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

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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%). For numbered affiliations see end of article.

INTRODUCTION

Retinoblastoma (RB) is typically discohesive, resulting in intraocular dissemination of tumour seeds in the subretinal or vitreous space on tumour growth.1 They are morphologically described as dust, sphere and cloud type, and especially the emergence of vitreous seeds is thought to worsen local tumour control.1-6 For example, the Reese-Ellsworth classification assigned the prognosis of eyes with vitreous seeds to the most unfavourable group, Vb group. 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.8-9 In contrast, the eighth edition American Joint Committee on Cancer (AJCC) staging system does not account for characteristics or distribution of RB seeds.10

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.2 3 5 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.1 Their small size and often diffuse distribution also prevent control with sequential aggressive local therapy.1 This has resulted in the need for external beam radiotherapy, periocular, and intravitreal chemotherapy to avoid enucleation.3 11 12

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).10 Its advantages include that AJCC-UICC was the first and only RB
staging system to incorporate intraocular and extraocular RB as well as heredity to predict both local treatment failure and metastasis-related mortality.\textsuperscript{10,13–14} 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.\textsuperscript{10} 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.\textsuperscript{13–15}

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.\textsuperscript{10,13–15} 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.\textsuperscript{13–15}

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, \textless{}5 mm of tumour or \textgreater{}5 mm) and the distribution of seeds (diffuse/local) and type of vitreous seeds (dust/sphere/cloud).

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 \textless{}5 mm from the base of any tumour. |
| cT1a         | Tumours \textless{}5 mm and further than 1.5 mm from the disc and fovea. |
| cT1b         | Tumours \textgreater{}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 \textgreater{}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 bulb.         |
| 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. |

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.

Treatment definitions
► The removal of treatment-naive 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 type characteristic was recorded, the predominant type with the highest degree was recorded.
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 (χ²(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%).
Clinical science

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 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 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 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.8 9 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.

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 | 1 year | 2 years | 5 years | 10 years |
|----------------|--------|---------|---------|---------|
| (A)            |        |         |         |         |
| 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 (43 to 52) | 14 (9 to 19) |
| (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.

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 |
|----------|---------------------------------|-----------|-------------|---------|
| (A) Univariate analysis | | | | |
| 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 1.59) | >0.99 |
| (B) Multivariate analysis | | | | |
| 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.

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.

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.\textsuperscript{10} 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.\textsuperscript{11} 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.\textsuperscript{15} 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 radioreistant due to hypoxia.\textsuperscript{1} 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 pericocular chemotherapy to induce seed regression.\textsuperscript{1–3 12 16 17} 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.\textsuperscript{12}

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 RB classification to account for distribution of RB seeds. Therefore, we recommend further analysis of the AJCC RB staging classification to account for distribution of RB seeds.

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Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as online supplemental information.

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