

## REVIEW ARTICLE



# Retinoblastoma: emerging concepts in genetics, global disease burden, chemotherapy outcomes, and psychological impact

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In this review we discuss several recent concepts regarding retinoblastoma control and its impact. In a cohort of 482 patients with solitary unilateral retinoblastoma revealed germline mutation in 16% and the likelihood of germline retinoblastoma was greater for younger children ( $\leq 1$  year versus (vs.)  $> 1$  year at presentation) with odds ratio (OR) 2.96 ( $p = 0.001$ ), and greatest for the youngest infants ( $\leq 3$  months vs.  $> 3$ –12 months) (OR 5.52) ( $p = 0.002$ ). Retinocytoma/retinoma, a benign variant of retinoblastoma, was studied in 78 tumours and demonstrated transformation into retinoblastoma in 9.2% by 5 years and 15.3% by 10 years and 20 years. An international global study on retinoblastoma over 1.5 years revealed 4351 new patients and 85% from low- and middle-income countries, notably with older age at detection and greater risk for metastasis. Management of retinoblastoma in 964 eyes using intravenous chemotherapy showed 20-year globe salvage at 96% in group A, 90% in group B, 90% in group C, 68% in group D, and 32% in group E eyes. The 5-year globe salvage with intra-arterial chemotherapy for 160 eyes (655 infusions) with retinoblastoma showed success in 100% for group B, 80% for group C, 78% for group D, and 55% for group E. The psychological impact of retinoblastoma on the parents revealed depression (73%), anxiety (64%), and/or stress (100%), and on the patient revealed deficits in quality of life issues. Retinoblastoma is a challenging disease and chemotherapy provides reliable tumour control and globe salvage. Continuing efforts to improve quality of life issues is important.

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## INTRODUCTION

Retinoblastoma is a dangerous malignancy that classically occurs in the eye(s) of children. In high-income countries, including the United States and most of Europe, this malignancy is commonly detected prior to invasion of the optic nerve, choroid, sclera, and orbit and systemic survival is favorable. However, in low and middle-income nations, particularly in Africa, this malignancy demonstrates evidence of invasive disease, with risks for local and remote metastasis and systemic chemotherapy is necessary for survival [1–6]. The management of retinoblastoma includes enucleation, methods of chemotherapy by various routes of intravenous, intra-arterial, intravitreal, and intracameral infusion, and focal therapies with plaque radiotherapy, cryotherapy, and laser photocoagulation/thermotherapy [1, 7, 8].

In this review, we will cover recently-published topics related to risk for germline mutation in children presenting with solitary unilateral retinoblastoma, risk for benign retinocytoma/retinoma transformation into active malignant retinoblastoma, retinoblastoma survival outcomes based on global income and the American Joint Committee on Cancer (AJCC) 8th edition, trilateral retinoblastoma screening, long-term globe salvage following intravenous and/or intra-arterial chemotherapy, and the psychological impact of this disease on the patient and the family.

### Germline mutation in unilateral solitary retinoblastoma

Previous publications have documented germline mutation in unilateral solitary retinoblastoma at approximately 7–33% of

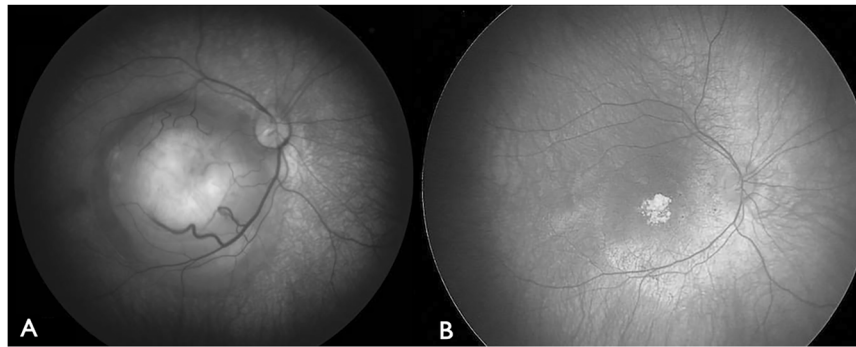
patients [9–13]. Schüler et al. reviewed 188 patients with solitary unilateral retinoblastoma and found 13% with genetic testing showing germline mutation [9]. Brichard et al. found similar 11% of 36 patients with solitary unilateral retinoblastoma showing germline mutation, and with mean age of 22 months at presentation [10]. Nichols et al. found 14% of 173 patients with sporadic unilateral retinoblastoma showing germline mutation [11]. Gregersen et al. reviewed a database from 1943 to 2013 of solitary unilateral retinoblastoma and found only 7% with germline mutation [12]. Berry et al. found 18% of 182 patients with solitary unilateral retinoblastoma without family history of retinoblastoma with germline mutation, several with mosaicism [13]. Others have noted up to 30% and 33% of solitary unilateral retinoblastoma with germline mutation [14, 15].

Shields et al. recently reviewed a large cohort of 482 patients with solitary unilateral retinoblastoma over nearly 50 years and found 16% were likely germline mutation based on positive family history, development of new tumours or bilateral disease, and the “gold standard” of genetic testing for germline mutation [16] (Fig. 1). They commented that genetic testing was not universally available so they used the all-inclusive term of “likely germline mutation”, based on the above features of family history, tumour multiplicity/bilaterality, as well as genetic testing. They found that likelihood for germline mutation in unilateral solitary retinoblastoma varied depending on age (0–1 year,  $> 1$ –2 years,  $> 2$ –3 years,  $> 3$  years) with results showing (29%, 17%, 8%, 9%,  $p = 0.001$ ). (Table 1) Further analysis into infants (0–3 months,  $> 3$ –6 months,

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**Fig. 1 Unilateral sporadic retinoblastoma in a child.** Unilateral sporadic retinoblastoma in a child of 13 months of age with a 17% risk for germline mutation (See Table 1). **A** Before and **(B)** after intra-arterial chemotherapy.

**Table 1.** Likelihood of germline mutation with solitary retinoblastoma based on patient age group at presentation in 482 cases.

Outcomes	Age Bracket				<i>p</i> value	Total
Outcomes for all patients of any age	Age 0–1 year	Age >1–2 years	Age >2–3 years	Age >3 years		Overall
	( <i>n</i> = 132)	( <i>n</i> = 122)	( <i>n</i> = 97)	( <i>n</i> = 131)		( <i>N</i> = 482)
	[ <i>n</i> (%)]	[ <i>n</i> (%)]	[ <i>n</i> (%)]	[ <i>n</i> (%)]		[ <i>N</i> (%)]
Likely germline disease*	<i>n</i> = 126	<i>n</i> = 117	<i>n</i> = 93	<i>n</i> = 126		<i>n</i> = 462
No	89 (71)	100 (85)	86 (92)	115 (91)	<b>0.001</b>	390 (84)
Yes	37 (29)	17 (17)	7 (8)	11 (9)		72 (16)
Outcomes for infants of ≤12 months of age	Age 0–3 months	Age >3–6 months	Age >6–9 months	Age >9–12 months		Total
	( <i>n</i> = 23)	( <i>n</i> = 27)	( <i>n</i> = 42)	( <i>n</i> = 40)		( <i>N</i> = 132)
	[ <i>n</i> (%)]	[ <i>n</i> (%)]	[ <i>n</i> (%)]	[ <i>n</i> (%)]		[ <i>N</i> (%)]
Likely germline disease*	<i>n</i> = 23	<i>n</i> = 25	<i>n</i> = 40	<i>n</i> = 37		<i>n</i> = 126
No	9 (39)	20 (80)	31 (76)	29 (78)	<b>0.009</b>	89 (71)
Yes	14 (61)	5 (20)	10 (24)	8 (22)		37 (29)

Bold *p* values indicate statistical significance.

\*Likely germline disease defined by positive family history of retinoblastoma, development of bilateral tumours or new tumours, and/or germline positive genetic testing.

Information adapted from Shields CL, Dockery PW, Ruben M, et al. Likelihood of germline mutation with solitary unilateral retinoblastoma based on patient age at presentation. Analysis of 482 consecutive patients. *J Pediatr Ophthalmol Strabism*. 2021. Jun 1;1–10. <https://doi.org/10.3928/01913913-20210414-02>. Online ahead of print [16].

>6–9 months, >9–12 months) with solitary unilateral retinoblastoma revealed results showing (61%, 20%, 24%, 22%,  $p = 0.009$ ).

These findings are relevant to decisions from ocular oncologists regarding patient management based on the presence or absence of germline disease. For patients with germline mutation, an attempt to conserve both eyes as well as protect from pinealoblastoma and second cancers is considered.

Currently, the use of next-generation sequencing (NGS) has advanced our understanding of retinoblastoma. Children with unilateral retinoblastoma could potentially be served with NGS of the cell free DNA (cfDNA) in the blood and aqueous humor to confirm the diagnosis of retinoblastoma and provide information on subtypes of retinoblastoma that might be at risk for recurrence following chemotherapy and impact treatment planning [17]. This form of “liquid biopsy” can be used for confirmation of diagnosis as well as monitoring tumour response during therapy.

#### Conditional risks for germline mutation in unilateral solitary retinoblastoma

Shields et al. further explored the 482 patients with solitary unilateral retinoblastoma specifically for new tumours (55 new tumours in 20 patients) using non-conditional and conditional analysis [18]. Comparison (new tumour vs. no new tumour development) revealed those with new tumour were younger at presentation (10 vs. 36 months,  $p < 0.001$ ), with family history of

retinoblastoma (35% vs. 3%,  $p < 0.001$ ), less advanced tumour ( $p = 0.012$ ), and greater macula location of first tumour (50% vs. 15%,  $p = 0.003$ ). Conditional risk for new tumours (at age 6, 9, 12, 18, 24 months) dynamically declined with increasing age (Table 2). Of those with new tumours, those that occurred ≤1 year from presentation were located more posteriorly whereas those that occurred >1 year from presentation were more likely to occur near the ora serrata. Importantly, patients ≤24 months at presentation demonstrated all new tumours by 24 months of age, whereas older patients (>24 months at presentation) showed new tumours up to 56 months of age.

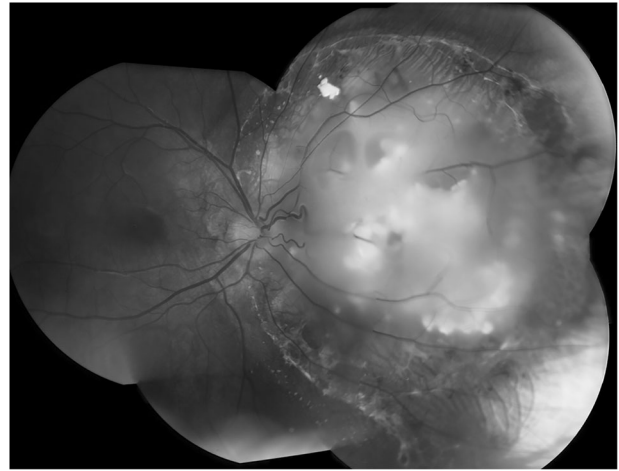
#### Retinocytoma/retinoma: risk for growth into retinoblastoma

Retinocytoma/retinoma refer to a benign variant of retinoblastoma, representing only 3% of all cases [19–24]. The older literature focused mostly on terminology and clinical features of this unique tumour [19–23]. In 2000, Singh et al. reviewed 24 tumours in 17 patients from our department and documented only 1 case (4%) with evidence of growth into retinoblastoma over median follow up of 4 years [24]. Dimaris et al. subsequently published on genomic instability in retinocytoma/retinoma at risk for transformation into retinoblastoma [25]. They showed that quiescent retinocytoma/retinoma demonstrated loss of both RB1 tumour suppressor gene alleles and low level genomic instability and high expression of senescent proteins that lead to stability in

**Table 2.** Non-conditional and conditional probability for new tumour development (either eye) in 482 patients presenting with solitary unilateral retinoblastoma.

Age at diagnosis	Conditional Risk @ Each Subsequent Time Point While Maintaining Solitary Unilateral Retinoblastoma										Age of Latest Initial New Tumour (months)
	Non-Conditional Risk at Presentation Total n (%)	@6 months n (%)	@9 months n (%)	@12 months n (%)	@18 months n (%)	@24 months n (%)	@30 months n (%)	@36 months n (%)	@48 months n (%)	@60 months n (%)	
0–3 months (n = 23)	8 (39)	4 (25)	2 (15)	2 (15)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	18.7
>3–6 months (n = 25)	5 (21)	4 (17)	3 (14)	1 (6)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	18.2
>6–9 months (n = 40)	2 (6)	2 (6)	2 (6)	2 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	17.8
>9–12 months (n = 37)	1 (3)	1 (3)	1 (3)	1 (3)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	23.4
>12–24 months (n = 112)	0 (0)					0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	na
>24–36 months (n = 91)	2 (2)						1 (1)	0 (0)	0 (0)	0 (0)	46.1
>36 months (n = 119)	2 (2)							1 (1)	0 (0)	0 (0)	55.9

Colors – no color – non-conditional risk from presentation; light gray – conditional risk low; dark gray – conditional risk absent; black – not applicable  
Information adapted from Shields CL, Dockery PW, Yaghy A, et al. Conditional analysis on new tumour formation with solitary unilateral retinoblastoma in 482 consecutive eyes. Saudi J Ophthalmol. 2022; in press [18].

**Fig. 2** Retinocytoma in a child. Spontaneously regressed retinoblastoma (retinocytoma) in a pre-teen child with low risk for transformation into retinoblastoma (See Table 3).

most cases, but instability could further lead to transformation into retinoblastoma.

Shields et al. looked into long-term clinical evidence of transformation of retinocytoma/retinoma into retinoblastoma in a fairly large cohort of these 78 benign tumours in 62 patients [26] (Fig. 2). At presentation with retinocytoma/retinoma, the median patient age was 5 years, older than most children with retinoblastoma. The retinocytoma/retinoma demonstrated median basal diameter of 6.0 mm and thickness of 2.3 mm without surrounding retinal pigment epithelial (RPE) alterations (31%) or with RPE alterations (69%). A comparative analysis based on age at presentation (<4 vs. ≥4 years) revealed younger patients being more likely Hispanic (19% vs. 2%,  $p = 0.04$ ) and with leukocoria (24% vs. 0%,  $p = 0.003$ ). A comparative analysis based on tumour focality (unifocal vs. multifocal) revealed unifocal tumour with lack of symptoms (62% vs. 25%,  $p = 0.03$ ), and greater median basal diameter (6.0 vs. 3.3,  $p = 0.003$ ) and thickness (2.5 vs. 1.5 mm,  $p = 0.006$ ) [26]. By Kaplan–Meier analysis, retinocytoma/retinoma transformation into retinoblastoma was found in 2.7% by 2 years, 9.2% by 5 years, 15.3% by 10 years and 20 years [26] (Table 3). The only factor predictive of transformation by multivariate analysis was increasing thickness ( $p = 0.003$ ) with hazard ratio of 2.83 per 1 mm increase in thickness.

#### Retinoblastoma: outcomes based on global income level

A 2009 survey of the world incidence of retinoblastoma by Kivela revealed the disease heavily concentrated (#/year) in Asia (4027 cases), Africa (1792 cases), and Latin America (622 cases) compared with Europe (414 cases), North America (258 cases), Japan (59 cases), and Oceania (21 cases) [5]. Mortality rate was greatest in Africa (70%), Asia (39%), and Latin America (20%) and least in Europe (5%), Japan (3%), and North America (3%) [5].

In 2020, The Global Retinoblastoma Group, led by Fabian et al. published a report on global retinoblastoma features by national income level and found that of 4351 new patients from 153 countries studied from June 2017 to December 2018, most (85%) were from low and middle-income countries [6]. The most common features included leukocoria (63%), strabismus (10%), and proptosis (7%). Those patients from high-income countries were diagnosed at median age of 14 months, 2% with extraocular tumour, and only <1% incidence of remote metastasis, compared to low-income countries with median age at presentation of 31 months, 49% with extraocular tumour, and 19% with remote metastasis [6]. They suggested that these concerning findings need to be addressed at a national or international level.

### Retinoblastoma: global retinoblastoma during Covid-19

In 2021, The Global Retinoblastoma Group, led by Fabian et al. published a letter to the editor on retinoblastoma management during the Covid-19 pandemic and noted that ~42% of the 194 participating centers reported restrictions for families to reach a retinoblastoma center and 40% also noted that management disruption occurred due to personnel or equipment problems [27]. Fortunately, most centers were able to continue intravenous chemotherapy (94%) and enucleation (90%), but intra-arterial chemotherapy was unavailable at 62% of centers.

### Retinoblastoma: outcomes based on AJCC 8th edition

There are several classification systems for retinoblastoma including the International Classification of Retinoblastoma (ICRB) and the American Joint Committee on Cancer (AJCC). The AJCC is currently in the 8th edition and Tomar et al. studied retinoblastoma based on the AJCC 8th edition using collaborative data in 2085 patients and found the 5-year Kaplan–Meier rate of survival decreased with increasing tumour category, revealing cT1a (100%), cT1b (98%), cT2a (98%), cT2b (96%), cT3 (89%), and cT4

(45%) [28]. Outcomes related to the ICRB are listed below under headings “Retinoblastoma: Long-term (20-year) outcomes following intravenous chemotherapy” and “Retinoblastoma: Long-term (20-year) outcomes following intravenous chemotherapy”.

### Retinoblastoma: screening for trilateral retinoblastoma

Trilateral retinoblastoma is a condition whereby a child with bilateral retinoblastoma develops germline-mutation-related pinealoblastoma or other intracranial neoplasm and this combination carries high risk for death [29, 30]. There is some evidence that systemic chemotherapy might reduce the incidence of pinealoblastoma in hereditary retinoblastoma [31]. Kivela provided a meta-analysis on the clinical features and outcomes of trilateral retinoblastoma in 106 cases [30]. He noted the median age at diagnosis of the brain neoplasm was 5 months and typically affected second or third generation families with retinoblastoma. Importantly they realized that routine neuroimaging with magnetic resonance imaging (MRI) could detect smaller tumours, associated with better 5-year survival.

De Jong et al. revisited screening for trilateral retinoblastoma in 138 cases and found 84% were symptomatic and 16% asymptomatic [32]. In those asymptomatic cases, 95% were diagnosed before age 40 months (Fig. 3). Overall, age at diagnosis of the pineal tumour did not correlate with age at diagnosis of the retinoblastoma [32]. They stated that MRI on a 6-month basis in cases of heritable retinoblastoma up until 3 years of age can detect pineal tumour, but it would take 311 MRI scans to find 1 asymptomatic pineal tumour and 776 MRI scans to save one life.

### Retinoblastoma: long-term (20-year) outcomes following intravenous chemotherapy

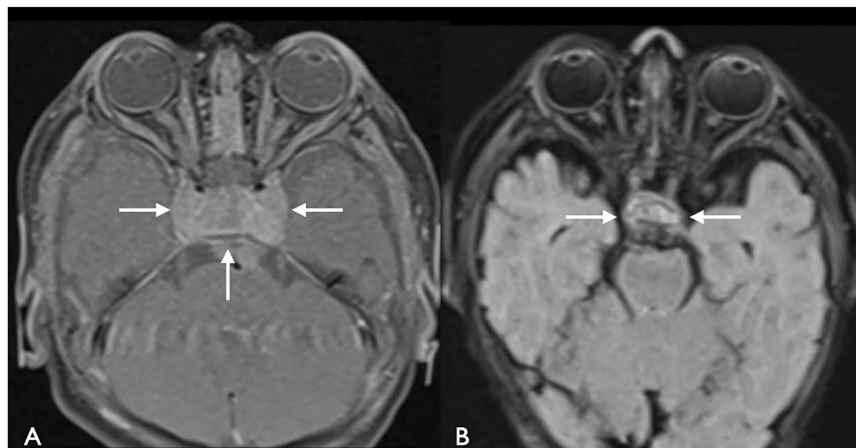
In the early 1990s, Kingston et al. noted that a certain systemic chemotherapy protocol, initially designed for neuroblastoma, was effective for retinoblastoma. They and others published initial observations on the efficacy of this approach [33–37]. In 2006, Shields et al. published results of intravenous chemotherapy (vincristine, etoposide, carboplatin) in 249 consecutive cases of retinoblastoma and found tumour control with globe salvage and (avoiding external beam radiotherapy) in 100% of group A, 93% of group B, 90% of group C, and 47% of group D eyes [38]. All group E eyes were enucleated.

In 2020, Shields et al. published on a larger cohort of 964 eyes in 554 patients treated with similar intravenous chemotherapy with Kaplan–Meier analysis demonstrating globe salvage (avoiding external beam radiotherapy) at 3 years in 96% of group A, 91% of group B, 91% of group C, 71% of group D, and 32% of group E eyes [39] (Figs. 4 and 5). This control and globe salvage was

**Table 3.** Kaplan–Meier estimates of transformation of retinocytoma/retinoma to retinoblastoma in 61 tumours of 48 patients.

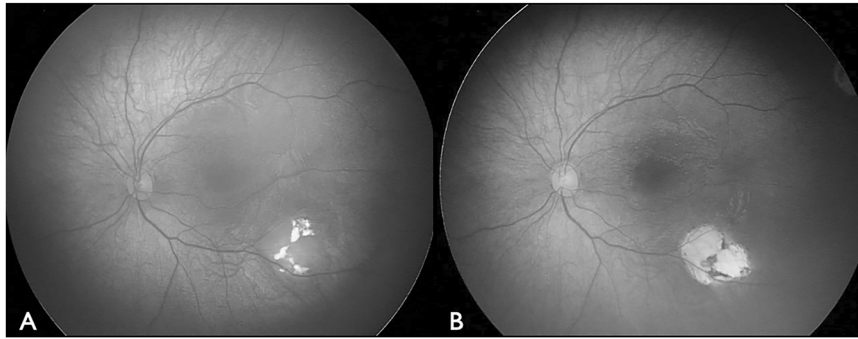
Year	Kaplan–Meier estimates % per patient	Kaplan–Meier estimates % per tumour
1	0%	0%
2	2.7%	2.1%
3	9.2%	6.9%
4	9.2%	6.9%
5	9.2%	6.9%
6	9.2%	6.9%
7	15.3%	10.8%
8	15.3%	10.8%
9	15.3%	10.8%
10	15.3%	10.8%
15	15.3%	10.8%
20	15.3%	10.8%

Information adapted from Shields CL, Srinivasan A, Alvarez JAL, et al. Retinocytoma/retinoma: Comparative analysis of clinical features in 78 tumours and rate of transformation into retinoblastoma over 20 years. *J AAPOS*. 2021 Jun;25(3):147.e1–147.e8. <https://doi.org/10.1016/j.jaapos.2020.11.024>. Epub 2021 May 26. PMID: 34051357 [26].

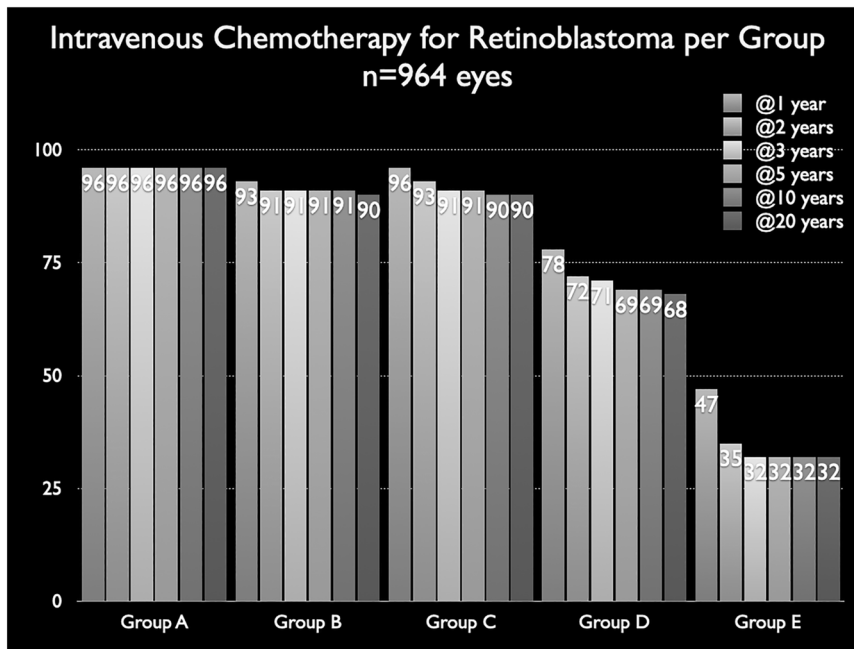


**Fig. 3** Trilateral retinoblastoma. Two-year old child with trilateral retinoblastoma and brain tumour (arrows) (A) before and (B) 2 months after high dose systemic chemotherapy.





**Fig. 4 Intravenous chemotherapy for retinoblastoma.** Intravenous chemotherapy plus transpupillary thermotherapy for Group B retinoblastoma showing control (A) before and (B) after treatment.



**Fig. 5 Intravenous chemotherapy for retinoblastoma per group in 964 eyes.** Globe salvage at 1, 2, 3, 5, 10, and 20 years by Kaplan–Meier analysis. (Data adapted from reference [39], Shields CL, Bas Z, Tadealli S, et al. Long-Term (20-year) real-world outcomes of intravenous chemotherapy (chemoreduction) for retinoblastoma in 964 eyes of 554 patients at a single Center. *Br J Ophthalmol.* 2020;104:1548-55.).

maintained at 20 years follow up. In order to preserve the eye(s), additional intra-arterial chemotherapy (IAC) or plaque radiotherapy was employed by year 2 in 5% of group A, 26% of group B, 28% of group C, 27% of group D, and 19% of group E eyes, with little further need beyond 2 years up to 20 years. Bas et al. studied outcomes in this cohort based on patient age and noted that younger patients demonstrated more lasting control than older patients [40]. As written in an editorial, the excellent control offered by intravenous chemotherapy has revolutionized retinoblastoma care [41].

#### Retinoblastoma: long-term (14-year) outcomes following intra-arterial chemotherapy

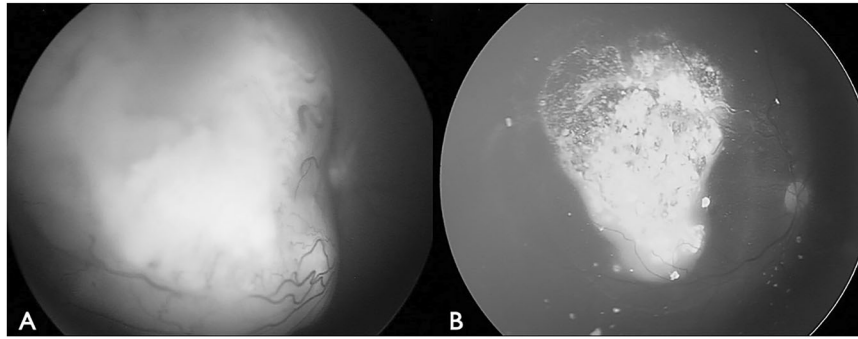
Intra-arterial chemotherapy is a targeted chemotherapy directly to the eye for retinoblastoma treatment. This modality can be used as primary or secondary treatment and can be applied to one or both eyes [42–47]. According to the International Classification of Retinoblastoma (ICRB), globe salvage as primary therapy has been highly successful for groups A, B, and C retinoblastoma, and moderately successful for groups D and E, depending on tumour extent [42–50]. A collaborative report on IAC for retinoblastoma from six international retinoblastoma centers using 4396

chemotherapy infusions in 1139 patients over a 10-year period found only 3 metastatic deaths (<1%) [49]. It is encouraged that this technique be performed only at experienced centers [50].

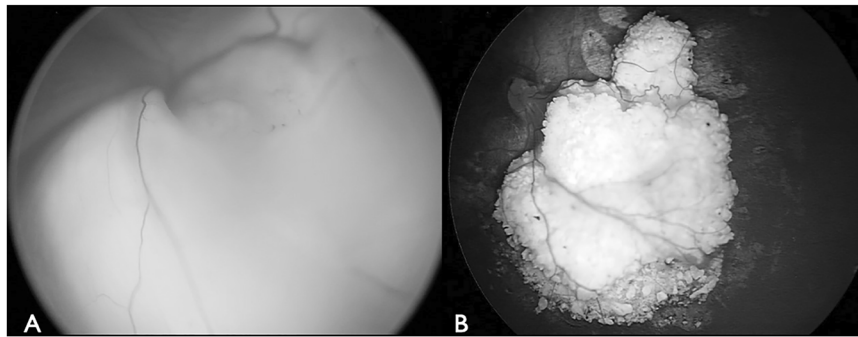
Shields et al. reported 14-year outcomes following primary or secondary IAC for retinoblastoma in 341 eyes treated with 1292 infusions [47]. Overall, Kaplan–Meier 5-year estimates of globe salvage was 74%. Of those treated with primary IAC ( $n = 160$  eyes, 655 infusions), 5-year globe salvage was 76%, including 100% for group B, 80% for group C, 78% for group D, and 55% for group E. (Figs. 6, 7 and 8) Of those treated with secondary IAC ( $n = 207$  eyes, 859 infusions), 5-year globe salvage was 71%. Complications (per catheterization) were minimal in this experienced team, including retinal ischemia (1%), choroidal ischemia (1%), neovascularization disc, retina, iris, or glaucoma (~1% each), and systemic ischemia (<1%). There was minimal difference in outcomes when evaluating by age, race, and sex.

#### Retinoblastoma: outcomes following intravitreal chemotherapy

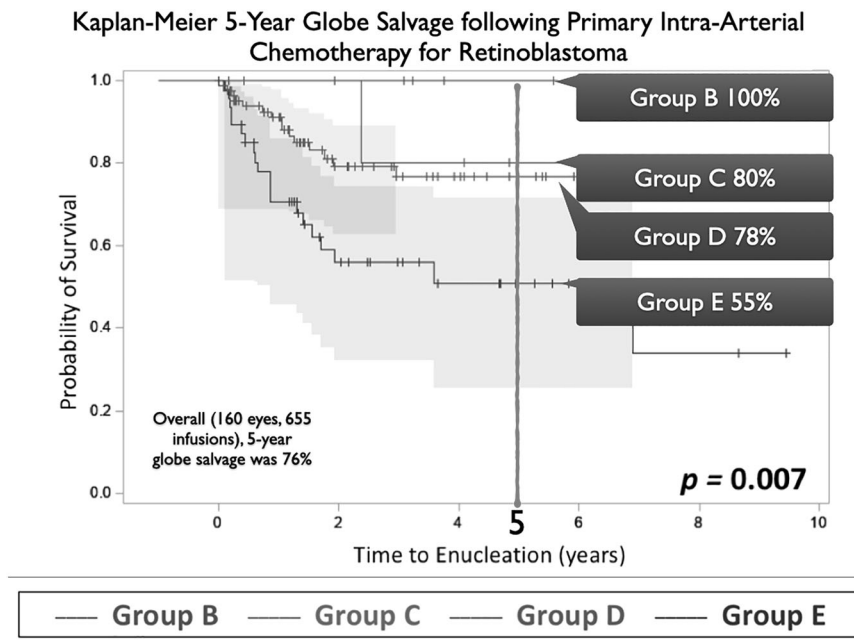
In the past, vitreous seeding from retinoblastoma was a particular concern as only radiotherapy or enucleation was available for treatment and many eyes were enucleated. In 2012, Munier et al.



**Fig. 6 Intra-arterial chemotherapy for large retinoblastoma.** Intra-arterial chemotherapy for Group D retinoblastoma with extensive subretinal seeding, showing control (A) before and (B) after treatment.



**Fig. 7 Intra-arterial chemotherapy for advanced retinoblastoma.** Intra-arterial chemotherapy for Group E retinoblastoma with extensive subretinal seeding for all clock hours and no view of the optic disc, showing control (A) before and (B) after treatment.



**Fig. 8 Intra-arterial chemotherapy for retinoblastoma per group in 160 eyes (655 infusions).** Globe salvage at 5 years by Kaplan-Meier analysis. (Data adapted from reference [47], Shields CL, Dockery PW, Yaghy A, et al. Intra-arterial chemotherapy for retinoblastoma in 341 consecutive eyes (1292 infusions): Comparative analysis of outcomes based on patient age, race, and sex. J AAPOS. 2021. [In press]).

[51] and Ghassemi and Shields [52] published the use of injection of chemotherapy into the vitreous cavity for management of retinoblastoma seeding with favorable results. Later, in 2016, Shields et al. reviewed 192 chemotherapy injections for retinoblastoma vitreous seeding and found 100% tumour control [53]. In 2017, Francis et al. collaborated with 10 international centers and

found complications of extraocular tumour seeding to be exquisitely rare, if proper safety precautions were employed [54].

#### **Psychological adaptation to retinoblastoma and vision loss**

Retinoblastoma not only affects the patient, but it can impact the entire family. A study by Collins et al. provided a thesis evaluation

of 138 parents of children with retinoblastoma using standardized self-reported psychological assessment indexes and found that most parents display depression (73%), anxiety (64%), and/or stress (100%) [55]. Severe parental depression is more commonly seen with those children who display multifocal retinoblastoma and those with less education and previous history of depression. These authors emphasized that the psychological status of the family is an important consideration when managing a family with retinoblastoma.

Parravano et al. provided a meta-analysis of 27 studies of 6992 patients with acquired visual acuity impairment in individuals over 18 years of age [56]. In their cohort, the mean age at evaluation was 76 years and results showed depression was common in patients, ranging from a prevalence of 24–34% in clinic-based and rehabilitation-based services [56]. They advised that ophthalmologists should recognize this common problem and address it with each patient and their health care professional.

Dhingra et al. reviewed health-related quality of life (HRQoL) in retinoblastoma survivors in India, studying physical, emotional, social, and school dimensions [57]. Compared to healthy siblings, they found affected survivors with lower HRQoL in all domains ( $p < 0.01$ ), especially the physical aspect.

## SUMMARY

What is known about this topic

- In a published cohort of 482 patients with solitary unilateral retinoblastoma, germline mutation was found in 16% patients and the likelihood of germline retinoblastoma was greater for younger children ( $\leq 1$  year versus (vs.)  $> 1$  year at presentation) ( $p = 0.001$ ) and greatest for youngest infants ( $\leq 3$  months vs.  $> 3$ –12 months) ( $p = 0.002$ ).
- An international global study on retinoblastoma during 2017 revealed 4351 new patients and 85% from low- and middle-income countries. They noted that low- and middle-income countries found patients with older age at detection and greater risk for metastasis, compared to high-income countries.
- Retinocytoma/retinoma is a benign and quite rare variant of retinoblastoma, and a study of 78 tumours demonstrated ultimate transformation into active retinoblastoma in 9.2% by 5 years and 15.3% by 10 years and 20 years.

What this study adds

- Management of retinoblastoma with systemic intravenous chemotherapy in 964 eyes revealed lasting 20-year globe salvage at 96% in group A, 90% in group B, 90% in group C, 68% in group D, and 32% in group E eyes.
- Management of retinoblastoma with intra-arterial chemotherapy in 160 eyes (655 infusions) revealed 5-year globe salvage was 100% for group B, 80% for group C, 78% for group D, and 55% for group E.
- The psychological impact of retinoblastoma on the parents revealed depression (73%), anxiety (64%), and/or stress (100%), and on the patient revealed deficits in quality-of-life issues.
- Retinoblastoma is a challenging disease and chemotherapy provides reliable tumour control and globe salvage. Continuing efforts to improve the psychology and quality of life is important.

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#### AUTHOR CONTRIBUTIONS

CLS, ZB: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work. CS, ZB, AL, AMVS, AS, SEL, JAS: Drafting the work or revising it critically for important intellectual content. Final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AL, AMVS, AS, SEL, JAS: Substantial contributions to the interpretation of data for the work.

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#### COMPETING INTERESTS

The authors declare no competing interests.

#### ADDITIONAL INFORMATION

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