

# Intravenous Chemoreduction or Intra-arterial Chemotherapy for Cavitory Retinoblastoma

## Long-term Results

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**Objective:** To assess the long-term results of chemotherapy for cavitory retinoblastoma.

**Methods:** Retrospective, nonrandomized, interventional case series of 26 cavitory retinoblastomas in 25 eyes of 24 patients. Retinoblastomas were treated with intravenous chemoreduction and/or intra-arterial chemotherapy. Main outcome measures included tumor control, globe salvage, and metastasis.

**Results:** Of 24 patients with cavitory retinoblastoma, the mean age at diagnosis was 16 months. The mean number of cavitory tumors per eye was 1 (median, 1; range, 1-2), with a mean tumor basal diameter of 13 (median, 13; range, 7-24) mm and mean tumor thickness of 7 (median, 6; range, 3-17) mm. The mean number of cavities per tumor was 2 (median, 2; range, 1-5), with a mean cavity diameter of 3

(median, 2; range, 1-10) mm. Related features included vitreous seeds in 7 tumors (27%), subretinal seeds in 6 (23%), and subretinal fluid in 13 (50%). Intravenous chemoreduction was used in 23 tumors (88%); intra-arterial chemotherapy, in 2 (8%); and both, in 1 (4%). After treatment, the mean reduction in tumor base was 22% and mean reduction in tumor thickness was 29%. Despite minimal reduction, tumor recurrence was noted in only 1 eye (4%), globe salvage was achieved in 22 (88%), and there were no cases of metastasis or death during 49 (range, 6-189) months of follow-up.

**Conclusion:** Despite minimal visible tumor response to chemotherapy, cavitory retinoblastoma displays relatively stable long-term results.

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**R**ETINOBLASTOMA IS A LIFE-threatening malignant neoplasm that manifests in the eye with features of painless leukocoria or strabismus. Intravenous chemotherapy or chemoreduction (CRD)<sup>1-19</sup> and intra-arterial chemotherapy (IAC)<sup>20-26</sup> currently play an important role in the management of retinoblastoma. For CRD, chemotherapeutic agents (vincristine sulfate, etoposide, and carboplatin) are given through an intravenous route, whereas for IAC, chemotherapy (usually melphalan hydrochloride) is delivered directly into the ophthalmic artery. In classic cases, clinically visible dramatic tumor regression is seen after CRD<sup>1,9,12,14,17-19</sup> and IAC,<sup>20,22,23,25</sup> with reduction of tumor thickness of 50% or more, leaving a partially calcified remnant in most cases.

Cavitory retinoblastoma, a rare low-grade variant of retinoblastoma<sup>27-30</sup> with ophthalmoscopically visible cavitory spaces, shows minimal response to CRD.<sup>27,28</sup> Despite its more subtle immediate reduction after CRD, the long-term results remain un-

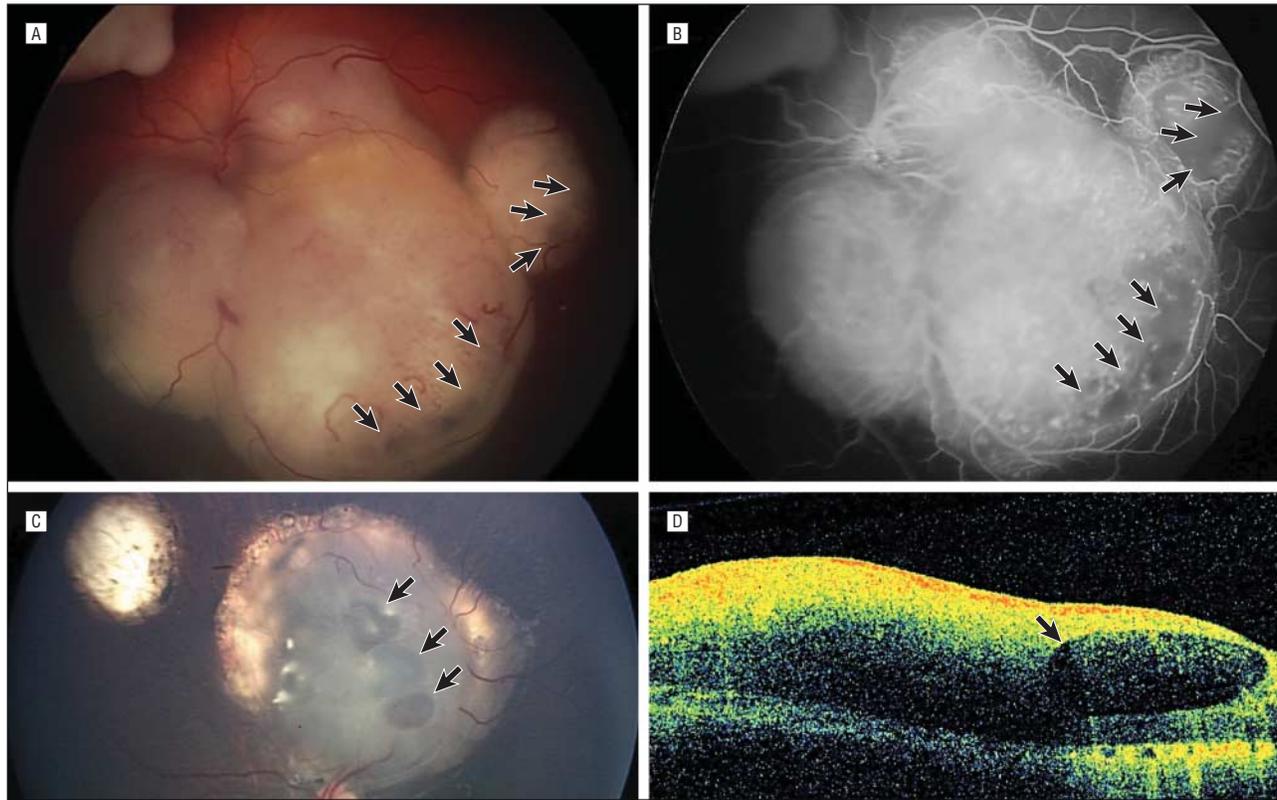
clear. In this report, we specifically review our long-term experience with CRD and IAC for cavitory retinoblastoma.

## METHODS

We reviewed the medical records of patients with retinoblastoma that was managed at the Oncology Service of the Wills Eye Institute from January 1, 1999, through July 31, 2011. Patients with the diagnosis of cavitory retinoblastoma and treatment with CRD or IAC were selected for further analysis (**Figure 1** and **Figure 2**). This was a retrospective, nonrandomized, noncomparative interventional case series. Institutional review board approval was obtained.

The patient data were reviewed for demographic information, clinical findings, treatment, and outcome. Each patient underwent evaluation for age at diagnosis (in months), sex (male or female), race (white, African American, Hispanic, or Asian), and hereditary pattern (familial or sporadic). Results of genetic testing (germline or somatic) were recorded whenever available. All prior treatments of the eye and previous CRD or IAC were recorded. A comprehensive ocular examination under an-

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**Figure 1.** Cavitory retinoblastomas before treatment. The tumors display gray lucent cavities (arrows) on clinical examination (A), shown as hypofluorescence (arrows) on fluorescein angiography (B). More pronounced gray lucent cavities (arrows) are demonstrated after chemoreduction (C) and on the optical coherence tomographic image (D).

esthesia was performed with assessment for laterality (unilateral or bilateral); intraocular pressure (measured by means of Schiötz tonometry); status of the anterior chamber, iris, ciliary body, optic nerve, choroid, retina, and vitreous; overall tumor growth pattern (exophytic, endophytic, or combined exophytic-endophytic); total number of tumors per eye; total number of cavitory tumors per eye; location of cavitory tumor; total number of cavities within each tumor; size of cavities; and location of cavities within each tumor. Each tumor was measured for greatest basal dimension and thickness using indirect ophthalmoscopy and ultrasonography; the presence of associated vitreous seeds (present or absent), percentage of retinal detachment (0-100%), and presence of subretinal tumor seeds (present or absent) were recorded. All findings were documented by large fundus drawing, fundus photography with a commercially available fundus camera (RetCam; Massie Industries), fluorescein angiography, and ultrasonography (Figure 1).

All patients were scheduled to receive CRD or IAC. For CRD, 6 monthly cycles of systemic intravenous chemotherapy with vincristine sulfate (0.05 mg/kg), etoposide (5 mg/kg), and carboplatin (18.6 mg/kg) were delivered. For IAC, 3 monthly cycles of melphalan hydrochloride (5 mg) were given. At the end of each chemotherapy cycle, ocular oncologic follow-up was performed by means of examination under anesthesia (Figure 2).

At each examination, the individual tumor response was judged as complete (no viable tumor), partial (some residual viable tumor), or none (completely viable tumor). On funduscopic examination, the tumor was determined to be viable if there was no change in the funduscopic appearance of the tumor. The tumor was considered to be nonviable or to demonstrate complete tumor response when it showed decreased basal dimensions and thickness, total or partial calcification, de-

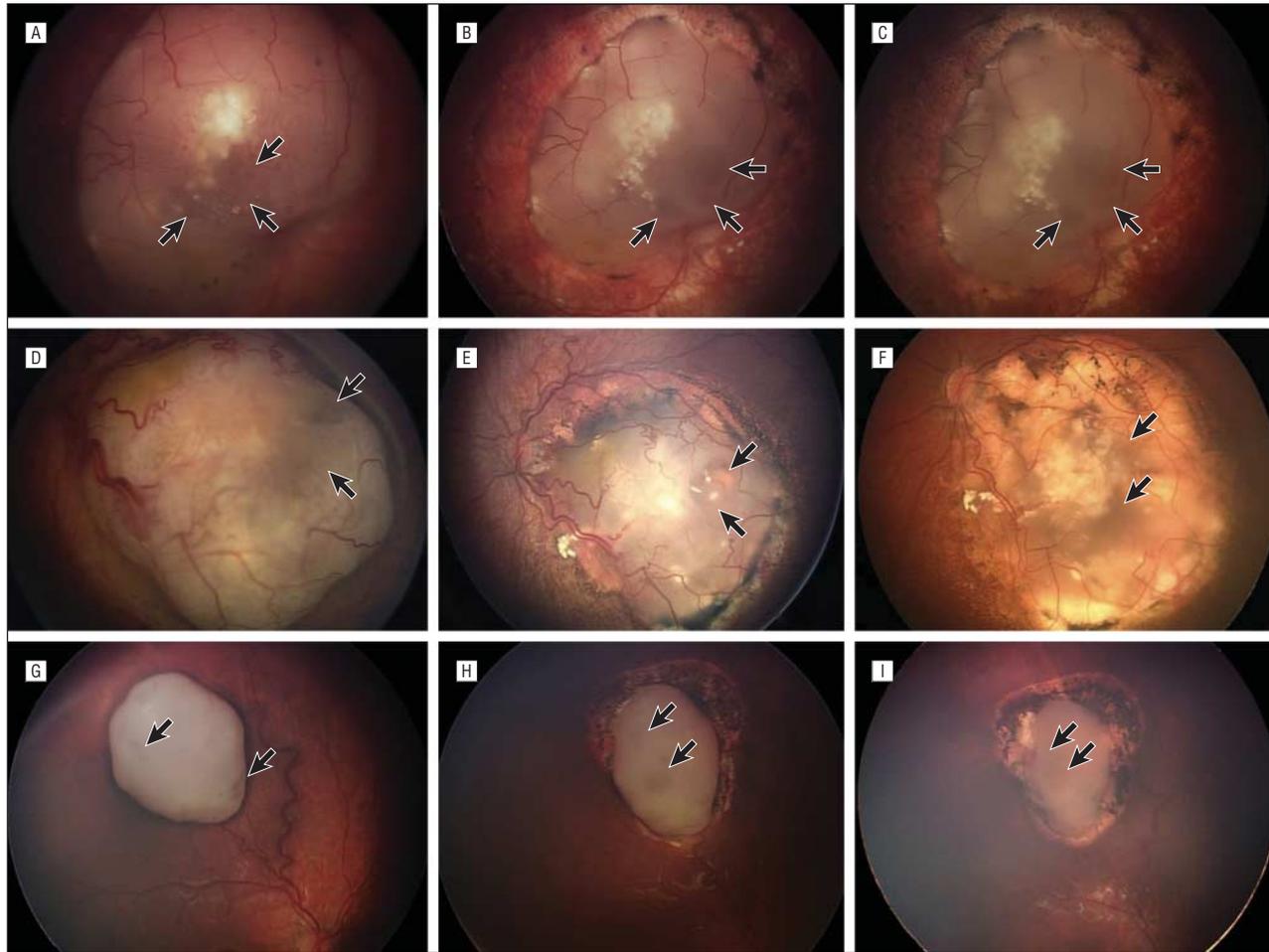
crease in the associated subretinal fluid, and surrounding areas of retinal pigment epithelial changes without areas of growth or recurrence.

Each cavitory tumor was measured for the greatest basal dimension, thickness, tumor regression pattern, and percentage of tumor replaced with calcium. The status of vitreous seeds (present, absent, or calcified), the status of subretinal seeds (present, absent, or calcified), and the percentage of residual subretinal fluid was noted. The percentage of decrease or increase in tumor base and thickness at the completion of chemotherapy and at the last follow-up date were calculated. Patient status at the last follow-up examination was also recorded (alive without metastasis, alive with metastasis, dead due to metastasis, or dead due to unrelated causes).

## RESULTS

Of 1591 patients with newly diagnosed retinoblastoma that was managed at the Oncology Service of the Wills Eye Institute from 1999 through 2011, 37 (2.3%) had cavitory retinoblastoma. Of these 37 patients, 13 were excluded because they had not received CRD or IAC or had a follow-up duration of less than 6 months. The remaining 24 patients displayed 26 cavitory retinoblastomas in 25 eyes. The mean patient age at presentation was 16 (median, 15; range, 6-35) months. The demographic data are listed in **Table 1**.

The tumor features are listed in **Table 2**. The mean number of cavitory retinoblastomas per eye was 1 (median, 1; range, 1-2), the mean tumor basal diameter was



**Figure 2.** Clinical course of cavitory retinoblastoma during chemotherapy in 3 cases. Findings are shown before treatment (A, D, and G), after 6 cycles of systemic chemotherapy (B, E, and H), and at the last follow-up visit (C, F, and I). Minimal to moderate change in tumor size is seen after treatment. The arrows indicate the cavities.

13 (median, 13; range, 7-24) mm, and the mean tumor thickness was 7 (median, 6; range, 3-17) mm. The mean number of cavities per tumor was 2 (median, 2; range, 1-5), with a mean cavity diameter of 3 (median, 2; range, 1-10) mm. Treatment variables are listed in **Table 3**. Twenty-three tumors (88%) were treated with CRD, 2 (8%) with IAC, and 1 (4%) with CRD and IAC. Adjuvant therapies are also listed in Table 3.

The mean percentage reduction in tumor diameter was 22% (median, 20%; range, 0-50%), and the mean percentage reduction in tumor thickness was 29% (median, 27%; range, 0-64%) during a mean follow-up duration of 49 (median, 20; range, 6-189) months. Outcomes are listed in **Table 4**. All 24 patients had at least 6 months of follow-up; 18 (75%), more than 1 year; 12 (50%), more than 3 years; and 9 (38%), more than 5 years. On follow-up, complete tumor response was found in 15 of 18 tumors (83%) at 1 year and in 9 of 9 tumors (100%) at 5 years. Overall, globe salvage was achieved in 22 eyes (88%). Enucleation was necessary for tumor recurrence (n=1), neovascular glaucoma (n=1), and optic nerve enhancement with suspected recurrence (later findings were negative) (n=1) (**Table 5**). We reviewed pathology results of the 3 enucleated eyes. In all 3 eyes, tumors were well differentiated with extensive areas of photorecep-

**Table 1. Demographic and Clinical Features of Patients Undergoing Chemotherapy for Cavitory Retinoblastoma**

Feature	Data (N = 24) <sup>a</sup>
Demographics	
Age, mo	
Mean	16
Median (range)	15 (6-35)
Sex	
Male	11 (46)
Female	13 (54)
Race	
White	19 (79)
African American	1 (4)
Hispanic	2 (8)
Asian	2 (8)
Clinical	
Laterality	
Unilateral	8 (33)
Bilateral	16 (67)
Heredity	
Sporadic	21 (88)
Familial	3 (13)
Genetic testing results <sup>b</sup>	
Somatic	4 (36)
Germline	7 (64)

<sup>a</sup>Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and might not total 100.

<sup>b</sup>Available in 11 patients.

**Table 2. Ocular Symptoms in Patients With Cavitory Retinoblastoma**

Symptom	Data (N = 26) <sup>a</sup>
Presenting concern <sup>b</sup>	
Leukocoria	13 (50)
Strabismus	12 (46)
Decreased vision	4 (15)
Duration of symptoms, wk	
Mean	17
Median (range)	17 (1-43)
Visual acuity	
Fixing and following light	16 (62)
Not fixing and following light	10 (38)
Intraocular pressure, mm Hg	
Mean	17
Median (range)	15 (10-42)
Associated findings <sup>b</sup>	
Neovascularization of iris	1 (4)
Secondary glaucoma	1 (4)
Vitreous seeds	7 (27)
Subretinal seeds	6 (23)
Retinal detachment	6 (23)
Basal diameter, mm	
Mean	13
Median (range)	13 (7-24)
Ultrasonographic thickness, mm	
Mean	7
Median (range)	6 (3-17)
Location of tumor epicenter	
Macula	10 (38)
Macula to equator	16 (62)
Tumor involving macula	
Yes	17 (65)
No	9 (35)
No. of total tumors per eye	
Mean	2
Median (range)	2 (1-6)
No. of cavitory tumors per eye	
Mean	1
Median (range)	1 (1-2)
No. of cavities per tumor	
Mean	2
Median (range)	2 (1-5)
Cavity diameter, mm	
Mean	3
Median (range)	2 (1-10)

<sup>a</sup>Unless otherwise indicated, data are expressed as number (percentage) of tumors.

<sup>b</sup>Percentages may not total 100 because some of the patients had more than 1 associated finding.

tor differentiation and had no viable tumor at the edges of the cavities. Of these 3 eyes, 1 had extensive focus of necrotic retinoblastoma with scattered foci of viable retinoblastoma in the anterior retina and subretinal space, and the remaining 2 eyes had no viable retinoblastoma. No metastasis or death occurred in any case.

### COMMENT

Retinoblastoma is known to respond dramatically to chemotherapy, including CRD<sup>1,9,12,14,17-19</sup> and IAC.<sup>20,22,23,25,26</sup> In a series of 457 tumors reported by Shields and associates,<sup>9</sup> the mean tumor reduction in

**Table 3. Treatment of Cavitory Retinoblastoma**

Treatment	No. (%) of Tumors (N = 26)
Chemotherapy <sup>a</sup>	
Systemic CRD (vincristine sulfate, etoposide, and carboplatin)	24 (92)
IAC (melphalan hydrochloride)	3 (12)
Adjuvant treatment <sup>b</sup>	
None	4 (15)
TTT	19 (73)
Cryotherapy	14 (54)
Subconjunctival carboplatin therapy	1 (4)
EBRT	3 (12)
Plaque brachytherapy	1 (4)

Abbreviations: CRD, chemoreduction; EBRT, external beam radiotherapy; IAC, intra-arterial chemotherapy; TTT, transpupillary thermotherapy.

<sup>a</sup>One patient had systemic CRD and subsequent IAC.

<sup>b</sup>Some of the patients had more than 1 adjuvant treatment. Of 26 tumors, 4 did not require any adjuvant treatment, 19 tumors needed additional TTT and/or cryotherapy, and 3 needed EBRT for complete tumor control.

basal diameter and thickness after CRD was 43% and 50%, respectively, with a tumor recurrence rate of 20%. Similar dramatic tumor responses have been found after IAC.<sup>20,22,23,25</sup> In a previous report of tumor response after CRD for cavitory retinoblastoma, the mean tumor reduction was 19% in basal diameter and 18% in tumor thickness, without tumor recurrence during a mean follow-up of 32 months.<sup>27</sup>

Cavitory retinoblastoma is a rare variant of retinoblastoma, which has ophthalmoscopically visible lucent cavities within the tumor.<sup>27</sup> The cavitory spaces appear hollow on ultrasonography and hypofluorescent on angiography (Figure 1).<sup>28</sup> Histopathologically, the cavitory spaces have been shown to represent areas of photoreceptor differentiation. Ts'o and colleagues<sup>29</sup> reviewed 300 eyes with retinoblastoma and found 18 tumors with associated photoreceptor differentiation in the adjacent area of cavitory spaces. Demirci et al<sup>31</sup> reviewed histopathologic findings in eyes with retinoblastoma treated with CRD and reported mean tumor reductions in basal diameter and thickness of only 17% and 32%, respectively, in well-differentiated tumors and, in contrast, tumor reductions of 35% in basal diameter and 55% in thickness in tumors that were not well differentiated. In 2004, our group<sup>27</sup> reported clinical features in 15 patients with cavitory retinoblastoma, and we found a relatively poor immediate clinical response of this variant to CRD. We concluded that cavitory retinoblastoma shows minimal visible response after CRD but speculated that this could be a sign of tumor differentiation. In a separate analysis of 68 cases of macular retinoblastoma treated with CRD and thermotherapy, tumor recurrence was found in 6 of 40 tumors (15%).<sup>32</sup> However, those tumors classified as cavitory showed only 1 recurrence in 26 tumors (4%) at 4 years.

In our present analysis, we confirm persistent long-term stability of cavitory retinoblastoma after CRD or IAC. Despite the relatively blunted clinical response with less dramatic shrinkage, long-term tumor control is typically achieved. We also observed that cavitory

**Table 4. Long-term Chemotherapy Results<sup>a</sup>**

Feature	Data <sup>b</sup>				
	Overall (N = 26)	At 1 y (n = 18)	At 5 y (n = 9)	At 10 y (n = 3)	At 15 y (n = 1)
Tumor response to chemotherapy					
Complete	23 (88)	15 (83)	9 (100)	3 (100)	1 (100)
Partial	2 (8)	2 (11)	0	0	0
None	1 (4)	1 (6)	0	0	0
Tumor recurrence	1 (4) <sup>c</sup>	1 (6) <sup>c</sup>	0	0	0
Vitreous seeds					
Recurrent	1 (4)	1 (6)	0	0	0
New	1 (4)	1 (6)	0	0	0
Subretinal seeds					
Recurrent	1 (4)	1 (6)	0	0	0
New	1 (4)	0	0	0	0
Reduction in basal diameter, %					
Mean	22	22	26	31	19
Median (range)	20 (0-50)	20 (0-50)	29 (8-50)	29 (19-44)	
Reduction in thickness, %					
Mean	29	29	34	29	18
Median (range)	27 (0-64)	23 (0-58)	30 (18-58)	20 (18-49)	
Regression pattern					
Type 1	2 (8) <sup>d</sup>	2 (11)	1 (11)	0	0
Type 2	4 (16) <sup>e</sup>	4 (22)	1 (11)	0	0
Type 3	20 (70) <sup>f</sup>	10 (56)	7 (78)	3 (100)	1 (100)
Type 4	0	0	0	0	0
Calcification, %					
Mean	36	35	48	53	90
Median (range)	20 (0-100)	20 (0-100)	50 (0-100)	50 (20-90)	
Residual retinal detachment	1 (4)	1 (6)	0	0	0

<sup>a</sup>There were no cases of metastasis or death.

<sup>b</sup>Unless otherwise indicated, data are expressed as number (percentage) of tumors.

<sup>c</sup>The solid tumor recurrence was in the noncavitary portion of the tumor.

<sup>d</sup>Both tumors underwent adjuvant transpupillary thermotherapy (TTT) and cryotherapy.

<sup>e</sup>Two tumors underwent no adjuvant treatment and 2 underwent TTT and cryotherapy.

<sup>f</sup>Fifteen tumors underwent TTT and/or cryotherapy; 2, no adjuvant therapy; and 3, external beam radiotherapy.

**Table 5. Globe Salvage and Enucleation**

Feature	No. (%) of Eyes (N = 25)
Globe salvage	22 (88)
Enucleation <sup>a</sup>	3 (12)
Reason for enucleation	
Diffuse vitreous seeds and vitreous hemorrhage	1 (4)
Neovascular glaucoma and total retinal detachment	1 (4)
Optic nerve enhancement on MRI	1 (4)

Abbreviation: MRI, magnetic resonance imaging.

<sup>a</sup>All patients who subsequently underwent enucleation also had multiple noncavitary tumors in the eyes.

retinoblastoma was less likely to display intrinsic calcification, subretinal fluid, vitreous seeds, or subretinal seeds.

In summary, we herein report a series of 26 cavitary retinoblastomas treated with chemotherapy (CRD and/or IAC), of which most showed only slight clinical reduction in tumor size. Despite minimal visible response to chemotherapy, cavitary retinoblastoma has a favorable long-term outcome with stable tumor regression and globe salvage. Based on these findings, aggressive or prolonged chemotherapy or adjunctive therapies are generally not necessary for cavitary reti-

noblastoma, although a dramatic response is not achieved. Long-term follow-up is advised for all cases because of the small risk of recurrence.

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