



# Intra-arterial chemotherapy for retinoblastoma in eyes with vitreous and/or subretinal seeding: 2-year results

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## ABSTRACT

**Background/aims** To review the effectiveness of intra-arterial chemotherapy for advanced intra-ocular retinoblastoma with vitreous and/or subretinal seeds in naive (untreated) and previously treated eyes.

**Methods** Retrospective study, approved by the institutional review board, of 76 eyes of 67 patients with retinoblastoma with subretinal and/or vitreous seeding treated with intra-arterial chemotherapy at Memorial Sloan-Kettering Cancer Center between May 2006 and August 2010.

**Results** Despite advanced intraocular disease with seeding, the majority (56/76) of eyes were saved; 20/76 eyes were enucleated. Among treatment-naïve eyes, the 2-year probability of ocular salvage was 83% (95% CI 27% to 97%) for eyes with subretinal seeding only, 64% (95% CI 24% to 87%) for eyes with vitreous seeding only, and 80% (95% CI 40% to 95%) for eyes with both. Among eyes that received previous treatment and had progressed, the 2-year probability of ocular salvage was 50% (95% CI 15% to 78%) for eyes with only subretinal seeding, 76% (95% CI 48% to 91%) for eyes with vitreous seeding only, and 54% (95% CI 20% to 79%) for eyes with both. Nine of 29 naïve eyes (31%) were cured with intra-arterial (super-selective ophthalmic artery infusion of chemotherapy) chemotherapy alone.

**Conclusion** Unlike radiation or systemic chemotherapy, intra-arterial chemotherapy can usually prevent the need for enucleation in naïve eyes with advanced intraocular retinoblastoma with seeding—especially if the seeding is subretinal. Treatment appears to be less effective in previously treated eyes when subretinal seeding is present (50% at 2 years), but may be more effective in eyes that failed to respond to previous systemic chemotherapy and have only vitreous seeding.

## INTRODUCTION

Although there are many different (and equally successful) strategies for curing retinoblastoma limited to the retina,<sup>1</sup> all strategies for managing advanced intraocular retinoblastoma are disappointing. Reese recognised this and therefore classified group V eyes (Va involving half the retina and Vb with vitreous seeding) as 'very unfavorable'.<sup>2</sup> The majority of group V eyes have always been enucleated primarily, and only 20–25% of treated eyes (with external beam irradiation) avoided enucleation. Multiagent chemotherapy for group V eyes has also been disappointing. Friedman *et al* reported that, after systemic chemotherapy, 75% of group V eyes progressed,<sup>3</sup> and Antonelli *et al* noted that none of the unilateral group V eyes treated in

Brazil could be salvaged after systemic chemotherapy.<sup>4</sup> Kim *et al* (and others) have suggested that systemic chemotherapy be used only for group I–III eyes because of the disappointing results (and toxicity) in more advanced eyes.<sup>5</sup>

The situation is even worse for Reese–Ellsworth group Vb eyes. Most are enucleated at diagnosis, but, with careful case selection (after enucleating most of these eyes), we demonstrated a 50% salvage rate with primary external beam irradiation.<sup>6</sup> Kaneko and Suzuki pointed out that systemic chemotherapy 'rarely cures vitreous seeds',<sup>7</sup> and Shields and colleagues demonstrated that the most important predictive factor for failure with systemic chemotherapy was seeding.<sup>8</sup>

Subretinal seeding was never part of the Reese–Ellsworth classification scheme, so there are no published data on the success/failure of primary external beam irradiation for eyes with subretinal seeding. Subretinal seeding is part of the newer international classification scheme; however, group D eyes (with vitreous and/or subretinal seeding >3 mm from a tumour) generally respond poorly to systemic chemotherapy. Gunduz and colleagues reported a success rate of 36% for eyes with seeding, but did not distinguish between vitreous seeding, subretinal seeding and eyes containing both.<sup>9</sup> The international classification does not put subretinal seeding in a different group from vitreous seeding, so there is no way to know the actual success of eyes treated in the modern chemotherapy world subcategorised by whether they have only vitreous seeds, only subretinal seeds, or a combination of both.

Seeding of any type in eyes that have been primarily treated with radiation or chemotherapy and progressed carries with it a dire prognosis for ocular salvage. Of Reese–Ellsworth group V eyes that were initially treated with radiation and progressed, only 2.2% could be salvaged with a second course of external beam irradiation.<sup>10</sup> The most encouraging report from England demonstrated that 29% of group Va eyes that failed to respond to systemic chemotherapy could be salvaged, but the authors stressed that they did not treat all eyes that failed to respond to chemotherapy, and enucleated some such eyes rather than try a course of salvage irradiation.<sup>11</sup> Only three eyes with vitreous seeding (group Vb) were salvaged.

We have previously reported on our experience with intra-arterial chemotherapy for the treatment of naïve eyes and eyes that progressed despite systemic chemotherapy.<sup>12–14</sup> In our report on our 4-year experience with intra-arterial chemosurgery, we noted that, for group V naïve eyes primarily

treated with intra-arterial chemosurgery, the Kaplan–Meier estimate of 2-year event-free survival was 80.5%. This group included patients in our initial institutional review board cohort who had advanced intraocular disease scheduled for enucleation. For group V eyes that had not responded to previous management (with systemic chemotherapy and/or external beam irradiation), we salvaged 51.5% of eyes at 4 years. That series, however, did not separate vitreous from subretinal seeds, so we undertook an analysis of all eyes with vitreous and/or subretinal seeding to determine the success, time course, and patient and ocular survival with intra-arterial chemotherapy as initial management and as salvage therapy for eyes with subretinal and/or vitreous seeds.

## MATERIALS AND METHODS

This is a retrospective, single institution, institutional review board-approved review of all retinoblastoma eyes with seeding treated at Memorial Sloan-Kettering Cancer Center between May 2006 and August 2010. The technique for intra-arterial chemotherapy has been described previously in detail.<sup>15</sup> Patients were evaluated with monthly examinations under anaesthesia with indirect ophthalmoscopy and RetCam imaging. The A and B ultrasound scan and modified electroretinogram (ERG) protocol (previously described<sup>15</sup>) were performed when clinically indicated. All statistical analyses were conducted using SAS software, V.9.2. The Kaplan–Meier method was used to estimate time to enucleation separately for treatment-naïve eyes and eyes that had received previous treatment. Median follow-up time was calculated for eyes that were not enucleated. The minimum length of follow-up for any patient was 1 year. Analyses were stratified by vitreous seeding only, subretinal seeding only, or both vitreous and subretinal seeding.

## RESULTS

There were 76 eyes of 67 patients included in this study (nine patients had bilateral disease). Patient-level characteristics are presented in table 1 and eye-level characteristics are presented in table 2. There were 20 enucleations overall, eight of which were in eyes with only vitreous seeding, five were in eyes with only subretinal seeding, and seven were in eyes with both vitreous and subretinal seeding. Median follow-up for surviving eyes was 2.04 years (range 0.19–5.04). Among treatment-naïve eyes, the 2-year probability of ocular salvage was 83% (95% CI 27% to 97%) for eyes with subretinal seeding only, 64% (95% CI 24% to 87%) for eyes with vitreous seeding only, and 80% (95% CI 40%

**Table 1** Patient-level characteristics overall and by vitreous seeding (VS), subretinal seeding (SRS) or both

	VS only (n=27)	SRS only (n=13)	Both VS and SRS (n=27)	Overall (n=67)
Age, median (IQR)	23.0 (6.0–95.0)	18.0 (3.0–41.0)	18.0 (5.0–62.0)	18.0 (3.0–95.0)
Sex, N (%)				
Female	14 (51.9)	3 (23.1)	19 (70.4)	36 (53.7)
Male	13 (48.1)	10 (76.9)	8 (29.6)	31 (46.3)
Family history, N (%)				
No	24 (88.9)	13 (100.0)	23 (85.2)	60 (89.6)
Yes	3 (11.1)	0 (0.0)	4 (14.8)	7 (10.4)
Years of follow-up, median (range)	1.8 (0.2–3.0)	2.2 (0.2–4.6)	1.6 (0.2–5.0)	1.7 (0.2–5.0)

to 95%) for eyes with both. Among eyes that received previous treatment, the 2-year probability of ocular salvage was 50% (95% CI 15% to 78%) for eyes with subretinal seeding only, 76% (95% CI 48% to 91%) for eyes with only vitreous seeding, and 54% (95% CI 20% to 79%) for eyes with both.

Two patients developed metastatic retinoblastoma (and have previously been reported on<sup>14</sup>) and are in remission. No patient died from disease, treatment-related complications or second cancers. No patient received external beam irradiation after intra-arterial chemotherapy.

Overall, 33 (43.4%) eyes received only one drug, 33 (43.4%) received two drugs, and 10 (13.2%) received three drugs during treatment. The number of cycles was dictated by the clinical response. Eyes with the best response received the fewest number of cycles. The majority (51 cases=67.1%) received three cycles or fewer.

Of the eyes that came to enucleation, some were retained for as long as 2.6 years; the median time for retention was 8.7 months (range 0.9–30.8).

## Electroretinogram

Flicker ERGs (30 Hz) were available before and after treatment with super-selective ophthalmic artery infusion of chemotherapy (SSOAIC) in 72 eyes. Improvement or worsening of the ERG was defined as >25 µV or <25 µV change. Forty-one eyes were unchanged, 14 were better, and 17 were worse.

## Additional treatments

Of the 76 eyes, 16 were cured with SSOAIC alone. Forty-three received supplemental laser, and 43 received supplemental

**Table 2** Eye-level characteristics overall and by vitreous seeding (VS), subretinal seeding (SRS) or both

	VS only (n=31)	SRS only (n=15)	Both VS and SRS (n=30)	Overall (n=76)
IC group, N (%)				
C	14 (45.2)	1 (6.7)	2 (6.7)	17 (22.4)
D	14 (45.2)	12 (80.0)	23 (76.7)	49 (64.5)
E	3 (9.7)	2 (13.3)	5 (16.7)	10 (13.2)
RE group, N (%)				
5A	0 (0.0)	8 (53.3)	0 (0.0)	8 (10.5)
5B	31 (100.0)	7 (46.7)	30 (100.0)	68 (89.5)
Previous treatment, N (%)				
No	9 (29.0)	6 (40.0)	14 (46.7)	29 (38.2)
Yes	22 (71.0)	9 (60.0)	16 (53.3)	47 (61.8)
Type of previous treatment, N (%)				
1–2 systemic chemo treatments	5 (22.7)	2 (22.2)	2 (12.5)	9 (19.1)
3–6 systemic chemo treatments	9 (40.9)	4 (44.4)	7 (43.8)	20 (42.6)
>6 systemic chemo treatments	2 (9.1)	0 (0.0)	1 (6.3)	3 (6.4)
EBR only	0 (0.0)	1 (11.1)	0 (0.0)	1 (2.1)
EBR + any systemic chemo	3 (13.6)	1 (11.1)	6 (37.5)	10 (21.3)
Local treatment only	3 (13.6)	1 (11.1)	0 (0.0)	4 (8.5)
Number of drugs, N (%)				
1	12 (38.7)	7 (46.7)	14 (46.7)	33 (43.4)
2	15 (48.4)	6 (40.0)	12 (40.0)	33 (43.4)
3	4 (12.9)	2 (13.3)	4 (13.3)	10 (13.2)
Number of cycles, N (%)				
≤3	19 (61.3)	12 (80.0)	20 (66.7)	51 (67.1)
>3	12 (38.7)	3 (20.0)	10 (33.3)	25 (32.9)

Chemo, chemotherapy; EBR, external beam irradiation; IC, international classification; RE, Reese-Ellsworth; SRS, sub-retinal seeds; VS, vitreous seeds.

cryotherapy. Nine received plaques. Of the 29 naive cases, nine (31%) received only SSOAIC. Fifteen received additional laser, 13 additional cryotherapy, and seven plaques.

## DISCUSSION

Seeding of retinoblastoma is widely recognised as the most common reason for enucleation in naive or previously treated retinoblastoma in developed countries. In Reese's day, 75% of cases were group V, and most were primarily enucleated. Of the primarily radiated cases, only 20% could be salvaged.<sup>15</sup> He did not publish results on success in group Va versus Group Vb (ie, with and without vitreous seeding), but success in group Vb eyes was even lower than the 20% figure. In those days, almost all cases of failed radiation resulted in enucleation, so they represent what we now refer to as 'naive' cases. As radiation techniques became more sophisticated, he (then Ellsworth and then Abramson) had experience with eyes that had received two and even three courses of radiation.<sup>10</sup> Most eyes that did not respond to the first course of radiation were enucleated. Of the eyes that had vitreous seeds after the first course of radiation, only 2.2% were salvaged. Unfortunately, 35% of patients who received second and third courses of radiation died from metastatic retinoblastoma.<sup>10</sup>

Reese carried out most of his work with the direct ophthalmoscope and did not include subretinal seeding in his classification scheme. When the international classification scheme was introduced, it was recognised that subretinal seeding was an important predictor of failure after primary treatment with systemic, multiagent chemotherapy. Group C eyes have 'minimal subretinal or vitreous seeding' and are defined as having 'subretinal fluid, present or past, without seeding involving up to ¼ retina, local fine vitreous seeding may be present close to discrete tumour and local subretinal seeding less than 3 mm (2DD) from the tumour'. Group D eyes have some (not necessarily all) of the following features: 'diffuse disease with significant vitreous or subretinal seeding'. They are defined as: 'subretinal fluid present or past without seeding, involving up to total retinal detachment, diffuse or massive vitreous disease may include 'greasy' seeds or avascular tumour masses, and diffuse subretinal seeding may include subretinal plaques or tumour nodules'. Multiple studies have confirmed that group D eyes fare less well than group C eyes, and statements such as 'systemic chemotherapy can rarely cure vitreous seeding'<sup>16</sup> are common in the literature. Using a slightly different new classification scheme, Shields *et al* reported that retinoblastoma recurred in 45% of group C and D eyes.<sup>17</sup> They emphasised that, of naive eyes with subretinal seeds treated with multiagent systemic chemotherapy, retinoblastoma recurred in 62% within 3 years. In another report from Philadelphia, these authors emphasised that the 'presence of vitreous seeds and subretinal seeds... were factors associated with the need for enucleation'. Of 75 eyes with group V disease, 32 required additional radiation and 32 were enucleated (some required both).<sup>18</sup> These results were echoed by Beck *et al*, who noted that systemic chemotherapy for groups IV and V was 'disappointing'.<sup>19</sup> In the past year, a 100% failure rate (requiring enucleation) of group D eyes managed with systemic chemotherapy was reported from China.<sup>20</sup>

There has been more than one international retinoblastoma classification scheme published and used in the past 10 years, causing some confusion in interpreting data.<sup>21</sup> Nonetheless, even earlier series by investigators in many countries produced discouraging results for group V (or D) eyes. Of 24 such eyes

treated in England, 20 required radiation and six required enucleation.<sup>22</sup> Of 21 such eyes, Murphree *et al* reported the need for radiation in seven eyes and enucleation in 17.<sup>23</sup> Of six such eyes, Greenwald *et al* reported the need for radiation in five and enucleation in three.<sup>24</sup> Rodriguez-Galindo *et al* reported that, of 15 such eyes, eight required radiation and eight enucleation.<sup>25</sup>

Although comparisons are difficult because definitions throughout these studies are not standardised, our results are both notable and informative. Although eyes with subretinal seeding generally fare poorly with systemic chemotherapy, they fared better with intra-arterial chemotherapy. Overall, 83% of such eyes that were treatment naive and 50% of such eyes that had been previously treated were estimated to be salvaged without radiation at 2 years. Intra-arterially treated eyes with vitreous seeding alone did well compared with older reports of systemic chemotherapy, with estimated 2-year salvage rates of 64% for treatment naive and 76% for previously treated eyes. Although the success rate for eyes with both subretinal and vitreous seeds that had been previously treated was low (54% at 2 years), considering that this group had already failed to respond to previous management with systemic chemotherapy, focal treatments and occasionally radiation with a plaque or external beam and faced enucleation, such salvage rates represent an important step in retinoblastoma management.

Vitreous and subretinal seeding remain a challenge for clinicians treating intraocular retinoblastoma, but the success of intra-arterial chemotherapy in salvaging eyes (without the need for external beam irradiation) is encouraging. Most eyes with either vitreous seeding and/or subretinal seeding were saved with intra-arterial chemotherapy. These are precisely the eyes that usually do not respond to primary systemic chemotherapy or external beam irradiation. Although the success rate may be lower in previously treated eyes that progress after systemic chemotherapy and/or external beam irradiation, enucleation can be avoided in the majority of such eyes.

Finally, eyes that failed to respond to SSOAIC treatment and progressed to enucleation were retained for as long as 2 1/2 years (median 8.7 months). In some cases, it was the patient's remaining eye. It is hoped that these additional months or years of vision were of value to these patients, even though the eye could not ultimately be saved.

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