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Prenatal versus Postnatal Screening for Familial Retinoblastoma

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Purpose: To compare overall outcomes of conventional postnatal screening of familial retinoblastoma and prenatal *RB1* mutation identification followed by planned early-term delivery.

Design: Retrospective, observational study.

Participants: Twenty children with familial retinoblastoma born between 1996 and 2014 and examined within 1 week of birth.

Methods: Cohort 1 included spontaneously delivered neonates examined within 1 week of birth and confirmed postnatal to carry their family's *RB1* mutant allele. Cohort 2 included infants identified by amniocentesis to carry their family's *RB1* mutant allele, and therefore scheduled for early-term delivery (36–38 weeks' gestation). Treatment for retinoblastoma was performed at the Hospital for Sick Children, Toronto, Canada.

Main Outcome Measures: Age at first tumor in each eye, eye stage, treatments given, ocular salvage, treatment success (defined as avoidance of enucleation, external-beam irradiation, or both), visual outcome, number of anesthetics, pregnancy or delivery complications, and estimated treatment burden.

Results: Vision-threatening tumors were present at birth in 4 of 8 infants in cohort 1 and in 3 of 12 infants in cohort 2. Eventually, all infants demonstrated tumors in both eyes. At the first treatment, 1 of 8 infants in cohort 1 had eyes in stage cT1a/cT1a or cT1a/cT0 (smallest and least vision-threatening tumors), compared with 8 of 12 infants in cohort 2 ($P = 0.02$). Null *RB1* germline alleles induced earlier tumors than low-penetrance alleles ($P = 0.03$). Treatment success was achieved in 3 of 8 children in cohort 1 compared with 11 of 12 children in cohort 2 ($P = 0.002$). Acceptable vision (better than 0.2 decimal) was achieved for 8 of 16 eyes in cohort 1 compared with 21 of 24 eyes in cohort 2 ($P = 0.014$). Useful vision (better than 0.1, legal blindness) was achieved for 8 of 9 children in cohort 1 compared with 12 of 12 children in cohort 2. There were no complications related to early-term delivery. Median follow-up was 5.6 years, cohort 1 and 5.8 years, cohort 2.

Conclusions: When a parent had retinoblastoma, prenatal molecular diagnosis with early-term delivery increased the likelihood of infants born with no detectable tumors, better vision outcomes, and less invasive therapy. Prenatal molecular diagnosis facilitates anticipatory planning for both the child and family. *Ophthalmology 2016;■:1–8 © 2016 by the American Academy of Ophthalmology*

Supplemental material is available at www.aaojournal.org.

Retinoblastoma, the most common primary ocular malignancy in children, usually is initiated when both alleles of the *RB1* tumor suppressor gene are inactivated in a precursor retinal cell, followed by progressive mutations in other specific genes.[1,2] Both alleles may be lost only in the retinal cell from which 1 tumor arises (nonheritable retinoblastoma), or, in 50% of children, a germline *RB1* mutation presents a predisposition for development of multiple retinal tumors during childhood and other cancers later in life. Ten percent of patients inherit a family-specific mutation from a parent.[1,3]

Children with an *RB1* germline mutation may have retinoblastoma(s) at birth, often in the posterior pole of the eye, a location that threatens vision.[4–7] Focal laser treatments near the optic nerve and macula may compromise vision. Most of these children are affected bilaterally, with either simultaneous or sequential detection of tumors.[4,6] Tumors developing later tend to be located peripherally, where focal treatment does not affect vision.[6,8] Low-penetrance (10% of families)[3] and mosaic[9] mutations result

in fewer tumors and a more frequent unilateral phenotype.[9] The timing of the first tumors after birth has not yet been studied.

The eighth edition of tumor, node, metastasis, and heritability cancer staging for retinoblastoma is predicted by a retrospective international survey to predict best the salvage of the eye(s), metastasis, and death.[10] To facilitate the transition from the international intraocular retinoblastoma classification,[11] previously the most accurate to predict eye salvage, the tumor, node, metastasis, and heritability and the international intraocular retinoblastoma classification features are compared in Table 1. Retinoblastoma is the first cancer to include heritability in cancer staging.

It is recommended that infants with a family history of retinoblastoma be examined for tumor detection as soon as possible after birth and repeatedly for the first few years of life, often under general anesthesia.[12] Early diagnosis when tumors are small (cT1) and treatable with less invasive therapies is thought to optimize salvage of the eye and

Table 1. The AJCC 8th Edition of the Tumor, Node, Metastasis, and Heritability Cancer Staging System for Retinoblastoma[10] Compared with the Previous Best Eye Staging, the International Intraocular Retinoblastoma Classification[11]

Category	Criteria	International Intraocular Retinoblastoma Classification Equivalent Category
cTX	Unknown evidence of intraocular tumor	
cT0	No evidence of intraocular tumor	0
cT1	Intraretinal tumor(s) with subretinal fluid ≤5 mm from the base of any tumor	
cT1a	Tumors ≤3 mm and farther than 1.5 mm from the disc and fovea	A
cT1b	Tumors >3 mm from or closer than 1.5 mm to the disc or fovea	B
cT2	Intraocular tumor(s) with retinal detachment, vitreous seeding, or subretinal seeding	
cT2a	Subretinal fluid >5 mm from the base of any tumor seeding	C/D
cT2b	Tumors with vitreous seeding, subretinal seeding, or both	C/D
cT3	Advanced intraocular tumor(s)	
cT3a	Phthisis or prephthisis bulbi	E
cT3b	Tumor invasion of the choroid, pars plana, ciliary body, lens, zonules, iris, or anterior chamber	E
cT3c	Raised intraocular pressure with neovascularization, buphthalmos, or both	E
cT3d	Hyphema, massive vitreous hemorrhage, or both	E
cT3e	Aseptic orbital cellulitis	E
cT4	Extraocular tumor(s) involving the orbit, including the optic nerve	
cT4a	Radiologic evidence of retrobulbar optic nerve involvement or thickening of the optic nerve or involvement of the orbital tissues	
cT4b	Extraocular tumor clinically evident with proptosis, an orbital mass, or both	
Heritability		
HX	Unknown or insufficient evidence of a constitutional RB1 gene mutation	
H0	Normal RB1 alleles in blood tested with demonstrated high-sensitivity assays	
H1	Bilateral retinoblastoma, retinoblastoma with an intracranial primitive neuroectodermal tumor (i.e., trilateral retinoblastoma), patient with familial trilateral retinoblastoma, history of retinoblastoma, or molecular definition of a constitutional RB1 gene mutation	

vision.[5,6,12] We have managed familial retinoblastoma by screening the fetus for the RB1 mutation of the proband parent. If the child carries the RB1 mutation and has a near 100% risk of bilateral tumors developing, we suggest delivery at early full term (37 weeks' gestation),[12] with full retinal examination on day 1. Further management is conventional screening and treatment. If the child does not carry the proband RB1 mutation, risk of retinoblastoma developing is the same as for the general population (<0.1%).[13]

The aim of this study was to review retrospectively the outcomes of children examined within 1 week of birth and shown to carry their family's RB1 mutant allele compared with those found to carry their family's RB1 mutant allele on prenatal testing and delivered early. We hypothesized that tumors that were diagnosed earlier would be smaller and easier to treat, with better visual outcomes.

Methods

Study Design

Research ethics board approval was obtained from the Hospital for Sick Children, Toronto, Canada. The study conformed to the tenets of the Declaration of Helsinki. Privacy was preserved by following the tricouncil policy statement privacy guidelines.[14] Data collected for children with familial retinoblastoma (family history of retinoblastoma and developed tumor) born between June 1, 1996, and June 1, 2014, included relation to proband; laterality of retinoblastoma in proband; gender; gestational age at birth; prenatal abdominal ultrasound results (if performed); delivery or perinatal complications; type of genetic sample tested and

results; penetrance of RB1 mutation; timing of first examination; age at and location of first tumor(s) in each eye; treatments used; tumor, node, metastasis, and heritability staging for eyes and child; international intraocular retinoblastoma classification[11] of each eye; active treatment duration; date of last follow-up; and visual outcome at last follow-up. The gestational age at birth for each child was calculated (39 weeks was considered full term). Eyes with vision-threatening tumors were defined as cT1b or worse. Treatments were summarized as focal therapies (laser therapy, cryotherapy, and periocular sub-Tenon's injection of chemotherapy) or systemic therapies (systemic chemotherapy or stereotactic external-beam irradiation). Active treatment duration (time from diagnosis to last treatment) and number of examinations under anesthesia (EUAs) were measured. Treatment success was defined as avoidance of enucleation or external-beam irradiation. Acceptable visual outcome was defined as visual acuity better than 0.2 decimal (Snellen equivalent, 20/100). Useful vision was defined as overall visual acuity better than 0.1 decimal in the better eye and legal blindness as overall visual acuity of 0.1 or worse in the best eye. Excluded from this study were children with a family history of retinoblastoma who were shown not to carry the familial RB1 mutant allele; no such child demonstrated retinoblastoma.

Data Analysis

Basic descriptive statistics were used for comparisons between patients screened postnatally (in the first week of life, cohort 1) and those provided prenatal testing and planned late preterm or early-term delivery (cohort 2). These included the Student t test, the chi-square test, the Fisher exact test, the Mann−Whitney U test, and Mood's median test. Correlations and Kaplan-Meyer survival graphs were plotted using Microsoft Excel 2007 (Microsoft Corp., Redmond, WA) and Prism 6 (Graphpad software, La Jolla, CA).
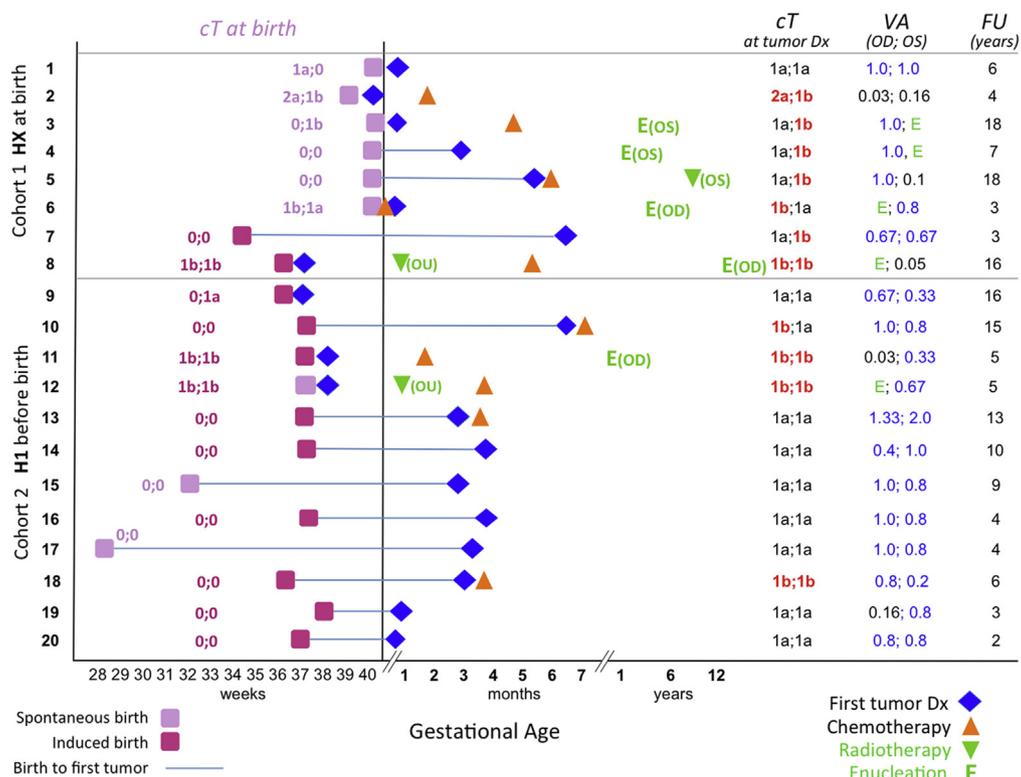
Figure 1. Graph showing tumor timing, therapy, and outcomes. Patients in cohort 1 who had an undefined inherited risk (HX) at birth and cohort 2 who carried the *RB1* mutation (H1) based on prenatal testing are plotted against age: at birth (pink squares), eighth edition clinical T stage (cT) per eye at birth (pink text), first tumor occurrence (blue diamonds), and invasive treatments (green text). cT at tumor diagnosis (cT1a, good prognosis [black]; cT1b, 2a, poorer prognosis [red]). Final visual outcome and follow-up (years) from diagnosis. Dx = diagnosis; FU = follow-up.

Results

Patient Demographics

Twenty children with familial retinoblastoma were reviewed (10 males, 10 females) and were eligible for this study (Fig 1). Diagnosis for cohort 1 (8 children; 40%) was by observation of the tumor or postnatal testing for the parental *RB1* mutation. Six were born full term and 2 were delivered late preterm because of pregnancy-induced hypertension (patient 7) or fetal ultrasound evidence of retinoblastoma[15] (patient 8). The 12 children (60%) in cohort 2 were diagnosed prenatally to carry their family's *RB1* mutation and referred to a high-risk pregnancy unit for elective late-preterm or early-term delivery: 3 were spontaneously premature (patients 10, 13, and 15; 28−37 weeks gestation) and 9 were delivered electively at 36 to 38 weeks gestation.

Molecular Diagnosis

All study participants were offspring of retinoblastoma probands. Nineteen probands were affected bilaterally and 1 was affected unilaterally (father 19). The familial *RB1* mutations were detected previously in routine care. Cohort 1 children (patients 1−8) were tested postnatal for their family's *RB1* mutation by blood samples; cohort 2 children (patients 10−21) were tested by prenatal amniocentesis at 16 to 33 weeks' gestation.

Null *RB1* mutations were present in 15 families. Five families had low-penetrance *RB1* mutations (whole-gene deletion, patient

18; weak splice-site mutations, patients 14, 17, and 20; and a missense mutation[16,17] patient 5; Supplemental Table S1, available at www.aaojournal.org). No proband in this study showed mosaic results for the *RB1* mutation. Eventually, all study participants were affected bilaterally. At birth, 8 of 15 infants with null *RB1* mutations had tumors affecting 13 of 30 eyes; 0 of 5 infants with low-penetrance mutations had tumors ($P = 0.02$ for eyes, $P = 0.1$ for children, Fisher exact test; Table 2).
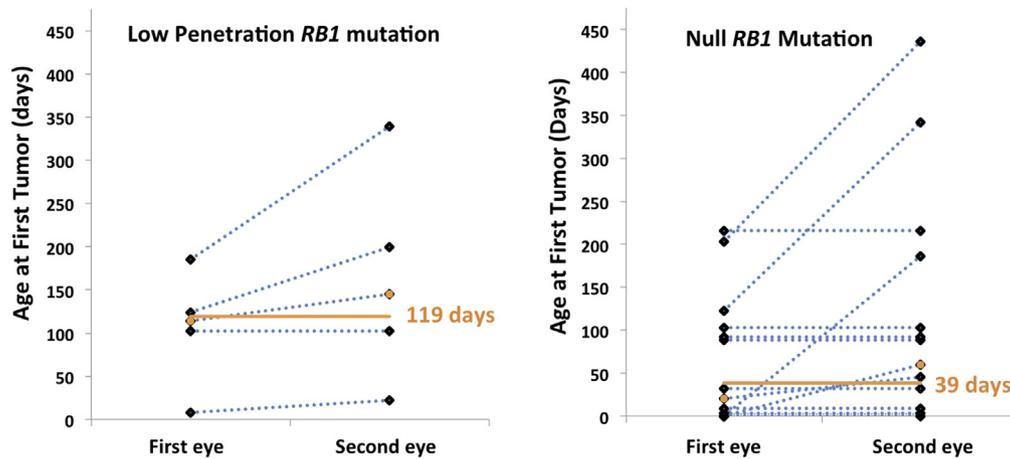
At the first tumor per child, children with null mutations tended to be younger (median age, 20 days) than those with low-penetrance mutations (median age, 114 days). At the first tumor per eye, children with null mutations (median age, 39 days) were

Table 2. Tumors Present at Birth and Type of *RB1* Mutation

RB1 Mutation	Eyes with Tumors at Birth				Children with Tumors at Birth			
	Yes	No	Total	% Yes	Yes	No	Total	% Yes
Null	13	17	30	43	8	7	15	53
Low penetrance	0	10	10	0	0	5	5	0
Total			40				20	
P value*		0.02[†]				0.1		

*Fisher exact test.
[†]Statistically significant.

Figure 2. Graphs showing the impact of *RB1* mutation penetrance on age at first tumor per eye. Children with null mutations were significantly younger (mean age, 83 days; median age, 39 days) than those with low-penetrance mutations (mean age, 134 days; median age, 119 days; *P* = 0.03, Mood's median test; medians in *orange*).

significantly younger than those with low-penetrance mutations (median age, 119 days; *P* = 0.03, Mood's median test; Fig 2).

Classification of Eyes at Birth

Of cohort 1 eyes, 8 of 16 had a tumor at birth, compared with 5 of 24 cohort 2 eyes (Table 3; Fig 1). At birth, a tumor was present in at least 1 eye in 5 of 8 cohort 1 patients and in 3 of 12 cohort 2 patients (Table 3; Fig 1). At birth, 6 of 16 eyes in cohort 1 had a vision-threatening tumor (cT1b or worse) compared with 4 of 22 cohort 2 eyes (Table 2).

Tumors detected at birth tended to be perimacular (cT1b), and tumors detected later were smaller and not vision threatening, as previously described[18,19] (Figs 1 and 3). When the first tumor was

Table 3. Outcome Parameters

| Parameter	Postnatal Positive Family History, Cohort 1		Prenatal *RB1* Mutation Carrier, Cohort 2		P Value
	No.	*%*	*No.*	*%*	
Per eye					
No. of eyes	16		24		
Tumor(s) at birth	8	50	5	21	0.09
Visual prognosis at birth					
cT1a, cT0	10	62	20	83	0.26
cT1b, cT2a	6	38	4	17	
Ocular salvage	12	75	23	96	0.13
Treatment success*	10	63	22	92	0.04[†]
Visual outcome					
Acceptable vision[‡]	8	50	21	88	0.01[†]
Poor vision	8	50	3	13	
Per child					
No. of children	8		12		
Tumor(s) at birth	5	63	3	25	0.17
Worst eye cT1a at first tumor diagnosis	1	13	8	67	0.02[†]
Treatment					
Focal therapy only	2	25	7	58	0.2
Systemic chemotherapy	6	75	5	42	
Treatment success*	3	38	11	92	0.02[†]
Ocular salvage	4	50	11	92	0.1
Visual outcome					
Useful vision[§]	7	88	12	100	1
Legally blind[‖]	1	13	0	0	

*Avoided enucleation or external-beam radiation.
[†]Significant result.
[‡]Vision >0.2 decimal in an eye.
[§]Vision >0.1 decimal in the better-seeing eye.
[‖]Vision ≤0.1 decimal in better-seeing eye.
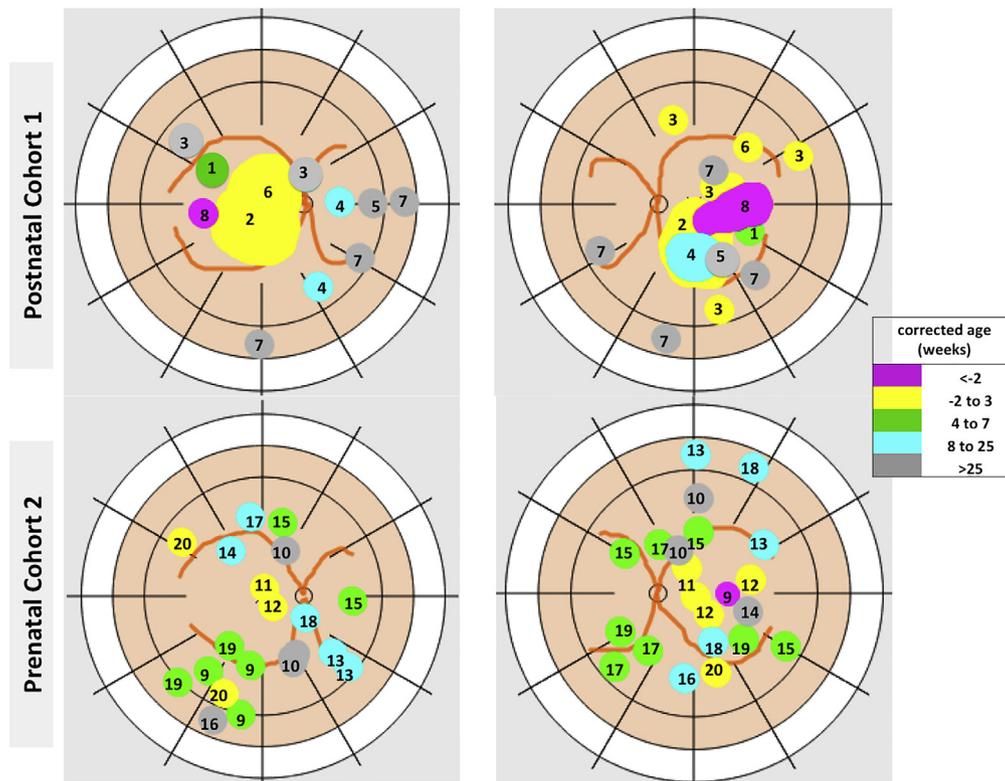
Figure 3. Topographic representation of the first tumor(s) in each eye for each cohort. The patient number is written on each tumor. The size of the graphic representation of the tumor is proportional to tumor size at diagnosis. Tumor color corresponds to corrected age in weeks at tumor diagnosis (see legend).

diagnosed, median age of the patient was 9 days for the 15 cT1b eyes (threatening the optic nerve and fovea, 6 with at least 1 tumor >3 mm), and the patients tended to be younger than 92 days for 24 cT1a eyes (tumors <3 mm and away from optic nerve and fovea). After correcting for gestational age when the first tumor was diagnosed per eye, the same tendency was observed (median age, 7 and 60 days, respectively).

At initial tumor diagnosis, 2 of 8 patients in cohort 1 had cT1a/cT1a or cT1a/cT0 eyes, compared with 8 of 12 in cohort 2 (*P* = 0.02, Fisher exact test; Fig 1; Table 3). At first diagnosis, tumors were not vision threatening (cT1a) in 7 of 16 cohort 1 eyes, compared with 17 of 24 cohort 2 eyes (Table 3). Vision-threatening tumor (cT1b or worse) was present at the first diagnosis in 6 of 16 cohort 1 eyes compared with 4 of 24 cohort 2 eyes (Fig 1; Table 3).

Cohort 1 showed larger and more posterior tumors than cohort 2 (Fig 3). Before 37 weeks gestation, 3 of 40 eyes showed tumors, all within the posterior pole. At 42 weeks gestation (2 weeks after full term), 15 of 40 eyes showed tumors, and in 12 of 15 eyes, the tumors were within the posterior pole.

Treatment Course

All infants were examined frequently from birth onward according to the National Retinoblastoma Strategy Guidelines for Care.[12] If there were no tumors at birth, each child was examined while awake every week for 1 month, every 2 weeks for 2 months, and after 3 months of age underwent an EUA every 2 to 4 weeks. If there was a tumor at birth, the children underwent an EUA every 2 to 4 weeks until control of tumors was achieved. Cohort 1

patients were treated with focal therapy (n = 8); chemotherapy using vincristine, carboplatin, etoposide, and cyclosporine (Toronto protocol[20]; n = 5); stereotactic radiation (n = 2); and enucleation of 1 eye (n = 4; Supplemental Table S1, available at www.aaojournal.org; Fig 1). Cohort 2 patients were treated with focal therapy (n = 12), chemotherapy (n = 5), and enucleation of 1 eye and stereotactic radiation (n = 1; Fig 1). Treatment by focal therapy alone (avoidance of systemic chemotherapy or external-beam irradiation) was possible in 2 of 8 cohort 1 patients and in 7 of 12 cohort 2 patients (Table 3).

The median active treatment duration was 523 days (range, 0−2101 days) in cohort 1, compared with 447 days (range, 0−971 days) in cohort 2 (*P* = 0.77, Mood's median test). The median number of EUAs was equal: 29 (range, 18−81) in cohort 1 and 29 (range, 20−41) in cohort 2 (*P* = 1, Mood's median test).

Outcomes

There were no pregnancy, delivery, or perinatal complications associated with spontaneous preterm, induced late-preterm, or early-term birth. Median follow-up was 5.6 years (cohort 1, 5.6 years; cohort 2, 5.8 years; Supplemental Table S1, available at www.aaojournal.org). At the last follow-up, the median age of cohort 1 was 10 years (range, 3−19 years) and that of cohort 2 was 9 years (range, 3−16 years).

Treatment success was achieved in 3 of 8 cohort 1 patients and in 11 of 12 cohort 2 patients (*P* = 0.02, Fisher exact test; Table 3). Kaplan-Meier 5-year ocular survival for cohort 1 was 62%, compared with 92% for cohort 2 (*P* = 0.03, log-rank [Mantel-Cox] test; Fig 4). One child (patient 6) in cohort 1 (11%) showed high-
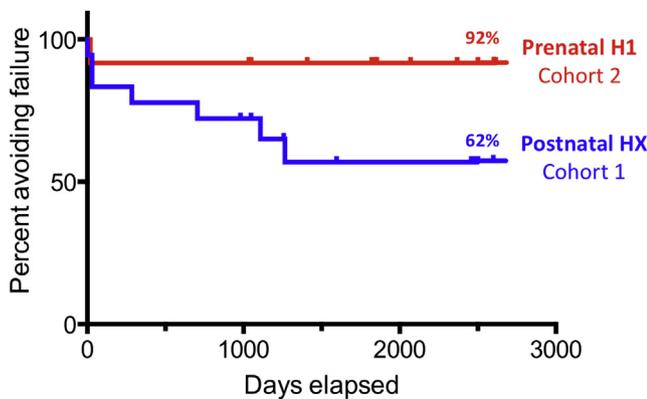
Figure 4. Kaplan-Meier treatment success (avoiding enucleation or radiation) curve of cohort 1 (an undefined inherited risk [Postnatal HX]; *blue*) was 62% compared with 92% for cohort 2 (*RB1* mutation carrier [Prenatal H1]; *red*; $P = 0.03$, log-rank, Mantel-Cox test).

risk histopathologic features[21–23] in the enucleated eye and received adjuvant treatment. The 1 eye enucleated in cohort 2 showed no high-risk features. All children were alive without metastases at the time of this report.

Legal blindness afflicted 1 of 8 cohort 1 children and no cohort 2 child (Table 3). Visual outcomes were considered acceptable (better than 0.2 decimal) for only 8 of 16 eyes in cohort 1 but 21 of 24 eyes in cohort 2 ($P = 0.01$, Fisher exact test; Table 3). Final visual acuity better than 0.5 decimal was achieved in 9 of 18 eyes in cohort 1 compared with 17 of 24 cohort 2 eyes ($P = 0.3$, Mood's median test).

Combined treatment success and good vision were documented in 8 of 16 cohort 1 eyes and in 21 of 24 cohort 2 eyes ($P = 0.02$, Fisher exact test; Fig 1). A trend toward a negative correlation was found between gestational age and final visual outcome ($r = -0.03$), with better visual outcome observed for earlier births.

Discussion

We report for the first time that elective early-term delivery of infants confirmed by prenatal *RB1* mutation testing to be at risk for familial retinoblastoma shows benefit for the child. Fewer and smaller tumors present at birth were treated as they emerged, resulting in better ocular and visual outcomes and requiring less intensive medical interventions, outweighing the theoretical risks of early delivery (Fig 1; Table 3).

It is now the standard of care[12] to identify 97% of germline *RB1* mutations in bilaterally affected probands and approximately 15% of unilateral probands who carry a germline gene mutation.[3,9] When the proband's unique mutation is known, molecular testing of family members determines which relatives also carry that mutation and therefore are at risk of developing retinoblastoma and other cancers. We report 12 infants identified in utero to carry the family's mutant *RB1* allele (cTxH1). Infants shown not to carry their family's mutation (not shown) required no interventions or cancer surveillance and were not included in this study. Amniocenteses (to collect a sample for genetic testing) were performed in the second half of pregnancy, when risks of miscarriage are low (range, 0.1%–1.4%).[24,25]

Our data confirm that the earliest tumors involve the perimacular region, threatening loss of central vision, whereas later-developing tumors tended to be peripheral (Fig 3), with less visual impact.[18,19,26] Smaller macular and perimacular tumors at diagnosis and treatment have better visual outcome because focal therapy options (laser or radioactive plaque) threaten the optic nerve and central vision. Systemic chemotherapy effectively shrinks tumors such that focal therapy can be applied with minimized visual damage. Patient 8 (cohort 1) had a tumor at 36 weeks' gestation detected by obstetrical ultrasound and was treated with reduced-dose chemotherapy as a newborn. Drug resistance ensued,[15] and ultimately the patient required enucleation at 14 years of age. Systemic chemotherapy in neonates is challenging because severe adverse effects may occur because of immature liver and kidney metabolism of drugs. Conventional dose-reduction chemotherapy for infants in the first 3 months of life[27] or single-agent carboplatin chemotherapy[28] opens the door to the selection of multidrug-resistant tumor cells, making later recurrences difficult to treat.[29–31] Periocular topotecan for treatment of small-volume retinoblastoma[32] may increase the effectiveness of focal therapy without facilitating resistance. Intra-arterial chemotherapy is not feasible in such small infants; the youngest age reported is 2 months.[33]

Imhof et al[6] screened children at risk of familial retinoblastoma starting 1 to 2 weeks after birth without molecular diagnosis and identified 17 retinoblastoma cases. At the first screening, 12 of 17 infants had retinoblastoma. At the first diagnosis, 14 of 34 eyes had a vision-threatening tumor, treatment failed in 12 of 34 eyes (the eyes required radiation, enucleation, or both), 1 child demonstrated metastasis, 20 eyes achieved vision better than 20/100, and 2 of 17 children achieved a best vision of worse than 20/200 (<0.1 decimal, legal blindness). In comparison of our cohort 2 eyes, 4 of 24 eyes showed vision-threatening tumors, treatment failed in 3 of 24 eyes, 21 of 24 eyes had vision better than 20/100, and no child had metastasis or legal blindness.

Early screening of at-risk infants with a positive family history as soon as possible after birth is the internationally accepted convention for retinoblastoma.[6,34] Rothschild et al[34] retrospectively reviewed 16 children who had undergone intensive screening (defined as the first week then every month up to 18 months) and demonstrated familial retinoblastoma: 15 of 16 were treated with systemic chemotherapy, 2 of 16 were treated with radiation, and 12 of 13 achieved vision better than 20/200 (no data provided on vision per eye). In our cohort 2, fewer children required systemic chemotherapy (5/12) and irradiation (1/12), with similar visual outcomes per child.

A concern with late-preterm or early-term delivery is its reported effect on neurological and cognitive development and later school performance.[35–37] The studies reporting on preterm and early-term babies tend to include many children with complex reasons for early delivery. In contrast, children with retinoblastoma are otherwise healthy babies, except for the cancer growing in their eye(s). Early-term delivery requires an interactive team of a neonatologist, ophthalmologist, and oncologist to reach the best timing for optimal outcome.[38] Neurocognitive development in

retinoblastoma patients can be affected by multiple factors, including blindness, multiple EUAs, and external-beam irradiation.[39,40] A comparative study is recommended to evaluate neurocognitive deficits after early delivery, taking into account vision outcomes and treatments required.

Counseling about reproductive risks is important for families affected by retinoblastoma, including unilateral probands.[41] Current optimized therapies result in very low mortality, and most retinoblastoma patients survive and may consider having children. Prenatal diagnosis enables preimplantation screening to ensure an unaffected child and informs parents who may wish to terminate an affected pregnancy.[42] It is our experience that retinoblastoma survivors and their relatives with full understanding of the underlying risks often are interested in early diagnosis to optimize options for therapy in affected infants. Because germline *RB1* mutations predispose to future second cancers, it may be worth investigating the role of cord blood banking for infants who are molecularly diagnosed prenatally with *RB1* mutant alleles as a potential stem-cell source in later anti-cancer therapy.

The small sample size, single institution, and observational retrospective data with lack of randomization limit this study. Despite the small number, we report the largest cohort of children with retinoblastoma diagnosed prenatally in comparison with previous case reports,[43–46] with multiple statistically significant outcomes. Prospective validation of these results will be considered in a multicenter study. We conclude that improved visual outcomes with decreased treatment-associated morbidity is achieved for infants at risk of familial retinoblastoma by prenatal molecular *RB1* mutation diagnosis and planned late-preterm or early-term delivery compared with those managed by postnatal molecular and clinical diagnosis.

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Abbreviations and Acronyms:
EUA = examination under anesthesia.

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