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### The American Joint Committee on Cancer Ophthalmic Oncology Task Force

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# Retinoblastoma seeds: impact on American Joint Committee on Cancer clinical staging

Ankit Singh Tomar,<sup>1</sup> Paul T Finger ,<sup>1</sup> Brenda Gallie ,<sup>2</sup> Tero Kivelä,<sup>3</sup> Ashwin Mallapatna,<sup>4,5</sup> Chengyue Zhang,<sup>6</sup> Junyang Zhao,<sup>6</sup> Matthew Wilson,<sup>7</sup> Rachel Brennan ,<sup>8</sup> Michala Burges,<sup>7</sup> Jonathan Kim,<sup>9</sup> Jesse L Berry ,<sup>10</sup> Rima Jubran,<sup>11</sup> Vikas Khetan,<sup>12</sup> Suganeswari Ganeshan,<sup>12</sup> Andrey Yarovoy,<sup>13</sup> Vera Yarovaya,<sup>13</sup> Elena Kotova,<sup>13</sup> Denis Volodin,<sup>13</sup> Yacoub Yousef ,<sup>14</sup> Kalle Nummi ,<sup>3</sup> Tatiana L Ushakova,<sup>15,16</sup> Olga V Yugay,<sup>15</sup> Vladimir G Polyakov,<sup>15,17</sup> Marco Antonio Ramirez-Ortiz,<sup>18</sup> Elizabeth Esparza-Aguiar,<sup>18</sup> Guillermo L Chantada,<sup>19</sup> Paula Schaiquevich,<sup>20</sup> Adriana C Fandiño,<sup>19</sup> Jason C Yam ,<sup>21</sup> Winnie W Lau,<sup>22</sup> Carol P Lam,<sup>22</sup> Phillipa Sharwood,<sup>23</sup> Sonia Moorthy,<sup>24</sup> Quah Boon Long,<sup>25</sup> Vera Adobea Essuman,<sup>26</sup> Lorna A Renner,<sup>27</sup> Ekaterina Semenova,<sup>1</sup> Jaume Català-Mora,<sup>28</sup> Maria Correa Llano,<sup>28</sup> Elisa Carreras,<sup>28</sup> The American Joint Committee on Cancer Ophthalmic Oncology Task Force

For numbered affiliations see end of article.

## Correspondence to

Dr Paul T Finger, Ophthalmic Oncology, New York Eye Cancer Center, New York, New York, USA; pfinger@eyecancer.com

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## ABSTRACT

**Aim** To investigate whether the American Joint Committee on Cancer (AJCC) clinical category cT2b needs to be subclassified by the type and distribution of retinoblastoma (RB) seeding.

**Methods** Multicentre, international registry-based data were collected from RB centres enrolled between January 2001 and December 2013. 1054 RB eyes with vitreous or subretinal seeds from 18 ophthalmic oncology centres, in 13 countries within six continents were analysed. Local treatment failure was defined as the use of secondary enucleation or external beam radiation therapy (EBRT) and was estimated with the Kaplan-Meier method.

**Results** Clinical category cT2b included 1054 eyes. Median age at presentation was 16.0 months. Of these, 428 (40.6%) eyes were salvaged, and 430 (40.8%) were treated with primary and 196 (18.6%) with secondary enucleation. Of the 592 eyes that had complete data for globe salvage analysis, the distribution of seeds was focal in 143 (24.2%) and diffuse in 449 (75.8%). The 5-year Kaplan-Meier cumulative globe-salvage (without EBRT) was 78% and 49% for eyes with focal and diffuse RB seeding, respectively. Cox proportional hazards regression analysis confirmed a higher local treatment failure risk with diffuse seeds as compared with focal seeds (hazard rate: 2.8;  $p < 0.001$ ). There was insufficient evidence to prove or disprove an association between vitreous seed type and local treatment failure risk ( $p = 0.06$ ).

**Conclusion** This international, multicentre, registry-based analysis of RB eyes affirmed that eyes with diffuse intraocular distribution of RB seeds at diagnosis had a higher risk of local treatment failure when compared with focal seeds. Subclassification of AJCC RB category cT2b into focal vs diffuse seeds will improve prognostication for eye salvage.

## INTRODUCTION

Retinoblastoma (RB) is typically discohesive, resulting in intraocular dissemination of tumour seeds in the subretinal or vitreous space on tumour growth.<sup>1</sup> They are morphologically described as dust, sphere and cloud type, and especially the emergence of vitreous seeds is thought to worsen local tumour control.<sup>1–6</sup> For example, the Reese-Ellsworth classification assigned the prognosis of eyes with vitreous seeds to the most unfavourable group, Vb group.<sup>7</sup> Similarly, the International Intraocular Retinoblastoma Classification and the International Classification for Retinoblastoma also account for the presence and extent of vitreous and subretinal seeds by dividing eyes according to focal (group C) or diffuse (group D) seeding.<sup>8,9</sup> In contrast, the eighth edition American Joint Committee on Cancer (AJCC) staging system does not account for characteristics or distribution of RB seeds.<sup>10</sup>

Despite advances in the conservative management of advanced RB, a major cause of local treatment failure remains the persistence or recurrence of resistant vitreous and subretinal RB seeding.<sup>2,3,5</sup> Vitreous and subretinal seeds can remain viable in the relatively avascular subretinal and vitreous environments and even grow to spheres. This environment has been thought to help RB seeds elude systemic and intra-arterial chemotherapy.<sup>1</sup> Their small size and often diffuse distribution also prevent control with sequential aggressive local therapy.<sup>1</sup> This has resulted in the need for external beam radiotherapy, periocular, and intravitreal chemotherapy to avoid enucleation.<sup>3,11,12</sup>

In 2018, the AJCC eighth edition provided a comprehensive, evidence-based RB staging system which was then adopted by the Union for International Cancer Control (UICC).<sup>10</sup> Its advantages include that AJCC-UICC was the first and only RB



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staging system to incorporate intraocular and extraocular RB as well as heredity to predict both local treatment failure and metastasis-related mortality.<sup>10 13 14</sup>

The AJCC Ophthalmic Oncology Task Force (OOTF) periodically updates RB staging based on the availability of significant medical evidence. In 2017, the AJCC-OOTF analysed the literature for the eighth edition AJCC RB staging system and found no statistically significant convincing evidence that focal and diffuse seeding should be separated.<sup>10</sup> However, since that time, new evidence has suggested that not all types of seeds nor their distributions are equal. Differences resulted in variation in the number of required intravitreal injections, the speed of seed-regression, and the rates of local treatment failure.<sup>16 12</sup>

Herein, we examine if clinical characteristics and intraocular distribution of RB seeds at presentation can be used to predict local treatment failure and improve RB staging.

## METHODS

This study was conducted in adherence to the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act of 1996. A total of 18 RB centres from 13 countries in 6 continents participated. Data from RB patients diagnosed between 5 January 2001 and 31 December 2013 were collected and entered into a secure online database and used to analyse RB seeding.

### The Registry

Select RB subspecialty AJCC-OOTF committee members developed the data fields employed in the internet-based registry to obtain statistically significant medical evidence and thus answer our questions about RB.<sup>10 13–15</sup> The scope of this study was limited to assessing the risk of local treatment failure based on the clinical type and intraocular distribution of RB seeds. Our internet database and security methods have been described in our prior registry publications.<sup>13–15</sup>

### Definitions

The eighth edition of the AJCC Cancer Staging Manual on RB was used to determine the primary clinical tumour (cT) extent (table 1). This study assessed clinically visible seeds assigned to category cT2b. The diagnostic and therapeutic protocols were determined by each centre. Data collected included: demographic and clinical information comprising size and location of the intraocular tumour, presence of glaucoma, iris neovascularisation, subretinal fluid (SRF, <5 mm of tumour or >5 mm) and the distribution of seeds (diffuse/local) and type of vitreous seeds (dust/sphere/cloud).

### Seed distribution

- ▶ Focal (within 3 mm of main tumour).
- ▶ Diffuse (beyond 3 mm of main tumour).

### Seed type

- ▶ Dust: small granules of vitreous opacity.
- ▶ Sphere: spherical shaped vitreous opacity.
- ▶ Cloud: dense collection of punctate vitreous opacities.

In this study, clinical vitreous seed type characteristics were divided into dust, sphere, and cloud. While these seed type characteristics were formalised after the closure of our registry, they were commonly used widely by participating centres.<sup>1</sup> Therefore, seed-type classification was analysed for all eyes where this information was entered. In cases where more than one seed

**Table 1** The American Joint Committee on Cancer (AJCC) eighth edition TNMH classification for retinoblastoma, Definitions for primary tumour staging (CT)

cTX	Unknown evidence of intraocular tumour
cT0	No evidence of intraocular tumour.
cT1	Intraocular tumour(s) with subretinal fluid ≤5 mm from the base of any tumour.
cT1a	Tumours ≤3 mm and further than 1.5 mm from the disc and fovea.
cT1b	Tumours >3 mm or closer than 1.5 mm to the disc and fovea.
cT2	Intraocular tumour(s) with retinal detachment, vitreous seeding or subretinal seeding.
cT2a	Subretinal fluid >5 mm from the base of any tumour.
cT2b	Tumours with vitreous seeding and/or subretinal seeding.
cT3	Advanced intraocular tumour(s).
cT3a	Phthisis or prephthisis bulbi.
cT3b	Tumour invasion of the pars plana, ciliary body, lens, zonules, iris or anterior chamber.
cT3c	Raised intraocular pressure with neovascularisation and/or buphthalmos.
cT3d	HypHEMA and/or massive vitreous haemorrhage.
cT3e	Aseptic orbital cellulitis.
cT4	Extraocular tumour(s) involving the orbit, including the optic nerve.
cT4a	Radiological evidence of retrobulbar optic nerve involvement or thickening of the optic nerve or involvement of the orbital tissues.
cT4a	Extraocular tumour clinically evident with proptosis and orbital mass.

cT, clinical tumour.

type characteristic was recorded, the predominant type with the highest degree was recorded.

### Treatment definitions

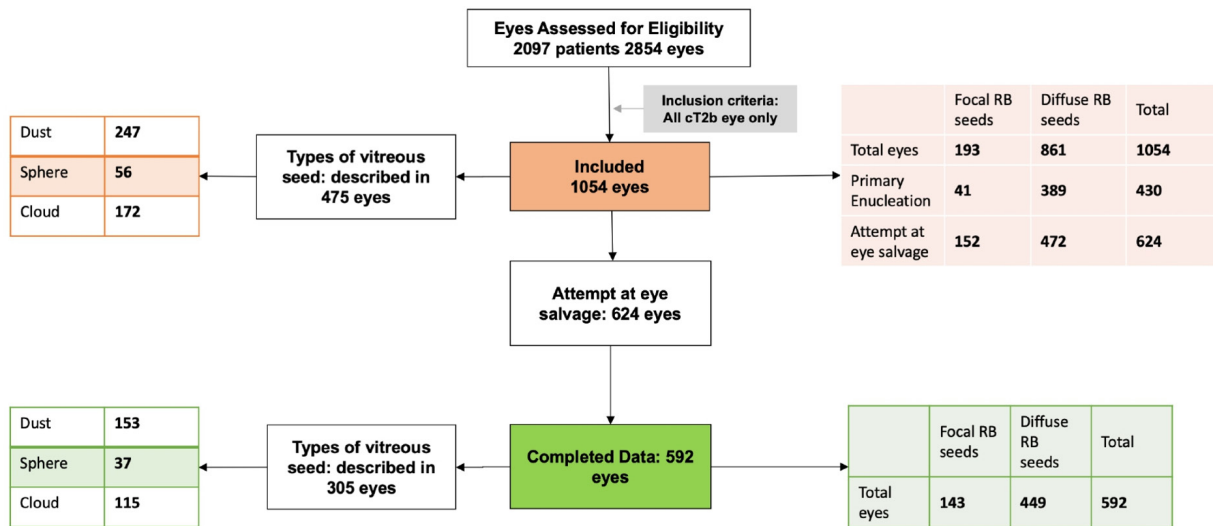
- ▶ The removal of treatment-naïve RB eyes was defined as primary enucleation.
- ▶ The removal of an eye after an attempt at eye salvage was defined as secondary enucleation, irrespective of the reason for enucleation (eg, recurrent tumour, significant residual disease, recurrent seeding and treatment complications).
- ▶ Local treatment failure after conservative treatment was defined as need for external beam radiation therapy (EBRT) or secondary enucleation.
- ▶ The follow-up time for each eye was defined as the time from diagnosis to last visit for salvaged eyes; or enucleation or EBRT, if the eye had to be enucleated or received EBRT, respectively.

Exclusion criteria included: if key variables, such as clinical variables essential for RB classification (tumour location, size, extent), treatment data (date and type of treatment) and outcome (globe salvage or primary/secondary enucleation) were missing or inconsistent.

A total of 2190 patients were enrolled from 18 ocular oncology centres across the world. Records with data sufficient for this study were available for 2085 patients (95.2%). Of these, all 1054 eyes staged as cT2b category were analysed.

### Statistical analysis

The median, range and IQR were used to describe continuous variables, and frequencies and proportions were employed for categorical variables. Kaplan-Meier plots, log-rank test for trend and Logistic and Cox proportional hazards regression models were used to test if distribution and type of RB seeding were



**Figure 1** CONSORT flow diagram of all retinoblastoma eyes with vitreous seeding. CONSORT, Consolidated Standards of Reporting Trials; RB, retinoblastoma

independently related to local treatment failure. The statistical analysis was performed using SPSS (V.26.0, IBM). Statistical significance was set at  $p < 0.05$ .

## RESULTS

### Demographic and clinical features

Median age at diagnosis was 16.0 months (mean, 20.5; SD, 20.6; IQR, 8–27; range, 1.0 month–13.6 years) and the median follow-up duration was 44.0 months (mean, 54.7; SD, 42.7; IQR, 20–81; range, 1 month to 14.6 years). Of the 1054 eyes, 535 (50.8%) had right eye involved and 579 (54.9%) had unilateral RB.

The distribution of predominant seeds was focal in 193 (18.3%) and diffuse in 861 (81.7%) eyes. The SRF was within 5 mm of the main tumour in 388 (36.8%) and beyond 5 mm in 666 (63.2%) eyes. The different types of vitreous seed were described in 475 eyes: dust 247 (52.0%), sphere 56 (11.8%) and cloud 172 (36.2%) eyes (figure 1).

### Treatment outcomes

Of the 1054 eyes, 430 (40.8%) underwent primary enucleation and 624 (59.2%) had an attempt at eye salvage. Of those, 428 (40.6%) eyes were salvaged and 196 (18.6%) required

secondary enucleation (table 2). There was a significant association between the distribution of RB seeds and treatment choice ( $\chi(1, N=1054)=37.400, p < 0.001$ ). RB eyes with diffuse seeds were more commonly treated with primary enucleation. The various treatment strategies employed for eye salvage included: systemic chemotherapy: 980 (93%), intra-arterial chemotherapy: 69 (6.5%) and primary EBRT: 5 (0.5%) eyes. Intravitreal chemotherapy was employed in 53 (5.0%) and periocular chemotherapy in 64 (6.0%) eyes.

### CUMULATIVE PROPORTION OF AVOIDING LOCAL TREATMENT FAILURE

#### Focal versus diffuse seed distribution

Of the 624 eyes, where eye salvage was attempted, 592 had complete data for globe salvage analysis. The distribution of seeds was focal in 143 (24.2%) and diffuse in 449 (75.8%) eyes. Associated SRF was within 5 mm from the main tumour in 237 (40.0%), and beyond 5 mm in 355 (60.0%) eyes. Though 375 (63.3%) eyes were salvaged, 217 (36.7%) were considered as local treatment failure (required secondary enucleation in 196 and EBRT in 21 eyes). The median follow-up duration was 22.0 months (mean, 36.7; SD, 39.4; IQR, 8–51; range, 1 month to 14.2 years). The 2-year and 5-year Kaplan-Meier cumulative proportions of avoiding local treatment failure by distribution of RB seeds were 83% (95% CI 80% to 86%) and 78% (95% CI 74% to 82%) for focal seeds and 60% (95% CI 57% to 63%) and 49% (95% CI 44% to 52%) for diffuse seeds, respectively. Diffuse seeds were associated with an increased risk of local treatment failure ( $p < 0.001$ , log-rank test for trend) as compared with focal seeds (table 3A, figure 2).

Cox proportional hazard regression univariable analysis confirmed that eyes with diffuse seeds (HR 2.8; 95% CI 1.9 to 4.1;  $p < 0.001$ ) had a greater risk relative to those with focal seeds, associated SRF  $> 5$  mm (HR 2.2; 95% CI 1.6 to 3.0;  $p < 0.001$ ) had a greater risk relative to those with SRF  $< 5$  mm and eyes of patients with unilateral disease (HR 1.9; 95% CI 1.4 to 2.4;  $p < 0.001$ ) had a greater risk of local treatment failure (need for EBRT or secondary enucleation) compared with those with bilateral disease (table 4A).

#### Vitreous seed type

The predominant vitreous seed type was noted in 305 eyes: dust in 153 (50.1%), spheres 37 (12.1%), and cloud in 115 (37.8%).

**Table 2** Treatment outcomes for eyes with retinoblastoma seeds by distribution

	Focal RB seeds, N (%)	Diffuse RB seeds, N (%)	Total, N (%)
Total eyes	193 (18.3)	861 (81.7)	1054
Primary enucleation	41 (21.2)	389 (45.2)	430 (40.8)
Attempt at eye salvage	152 (78.8)	472 (54.8)	624 (59.2)
Eye salvage	124 (64.2)	304 (35.3)	428 (40.6)
Secondary enucleation	28 (14.5)	168 (19.5)	196 (18.6)

Association between the distribution of seeds and treatment choice:  $\chi(1)=37.400, p < 0.001$ . RB, retinoblastoma.

**Table 3** (A) Kaplan-Meier cumulative proportion of avoiding local treatment failure according to distribution of retinoblastoma seeding, (B) Kaplan-Meier cumulative proportion of avoiding local treatment failure according to type of retinoblastoma vitreous seeding

Classification	Kaplan-Meier point estimates (95% CI), %			
	1 year	2 years	5 years	10 years
<b>(A)</b>				
All eyes (n=592)	70 (68 to 72)	66 (64 to 68)	57 (54 to 60)	25 (20 to 30)
Focal (n=143)	85 (82 to 88)	83 (80 to 86)	78 (74 to 82)	66 (59 to 73)
Diffuse (n=449)	65 (63 to 67)	60 (57 to 63)	49 (44 to 52)	14 (9 to 19)
<b>(B)</b>				
Dust (n=153)	74 (70 to 78)	66 (61 to 71)	47 (39 to 55)	38 (28 to 48)
Sphere (n=37)	51 (42 to 60)	47 (38 to 56)	47 (38 to 56)	8 (4 to 12)
Cloud (n=115)	69 (64 to 74)	67 (62 to 72)	50 (42 to 58)	Not available

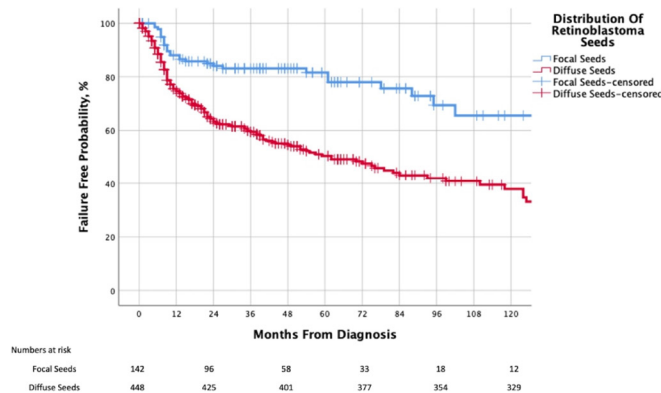
(A) Log-rank test for trend:  $p < 0.001$ .  
 (B) Log-rank test for trend, overall comparison:  $p = 0.06$ , Wilcoxon (Gehan) Statistic:  $p = 0.033$ , Tarone-Ware:  $p = 0.04$   
 N, Number.

The 2-year and 5-year Kaplan-Meier cumulative proportions of avoiding local treatment failure by type of RB vitreous seeds were 66% (95% CI 61% to 71%) and 47% (95% CI 39% to 55%) for dust, and 47% (95% CI 38% to 56%, for both 2-year and 5-year) for sphere, and 67% (95% CI 62% to 72%) and 50% (95% CI 42% to 58%) for cloud, respectively. The overall p value for this analysis was log rank:  $p = 0.06$ , Wilcoxon (Gehan) Statistic:  $p = 0.033$ , Breslow:  $p = 0.03$  and Tarone-Ware:  $p = 0.04$  (table 3B, figure 3). We did not have enough evidence either to prove or disprove the possibility that there was no statistically significant difference in the risk of local treatment failure between the three groups.

Cox proportional hazard regression univariable analysis revealed that eyes with spherical vitreous seeds are associated with a higher risk of local treatment failure (HR 1.8; 95% CI 1.1 to 3.0;  $p = 0.031$ ) as compared with dust. However, there was no increased risk of local treatment failure with cloud ( $p = 0.99$ ) compared with dust.

**Multivariate analysis**

Multivariable Cox regression showed a greater risk of local treatment failure in eyes in diffuse seeds (HR 1.6; 95% CI 1.2 to 2.3;  $p = 0.002$ ) compared with eyes with focal seeds, as were the patients with unilateral disease (HR 1.8; 95% CI 1.3 to



**Figure 2** Kaplan-Meier curve showing the cumulative proportion of salvaged eyes (without need for EBRT), by distribution of retinoblastoma seeding in clinical category cT2b eyes. EBRT, external beam radiation therapy.

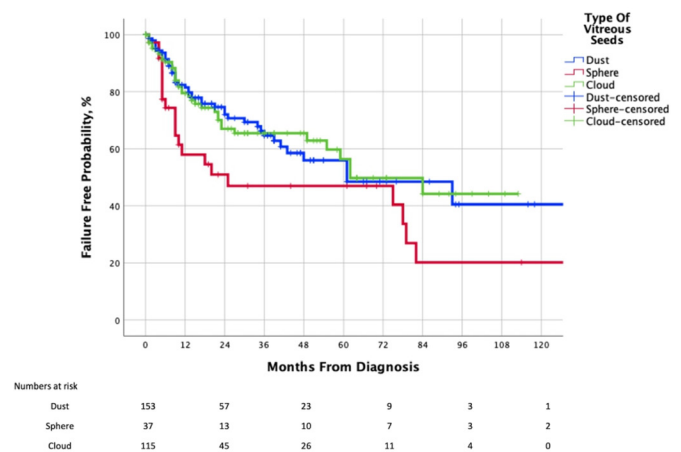
**Table 4** Cox proportional hazards regression model in retinoblastoma eyes for association of retinoblastoma clinical features with local treatment failure

Variable	Eyes in category, no (total=592)	Reference	HR (95% CI)	P value
<b>(A) Univariate analysis</b>				
Diffuse seeding	n=449	Focal seeding	2.80 (1.89 to 4.14)	<0.001
Unilateral	n=213	Bilateral	1.85 (1.40 to 2.42)	<0.001
SRF >5 mm	n=355	SRF <5 mm	2.20 (1.64 to 2.95)	<0.001
Sphere	n=37	Dust	1.77 (1.05 to 2.97)	0.031
Cloud	n=115	Dust	1.00 (0.64 to 1.55)	>0.99
<b>(B) Multivariate analysis</b>				
Diffuse	n=449	Focal	1.64 (1.20 to 2.26)	0.002
Unilateral	n=213	Bilateral	1.76 (1.34 to 2.31)	<0.001
SRF >5 mm	n=355	SRF <5 mm	2.20 (1.45 to 3.35)	<0.001
SRF, subretinal fluid.				

2.3;  $p < 0.001$ ) compared with those with bilateral disease and associated SRF >5 mm (HR 2.2; 95% CI 1.5 to 3.4;  $p < 0.001$ ) compared with those with SRF <5 mm (table 4B).

**DISCUSSION**

Herein, we present an analysis of a multicentre, international, internet-based registry used to answer the question: Does the distribution and clinical characteristics of RB seeds affect local treatment failure and thus suggest that AJCC cT2b category should be further subdivided? We found that at presentation, diffuse RB seeding was significantly associated with increased risk of local treatment failure (defined as need for EBRT or secondary enucleation). When compared with focal RB-seeding, diffuse seeding was associated with a 2.8-fold risk of eventual local treatment failure. The clinical characteristics of vitreous seed type did not significantly increase the risk of secondary enucleation or need for EBRT. Though unrelated to seed type or distribution, the presence of SRF >5 mm has been a component of other staging systems (eg, WEH, CHLA) related to globe salvage.<sup>8,9</sup> Separate analysis found that the presence of SRF >5 mm at presentation also affected local control, having a 2.2-fold risk of local treatment failure compared with SRF <5 mm.



**Figure 3** Kaplan-Meier curve showing the cumulative proportion of salvaged eyes (without need for EBRT), by type of retinoblastoma vitreous seeding in clinical category cT2b eyes. EBRT, external beam radiation therapy.

The eighth edition AJCC staging system for RB was derived by the AJCC-OOTF through international consensus after evaluating evidence-based data.<sup>10</sup> The AJCC manages a dynamic, ever-evolving staging system where multicentre international committees of subspecialists regularly convene to modify the staging. Our study provides statistically significant evidence that eyes with focal and diffuse seeding carry significantly different risks of local treatment failure. Therefore, a subcategory description should be considered in subsequent editions of the AJCC RB staging.

The eighth edition AJCC staging system for RB for risk of metastatic mortality demonstrated no difference between clinical categories cT2a and cT2b, reaffirming the fact that presence of RB seeding does not impact the overall risk of mortality.<sup>13</sup> The main impediment in RB eyes with seeds has been local tumour control, with need for multiple treatments to tackle recurrent and resistant seeds. In addition, our recent national income-based evaluation of RB presentation across the world revealed that cT2b category was one of the most common RB stages at presentation.<sup>15</sup> The large size and resultant heterogeneity of this category supports the need for further analysis to determine useful subclassification.

The worse outcomes associated with diffuse seeding have been attributable to their inaccessibility to focal therapy and poor reach of systemic treatments into avascular spaces. These seeds may also be radioresistant due to hypoxia.<sup>1</sup> The presence of extensive SRF can complicate the use of intravitreal chemotherapy for vitreous seeds and laser treatment for subretinal seeds. Further, various studies have reviewed the impact of morphology of RB seeds on the efficacy of intravitreal and periocular chemotherapy to induce seed regression.<sup>1–3 12 16 17</sup> In contrast, we could not conclusively prove or disprove a significant relationship between the type of vitreous seeds and risk of local treatment failure. This result should be interpreted cautiously since we had limited details of specific treatment modalities, the number of intravitreal injections, the drugs employed or specific focal treatment of subretinal seeds. In addition, some RB eyes may require enucleation for many reasons despite complete regression of seeds. For example, in a recent study, 32% eyes (groups D and E) were treated with secondary enucleation, despite a 100% successful treatment of seeds.<sup>12</sup>

Limitations of our study include that the data was collected between 2001 and 2013 which does not account for the current use of intra-arterial chemotherapy and intravitreal chemotherapy. In addition, the RB seeding localisation was not separated as vitreous or subretinal, preventing a location-based independent local failure risk assessment. Our retrospective design used locally defined diagnostic and treatment modalities, limiting our ability to analyse specific chemotherapeutic agents. The registry did not collect data on patterns of seed regression or time to regression and hence they could not be analysed in this manuscript.

Strengths of this study include that it used a multicentre, international registry to accrue a large number of patients. There were enough patients to provide statistically significant evidence used to answer an outstanding question on a rare disease. Specifically, it answered a question that may be used to improve the AJCC and UICC staging system for RB.

This study revealed evidence that the distribution of vitreous and subretinal seeding was predictive of risk of need for secondary enucleation or EBRT. Specifically, it revealed that the diffuse seeds carried a higher risk of local treatment failure compared with focal RB seeds. Therefore, we recommend further analysis of the AJCC RB classification to account for distribution of RB seeds.

#### Author affiliations

<sup>1</sup>Department of Ocular Tumor and Orbital Disease, New York Eye Cancer Center, New York, New York, USA

- <sup>2</sup>The Eye Cancer Clinic, Princess Margaret Cancer Centre, and Department of Ophthalmology and Vision Sciences, Hospital for Sick Children, Toronto, Ontario, Canada
- <sup>3</sup>Ocular Oncology Service, Department of Ophthalmology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
- <sup>4</sup>Department of Ophthalmology and Vision Sciences, Hospital for Sick Children, Toronto, Ontario, Canada
- <sup>5</sup>Department of Ophthalmology and Vision Sciences, Narayana Nethralaya, Bangalore, Karnataka, India
- <sup>6</sup>Pediatric Oncology Center, Beijing Children's Hospital, Beijing, China
- <sup>7</sup>Ophthalmic Oncology, Department of Ophthalmology Hamilton Eye Institute, The University of Tennessee Health Science Center, Memphis, Tennessee, USA
- <sup>8</sup>Department of Ophthalmology, St Jude Children's Research Hospital, Memphis, Tennessee, USA
- <sup>9</sup>USC Roski Eye Institute, Keck Medical School of the University of Southern California, and The Vision Center at Children's Hospital Los Angeles, Los Angeles, California, USA
- <sup>10</sup>Department of Pediatrics, Children's Hospital Los Angeles, Los Angeles, California, USA
- <sup>11</sup>Cancer and Blood Diseases, Children's Hospital Society of Los Angeles, Los Angeles, California, USA
- <sup>12</sup>Vitreous Retinal Services, Sankara Nethralaya, Chennai, Tamil Nadu, India
- <sup>13</sup>Ocular Oncology Department, S Fyodorov Eye Microsurgery Federal State Institution, Moskva, Moskva, Russian Federation
- <sup>14</sup>Department of Surgery (Ophthalmology), King Hussein Cancer Center, Amman, Jordan
- <sup>15</sup>Pediatric Oncology and Hematology, N N Blokhin NMRCO, Moskva, Russian Federation
- <sup>16</sup>Russian Academy of Postgraduate Medical Education, Moskva, Russian Federation
- <sup>17</sup>Russian Academy of Sciences, Moskva, Russian Federation
- <sup>18</sup>Department of Ophthalmology, Hospital Infantil de Mexico Federico Gomez, Mexico City, Mexico
- <sup>19</sup>Ophthalmology, Paediatric Hospital Dr Juan Garrahan Library, Buenos Aires, Argentina
- <sup>20</sup>Precision Medicine Coordination Hospital J. P. Garrahan, and CONICET (National Scientific and Technical Research Council), Buenos Aires, Argentina
- <sup>21</sup>Ophthalmology and Visual Sciences, The Chinese University of Hong Kong Faculty of Medicine, Hong Kong, Hong Kong
- <sup>22</sup>Department of Ophthalmology and Visual Sciences, Hong Kong Eye Hospital, Hong Kong, Hong Kong
- <sup>23</sup>Save Sight Institute, Discipline of Ophthalmology, The University of Sydney Sydney Medical School, Sydney, New South Wales, Australia
- <sup>24</sup>Retinoblastoma Unit, Department of Oncology, Hospital Sant Joan de Déu. Esplugues de Llobregat, Barcelona, Spain
- <sup>25</sup>KK Women's and Children's Hospital, Singapore
- <sup>26</sup>Department of Child Health, University of Ghana Medical School, Accra, Ghana
- <sup>27</sup>Department of Child Health, University of Ghana Medical School, Accra, Greater Accra, Ghana
- <sup>28</sup>Ophthalmology, Hospital Sant Joan de Deu, Barcelona, Catalunya, Spain

**Twitter** Paul T Finger @#paulfingermd, Guillermo L Chantada @gchantada and Adriana C Fandiño @seeds

**Collaborators** American Joint Committee on Cancer Ophthalmic Oncology Task Force members: Paul T. Finger, MD (Chair) (New York Eye Cancer Center, New York); Sarah E. Coupland, MBBS, PhD, FRCPath (Vice Chair) (Royal Liverpool University Hospital, Liverpool, United Kingdom); Daniel M. Albert, MD, MS (Oregon Health and Sciences University, Portland); Anush G. Amiryani, MD, and Svetlana Saakyan, MD (Moscow Helmholtz Research Institute of Eye Disease, Moscow, Russian Federation); Claudia Auw-Hädrich, MD (University of Freiburg, Freiburg, Germany); Diane Baker, CTR (American Joint Committee on Cancer, Chicago, Illinois); Raymond Barnhill, MD, MSc (UCLA Medical Center, Los Angeles); José M. Caminal, MD, PhD (Bellvitge University Hospital, Hospitalet de Llobregat, Barcelona, Spain); William L. Carroll, MD (New York University Cancer Institute—New York University Langone Medical, New York); Nathalie Cassoux, MD, PhD, Laurence G. Desjardins, MD, François Doz, MD, MSc, and Gaëlle Pierron, PhD (Institut Curie, Paris, France); Jaume Catalá-Mora, MD (SJD Barcelona Children's Hospital, Hospital Sant Joan de Déu, Barcelona, Spain); Guillermo Chantada, MD (Hospital JP Garrahan, Buenos Aires, Argentina); Patricia Chévez-Barrios, MD (Houston Methodist Hospital, Houston, Texas); R. Max Conway, MD, PhD (Save Sight Institute, Sydney, Australia); Bertil E. Damato, MD, PhD (University of California, San Francisco, San Francisco); Hakan Demirci, MD (Kelllogg Eye Center, Ann Arbor, Michigan); Jonathan J. Dutton, MD, PhD (University of North Carolina, Chapel Hill); Bitá Esmali, MD, Víctor G. Prieto, MD, PhD, and Michelle Williams, MD (University of Texas MD Anderson Cancer Center, Houston); Brenda L. Gallie, MD (Hospital for Sick Children, Toronto, Ontario, Canada); Gerardo F. Graue, MD (Instituto de Oftalmología Fundación Conde de Valenciana, Mexico City, Mexico); Hans E. Grossniklaus, MD (Emory Eye Center, Atlanta, Georgia); Steffen Heegaard, MD, PhD (University of Copenhagen, Glostrup Hospital, Copenhagen,

Denmark); Leonard M. Holbach, MD (University Erlangen, Nürnberg, Germany); Santosh G. Honavar, MD (Centre For Sight Super-Specialty Eye Hospital, Hyderabad, India); Martine J. Jager, MD, PhD (Leiden University Medical Center, Leiden, the Netherlands); Tero Kivelä, MD, FEBO, and Emma Kujala, MD (Helsinki University Hospital, Helsinki, Finland); Livia Lumbroso-Le Rouic, MD (Institute Claudius Regaud Medical Center, Toulouse, France); Ashwin C. Mallipatna, MBBS, MS, DNB (Hospital for Sick Children, Toronto, Canada); Giulio M. Modorati, MD (San Raffaele Hospital, Milan, Italy); Francis L. Munier, MD (Jules-Gonin Eye Hospital, Lausanne, Switzerland); Timothy G. Murray, MD, MBA (Murray Ocular Oncology and Retina, Coral Gables, Florida); Anna C. Pavlick, MD (Weill Cornell College of Medicine, New York); Jacob Pe'er, MD (Hebrew University, Hadassah Ein Karem Hospital, Jerusalem, Israel); David E. Pelayes, MD (Buenos Aires University, Buenos Aires, Argentina); Manuel Jorge Rodriguez, MD (Mayo Clinic, Jacksonville, Florida); Wolfgang A.G. Sauerwein, MD, PhD (University Hospital Essen, Essen, Germany); Ekaterina Semenova, MD (The New York Eye and Ear Infirmary of Mount Sinai, New York); Stefan Seregard, MD (St Erik's Eye Hospital, Karolinska Institute, Stockholm, Sweden); Carol Shields, MD (Wills Eye Institute, Philadelphia, Pennsylvania); E. Rand Simpson, MD, FRCS(C) (Mount Sinai Hospital, Toronto, Ontario, Canada); Arun D. Singh, MD (Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio); Shigenobu Suzuki, MD, PhD (National Cancer Center Hospital, Tokyo, Japan); Mary Kay Washington, MD, PhD (Vanderbilt University Medical Center, Nashville, Tennessee); Valerie A. White, MD, MHSc, FRCP(C) (Vancouver Coastal Health Research Institute, Vancouver, British Columbia, Canada); Mathew W. Wilson, MD (University of Tennessee Health Science Center, Memphis); Christian W. Wittekind, MD (Institut für Pathologie der Universität, Leipzig, Germany); and Vivian Yin, MPH (Memorial Sloan Kettering Cancer Center, New York, New York).

**Contributors** AST: Study conception and design, analysis and interpretation of data, and drafting of manuscript. PTF: Study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, and critical revision. BG: Study conception and design, acquisition of data, analysis and interpretation of data and critical revision. TK: Study conception and design, acquisition of data, analysis and interpretation of data and critical revision. AM: Study conception and design, acquisition of data, analysis and interpretation of data and critical revision. CZ: Study conception and design, acquisition of data and critical revision. JZ: Study conception and design, acquisition of data and critical revision. MW: Study conception and design, acquisition of data and critical revision. RB: Study conception and design, acquisition of data and critical revision. MB: Study conception and design, acquisition of data, and critical revision. JWK: Study conception and design, acquisition of data, and critical revision. JLB: Study conception and design, acquisition of data, and critical revision. RJ: Study conception and design, acquisition of data, and critical revision. VK: Study conception and design, acquisition of data, and critical revision. GS: Study conception and design, acquisition of data, and critical revision. AY: Study conception and design, acquisition of data, and critical revision. VY: Study conception and design, acquisition of data, and critical revision. EK: Study conception and design, acquisition of data, and critical revision. DV: Study conception and design, acquisition of data, and critical revision. AY: Study conception and design, acquisition of data, and critical revision. KPN: Study conception and design, acquisition of data, and critical revision. TLU: Study conception and design, acquisition of data and critical revision. OYV: Study conception and design, acquisition of data and critical revision. MAR-O: Study conception and design, acquisition of data, and critical revision. EE-A: Study conception and design, acquisition of data, and critical revision. GLC: Study conception and design, acquisition of data and critical revision. PS: Study conception and design, acquisition of data and critical revision. ACF: Study conception and design, acquisition of data and critical revision. JCY: Study conception and design, acquisition of data and critical revision. WWL: Study conception and design, acquisition of data and critical revision. CPL: Study conception and design, acquisition of data and critical revision. PS: Study conception and design, acquisition of data, and critical revision. SM: Study conception and design, acquisition of data, and critical revision. QBL: Study conception and design, acquisition of data and critical revision. VE: Study conception and design, acquisition of data and critical revision. LAR: Study conception and design, acquisition of data and critical revision. ES: Study conception and design, acquisition of data and critical revision. JC-M: Study conception and design, acquisition of data, and critical revision. MCL: Study conception and design, acquisition of data, and critical revision. EC-B: Study conception and design, acquisition of data and critical revision.

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#### ORCID iDs

Paul T Finger <http://orcid.org/0000-0002-8111-3896>  
 Brenda Gallie <http://orcid.org/0000-0003-0503-4528>  
 Rachel Brennan <http://orcid.org/0000-0002-2090-4395>  
 Jesse L Berry <http://orcid.org/0000-0002-8907-9100>  
 Yacoub Yousef <http://orcid.org/0000-0001-7750-6454>  
 Kalle Nummi <http://orcid.org/0000-0002-9497-1822>  
 Jason C Yam <http://orcid.org/0000-0002-2156-1486>

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