, et al. Retinoblastoma in Turkey: survival and clinical characteristics 1981-2004. Pediatr Int 2006; 48: 369-373.
15. Naseripour M, Nazari H, Bakhtiari P, Modaress-zadeh M, Vosough P, Ausari M. Retinoblastoma in Iran: outcomes in terms of patients survival and globe survival. Br J Ophthalmol 2009; 93: 28-32.
16. Shanmugam MP, Biswas J, Gopal L, Sharma T, Nizamuddin SH. The clinical spectrum and treatment outcome of retinoblastoma in Indian children. J Pediatr Ophthalmol Strabismus 2005; 42: 75-81.
17. Owoeye JF, Afolayan EA, Ademola-Popoola DS. Retinoblastoma- a clinico-pathological study in Ilorin, Nigeria. Afr J Health Sci 2006; 13: 117-123.
18. Rai P, Narsani AK, Lohana MK, Memon MA. Too late presentation of 53 patients with retinoblastoma: a big challenge. Int J Ophthalmol 2009; 9: 221-230.
19. Badhu B, Sah SP, Thakur SK, Dulal S, Kumar S, Sah RP, et al. Clinical presentation of retinoblastoma in Eastern Nepal. Clin Experiment Ophthalmol 2005; 33: 386-389.
20. Patikulsila P, Patikulsila D. Retinoblastoma at Maharaj Nakorn Chang mai hospital; A 7- year study. Changmai Med Bull 2001; 40: 167-172.
21. Sahu S, Banavali SD, Pai SK, Nair CN, Kurkure PA, Advani SH. Retinoblastoma: problems and perspectives from India. Pediatr Hematol Oncol 1998; 15: 501-508.
22. Chantada G, Fandino A, Manzitti J, Urrutia L, Schvartzman E. Late diagnosis of retinoblastoma in a developing country. Arch Dis Child 1999; 80: 171-174.
23. Shields CL, Lally SE, Leahey AM, Jabbour PM, Caywood EH, Shields JA. Targeted retinoblastoma management: when to use intravenous, intra-arterial, periocular, and intravitreal chemotherapy. Curr Opin Ophthalmol 2014; 25: 474-485.
24. Song JS, Lee JK, Lee TW. Treatment and prognosis of retinoblastoma; clinicopathologic analysis of 101 cases. J Korean Ophthalmol Soc 1998; 39: 393-405.
25. Kao LY, Su WW, Lin YW. Retinoblastoma in Taiwan: survival and clinical characteristics 1978-2000. Jpn J Ophthalmol 2002; 46: 577-580.
26. Sun XL, Yokoyama T, Minoda K, Sakuma A. Immunohistochemical studies of retinoblastoma. Jpn J Ophthalmol 1990; 34: 149-157.
27. Karim MM, Yamamoto M, Itoh H. Retinoblastoma: clinical and immunocytochemical observations. Kobe J Med Sci 1996; 42: 151-161.
28. Kashyap S, Sethi S, Meel R, Pushker N, Sen S, Ghose S, et al. A Histopathologic analysis of eyes primarily enucleated for advanced intraocular retinoblastoma from a developing country. Arch Pathol Lab Med. 2012; 136: 190-193.