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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*

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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

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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).