

# **The UCSF Documentation System for Retinoblastoma: Preparing to Improve Staging Methods for This Disease**

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## 21 **Abstract**

### 22 ***Background/Aims***

23 Current retinoblastoma staging systems do not adequately describe the disease, especially in  
24 eyes with multiple tumors. The aims of this study were to develop methods for documenting  
25 individual tumors and scoring disease burden over time.

### 26 ***Methods***

27 A coding system was devised to describe each tumor according to affected eye, meridian,  
28 antero-posterior location, activity, growth pattern, type of seed, and treatment. A scoring  
29 system for quantifying disease burden was developed, taking account of tumor number, size,  
30 spread and secondary effects on the eye.

### 31 ***Results***

32 Our coding system allowed contemporaneous tumor documentation, producing datasets that  
33 enabled generation of fundus diagrams, Kaplan-Meier curves, and tables summarizing disease  
34 progression in individual tumors and eyes. Our data showed disparities between ocular and  
35 tumor documentation, for example, indicating earlier tumor development in the left eye but  
36 younger age at presentation if disease was worse in the right eye. Actuarial rates of local  
37 treatment failure were lower when individual tumors were analyzed than when data were  
38 reported in terms of whole eyes.

### 39 ***Conclusion***

40 Our methods for documenting individual retinoblastomas have facilitated review of patients'  
41 progress in our routine practice and may provide data that could be used to refine  
42 retinoblastoma classifications in the future.

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## Introduction

As with other diseases, full documentation of retinoblastoma is essential for planning treatment, evaluating quality of care, performing clinical trials, and predicting outcomes.

Several systems for staging retinoblastoma exist.[1-3] These have several limitations. First, they do not fully describe eyes harboring multiple tumors, which are often treated differently from each other and which vary in their growth pattern and response to therapy. Second, current classifications are designed to categorize disease at presentation, not change over time. Third, present staging systems do not reflect recent advances in intra-arterial and intra-vitreous chemotherapy. For example, the type of vitreous seed (i.e., dust, spheres or clouds) may be a better prognostic indicator than the distance of furthest seed from tumor surface. Fourth, they do not take into account the number of tumors in an eye. A 'Group A' eye with only one tumor may not have the same prognosis as an eye with 'Group A' disease and multiple tumors. Finally, they do not take into account the tendency for a patient to develop new tumors after initial treatment, this tendency varying greatly between individuals. Retinoblastoma documentation needs to be more comprehensive to allow staging systems to continue to evolve in response to novel therapies and research findings.

We devised a system for coding individual tumors, also documenting tumor activity. Such a system allows the patient's history to be reviewed quickly, indicating which tumors were active most recently, how each of these was treated, and when such treatment was administered.

The aims of this study were to develop methods for documenting retinoblastoma according to each individual tumor and scoring disease burden.

## **Patients and Methods**

The coding system was developed prospectively with data from the first 40 newly-diagnosed patients treated for retinoblastoma at the University of California San Francisco between June 2013 and December 2017. Patients were excluded if treatment had been initiated elsewhere or before June 2013, because of insufficient data. The cohort comprised 20 patients (9 female, 11 male) with somatic retinoblastoma and 20 patients with a germline mutation (12 female, 8 male), the latter presenting with 103 tumors in 37 eyes. The supplementary table S1 summarizes baseline status, treatment, and outcomes.

The first examination under anesthesia (EUA) included: tonometry; measurement of corneal diameter; portable slit-lamp examination of the anterior chamber and lens; binocular indirect ophthalmoscopy; measurement of basal tumor diameter and thickness by B-scan ultrasonography (Eye Cubed, Ellex, Adelaide, Australia); optical coherence tomography (OCT) in selected cases (Bioptigen, Durham, NC, USA); and photography with RetCam (RetCam, Pleasanton, CA, USA). Fundus drawings were prepared on an iPad tablet using drawing software (Adobe, San Jose, CA, USA) and a template designed by us and made available at [www.oculonco.com](http://www.oculonco.com)) (Fig. 1a & Fig 1b). These drawings were uploaded into our electronic medical records as with other images and documents. Magnetic resonance imaging of the brain and orbits was performed on the same day as the first EUA or on the previous day. Subsequent

EUAs included binocular indirect ophthalmoscopy, fundus photography, fundus drawings and, in selected cases, optical coherence tomography and ultrasonography.

All patients underwent investigation for germline *RB1* alternations. If enucleation was performed, harvested tumor was also analyzed for *RB1* alterations. (Invitae, San Francisco, CA, USA; Impact Genetics, Bowmanville, ON, Canada).

Small tumors (i.e., diameter  $\leq 3$  mm) were treated with cryotherapy if anterior and with laser if posterior. In the early part of the study, tumors considered too large for such focal therapy were treated with systemic chemotherapy, if bilateral, or intra-arterial chemotherapy if unilateral; however, this changed to intra-arterial chemotherapy for all patients. Vitreous seeds unresponsive to systemic or intra-arterial chemotherapy were treated with intra-vitreous chemotherapy. Enucleation was reserved for Group E eyes and those unresponsive to eye-conserving therapy.

Each tumor was coded with a single letter for each item according to: affected eye (Left, Right); meridian in clock minutes; antero-posterior tumor location (Both disc & fovea, Fovea, Disc, Macula not involving fovea, Posterior retina not involving disc, Equator, Anterior retina [i.e., pre-equatorial retina], Ora, Uncertain); and status (New, Larger, Persistent, Diminished, Inactive, Uncertain). Uncertain tumor meridian was coded as 00 (e.g., when the tumor filled the eye). The disc was recorded as being involved if visible tumor extended to the disc margin or if the optic disc was obscured by tumor. Tumors were categorized as: exophytic (X); endophytic

110 (N); mixed (M); vitreous seeds (V); subretinal (S); and uncertain (U). We categorized tumor  
111 configuration at first visit as 'mixed' if the internal limiting membrane was breached. To enable  
112 automated fundus diagrams, diffuse subretinal seeds were documented circumferentially in 5-  
113 minute intervals (e.g., 5, 10, 15, etc.) whereas with isolated subretinal seeds the actual  
114 meridian was documented. Both treated and inactive tumors were sub-categorized as: calcific  
115 ('cottage cheese') (1); fish-flesh (2); mixed (3); flat (4) and invisible (0), in keeping with  
116 conventional practice. Regressing tumors were categorized as fish flesh (Type 2) if calcifications  
117 within the tumor were minimal and non-confluent. Vitreous seeds were sub-categorized as:  
118 dust (D); spheres (S); and clouds (C).[4] Their activity was categorized as (New, Larger,  
119 Persistent, Diminished, Inactive, and Uncertain). Location of diffuse vitreous seeds was  
120 documented by affected quadrant (i.e., 7, 22, 37 and 52 clock minutes) whereas with isolated  
121 vitreous seeds the actual meridian was recorded, with documentation of the retinal zone when  
122 the seeds were close to the retina. Vitreous seeds were categorized as calcified (1); amorphous  
123 (2); mixed (3); and invisible (0). Treatment was coded as: arterial chemotherapy (A);  
124 cryotherapy (C); enucleation (E); laser therapy (L); systemic chemotherapy (S); and vitreal  
125 chemotherapy (V). When multiple therapeutic modalities were administered simultaneously,  
126 these were listed alphabetically. For example, an new, infero-temporal, pre-equatorial,  
127 exophytic tumor in the right eye treated with cryotherapy in a patient who also received  
128 systemic chemotherapy was coded as R35AXN,CS. Tumors were categorized as 'recurrent' only  
129 if previous examination had suggested total inactivity; otherwise, they were classified as  
130 'persistent', 'diminished' or 'larger'. Ocular morbidity, such as glaucoma, retinal detachment  
131 and uveitis, were also recorded.

Eyes were scored as shown in Table 1 so as to indicate the disease burden at each examination.

Findings were documented in our hospital's electronic medical records (APeX, EPIC Systems, Verona, WI, USA). After 2013 these were entered into Document Flowsheets, which we customized to serve as a registry. Data were exported to SPSS (IBM SPSS Statistics for Macintosh, Version 22.0, Armonk, NY, USA) for statistical analysis. Fundus diagrams were generated automatically from numerical data using Stata (Release 14.2 for Mac, StataCorp, College Station, TX, USA)(Fig. 1c). Drawings were uploaded into our electronic medical records and included in our reports. This study complied with the Health Insurance Portability and Accountability Act (HIPAA). Approval of the UCSF Institutional Review Board was obtained (No: 16-19878).

## Results

Figure 2 shows how our coding system enables documentation of tumor locations within each eye. For example, Figure 2a demonstrates how tumors were more common medially and how those detected at a later age tended to be more anterior. Figure 2b, shows the location of new tumors developing after completion of intra-arterial chemotherapy in patients with germline disease.

Figure 3 shows how this coding system would facilitate investigation of age at detection of each tumor. For example, in a cohort of 55 germline retinoblastomas detected after the first examination, such analysis indicates that post-equatorial tumors are detected at a younger age

than anterior tumors (Figure 3a). Figure 3b suggests that tumors in the left eye tend to be detected at a younger age than those in the right eye. This result is different from that of Figure 3c, which suggests that patients present at a younger age when the disease is more advanced in the right eye.

As expected, reported recurrence rates were lower when reported in terms of tumors than in terms of eyes. Kaplan-Meier analysis indicates that recurrences occurred in 29.9% of 61 eyes that had not undergone primary enucleation. These 61 eyes harbored 156 tumors, 11.1% of which had recurred.

Table 2 shows how our coding system aids detailed review of patients' previous treatment, providing information on the location, growth pattern, treatment and outcome of each tumor at every examination. It summarizes the history of a baby girl presenting with bilateral retinoblastoma at the age of 6 months. The right eye was enucleated after one dose of systemic neoadjuvant chemotherapy. The left eye was found to have 5 exophytic retinal tumors and 2 tumors that had perforated the internal limiting membrane, with dusty vitreous seeding infero-temporally and medially. The patient received three doses of systemic chemotherapy in addition to laser therapy to most lesions. At the age of 12 months, a new exophytic tumor was noted in the infero-temporal equatorial retina and this was treated with laser. At the age of 15 months, a suspicious lesion in the infero-nasal, post-equatorial retina was lasered, as a precaution. At the age of 14 months, two recurrences, consisting of fish flesh and calcification, were noted in the temporal and infero-temporal equatorial region of the left eye and these



were treated with laser, the infero-temporal lesion in the 20-minute meridian ('4 o'clock') subsequently receiving cryotherapy and laser treatment. Another recurrence, located in the horizontal, medial, equatorial region, was diagnosed at the age of 24 months, and this was treated with laser therapy and cryotherapy. No further tumor activity was noted over the next 10 months, until shortly before the close of the study. This table also showed how scores varied with the disease burden.

## **Discussion**

### ***Main outcomes***

We have devised a system for coding the location and behavior of individual tumors in retinoblastoma-affected eyes. We have also developed a method for scoring disease burden in affected eyes and to document change over time.

### ***Strengths and weaknesses***

Our treatment selection shifted from systemic to intra-arterial chemotherapy during this project; however, since we were not evaluating therapy this did not detract from our study.

### ***Methods***

Drawings were made on a tablet because it was easier to see the images in the darkened room and to avoid fragments from color pencils and erasers from contaminating the operative field. Further, these digital images aided oral communication with the patients' relatives immediately

198 after each EUA and were easily uploaded into electronic health records and incorporated into  
199 reports, which were copied to the parents.

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201 In our scoring system, predictive factors were categorized and scored to derive groupings  
202 similar to current IRC systems. However, continuous data were nevertheless documented to  
203 enable future development of tumor staging. For example, IRC systems do not differentiate  
204 between tumors that are 3 mm thick and those that have a thickness of, say, 10 mm. Tumor  
205 diameter and thickness were documented separately because following treatment tumor  
206 thickness may regress differently from tumor base. We did not use tumor volume in our system  
207 because its estimation was subjective and because it related to ocular volume, which was not  
208 measured; therefore, we preferred to rely on tumor thickness. Although tumor dimensions and  
209 distances from disc and fovea were documented, these were not included in the tumor codes  
210 to avoid such codes from becoming unwieldy. Tumor growth and regression were mostly  
211 categorized according to ophthalmoscopic appearances; this is in keeping with conventional  
212 practice, because ultrasonographic measurements of every tumor are not routinely obtained in  
213 follow-up EUAs. Circumferential tumor localization was documented in clock minutes because  
214 these were easier to image mentally than degrees and more precise than clock hours.

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216 Vitreous seeds were categorized by type because these vary in their chemo-responsiveness.  
217 Locations of vitreous and subretinal seeds were categorized by quadrant and clock hour  
218 respectively to enable computer-generated fundus diagrams. Further studies are required to  
219 refine seed categorization, ideally describing severity more fully.

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Our system also allowed documentation of other factors, such as glaucoma, uveitis, retinal detachment, extra-ocular spread and optic nerve involvement. We categorized intraocular pressure only according to tonometry, without including ‘Buphthalmos’ because this was secondary to intraocular pressure. Retinal detachment was recorded as a continuous variable to enable future development.

**Results**

The clinical results reported in this article are intended to demonstrate the potential of our coding system for retinoblastoma and not to make any inferences regarding therapeutic efficacy.

Table 2 shows how the entire ocular history can be summarized in one table so that it is possible for the clinician to review each tumor individually. If the patient had glaucoma, extraocular spread or other adverse factors, these would have been listed in an additional column. Table 2 also shows how the disease stage improved over time; however, it also shows how the scores varied widely within the IRC B Grouping, which therefore does not seem to describe the disease burden precisely. In examinations 16 to 20, the disease in the left eye was categorized as ‘A’ in the absence of any viable tumors and this was meant to reflect some risk of new tumor formation. This was done to emulate the TNM staging system but requires further evaluation.[5]

Kaplan-Meier analyses suggest that in eyes with multiple tumors, local tumor control is described more precisely when outcomes are reported by tumor than by eye.

Our system for localizing tumors demonstrated a higher prevalence of medial tumors, which has been reported previously.[6] This is in keeping with the higher density of cones in the medial retina and evidence that retinoblastomas arise from cone precursors.[7, 8]

#### ***Further studies***

Our coding system is intended only as a method for documenting retinoblastomas in greater detail so as to provide data that might in future be useful to any groups or individuals striving to improve existing classifications so that these do not lose relevance when new therapies are developed (e.g., intra-vitreous chemotherapy). It is not the aim of this study to develop or propose a new classification.

As mentioned, our scoring system is designed to categorize affected eyes into groupings similar to those of the IRC. We are currently evaluating it in a larger cohort of patients. There is scope for further studies to adjust the scoring of each risk factor according to the outcome this factor is intended to predict (i.e., visual acuity, ocular conservation, mortality). For example, foveal involvement should predict visual acuity but not patient survival. There is also a need to determine whether our approach usefully allows prognostication to be revised according to the findings of each successive examination, as well as the patient's age and type of mutation. It is hoped that our proposals will be further refined and validated with data from other centers,

following standardized protocols.[9] Prospects for such studies would be improved by the development of software programs to enable clinicians to collect data contemporaneously, effortlessly, efficiently, and accurately.

## **Conclusions**

We have developed a coding system for documenting individual tumors and scoring disease burden in eyes affected by retinoblastoma. Further studies are needed to enhance the ergonomics of this system and to validate it in other centers.

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## **Legends to Figures**

Figure 1. Multiple retinoblastomas in both eyes of an African-American baby boy. Fundus drawings of (a) right eye and (b) left eye, prepared on a tablet during the examination under anesthesia, depicting the exophytic tumor as light green, endophytic tumor as medium green, and vitreous seeds as dark green; (c) Fundus diagram, generated with Stata, depicting the

exophytic tumors in blue, endophytic tumor in orange and vitreous seeds in red. The text was added using Powerpoint.

Figure 2. Computer-generated fundus diagrams showing (a) germline tumor locations according to age when new tumors were detected, with red circles, orange diamonds, green triangles and purple squares representing tumors found at 0-6 months of age, >6-12 months, >12-18 months and >18 months, respectively, and (b) the location of new germline tumors developing after completion of intra-arterial chemotherapy. The numbers in red indicate are the case numbers. The blue circles indicate new tumors developing before completion of intra-arterial chemotherapy and those developing in eyes without this treatment.

Figure 3. Age at detection of each new germline tumor after the first examination, according to (a) antero-posterior tumor location and (b) affected eye. (c) Age at presentation, according to worst affected eye.

### **Legends to Tables**

Table 1. Tentative system for scoring eyes and individual tumors to categorize retinoblastoma-affected eyes in grouping similar to the International Retinoblastoma Classification.

Table 2. Clinical history of a baby girl presenting with bilateral retinoblastoma at the age of 6 months.

308     Supplementary Table. Ocular status, according to (a) eye and (b) tumor at presentation and (c)  
309     at close of study.

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