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Clinical spectrum and treatment outcome of retinoblastoma with Group D and E diseases

A single institution retrospective review

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Abstract

The purpose of our study was to evaluate the ocular survival and event-free survival after multimodal therapy for group D and E of retinoblastoma (RB). Enucleation of group D and E is controversial as the risks of chemotherapy must be weighed against the potential for vision.

A 10-year retrospective study from one center of 86 patients with advanced intraocular disease defined as International Classification Retinoblastoma (ICRB) group "D" or "E." Cases with visible extraocular extension at diagnosis were excluded. Ocular survival and patient survival were assessed. Indirect ophthalmoscopy at examination under anesthesia to visualize the tumor was used to evaluate clinical response.

The median onset age in 86 patients with group D or E eye was 16 months (1–167 months). There were 29 (34%) bilateral cases. Leukocoria was the most common presentation sign (61%). Chemoreduction was primarily used in the treatment of intraocular RB. Selective ophthalmic arterial injection (SOAI) was applied as a component of multimodal therapy in 34 of the 86 cases. The globe preservation rate in patients with group D or E eyes was 19%. Using chemoreduction for advanced eyes, more eyes are being preserved which enables 70% 5-year ocular survival in patients with group D eyes.

In triaging appropriate patients, multidisciplinary strategy can reduce tumor size with chemoreduction and consolidate the regressed tumor with local ophthalmic therapy to ensure globe salvage.

Abbreviations: COG = Children's Oncology group, EBRT = external beam radiotherapy, ICRB = International Classification Retinoblastoma, RB = Retinoblastoma, RE = Reese–Ellsworth, SOAI = Selective ophthalmic arterial injection.

Keywords: chemoreduction, enucleation, retinoblastoma, selective ophthalmic arterial injection

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1. Introduction

Clinicians have sought to improve the success rate of eye preservation and salvage useful vision. Chemoreduction is the commonly used frontline management option for intraocular retinoblastoma (RB),[1] and it has no late side effects following external beam radiotherapy (EBRT). Chemotherapy can cure not only recurrence but also primary tumors. However, systemic chemotherapy can rarely cure vitreous seeding, but selective ophthalmic artery injection (SOAI) using melphalan with additional topotecan and/or carboplatin can achieve globe salvage for advanced intraocular RB.[2] Therefore, the study was conducted to evaluate the efficacy and safety of multimodal therapy for eradication of vitreous seeds and maintenance of visual function.

The experts have an expanding armamentarium to treat advanced intraocular disease, which includes chemotherapy administered through different routes of administration.[2] Repetitive SOAI followed by delayed enucleation might increase the chance of developing metastasis in potentially high risk cases.[3] Fundoscopy measurements to obtain images of the retinal surface for guiding treatment decisions are becoming increasingly available.

2. Methods

2.1. Patients and disease characteristics

A retrospective study of children diagnosed with intraocular RB from 2007 to 2016 at Chang Gung Memorial Hospital was undertaken. Advanced RB was defined as International Classifi-

cation of Retinoblastoma (ICRB) Groups "D" or "E" using the Children's Oncology group (COG) version. Computerized tomography and/or magnetic resonance imaging of the orbit and brain were performed to exclude gross optic nerve and central nervous system involvement. All patients underwent dilated fundus examination under general anesthesia before chemoreduction and were assessed based on the International Classification of Retinoblastoma (ICRB). The clinical findings were assessed using fundus photography (RetCam camera; Clarity Medical Systems, Pleasanton, CA). Only groups D and E eyes with more than 12 months' follow-up were analyzed. Clinical spectrum and treatment outcome were studied. The collected data included information on demographics, clinical findings, management, and treatment outcomes. The exclusion criteria were follow-up time of <6 months, extraocular RB at initial presentation, or trilateral RB. The patients and their families were informed of the possible risks and benefits of chemoreduction, and written informed consent was given by parents/guardians in all cases.

2.2. Study definitions

Primarily enucleated eyes were defined as eyes that were enucleated fewer than 30 days after coming to Chang Gung Memorial Hospital. The criteria for secondary enucleation were not well defined but were dominated by refractory subretinal and vitreous seeding, vitreous hemorrhage and secondary glaucoma. Secondary enucleation was performed if there was failure of local tumor control following chemoreduction and local treatment in group D and E eyes, that is, progressive tumor growth or tumor recurrence. Clinical parameters such as patients' and tumor characteristics were analyzed at baseline before the administration of treatment. The suitability of the fit of ICRB grouping was reviewed by the expert ophthalmologist, Dr Kao.

Subjects were censored at the time of enucleation, end of therapy, death, lost to follow-up, or at the end of the study period. The timing, number and type of salvage treatment were recorded. Ocular consolidation treatments included diode laser photocoagulation, transpupillary thermotherapy (TTT), cryotherapy, subtenon carboplatin injection, and SOAI.[4,5]

2.3. Treatment schema and follow-up

The treatment modalities included primary enucleation alone, vision-preserving treatment, and enucleation with salvage chemotherapy and/or ERBT. Vision-preserving treatment included chemoreduction and ocular consolidation treatment. Chemoreduction was primarily used in the treatment of intraocular RB. Patients with overt extraocular disease or metastatic spread were not included in this analysis. The chemotherapy protocol, including 6 cycles of intravenous cyclophosphamide, vincristine, etoposide, and carboplatin, is administered every 21 days.[6] Most patients received additional TTT, some received local treatment with laser coagulation, cryotherapy, intra-arterial and intravitreal chemotherapy. Treatment failure was defined as tumor progression, extrascleral extension, or local recurrence. At any suggestion of tumor progression, the eye needs enucleation or EBRT.

Written informed consent was obtained from parents/legal guardians and assent from the child where appropriate as per institutional guidelines. Institutional review board approval was required at the treating institution before starting data collection. All chemotherapy drugs used were approved by the Pediatric Oncology Review Board.

2.4. Statistical analysis

We analyzed comparisons between age groups, bilateral, and unilateral disease using the Mann–Whitney *U* test. We analyzed the correlation between these variables with the chi-square test. Kaplan–Meier survival data with the log-rank test were used to evaluate ocular survival (defined as survival of the eye; no enucleation), and the Mantel–Cox test was used to compare survival curves. An event was defined as enucleation or EBRT. Ocular survival was defined per patient or per eye as the time interval from date of study entry to date of enucleation or date of last follow-up. In all cases, 95% confidence intervals were used and 5-year ocular survival was analyzed.

3. Results

In our study, charts of 91 patients were reviewed during a study period of 10 years. Four patients were excluded because enucleation had been performed as the primary treatment at another hospital. One with extraocular extension was confirmed by an ophthalmic pathologist. Demographics and clinical features of the 86 patients were summarized in Table 1. The median age at first diagnosis of RB was 16 months. Of the 115 eyes with intraocular diseases, those treated with primary therapy eyes were classified according to the ICRB classification as group A (n=6), B (n=10), C (n=8), D (n=12), or E (n=79). The majority of affected eyes were group E (69%), followed by group D (10%), group C (7%), group B (9%), and group A (5%).

The median onset age in 81 patients with group D or E eye was 16 months (1–167 months). Leukocoria was the most common presentation sign (74%). Chemoreduction was primarily used in the treatment of intraocular RB. The goal was to shrink the tumor to facilitate local treatment methods. SOAI was applied as a part of multimodal therapy in 27 of the 81 cases.

The ICRB and treatment of each eye is summarized in Table 2, data are shown separately for the unilateral or bilateral group. Of the 66 eyes managed with vision-preserving therapy, 23 eyes developed progressive disease during the course of treatment and were subsequently enucleated. In our study, as opposed to 100% enucleation, globe salvage was achieved 73% for group D eyes and 44% for group E eyes with vision-preserving therapy.

Ocular survival curves were significantly different ($P=.03$), with 5-year survival of respectively 74.3% in group D (95% CI, 56.0–92.6%) versus 42.9% in group E (95% CI, 29.1–56.6%) (Fig. 1). Ocular survival curves were not significantly different ($P=.17$), with 5-year survival of respectively 37.4% in bilateral eyes (95%CI, 22.7–52.2%) vs 52.1% in unilateral eyes (95% CI, 30.4–73.9%) (Fig. 2).

4. Discussion

RB grouping as determined by ICRB classification is the strongest predictor of ocular salvage. With the intended use of chemoreduction and local therapy, patients can be treated without histopathological confirmation for assessment of risk factors for disease dissemination and prognosis.[7] The ICRB and Reese–Ellsworth (RE) classifications had been found to be rationally concordant when the classifications were further subdivided into A–B–C vs D–E for the ICRB classification and I through IV vs V

Table 1

Patients demographic features (115 eyes of 86 patients).

Feature	n	Percentage
Age (months) (median, range)	16 (1–167)	
Gender		
Male	48	56
Female	38	44
Age at retinoblastoma diagnosis		
<1 yr	32	37
1–2 yr	31	36
>2 yr	23	27
Laterality		
Unilateral	57	66
Bilateral	29	34
Eye affected		
Right	53	46
Left	62	54
Presenting signs		
Leukocoria	60	61
Impaired vision	8	9
Strabismus	8	9
Red eyes	4	5
Sore eyes	2	2
Floaters	1	1
Glaucoma	1	1
Swollen eyelid	1	1
Follow-up of retinopathy of prematurity	1	1
Treatment for retinoblastoma		
Primary enucleation	44	51
Secondary enucleation	23	27
Chemoreduction	44	51
Selective ophthalmic arterial injection	34	40
Local ophthalmic therapy	34	40
External beam radiotherapy	17	20
Vital status at the end of follow-up		
Alive	79	92
Dead	7	8

for the RE classification.[8] The overall survival and event-free survival in both groups were parallel. The presence of vitreous or subretinal seeding is the key feature for enucleation (groups A–B–C) from those containing more advanced tumors (groups D–E) with a high risk.[9] However, there is still no consensus over the best chemotherapy protocol. Multiple treatment modality had augmented the chemotherapy effect and enhanced the success rate. Given its relative rarity, data on enucleation-free survival for eyes with group D and E are limited. Rarity of RB has precluded randomized clinical trials in this patient population, and treatment has been based upon small case series and expert opinions.

There is a paucity of studies on visual outcomes in ICRB Group D and E eyes. The majority of D and E eyes worldwide are primarily enucleated, because disease is difficult to cure with systemic chemotherapy. For D eyes salvaged with systemic chemotherapy, visual acuity is usually poor.[10] The tumor in group E eyes is extensive and has destroyed the eye, which are rarely salvageable and required enucleation as the primary treatment. The ICRB can be of assistance in predicting chemoreduction success for RB.[8] Chemotherapy is effective for RB and the targeted treatment route depends on the clinical features and anticipated outcomes.[11]

Unilateral group D or E RB most often requires enucleation. Enucleation is an excellent way to cure RB confined to the eye. However, there are a few significant limitations or clinical problems to be solved. First, risk stratifications for the inclusion criteria in our studies were based on the conventional clinical parameters (age, the presence of metastasis, significant residual tumor). Second, the number of patients enrolled in our single institution was low due to the rarity of RB.

The results were heterogeneous: Retrospective analysis suggests a beneficial role of chemoreduction in RB with group D and E eyes, but this role has been debated given the long-term sequelae of chemotherapy in infants and young children that constitute majority of the patients with RB. Even if a control group of patients treated with enucleation was not included in this study, our results are comparable with the literature, as reported group E with enucleation-free is over 40%.

Several limitations of this study exist, including the single-center, retrospective nature, and small sample size. It is difficult to draw robust conclusions on the benefits of different treatment regimens on clinical outcome. It is arguable, as to whether or not to give chemotherapy to patients with early stage tumors in lower doses or shorter durations.[12,13]

Table 2

Classification and treatment (115 eyes of 86 patients).

			Treatment		
Group	ICRB	n (%)	Primary enucleation alone	Vision-preserving treatment	Enucleation with salvage chemotherapy and/or ERBT
Unilateral	A	0	0	0	0
	B	3 (5%)	0	3	0
	C	1 (2%)	0	1	0
	D	6 (11%)	1	5	0
	E	47 (82%)	30	9	8
	Total	57	31	18	8
Bilateral	A	6 (10%)	0	3	3
	B	7 (12%)	0	6	1
	C	7 (12%)	0	6	1
	D	6 (10%)	0	6	0
	E	32 (56%)	2	27	3
	Total	58	2	48	8

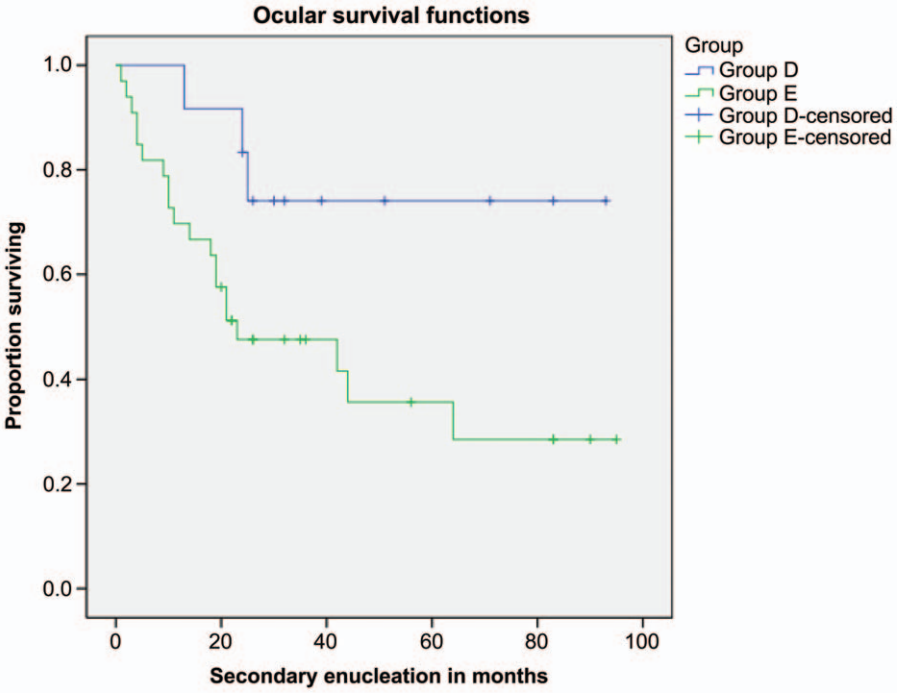

Figure 1. Enucleation-free survival rate in patients with retinoblastoma was notable between group D and group E.

Our experience in RB with group D and E eyes suggests that chemoreduction followed by local treatment might offer the hope of circumventing the need for enucleation without jeopardizing survival rates. At present, it does not appear justifiable to use this treatment except in appropriately designed controlled trials. However, this hypothesis needs to be addressed in future studies.

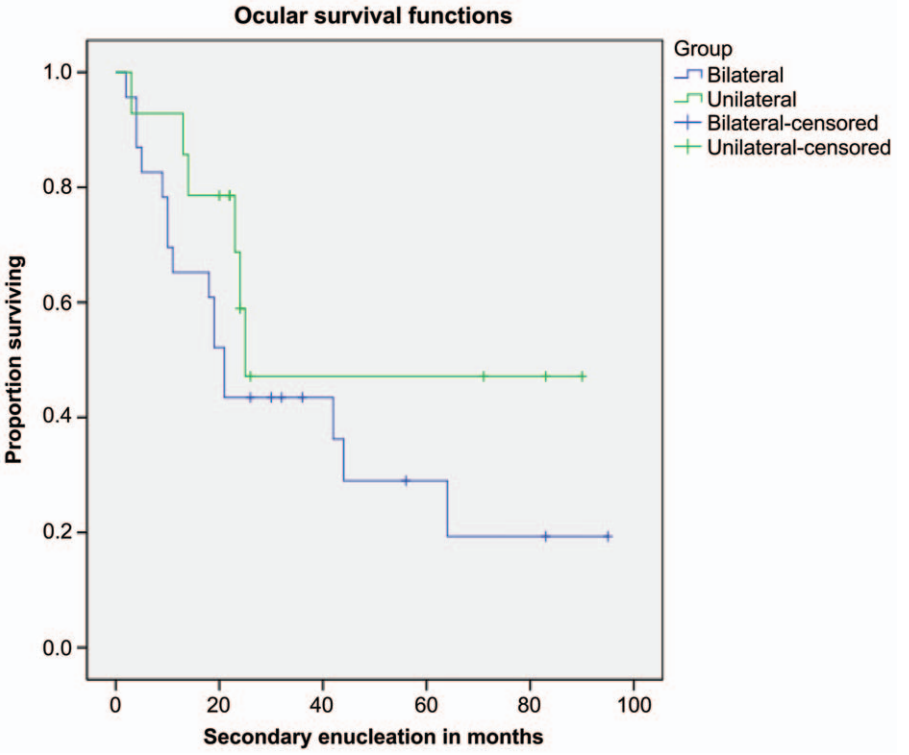

Figure 2. Enucleation-free survival rate in patients with retinoblastoma was not significantly different between unilateral eye and bilateral eyes.

Author contributions

LY Kao and YJ Tsai contributed to the conception of the work. PY Weng and SH Yang searched the literature and extracted the data. SH Chen and CK Tseng wrote the manuscript. PK Tsay developed the theoretical formalism, performed the analytic calculations and performed the numerical simulations. TH Jaing revised the manuscript and produced the final version. All authors read and approved the final manuscript.

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