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Classification of Vitreous Seeds in Retinoblastoma

Correlations with Patient, Tumor, and Treatment Characteristics

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Purpose: To evaluate the patient, disease, and tumor characteristics of the 3 morphologically distinct groups of vitreous seeds in retinoblastoma presenting for treatment with ophthalmic artery chemosurgery (OAC): dust (class 1), spheres (class 2), and clouds (class 3) in primary and recurrent vitreous seeds.

Design: Retrospective cohort study of patients treated for vitreous seeds at Memorial Sloan Kettering Cancer Center between May 2006 and March 2015.

Participants: A total of 135 eyes with active vitreous seeds, presenting for primary treatment with OAC or with recurrent vitreous disease.

Methods: Vitreous seeds were classified into 3 groups: dust, spheres, and clouds. Indirect ophthalmoscopy, fundus photography, ultrasonography, and ultrasonic biomicroscopy were used to locate and evaluate the extent of retinal and vitreous disease. Patient and disease characteristics (age, laterality of disease, treatment status) were compared among classification groups. A 2-tailed Fisher exact test and paired Student *t* test were used for statistical analysis.

Main Outcome Measures: Age of patient, laterality of disease, location of retinal disease, extent of vitreous disease, and treatment status.

Results: Primary treated disease: Patients with eyes containing class 3 (cloud) vitreous seeds were significantly older than patients with class 1 or 2 seeds ($P < 0.05$). The median age of patients with class 1, 2, and 3 seeds was 11, 15.5, and 32 months, respectively. Eyes containing class 3 seeds were significantly more likely to occur in the equator-ora region of the fundus ($P < 0.0001$), in a diffuse pattern ($P < 0.0001$), and in patients with unilateral disease ($P < 0.05$), compared with class 1 and 2 seeds. Recurrent disease: Recurrent vitreous seeds were significantly more common to class 2 ($P < 0.05$), occurring in a diffuse pattern ($P = 0.01$) and in patients with bilateral disease ($P < 0.001$).

Conclusions: The 3 classes of vitreous seeds have distinct clinical characteristics associated with the age of patient, laterality of disease, and extent and location of tumor-producing seeds. Furthermore, recurrent vitreous seeds appear to have a unique clinical profile compared with seeds receiving primary treatment. *Ophthalmology 2016;■:1–5 © 2016 by the American Academy of Ophthalmology.*

A number of temporal and spatial relationships have been established in retinoblastoma, particularly with regard to patient age at diagnosis and intraocular tumor location.[1,2] For example, it is known that patients with germline (usually bilateral) disease typically present at a younger age, with multifocal tumors, compared with patients with (usually unilateral and single foci) disease restricted to a somatic mutation. Stallard[3] recognized that new tumor foci may form after diagnosis of the presenting tumor, and these subsequent tumors typically are peripheral to the presenting disease. These temporal and spatial relationships focus on retinal disease, and little is known about how these principles may apply to vitreous disease.

As our success rate for treating vitreous disease has improved with the use of intravitreal chemotherapy, so too has our knowledge of vitreous seeds. On the basis of their distinct morphologic characteristics, vitreous seeds can be classified as follows: dust (class 1), spheres (class 2), and clouds (class 3).[4,5] With intravitreal melphalan, each seed class varies not only in the amount and dose of intravitreal melphalan used to control the seeds but also in regression pattern and time to final response to treatment.[5] A similar analysis has not been reported for seed response to ophthalmic artery chemosurgery (OAC). The present study evaluated whether there are additional clinical features that distinguish these classes of vitreous seeds, particularly with regard to the age of patient, laterality of disease,

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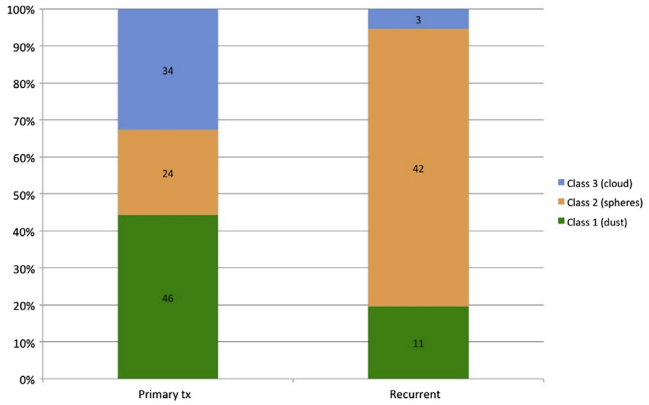

Figure 1. Seed classification according to treatment status. This chart demonstrates the distribution of seed classes for both primary treated and recurrent vitreous seeds.

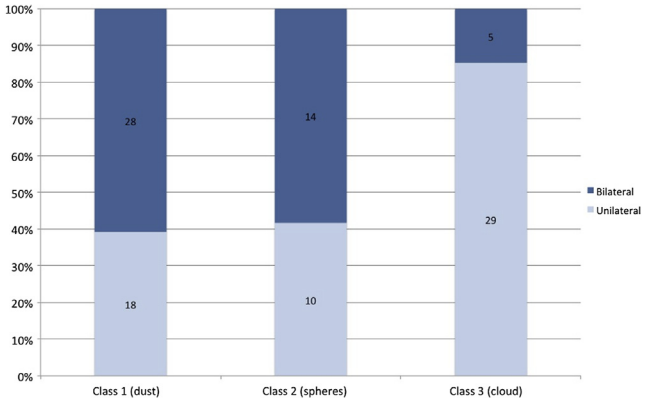

Figure 2. Seed classification and laterality of disease. This chart demonstrates the laterality of retinoblastoma for each seed class.

intraocular tumor location, extent of disease, and treatment status.

Methods

This Memorial Sloan Kettering Institutional Review Board–approved retrospective study included all eyes with active vitreous seeds presenting for primary treatment with OAC or with recurrent vitreous disease at Memorial Sloan Kettering Cancer Center from May 30, 2006, to March 25, 2015. Informed consent was obtained for each patient from a guardian, caregiver, or parent. The study was Health Insurance Portability and Accountability Act compliant. Research adhered to the tenets of the Declaration of Helsinki.

A total of 360 eyes of 289 patients were retrospectively reviewed for vitreous seeds. Eyes were excluded if there was an absence of active vitreous seeds, if vitreous hemorrhage precluded an assessment of the fundus, if clinical history was insufficient, or if fundus photography was unavailable to judge vitreous seed status. The clinical status was reviewed using clinical notes documented during the examination under anesthesia with indirect ophthalmoscopy, RetCam fundus photography (Clarity, Pleasanton, CA), B-scan ultrasonography (OTI Scan 2000 Ophthalmic Technologies, North York, ON, Canada), and ultrasonic biomicroscopy (OTI Scan 2000 Ophthalmic Technologies). Although all eyes presented for and received treatment with OAC, some eyes may have subsequently received intravitreal chemotherapy. Unlike our prior publication on this topic, this present study does not report on the response to treatment.[5]

Patient data included age, sex, laterality, and treatment status. Treatment status was divided into eyes receiving primary treatment (these eyes could be naïve to treatment or could have received prior treatment with intra-arterial chemosurgery at an outside hospital or systemic chemotherapy, but contain seeds that were not from a new source or deemed recurrent: e.g., an eye that received a cycle of systemic chemotherapy while arranging travel to our center) and eyes with recurrent vitreous disease (defined as recurrent tumor after 2 months of progression-free follow-up at monthly examinations at an outside hospital, or after OAC at our institution). Tumor data included Reese-Ellsworth classification, International Classification using the Children's Oncology grouping, seed classification (class 1 = dust, class 2 = spheres ± dust, or class 3 = clouds ± spheres or dust), extent of disease (localized [≤1 quadrant] or diffuse [>1 quadrant]), and location of retinal tumor/source of vitreous seeds (defined by tumor center located in macula or macula-equator or equator-ora; tumors nasal to the disc could be defined only as macula-equator or equator-ora).

The interobserver variability of vitreous seed classification is unknown. However, the system is purposefully based on morphologic features (much in the same way that the existing classification systems for retinoblastoma are constructed) and as such, places emphasis on objective clinical characteristics.

Table 1. Median, Mean, and Range of Age at Presentation of Primary or Recurrent Vitreous Disease

Treatment Status	No. of Eyes	Age* (mos)	1 (Dust)	2 (Spheres)	3 (Cloud)
Primary	104	Median	**11**	**15.5**	**32**
		Mean	**12.8**	**19.2**	**39.3**
		Range	3–41	5–59	6–120
Recurrent	56	Median	31	34.4	85
		Mean	27.2	48.1	102.7
		Range	11–41	15–215	31–192

*Age at presentation of primary or recurrent vitreous disease. Bold numbers represent those that are statistically significant at $P < 0.05$.

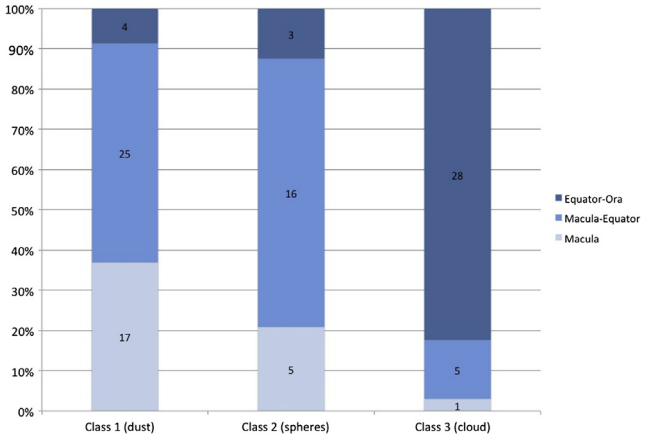

Figure 3. Seed classification and location of tumor. This chart demonstrates the location of the tumor producing seeds for each seed class.