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Retinoblastoma in Hong Kong from 2008 to 2019: looking back and moving forward

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Abstract

Purpose: To report the incidence, clinical features, and treatment outcomes of retinoblastoma at a tertiary referral center in Hong Kong.

Methods: Medical records of all patients with retinoblastoma presenting to Hong Kong Eye Hospital from 2008 to 2019 were reviewed.

Results: 75 eyes in 55 patients were treated for retinoblastoma during the 10-year study period. The mean age at presentation was 19.8±16.4 months. The mean duration of symptoms before diagnosis was 1.1±2.1 months. The most common presenting sign was leukocoria and/or strabismus (n=33, 60.1%). 65% of patients presented with advanced disease of groups D and E. The tumor was unilateral (n=35, 63.6%), bilateral (n=18, 32.7%), or trilateral (n=2, 3.6%). The enucleation rate was 0% in groups A to C, 70% in group D, and 93.3% in group E. With the introduction of intra-arterial chemotherapy since 2016, the globe salvage rate has increased from 29.4% to 33.3% in group D eyes and from 4.5% to 12.5% in group E eyes. The overall globe salvage rate was 40.0%, and the overall 5-year survival rate was 100%.

Conclusions: The prognosis of retinoblastoma is good in cases with early detection and appropriate treatment. Unfortunately, most patients presented with relatively advanced disease, which lowers the overall globe salvage rate. There is a need for enhanced public awareness and education for healthcare professionals to facilitate early detection and improve ocular outcomes for children with retinoblastoma.

Key words: Eye enucleation; Hong Kong; Incidence; Retinoblastoma; Treatment outcome

Introduction

Retinoblastoma is the most common intraocular malignancy of childhood[1] and constitutes 3% of all pediatric cancers,[2], with the incidence ranging from 1 in 15000 to 20000 live births.[3,4] The most common presenting signs and symptoms are leukocoria and strabismus, followed by glaucoma, decreased visual acuity, orbital cellulitis, and others.[5] Retinoblastoma is often diagnosed in relatively later stages,[5] as early detection requires vigilant screening and public awareness.

Once detected, treatment for retinoblastoma is multimodal and dictated by the stage of the disease, laterality, presence of extraocular extension, and visual prognosis. Management of retinoblastoma has evolved over the past four decades. In the 1970s, enucleation was important for ensuring survival. Enucleation remains relevant for advanced retinoblastoma, particularly in Asia and Africa. In the 1980s, external beam radiotherapy was widely used, but risks of radiation-related secondary malignancies have led to its reduced use. In the 1990s to 2000s, systemic intravenous chemotherapy was

used, typically with combinations of vincristine, etoposide, and carboplatin.[6] Currently, systemic chemotherapy remains popular for intraocular retinoblastoma control as well as prevention of systemic metastasis. In general, earlier presentation is associated with improved prognosis in terms of patient survival and globe salvage rates. With advancements in globe salvage techniques and new treatments, the prospect of preserving the eye even in advanced disease has steadily improved. In the recent decade, intra-arterial chemotherapy (IAC) and other forms of locally delivered chemotherapy and combination therapies have been explored.

To the best of our knowledge, there has been one study describing clinical features and treatment outcomes of retinoblastoma in Hong Kong in 2008.[7] The present study was conducted to report updated epidemiological data, advances in treatment, and management outcomes for retinoblastoma from 2008 to 2019.

Patients and methods

In Hong Kong, most patients with retinoblastoma are managed in the Kowloon Central Cluster by a multidisciplinary team of pediatricians, ophthalmologists, pediatric oncologists, radiologists, pathologists, social workers, and volunteers from non-governmental organizations. We retrospectively reviewed records of all patients with retinoblastoma treated at Hong Kong Eye Hospital from January 2008 to January 2019. Data were retrieved from the Hospital Authority clinical management system and included sex, age at diagnosis, presenting symptoms or signs, laterality, presenting stage, family history, treatment modality, recurrence rate, survival rate, and results of genetic testing.

Each of the eyes was classified according to the International Classification of Retinoblastoma (ICRB) [**Table 1**]. If such classification was not available, RetCam (Natus Medical, Pleasanton [CA], USA) photography on first presentation was used for tumor grading according to the documented tumor size and features. The diagnosis of retinoblastoma was confirmed by dilated fundus examination, ultrasonography, and magnetic resonance imaging, which aids the identification of poor prognostic features such as pineal gland involvement, extra-scleral extension, and optic nerve spread.[8] We included only those patients who were followed up for at least 1 year after diagnosis was made.

Table 1. International Classification of Retinoblastoma

Group A	Retinoblastoma ≤3 mm (in basal dimension or thickness)
Group B	Retinoblastoma >3 mm (in basal dimension or thickness) or • Macular location (≤3 mm to foveola) • Juxtapupillary location (≤1.5 mm to disc) • Additional subretinal fluid (≤3 mm from margin)
Group C	Retinoblastoma with: • Subretinal seeds ≤3 mm from tumor • Vitreous seeds ≤3 mm from tumor • Both subretinal and vitreous seeds ≤3 mm from tumor
Group D	Retinoblastoma with: • Subretinal seeds >3 mm from tumor • Vitreous seeds >3 mm from tumor • Both subretinal and vitreous seeds >3 mm from retinoblastoma
Group E	Extensive retinoblastoma occupying >50% globe or with: • Neovascular glaucoma • Opaque media from hemorrhage in the anterior chamber, vitreous, or subretinal space • Invasion of postlaminar optic nerve, choroid (>2 mm), sclera, orbit, anterior chamber

Treatment modalities included chemotherapy (systemic, intra-arterial, and intravitreal mode of delivery), focal therapy with laser or cryotherapy, and enucleation. Radiotherapy was avoided owing to the lifetime risk of secondary malignancies, and the option of plaque radiotherapy was not provided. In our center, IAC has been introduced since 2016 and is currently offered to patients for salvage treatment in bilateral disease and selected patients with ICRB groups C or D localized unilateral retinoblastoma. Intravitreal chemotherapy is offered occasionally as a combination therapy for recurrent vitreous seeding following incomplete control with other methods. Systemic chemotherapy is often given as a chemoreduction regimen in bilateral retinoblastoma, as combination therapy for resistant or recurrent unilateral cases, or as a bridging therapy in neonates who are too young for IAC or surgery. Agents used were a combination of carboplatin, etoposide, and vincristine, given every 21 to 28 days for up to 4 to 6 cycles.[9] After a few cycles of chemotherapy, focal therapy (laser therapy or cryotherapy) is applied when there is a significant reduction in tumor size with improved laser uptake.

Results

75 eyes in 35 boys and 20 girls of Chinese ethnicity were treated for retinoblastoma at our hospital during 2008-2019. The incidence of retinoblastoma in Hong Kong during the study period was estimated to be 1 per 14309 live births, based on 787000 live births during the study period.[10]

The mean age at presentation was 19.8±16.4 months (23.2±17.3 months for unilateral cases and 13.1±13.1 months for bilateral cases). The mean duration of symptoms before diagnosis was 1.1±2.1 months. Upon presentation to an ophthalmologist, retinoblastoma was suspected after clinical examination, and there was no misdiagnosis.

The most common presenting sign was leukocoria (n=25, 45.5%), followed by decreased visual acuity (n=6, 10.9%), strabismus (n=4, 7.3%), and combined leukocoria and strabismus (n=4, 7.3%). In two (3.6%) patients, the diagnosis was picked up during screening for positive family history.

The tumor was unilateral (n=35, 63.6%), bilateral (n=18, 32.7%), or trilateral (n=2, 3.6%). The ICRB group at presentation was A in 8 eyes (10.7%), B in 8 eyes (10.7%), C in 4 eyes (5.3%), D in 20 eyes (26.7%), E in 30 eyes (40.0%), and not available in the remaining 5 eyes (6.7%). More

patients presented in the later groups (D and E) than in the earlier groups (A to C), and this trend had not changed over the study period.

Five (9.1%) patients had a positive family history for retinoblastoma, but four of them had no available data regarding this. The remaining 46 (83.6%) patients were not observed to have the disease in the family prior to the index case. Genetic testing was performed in 38 (69.1%) patients: 22 (57.9%) had non-germline mutation and 16 (42.1%) had germline mutation.

42 (56.0%) eyes underwent primary enucleation. In three (9.1%) eyes, chemoreduction with focal therapy was attempted but failed and eventually required enucleation. The rate of enucleation was proportionally related to the presenting stage (0% in groups A to C, 70% in group D, and 93.3% in group E) [**Table 2**].

32 (58.2%) patients were given systemic chemotherapy, and two (3.6%) received radiotherapy (external beam radiotherapy or plaque radiotherapy) in overseas centers. Intravitreal melphalan was administered in two patients with resistant vitreous seeding despite systemic chemotherapy, IAC, and focal laser. IAC was used in seven patients as salvage therapy when first-line systemic chemotherapy or local therapy could not control the disease.

Four patients developed complications from IAC. One patient developed transient cellulitis and lid swelling, which resolved spontaneously 3 weeks after IAC. One patient developed ischemic optic neuropathy after three cycles of IAC and required a course of pulsed methylprednisolone followed by prolonged oral steroid and intravitreal anti-VEGF injection to control the disc swelling. Two patients developed ischemic retinopathy and neovascular glaucoma with vitreous hemorrhage after three and six cycles, respectively, of IAC in an overseas center; the involved eye was eventually enucleated due to high-risk features. With the introduction of IAC in Hong Kong since 2016, the globe salvage rate has improved from 29.4% to 33.3% in group D eyes and from 4.5% to 12.5% in group E eyes (**Table 2**).

Table 2. Enucleation rate and globe salvage rates before and after introduction of intra-arterial chemotherapy in 2016

Presenting stage*	No. (%) of eyes		
	Enucleation rate	Globe salvage rate before 2016	Globe salvage rate after 2016
Group A (n=8)	0 (0)	6/6 (100)	2/2 (100)
Group B (n=8)	0 (0)	7/7 (100)	1/1 (100)
Group C (n=4)	0 (0)	3/3 (100)	1/1 (100)
Group D (n=20)	14 (70)	5/17 (29.4)	1/3 (33.3)
Group E (n=30)	28 (93.3)	1/22 (4.5)	1/8 (12.5)

** Staging in 5 eyes was not documented*

Six patients received post-enucleation chemotherapy for high-risk features, including tumor invasion posterior to lamina cribosa of the optic nerve, ≥3 mm of choroidal invasion, and any degree of optic nerve and uveal invasion on pathological examination after enucleation.[11,12] These patients had group E eyes on presentation, but there were no features suspicious of choroidal invasion or optic nerve invasion detected on preoperative magnetic resonance imaging. The overall globe salvage rate was 40.0%, and the 5-year survival rate was 100% including the two patients with trilateral retinoblastoma.

Discussion

Consistent with the literature,[13-17] in the present study, the most common presenting symptoms were leukocoria and/or strabismus (60.1%), and the mean age at presentation was younger in bilateral cases than unilateral cases (13.1±13.1 months vs 23.2±17.3 months). Compared with studies in other Asian centers,[18-21,26-29] in the present study, the mean duration of symptoms before diagnosis was 1.1±2.1 months, and the diagnosis of retinoblastoma was suspected upon presentation to an ophthalmologist, with no misdiagnosis. This is likely due to the centralized management model in a quaternary referral center with relatively high awareness among ophthalmological staff. In addition, most patients had advanced retinoblastoma (groups D and E) at presentation and there was no improvement in early detection over the years. As early-stage disease carries a much higher globe salvage rate and better survival prognosis, there is a need for more public education and healthcare professional awareness to enable early detection of disease.

In the present study, the 5-year overall survival rate of retinoblastoma was 100%, which is consistent with the 95% reported in Europe,[22,23] and the >96% in the United States,[24] and is higher than the 35% to 86% in most parts of Asia.[25-29] Traditionally, trilateral retinoblastoma (intraocular retinoblastoma combined with a histologically similar brain tumor – most commonly in the pineal gland) is associated with poor prognosis.[30] However, facilitated by early detection and the use of high-dose chemotherapeutic agents with stem cell rescue and radiotherapy, the 5-year survival of patients with pineal and non-pineal trilateral retinoblastoma has increased substantially from 6% to 44% from 1995 onwards.[31] In the present study, the two patients with trilateral retinoblastoma exhibited rapid tumor control and regression with high-dose chemotherapy with vincristine, carboplatin, etoposide, and cyclophosphamide (according to the COG ARET0321 protocol) for six cycles along with autologous stem cell transplant.[32] In one patient the more severe eye was enucleated, and in the other patient total regression of tumors in both eyes occurred after chemotherapy alone without the need for enucleation. Both patients have remained in remission for 2 years and 9 years, respectively.

Over the last decade, advances in the globe salvage therapies have improved disease control and minimized late effects of systemic chemotherapy. In addition, IAC and intravitreal chemotherapy have improved treatment outcomes for

advanced retinoblastoma. Shields and Shields[6] reported that primary therapy with IAC was better than systemic chemotherapy alone and was successful in 100% of group C eyes, 100% of group D eyes, and 33% of group E eyes. IAC was effective in inducing 92% of solid tumor regression and controlling 80% to 95% of subretinal seeds.[6] Since the introduction of IAC in our center in 2016, the globe salvage rate for unilateral and bilateral retinoblastoma has increased from 29.4% to 33.3% in group D eyes and 4.5% to 12.5% in group E eyes. Besides IAC, intravitreal chemotherapy is available as a second-line therapy in patients with resistant vitreous seeding. Suzuki et al[33] achieved a globe salvage rate of nearly 51% in the largest series of intravitreal melphalan at 8 micrograms for eyes with vitreous seeding. However, they reported one case of metastasis (0.4%) and suggested that intravitreal chemotherapy should be combined with triple freeze-thaw cryotherapy upon needle withdrawal at the injection site. We used intravitreal melphalan to control resistant vitreous seeding in two patients who remained recurrence-free at 2 and 4 years of follow-up, respectively. Our rate of globe salvage for groups A, B, and C eyes is comparable to that of most developed countries, with the exception of group D eyes.[34-37] The primary goal of retinoblastoma treatment is to preserve life, and hence enucleation remains a favored option as opposed to globe salvage therapy among parents. In Hong Kong, IAC is a relatively new treatment modality and is limited by manpower and logistical requirements, and hence it has only been used as a salvage therapy or secondary treatment in resistant or recurrent cases. More funding is needed to widen the use of IAC.

Nonetheless, IAC must be used with caution. Our series reported ischemic retinopathy and optic neuropathy after >3 cycles of IAC for globe salvage therapy. Despite having a lower rate of systemic side effects of chemotherapy such as neutropenia and fever, IAC has increased local effects ranging from eyelid edema to lower limb ischemia, arterial dissection, and retroperitoneal bleeding. There is also the risk of missing or downgrading high-risk characteristics such as choroidal or optic nerve invasion, which can only be revealed by pathological examination after enucleation. Long-term data on risk for systemic metastases are lacking, although a multicenter retrospective survey reported the risk of metastatic death to be <1% with IAC.[38]

Genetic testing was performed in 69% of our patients, which is lower than that reported in European or North American centers.[39,40] This is partially explained by the relatively high cost of genetic testing, which is offered on a self-financed basis with a limited number of families fulfilling financial criteria for subsidies from non-governmental organizations such as the Children's Cancer Fund. With the establishment of the Hong Kong Children's Hospital, we hope that there is wider availability of genetic testing and counseling to families, fast track imaging and IAC services, and increased use of local chemotherapy and other globe salvage techniques, as well as more frequent multidisciplinary interactions with pediatricians, clinical psychologists, and social workers; and more collaboration with non-governmental organizations such as Children's Cancer Fund to promote awareness among parents, general practitioners, and pediatricians for earlier referral and identification of retinoblastoma symptoms. Early detection and treatment are keys to better outcomes. Our team has launched a series of public education campaigns targeted to the general public, primary healthcare doctors, and pediatricians to educate and raise public awareness on the importance of early detection and referral of cases of retinoblastoma.

There are limitations to this study. Hong Kong Eye Hospital is a tertiary referral center for retinoblastoma in Hong Kong, but patients who attended private ophthalmic centers and were managed elsewhere or overseas were not included in the database, and therefore their disease outcomes were not known.

Conclusion

The prognosis of retinoblastoma is good in cases with early detection and appropriate treatment. Increased availability of local chemotherapy delivery such as IAC has improved the overall globe salvage rate, especially in groups C or D advanced disease. Unfortunately, most patients still presented with relatively advanced disease, which lowers the overall globe salvage rate. There is a need for enhanced public awareness and education for healthcare professionals to facilitate early detection and improve ocular outcomes for children with retinoblastoma.

Author contributions

Concept or design: all authors
Acquisition of data: EW, AC, WL
Analysis or interpretation of data: EW, AC
Drafting of the article: EW, AC
Critical revision for important intellectual content: all authors

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As Editors of the Journal, WL and JY were not involved in the peer review process for this article. All other authors have no conflicts of interest to disclose.

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Ethics approval

This study was approved by the Kowloon Central / Kowloon East Cluster Research Ethics Committee (reference: KC/KE-20-0035/ER-3).

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