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Management and Outcomes of Retinoblastoma Cases Presenting to Children's Hospital Westmead, Sydney Between 2008 and 2018

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Abstract: This retrospective review reports on the management and outcomes of retinoblastoma in children treated at Children's Hospital Westmead (CHW), Sydney. Results were compared to those of a previous retrospective review of RB cases presenting between 1974 and 2005 at the same centre, which was published in this journal. A retrospective review of all cases of retinoblastoma presenting to the Children's Hospital Westmead Medical between 2008 and 2018 was conducted. 67 patients were included in the study with a mean age at presentation of 23.5-months and 9.2-months for unilateral and bilateral disease respectively. All patients in our cohort were offered genetic testing. The rate of germline *RB1* mutation in our cohort was 29% for unilateral disease and 86% for bilateral disease. Mean follow-up period was 48 months. Globe salvage rates in patients with bilateral disease was 57%, compared to the previous study which was 47%. The most common treatment-related ocular complication was strabismus. Our cohort had only one patient develop metastatic disease and one patient who presented with trilateral disease, which was a case of delayed presentation and was the only mortality in the study. Morbidity and mortality rates in our cohort are on par with other tertiary centres internationally. There has been a significant improvement in globe salvage rate with our current management protocol. As intra-arterial chemotherapy is implemented into the treatment regime at CHW, these results will provide a benchmark to ensure that the excellent standards of care and outcomes are maintained.

Keywords: Retinoblastoma, Chemotherapy, Enucleation

1. Introduction

Retinoblastoma (RB) is the most common intraocular cancer in childhood with an incidence of one per 15,000 to 20,000 live births. [1] Its pathogenesis lies in a bi-allelic mutation of the *RB1* tumour suppressor gene, which permits malignant transformation of primitive retinal cells. [2-4] A small proportion are due to NMYC gene amplification. [5] Left untreated, RB is almost always fatal [6], but with improvements in detection and treatment, overall survival rates for patients in the developed world with access to appropriate tertiary care are now >95%. [7, 8] Current management strategies for RB are therefore focused on salvaging vision without compromising patient survival. [7, 8] In particular, the evolution of chemotherapy (systemic and local) combined with focal laser treatment and cryotherapy has led to increasingly successful treatment of RB without the need for primary enucleation, which, while a safe and valid treatment in some cases, usually comes at the expense of vision. [7-11]

Additionally, genetic testing for retinoblastoma is now readily available and significantly influences the management of retinoblastoma-affected families in the form of genetic counselling, pre-implantation genetic diagnosis and pre/post-natal genetic screening. [12, 13]

This retrospective review reports the diagnosis, management, and clinical outcomes of retinoblastoma in children presenting to The Children's Hospital at Westmead (CHW) in New South Wales, Australia between 2008 and 2018. As a tertiary referral centre, CHW is referred almost all newly presenting case of retinoblastoma in NSW. We are also referred patients from interstate and overseas centres who require further complex multi-disciplinary management. On average, CHW manages approximately 6-7 new cases per year.

The results of this study were compared to a retrospective review of RB cases that presented between 1974 and 2005 at CHW. [14] It has allowed us to demonstrate that, under our current treatment protocols, our morbidity and mortality rates align with other major international RB treatment centres. This data provides an important benchmark as we assess the effect of newer treatment modalities such as intra-arterial chemotherapy.

2. Methods

Medical records of all patients 16 years or younger presenting to CHW between January 2008 and December 2018 with retinoblastoma were reviewed retrospectively. This included local, interstate patients and those referred from overseas institutions. Retrospective data were manually collected using electronic medical records and paper records as required.

De-identified data was collected regarding patient demographics, clinical presentation, diagnosis, clinical staging, family history, the results of genetic testing, primary and secondary treatment modalities and outcomes including mortality, visual acuity, and ocular and systemic side-effects. Records were reviewed to determine last follow-up, the results of surveillance scans (MRI surveillance) as well as ocular and systemic short, medium, and long-term outcomes. This included reviewing images from examinations under anaesthesia using RetCam photography (Clarity Medical Systems – California, USA). If patients were transferred from interstate or overseas facilities, details of any prior treatments were also recorded as available. Data were analysed using SPSS software version 25 (SPSS Inc- Illinois, USA).

Each eye with a retinoblastoma was categorised according to the International Intraocular Retinoblastoma Classification (IIRC) into groups A, B, C, D, E or unknown if enough data could not be collected to accurately classify them into one of the categories. [15, 16] Patients were then classified according to the more advanced eye for analysis. The classification system is summarised in Table 1.

Table 1. *International Intraocular Retinoblastoma Classification (IIRC)[16].*

	International Intraocular Retinoblastoma Classification (IIRC)
Group A (very low risk)	All tumours are 3 mm or smaller, confined to the retina and at least 3 mm from the foveola and 1.5 mm from the optic nerve. No vitreous or subretinal seeding is allowed.
Group B (low risk)	Eyes with no vitreous or subretinal seeding and discrete retinal tumour of any size or location. Retinal tumours may be of any size or location not in group A. Small cuff of subretinal fluid extending ≤5 mm from the base of the tumour is allowed.
Group C (moderate risk)	Eyes with focal vitreous or subretinal seeding and discrete retinal tumours of any size and location. Any seeding must be local, fine, and limited so as to be theoretically treatable with a radioactive plaque. Up to one quadrant of subretinal fluid may be present.
Group D (high risk)	Eyes with diffuse vitreous or subretinal seeding and/or massive, non-discrete endophytic or exophytic disease Eyes with more extensive seeding than Group C Massive and/or diffuse intraocular disseminated disease including exophytic disease and >1 quadrant of retinal detachment. May consist of 'greasy' vitreous seeding or avascular masses. Subretinal seeding may be plaque-like.
Group E (very high risk)	Eyes that have been destroyed anatomically or functionally with one or more of the following: Irreversible neovascular glaucoma, massive intraocular haemorrhage, aseptic orbital cellulitis, tumour anterior to anterior vitreous face, tumour touching the lens, diffuse infiltrating retinoblastoma and phthisis or pre-phthisis

Primary treatment was defined as the treatment used for tumours found at the baseline examination. Secondary treatment was defined as any further treatment used to treat recurrence of the original tumours or the development of new tumours. The Ophthalmology Unit and the Cancer Centre for Children at CHW employed systemic treatment modalities including intravenous chemotherapy, external beam radiotherapy and high dose chemotherapy autologous stem cell rescue as well as local treatments such as retinal laser or cryotherapy, sub-tenon or intravitreal chemotherapy injections. At the time of this study our centre local intra-arterial chemotherapy (IAC) had not been introduced on site and a small cohort of patients with severe disease refractory to our treatments were referred to one other centre interstate for IAC and data was collected accordingly.

This study was approved by the human research ethics committee of The Children's Hospital at Westmead (HREC reference: 2019/ETH00525).

3. Results

A total of sixty-seven patients presented to CHW with retinoblastoma between January 2008 and December 2018. All sixty-seven patients (44 with unilateral and 23 with bilateral disease at presentation) were included in this study. The most common reason for presentation was leukocoria (73%) and the median age at diagnosis was 13 months (range 0-74 months). Fifty-eight (87%) patients resided locally within the New South Wales, whilst 5 (7%) were referred from interstate and 3 (5%) from overseas centres. Fifty-three (79%) were diagnosed with retinoblastoma at CHW whilst the remaining fourteen (21%) patients were diagnosed

elsewhere and referred to CHW for further investigation and management.

The mean age at presentation was 23.5 (±21) months for unilateral disease compared with 9.2 (±9.1) months in those with bilateral disease. The most common presenting clinical sign in our cohort was leukocoria, which was present in 49 patients (73%). Following this, strabismus was the next most common presenting sign and was present in nine (13%) patients, although only one of these had strabismus alone, the remaining eight presented with strabismus and leukocoria. Six patients (9%) had their tumours detected through early surveillance either due to a known family history and/or a known *RB1* mutation detected by prenatal genetic testing.

Magnetic resonance imaging (MRI) was used as the first diagnostic imaging modality to make the diagnosis of RB in 75% of patients. Computed tomography (CT) was performed to initially make the diagnosis in nine patients (13%) and ultrasound scan (USS) in two (3%). Three patients (4%) underwent examination under anaesthetics (EUA) prior to any diagnostic imaging, however all patients, regardless of how they were diagnosed went on to have EUAs. The small number of CT scans performed at diagnosis were carried out in other centres prior to their referral to our service. Due to the elevated risk of secondary malignancies in children with an underlying *RB1* gene mutation, CT scan was not used in children presenting to or subsequently referred to CHW as part of their diagnostic imaging workup or ongoing surveillance to avoid unnecessary radiation exposure. [17, 18] There were three (4%) patients referred to our institution from other centres where data regarding primary imaging modality was missing.

Table 2. *Patient demographics and International Intra-ocular Retinoblastoma Classification (IIRC) of patients presenting with unilateral disease.*

Unilateral disease at presentation (n = 44)							
IIRC Classification (%)	**IIRC-A 2 (4.5)**	**IIRC-B 7 (15.9)**	**IIRC-D 22 (50)**	**IIRC-E 11 (25)**	**Unknown* 1 (2.3)**	**Retinocytoma# 1 (2.3)**	**Total 44**
Mean age at presentation in months (range)	2.5 (2-3)	15.3 (0-66)	19.5 (2-57)	37.7 (16-66)	10	74	23.5 (0-74)
Male (%)	1 (50)	4 (57)	6 (27)	3 (27)	1 (100)	0 (0)	15 (34)
Female (%)	1 (50)	3 (43)	16 (73)	8 (73)	0 (0)	1 (100)	29 (66)
Mean Follow up in months (range)	40.5 (11-70)	65.6 (6-128)	33.8 (8-79)	49.3 (5-124)	43	36	46.0 (1-128)

* Diagnosis and primary treatment overseas, IICR classification unavailable

Retinocytoma is a benign neoplasm arising from the retina.

Table 3. *Patient demographics and International Intra-ocular Retinoblastoma Classification (IIRC) in the more severe eye of patients presenting with bilateral disease.*

Bilateral disease at presentation (n = 23)					
IIRC Classification (%)	**IIRC-B 4 (17.4)**	**IIRC-D 12 (52.2)**	**IIRC-E 5 (21.7)**	**Unknown 2 (8.7)***	**Total 23**
Mean age at presentation in months (range)	0.3 (0-1)	8.8 (2-32)	13.8 (1-25)	18 (15-21)	9.2 (0-32)
Male (%)	2 (50)	8 (66)	2 (40)	1 (50)	13 (57)
Female (%)	2 (50)	4 (33)	3 (60)	1 (50)	10 (43)
Mean Follow up in months (range)	77.5 (21-101)	40.2 (6-108)	48.6 (11-98)	70.5 (36-105)	51 (6-108)

* Diagnosis and primary treatment overseas, IICR classification unavailable

Six patients (9%) had a positive family history of retinoblastoma (a parent in all cases) and all these patients had germline *RB1* mutations detected on genetic testing. Two of these patients presented with unilateral disease (detected through early screening from the first day of life) and four presented with bilateral disease. All patients in our cohort were offered genetic testing. The families of two patients (3%) declined testing and one patient died before genetic testing could be performed (the only child in the series who died). The incidence of germline *RB1* mutation in patients who underwent testing was 45%. Twenty-three patients who had germline *RB1* mutation detected did not have a family history of RB and eight of these (35%) had unilateral disease on presentation, highlighting the importance of genetic testing regardless of whether the patient has unilateral or bilateral disease at presentation. Two patients, both with bilateral disease on presentation were found to have a 13q4 deletion. Two patients both with unilateral disease on presentation had mosaic *RB1* mutations. Patients with no pathogenic *RB1* mutation detected in their blood who did not undergo an enucleation and therefore did not have tumour tissue available for genetic testing were classified as somatic (that is, no germline *RB1* mutation or 13q4 deletion) for the purposes of this study. Twenty-five patients were classified as somatic with twenty-four presenting with unilateral disease and only one with bilateral disease. Three patients had variants of unknown significance (VOUS) detected in either the tumour and/or blood and were therefore classified as unknown as the pathogenicity of these mutations has not yet been confirmed.

Of forty-four patients presenting with unilateral disease, thirty-one (70.5%) underwent either primary or secondary enucleation and thirteen (29.5%) did not require enucleation (see table 4). Of twenty-three patients presenting with bilateral disease, ten (43.5%) patients underwent primary or secondary unilateral enucleation and two (8.7%) underwent bilateral enucleation. Mean time to primary enucleation (n=31) was 4.89 days. All eyes classified as IIRC-E (n=16) underwent primary enucleation (see tables 4 and 5). Six of these (37.5%) had high risk pathological staging and therefore received six cycles of primary chemotherapy. Of

the twenty-two unilateral IIRC-D eyes, eleven (50%) underwent enucleation and one (4.5%) had high risk pathological staging and therefore received six cycles of primary chemotherapy.

Table 4. *Treatment modalities used for patients presenting with unilateral disease.*

Unilateral disease at presentation (n = 44)							
	IIRC-A (n =2)	**IIRC-B (n =7)**	**IIRC-D (n =22)**	**IIRC-E (n =11)**	**Unknown (n =1)**	**Retinocytoma (n =1)**	**Total (n=44)**
Enucleation (%)							
Primary Enucleation	0 (0)	0 (0)	11 (50)	11 (100)	1 (100)	0 (0)	23 (52)
Secondary Enucleation	0 (0)	1 (14)	7 (32)	0 (0)	0 (0)	0 (0)	8 (18)
No Enucleation	2 (100)	6 (86)	4 (18)	0 (0)	0 (0)	1 (100)	13 (30)
Chemotherapy (%) *							
Primary Chemotherapy *	1 (50)	7 (100)	12 (55)	5 (45)	0 (0)	0 (0)	25 (57)
Secondary Chemotherapy	0 (0)	1 (14)	1 (5)	0 (0)	0 (0)	0 (0)	2 (5)
No Chemotherapy	1 (50)	0 (0)	10 (45)	6 (55)	1 (100)	1 (100)	19 (43)
Focal Therapy (%) #							
Received Focal therapy	2 (100)	3 (43)	3 (14)	0 (0)	0 (0)	0 (0)	8 (18)
No Focal therapy	0 (0)	4 (57)	19 (86)	11 (100)	1 (100)	1 (100)	36 (82)

* - Primary chemotherapy protocol at CHW includes Vincristine, Etoposide and Carboplatin with growth factor support.
# - Focal therapy consisted of retinal cryotherapy and laser therapy (Retinal Frequency Doubled Neodymium-doped Yttrium-Aluminium-Garnet laser 532nm).

Other secondary treatments used in patients presenting with unilateral disease (not contained in table 4) included external beam radiotherapy and autologous stem cell transplant in one patient with IIRC-D disease who underwent enucleation with low-risk histopathology and subsequently developed orbital and lung metastases. One patient with IIRC-D disease received additional sub-tenons injections of topotecan. One patient with IIRC-B disease received secondary intravitreal injections of Melphalan.

Table 5. *Treatment modalities used for patients presenting with bilateral disease.*

Bilateral disease at presentation (n = 23)					
	IIRC-B (n =4)	**IIRC-D (n =12)**	**IIRC-E (n =5)**	**Unknown (n =2)**	**Total (n=23)**
Enucleation (%)					
Primary Enucleation	0 (0)	1 (8)	5 (100)	2 (100)	8 (35)
Secondary Enucleation	0 (0)	2 (17)	0 (0)	0 (0)	2 (9)
Bilateral Enucleation	0 (0)	0 (0)	1 (20)	1 (50)	2 (9)
No Enucleation	4 (100)	9 (75)	0 (0)	0 (0)	13 (57)
Chemotherapy (%) *					
Primary Chemotherapy*	4 (100)	12 (100)	5 (100)	0 (0)	21 (91)
Secondary Chemotherapy	2 (50)	6 (50)	3 (60)	0 (0)	11 (48)
No Chemotherapy	0 (0)	0 (0)	0 (0)	2 (100)	2 (9)
Focal Therapy (%) #					
Received Focal therapy	4 (100)	10 (83)	3 (60)	1 (50)	18 (78)
No Focal therapy	0 (0)	2 (17)	2 (40)	1 (50)	5 (22)

* - Primary chemotherapy regime in CHW was a combination of Vincristine, Etoposide and Carboplatin with growth factor support.
# - Focal therapy consisted of Cryotherapy and laser therapy (Retinal Frequency Doubled Neodymium-doped Yttrium-Aluminium-Garnet laser 532nm).

Other secondary treatments used in patients presenting with bilateral disease (not contained in table 5) included external beam radiotherapy in six patients (three with IIRC-D disease and three with IIRC-E disease). Autologous stem cell transplantation was used in one patient with trilateral disease at presentation (this patient has been included in the bilateral disease table 5) and worse eye classified as IIRC-E disease. One patient with bilateral IIRC-D disease had sub-tenon as well as intravitreal injections of topotecan. Whilst CHW did not perform intra-arterial chemotherapy at the time of the study, two patients with bilateral disease were referred to an interstate centre to receive intra-arterial melphalan (one with IIRC-D disease and one with IIRC-E disease). Both patients had received intravitreal injections of Melphalan prior to this. One additional patient with bilateral IIRC-D disease received intravitreal injection of Melphalan but did not require intra-arterial Melphalan.

The mean follow-up period was 48 (±35) months. Fifty-six (84%) patients were still being followed up at CHW Eye Clinic while eight (12%) have returned for follow-up to their referring institution, two (3%) have been lost to follow-up and one (1%) patient died. Functional visual acuity (defined as binocular visual acuity or monocular if one eye enucleated) at last follow up was better than or equal to 6/12 in 43 (64%) patients, and better than or equal to 6/60 for 50 (75%) of patients. Three patients (4%) had a functional vision worse than 6/60 on last follow up and the visual outcome for 14 (21%) patients is unknown due to incomplete documentation

or follow-up at another institution that could not be obtained.

Ocular adverse outcomes within our study included five (7.5%) patients who developed ptosis, two (3%) who developed a cataract and six (9%) children who developed strabismus. Socket-related pathology (Implant extrusion, post-enucleation socket syndrome and orbital cellulitis) occurred in six patients (19% of enucleated eyes).

During this 10-year review period, two patients developed sensorineural hearing loss secondary to chemotherapy (Carboplatin). One patient developed metastatic disease and one patient had trilateral disease at presentation. This patient had a delayed presentation and was the only patient in the cohort to present with trilateral disease and to die.

4. Discussion

The treatment of RB has evolved and is now focused on optimisation of vision and globe salvage, whilst maintaining excellent overall survival. [7, 8] Chemotherapy (systemic and local) combined with focal laser treatment and/or cryotherapy is routinely used in the successful treatment of bilateral and select unilateral cases of RB without the need for enucleation. [19-21] This study adds to the growing body of evidence regarding RB management and allows for benchmarking and comparison with a previous retrospective review conducted at CHW, of patients presenting with RB between 1974 and 2005. [14] This is particularly important as treatment modalities in Australia move increasingly towards the utilisation of intravitreal and intra-arterial chemotherapy.

Over the 12-year study period there was on average 5.6 new presentations per year compared to 4.6 per annum between 1974 and 2005. [14] This increase in presentation correlates with the population growth within New South Wales and an increase in interstate referrals. The median age at diagnosis was 13 months in our study compared to 15 months between between 1974 and 2005 which may reflect improved screening protocols. [14] This is in-line with a multi-centre global study showing a median diagnosis age of 17-months worldwide. [22]

In terms of management protocols, the intravenous chemotherapy (IVC) regime for CHW currently in use is vincristine, etoposide and carboplatin ("JOE"), every three weeks for three to six cycles. Whilst 33 out of the 43 patients who received chemotherapy between 1974 and 2005 received a similar regime, the remaining ten were treated with single agents or methotrexate. [14] All patients in our cohort received the "JOE" protocol. Another change in treatment protocol is the reduced use of external beam radiotherapy. In the previous study, 35 patients received external beam radiotherapy, compared to 7 patients in our cohort. During the period of the study, CHW reserved the use of external beam radiotherapy for refractory disease or extra-ocular disease only.

In patients presenting with unilateral disease, treatment to preserve the eye was attempted in 21 (47%) of patients. It was successful in 13 patients, the remaining 8 eventually requiring enucleation. The globe salvage rate of 30% in unilateral disease in our centre is in line with other tertiary centres globally which range from 7-40%. [23-25] This salvage rate, compares favourably to the 8% salvage rate our centre between 1974 and 2005 [14] and reflects the significant improvement in treatment modalities and outcomes.

In patients presenting with bilateral disease, globe-salvage treatment was successful in 13 (57%) patients. This is compares with a 47% globe preservation rate in our centre between 1974 and 2005, [14] and is in line with other tertiary centres reporting salvage rates ranging between 28-52%. [25-27] The globe salvage rate amongst patients with IIRC D & E was 26% (13 from 50). During the period of this study, CHW did not routinely use IAC for primary treatment of patients with IIRC D & E disease. The majority of patients with group E disease were treated with enucleation. Intra-arterial chemotherapy was reserved for refractory cases where other treatment modalities had failed. This small cohort of patients were referred to an interstate institution (the Royal Children's Hospital Melbourne) to receive this treatment. Intra-arterial chemotherapy is employed as a primary treatment in centres outside Australia. [28, 29] A recent study from Jules-Gonin Eye Hospital (Lausanne, Switzerland) showed the use of first-line IAC to have shorter treatment duration, better ocular survival and visual acuity compared to group D patients who were treated with other chemotherapy regimens. [30] Similarly, another study from Wills Eye Hospital in Philadelphia examining group D or E patients who had undergone initial IVC therapy followed by subsequent IAC therapy due to recurrence showed a 57% globe salvage rate at 2 years follow up. [30] CHW is now performing IAC and this study provides an essential benchmark of outcomes prior to the implementation of changes to our treatment protocol.

The vast majority of patients in our cohort presented with leukocoria. There were, however, a few atypical presentations that warrant further discussion. The most atypical presentation of RB in our cohort was a patient who presented with leukocoria, raised intraocular pressure and anterior segment inflammation. This patient was therefore classified as group "E" disease and underwent primary enucleation. However, the histopathology did not reveal any anterior chamber tumour cells, instead revealing a sub-acute inflammatory reaction. Another patient presented with unilateral orbital cellulitis including chemosis and the MRI reported "signs of early extension into the retro-orbital space". This patient underwent enucleation of this eye; however, histopathology staging was pT2a with orbital cellulitis present but no signs of tumour extension into the retro-orbital space. This highlights the importance of timely and accurate pathology in guiding treatment.

There were several outliers in our patient cohort that warrant specific discussion. Firstly, two patients in our study underwent bilateral enucleations. One patient had bilateral enucleations as primary treatment overseas prior to presentation to CHW. We did not have details about the classification of these eyes prior to enucleation. Another

patient presented to our centre with pre-septal cellulitis and leukocoria. This patient had been diagnosed interstate with bilateral disease (IIRC B and IIRC E eyes). They had germline mutation without any family history and underwent primary enucleation of the eye with IIRC E disease with adjuvant systemic chemotherapy. Histopathology of the enucleated eye revealed cT3e disease. This patient later required enucleation of the contralateral eye having demonstrated refractory disease after receiving 24 subsequent cycles of secondary intravenous chemotherapy, focal treatment (retinal laser and cryotherapy), IAC Melphalan and external beam radiotherapy.

In our cohort, one patient (1.5%) developed metastatic disease, 6-months following primary enucleation. By comparison, a multicentre, International Collaborative Study reported a 5.2% rate of metastasis, with a median time from presentation to metastasis development of 9.5 months. [22] Our study has a median follow up time of 37 months, which is adequate to capture metastatic disease in most patients. Only seven (10%) of patients in our cohort had a follow up period of less than 9.5 months.

The patient who developed metastatic disease in our cohort the first presented with unilateral disease IIRC-D and underwent enucleation with histopathology reporting pT1 without orbital disease. Given the histopathology, the patient did not receive primary adjuvant chemotherapy. They went on to develop secondary orbital disease and lung metastases 6-months post-enucleation, which was treated successfully with secondary chemotherapy and autologous bone marrow transplantation. This patient remained disease-free at 3 years follow up.

Presentation with pineal (trilateral) RB has been reported in the literature as 0.8% of RB presentations. [31] One patient in our series had delayed presentation and trilateral disease at the time of primary diagnosis. There was an eleven-month history of leukocoria and abnormal visual behaviour with multiple visits to their primary care physician. At the time of presentation to CHW the patient had bilateral disease (IIRC-A and IIRC-E) and underwent prompt enucleation of the worse eye. Pathology on enucleation was pT3b; the tumour had extensively involved the choroid, optic nerve head and the optic nerve up to 0.6mm beyond the lamina cribrosa. It has previously been shown that delay between presentation and diagnosis of >6-months is often predictive of high-risk retinoblastoma on histopathology. [32] This highlights the importance of education of primary healthcare physicians and nurses to enable early identification of leukocoria and timely referral.

Genetic testing was offered to all patients in our cohort. The rate of germline mutations in our cohort (29% of unilateral presentations and 86% of bilateral presentations) is in line with the literature where the detection of germline mutations in unilateral disease ranged between 13-33% compared to bilateral disease at 92-94%. [13, 23, 33] Genetic testing plays a pivotal role in informing patients and their families about the risk to future offspring as well as identifying siblings at risk of disease. Prenatal genetic testing is also available for the offspring of patients with a history of RB, which means that babies identified as having an *RB1* mutation in utero can undergo surveillance (in the form of retinal examination) as early as the first day of life. With the shift towards globe salvage therapies, genetic classification and counselling of patients may become more challenging in the absence of tumour tissue availability for genetic testing. VOUS (variants of unknown significance) add to the complexity of genetic counselling, particularly when there is no primary tumour tissue available for analysis. In these cases, determination of pathogenicity is difficult. These cases are therefore not classified as germline as they do not have a known pathogenic mutation, however this will change in the future as VOUS are correctly assigned a pathogenic label.

Six patients had a family history of Rb in one parent prompting careful prenatal screening and/or surveillance from birth in the form of regular (4-6 weekly) dilated fundus examinations. Disease was therefore detected early (range between 1-day and 115-days old) in these patients. Two of these patients had an *RB1* mutation detected on amniocentesis, the remaining four had subsequent genetic testing shortly after birth and all had germline mutations as expected. Three of the patients with positive family histories had bilateral disease at the time of diagnosis, all of which were classified as either A or B eyes. The remaining three patients had unilateral, unifocal disease at the time of diagnosis (two A eyes and one B eye). Patients who undergo such surveillance have their disease detected extremely early relative to the rest of the cohort and often have unilateral, unifocal tumours at presentation.

One limitation of our study is the duration of follow-up data collected. Given that metastases and adverse outcomes can occur months to years following therapy, there is a possibility that we are under-reporting these due to the variable length of follow-up especially on patients presenting in the latter years of the study and those patients who were referred from interstate or overseas who have since returned to their place of origin. We are continuing to collect data on these patients so that future studies can report on longer-term follow-up outcomes.

5. Conclusion

This study has provided an essential benchmark for our outcomes in the management of retinoblastoma. Results show that our standard of care is on par with other major tertiary centres around the world and also that there has been a significant improvement in outcomes when we compare to the previous study conducted at this hospital. As we move forward and implement intra-arterial chemotherapy into our treatment regime, we will be able to compare outcomes from the next cohort of patients to those found in this study, thus ensuring that we maintain our excellent standard of care.

Conflict of Interest

The authors declare that they have no competing interests.

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