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Retrospective Retinoblastoma Activity Index Validation (RRAIV): A Digital Solution to Standardize Outcome Measures in Clinical Trials for Intraocular Retinoblastoma

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Study Protocol
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Principal Investigator (PI):

Dr. Brenda Gallie, MD, FRCSC
brenda.gallie@sickkids.ca
416.813.7654, Extension: 203287

Co-Investigator:

Furqan Shaikh, MD, MSc, FRCPC
furqan.shaikh@sickkids.ca
416.813.7654, Extension: 20886

Research Team:

Mei Chen, Clinical Project Coordinator MASc; mei.chen@sickkids.ca
Sameh Soliman, Research Fellow, MD, sameh.soliman@sickkids.ca
Maxwell Gelkopf, Research Student, BSc; maxwell.gelkopf@sickkids.ca
Isabella Janušonis, Research Student; isabella.janusonia@sickkids.ca

Research Coordinator:

Kaitlyn Flegg, MSc
kaitlyn.flegg@sickkids.ca
416.813.7654, Extension: 203287
Study Site:
The Hospital for Sick Children

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1. BACKGROUND

Retinoblastoma is an aggressive childhood cancer of the eye, affecting ~8,000 children annually (approximately 1/17,000 live births).[1] The retinoblastoma tumor is caused by biallelic pathogenic allele of the *RB1* gene, with approximately half of all retinoblastoma patients carrying one predisposing pathogenic *RB1* allele in constitutional cells.

Retinoblastoma centres around the world largely operate independently, with few collaborative research trials and data-sharing. Variations in staging systems, treatments, and outcome measurements and communication challenges all contribute to unequal quality care and outcomes.

In other pediatric solid cancers, standardized measures of tumour response, such as Response Evaluation Criteria Solid Tumors (RECIST)[2] indicate the primary outcome in trials of novel agents. However, RECIST cannot be applied to retinoblastoma due to the unique multifocality and focal spread within each affected eye. The retinoblastoma tumour can be viewed directly through the dilated pupil, very often seen first by parents as a white glow in the pupil (leukocoria). The diagnosis is confirmed under anesthesia (EUA). Clinical staff record digital wide-angle images of the whole retina and with optical coherence tomography find new tumors so small that they are invisible. Since the 1950s the key tool in managing retinoblastoma was the hand-drawn retinal diagram on paper forms with colored pencils to record the key clinical features of the intraocular disease in each eye.

Since 2003, digital retinal drawings have been stored on an electronic system called the electronic Cancer Care for Retinoblastoma (eCCrb) housed within SickKids. We propose to retrospectively use these drawings to validate and determine the weight of the modifying factors based on outcomes of successful eye salvage and avoid metastasis.

Having a standardized retinoblastoma response criterion to therapies will allow comparisons of different treatment outcomes. This will accelerate the rate of development of new treatments and technologies for treating retinoblastoma. With the Retinoblastoma Activity Index (RAI) score calculated at every patient encounter, clinicians and researchers will have a representation of the tumour activity across time in the DEPICT HEALTH database that is the successor of eCCrb. This will also be useful to share with families to help them understand their child's disease status and treatment response.

The widely accepted measure of successful treatment of retinoblastoma is the salvage of an eye without use of external beam radiation.[3] While eye salvage is a meaningful outcome, it is affected by many variables not directly related to treatment (parental preference, institutional culture, visual potential of either eye, etc.) and does not facilitate an objective comparison of different treatments. Therefore, there it is important to develop a standardized treatment response assessment measure, analogous to RECIST[2] but tailored specifically to the unique complexities and features of retinoblastoma.

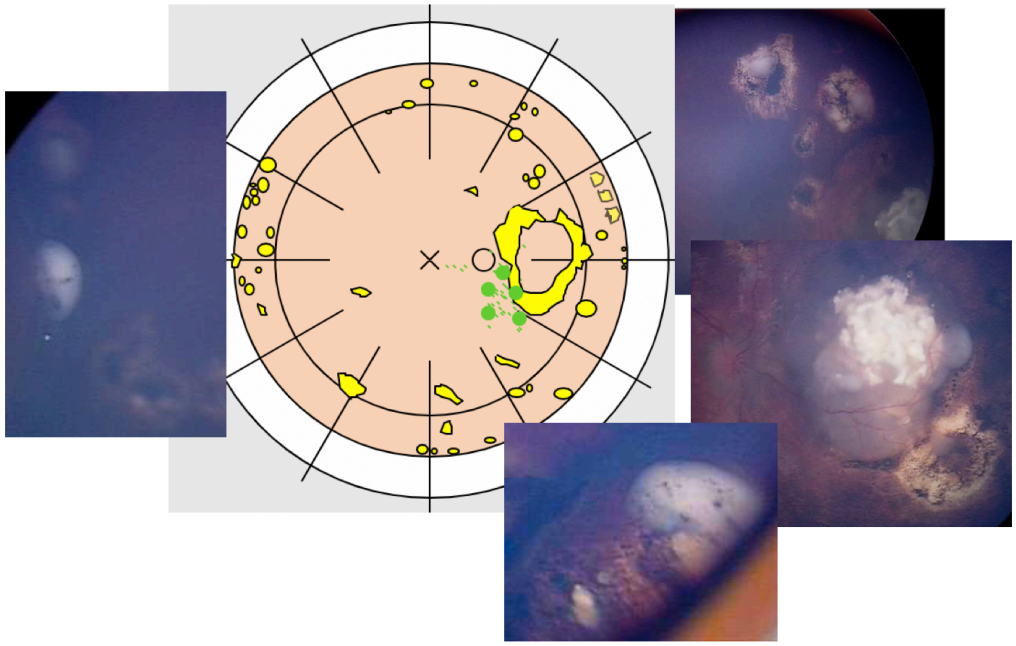

Figure 1. The hand drawn diagram in the middle cumulatively encapsulates the disease status, clinically interpreted from the tumour digital images taken during the exam under anesthesia; yellow represents active tumours while green represents vitreous seeds.

We propose a novel method to quantify tumour severity by taking the total area of the yellow pixels in the digitally drawn images in – as the basic measure for the RAI. A simple, straight forward algorithm will read the drawing and output a number from 0 to 100 indicating the percent of area covered by the yellow tumour relative to the total area of the retina. Next, evidence supported by published data relative to likelihood of saving an eye will be factored in, to modify the RAI, and arrive at the full RAI as a predictor of success to save and eye without metastases.

2. STUDY PURPOSE AND OBJECTIVES

The primary objective of this study is to develop an algorithm that will optimize the retinoblastoma represented in RAI score to predict eye outcomes.

3. HYPOTHESIS

The RAI can approximate disease status and correlate with treatment outcomes.

4. STUDY DESIGN AND METHODOLOGY

4.1 General Study Design

This study is a retrospective review of digital retinal drawings in order to iteratively develop, test, and validate algorithms for calculating the RAI.

Retinal drawings and treatment outcomes will be retrieved from files in eCCrb. (Missing information will be filled in with data from SickKids medical records) (EMR and historic "Red Charts" for Retinoblastoma (in Department of Ophthalmology and Vision Science, DOVS). No identifying patient information (PHI) will be collected except the Medical Record number corresponding to a Study Participant Number which will be stored in a separate key excel document, on a password protected computer, in a locked office. Number and dates of encounters with studied drawings will be collected.

An image processing script will be developed using Python as the programming language. The algorithm will be used to quantify tumour by measuring the total area of the tumour (marked yellow) and calculate its relative area compared to the entire retina area. Modifying factors such as the coverage of the macula, optic nerve, and anterior extension beyond the retina will be assessed and incorporated into the outcome modifying factors (see data collection sheet A). We will develop the tool to enable this calculation, see methods section for detailed steps.

We will treat each eye of the patient as its own entity, due to the fact that clinical decision of each eye is considered separately according to its independent disease. The worst eye at initial diagnosis will the study eye for the systemic outcome of metastasis.

4.2 Inclusion Criteria

- SickKids patients who have been treated for retinoblastoma and are included in eCCrb, diagnosed since 2003-01-01.
- The eye is included if it had a minimum of 4 completed high quality retinal drawings available in eCCrb (one must be at the baseline staging examination under anesthesia); high quality is defined as a completed retinal drawing consistent with clinical images.

4.3 Exclusion Criteria

- Patients who received cancer staging outside of SickKids, due to treatment prior to arrival at SickKids and absence of baseline eCCrb retinal drawings.
- Patients added to eCCrb retrospectively, due to variations in quality of retinal drawings.
- Patients who have been bilaterally enucleated before their 4th retinal drawing.
- Patients who have extraocular disease at diagnosis since this modifies their overall management.

4.4 Study Procedures

Clinical data will be retrieved from eCCrb, recorded in a password protected excel document and stored on a password locked computer in a secure SickKids office. The data will be de-identified on collection; a key will be created to link the patient ID to the patients' hospital number – this key will be kept separately from the data collection sheet.

RAI algorithm development:

The image processing script will be built with Python and accompanying open-source libraries (TensorFlow, OpenCV, Numpy, and Scikit-Learn) The script will read the retinal images (pixel-by-pixel) and quantify the amount of yellow and green area (indicating tumour and vitreous seed area, respectively) in the drawing. The scripts for the modifying factors will be developed similarly, using the open-source tool boxes and calculating the percentage of the optic nerve and macula covered. See Figure 2 for a sample image and calculation.

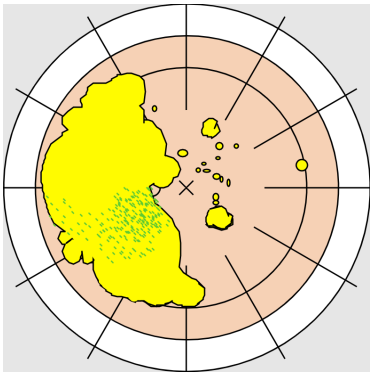

Figure 2. Sample image and calculation in this sample retinal image, the yellow tumour is calculated by RAI to cover 17.33% of the eye. The optic nerve is partially covered.

Literature evaluation for evidence-based modifier factors for retinoblastoma

Recent evidence reveals importance of visualization of the optic nerve and macula to support safe attempt at salvage of an eye with retinoblastoma.[4] The TNMH most recent edition summarizes the literature on eye features that correlate with risk for metastasis and extraocular tumor extension.[5] These and other recent literature will be incorporated into the "weight" of eye clinical features in the RAI.

Collect data on Modifying variables in participant records to be collected from eCCrb and the EMR and Red Chart if:

- Tumour is touching or covering the optic nerve (this is a route of metastasis)
- Tumour is touching or covering the macula (this is indicative of low vision potential)
- Tumour is manifested in the anterior compartment of the eye
- Presence and quantity of vitreous seeds (an adverse situation to control intraocular disease)
- Bilateral or unilateral of disease (modifies extent to which eye salvage is pursued)
- Vision at presentation (converted from various techniques to digital visual acuity)

Outcome variables:

- Occurrence of metastatic disease
- Salvage of the eye [Y/N]
- Final vision (converted from various techniques to digital visual acuity)

The RAI algorithm will be iteratively calculated with the input variables (in-drawing yellow, active tumor and green, vitreous seeds; and various weighting clinical modifying features) to optimize the RAI prediction of the outcome measures (summed as saving of the eye without metastasis).

4.5 Date Range

This study will include charts ranging from 01-01-2003 to 01-11-2019 (eCCrb was used clinically since 2003).

4.6 Participant Selection

eCCrb records with eligibility criteria will be identified by a member of the research team who is listed on the REB application.

4.7 Data Sources

This study will use retinal drawings from eCCrb, the “Red Chart for Retinoblastoma” a key record including retinal drawings in SickKids since 1985, and EPIC for current patients and outcomes. No tissue samples or lab values will be collected. See data collection sheet.

4.8 Primary and Secondary Objectives

The **Primary Objective** is to approximate the optimal weighting to assign each variable by determining the association between the RAI score and patient outcomes in the Primary Participant Group.

The **Secondary Objective** is to validate in a retrospective dataset (the Second Participant Group), if the RAI predicts which eyes would ultimately be salvaged, how many invasive therapies were required to save the eye, and what eyes could have been expected to fail salvage.

4.9 Statistical Methods/Data Analysis

Tumour area calculation, modifying variables and eye outcomes will be summarized using descriptive statistics, see data collection sheet.

See specific steps for calculating the RAI are as follows:

Step1: Calculate the area and quantify the area covered by the tumour and vitreous seeds.

Step 2: Assess whether if the optic nerve or touched is covered by using a customized optic nerve detector tool and measuring the coverage percent of the optic nerve. The development of this tool will be done using Python, leveraging python libraries: TensorFlow, OpenCV, Numpy, and SciKit-Learn.

Step 3: Conduct similar processes for the anterior extension of tumour and macula and assess its coverage by tumour.

Step 4: Visualization of the results above will be done via d3.js.

Statistical clustering methods such as random forest will also be used to predict similar clusters of patients based on TNMH 8th edition cancer staging for each eye, and assess which variables are the most determinant of outcomes. Correlation calculation will be conducted via Python, SciKit-Learn and SPSS.

5. DATA PRIVACY

Proper safeguarding techniques to protect confidentiality of the data will be employed; data will be protected and safeguarded as per SickKids policy:

- Issue a unique study ID code for each participant.
- Protect identifiable information (i.e., participant name) in a code-breaking log, which will be stored separately from study data.
- Limit access to identifying information.
- Store all data using a two-lock system.
- Store all data for 7 years from last publication.
- Securely destroy all data:
- Electronic records will be destroyed by contacting the SickKids help desk
- Paper records will be disposed in SickKids confidential bins.

- Old CDs, DVDs, videos, USB keys, external hard drives and other technology will be sent to the repair center for destruction

6. REFERENCES

1. Dimaras H, Corson TW, Cobrinik D, et al. Retinoblastoma. *Nat Rev Dis Primers.* 2015;1:15021.
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3. Chan HS, Gallie BL, Munier FL, Beck Popovic M. Chemotherapy for retinoblastoma. *Ophthalmology clinics of North America.* 2005;18(1):55-63, viii.
4. Kletke SN, Feng ZX, Hazrati LN, Gallie BL, Soliman SE. Clinical Predictors at Diagnosis of Low-Risk Histopathology in Unilateral Advanced Retinoblastoma. *Ophthalmology.* 2019;126(9):1306-1314.
5. Mallipatna A, Gallie BL, Chévez-Barrios P, et al. Retinoblastoma. In: Amin MB, Edge SB, Greene FL, eds. *AJCC Cancer Staging Manual.* Vol 8th Edition. New York, NY: Springer; 2017:819-831.

CODE BREAKER	
Participant ID	**Hospital MRN #**

DATA COLLECTION SHEET

			RAI per encounter		
					Modifiers
Participant ID	**Tumour %**	**Staging or Treatment**	**Encounter Date [yy/mm/dd]**	**Bilateral/ Unilateral**	**Study Eye [OD/OS]**

			Patient	
			Eye outcomes	
Tumour touching/covering optic nerve	Tumour touching/covering macula	Anterior tumour	Eye (Enucleation, Visual Acuity)	Number of treatment modalities used

Outcomes			Notes
Child outcome			
Metastatic disease [Y/N]	Outcome Life (Alive, Death)	Total # of EUAs	

BUDGET AND JUSTIFICATIONS

Item	Price	Justification
Clinical Research Project Coordinator	$45,962	(0.6 FTE X $62790), 22% benefits
Modification of DEPICT HEALTH for RAI by UHN Health Research Informatics	$14,083	Develop modifications to automate RAI from retinal drawings
Total:	$60,000	