Assessing characteristics of retinoblastoma on visual acuity: a cohort study

Master thesis

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ABSTRACT

Background: Retinoblastoma is a curable eye cancer with high survival rates (>90%) when diagnosed and treated early. Visual prognosis is affected by tumour classification, location, treatment and heredity. While newer treatment modalities enhance globe salvaging and vision preservation, the long-term clinical outcomes of visual acuity (VA) and functional vision are still understudied, leading to challenges for parents in understanding their child's vision.

Aim: To investigate the different factors influencing VA outcomes and functional vision in patients diagnosed with retinoblastoma.

Methods: This retrospective observational cohort study included all patients with retinoblastoma from a national centre between 1991-2015. Patients with missing data on treatment modality and inaccurate VA measurements were excluded. VA outcomes were measured at ages 7, 12, and 18 using the LogMAR scale with recognition acuity. Functional vision was assessed using the international PEDIG scale for visual impairment (VI). Effects of tumour classification, location, treatment modalities and heredity on VA outcomes were analysed.

Results: This study included 271 patients with 379 retinoblastoma-diagnosed eyes. At age 7, enucleation rate was 60% (229 eyes), with 18% experiencing VI. Tumour classification, location, treatment, and heredity were strongly associated with VA outcomes ($p<0.001$). Familial heredity showed the best VA outcomes (LogMAR 0.20), sporadic heredity had severe VI prevalence (31%), and sporadic non-hereditary had high enucleation rates (93%). Foveal tumours resulted in poor VA outcomes (LogMAR 1.80), while peripheral tumours had better outcomes (LogMAR 0.00). Tumour classification, location and treatment are correlated with each other ($p<0.001$). Therefore influencing VA and leading to increased VI in advanced-staged tumours and more aggressive treatments.

Conclusion: Patients with retinoblastoma exhibited high rates of blindness due to enucleation, but maintained high functional vision without VI (82%). Heredity played a vital role, showing the importance of early screening. Tumour location significantly impacted VA outcomes with localization closer to the macula resulting in poorer vision. Less severe tumours received less aggressive treatments, leading to better VA outcomes.

Recommendations: The findings of this study provide valuable insights for personalized support, highlighting the urgent need for a new classification system considering vision preservation and further exploration of vision-related quality of life effects.

Keywords: Retinoblastoma, Paediatric Cancer, Oncology, Visual Acuity

Samenvatting

Achtergrond: Retinoblastoom is een geneesbare oogkanker met hoge overlevingskansen (>90%) indien vroeg behandeld. Tumorclassificatie, locatie, behandeling en erfelijkheid hebben invloed op de visuele prognose. Nieuwere behandelmethoden dragen bij aan behoud van oog en zicht, maar lange termijn resultaten van gezichtsscherpte en functioneel zicht zijn nog onvoldoende bestudeerd, wat ouders uitdaagt bij het begrijpen van het zicht van hun kind.

Doel: Onderzoeken van factoren welke gezichtsscherpte en functioneel zicht beïnvloeden bij patiënten met retinoblastoom.

Methoden: Retrospectieve observationele cohortstudie omvatte alle patiënten met retinoblastoom van het nationaal centrum (1991-2015). Patiënten zonder behandelingsgegevens en onnauwkeurige visusmetingen werden uitgesloten. Gezichtsscherpte werd gemeten op 7, 12 en 18 jaar met behulp van de LogMAR-schaal. Functioneel zicht werd beoordeeld met behulp van de internationale PEDIG-schaal voor visuele beperking (VI). Effecten van tumorclassificatie, locatie, behandelingen en erfelijkheid zijn meegenomen in de analyses.

Resultaten: De studie omvatte 271 patiënten en 379 ogen gediagnosticeerd met retinoblastoom. Op 7-jarige leeftijd was het enucleatiepercentage 60% (229 ogen), met 18% VI. Tumorclassificatie, locatie, behandeling en erfelijkheid zijn geassocieerd met gezichtsvermogen ($p<0.001$). Familiaire erfelijkheid toonde het beste zicht (LogMAR 0.20), sporadische erfelijkheid een hoge prevalentie van ernstige VI (31%) en sporadische niet-erfelijke patiënten hoge enucleatiepercentages (93%). Foveale tumoren resulteerden in slecht zicht (LogMAR 1.80), terwijl perifere tumoren betere resultaten hadden (LogMAR 0.00). Tumorclassificatie, locatie en behandeling zijn met elkaar gecorreleerd ($p<0.001$). Dit beïnvloedt het zicht en leidt tot een verhoogde VI bij tumoren in een gevorderd stadium en bij agressievere behandelingen.

Conclusie: Patiënten met retinoblastoom hebben een hoog percentage blindheid als gevolg van enucleatie, maar behielden een hoog functioneel zicht zonder VI (82%). Erfelijkheid speelde een essentiële rol, waarbij het belang van vroegtijdige screening werd benadrukt. Tumorlocatie had een aanzienlijke invloed op gezichtsscherpte, vooral bij locaties dichter bij de macula, wat resulteerde in slechter zicht. Minder ernstige tumoren kregen minder agressieve behandelingen, wat leidde tot beter zicht.

Aanbevelingen: De bevindingen van deze studie bieden waardevolle inzichten voor gepersonaliseerde ondersteuning bij patiënten en benadrukken de dringende noodzaak van een nieuw classificatiesysteem welke rekening houdt met het behoud van het zicht. Bovendien is verder onderzoek naar de effecten van zicht op kwaliteit van leven gewenst.

Trefwoorden: Retinoblastoom, Kinderkanker, Oncologie, Visus

INTRODUCTION

In the Netherlands one in 17.000 children is born with Retinoblastoma (Rb)[1]. Rb is the most common malignant intraocular paediatric tumour, which can be lethal if left untreated[2]. When a child is diagnosed with Rb, there is a 60% chance of having a non-hereditary, and 40% chance of having a hereditary form[3]. The hereditary form can occur as sporadic, first generation/patient in a family, or as familial Rb hereditary[4]. Non-hereditary Rb typically presents unilaterally, while hereditary Rb can present either as unilateral or bilateral and often with multiple tumours[5]. Currently, Rb has a high survival rate (>90%), which is achieved by early diagnosis and, in case of advanced disease, by a more aggressive approach through removal of the eye (enucleation)[6]. Earlier identification leads to better tumour control, patient survival and better visual acuity (VA)[7].

Rb is considered a curable cancer, and treatments are aimed at saving the child`s life. Subsequently, choices for preservation and optimizing visual outcomes are made[8]. The management of Rb has drastically changed over the years. Enucleation used to be the only treatment option[9]. With the advent of new treatment options, in addition to an improved survival rate, the globe salvage rate has also continued to improve, allowing us to include the decision on treatment for vision preservation[10].

The first available type of treatment for globe salvage was external beam radiotherapy (EBRT). EBRT is also used in cases of extra-ocular tumour growth, orbital recurrence, and positive optic nerve margin[11]. In severe cases, eyes could be preserved, but visual outcome would remain poor depending on tumour location and late side effects of the treatment[12]. Visual outcome can be compromised, for example due to radiation retinopathy, cataract and, keratopathy[11]. Due to the extreme side effects, EBRT is no longer the first treatment option in globe salvaging[13]. Facial disfigurement affects the patient's appearance to such an extent that quality of life is also compromised[14].The eventual development of second primary tumours in the irradiated field in hereditary patients is one of the most dangerous side effects of EBRT, which may still eventually lead to death[15].

A newer form of treatment that emerged afterwards is systemic chemotherapy, which must be combined with local treatment[8,16]. The degree of late side effects is much lower with this therapy, and vision is most often stable throughout life[17]. For small tumours, local treatment options are cryotherapy, plaque radiotherapy, and laser photocoagulation. Since 2010, the treatment with selective intra-arterial chemotherapy (SIAC) is added to the management of Rb, allowing for better preservation of eyes that previously had to be enucleated with no need for systemic chemotherapy to be applied aswell[18]. A side effect that has a strong

influence on VA outcome is the development of chorioretinal ischemia and atrophy[19]. Despite the limited prognosis for vision, many parents prefer globe salvage treatments over enucleation because of the potential psychosocial consequences associated with enucleation, that distress families[20,21].

Rb affecting the macular region, will lead to VA decrease[12,22–24]. In addition, VA decrease can also develop due to amblyopia, which can be superimposed on the underlying organic ocular disease. Besides organic amblyopia[25], functional amblyopia[26] can be present, which can be reversible with occlusion therapy[27].

The current understanding of VA outcomes in Rb is limited and lacks precision[16,28]. Factors like tumour location, classification, and treatment modality contribute to the variability of VA outcomes, but existing literature is based on small sample sizes and outdated treatment[12,22–24,28]. Most studies focus on monocular vision, neglecting crucial data related to the patient's daily life functioning. Limited studies that consider both eyes' VAs also suffer from small sample sizes[22,23]. For example, a study with 22 patients found that 23% of 4-year-olds had visual impairment (VI), with 81% requiring enucleation[23]. Another study of 8-year-old patients with bilateral Rb reported a complete blindness rate of 22%[22]. To capture a comprehensive understanding, it is essential to consider binocular or functional vision, which encompasses the visual capabilities of the patient's better eye.

Having a clear view on the expected VA outcome and functional vision after Rb diagnosis or treatment is challenging for healthcare practitioners due to the complex interplay of various Rb associated factors. As a result, parents often find it challenging to understand what their child's vision will be like both in childhood and adulthood. Identifying key factors that influence visual outcomes, will bring more clarity to clinical practice, which can aid healthcare practitioners in providing parents with informative and reliable guidance regarding the expected VA outcome of their child with Rb.

The aim of this study is to investigate the different factors influencing VA outcomes and functional vision in patients diagnosed with Rb.

METHODS

Study design and setting

This retrospective observational cohort study was conducted at the Dutch Retinoblastoma Expertise Centre of Amsterdam UMC, the sole Rb expertise centre in the Netherlands since 1991[29]. Electronic patient files of the Dutch Rb cohort were searched for individuals diagnosed between January 1991 and December 2015. Patients with Rb received regular monitoring for recurrences in early childhood, and those born to parents with familial hereditary Rb underwent preventive screening from birth. The orthoptist examined the children at least once a year, while adult patients underwent ophthalmic checks every two years. The data used in this study were collected as part of routine medical care, and no additional interventions were conducted specifically for this study.

Participants and study size

The incidence of Rb in the Netherlands is approximately ten new cases per year. For the current study, all patients diagnosed with Rb between 1991 and 2015 in the Dutch Rb cohort were included, providing an estimated sample size of around 240 patients. Patients born until 2015 were included, in order to ensure the necessary 'adult-like' VA outcome that can be measured at age 7[30–32]. Exclusion criteria were missing data regarding treatment modality or inaccurate VA measurements. To ensure data quality and accuracy, the patients excluded by two researchers (D.L. and N.B) were assessed a second time by two other experts (A.M. and H.M.J), with any ambiguities or uncertainties being resolved through discussion.

Variables

The study focused on variables in Rb, including tumour location, classification, treatment and heredity. Heredity was classified as non-hereditary sporadic, hereditary sporadic, or hereditary familial[33]. Tumour location categories included foveal, juxtafoveal macular, papillo-macular, or peripheral[33]. The International Classification of Retinoblastoma (ICRB) was used to determine the severity of Rb based on treatment failure risk[34]. An ophthalmologist with expertise in Rb determines the classification at the initial visit. Treatment modalities were classified as enucleation, EBRT, SIAC, local treatment (plaque radiotherapy, cryotherapy, and laser photocoagulation), or local treatment with systemic chemotherapy (e.g., thermo-chemotherapy). Treatment selection depended on the Rb classification and tumour location.

Data sources / measurement

Data on VA can be collected in either resolution or recognition acuity[31]. The 'adult-like' VA was measured in recognition acuity, for example, with a letter acuity card. It is difficult to determine when a child's visual function is fully adult-like[31]. Letter acuity is indicated to be at adult value at the age of 5[35] or 6[30]. Other studies on multiple versions of recognition acuity have shown that it reaches its optimum development between the ages of 7 and mid-teens[31,32]. Hence, a minimum age of 7 years was selected to enable comparison with adult-like VA. Furthermore, monocular distance VA measurements were conducted at ages 12 and 18 using an ETDRS chart (letter acuity) by an orthoptist and converted to the logarithm of MAR (logMAR) for data analysis[36]. VA is a continuous parameter which also contains some qualitative measures of poor vision. Qualitative VA like counting fingers, hand motion, light perception and no light perception were converted to a decimal acuity (Appendix 1)[37–39]. In case of enucleation of an eye, VA outcome was considered equivalent to no light perception. The healthy eyes functioned as a control group and was used to calculate the functional vision outcome on patient level. Functional vision in daily life was determined based on the best VA outcome of both eyes, and thereafter categorized into three groups using the standardised Pediatric Eye Disease Investigator Group (PEDIG)[40–43] scale for visual impairment (Appendix 1).

Statistical methods

Demographic and clinical data were analysed using R Studio version 2022.7.2.576[44]. Descriptive statistics were applied to the demographic data, presenting measures of central tendency. Due to a non-normally distributed dataset a median and 95% Confidence Interval (CI) was displayed for the total Rb population and Inter Quartile Range (IQR) for the variables affecting VA outcome.

Kruskal-Wallis two-sided test was used to investigate the correlation between the age of diagnosis and heredity status for comparisons between clinical characteristics.

The association between the VA outcome and the Rb variables (heredity, tumour classification, location and treatment) was examined using Fisher's exact test due to a cell count of less than 5 in more than 20% of the cells. The effect size of these tests was assessed using Cramer's V test, scaled from 0 (no association) to 1 (complete association)[45]. A p-value of <0.05 was considered statistically significant.

Reporting and Ethical statement

This cohort study adhered to the 'Strengthening the reporting of observational studies in epidemiology' (STROBE) [46] guideline for reporting and followed the principles of the Helsinki Declaration (2013) [47]. As it involved analysing pre-collected data from routine visits, it was not subject to the Medical Research Involving Human Subjects Act (WMO). Approval was obtained from the Medical Ethics Committees (METC) of Amsterdam UMC (MEC-2015-109) after obtaining parental consent for inclusion in the Dutch Retinoblastoma Register.

RESULTS

A total of 291 patients (151 males [56%]) were part of the Dutch Retinoblastoma Cohort during the data collection. After screening, 20 patients were excluded. Ten patients deceased before the age of 7 years. Nine were lost to follow up leaving no VA measurements, four of these did not show up at regular visits and the other five moved and had controls at other hospitals. One patient was excluded with inaccurate VA measurements due to intellectual disability. Figure 1 shows the presenting characteristics of the patients, including their age, sex, age at diagnosis, heredity status, and the distribution of the classified tumour. Of the included 271 patients, 379 eyes were diagnosed with Rb, with a median age of diagnosis at 14 months. Most of the tumour stages were classified as stage D (39%, 149 eyes). Sporadic non-hereditary was the most common heredity form of Rb (51%, 138 eyes). The mean age of Rb diagnosis was 1.19 [95%CI 0.1-5.5] years for all patients.

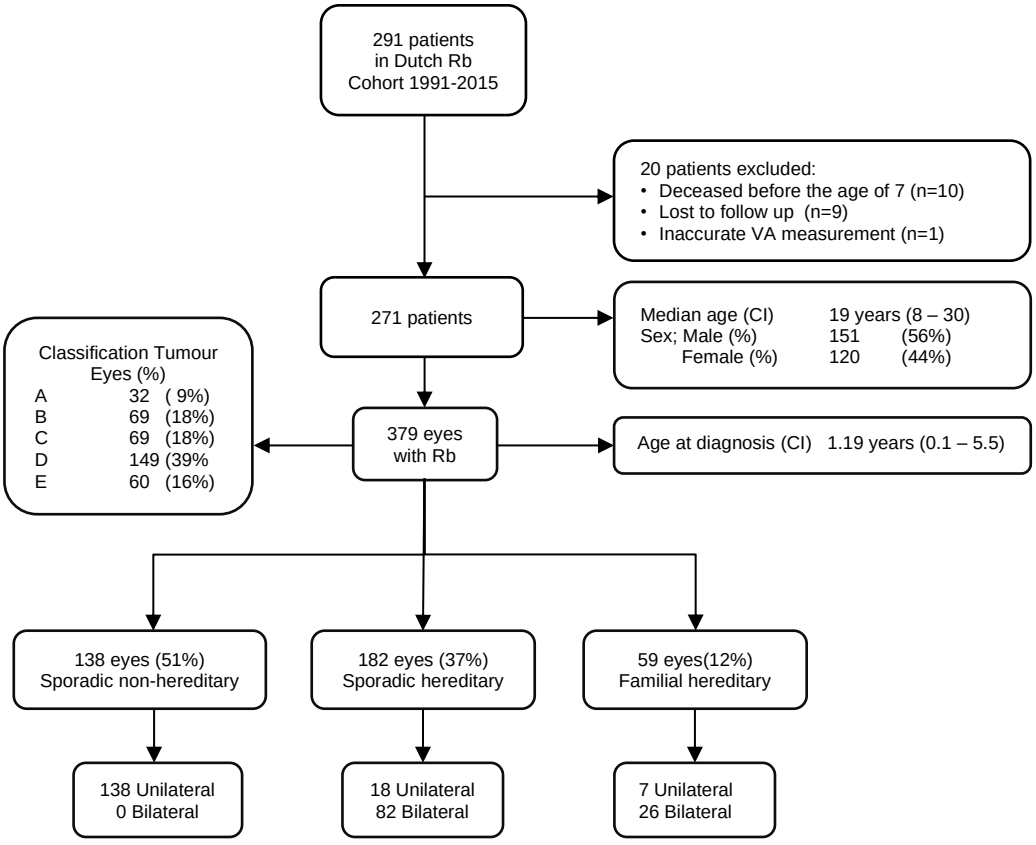

***Figure 1**. Figure of demographic data of Rb patients.*

Rb = Retinoblastoma; N= number of patients; CI = 95% Confidence Interval; VA = Visual Acuity

VA outcome and functional visiosn

Visual acuity outcome is in 80% of the eyes lower than LogMAR 0.3 and in 76% lower than LogMAR 0.7. The median VA outcome for all eyes diagnosed with Rb, including the enucleated eyes, is LogMAR ≥3 [CI ≥3-0.0] at age 7 (table 1). The functional vision per patient, assessed by the VA outcome for the eye with better VA outcome per patient, is LogMAR 0.00[CI 2.80-0.20]. According to the measures of the PEDIG scale for VI[40–43], 82% (222 of 271) of all Rb patients at age 7 had no VI (LogMAR ≤0.2). At this age, 5% were moderately visually impaired (LogMAR 0.3–0.6) and 13% are severely visually impaired (LogMAR ≥0.7).

***Table 1**. Median VA outcome of all eyes with and without Rb*

Visual acuity outcome						
Age	**Eyes***	**Eyes with Rb**** [CI]		**Eyes***	**Eyes without Rb**** [CI]	
		Decimal acuity	**LogMAR**		**Decimal acuity**	**LogMAR**
7	377	0.00 [0.00 – 1.00]	≥3 [≥3 – 0.00]	157	1.00 [0.80 – 1.20]	0.00 [0.10 – -0.08]
12	312	0.00 [0.00 – 1.20]	≥3 [≥3 – -0.08]	119	1.20 [1.00 – 1.60]	-0.08 [0.00 – -0.20]
18	225	0.00 [0.00 – 1.20]	≥3 [≥3 – -0.08]	69	1.20 [1.00 – 1.60]	-0.08 [0.00 – -0.20]

Functional Vision						
Age	**Patients***	**Vision of the best eye**** [CI]		**PEDIG scale**		
		Decimal acuity	**LogMAR**	**Severe VI**	**Moderate VI**	**No VI**
7	264	1.00 [0.01 – 1.20]	0.00 [2.00 – -0.08]	13%	5%	82%
12	218	1.00 [0.01 – 1.60]	0.00 [2.00 – -0.20]	13%	5%	82%
18	146	1.20 [0.00 – 1.60]	-0.08 [≥3 – -0.20]	23%	5%	72%

Rb = Retinoblastoma; CI = Confidence interval; * = number of eyes of which VA could be determined; ** = All data presented as median [CI]; PEDIG = Pediatric Eye Disease Investigator Group; VI = Visual Impairment

The results presented in Table 1 were calculated from the total Rb population, which includes blindness due to enucleation and comprises 60% of Rb eyes (229 eyes). The VA outcome and functional vision of the remaining preserved eyes (40%, 150 eyes) are presented in Table 2. The median VA outcome is LogMAR 0.15[IQR 1.00-0.00] at age 7.

***Table 2.** Median VA outcome of preserved eyes with Rb*

Visual acuity outcome				
Age	**Enucleation** n (%)	**Eyes***	**Preserved eyes with Rb** [IQR]	
			Decimal acuity	**LogMAR**
7	229	148	0.70 [0.10 – 1.00]	0.15 [1.00 – 0.00]
12	192	120	0.65 [0.05 – 1.00]	0.19 [1.30 – 0.00]
18	143	82	0.75 [0.05 – 1.15]	0.13 [1.30 – -0.06]

Rb = Retinoblastoma; IQR = Inter Quartile Range; *= number of eyes with Rb without enucleations of which VA could be determined; ** = All data presented as median [CI]; PEDIG = Pediatric Eye Disease Investigator Group; VI = Visual Impairment

The VA outcome has remained relatively stable from ages 7 to 18. Of the total of 379 eyes, only eight eyes had a decreased VA outcome over time. Six out of the eight eyes received local treatment, particularly around the macula. The other two underwent EBRT of which one

received this treatment after the age of 7. Conversely, there were a total of four out of the 379 eyes whose VA outcome improved over time after EBRT treatment.

VA outcome and functional vision in heredity forms

Age of diagnosis varied among the different heritability types, as shown in Figure 2. The median age of diagnosis for familial, sporadic hereditary and sporadic non-hereditary was 0.16[95%CI 0.02-1.8], 0.9[95%CI 0.12-3.6] and 2.1[95%CI 0.3-6.9] years, respectively. There was a significant difference in age of diagnosis between the three heredity types ($p<0.001$) and within each group ($p<0.001$).

Bilateral Rb was present in 40% of the patients (n=108), of which 82 patients were diagnosed with sporadic hereditary and 26 with familial hereditary Rb.

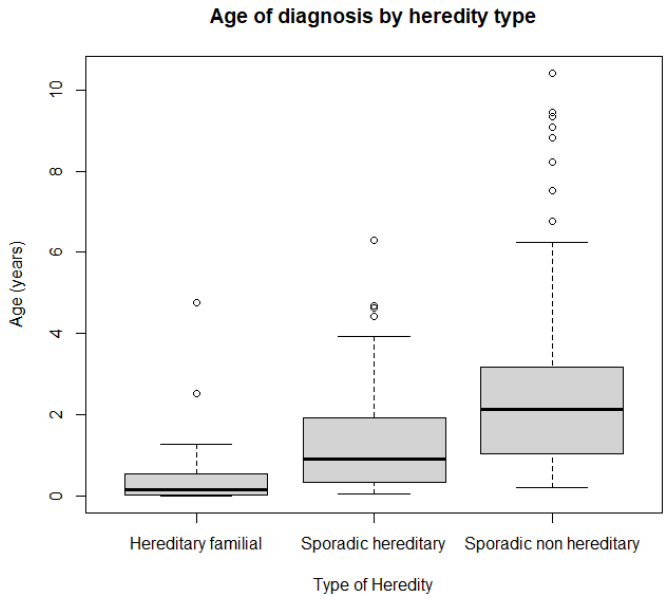

***Figure 2**. Age of diagnosis categorized by heredity type; familial, sporadic heredity and sporadic non-hereditary with a significant difference in age of diagnosis between the three heredity types ($p<0.001$) and within each group ($p<0.001$).*

The median VA outcome for familial heredity is LogMAR 0.2[IQR 1.70-0.00], sporadic hereditary LogMAR ≥3[≥3-0.20], and sporadic non-hereditary LogMAR ≥3[≥3-≥3] (table 3). At ages 12 and 18, there were no cases of severe VI in the sporadic non-hereditary group. In the familial hereditary group, 10% had severe VI age 18, and in the sporadic heredity group, 38% had severe VI.

Table 3. *Median VA outcome of all Rb eyes in different heredity forms*

Visual acuity outcome							
Heredity type	**Age**	**Eyes***	**VA Outcome / eye** [IQR]				
			Decimal acuity	**LogMAR**			
Familial hereditary	7	59	0.60 (0.02 – 1.00)	0.20 (1.70 – 0.00)			
	12	52	0.60 (0.02 – 1.00)	0.20 (1.70 – 0.00)			
	18	39	0.60 (0.02 – 1.00)	0.20 (1.70 – 0.00)			
Sporadic hereditary	7	181	0.00 (0.00 – 0.60)	≥3 (≥3 – 0.20)			
	12	148	0.00 (0.00 – 0.50)	≥3 (≥3 – 0.30)			
	18	109	0.00 (0.00 – 0.40)	≥3 (≥3 – 0.40)			
Sporadic non hereditary	7	137	0.00 (0.00 – 0.0)	≥3 (≥3 – ≥3)			
	12	112	0.00 (0.00 – 0.0)	≥3 (≥3 – ≥3)			
	18	77	0.00 (0.00 – 0.0)	≥3 (≥3 – ≥3)			
Functional vision							
Heredity type	**Age**	**Patients****	**At patient level (based on best eye)**** [IQR]		**PEDIG scale**		
			Decimal acuity	**LogMAR**	**Severe VI**	**Moderate VI**	**No VI**
Familial hereditary	7	33	1.00 (0.80 – 1.00)	0.00 (0.10 – 0.00)	9%	9%	82%
	12	29	1.00 (0.80 – 1.20)	0.00 (0.10 – -0.08)	3%	14%	83%
	18	22	1.00 (0.80 – 1.20)	0.00 (0.10 – -0.08)	10%	14%	76%
Sporadic hereditary	7	100	0.80 (0.20 – 1.00)	0.10 (0.70 – 0.00)	31%	8%	61%
	12	81	0.90 (0.10 – 1.20)	0.05 (1.00 – -0.08)	33%	9%	58%
	18	58	0.95 (0.05 – 1.20)	0.02 (1.30 – -0.08)	38%	7%	55%
Sporadic non hereditary	7	138	1.00 (1.00 – 1.20)	0.00 (0.00 – -0.08)	0%	2%	98%
	12	111	1.20 (1.00 – 1.20)	-0.08 (0.00 – -0.08)	0%	0%	100%
	18	75	1.20 (1.20 – 1.20)	-0.08 (-0.08 – -0.08)	0%	0%	100%

Rb = Retinoblastoma; IQR = Inter Quartile Range; PEDIG = Pediatric Eye Disease Investigator Group; VI = Visual Impairment;

* = number of eyes with Rb of which VA could be determined; Rb Pat = Number of patients with Rb in this category;

** = Total amount of patient numbers in each age category

Table 4 presents the VA outcome of the preserved eyes in the different heredity forms. In the familial Rb group, a total of six eyes (10%) were enucleated. Among the 53 eyes that were not enucleated, the median VA outcome is LogMAR 0.10[IQR 0.82–0.00]. The sporadic heredity had 94 eyes (52%) enucleated, and the VA outcome of the preserved 87 eyes has a median LogMAR of 0.19[IQR 1.00–0.00]. For the sporadic non-hereditary Rb group, 93% of the eyes were enucleated (129 eyes), and the VA outcome of the eight preserved eyes is LogMAR 0.80[IQR 1.90–0.70].

A moderate association (V=0.337) was found between the VA outcome and heredity using the Fisher`s exact test (two-sided p<0.001).

***Table 4**. Median VA outcome of preserved eyes in different heredity forms*

Visual acuity outcome					
Heredity type	**Age**	**Enucleations** n (%)	**Eyes***	**VA Outcome / eye** [IQR] **Decimal acuity**	**LogMAR**
Familial hereditary	7	6 (10%)	51	0.80 [0.15 – 1.00]	0.10 [0.82 – 0.00]
	12	6 (12%)	46	0.80 [0.33 – 1.00]	0.10 [0.48 – 0.00]
	18	6 (15%)	33	0.80 [0.30 – 1.00]	0.10 [0.52 – 0.00]
Sporadic hereditary	7	94 (52%)	86	0.65 [0.10 – 1.00]	0.19 [1.00 – 0.00]
	12	81 (54%)	67	0.70 [0.08 – 1.00]	0.15 [1.10 – 0.00]
	18	62 (57%)	47	0.70 [0.05 – 1.20]	0.15 [1.30 - -0.08]
Sporadic non hereditary	7	129 (93%)	8	0.02 [0.01 – 0.19]	0.80 [1.90 – 0.70]
	12	105 (94%)	7	0.02 [0.02 – 0.31]	0.80 [1.90 – 0.51]
	18	75 (97%)	2	0.03 [0.03 – 0.04]	0.50 [1.60 – 1.40]

n = number of enucleated eyes; % = amount of patients receiving enucleation. Calculated: number of enucleations divided by complete group of related heredity type; IQR = Inter Quartile Range; * = number of eyes of which VA could be determined.

VA Outcome and classification

The VA outcome categorized according to ICRB classification shows that the median VA outcome at classification A is logMAR 0.00[IQR 0.10-1.00] after which it decreases once the classification becomes higher (Table 5). Classification B has a median outcome of 0.22[IQR 1.00-0.00] and classification C LogMAR 1.70[IQR ≥3-0.48]. The median VA outcome for classification D and E are both ≥3 [IQR ≥3-≥3].

***Table 5.** VA outcome of preserved eyes with Rb categorized per classification type*

Visual acuity outcome				
Class*	**Age**	**Eyes***	**VA Outcome** median [IQR] **Decimal acuity**	**LogMAR**
A	7	32	1.00 [0.80 – 1.00]	0.00 [0.10 – 1.00]
	12	25	1.00 [0.90 – 1.20]	0.00 [0.05 - -0.08]
	18	17	1.00 [1.00 – 1.20]	0.00 [0.00 - -0.08]
B	7	69	0.60 [0.10 – 1.00]	0.22 [1.00 – 0.00]
	12	55	0.60 [0.10 – 1.00]	0.22 [1.00 – 0.00]
	18	37	0.60 [0.30 – 1.20]	0.22 [0.53 - -0.08]
C	7	69	0.02 [0.00 – 0.33]	1.70 [≥3 – 0.48]
	12	57	0.02 [0.00 – 0.30]	1.70 [≥3 – 0.53]
	18	41	0.02 [0.00 – 0.10]	1.70 [≥3 – 1.00]
D	7	149	0.00 [0.00 – 0.00]	≥3 [≥3 – ≥3]
	12	129	0.00 [0.00 – 0.00]	≥3 [≥3 – ≥3]
	18	100	0.00 [0.00 – 0.00]	≥3 [≥3 – ≥3]
E	7	60	0.00 [0.00 – 0.00]	≥3 [≥3 – ≥3]
	12	46	0.00 [0.00 – 0.00]	≥3 [≥3 – ≥3]
	18	30	0.00 [0.00 – 0.00]	≥3 [≥3 – ≥3]

Class* = Classification type according to The International Classification of Retinoblastoma (ICRB). Ranked from A (very low risk) to E (very high risk) of treatment failure with systemic chemotherapy combined with local therapy [34,48];
IQR = Inter Quartile Range; * = number of eyes of which VA could be determined, enucleations are excluded.

A strong association (V=0.523) was found between the VA outcome and classification using the Fisher`s exact test (two-sided p<0.001).

VA outcome and functional vision in tumour locations

Table 6 displays the VA outcomes of preserved eyes per tumour zone. The maximum VA outcome is 1.0 LogMAR when a tumour affects the fovea. If the tumour is juxtafoveal, the maximum VA outcome is 0.15 LogMAR at age 7 and 0.4 LogMAR at 18 years for patients treated with laser photocoagulation. For a tumour located in the papillomacular zone, the maximum VA outcome is -0.08 LogMAR, the same as a tumour in the peripheral zone. A tumour only in the peripheral zone does not result in a VA outcome below 0.5 LogMAR.

***Table 6**. VA outcome of preserved eyes with Rb in different retinal locations*

Visual acuity outcome				
Tumour location	**Age**	**Eyes***	**VA Outcome / eye** [IQR] **Decimal acuity**	**LogMAR**
Foveal	7	34	0.02 (0.01 – 0.04)	1.80 (2.22 – 1.39)
	12	27	0.02 (0.02 – 0.05)	1.80 (1.80 – 1.30)
	18	20	0.02 (0.01 – 0.05)	1.80 (2.48 – 1.30)
Juxta	7	57	0.02 (0.02 – 0.10)	1.80 (1.80 – 1.00)
Foveal /	12	44	0.05 (0.02 – 0.10)	1.30 (1.80 – 1.00)
Macular	18	32	0.05 (0.02 – 0.10)	1.30 (1.80 – 1.00)
Papillo	7	94	0.40 (0.05 – 0.90)	0.40 (1.30 – 0.05)
Macular	12	77	0.40 (0.05 – 0.90)	0.40 (1.30 – 0.05)
	18	56	0.30 (0.05 – 0.93)	0.50 (1.30 – 0.03)
Peripheral	7	92	0.90 (0.40 – 1.0)	0.05 (0.40 – 0.00)
	12	81	1.00 (0.40 – 1.20)	0.00 (0.40 – -0.08)
	18	60	1.00 (0.18 – 1.20)	0.00 (0.75 – -0.08)

Rb = Retinoblastoma; IQR = Inter Quartile Range from 25-75%; * = number of eyes of which VA could be determined, enucleations are excluded. Patient number decreases with age due to amount of patient not reaching the stated age.

A strong association (V=0.638) was found between the VA outcome and location using the Fisher`s exact test (two-sided p<0.001).

VA Outcome and side effects in treatment modalities

Out of the total 382 eyes, 229 (60%) underwent enucleation, of which ten patients required bilateral enucleation (table 7). All ten patients had sporadic hereditary Rb, and in these eyes, the tumour stage was classified as stage C for 5% (1 eye), stage D for 70% (14 eyes), and stage E for 25% (5 eyes).

Table 7. *VA outcome in the different treatment groups*

Treatment	**Age**	**Eyes***	**VA Outcome** median [IQR]	
			Decimal acuity	**LogMAR**
EBRT	7	56	0.35 [0.09 – 0.73]	0.46 [1.05 – 0.14]
	12	49	0.40 [0.05 – 0.80]	0.40 [1.30 – 0.10]
	18	38	0.25 [0.05 – 0.80]	0.60 [1.30 – 0.10]
SIAC	7	17	0.02 [0.01 – 0.20]	1.70 [2.00 – 0.70]
	12	6	0.08 [0.03 – 0.78]	1.10 [1.52 – 0.11]
	18	0	NA	NA
Local treatment	7	45	1.00 [0.70 – 1.00]	0.00 [0.15 – 0.00]
	12	42	1.00 [0.60 – 1.20]	0.00 [0.22 - -0.08]
	18	29	1.00 [0.60 – 1.20]	0.00 [0.22 - -0.08]
Thermo chemotherapy	7	22	0.75 [0.05 – 1.00]	0.13 [1.30 – 0.00]
	12	18	0.75 [0.03 – 1.00]	0.13 [1.52 – 0.00]
	18	8	0.20 [0.02 – 1.00]	0.70 [1.70 – 0.00]

Rb = Retinoblastoma; EBRT = external beam radiotherapy; SIAC = selective intra-arterial chemotherapy; IQR = Inter Quartile Range from 25-75%; * = number of eyes of which VA could be determined. Patient number decreases with age due to amount of patient not reaching the stated age; NA = Not Applicable due to not yet using SIAC at that time.

Two eyes treated with SIAC exhibited side effects, with one eye developing cataract and the other eye having retinal and vitreous haemorrhages. Eyes treated with EBRT demonstrated an increased occurrence of complications over time, including radiation cataract (35 eyes), radiation keratopathy (19 eyes), and radiation retinopathy (12 eyes).
Patients who underwent laser photocoagulation as a treatment for a tumour near the macular region experienced a decrease in VA outcome at 12 and 18 years, in comparison to the age of 7.

A strong association (V=0.557) was found between the VA outcome and treatment using the Fisher`s exact test (two-sided $p<0.001$).

Rb associated factors

Heredity, tumour classification, location, and treatment are strongly associated with VA outcome ($p<0.001$). Between these factors, there is also a high degree of association between tumour classification, location, and treatment (Figure 3). Heredity is not associated with the other factors.

	Heredity	**Classification**	**Location**	**Treatment**
Heredity	-	P = 0.597 V = 0.09	P = 0.472 V = 0.08	P = 0.764 V = 0.08
Classification	P = 0.597 V = 0.09	-	P < 0.001 V = 0.467	P < 0.001 V = 0.452
Location	P = 0.472 V = 0.08	P < 0.001 V = 0.467	-	P < 0.001 V = 0.410
Treatment	P = 0.764 V = 0.08	P < 0.001 V = 0.452	P < 0.001 V = 0.410	-

- = Not feasible otherwise this variable is compared. = not statistically significant associated

Figure 3. *Associations among variables*

DISCUSSION

Current study highlights four key factors that contribute to the VA outcome and functional vision in patients with Rb, providing more clarity to clinical practice and giving valuable information for parents. Firstly, heredity played a significant role in the VA outcome, with familial hereditary Rb demonstrating the most favourable outcome. Therefore, showing the value of early screening. Secondly, the choice of treatment modality is associated with the third factor tumour classification, enabling localized treatment for less severe tumours and yielding improved VA outcomes. Fourth, the location of the tumour remains a critical determinant of the VA outcome, with tumours located closer to the fovea showing the poorest VA outcomes.

This study presents findings from the largest cohort of patients with Rb to date, offering a comprehensive understanding of variation in VA outcomes. Previous studies reported overall VA outcomes for the entire patient group, ranging from 23% to 74% with a VA outcome <0.3 LogMAR and enucleation rates between 31% and 82%[12,22–24,49]. In our study, 76% of patients achieved a VA outcome <0.3 LogMAR, with a 60% enucleation rate. However, it should be noted that our cohort included 271 patients with Rb, in contrast to the smaller studies (ranging from 11 to 24 patients[12,23,24,27]) focusing on specific subpopulations (e.g. macular tumours[24,27], hereditary Rb[49], treatment specific[12,49]). Among the preserved eyes, 59% had a VA outcome <0.3 LogMAR. Functional vision assessment for both eyes at the patient level is rare. In our cohort, 82% had no VI. Other studies, limited to hereditary Rb, reported 26%[22] up to 54%[49] with no VI. Within our hereditary Rb patients, 34% had no VI.

Comparing the different factors contributing to VA outcome with other studies, there is one larger study, relatively outdated, which included 116 patients with hereditary Rb[22]. Reporting a 55% enucleation rate, in comparison, our study observed an enucleation rate of 41% for hereditary Rb. The differences may be attributed to the practice of referring patients to specialist centres where enucleation was often the initial treatment for the first affected eye. Our findings supports the importance of early screening[33,50], leading to earlier diagnosis and better VA outcomes in our cohort for familial Rb.

Consistent with previous research[12,22–24], our study confirms that tumours in the fovea have the poorest prognosis, not exceeding 1.0 LogMAR. However, as literature depicts not all macular tumours lead to the wordt prognosis [24], we observed that juxta-foveal tumours could achieve a maximum VA outcome of 0.4 LogMAR. Nevertheless, our longitudinal data revealed a decline in VA outcome over time for macular tumours treated with laser

photocoagulation, indicating the progression of scar formation as a consequence of the treatment[51].

The VA outcome in Rb varied depending on the treatment approach. Initially, EBRT was commonly used for eye preservation but had immense side effects[13,15]. Newer techniques prioritize both globe salvaging and vision preservation. Local treatment had the best VA outcomes. SIAC had poorer outcomes which was primarily used in advanced-stage tumours and is a relatively new treatment whereby a smaller patient group existed in this cohort. Limited research exists, Rishi et al. (2020)[52] reported a VA outcome of LogMAR ≤1.0 in 62% of the patients, which is comparable with our study's finding of 71%.

The current study offers an important advantage by including the VA outcome of the healthy eye, providing valuable insights for healthcare practitioners and making it highly relevant to clinical practice. This information can help parents understand their child's daily functional vision. In contrast to other studies focusing on VA outcomes in affected eyes[12,22–24,49], our study considers both eyes, providing a comprehensive understanding of VI in daily life. Furthermore, the study's inclusion of the entire cohort of patients with Rb avoids selection bias towards severe cases, in contrast from previous studies where patients had already undergone enucleation elsewhere before evaluation at the expertise centre[22]. Additionally, the study benefits from a relatively long follow-up period, allowing for VA outcome assessment at multiple ages.

Despite its strengths, our study has a few limitations. Different treatment modalities were used over time, making it difficult to compare VA outcomes across different time periods. While subgroups were established to address this issue, smaller groups were eventually analyzed. Furthermore, the study did not take into account newer treatment options such as intravitreal chemotherapy, as it was not utilized at our center of excellence until after the study's inclusion period ended in 2015[53]. The study's retrospective design limits control over data collection, relying on existing data without additional assessment of the actual impact of patients' vision on their quality of life. Although VA outcomes of both eyes were collected, binocular vision and the impact of unilaterality on quality of life were not examined as well[20,21].

Implications for clinical practice and future research

This study provides valuable insights into expected vision outcomes for patients with Rb, enhancing counseling for parents. The findings enable personalized support in home and school settings, supporting information provided towards healthcare workers. Further research is needed to develop a prediction model that combines the study's findings and explores the relationship between heredity, as a separate factor, and the correlation between tumour location, classification, and treatment. As new treatment options emerge, including vision preservation in Rb management becomes increasingly important. Furthermore, as we are on the verge of making vision preservation decisions in addition to patient survival and globe salvage, there is a pressing need for a new classification system that considers factors associated with vision outcomes like tumour location. Additionally, studies evaluating quality of life, impact of vision, and unilateral enucleation can offer valuable insights for this future perspectives.

CONCLUSION

Patients diagnosed with Rb experience a high rate of functional vision without VI in 82% of cases. However, the enucleation rate is significant at 60%, resulting in blindness in the affected eye. Heredity played a crucial role, with sporadic non-hereditary Rb having a 93% likelihood of requiring enucleation. However, functional vision remains good (LogMAR 0.00) in this group due to the unilateral nature of non-hereditary cases. Early screening benefits familial hereditary Rb, leading to VA outcome of LogMAR 0.20. Prognosis is primarily determined by tumour location, with macular tumors associated with the poorest VA outcomes. Ongoing research is necessary to accurately assess VA outcomes and treatment effectiveness in specific subgroups receiving the latest treatment options.

Expected vision outcomes facilitates personalized support, but require further exploration to combine study findings. A classification system that takes vision preservation into account is necessary. Assessing quality of life, and the impact of vision, and unilateral enucleation is essential for future research.

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APPENDIX

Appendix 1

PEDIG scale for VI	Snellen ratio	Decimal acuity	LogMAR
No VI	20/20	≥1	≤0
	20/25	0.8	0.1
	20/32	0.6	0.2
Moderate VI	20/40	0.5	0.3
	20/80	0.25	0.6
Severe VI	20/100	0.2	0.7
	20/200	0.1	1.0
	20/400	0.05	1.3
	20/1500 (CF)	0.014	1.8
	20/4000 (HM)	0.0052	2.3
	LP+	0.0016	2.8
	LP-	0	≥3

*PEDIG = Pediatric Eye Disease Investigator Group; VI = Visual Impairment; CF = Counting Fingers; HM = Perception of Hand Movement; LP+ = Light perception; LP- = No light perception

Visual acuity scale for visual impairment. This scale shows the category range adapted for low vision**.** VA is depicted in measures of Snellen ratio, LogMAR en Decimal acuity. Qqualitative VA like counting fingers, hand motion, light perception and no light perception a conversion to LogMAR and Decimal acuity is added[37–39]. The Pediatric Eye Disease Investigator Group (PEDIG)[40–43] scale for visual impairment is used to categorize the VA into three groups: ≤0.2, 0.3–0.6 and ≥0.7 logMAR.