Conditional analysis on new tumor formation with solitary unilateral retinoblastoma in 482 consecutive patients

Carol L. Shields, Philip W. Dockery, Megan Ruben, Madalyne A. Sunday, Martin Calotti, Antonio Yaghy

Abstract:

PURPOSE: The objective of the study was to understand dynamic risk (conditional analysis based on patient age) for new tumor development in patients with solitary unilateral retinoblastoma.

METHODS: This was a retrospective analysis.

RESULTS: Of 482 patients with solitary unilateral retinoblastoma, 55 new tumors developed in 20 patients (4%). Comparison (new tumor vs. no new tumor development) revealed those with new tumor demonstrated younger mean age at presentation (10 vs. 36 months, \(P < 0.001\)), greater likelihood of family history of retinoblastoma (35% vs. 3%, \(P < 0.001\)), and greater probability of primary tumor location in the macula (35% vs. 3%, \(P = 0.003\)). Conditional risk for new tumors (at age 6, 9, 12, 18, and 24 months) declined for those who presented at 0–3 months old (25%, 15%, 15%, 8%, and 0%), >3–6 months old (17%, 14%, 6%, 6%, and 0%), >6–9 months old (not applicable [na], 6%, 6%, 0%, and 0%), and >9–12 months (na, na, 3%, 3%, and 0%). Younger patients showed greater development of bilateral tumors (\(P < 0.001\)). Of patients with new tumors, those that occurred within 1 year from presentation were located in the preequatorial region in 46%, whereas those that occurred more than 1 year from presentation were preequatorial in 78%. Patients ≤24 months at initial presentation demonstrated all new tumors by 24 months of age. Older patients (>24 months at presentation) showed new tumors up to 56 months of age.

CONCLUSION: Children (≤24 months) with solitary unilateral retinoblastoma showed decreasing risk for new tumors up to 24 months of life. Later onset of new tumor was more likely located in preequatorial region.

Keywords: Conditional analysis, eye, new tumor, retina, retinoblastoma, solitary, unilateral

Introduction

Solitary unilateral retinoblastoma can be the initial manifestation of germline retinoblastoma in which multiple subsequent tumors can arise in one or both eyes.[1] On the other hand, solitary unilateral retinoblastoma can also represent somatic mutation with only a single solitary tumor and no further tumors. This differentiation is important as germline retinoblastoma implies additional long-term concerns such as multiple new retinoblastomas, pinealoblastoma or neuroblastic tumors of the brain, and second cancers in remote parts of the body.[2–11]

Prior publications have indicated that solitary unilateral retinoblastoma in younger (versus older) patients carries a higher likelihood of germline mutation and a higher rate of subsequent new tumors in the ipsilateral and/ or contralateral eyes.[8] In one analysis, a comparison of 132 infants categorized according to quartiles (0–3 months vs. >3–6 months, vs. >6–9 months vs. >9–12 months), with solitary unilateral retinoblastoma, revealed decreasing likelihood of germline mutation (61% vs. 20% vs. 24% vs. 22%, \(P = 0.009\)) and decreasing rate of new retinoblastomas (35% vs. 20% vs. 5% vs. 3%, \(P = 0.004\).[8] When reviewing the entire cohort of 482 patients with solitary unilateral retinoblastoma, those ≤1 year (vs. >1 year) at presentation demonstrated 2.96
odds ratio (OR) \(P = 0.001\) for likelihood of germline retinoblastoma and 6.89 OR \(P < 0.001\) for new tumors.8

The previous probabilities were static estimates from date of presentation (nonconditional estimates). In this current analysis, we further explore dynamic estimates (conditional estimates) for those who maintained solitary unilateral retinoblastoma at specific timepoints (age 6, 9, 12, 18, 24, 30, 36, 48, and 60 months) to track the declining estimates for new tumor development over time.

**Methods**

The medical records from the Ocular Oncology Services at Wills Eye Hospital, Thomas Jefferson University, Philadelphia, PA USA, were retrieved for all patients with retinoblastoma from June 16, 1972, to June 3, 2020, and specifically selecting those with unilateral retinoblastoma at presentation. Inclusion criteria contained all new patients with unilateral retinoblastoma treated at our facility, whereas exclusion criteria encompassed those patients who received initial treatment elsewhere. This study was approved by the Institutional Review Board of Wills Eye Hospital, adhered to the tenets of the Declaration of Helsinki, and complied with the Health Insurance Portability and Accountability Act. Informed consent was obtained from all patients/families.

All patients were examined by a trained ocular oncologist (CLS), using indirect ophthalmoscopy, large fundus drawings, and ophthalmic imaging, including external photography, ultrasonography, fundus photography, fluorescein angiography, and optical coherence tomography at initial examination and for documentation, as needed at each subsequent examination. Magnetic resonance imaging was performed for evaluation of the orbit and brain when necessary. Each tumor was imaged, sized, and localized in the retina.

Data were recorded at each examination and documented on the patient’s chart. The demographic data in this analysis included patient age (months), race (Caucasian, African American, Hispanic, Asian Indian, Asian Oriental, and others/unknown), and sex (male, female). The involved eye (right, left), family history of retinoblastoma, and retinoblastoma genetic status (germline, somatic) were also documented.

The clinical features at presentation included the International Classification of Retinoblastoma (ICRB)8 group for each eye, largest tumor basal dimension (millimeters [mm]), tumor thickness (mm), main tumor anteroposterior location (macula, macula to equator, equator to ora, ciliary body, and iris), and main tumor quadrantic location (macula, superior, nasal, inferior, and temporal).

The treatment parameters were recorded. Retinoblastoma was managed by one or more of the following therapies including enucleation, intravenous chemotherapy (IVC; vincristine, etoposide, and carboplatin), intra-arterial chemotherapy (IAC; melphalan, topotecan), external beam radiotherapy, proton beam radiotherapy, plaque radiotherapy, and/or focal nonirradiative methods (laser photocoagulation, transpupillary thermotherapy, and cryotherapy). Supplementary treatments such as intravitreal chemotherapy (melphalan and/or topotecan) and focal non-irradiative therapy (laser photocoagulation, transpupillary thermotherapy, and cryotherapy) were used when necessary.

The main outcome was a conditional analysis of the formation of new retinoblastomas in either the ipsilateral or contralateral eye based on age survived (6, 9, 12, 18, 24, 30, 36, 48, and 60 months) without new tumors after presentation.

For each new tumor that was found after diagnosis, the following information was documented: age (months), tumor laterality (ipsilateral, contralateral), tumor anteroposterior location (macula, macula to equator, equator to ora), tumor quadrantic location (macula, superior, nasal, inferior, and temporal), tumor basal dimension (mm), and tumor thickness (mm). Secondary outcomes included trends in location of new tumors (anteroposterior, quadrantic) and size of new tumors (basal dimension, thickness) based on age at new tumor development and interval from initial presentation to the time of new tumor development.

Statistical analysis was performed using SAS Software Suite (version 9.4; SAS Institute, SAS Cary, NC, USA). Continuous variables were expressed as mean (median, range). The one-sample Shapiro-Wilk test was used to assess the normality of distribution. Comparison between groups was performed using the one-way ANOVA test for continuous variables with normal distribution and Kruskal-Wallis test for continuous variables without normal distribution. Comparison of categorical variables was performed using the likelihood ratio Chi-square test and Fisher’s exact test when indicated. Nonconditional and conditional analysis was assessed using Kaplan-Meier analysis of new tumor formation based on age survived without any new tumors after presentation. Cox regression analysis for competing risks was performed with no significant discrepancies from Kaplan-Meier analysis. Binary logistic regression analysis was performed to identify factors potentially predictive of new tumor formation, which could act as confounders. Variables found to be significant in univariate analysis at a level of \(P < 0.10\) were entered into multivariate multiple regression models using the stepwise Wald method, which further excluded variables noncontributory to the fit of the model \(P > 0.05\). Trends in location and size of new tumors were assessed using multivariate linear regression. \(P < 0.05\) was considered statistically significant for results of multivariate multiple regression.

**Results**

There were 482 consecutive patients with solitary unilateral retinoblastoma managed on the Ocular Oncology Service at Wills Eye Hospital, Philadelphia, PA, USA, over a 48-year period. Demographic features are listed in eTable 1. A comparison of patients (new tumor vs. no new tumor development) revealed differences in median age at
presentation (4.2 months vs. 23.5 months, \( P < 0.001 \)) and presence of family history of retinoblastoma (35\% vs. 3\%, \( P < 0.001 \)). There was no difference in development of new tumor based on patient race, sex, or involved eye.

The clinical features of the presenting tumor are listed in eTable 2. A comparison of patients (new tumor vs. no new tumor development) revealed those with new tumor demonstrated less advanced ICRB group \( (P = 0.012) \) and higher rate of macular tumor location (50\% vs. 15\%, \( P = 0.003 \)). There was no difference in development of new tumor based on tumor basal dimension or tumor thickness.

The treatment modalities are listed in eTable 3. A comparison of patients (new tumor vs. no new tumor development) revealed those with new tumor demonstrated differences in primary treatment \( (P = 0.002) \), including a higher rate of IVC (55\% vs. 19\%) and a lower rate of enucleation (10\% vs. 34\%). Those with new tumors following enucleation occurred in the opposite eye in all cases. There was no difference in type of secondary or tertiary treatment, and no difference in those who received surgical or radiation treatment. Patients with new tumor development underwent more total treatments (median: 2 vs. 1, \( P = 0.005 \)) and a higher percentage of medical treatments (85\% vs. 61\%, \( P = 0.021 \)).

Conditional analysis of new tumor formation based on patient age at diagnosis is listed in Table 1. When stratified into seven age categories based on age at diagnosis (0–3 months vs. 3–6 months vs. 6–9 months

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eTable 1: Conditional Analysis of New Tumor Formation in 482 Patients Presenting with Solitary Unilateral Retinoblastoma. Demographic Features

| Demographic features | New tumor development \( (n=20), n (%) \) | No new tumor development \( (n=462), n (%) \) | \( P \) | Total \( (n=482), n (%) \) |
|----------------------|--------------------------------|---------------------------------|-----|-----------------|
| Age \( (\text{months}) \) | Mean (median, range) | 10.3 (4.2, 0.5-52.3) | 35.5 (23.5, 0.8-861.3) | <0.001 | 34.0 (23.0, 0.5-861.3) |
| Race | | | | | |
| Caucasian | 15 (75) | 292 (63) | 0.428 | 307 (64) |
| African American | 2 (10) | 52 (11) | 54 (11) |
| Hispanic | 2 (10) | 40 (9) | 42 (9) |
| Asian Indian | 0 | 10 (2) | 10 (2) |
| Asian oriental | 0 | 52 (11) | 52 (11) |
| Other/unknown | 1 (5) | 16 (3) | 17 (4) |
| Sex | | | | | |
| Male | 12 (60) | 229 (50) | 0.359 | 241 (50) |
| Female | 8 (40) | 233 (50) | 241 (50) |
| Involved eye | | | | | |
| Right | 10 (50) | 227 (49) | 0.940 | 237 (49) |
| Left | 10 (50) | 235 (51) | 245 (51) |
| Family history | | | | | |
| No | 13 (65) | 448 (97) | <0.001 | 461 (96) |
| Yes | 7 (35) | 13 (3) | 20 (4) |

Bold values indicate statistical significance

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eTable 2: Conditional Analysis of New Tumor Formation in 482 Patients Presenting with Solitary Unilateral Retinoblastoma: Clinical Features

| Clinical features | New tumor development \( (n=20), n (%) \) | No new tumor development \( (n=462), n (%) \) | \( P \) | Total \( (n=482), n (%) \) |
|------------------|--------------------------------|---------------------------------|-----|-----------------|
| ICRB \( (n=482 \text{ eyes}) \) | | | | |
| Group A | 1 (6) | 1 (<1) | 0.012 | 2 (1) |
| Group B | 4 (25) | 19 (6) | 23 (6) |
| Group C | 0 (0) | 21 (6) | 21 (6) |
| Group D | 6 (38) | 109 (32) | 115 (32) |
| Group E | 5 (31) | 189 (56) | 194 (55) |
| Spontaneously regressed at presentation | 0 | 14 (4) | 0.261 | 14 (4) |
| Tumor characteristics | | | | |
| Largest basal dimension (mm), mean (median, range) | 15.9 (18.0, 1.0-24.0) | 17.9 (20.0, 1.0-24.0) | 0.320 | 17.8 (20.0, 1.0-24.0) |
| Thickness (mm), mean (median, range) | 7.9 (9.3, 0.3-16.0) | 9.9 (10.0, 0.0-20.5) | 0.085 | 9.9 (10.0, 0.0-20.5) |
| Tumor epicenter location\* | | | | |
| Macula | 10 (50) | 75 (15) | 0.003 | 85 (18) |
| Macula to equator | 9 (45) | 355 (78) | 364 (76) |
| Equator to ora | 1 (5) | 27 (6) | 28 (6) |

\*Two patients were excluded because there was no view of the fundus. Two tumors were located on the iris. One tumor was located on the ciliary body. Bold values indicate statistical significance. ICRB: International Classification of Retinoblastoma
vs. 9–12 months vs. 12–24 months vs. 24–36 months vs. >36 months), the probability of developing at least one subsequent new tumor was 39%, 21%, 6%, 3%, 0%, 2%, and 2%, respectively. For patients diagnosed within the first year of life, if they survived to their first birthday with no new tumor development, the probability of developing at least one subsequent new tumor was 15%, 6%, 6%, and 3%, respectively, for each of the first four age categories. For patients diagnosed within the first 2 years of life, if they survive to their second birthday with no new tumor development, no subsequent new tumors were found in this population.

Critical time points and quantitative assessment of new tumor formation are listed in Table 2. When stratified into seven age categories based on age at diagnosis (0–3 months vs. 3–6 months vs. 6–9 months vs. 9–12 months vs. 12–24 months vs. 24–36 months vs. >36 months), the mean age at time of initial new tumor ($P = 0.025$) and the mean age at time of final new tumor ($P = 0.047$) trended with age at diagnosis, but the interval from diagnosis to initial new tumor ($P = 0.718$) and the interval from diagnosis to final new tumor ($P = 0.208$) did not correlate with age at diagnosis. Younger patients were more likely to develop bilateral disease ($30\%$ vs. $20\%$ vs. $3\%$ vs. $0\%$ vs. $0\%$ vs. $0\%$ vs. $1\%$, $P < 0.001$). For patients who developed new tumors ($n = 20$), there was no statistical difference between the number of new tumors and age at diagnosis ($P = 0.172$).

Clinical features of new tumors are listed in Table 3. Comparison by age at diagnosis (0–3 months vs. 3–6 months vs. 6–9 months vs. 9–12 months vs. 12–24 months vs. 24–36 months vs. >36 months) revealed that older patients develop tumors with larger basal dimension ($0.8$ mm vs. $1.4$ mm vs. $0.7$ mm vs. $7.0$ mm vs. $0.0$ mm vs. $6.5$ mm vs. $4.1$ mm, $P = 0.020$). There was no difference in ipsilateral/contralateral eye involvement, tumor location, or tumor thickness.

Trends in clinical features of new tumors are listed in Table 4. A comparison based on age at development of each new tumor
Table 1: Nonconditional and conditional analysis of probability for development of new tumors in ipsilateral or contralateral eye in 482 patients presenting with solitary unilateral retinoblastoma

| Age at diagnosis (months) | Nonconditional risk at presentation | Conditional risk at each subsequent time point while maintaining solitary unilateral retinoblastoma | Age of latest initial new tumors (months) |
|---------------------------|-------------------------------------|-------------------------------------------------------------------------------------------------|------------------------------------------|
| Total, n (%)              | At 6 months, n (%)                  | At 9 months, n (%)                             | At 12 months, n (%)                      | At 18 months, n (%)                       | At 24 months, n (%)                       | At 30 months, n (%)                       | At 36 months, n (%)                       | At 48 months, n (%)                       | At 60 months, n (%)                       |<0.001                                  |
|                           | 8 (39)                              | 4 (25)                                         | 2 (15)                                   | 2 (15)                                   | 1 (8)                                   | 0                                       | 0                                       | 0                                       | 0                                       | 18.7                                   |
| 0-3 (n=23)                | 5 (21)                              | 6 (44)                                        | 2 (25)                                   | 2 (25)                                   | 1 (10)                                  | 0                                       | 0                                       | 0                                       | 0                                       | 23.4                                   |
| >3-6 (n=25)               | 2 (6)                               | 2 (12)                                        | 2 (12)                                   | 2 (12)                                   | 0                                       | 0                                       | 0                                       | 0                                       | 0                                       | 17.8                                   |
| >6-9 (n=40)               | 1 (3)                               | 1 (3)                                         | 1 (3)                                    | 0                                       | 0                                       | 0                                       | 0                                       | 0                                       | 0                                       | 24.3                                   |
| >9-12 (n=37)              |                                   |                                               |                                         |                                         |                                         |                                         |                                         |                                         |                                         |<0.001                                  |
| >12-24 (n=112)            | 0                                   |                                               |                                         |                                         |                                         |                                         |                                         |                                         |                                         | NA                                     |
| >24-36 (n=91)             | 2 (2)                               |                                               |                                         |                                         |                                         |                                         |                                         |                                         |                                         | 46.1                                   |
| >36 (n=119)               | 2 (2)                               |                                               |                                         |                                         |                                         |                                         |                                         |                                         |                                         | 55.9                                   |
| NA: Not applicable        |                                    |                                               |                                         |                                         |                                         |                                         |                                         |                                         |                                         |                                        |

Table 2: Critical time points and quantitative assessment of onset and interval of new tumor formation in 482 patients presenting with solitary unilateral retinoblastoma

| Critical time points | Age at diagnosis (months) | P | Total population (n=482) |
|----------------------|---------------------------|---|--------------------------|
|                      | 0-3 (n=23)                |   | 16.8 (11.4, 19.5)        |
|                      | 3-6 (n=25)                |   | 19.1 (15.6, 22.6)        |
|                      | 6-9 (n=40)                |   | 47.8 (42.5, 53.1)        |
|                      | 9-12 (n=37)               |   | 50.8 (45.5, 56.1)        |
|                      | 12-24 (n=112)             |   | 48.5 (43.2, 53.8)        |
|                      | 24-36 (n=91)              |   | 58.0 (52.7, 63.3)        |
|                      | >36 (n=119)               |   | 63.5 (58.2, 68.8)        |

*Only eyes that developed at least one new tumor after initial presentation were included in this analysis (n=20), Bold indicates statistical significance. NA: Not applicable

revealed an increase in age correlated with an increase in tumor basal dimension and tumor thickness, with each additional year of age leading to new tumors with 1.00 mm larger diameter (P < 0.001) and 0.55 mm thicker (P = 0.001). There was no difference per age in tumor location. A comparison based on interval from diagnosis to development of new tumor revealed that an increase in time from presentation was associated with more anterior tumor location with an incremental annual increase of pre-equatorial tumors by 31.7% compared to postequatorial tumors (P = 0.041). More specifically, 46% of new tumors that developed within the 1st year following diagnosis were pre-equatorial compared to 78% of new tumors that develop at 1 year or beyond after diagnosis [Figure 1]. There was no difference in tumor quadratic location or tumor size based on interval from diagnosis to development of new tumor.

**Discussion**

Conditional risks are dynamic and change based on the duration of patient follow-up. In this analysis, we explored conditional risk for new tumors in patients, mostly young children, who had presented with a solitary unilateral retinoblastoma. It is well established that new
tumor development tends to manifest in younger patients at presentation ($P < 0.001$), those with family history of retinoblastoma ($P < 0.001$), and those with macular tumor involvement ($P = 0.003$) [eTables 1 and 2]. In this analysis, the new tumor location was associated with time of onset. For example, those who developed new tumor at $\leq$ 12 months from initial diagnosis demonstrated 54% post-equatorial and 46% pre-equatorial location, compared to those who developed new tumor >12 months from diagnosis where only 22% new tumor location was post-equatorial and 78% pre-equatorial [Figure 1]. Thus, the longer the surveillance for new tumor, the more carefully one should examine the pre-equatorial retina, especially near the ora serrata.

Children with solitary unilateral retinoblastoma are closely followed by ocular oncologists in their first 3 years of life. In this analysis, using conditional risk evaluation, we noted that children who presented at $\leq$ 3 months of age and survived without new tumor to 12 months demonstrated a 15% chance for new tumors, while those $>3$–6 months old at presentation who survived without new tumor to 12 months demonstrated a 6% chance for new tumors, and the risk further decreased with older infant age. Importantly, children who presented $\leq$ 24 months old and survived without new tumor to 24 months of age demonstrated no further risk for new tumors. This suggests that close follow-up of the youngest children is essential and when the patient reaches 24 months of age, the risk for new tumor is minimal and less stringent follow-up thereafter could be considered. This is valuable as following a child with solitary unilateral retinoblastoma involves examination under anesthesia, and reducing the frequency of evaluations after 24 months could be suggested.

For those children with solitary unilateral retinoblastoma who present at age >24 months, the rate of new tumor is low overall (2%) and the conditional risk for new tumors in those that reach 48 months without new tumor is lower yet ($\leq$ 1%). In this older age group, less intense monitoring is warranted and the realization that a new tumor could be in the far periphery of the retina should be understood.

New tumors can be difficult to detect, especially when realizing that the median basal dimension was 1.0 mm and median thickness was 0.8 mm. In a cursory examination, these tiny lesions can be overlooked so careful scrutiny of the fundus with scleral depressed examination, complemented with ophthalmic imaging using ultrasonography and optical

Table 3: Clinical features of new tumor development in 482 patients presenting with solitary unilateral retinoblastoma

| New tumor features | Age at diagnosis (months) | Total population |
|-------------------|---------------------------|-----------------|
|                   | 0-3 $n=32$ | 3-6 $n=13$ | 6-9 $n=3$ | 9-12 $n=1$ | 12-24 $n=0$ | 24-36 $n=2$ | >36 $n=4$ | $P$ |
| Ipsilateral       | 8 (25)     | 4 (31)     | 2 (67)     | 1 (100)    | 0          | 2 (100)    | 2 (50)     | 0.091 |
| Contralateral     | 24 (75)    | 9 (69)     | 1 (33)     | 0          | 0          | 2 (50)     | 36 (65)    |       |
| Macula            | 1 (3)      | 0          | 0          | 0          | 0          | 0          | 0.506      |
| Macula to equator | 14 (44)    | 5 (38)     | 2 (67)     | 0          | 0          | 1 (50)     | 26 (47)    |       |
| Equator to ora    | 17 (53)    | 8 (62)     | 1 (33)     | 1 (100)    | 0          | 1 (50)     | 28 (51)    |       |
| Macula            | 1 (3)      | 0          | 0          | 0          | 0          | 0          | 0.907      |
| Superior          | 6 (19)     | 4 (31)     | 2 (67)     | 0          | 0          | 1 (25)     | 13 (24)    |       |
| Nasal             | 13 (41)    | 5 (38)     | 0          | 0          | 1 (50)     | 1 (25)     | 20 (36)    |       |
| Inferior          | 8 (25)     | 2 (15)     | 1 (33)     | 1 (100)    | 0          | 1 (50)     | 14 (25)    |       |
| Temporal          | 4 (13)     | 2 (15)     | 0          | 0          | 0          | 1 (25)     | 7 (13)     |       |
| Basal dimension (mm), mean (median, range) | 0.8 (0.8, 1.4 (1.5, 0.7 (0.1, 7.0 (7.0, 0.0 (0.0, 6.5 (6.5, 4.1 (3.0, 0.2-3.0) 0.2-1.0) 7.0-7.0) 0.0-0.0) 5.0-8.0) 0.3-10.0) | $0.020$ | 1.5 (1.0, 0.1-10.0) |
| Thickness (mm), mean (median, range) | 0.6 (0.5, 0.9 (1.0, 0.7 (1.0, 5.0 (5.0, 0.0 (0.0, 4.0 (4.0, 2.3 (1.2, 0.1-2.0) 0.1-2.0) 5.0-5.0) 0.0-0.0) 2.0-6.0) 0.3-6.0) | 0.061 | 1.0 (0.8, 0.1-6.0) |

| Bold indicates statistical significance |

Table 4: Trends in clinical features of new tumor development in 482 patients presenting with solitary unilateral retinoblastoma

| New tumor features | Age at development of each new tumor | Interval from diagnosis to development of each new tumor |
|-------------------|-------------------------------------|--------------------------------------------------------|
|                   | Incremental change per year $P$     | Incremental change per year $P$                         |
| Tumor location, anteroposterior* | $-6.9\%$ | 0.292 | +31.6\% | 0.041 |
| Tumor location, quadratic | NA | 0.625 | NA | 0.917 |
| Basal dimension (mm)* | 1.00 | $<$0.001 | 0.51 | 0.406 |
| Thickness (mm)* | 0.55 | 0.001 | 0.56 | 0.146 |

*Expressed as percent change from post-equatorial to pre-equatorial tumors per year, †Expressed as change in millimeters per year, Bold indicates statistical significance. NA: Not applicable
coherence tomography, can be employed. While the new tumors in older patients seem to be larger compared to younger patients, this effect is most likely the result of longer interval between each examination.

Limitations to this evaluation include the retrospective design and inclusion of all patients in our service with solitary unilateral disease, managed with various methods over many years. There could be underestimation of true conditional risks for new tumors in that chemotherapy, radiotherapy, or enucleation could have precluded the development of new tumors. However, this analysis does represent “real world” experience in a large cohort of patients with retinoblastoma as generally patients require several treatment methods over several months to control this disease.

CONCLUSION
All children who present with solitary unilateral retinoblastoma should be followed for new tumors, especially those that are younger at presentation, with family history of retinoblastoma, and those with macular tumors. Most younger patients (≤12 months at presentation) with solitary unilateral retinoblastoma who develop new tumors will demonstrate all new tumors by 24 months. Those who are older at presentation display less risk for new tumors. Overall, the longer the time interval between initial tumor and new tumor, the more peripheral, the new tumor will be located in the retina.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Dimaras H, Corson TW, Cobrinik D, White A, Zhao J, Munier FL, et al. Retinoblastoma. Nat Rev Dis Primers 2015;1:15021.
2. Nichols KE, Walther S, Chao E, Shields C, Ganguly A. Recent advances in retinoblastoma genetic research. Curr Opin Ophthalmol 2009;20:351-5.
3. Thériault BL, Dimaras H, Gallie BL, Corson TW. The genomic landscape of retinoblastoma: A review. Clin Exp Ophthalmol 2014;42:33-52.
4. Benavente CA, Dyer MA. Genetics and epigenetics of human retinoblastoma. Annu Rev Pathol 2015;10:547-62.
5. Berry JL, Lewis L, Zolfaghari E, Green S, Le BH, Lee TC, et al. Lack of correlation between age at diagnosis and RB1 mutations for unilateral retinoblastoma: The importance of genetic testing. Ophthalmic Genet 2018;39:407-9.
6. Shields JA, Shields CL. Intraocular tumors. An Atlas and Textbook. 3rd ed. Philadelphia: Lippincott Wolters Kluwer; 2016. p. 349-71.
7. Ramasubramanian A, Shields CL, editors. Retinoblastoma. New Delhi, India: Jaypee Brothers Medical Publishers; 2012. p. 80-118.
8. Shields CL, Dockery PW, Ruben M, Yaghy A, Sunday MA, Duffner E, 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;58:355-64.
9. Shields CL, Shields JA. Basic understanding of current classification and management of retinoblastoma. Curr Opin Ophthalmol 2006;17:228-34.
10. Schüler A, Weber S, Neuhäuser M, Jürklies C, Lehnert T, Heimann H, et al. Age at diagnosis of isolated unilateral retinoblastoma does not distinguish patients with and without a constitutional RB1 gene mutation but is influenced by a parent-of-origin effect. Eur J Cancer 2005;41:735-40.
11. Brichard B, Heusterspreute M, De Potter P, Chantrain C, Vermlyen C, Sibille C, et al. Unilateral retinoblastoma, lack of familial history and older age does not exclude germline RB1 gene mutation. Eur J Cancer 2006;42:65-72.