

# Anterior Chamber Invasion in Retinoblastoma: Not an Indication for Adjuvant Chemotherapy

Kummamuri V. Sreelakshmi,<sup>1</sup> Anita Chandra,<sup>2</sup> Subramanian Krishnakumar,<sup>3</sup> Viswanathan Natarajan,<sup>4</sup> and Vikas Khetan<sup>1</sup>

<sup>1</sup>Shri Bhagawan Mahavir Vitreoretinal Services, Sankara Nethralaya, Chennai, India

<sup>2</sup>Department of Medical Oncology, Sankara Nethralaya, Chennai, India

<sup>3</sup>Department of Larsen and Toubro Ocular Pathology, Sankara Nethralaya, Chennai, India

<sup>4</sup>Department of Statistics, Sankara Nethralaya, Chennai, India

Correspondence: Vikas Khetan, Shri Bhagawan Mahavir Vitreoretinal Services, Sankara Nethralaya, 18 College Road, Nungambakkam, Chennai, India; drkkhetan@yahoo.com.

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**PURPOSE.** In retinoblastoma, adjuvant chemotherapy after enucleation is given in eyes with histopathological high-risk features (HRFs) to reduced mortality. Anterior chamber seeds (AC seeds) on histopathological evaluation are a contentious finding. This study attempts to determine the effect of AC seeds on the survival rate.

**METHODS.** This is a retrospective case record review. Eyes were divided into four groups: those with neither AC seeds nor HRFs, those with only HRFs, those with only AC seeds, and those with both HRFs and AC seeds. The groups were compared for demographic and clinical features and survival curves were plotted for each.

**RESULTS.** For the 212 eyes included in the study, mean age was  $30.5 \pm 36.8$  months. Children with only AC seeds were significantly older ( $75.3 \pm 94.6$  months) ( $P = 0.004$ ). Chemotherapy was administered in 81 (38.2%) of 212 eyes; 16 (13.7%) of 117 eyes without HRF and in 65 (68.4%) of 95 eyes with HRFs ( $P < 0.001$ ). The survival rate at 1, 3, and 5 years was the highest for the group with only AC seeds, although the difference was not statistically significant.

**CONCLUSIONS.** We conclude that AC seeds do not, by themselves, constitute an independent risk factor for metastasis. These children need not be treated with immediate adjuvant chemotherapy, but, instead, can be followed with regular screening for metastasis. However, AC seeds are seen in only a small proportion of enucleated eyes. A larger study would better validate our study results.

**Keywords:** retinoblastoma, anterior chamber seeds, adjuvant chemotherapy, high-risk features

Retinoblastoma is the most common pediatric intraocular malignancy.<sup>1,2</sup> It also has the highest survival rate; nearly 95% in developed countries. Intra-arterial and intravitreal chemotherapy have even enabled globe and vision salvage, albeit in a select group of patients. However, the survival rate in developing countries ranges from 40% to 79%,<sup>3</sup> a large percentage of eyes still undergo primary enucleation, and systemic metastasis remains an important cause of mortality. Studies have enumerated various clinical and histopathological factors postulated to increase the risk of metastasis and thus increase mortality. Adjuvant chemotherapy significantly reduces the mortality in this group of children. Clinical features that have been evaluated as predictors for systemic metastasis include older age at presentation, increased time lag between onset of symptoms and presentation, glaucoma, exophytic growth pattern, buphthalmos,<sup>4</sup> and neovascularization of iris.<sup>5</sup> Massive invasion of choroid, optic nerve, sclera, and ciliary body as seen on histopathological evaluation (HPE) are considered to be high-risk features (HRFs).<sup>6-8</sup>

Anterior chamber seeding (AC seeds) as seen on HPE is a contentious risk factor. There have been no large case series that have evaluated the effect of isolated AC seeds on systemic metastasis and mortality. We have observed that AC seeds are

not an independent risk factor for metastasis.<sup>9</sup> This current study attempts to determine survival rate of patients with AC seeds with and without HRFs and compare it with similar groups without AC seeds.

## MATERIALS AND METHODS

This was a retrospective case series. Approval by the institutional review board and ethics committee was taken. The tenets of the Declaration of Helsinki were followed. Histopathological records of all eyes enucleated for retinoblastoma between January 2008 and December 2013 were reviewed. Preparation of specimens for histopathological examination followed the guidelines given by International Retinoblastoma Staging and Working Group.<sup>10</sup> HRFs were searched for in each eye. HRFs were defined as choroidal invasion more than 3 mm or full-thickness invasion, post-laminar optic nerve invasion, focal choroidal invasion of less than 3 mm but with prelaminar or laminar invasion, scleral invasion, and ciliary body invasion.<sup>11-13</sup> Extra scleral extension or involvement of optic nerve transection end constituted microscopic residual disease. These were eliminated from the



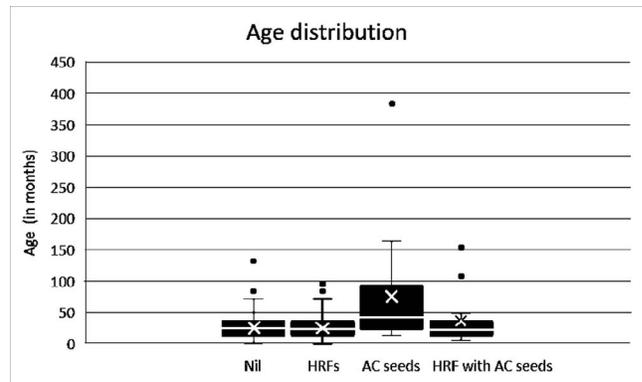
**TABLE 1.** Chemotherapy Regimen, Administered in Six Cycles, 3 to 4 Weeks Apart

Drug	Dosage
Vincristine	0.05 mg/kg as intravenous bolus on day 1
Carboplatin	28 mg/kg in 100 mL 5% dextrose over 1 hour on day 1
Etoposide	12 mg/kg in 100 mL 0.9% normal saline over 1 hour, on days 1 and 2

study. AC seeds included tumor cell clusters on endothelium, tumor cells on surface of iris, iris stromal infiltration, and tumor cells in anterior chamber. Anterior chamber angle invasion, ectropion uveae, and neovascularization of iris were not considered as AC seeds.

There were 260 eyes that were enucleated for retinoblastoma during the study period. Eyes that had features of microscopic orbital retinoblastoma were identified and eliminated from the study; seven eyes. When there was a history of chemotherapy before enucleation, as chemotherapy reduction or as neoadjuvant chemotherapy, those eyes were excluded from the study, as chemotherapy is known to result in downgrading of the histopathological features; 41 eyes. Although there were no bilateral primary enucleations during the study period, in secondary enucleation in a bilaterally affected patient, only the first eye was considered for analysis, as in all cases, the child received chemotherapy in an attempt to salvage the second eye before undergoing enucleation. There were 212 eyes with intraocular retinoblastoma that underwent primary enucleation and were included in this study. Clinical records of these children were reviewed and demographic data, clinical features, retinoblastoma grading according to the International Intraocular Retinoblastoma Classification (IIRC),<sup>14</sup> investigations, treatment history, duration of follow-up, and development of adverse events were documented. At diagnosis, all patients underwent full ophthalmological examination under anesthesia and magnetic resonance imaging of the brain and orbit was performed in all cases at presentation and annually. Metastasis workup in the form of bone marrow cytology with lumbar puncture and cerebrospinal fluid analysis with spinal tap was done in children with clinical or radiological suspicion of metastasis at presentation and repeated at 6-month intervals until the child was 5 years of age. Chemotherapy was in the form of six cycles of a standard three-drug regimen given at 3- to 4-week intervals (Table 1). The dosage was determined after consultation with an oncologist before every cycle and was adjusted in children younger than 1 year. Before each cycle of chemotherapy, complete hematology workup was done and abnormal parameters, such as anemia, were treated before proceeding with the chemotherapy. Local therapy in the form of cryotherapy or trans pupillary thermotherapy was initiated for the other eye in bilateral cases.

Eyes were divided into four groups based on histopathological features; those without HRFs and AC seeds, those with only AC seeds, those with only HRFs, and those with HRFs and AC seeds. Comparison of demographic data and survival curves was made between the groups. Survival curve was calculated from the date of enucleation to date of last visit. Metastasis and deaths during follow-up were counted as adverse events. Patients lost to follow-up were censored while constructing the survival curves. Presence of postlaminar invasion of the optic nerve, choroidal invasion >3 mm, choroidal invasion of <3 mm along with any amount of optic nerve invasion, and scleral invasion were each counted as one risk factor. When both choroidal invasion >3 mm and postlaminar invasion were

**FIGURE 1.** Box and whisker plot demonstrating distribution of age in the four histopathological groups. Nil indicates no HRFs or AC seeds.

present, they were counted as two risk factors. Distribution of HRFs in the four groups was also analyzed.

SPSS 14.0 software (IBM SPSS Statistics, IBM Corporation, Chicago, IL, USA) was used for the statistical analysis. Independent samples *t* test or Mann-Whitney *U* Test was performed to compare mean value between two groups. One-way ANOVA was used to compare the mean values for more than two groups. Bonferroni test was used for post hoc analysis. Fisher exact test and  $\chi^2$  chi square test for independence were used to compare proportions. The proportion of children free of adverse events (metastasis, death) was calculated using the Kaplan Meier curve, separately for each group. Date of enucleation was the starting point of the survival curve.

## RESULTS

Of the 212 eyes, there were 99 (46.7%) eyes with no HRFs on HPE, 18 (8.5%) eyes with only AC seeds, 77 (36.3%) eyes with only HRFs, and 18 eyes (8.5%) with HRFs with AC seeds.

### Demographic Variables and Clinical Features

For the whole cohort, the mean age was  $30.5 \pm 36.8$  months. Mean age among the groups was  $26.5 \pm 22.5$  months for the group with no HRFs,  $75.3 \pm 94.6$  months for the group with AC seeds,  $29.96 \pm 19.57$  months for the group with only HRFs, and  $35.0 \pm 37.8$  months for the group with HRF with AC seeds. There was a statistically significant difference in the distribution of age in the four subgroups ( $P < 0.001$ ). Children with only AC seeds were significantly older than the other three groups ( $P = 0.004$ ). Of the 18 children in the group with only AC seeds, 6 (33%) were younger than 3 years, 8 (45%) were 3 to 9 years of age, and 4 (22%) were 9 years old or older. The mean plot for age distribution among the groups is shown in Figure 1.

The distribution of bilateral retinoblastoma ranged from 19.19% to 22.2% in the three groups and was considerably lower, 5.5% (one eye), in the group with only AC seeds, although not reaching statistical significance. Gender distribution and follow-up period were comparable among groups. In all four groups, percentage of group E tumors was more than that of grade D tumors, although this difference did not reach statistical significance in eyes with no HRFs or AC seeds. Patient characteristics are described in Table 2.

Eyes with only AC seeds on HPE were compared with eyes having HRF with AC seeds for clinical presentation and pattern of AC seeding on histopathology. Although duration of

TABLE 2. Relevant Demographic, Clinical, and Histopathological Characteristics of the Four Histopathological Groups

Characteristics	Nil	AC Seeds	HRF	AC Seeds With HRF	P
No. of eyes	99	18	77	18	
Age, mo, mean	26.5 ± 22.5	75.3 ± 94.6	29.96 ± 19.57	35.0 ± 37.8	<0.001
Age, mo, median	24	42	24	24	
Male, %	54.5	50	64.9	72.2	0.2805
Bilateral, %	19.19	5.5	20.78	22.2	0.4924
Group D, n (%)	44 (44.4)	4 (22.2)	32 (41.6)	3 (16.7)	
Group E, n (%)	55 (55.6)	14 (77.8)	45 (58.4)	15 (83.3)	
Group distribution, P value	0.1179	0.0009	0.0362	0.0001	
Chemotherapy, n (%)	14 (14.1)	2 (11.1)	49 (63.6)	16 (88.9)	
Follow-up, y	3.89 ± 1.94	3.99 ± 2.3	3.6 ± 2.11	3.36 ± 2.28	0.7538
1-y survival rate	0.99	1.00	0.93	0.77	
3-y survival rate	0.99	1.00	0.91	0.71	
5-y survival rate	0.99	1.00	0.88	0.71	
Deaths, n	1	0	7	5	

symptoms to enucleation was longer in patients with both features on HPE, the difference was not statistically significant. When all 36 eyes with AC seeds on HPE were analyzed, iris surface was the most common location of retinoblastoma cells seen in 21 (58.3%) of the 36 eyes. The second most common location was the anterior chamber itself, seen in 15 (41.7%) of the 36 eyes, followed by angle-Trabecular meshwork complex and iris infiltration seen in 12 (33.3%) of 36 each. This distribution was comparable between the two groups. Details are described in Table 3. Among the 18 eyes with only AC seeds on histopathology, 2 (38.9%) eyes had only anterior segment mass and the posterior segment was completely within normal limits. Diffuse infiltrating retinoblastoma was diagnosed in one eye.

Eyes with HRFs were compared with eyes with HRFs and AC seeds for the number of HRFs in the eye at HPE. The latter had a significantly higher number of HRFs than the former ( $P =$

0.001). In eyes with only HRFs, 40 (51.9%) of 77 eyes had only one risk factor, whereas there were three risk factors in 8 (44.4%) of 18 eyes with AC seeds and HRFs. Only 9 (11.7%) of 77 eyes with only HRFs had three risk factors. This distribution is shown in Figure 2.

Systemic chemotherapy comprised the vincristine-etoposide-carboplatin regimen. This was administered to 81 (38.2%) of 212 patients in the study. Chemotherapy was given in 16 (13.7%) of the 117 patients who had no HRFs (with or without AC seeds) on HPE. Chemotherapy was administered in these patients for chemoreduction for the contralateral eye in bilateral retinoblastoma. Chemotherapy was advised in all 95 patients with HRFs, and six cycles of chemotherapy were completed in 65 (68.4%) of the 95 patients, and 26 patients in this group received zero to four cycles of chemotherapy. Only 5 of the 26 children had follow-up of less than a year and 2 of these 5 children were lost to follow-up immediately after enucleation. Chemotherapy was administered to two patients who had only AC seeds, one who had bilateral retinoblastoma and the other who had inadvertently been subjected to AC tap elsewhere before being diagnosed to have retinoblastoma. Distribution of chemotherapy in the four groups is shown in Table 2.

There were 13 deaths in this case series. In 12 of the 13 of these cases, HRFs were observed in the enucleated specimen. Histopathological HRFs in these 13 cases included massive choroidal invasion in nine eyes and post laminar optic nerve invasion in eight eyes. There were five eyes with massive choroidal invasion as well as postlaminar invasion. In four of these cases, AC seeds were present in the enucleated specimen in addition to other HRFs. All 13 cases had received adjuvant chemotherapy, and 3 of the 13 had also received external beam radiation therapy (EBRT).

### Survival Curve

A survival curve was plotted for each of the four groups of eyes (Fig. 3). Occurrence of metastasis or death was taken as an adverse event for the construction of the survival curve and children lost to follow-up were censored at the last follow-up date. The survival rate at 1-year, 3-year, and 5-year follow-up for each of the four groups is given in Table 2. Survival curve of the group with only AC seeds was highest, followed by patients with no HRFs or AC seeds, followed by those with HRFs and finally those with HRFs and AC seeds. The difference of survival rate among the groups was not significant.

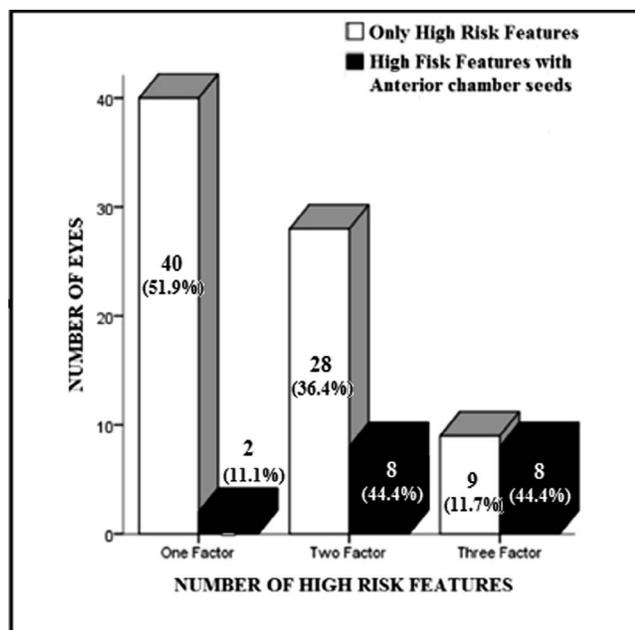


FIGURE 2. Bar chart representing number of HRFs in eyes with only HRFs and eyes with HRFs and AC seeds.

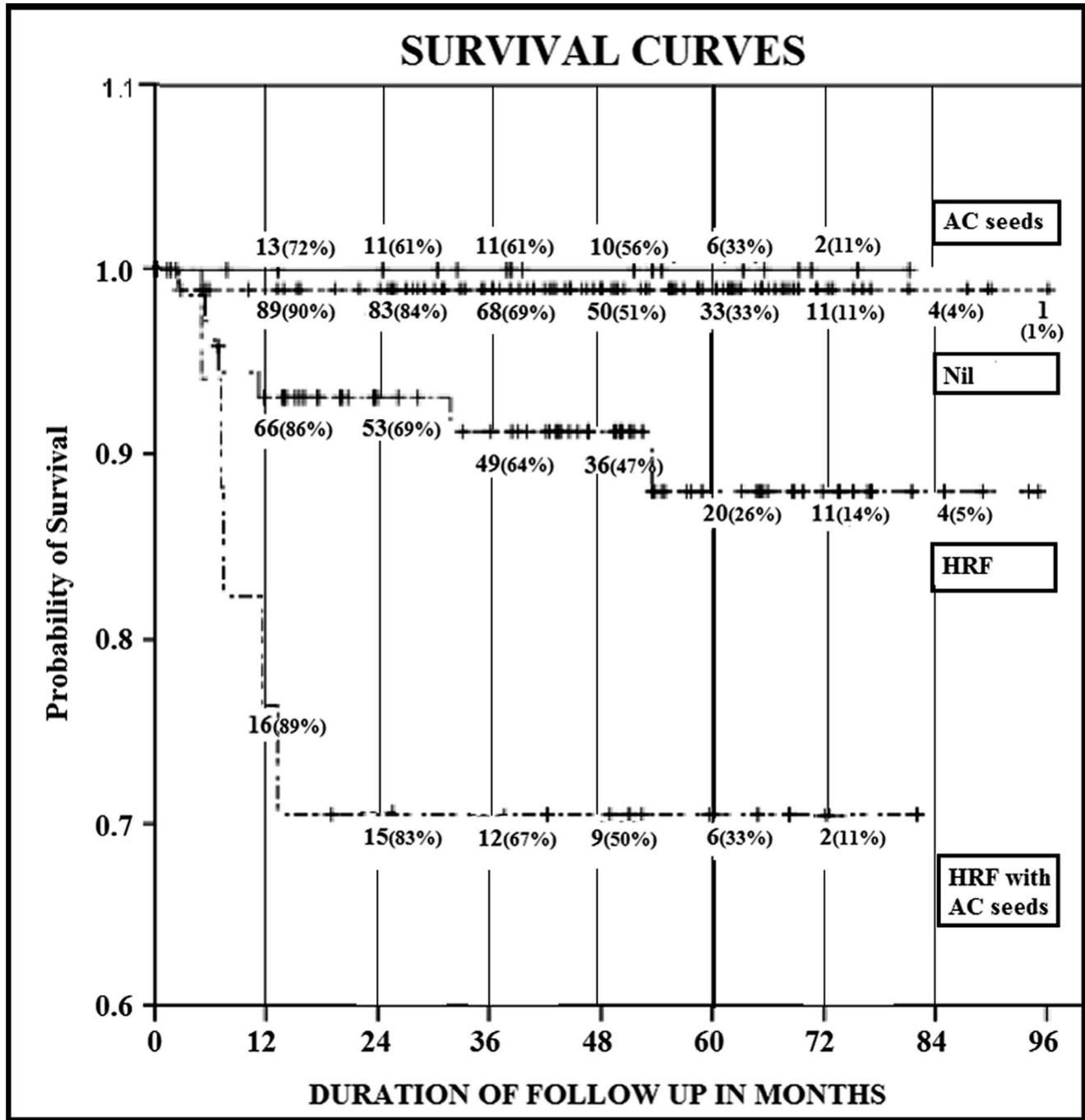


FIGURE 3. Survival curve of the four histopathological groups.

**DISCUSSION**

Current management techniques for retinoblastoma have improved the survival rates in retinoblastoma; of the child, the globe, and the vision. Mortality is most commonly consequent to microscopic residual disease and adjuvant chemotherapy is an effective tool to eradicate presumed micrometastases before they clinically manifest and to thus reduce mortality. However, chemotherapy is not without side effects. Common side effects include anemia, thrombocytopenia, and neutropenia, potentially requiring hospitalization and transfusions. Other significant, but controversial side effects include a risk of secondary malignancies and ototoxicity.

Although children with heritable retinoblastoma are at risk of secondary cancer due to the innate genetic predisposition, the risk is increased with the use of chemotherapy agents.<sup>15</sup> Malignancies observed at a mean of 11 years' follow-up were osteosarcoma, rhabdomyosarcoma, melanoma, glioma, and acute promyelocytic leukemia. There have also been reports of acute myelogenous leukemia.<sup>16</sup>

It is thus important to identify the eyes at high risk of developing metastasis to reduce the risk of metastasis without the consequent side effects.<sup>11</sup> Although massive choroidal invasion, postlaminar optic nerve invasion, and scleral invasion are accepted histopathological HRFs purported to increase risk of metastasis,<sup>17-19</sup> anterior chamber seeding is a contentious

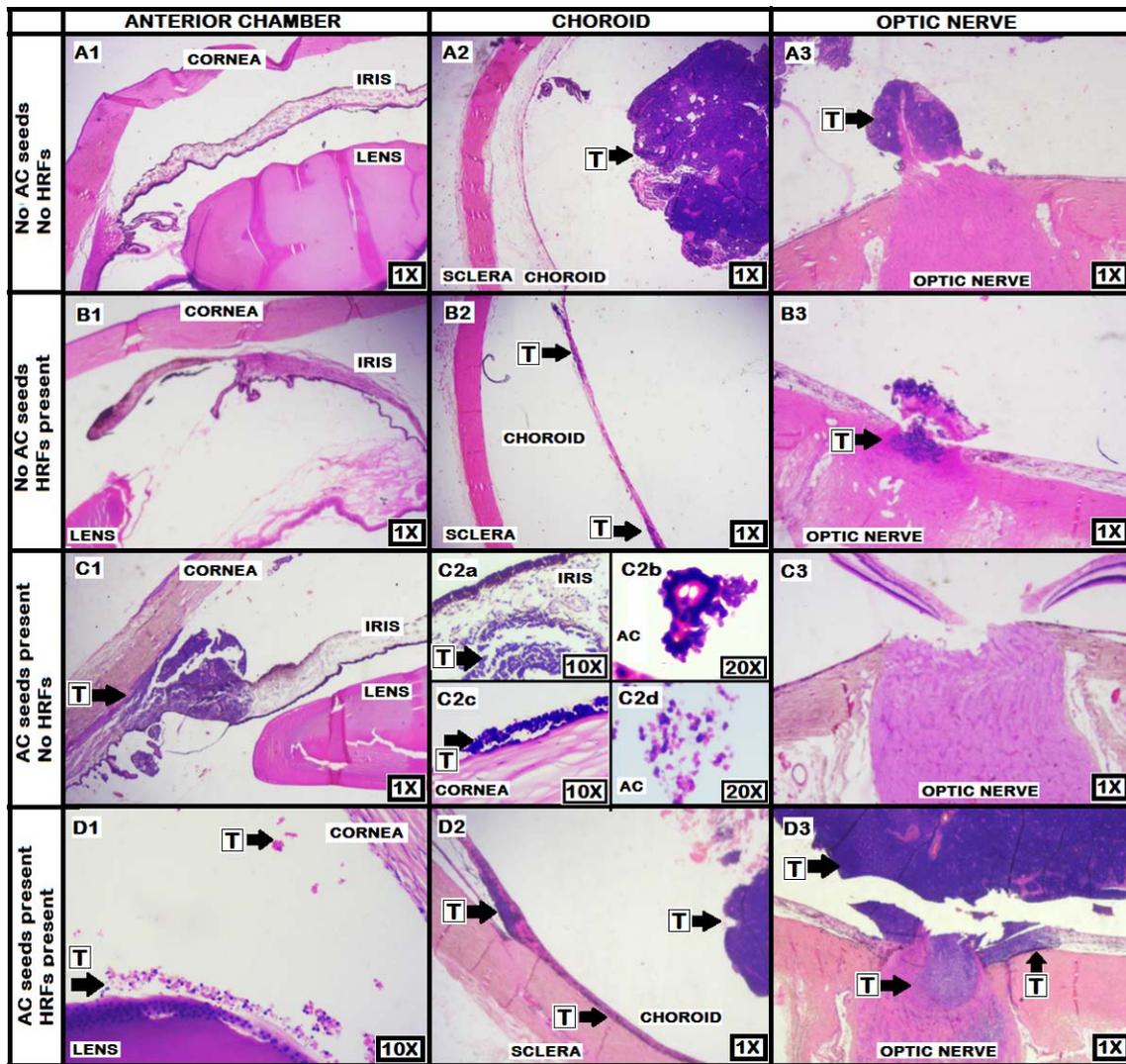


FIGURE 4. Representative microphotographs of histopathological features of the four groups included in the study. The horizontal panels represent the four histopathological groups and the vertical panels, the histopathological sections of anterior chamber, choroid, and optic nerve of the four groups. C2a-d do not show choroidal invasion, which was absent, and instead show magnified view of anterior chamber invasion. All slides are stained with hematoxylin and eosin. The magnification is given in the lower right-hand corner. Black arrows headed by letter T point toward the tumor cells in all panels. T, tumor cells.

histopathological finding. Determination of structures whose involvement constitutes AC seeds is also a gray area. Figures 4C2a-d demonstrate invasion of various anterior chamber structures by the tumor cells.

Seeds in the anterior chamber, on corneal endothelium and iris surface and stroma are well accepted as AC seeds; however, involvement of trabecular meshwork and ciliary body is contentious. In an article by Baroni et al,<sup>20</sup> AC seeds were

TABLE 3. Clinical and Histopathological Features in Eyes With AC Seeds, With and Without HRFs

Characteristics	AC Seeds With HRF	AC Seeds	P
Duration of symptoms to enucleation, mo, mean ± SD	6.63 ± 8.75	3.08 ± 3.17	0.254
AC seeds seen clinically, n (%)	9 (50)	7 (43.7)	1
Presence of NVI clinically, n (%)	2 (11.1)	6 (33.3)	
Mean IOP before enucleation, mm Hg, mean ± SD	38.5 ± 18.15	31.24 ± 13.23	0.3
Location of AC seeds			
Adhered to cornea, n (%)	1 (5.6)	1 (5.6)	1
In anterior chamber, n (%)	7 (38.9)	8 (44.4)	0.7353
On iris surface, n (%)	10 (55.6)	11 (61.1)	0.7353
Iris infiltration, n (%)	6 (33.3)	6 (33.3)	1
Trabecular meshwork, n (%)	7 (38.9)	5 (27.8)	0.4795

AC seeds, anterior chamber seeds; HRF, high risk features; NVI, neovascularisation of iris.

**TABLE 4.** Comparison of Treatment Protocols Followed by Various Studies in the Management of AC Seeds Seen on Histopathology After Enucleation

Authors	Year	Enucleation	Definition of AC Seeds	Whether to Treat	No. of Cycles	Chemotherapy Regimens
Honavar et al. <sup>18</sup>	2002	P	Iris, AC, CB	Yes	6–12	VDCy/VEC
Chantada et al. <sup>22</sup>	2004	P	Iris, AC, CB	No	NA	VDCy/VECCy/ VIECCy
Baroni et al. <sup>20</sup>	2012	P, S	Iris, AC, CB	No	NA	VCyD/VCyE/VCyICE
Aerts et al. <sup>21</sup>	2013	P	Iris, CB	Yes	4	EC, VCy Alternating
Sullivan et al. <sup>23</sup>	2014	P	Iris, AC, CB	Yes	4	VDCG
Kaliki et al. <sup>12</sup>	2015	P	Iris, AC	Yes	6	NA
Fabian et al. <sup>13</sup>	2017	S	Iris, AC, CM, CB	Yes	4	IVD/TVD/Thiotepa

AC, anterior chamber; C, carboplatin; CB, ciliary body; CM, ciliary muscle; Cy, cyclophosphamide; D, doxorubicin; E, etoposide; G, granulocyte colony-stimulating factor; I, ifosfamide; P, primary; S, secondary; T, topotecan; V, vincristine.

not considered an HRF and chemotherapy was administered only if concomitant HRFs were present. However, AC seeds alone were not analyzed independently. In an article by Khelifaoui et al.,<sup>7</sup> AC seeds, although identified as a risk factor for metastasis in the multivariate analysis, did not remain risk factors once eyes with extra scleral or resection line involvement were excluded. Presence of AC seeds has been considered an HRF and treated with six cycles of chemotherapy in a few studies,<sup>18</sup> considered to be of intermediate risk for development of metastasis and treated with four cycles of chemotherapy in a few studies<sup>13,21</sup> and not considered a risk factor for metastasis and monitored for metastasis without chemotherapy in a few studies<sup>15</sup> (Table 4). In most of the studies, AC seeds have not been independently analyzed for effect of adjuvant chemotherapy, and when analyzed, the number of eyes was too small to comment on the effect of chemotherapy.

In this study, we compared the survival rates of eyes with no HRFs, only AC seeds, only HRFs, and AC seeds with HRFs to demonstrate the good survival rate of eyes with AC seeds alone. A study by Kaliki et al.<sup>12</sup> reported AC seeds in 36 (23%) of 157 eyes with anterior chamber seeding in 6% and iris infiltration in 3%. This was comparable to 16.9% eyes with AC seeds seen in our case series with iris infiltration being observed in 5.7% and anterior chamber seeds in 7.1%. In a study by Honavar et al.,<sup>18</sup> 21% of cases showed AC tumor seeding, although only unilateral sporadic retinoblastomas were included in that series.

We observed a higher age (mean and median) at time of clinical diagnosis in those eyes that had only AC seeds. Children with sporadic unilateral retinoblastoma are known to present at an older age than those with bilateral retinoblastoma, and in this group, with the exception of one, all had unilateral retinoblastoma. In this group, there were two eyes that had the tumor in the anterior chamber only, with no tumor in the posterior chamber, representing diffuse anterior retinoblastoma, whereas one eye had the diagnosis of diffuse infiltrating retinoblastoma. This presentation of retinoblastoma is known to occur in a relatively older group of children. There was no significant difference in the distribution of other demographic variables among the groups. Presence of AC seeds alone was associated with a reduced duration of symptom to enucleation period as compared with when HRFs were also present, although the difference did not reach statistical significance. There was a statistically significant difference in the distribution of group D and group E tumors among the groups ( $P = 0.0015$ ). The percentage of group E tumors was higher than group D tumors in all four groups. However, the difference was statistically significant in three groups: those with AC seeds, AC seeds with HRFs, and those with HRFs. Massive choroidal invasion and optic nerve

invasion are appreciated on histopathology and cannot be determined clinically. They do not influence the clinical grading of the eyes directly. However, presence of AC seeds can be appreciated clinically as well as on HPE and their presence upgrades the retinoblastoma to grade E, thus explaining the higher percentage of grade E tumors in these eyes.

Survival rate of all the four groups did not show statistically significant difference, reflecting the overall good prognosis of retinoblastoma. Survival rate of eyes with no HRFs and no AC seeds was similar to that with eyes with only AC seeds representing lack of effect of AC seeds on mortality in these children. Survival rate of eyes with HRF and AC seeds was lower than that of eyes with only HRFs, although not reaching statistical significance. This could be due to asymmetrical distribution of number of HRFs. Although eight (44.4%) eyes with HRFs and AC seeds had at least three HRFs in the enucleated specimen, only nine (11.7%) eyes with only HRFs had three HRFs on HPE.

AC seeds may merely represent spillover of tumor activity into anterior chamber, especially when the original focus of retinoblastoma is anterior and the early involvement of anterior chamber is to be expected. Here anterior chamber involvement represents only the anterior location of the tumor and not the grade of the tumor or degree of anaplasia. Diffuse anterior retinoblastoma represents another entity in which the tumor involves only the anterior segment of the eye. These children are typically older (6 to 12 years of age) at diagnosis.<sup>24</sup> They are often sporadic, although a recent case report described a heritable form. Although Herwig et al.,<sup>25</sup> Longmuir et al.,<sup>26</sup> and Garner et al.<sup>27</sup> treated diffuse anterior retinoblastoma with enucleation followed by adjuvant chemotherapy and radiotherapy, Khetan et al.<sup>28</sup> treated with enucleation alone and did not report a recurrence at time of publication. A recent report by Shields et al.<sup>29</sup> described successful globe salvage in three such cases wherein only two of the three cases received systemic chemotherapy and none developed metastasis over a follow-up of 35 months.

Studies have shown that metastasis, after enucleation, usually occurs within 5 years.<sup>2</sup> A study had identified 6.4 months in unilateral cases and 14.2 months in bilateral cases as the median time to development of metastasis.<sup>30</sup> In a study by Shields et al.,<sup>31</sup> 78.2% of recurrences occurred within the first year of diagnosis of retinoblastoma, whereas the median time to death was 10 months in that series. In our case series, 80 (37.7%) of the 212 eyes had a follow-up of 1 year, and in the group with AC seeds alone, 89.9% had a follow-up of more than a year and during this period, none developed metastasis.

## CONCLUSIONS

There is lack of consensus on AC seeds as high-risk prognosticators. In this study, we presented a series of 18 cases of AC seeds, 89% of whom were successfully managed without adjuvant chemotherapy for a mean period of 3.99 years. There were no relapses or metastases in this group of children. We therefore conclude that AC seeds do not, by themselves, constitute an independent risk factor for metastasis, and that all children with AC seeds alone on histopathological examination need not be treated with immediate adjuvant chemotherapy. Instead, they can be followed with regular screening for metastasis. However, AC seeds are seen in only a small proportion of enucleated eyes and rate of metastasis in retinoblastoma is low. A larger study would better validate our study results.

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