

INTRAARTERIAL CHEMOTHERAPY FOR RETINOBLASTOMA

History, technique, and update on outcomes.

BY RYAN S. KIM, BA; MARK J. DANNENBAUM, MD; AND AMY C. SCHEFLER, MD



Retinoblastoma is a rare malignant disease encountered in the pediatric population. Annually, an estimated 250 to 350 new cases of retinoblastoma are reported in the United

States.¹ Less advanced cases may be treated with focal therapies such as laser ablation or cryotherapy alone, but retinoblastoma with International Classification of Retinoblastoma (ICRB) grades of D or E usually require more invasive treatment, such as intraarterial chemotherapy (IAC).

Advances in the technique used to administer IAC have dramatically improved treatment outcomes and eye salvage rates for retinoblastoma across all ICRB groups (A through E) since the early 2000s. In this article, we briefly discuss the history and procedure of IAC and review the outcomes reported from recent large studies.

HISTORY OF IAC

In 1954, Reese and colleagues performed the first form of IAC for retinoblastoma by directly injecting triethylene melamine into the internal carotid arteries of patients to maximize the local concentration of chemotherapy.² In 2004, Japanese investigators reported a technique of temporarily occluding the distal flow in the internal carotid artery with a balloon and then injecting melphalan into the ophthalmic artery.³ In 2008, by using newer catheter technology, Abramson et al proposed a new method for superselective catheterization of the ophthalmic artery that many large centers in the world use today with slight variations.⁴

PROCEDURE OF IAC

IAC is performed under general anesthesia. After a 4-French pediatric arterial sheath is inserted into the femoral artery, 70 IU/kg to 75 IU/kg heparin is administered to prevent coagulation. A 1.3-mm diameter 4-French catheter

is used to catheterize the ipsilateral internal carotid artery, and angiograms are taken to visualize the angioanatomy and guide the accurate placement of the catheter into the ostium of the ophthalmic artery.

Once selective catheterization is complete, superselective injection with dye is performed to confirm the final position of the microcatheter and the flow into the ophthalmic artery without reflux into the ipsilateral internal carotid artery.

In some cases, the ophthalmic artery is not fully developed, or the access angle from the internal carotid artery is too acute, making it inappropriate for selective catheterization. In such cases, one of two alternative routes can be taken to achieve catheterization. The first option is to access the ophthalmic branch of the ipsilateral middle meningeal artery if sufficient flow to the globe has been established. The second option is the Japanese technique (mentioned above) of occluding the distal flow of the internal carotid artery with a balloon and injecting the chemotherapy indirectly into the ophthalmic artery.

Melphalan is the primary chemotherapeutic agent for IAC, but topotecan or carboplatin can be administered along with or instead of melphalan, depending on the patient's previous therapeutic history and his or her



AT A GLANCE

- Intraarterial chemotherapy (IAC) has been effective as primary therapy for treatment-naïve eyes with retinoblastoma and as a secondary therapy after previous failed treatments.
- IAC is a highly localized treatment modality with lower systemic effects than systemic chemotherapy.
- Reports of the treatment of retinoblastoma with IAC affirm the procedure's safety and efficacy.

TABLE. OUTCOMES OF IAC IN SELECTED STUDIES

Study	No. of Eyes	Total No. of Chemotherapy Injections; Median; Range per Patient	Drugs	% of Successful Catheterization (n/n)	Median Follow-up (months)	No. of Enucleated Eyes per Group	No. of Metastases After IAC; No. of Metastatic Deaths
Gobin ⁵	95	289; 3; 1-7	melphalan, topotecan, carboplatin, methotrexate	98.5% (255/259)	13	RE group I-IV: None RE group V: 19	2 (average of 8 months); 0
Suzuki ⁶	408	1452; 3; 1-18	melphalan	98.8% (1452/1469)	74	group A: 0/5 group B: 14/130 group C: 10/30 group D: 114/216 group E: 14/18 9 lost to follow-up	8; 8
Venturi ⁷	39	140; NA; 1-9	melphalan	92.1% (140/152)	13	RE group Vb: 8 Total: 8/34 2 lost to follow-up	0; 0
Shields ⁸	70	197; 3; 1-7	melphalan, topotecan, carboplatin	99.5% (197/198)	19 (mean)	Primary IAC: group B: 0/1 group C: 0/4 group D: 1/17 group E: 9/14 Secondary IAC: 13/34 Total: 23/70 eyes	0; 0
Taich ⁹	27	66; NA; NA	melphalan, topotecan	NR	11.7	9/27 eyes	0; 0
Ghassemi ¹⁰	24	33; NA; NA	melphalan, topotecan, carboplatin	80.5% (33/41)	14.6	group B: 0/1 group C: 2/2 group D: 6/18 group E: 1/3 Total: 9/24 eyes	0; 0
Akyüz ¹¹	56	124; NA; 1-7	melphalan	NR	11.9	Primary IAC: 3/12 Secondary IAC: 16/44 Total: 19/56 eyes	Unknown; 2
Total	719	2301; NR; NR	NR	98% (2077/2119)	NR	239/708* enucleated total group B: 14/132 group C: 12/36 group D: 121/251 group E: 24/35	10; 10

Abbreviations: IAC, intraarterial chemotherapy; ICRB, International Classification of Retinoblastoma; RE, Reese-Ellsworth; NA, not applicable; NR, not reported

*11 of 719 eyes total were lost to follow-up. The number of enucleations per ICRB group includes data from only three studies^{6,8,10} that followed the ICRB system and provided detailed post-IAC outcomes for each ICRB group.

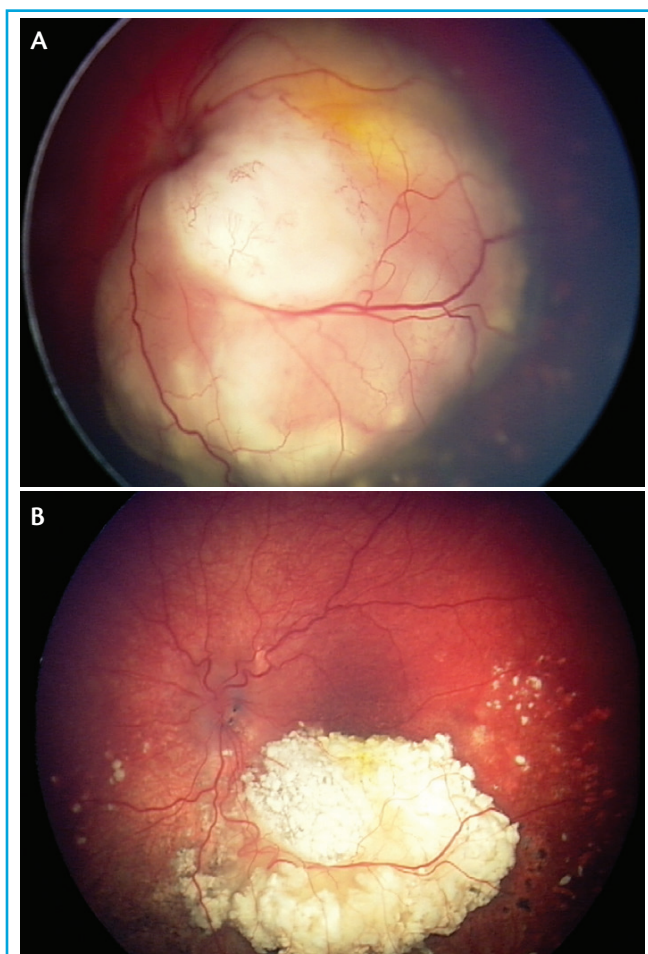


Figure 1. Fundus photo of the left eye of a 6-month-old child at retinoblastoma diagnosis. A large, white, dome-shaped tumor involving the temporal and inferotemporal quadrants posteriorly, obscuring the optic nerve, is evident. The vessels are engorged over the lesion (A). Fundus photo of the same eye after two cycles of IAC with a combination of melphalan, topotecan, and carboplatin. Note the treated retinoblastoma lesion with type 1 regression pattern along the inferotemporal arcade (B).

response to each drug (Figures 1 and 2). Chemotherapeutic drugs are diluted with 20 mL to 30 mL saline and are injected through a 1-cc microsyringe in a repetitive, pulsatile manner over 30 minutes for homogeneous drug delivery. After the injection, a superselective ophthalmic artery angiogram is performed through a microcatheter to verify patency of the artery (Figure 3), followed by an angiogram performed through a guide catheter in the internal carotid artery to evaluate the intracranial vasculature distally.

Before the procedure is completed, a femoral angiogram is performed. If there is a significant spasm of the vessel, then 50 mg to 200 mg nitroglycerin is infused into the femoral

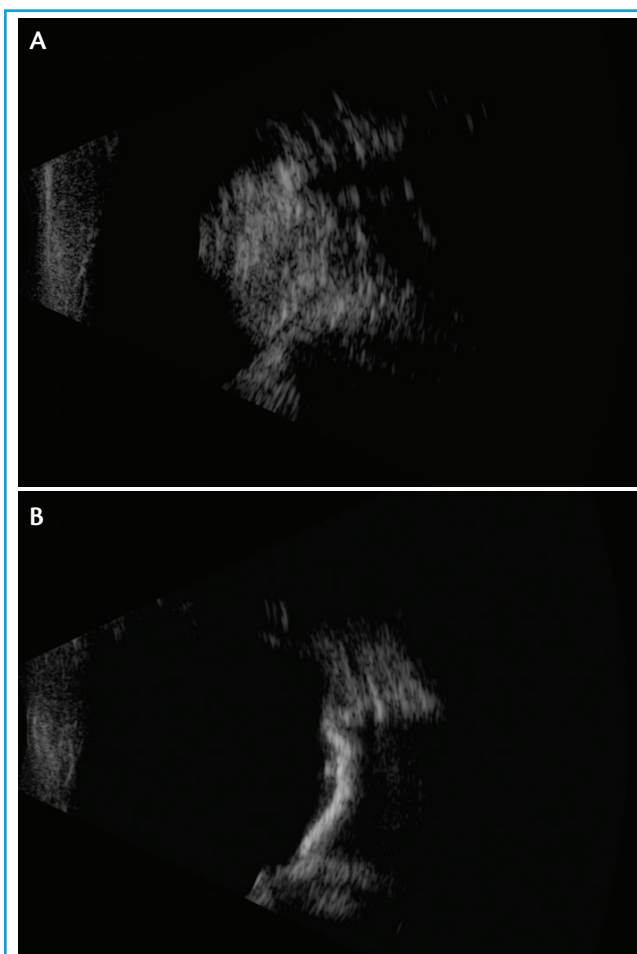


Figure 2. B-scan of the eye pictured in Figure 1 before IAC. A large, dome-shaped, partially calcified lesion extends from 2:30 to 6:00 posteriorly with dimensions of 14.5 mm by 19 mm in base and 9.7 mm in height. The lesion is hanging over the optic nerve. No vascularity is noted (A). B-scan image at 6 months postop showing the highly calcified scar (B).

artery sheath. The femoral sheath is then removed, and hemostasis is achieved using manual compression. The patient is usually discharged the same day or the day after, assuming no major complications arise during patient monitoring.

INDICATIONS FOR IAC

Multiple studies have demonstrated that IAC can be effective as primary therapy for treatment-naïve eyes or as secondary therapy after previously failed treatments, including systemic chemotherapy. IAC is particularly successful for eyes with more advanced disease (ICRB group D or E) compared with other treatment modalities, including systemic chemotherapy, external beam radiation (EBR), laser, and cryotherapy. Tandem therapy (bilateral chemotherapy in one session) can be used in

patients with bilateral retinoblastoma.

Patients who are relatively contraindicated for IAC include small infants weighing less than 6 kg, patients who have known metastatic retinoblastoma, patients who have neovascular glaucoma with vitreous hemorrhage and no view to the posterior segment, and patients who are unable to complete an extended treatment regimen (often lasting 1-2 years) due to financial or travel constraints.

REVIEW OF OUTCOMES

Since the middle of the preceding decade, multiple studies have reported outcomes of IAC for retinoblastoma. For the purpose of this article, we selected seven representative studies that are nonduplicative, that included more than 20 patients, and that were published in the past 5 years (Table).⁵⁻¹¹

In total, 719 eyes of 620 patients received IAC in these studies. The total rate of successful catheterization, excluding two studies with unknown success rates, was 98%. After successful catheterization, a total of 2301 individual drug injections were administered to patients. Three studies used only melphalan; one study used melphalan and topotecan; two studies used melphalan, topotecan, and carboplatin; and one study used melphalan, topotecan, carboplatin, and methotrexate.

The overall globe salvage rate was 66.2% (469 of 708 eyes; 11 patients were lost to follow-up^{6,7}). In the three reports that followed the ICRB system and provided detailed outcomes, 118 out of 132 group B eyes (89.3%), 24 out of 36 group C eyes (66.7%), 130 out of 251 group D eyes (51.8%), and 11 out of 35 group E eyes (31.4%) were salvaged. No enucleations were reported for group A eyes. A total of 10 patients with metastases were reported, as were 10 metastatic deaths.

Systemic Complications

Procedure-related nonocular complications such as groin hematoma, neurologic impairment, seizure, stroke, cerebral or femoral ischemia—all of which have been reported in the adult neurointerventional literature—are rare. Transient bronchospasm during the procedure is common and is thought to be related to the stimulation of the intracranial vasculature by microcatheters.¹² Patients who have undergone previous systemic chemotherapy appear to have an increased chance of developing grade 3 or 4 neutropenia after IAC. Incidence of metastatic retinoblastoma after IAC is also reported infrequently; within the seven studies included in this article, 10 metastases occurred in 620 patients, a rate of 1.6%. One recent review publication noted that there may be children with metastases whose cases have not been reported in the literature, but these have not been confirmed in any peer-reviewed papers and may

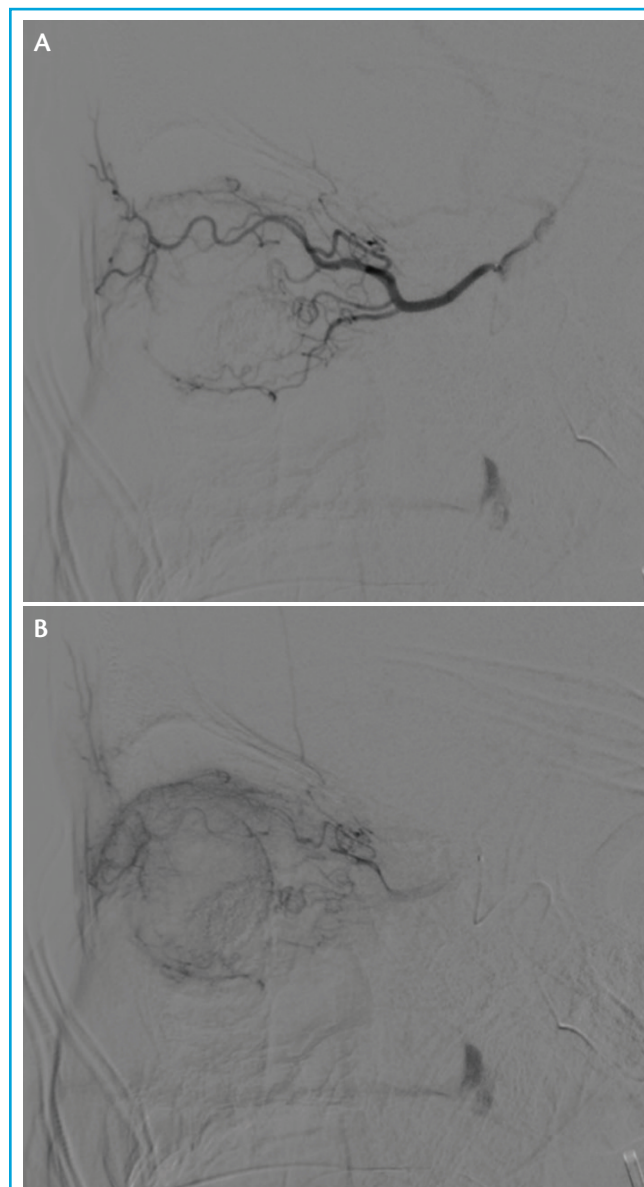


Figure 3. Image of superselective microcatheter injection (early phase) demonstrating opacification of the left ophthalmic artery, lateral view (A). Superselective microcatheter injection (late phase) demonstrating opacification of the ophthalmic artery, lateral view. The choroidal blush and the shadow of the globe and orbital structures are well visualized (B).

represent patients who did not complete the recommended treatment regimen.¹³

Ocular Complications

Eyelid edema, vitreous hemorrhage, hyperemia of the forehead, and temporary thinning or loss of eyelashes may occur postoperatively but are often transient. Changes in

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the retinal pigment epithelium are often a sign of disease resolution. Reported ocular complications include retinal artery occlusions, enophthalmos, choroidal occlusions, ophthalmic artery obstructions, vitreous hemorrhage, neovascular glaucoma, and retinal drug toxicity. Multiple authors have reported that ocular complications decrease with increasing levels of experience with this technique on the part of the neurointerventionalist.

A HIGHLY POTENT TECHNIQUE

Treatment of intraocular retinoblastoma has undergone rapid progress in the past decade. The globe salvage rate for unilateral group D retinoblastoma has been reported as between 78% and 91%.^{14,15} Furthermore, IAC helps prevent some serious adverse events caused by EBR and systemic chemotherapy, especially in patients who have a germinal RB1 mutation. It is well known that patients with Reese-Ellsworth group Vb disease who undergo EBR experience a higher risk of secondary cancer development compared with those who do not undergo EBR, due to the effects of ionizing radiation.¹⁶ In contrast, IAC is a highly localized treatment modality with comparatively lower systemic effects.

Outcomes of IAC for retinoblastoma have been outstanding. A review of patients treated in four large centers reported that only one of 634 patients treated with IAC died of metastatic retinoblastoma.¹⁷ Suzuki and colleagues, who have the longest period of follow-up (median 74 months), reported that the rate of metastasis in their study was stable, with 4.8% at 10 years and 5.8% at 15 years of follow-up.⁶

Nevertheless, there is always room for improvement with IAC techniques and the reporting of results for patients with retinoblastoma. Two classification systems (Reese-Ellsworth and ICRB) are used to categorize the severity of retinoblastoma at presentation, making it difficult to compare studies or perform meta-analyses. Also, because IAC

for retinoblastoma was developed without randomized multicenter trials, treatment protocols are not standard. Doses of drugs, the lower limit of patient size, the use of tandem therapy for bilateral cases, and the number of cycles vary widely among centers. Although multicenter collaborations are ideal, they are difficult to organize given the rare and variable nature of the disease. Nonetheless, most of the studies published on the subject of IAC for treatment of intraocular retinoblastoma reaffirm the safety and efficacy of this highly potent technique. ■

1. Scheffer AC, Abramson DH. Retinoblastoma: what is new in 2007–2008. *Curr Opin Ophthalmol*. 2008;19(6):526–534.
2. Reese AB, Hyman GA, Merriam GR Jr, et al. Treatment of retinoblastoma by radiation and triethylenemelamine. *AMA Arch Ophthalmol*. 1954;53(4):505–513.
3. Yamane T, Kaneko A, Mohri M. The technique of ophthalmic arterial infusion therapy for patients with intraocular retinoblastoma. *Int J Clin Oncol*. 2004;9(2):69–73.
4. Abramson DH, Dunkel IJ, Brodie SE, et al. A phase I/II study of direct intraarterial (ophthalmic artery) chemotherapy with melphalan for intraocular retinoblastoma: initial results. *Ophthalmology*. 2008;115(8):1398–1404, 1404.e1.
5. Gobin YP, Dunkel IJ, Marr BP, et al. Intra-arterial chemotherapy for the management of retinoblastoma: four-year experience. *Arch Ophthalmol*. 2011;129(6):732–737.
6. Suzuki S, Yamane T, Mohri M, Kaneko A. Selective ophthalmic arterial injection therapy for intraocular retinoblastoma: the long-term prognosis. *Ophthalmology*. 2011;118(10):2081–2087.
7. Venturi C, Bracco S, Cerase A, et al. Superselective ophthalmic artery infusion of melphalan for intraocular retinoblastoma: preliminary results from 140 treatments. *Acta Ophthalmol*. 2013;91(4):335–342.
8. Shields CL, Manjandavida FP, Lally SE, et al. Intra-arterial chemotherapy for retinoblastoma in 70 eyes: outcomes based on the international classification of retinoblastoma. *Ophthalmology*. 2014;121(7):1453–1460.
9. Taich P, Ceciliano A, Buitrago E, et al. Clinical pharmacokinetics of intra-arterial melphalan and topotecan combination in patients with retinoblastoma. *Ophthalmology*. 2014;121(4):889–897.
10. Ghassemi F, Ghanaati H, Karkhaneh R, et al. Outcome of retinoblastoma following limited sessions of intra-arterial chemotherapy in Iran. *Iran J Radiol*. 2014;11(3):e16958.
11. Akyüz C, Kiratlı H, Sen H, et al. Intra-arterial chemotherapy for retinoblastoma: a single-center experience. *Ophthalmologica*. 2015;234(4):227–232.
12. Kato MA, Green N, O'Connell K, et al. A retrospective analysis of severe intraoperative respiratory compliance changes during ophthalmic arterial chemosurgery for retinoblastoma. *Paediatr Anaesth*. 2015;25(6):595–602.
13. Yousef YA, Soliman SE, Astudillo PP, et al. Intra-arterial chemotherapy for retinoblastoma: a systematic review [Published online ahead of print March 17, 2016]. *JAMA Ophthalmol*.
14. Shields CL, Jorge R, Say EA, et al. Unilateral retinoblastoma managed with intravenous chemotherapy versus intra-arterial chemotherapy. Outcomes based on the International Classification of Retinoblastoma. *Asia Pac J Ophthalmol (Phila)*. 2016;5(2):97–103.
15. Abramson DH. Retinoblastoma: saving life with vision. *Annu Rev Med*. 2014;65:171–178.
16. Scheffer AC, Kleiner RA, Abramson DH. Genes and environment: effects on the development of second malignancies in retinoblastoma survivors. *Expert Rev Ophthalmol*. 2008;3(1):51–61.
17. Abramson DH, Shields CL, Munier FL, Chantada GL. Treatment of retinoblastoma in 2015: agreement and disagreement. *JAMA Ophthalmol*. 2015;133(11):1341–1347.

Mark J. Dannenbaum, MD

- neurosurgeon at the University of Texas McGovern Medical School, Mischel Neuroscience Institute, Memorial Hermann Hospital, all in Houston
- financial interest: none acknowledged
- mark.dannenbaum@uth.tmc.edu

Ryan S. Kim, BA

- research assistant at Retina Consultants of Houston; medical student at the University of Texas McGovern Medical School, both in Houston; planning to matriculate in the fall of 2016
- financial interest: none acknowledged
- ryan.sangwoo.kim@gmail.com

Amy C. Scheffer, MD

- surgeon at Retina Consultants of Houston; surgeon at Children's Memorial Hermann Hospital, both in Houston, Texas
- financial interest: none acknowledged
- +1-713-524-3434; acsmd@houstonretina.com