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Clinical Features, Treatment, and Outcomes of Retinoblastoma in China

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Abstract

Background This review determined clinical features and treatment outcomes of retinoblastoma patients in China, which ranks second in incidence globally and is among the countries listed to produce 4,000 new cases of the estimated world's retinoblastoma cases in 2023.

Methods A search was done using different databases for literatures on retinoblastoma in China published from 2010 to 2020. The articles were then reviewed for clinical features, treatment, and outcomes.

Results Ten articles that included 3,702 patients involving ~4,412 eyes seen in China from 1957 to 2019 were analyzed. Median age at consult ranged from 18 to 30 months and mean lag of consultation was 4 to 6 months. More males were affected (58%). Seventy-nine percent had unilateral disease. Retinoblastoma was assumed intraocular in 4,123(89%) eyes with ≥996(22%) belonging to group E of International Intraocular Retinoblastoma Classification/International Classification of Retinoblastoma. Extraocular extension was present in 415 (9%) eyes with 845 patients having direct extraocular extension, while 54 had distant metastasis. Enucleation was the most used treatment procedure specially in unilateral disease done in at least 2,781 (74%) eyes. Median follow-up period ranged from 14 to 47 months. Functional vision was retained in 48 (2%) eyes. Globe salvage rate for group A to D eyes ranged from 56 to 100%. Highest globe salvage rate for group D was 87% and 70% for group E. Overall survival rate was 1,655/1898 (87%), ranging from 81 to 100%. Overall mortality was 4%.

Discussion Clinical profile and management options for retinoblastoma in China changed overtime improving outcomes. Globe salvage and survival rate were high for those with intraocular disease.

Keywords
- retinoblastoma
- clinical features
- treatment
- outcomes
- China

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Introduction

China ranks second to India in retinoblastoma incidence globally and is among the six Asian countries listed to be the source of almost 4,000 new cases of the retinoblastoma cases in 2023.[1] The clinical profile and treatment outcomes of retinoblastoma change in every country and overtime. Treatment has shifted from enucleation and external beam radiotherapy (EBRT) to systemic chemotherapy and globe salvage procedures that in turn improved outcomes in the past decade. This paper aimed to review the recent clinical presentation, management options, and the outcomes of retinoblastoma patients in China based on the literatures published in the past decade. This review is part of a series made to determine the recent clinical profile and treatment outcomes of retinoblastoma in the six Asian countries listed by Usmanov and Kivela.[1]

Subjects and Methods

A search for articles published from 2010 to 2020 on retinoblastoma in China using the PubMed, EMBASE, Scopus, Science Direct, Google scholar, and Web of Science databases and the terms "retinoblastoma," "China," "clinical," "presentation," "treatment," and "outcome" in different combinations. Abstracts were reviewed for clinical presentation, treatment, and outcomes of retinoblastoma. Articles with no clinical presentation as well as those with significant overlap in patient database based on authors, study site, and duration were excluded. Only the articles with the longest duration or with the most patients were included. Articles that were not written in English were also excluded. Six articles were included in the initial search, while four more were added after the second search. Eight were observational studies, while two were interventional. All were retrospective studies that included 3,702 patients involving around 4,412 eyes seen in China from 1957 to 2019.

The following data were collected, if available: age at consult or diagnosis, age at onset or first not of presenting symptom, lag time, gender, laterality, family history, level of involvement, chief complaint, retinoblastoma classification and staging systems, treatment procedures done, and outcomes. Mean, median, range, standard deviation, and percentage were computed using Microsoft Excel Ver. 3 2013 (Microsoft Corp.; Redmond, Washington, United States).

Results

There were no significant differences in median age of onset between the Han and the minority groups ($p = 0.66$).[2] However, the median lag time (5 months vs. 2, $p < 0.047$) was longer in the minority groups as a result of the longer travel time from home to hospital (4 days vs. 1, $p < 0.0001$).[2] Patients from Tibet were found to have longer travel time from home to hospital (6 days vs. 1, $p < 0.0001$), longer lag time (12 months vs. 2, $p < 0.0001$), higher proportion of extraocular disease ($p < 0.04$), and lower survival rate ($p < 0.04$) than those who were not from Tibet.[2]

Clinical Presentation

The median age at consult ranged from 18 to 30 months (►**Table 1**). Gao et al registered the highest number of retinoblastoma patients who were more than 5 years old at 8% with one patient having bilateral disease.[2] Median age at consultation decreased significantly from 1957–1996 to 1997–2006 ($p < 0.001$).[3] Median age at onset of initial symptoms (8 months vs. 23, $p < 0.001$) and at consultation (14 months vs. 27, $p < 0.001$) of patients with bilateral disease was younger compared with those with unilateral disease.[2,4,5] However, the overall lag time was similar for both groups ($p = 0.18$).[2] The mean lag of consultation was 4 to 6 months. The mean lag time decreased from 1957–1986 to 1987–2006.[3] There was no significant difference in mean lag of consultation between genders (4 months vs. 4, $p = 0.67$).[4]

More males were affected than females at 58%, although prevalence of retinoblastoma was found not to be associated with gender ($p = 0.30$).[3] Seventy-nine percent had unilateral disease. Only 1% reported family history of retinoblastoma. Family history of retinoblastoma among patients with bilateral disease was significantly higher than those with unilateral (9 vs. 1%, $p < 0.01$).[6] Retinoblastoma was assumed to be intraocular in 4,123 (89%) eyes based on reported deaths from metastasis since there was no report on staging. Similarly, two of the articles were on intraarterial chemotherapy (IAC) that was primarily indicated for intraocular retinoblastoma. Some articles including the interventional ones limited their inclusion criteria to intraocular disease.[7] At least 996 (22%) eyes of those with intraocular disease belonged to group E of International Intraocular Retinoblastoma Classification (IIRC) or International Classification of Retinoblastoma (ICRB).

Extraocular extension was present in at least 415 (9%) of the eyes. The proportion of extraocular disease decreased significantly from 1956–1961 to 2002–2006 ($p < 0.001$). Cerebrospinal fluid analysis and bone marrow biopsy were done for those with group E disease.[8] Leukocoria remained the most common presenting symptom among at least 2266 (58%) patients. Patients who presented with leukocoria were significantly younger than those without (23 ± 15 vs. 30 ± 25 months, $p < 0.02$).[4] However, patients who presented with strabismus ($p < 0.05$) and blurring of vision ($p < 0.00$) were significantly older than those who did not have them.[4] Patients who presented with strabismus ($p < 0.02$) and exophthalmos ($p < 0.02$) had significantly longer lag time.[4] At least 845 patients had direct extraocular extension, while 54 had distant metastasis.

Treatment

Nine articles with 3,250 patients involving 3,875 eyes had data on treatment. Treatment was refused for 17 eyes (►**Table 2**). Local treatment procedures, mostly laser photocoagulation and cryotherapy, were given to 553 (~14%) eyes. Enucleation was the most used treatment procedure specially in unilateral disease done in at least 2,781 (74%) eyes with at least 168 (~4%) eyes receiving it as a secondary procedure.[2] High-risk features (HRF) were seen in 706 (18%)

Table 1 Clinical features of retinoblastoma patients from China

Clinical features	Bai et al, 2011[3]	Luo et al, 2015[4]	Gao et al, 2011[7]	Huang et al 2013[6]	Gao et al, 2016[2]	Jin et al 2018[8]	Chen et al 2016[11]	Jin et al 2017[5]	Xiao et al 2019[9]	Xu et al 2020[10]
	1957–2006	2003–2011	2005–2009	2005–2009	2006–2015	2009–2017	2011–2013	2013–2016	2016–2019	2013–2017
	Capital Medical University, Beijing	Sun Yat-sen University, Guangzhou	Fudan University, Shanghai	Capital Medical University, Beijing	Sichuan University, Changdu	Beijing's Children Hospital, Beijing	Women and Children Medical Center, Guangzhou	Quanzhou Maternal and Child Health Hospital, Fujian	Sun Yat-sen University, Guangzhou	Bright Eye Hospital, Chongqing
Child/Eye	1230 /1234	314/399	133/159	684/885	253/296	356/486	73/107	436/610	138/138	85/98
Mean age at consult (in months)	33 ± 22	24 ± 18	26	26 ± 20	–	–	–	–	28	16 ± 1
Median (range)	30 (1–168)	–	23 (2–134)	23 (0–216)	25 (1–617)	18 (1–84)	20 (4–95)	18 (1–390)	–	–
Mean lag of consult (in months)	6 ± 7	4 ± 6	–	–	–	4 ± 2	–	–	–	–
Median (range)	3 (1–48)	(0–48)	–	–	2 (0–48)	–	–	1 (0–96)	–	–
Sex										
Male	702 (57%)	197 (63%)	83 (62%)	400 (58%)	143 (57%)	193 (54%)	31 (42%)	255 (58%)	71 (51%)	51 (60%)
Female	528 (43%)	117 (37%)	50 (38%)	284 (42%)	110 (43%)	163 (46%)	42 (58%)	181 (42%)	67 (49%)	35 (40%)
Laterality										
Unilateral	1200 (98%)	229 (73%)	107 (80%)	483 (71%)	203 (80%)	226 (63%)	35 (33%)	262 (60%)	138	74 (87%)
Bilateral	30 (2%)	85 (27%)	26 (20%)	201 (29%)	50 (20%)	130 (37%)	72 (67%)	174 (40%)	–	12 (13%)
Family history	–	–	9 (7%)	21 (3%)	4 (2%)	–	–	2 (0.5%)	–	12 (14%)
Involvement (eye)		Child								
Intraocular	1032 (84%)	281[a]	159 (100%)	723 (82%)	272 (92%)	486	107[b]	602[b]	138[b]	98[b]
Extraocular	197 (15%)	33[a]	0	162 (18%)	24 (8%)	–	0	8[b]	0	0
Unknown	5 (1%)	–	0	0	0	–	–	–	0	0
Leukocoria	827 (67%)	242 (77%)	93 (70%)	482 (70%)	182 (71%)	–	–	340	100 (72%)	–
IIRC (eye)			ICRB	IRC					ICRB	
A	↑	9	9 (6%)	↑	0	7	–	–	–	–
B	808 (78%)	136	14 (9%)	134 (18%)	8 (3%)	36	11	–	–	–
C	↓	52	4 (2%)	↓	20 (7%)	33	11	–	–	–

(*Continued*)

Table 1 (*Continued*)

Clinical features	Bai et al, 2011[3]	Luo et al, 2015[4]	Gao et al, 2011[7]	Huang et al 2013[6]	Gao et al, 2016[2]	Jin et al 2018[8]	Chen et al 2016[11]	Jin et al 2017[5]	Xiao et al 2019[9]	Xu et al 2020[10]
D	224 (22%)	66	29 (18%)	244 (34%)	69 (25%)	248	56	–	138	75
E	↓	159	103 (65%)	345 (48%)	175 (65%)	162	29	–	↓	23
IRSS (child)										Eye
0	–	–	–	–	–	↑	–	–	–	79[c]
1	520[c] eyes	44	–	–	–	349	–	–	–	17[c]
2	517[c] eyes	12	–	–	–	↓	–	–	–	–
3	197[c] eyes	18	–	101[c] (15%)	–	–	–	–	–	–
4	–	3	1[c]	32[c] (5%)	–	7[b]	–	–	–	2[c]

Abbreviations: ICRB, International Classification of Retinoblastoma; IIRC, International Intraocular Retinoblastoma Classification; IRC, International Retinoblastoma Classification; IRSS, International Retinoblastoma Staging System.
[a]Derived from the 33 patients with IRSS stage 2–4.
[b]Assumed based on available data on intraocular grading and presence of metastasis.
[c]Derived from available data on enucleated eye, presence of high-risk features and extent of metastasis.

enucleated eyes. Other presenting symptoms except leukocoria were associated with increased risk for HRF (41 vs. 18%, $p < 0.007$).[9] There was no significant difference in the mean age at consult ($p = 0.9$) or at enucleation ($p = 0.6$) between those with no HRF and with HRF.[9] Similarly, there was no significant difference between those with no HRF and with HRF in terms of ethnicity (Han vs. others, $p = 0.4$), parents' educational level ($p = 0.3$), household income (<3000 Renminbi [RMB] vs. ≥3000, $p = 0.4$), medical insurance coverage ($p = 0.4$), and patient's birth place (rural vs. urban, $p = 0.3$).[9] There was also no significant difference in overall lag time between those with no HRF and those with HRF ($p = 0.06$).[9] Fourteen orbits were exenterated. In the series of Jin et al, six patients were mismanaged and underwent pars plana vitrectomy.[8]

However, in Gao's series, chemotherapy in all forms overtook enucleation as the most commonly performed procedure for retinoblastoma in 2014 to 2015.[2] Systemic chemotherapy was given to at least 1061 (33%) patients with 149 (5%) receiving it as a secondary procedure. Two regimens of systemic chemotherapy were used. For primary mass reduction (regimen 1), the regimen consisted of 0.05 mg/kilogram (mg/kg) vincristine on day 1, 5 mg/kg etoposide on days 1 and 2, and 18.6 mg/kg carboplatin (VEC) on day 1 given for 6 cycles with 3 to 4 weeks interval.[4] For extraocular disease (regimen 2), the regimen was increased to 0.25 mg/kilogram (mg/kg) vincristine on day 1, 12 mg/kg etoposide on days 1 and 2, and 28 mg/kg carboplatin on day 1.[4] Carboplatin dose depended on the kidney test or glomerular filtration rate.[7] IAC was given to 205 eyes. Periocular chemotherapy was reportedly done in one eye, while there was no report of intravitreous chemotherapy administered. IAC with local therapy was used either as primary treatment or as an adjuvant to systemic primary chemotherapy for unilateral or bilateral grade D and E eyes every 3 to 4 weeks.[10] The number of cycles used depended on the response. The average number of cycles was 3 to 3.5.[10,11] Chen et al used two IAC regimens melphalan alone of not more than 0.5 mg/kg and melphalan with 1 mg of topotecan.[11] The former regimen was less effective in avoidance of enucleation than the latter ($p < 0.001$).[11] IAC was also found to significantly increase globe salvage rate as primary treatment than as adjuvant (93 vs. 79%, $p < 0.001$).

Xu et al used a different regimen where melphalan and carboplatin at 20 mg were given during the first and third IAC sessions, while melphalan and topotecan at 0.5 to 1 mg were given on the second and fourth sessions. The use of melphalan did not exceed 0.5 mg/kg and regulated based on the tumor's and patient's response.[10] For those who were treated first with systemic chemotherapy, regimen 1 was given weekly for 3 to 6 weeks prior to the IAC. Systemic chemotherapy was discontinued if with progression of tumor size or seeding and enucleation was done.[10] Tumor size was measured using ocular ultrasound.[10]

Systemic chemotherapy with IAC significantly reduced tumor diameter ($p < 0.001$) and thickness ($p < 0.001$) more than IAC.[10] However, it did not significantly increased globe salvage rate (86 vs. 80%, $p = 0.58$) or decrease relapse (12 vs.

Table 2 Treatment of retinoblastoma patients from China

Treatment	Bai et al 2011[3]	Gao, et al 2011[7]	Huang et al 2013[6]	Gao et al 2016[2]	Jin et al 2018[8]	Chen et al 2016[11]	Jin et al 2017[5]	Xiao et al 2019[9]	Xu et al 2020[10]
	1957–2006	2005–2009	2005–2009	2006–2015	2009–2017	2011–2013	2013–2016	2016–2019	2013–2017
Child/eye	1230/1234	133/159	684/885	253/296	356/486	73/107	436/610	138/138	85/98
Denial of any treatment (child)	–	–	–	17 eyes	–	–	–	–	–
Local therapy (laser, cryotherapy)	–	36	121	42	284	12	–	–	58
Primary enucleation	1234	123[a]	809	206 + 6	72	–	95 children	138	–
Secondary enucleation	Type NS	6	type NS	7	115	23	–	Type NS	17
Exenteration	–	–	–	14	–	–	–	–	–
Primary chemotherapy	–	–	515	–	284	64	–	–	49
Adjuvant chemotherapy	–	45	type NS	104	–	–	–	–	–
Intraarterial chemotherapy	–	–	–	–	–	107	–	–	98
Periocular chemotherapy	–	–	–	–	–	1	–	–	–
Primary EBRT	–	–	–	–	–	–	–	–	0
Adjuvant EBRT	–	NS	–	6 + 4	–	–	–	–	0
High-risk histologic characteristic requiring added treatment (eye)	517	45[a]	49	35	–	–	–	60	–

Abbreviations: EBRT, external beam radiotherapy; NS, not specified.
[a]From 78 eyes enucleated and 45 eyes enucleated primarily but assumed to have high-risk features thus requiring adjuvant therapy.
[b]Assumed based on available treatment protocol in the article.

18%, $p = 0.58$) when used together.[10] Only ten orbits received EBRT as an adjuvant treatment. However, this may be because some of the articles excluded prior EBRT treatment to their population.

For unilateral group A–C and some group D eyes, cryotherapy, transpupillary thermotherapy, and laser with or without systemic primary systemic chemotherapy were done.[4] Laser was used for mass with diameter of less than 3 mm and thickness of less than 2 mm located posterior to the equator, while cryotherapy was used for those anterior to the equator. EBRT or orbital apex implantation of radioactive seed was also offered.[6] For unilateral advanced group D and E, primary enucleation was done.[4] For those who refused enucleation, regimen 1 was offered with the higher dose of 26 mg/kg carboplatin.[8] After the second cycle, the eye was then reassessed for response. Enucleation was done If response was insufficient (e.g. thickening of the optic nerve on imaging, inability to see the optic nerve on fundoscopy from mass involvement of the optic nerve herve head or from vitreous hemorrhage, no reduction in tumor size, note of mass growth, or development of vitreous seeding).[8] For those with HRF, regimen 1 was initiated 4 weeks after enucleation.[8] HRF include tumor invasion of the choroid 3 mm or more in diameter, postlamina of the optic nerve, or of the inner fibers of the sclera.[3,9] HRF also include involvement of the optic nerve posterior to the lamina and positive resection margin and the anterior chamber.[3] Huang et al used 3 to 6 cycles of systemic chemotherapy composed of 600 mg/m^2 carboplatin on day 1 and 1.5 mg/m^2 and 200 mg/m^2 etoposide imatinib platinum glycosides on day 2 as adjuvant.[6] For bilateral cases, primary systemic chemotherapy was often given.[4] Secondary enucleation was done in uncontrolled group E eyes.[4] Periorbital carboplatin was injected at 20 mg/20mL to bilateral cases with advanced disease.[4] The proportion of enucleated eyes with HRF decreased significantly from 1956–1961 to 2002–2006 ($p < 0.001$).[3]

For extraocular cases, enucleation and high-dose adjuvant chemotherapy were used.[4] EBRT was also given to the affected orbit and to the site of metastasis accordingly.[4] Periocular carboplatin was also used.[4] Autologous stem cells from peripheral blood were also transplanted for patients with extraocular disease and those with recurrence.[6] For those with intracranial metastasis, intrathecal cytarabine, methotrexate, and dexamethasone were given.[6]

For those receiving chemotherapy, patients were monitored thru regular testing for hepatotoxicity (etoposide), nephrotoxicity (etoposide and carboplatin), myelosuppression (vincristine, etoposide and carboplatin), and ototoxicity (carboplatin).[5] Kidney and hearing testing were repeated on the 3rd and 6th month of chemotherapy.[7] All patients developed bone marrow suppression with 18 patients requiring blood components transfusion.[8] Reversible hearing loss was also reported.[8] Side effects that were seen in patients who underwent systemic chemotherapy and IAC include fever, abdominal discomfort, and myolesuppression.[10] Ocular complications of IAC included lid swelling and droopiness, strabismus, enophthalmos, excessive tearing, subretinal hemorrhage, cataract, vitreous hemorrhage, and spasm of ophthalmic artery.[10,11] There were no significant differences in side effect profiles between those who received IAC alone to those who received systemic chemotherapy with IAC.[10] Patients undergoing chemotherapy were given sulfamethoxazole-trimethoprim to prevent pneumonia from *Pneumocystis carinii*.[7]

Follow-up protocol for patients who were ≤1-year-old was monthly on the 1st year, every 2 months on the 2nd year and every 3 months on the 3rd year after the last treatment.[10] For older patients, they were followed every 2 months on the 1st year, every 3 months on the 2nd year, and every 6 months on the 3rd year.[10] Long-term follow-up was also pointed out by Huang et al since they had a patient who developed retinoblastoma on the other eye after 7 years.[6]

Levels of vascular endothelial growth factor (VEGF), neurone-specific enolase (NSE), livin and survivin were also monitored using enzyme-linked immunoassay.[10] Those who received systemic chemotherapy with IAC had significantly lower levels of VEGF ($p < 0.002$), NSE ($p < 0.001$), livin ($p < 0.007$), and survivin ($p < 0.017$) than those who received IAC alone.[10] Neuron-specific nicotinic acid esterase was also monitored in the different grade and a significant difference in its level was found between grades ($p < 0.05$).[6]

Outcomes

Seven articles with 1,898 patients involving 2,430 eyes had data on outcomes. Median follow-up period ranged from 14 to 47 months. There were 34 patients lost to follow-up, while 51 patients abandoned prescribed treatment (►**Table 3**). Functional vision was retained in 48 (2%) eyes. Globe salvage rate for group A to D eyes ranged from 56 to 100%. Highest globe salvage rate for group D was 87 and 70% for group E. Overall survival rate was 1,655/1898 (87%), ranging from 81 to 100%. Overall mortality was 4%. Kaplan–Meier survival probability was 88% in 3 years, ranged from 81 to 98% in 5 years and 75% in 10 years.

Survival rate was not different from patients from urban areas to those from rural areas.[2] There was no significant difference in survival rates between male and female (83 vs. 78%, $p = 0.67$).[4] Patients who presented with exophthalmos had significantly lower survival rate in 5 years than those without (18 vs. 84, $p < 0.00$).[4] There was no significant difference in survival rates between unilateral and bilateral disease (83 vs. 76%, $p = 0.34$).[4] There was higher survival rate in patients who consulted within 6 months from initial onset of symptoms than those who consulted after more than 6 months (84% vs 65%, $p < 0.01$).[4] The survival rate of those with extraocular group manifesting as exophthalmos was lower than those with intraocular disease (18 vs. 84%, $p < 0.0008$).[4]

Discussion

This review summarized the clinical presentation, treatment, and outcomes of retinoblastoma patients in China included in literatures published from 2010 to 2020 and highlighted the changes that occurred to them overtime. This

Table 3 Outcomes of retinoblastoma patients from China

	Luo et al 2015[4]	Gao et al 2011[7]	Huang et al 2013[6]	Gao et al 2016[2]	Jin et al 2018[8]	Chen et al 2016[11]	Xu et al 2020[10]
	2003–2011	2005–2009	2005–2009	2006–2015	2009–2017	2011–2013	2013–2017
Child/eye	314/399	133/159	684/885	253/296	356/486	73/107	85/98
Median follow-up (in months)	33 (1–110)	26 (8–60)	27 (3–53)	16 (0–119)	47 (1–96)	14 (3–28)	–
Vision	–	–	–	–	–	–	48
Globe salvage							
A	–	↑	↑	–	–	–	–
B	–	↑	117 (97%)	89%	–	11 (100%)	–
C	–	30 (83%)	↓	67%		11 (100%)	–
D	–	↓	128 (56%)	24%	149 (60%)	44 (79%)	65 (87%)
E	–	–	22 (8%)	–	55 (34%)	18 (62%)	16 (70%)
Treatment abandonment	–	–	34	14	3	0	0
Lost to follow-up	–	–	34	–	–	0	0
Alive	254 (81%)	132 (99%)	586 (95%)	230 (91%)	342 (96%)	73	83 (98%)
Expired	–	1 (1%)	30 (5%)	23 (9%)	14 (4%)	0	2 (2%)
KM survival prob							
3	–	–	–	88%	–	–	–
5	81%	98%	95%	81%	95%	–	–
10	–	–	–	75%	–	–	–

review included papers from eye centers in the different parts of China for better representation. Similarly, data available on ethnicities, accessibility to eye care, and other factors contributory to the outcomes of patients were included. Diagnostic procedure and treatment regimens are summarized that can be used by other countries in managing retinoblastoma.

Tibetans were found to have lower survival rate ($p < 0.04$) due to the higher proportion of extraocular disease in them from a longer lag time.[2] The median age at consult in China was generally similar to the findings that 90 to 95% of retinoblastoma cases are diagnosed in patients <5 years of age.[12] However, retinoblastoma still needs to be considered even for patients aged >5 years as there were centers with >5% retinoblastoma patients older than 5 years when diagnosed. Although median delay of consultation decreased overtime, it was still long at 4 to 6 months. Delay was similar in unilateral and bilateral disease despite bilateral disease presenting at an earlier age indicating that there are constant factors that lead to delay. These factors have to be addressed since longer lag time leads to more extraocular disease.[2]

Males were more affected at 58% similar to India despite the disease having no reported global sex preponderance. Huang et al attributed this to the higher number of males in China.[6] However, Gao et al suggested that this maybe secondary to tradition that males are more likely to receive specialized care than female.[7] However, there was no significant difference in mean lag of consultation between genders (4 months vs. 4, $p = 0.67$).[4] There was also no significant difference in survival rates between males and females (83 vs. 78%, $p = 0.67$).[4]

Unilateral disease (79%) outnumbered bilateral disease. However, Chen et al had a high proportion of patients with bilateral disease (67%), higher than Kaliki et al's (43%) in India.[11,13] Family history, common in bilateral disease, was lower though than other Asian countries including in India.[14,15] Leukocoria remained the most common presenting symptom and, if not associated with other symptoms, exhibited higher survival rate at 85%. This was attributed to leukocoria being a sign that the retinoblastoma was being exophytic and decreasing the change of posterior extension.[4]

As preferred therapeutic procedures changed over time, new classification systems were also introduced such as the IIRC and ICRB.[16,17] Six articles used the IIRC, while two used the ICRB. One used an International Retinoblastoma Classification (IRC), while another did not use any classification system. Only one articles used the International Retinoblastoma Staging System, while three used the pathologic system of the TNM classification.[2–4,6] There were no standard classification and staging system used. This should be addressed since standardizing retinoblastoma reporting can paint a clearer picture of the clinical profile of the patients in China and it can better assist in the creation of treatment protocols. Around 40% (≥2145 eyes: 1,286 [IIRC], 589 IRC and 270 (ICRB) had advanced intraocular disease (grade D and E eyes), lower than India's 56%.[18] At least 415 (9%) patients had extraocular

disease, higher than reported by Jubran et al in Los Angeles, California, at 5%[19] but below the reported rates in India (~17%), Mexico (29%), and Malaysia (55%).[20,21] Despite lower proportion of extraocular disease as a result of exclusion in some of the articles reviewed, many authors claimed that patients with advanced disease were commonly seen.

NSE, a derivative of neuroectodermal or neuroendocrine tumors, was found elevated in patients with extraocular retinoblastoma or those with distant metastasis.[6] As such, Huang et al suggested its use as a marker for extraocular disease.[6] Other markers used for monitoring extraocular activities were survivin, livin, and VEGF.[10] They were found to be lower when IAC and systemic chemotherapy were used together compared to when IAC was used alone.[10] These markers are not commonly used in other countries for diagnosing and monitoring retinoblastoma patients.

Enucleation was the most used treatment procedure specially in unilateral disease. This can be explained by the inclusion of a large clinicopathologic article in the study. There was no significant difference in the mean age at consult, at enucleation, ethnicity, parents' educational level, household income, medical insurance coverage and patient's birth place, and overall lag time between those with no HRF and those with HRF.[9] Lag time from the time of diagnosis to intervention was correlated to increased proportion of HRF. This was explained by the health system of China where despite being diagnosed early in the primary level, the patient had to be enucleated in a tertiary institution. Factors like enucleation hesitancy, finances, and surgery scheduling were also contributory.[9] There were centers where chemotherapy had overtaken enucleation as the most used treatment. Chemotherapy was delivered mostly intravenously and intraarterially. However, there were only limited centers with the expertise and equipment to perform said procedures especially IAC.[10,11] Gao et al gave adjuvant chemotherapy and radiotherapy even for IIRC group B and C eyes.[2] Treatment depended on laterality, extent, and patient preference. Luo et al presented two systemic VEC regimens, one for intraocular mass reduction and the other for extraocular.[4] For unilateral disease belonging to groups A to C, eyes were treated with focal therapy, with or without chemotherapy and EBRT or local radiotherapy.[4] For unilateral disease belonging to groups D and E, patients were primarily offered enucleation.[4] For those who refuse, a higher dose VEC was given. If not responsive, enucleation was again offered.[5] For enucleated with HRF, a different regimen of systemic chemotherapy of carboplatin and etoposide imatinib platinum glycoside was used.[6] For bilateral disease, systemic chemotherapy was a mainstay.[4] Periocular carboplatin was also administered in eyes with advanced disease.[4] For uncontrolled advanced disease, the eye was enucleated.[4] Although the indication for IAC use was not listed, IAC was used as primary or adjuvant treatment in treating Grade A to E eyes.[10]

For extraocular cases, enucleation, high-dose systemic chemotherapy, EBRT to orbit and site of metastasis, periocular chemotherapy, and autologous stem cells transplantation were used.[4,6] For those with intracranial metastasis, intrathecal cytarabine, methotrexate, and dexamethasone were given.[6] Overtreatment even without indication can predispose patients to more long-term side effects, secondary neoplasm, and lower quality of life in the future.[5] As such, standard guidelines need to be established or followed. Refusal for treatment including enucleation and treatment abandonment in China was low, a common occurrence in other Asian coutries.[21–23] However, some articles used treatment refusal and abandonment as exclusion criteria which may explain the low numbers.

Conclusion

The clinical profile of retinoblastoma patients in China changed overtime with the age of consult being younger and extraocular extension was low. Although enucleation remained the most common procedure, chemotherapy in all forms had been used at almost the same rate. Globe salvage rate and overall survival rate were high and opportune for a country that ranks second in annual retinoblastoma incidence.

Conflict of Interest
None declared.

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