Original Article

Management of retinoblastoma in older children (>5 years) using intra-arterial chemotherapy: Comparison of outcomes to prechemotherapy and intravenous chemotherapy eras

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Purpose: Intra-arterial chemotherapy (IAC) has emerged as an effective treatment for retinoblastoma (RB) however, little information exists regarding its use in older patients (>5 years). In the present study, we evaluate the use of IAC (2008–2018) for RB in older patients and compare the outcomes to those in the prechemotherapy (<1994) and intravenous chemotherapy (IVC) (1994–2007) eras. **Methods:** A retrospective analysis of all patients older than 5 years treated with IAC for RB from 2008–2018. Comparisons were made to 26 active RB cases in older children treated in the prechemotherapy era and to 12 active RB cases treated in the IVC era. **Results:** There were 13 eyes with RB in 13 older patients treated in the IAC era. The median patient age was 6.8 years. Tumor response was achieved in all 13 eyes at a median interval of 1.1 months from first IAC. Globe salvage was achieved in eight eyes with five eyes requiring enucleation. At 14 months, median follow-up after IAC, there was no metastasis or death. Compared to the prechemotherapy era, those in the IAC era demonstrated significant reduction in need for enucleation ($P < 0.001$) and EBRT or enucleation ($P < 0.001$). Compared to the IVC era, there was significant reduction in need for EBRT ($P = 0.02$) and EBRT or enucleation ($P = 0.03$) and similar avoidance of metastasis ($P > 0.99$) and death ($P > 0.99$). **Conclusion:** Older patients with RB managed in the IAC era demonstrated reduced need for EBRT or enucleation compared to those managed in the IVC or prechemotherapy eras, with no instance of metastasis or death.

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_642_19

Quick Response Code:

Key words: Children, eye, IAC, older, retinoblastoma

A majority (95%) of retinoblastoma (RB) cases occur in children under the age of 5 years; however, RB can be present in older children and even manifest in adults, with the oldest published patient demonstrating newly diagnosed RB at 74 years of age.[1-8] Older children and adults with newly diagnosed RB tend to present with more disease, often requiring enucleation. In a literature search of 45 published cases of adult-onset RB from 1919 to 2015, globe salvage was achieved in only two cases (4%).[1]

The efficacy and safety of intra-arterial chemotherapy (IAC) have been established in several studies;[9-16] revealing approximately 67% globe salvage even with advanced eyes and minimal local toxicity to the globe, especially in recent years, as published from our center and others.[14-16] However, little information is available on the results of IAC for older children and adults. In this retrospective analysis, we explore the use of IAC for RB in older patients and compare results to previously published reports representing data from the prechemotherapy era (<1994)[2] and the intravenous chemotherapy (IVC) era (1994–2007).[17]

Methods

This analysis was compliant to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the Wills Eye Hospital, Philadelphia, Pennsylvania. All patients from the ocular oncology service with RB and age ≥5 years were reviewed. Those treated with IAC as a primary or secondary measure were selected for analysis. Patients less than 5 years of age were excluded from the study. This analysis was compliant to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the Wills Eye Hospital, Philadelphia, Pennsylvania.

All patients were examined under anesthesia when necessary, using indirect ophthalmoscopy and fundus details were documented using large fundus drawings, external photography, wide-angle fundus photography, fluorescein angiography, B-scan ultrasonography, and optical coherence tomography. The procedure for IAC has been described elsewhere.[9,10]

Recorded data included age at diagnosis, race, sex, symptom, hereditary pattern of RB (familial, sporadic), affected eye (right, left, both), age at treatment, and visual acuity. Each eye was classified according to the International Classification for International Classification for Retinoblastoma (ICRB).[18,19] Each

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Received: 31-Mar-2019 Revision: 29-May-2019
Accepted: 10-Jul-2019 Published: 22-Nov-2019

Cite this article as: Selzer EB, Welch RJ, Jabbour P, Leahey AM, Shields CL. Management of retinoblastoma in older children (>5 years) using intra-arterial chemotherapy: Comparison of outcomes to prechemotherapy and intravenous chemotherapy eras. Indian J Ophthalmol 2019;67:2005-11.

tumor was evaluated for largest basal dimension, thickness, proximity to the optic disc, and foveola (in mm), associated subretinal or vitreous seeds, macular subretinal fluid, and anterior segment tumor. Treatment with IAC was characterized by a number of cycles, agents used (melphalan, topotecan, carboplatin), and cumulative dose. Additional treatments including intravitreal chemotherapy, IVC, plaque radiotherapy, and external beam radiation therapy (EBRT) were noted. After each cycle of IAC, tumor response was observed clinically and documented photographically and ultrasonographically. Visual acuity following treatment was documented.

Comparisons to historical data were performed to evaluate differences in the need for EBRT, enucleation, EBRT or enucleation, and the development of metastasis and death. All 13 cases were compared to 26 active RB cases in older children treated in the prechemotherapy era,[2] and 10 of the 13 cases (those with unilateral RB only) were compared to 12 active unilateral RB cases in a series treated with IVC.[17] Data were compiled in Microsoft Excel (2016) and measures of central tendency were calculated. Statistical comparisons were made using a two-sided Fisher's exact test. P values < 0.05 were considered statistically significant.

Results

In this study, there were 13 eyes with RB in 13 older patients (>5 years) that received IAC. Patient demographic and clinical features are listed in Table 1. The median patient age at the time of IAC was 6.8 years (mean 10.1, range 5.2-32.3 years). The patients were male (7/13, 54%) and white (11/13, 84%). The median visual acuity on presentation was 20/100 (mean 20/400, range 20/20-light perception (LP)). Patients presented a median of 1 tumor per eye (mean 1.5, range 1–8). The eyes were classified as either group D (n = 9, 69%) or group E (n = 4, 31%) according to ICRB [Fig. 1]. Three patients had bilateral RB, but only one eye was treated with IAC in each case.

The median largest basal tumor dimension was 16 mm (mean 15.2, range: 7–24 mm) with a median thickness of 7 mm (mean 7, range 3–14 mm) as measured by ultrasonography. Tumors were a median of 2 mm from the foveola (mean 3.5, range 0–9 mm) and 3 mm from the optic disc (mean 3.6, range 0–10 mm). Vitreous seeding was present in 12 patients (92%), subretinal seeding in six patients (46%), and no view of the retina in three patients (23%). Anterior segment seeding was present in three patients (23%).

Treatment and outcomes are listed in Table 2. Intra-arterial chemotherapy was primary therapy (n = 8, 62%) or secondary therapy (n = 5, 38%). Previous treatments included IVC (n = 4), plaque radiotherapy (n = 1), intravitreal chemotherapy (n = 1), or EBRT (n = 1). The median number of IAC cycles was 3 (mean 3.6, range 2–7 cycles). A median cumulative dose of 20 mg of melphalan (mean 19.6, range 10–45 mg), 3 mg topotecan (mean 2.6, range 1–4 mg), and 0 mg of carboplatin (mean 9.2 mg, range 0–120 mg).

Initial tumor response was observed in all 13 eyes at a median interval of 1.1 months (mean 1.3, range 0.9–2.3 months) [Fig. 1]. The globe was salvaged in eight eyes (62%) and enucleation was necessary in five eyes (38%) for reasons of recurrence of solid tumor (n = 2), vitreous seeds (n = 2), or subretinal seeds (n = 1). Two of the three eyes with anterior segment seeding were enucleated due to recurrent seeding. There was no instance of metastasis or death after a median follow-up of 14 months. Of the eight eyes in which globe salvage was achieved, the median

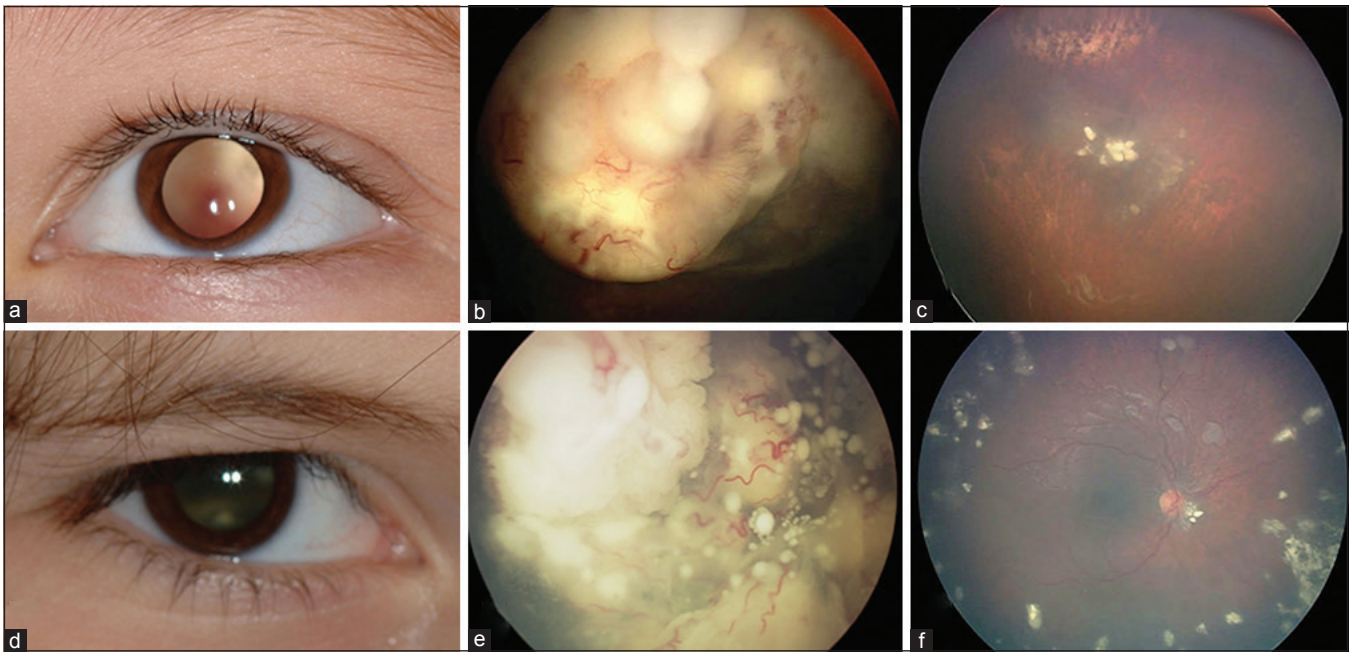

Figure 1: Retinoblastoma in older children. A 71-month-old female with unilateral leukocoria (a) and funduscopy (b) demonstrating a large group D retinoblastoma. Following six cycles of intra-arterial chemotherapy and six intravitreal chemotherapy injections, (c) the tumor demonstrated rapid reduction, but recurrent subretinal seeds lead to enucleation per parent request. An 81-month-old female with unilateral leukocoria (d) and funduscopy (e) demonstrating a large group E retinoblastoma. Following four cycles of intra-arterial chemotherapy and six intravitreal chemotherapy injections, (f) tumor control was achieved with ultimate globe salvage

Table 1: Intra-arterial chemotherapy (IAC) for retinoblastoma in older patients (>5 years): Patient demographics and clinical features at the time of IAC

Features	Number (%), *n*=13 eyes, 13 patients
Median age at RB diagnosis, years (mean, range)	6.7 (9.4, 2.5-28.9)*
Median age at IAC, years (mean, range)	6.8 (10.1, 5.2-32.3)
Sex	
Male	7 (54)
Female	6 (46)
Race	
White	11 (84)
Black	1 (8)
Asian	1 (8)
Laterality	
Unilateral RB	10 (77)
Bilateral RB	3 (23)
Eye treated with IAC, n=13 eyes	
Right eye	10 (77)
Left eye	3 (23)
ICRB group of the eye treated with IAC	
A	0 (0)
B	0 (0)
C	0 (0)
D	9 (69)
E	4 (31)
Visual acuity at IAC, median (mean, range)	20/100 (20/400, 20/20-LP)
Number of tumors per eye, median (mean, range)	1 (1.5, 1-8)
Median largest basal diameter, mm (mean, range)	16 (15.2, 7-24)
Median thickness by ultrasound, mm (mean, range)	7 (7.0, 3-14)
Median distance to fovea, mm (mean, range)	2 (3.5, 0-9)
Median distance to optic disc, mm (mean, range)	3 (3.6, 0-10)
Vitreous seeding	
Present	12 (92)
Absent	1 (8)
Subretinal seeding	
Present	6 (46)
Absent	4 (31)
No view	3 (23)
Anterior segment seeding	
Present	3 (23)
Absent	10 (77)

*One patient was diagnosed at age 2.5 years and treated with systemic chemotherapy and plaque radiation; he was not treated with IAC until age 5.8 years.
IAC=Intra-arterial chemotherapy; RB=Retinoblastoma; ICRB=International Classification of Retinoblastoma; mm=millimeter

visual acuity was 20/400 (mean: 20/400, range 20/30-light perception). Each patient course is listed in Table 3.

In Table 4, a comparison of these 13 older patients with RB managed with IAC versus 26 older patients with active RB treated in the prechemotherapy era is listed. Patients treated with IAC demonstrated a significant reduction in need for enucleation (P value <0.001) and EBRT or enucleation ($P < 0.001$), along with insignificant reductions in the need for EBRT ($P = 0.07$). There was no difference in prevention of metastasis ($P = 0.28$) or death ($P = 0.28$).

In Table 5, a comparison of 10 older patients with unilateral RB treated with IAC versus 12 older patients with unilateral RB (Reese-Ellsworth group V) treated with IVC is listed. There was significant reduction in need for EBRT (P-value = 0.02) and EBRT or enucleation ($P = 0.03$) in those treated with IAC, insignificant reduction in enucleation ($P = 0.23$). There was no difference in prevention of metastasis ($P > 0.99$) or death ($P > 0.99$).

Discussion

There have been few published series on the topic of RB in older children.[1-8] In most series, management was enucleation for all subjects.[1-8] The largest published series of RB in older patients revealed enucleation in 24 out of 26 cases (92%),[2] and a review of published case reports and case series revealed enucleation in 43 of 45 cases (96%).[1] In those large cohorts, metastases occurred in 15% and death in 7%.[1,2] An additional comprehensive study in 1986, on the effect of age at diagnosis of RB on patient survival in 1147 patients, revealed retinoblastoma-related mortality for young patients (0–1 years) was 4.6%, for intermediate age patients (1–2 years) was 8.9%, for older patients (2–7 years) was 19%, and for the oldest

Table 2: Intra-arterial chemotherapy (IAC) for retinoblastoma in older patients (>5 years): Treatments and outcomes

Features	Number (%), *n*=13 eyes
Type of IAC treatment	
Primary	8 (62)
Secondary	5 (38)
Treatment before IAC	
None	8
IVC	4
IVT	1
External beam radiotherapy	1
Plaque*	1
Treatments following initial IAC	
None	2
IVT	5
Enucleation	2
IVT + enucleation	2
IVT + plaque	1
IVT + plaque + enucleation	1
Total number of IAC cycles, median (mean, range)	3 (3.6, 2-7)
Cumulative melphalan dose, mg, median (mean, range)	20 (19.6, 10-45)
Cumulative topotecan dose, mg, median (mean, range)	3 (2.6, 1-4)
Cumulative carboplatin dose, mg, median (mean, range)†	0 (9.2, 0-120)
Total number of IVT injections, median (mean, range)	4 (3.8, 0-6)
Cumulative melphalan dose, µg, median (mean, range)	92.5 (79.2, 0-145)
Cumulative topotecan dose, µg, median (mean, range)	0 (28.3, 0-120)
Initial tumor response achieved	13 (100)
Median time to tumor response after initial IAC, months (mean, range)	1.13 (1.26, 0.90-2.33)
Median length of follow-up after IAC, months (mean, range)	13.8 (16.5, 1.9-39.8)
Enucleation	5 (38)
Metastasis	0 (0)
Death	0 (0)

IAC=Intra-arterial chemotherapy; IVC=Intravenous chemotherapy; IVT=Intravitreous chemotherapy; Plaque=Radioactive iodine brachytherapy with tumor apex dose of 35 Gy; *This patient received 3 plaques prior to IAC with tumor apex doses of 40 Gy, 40 Gy, and 35 Gy; mg=Milligram; †Carboplatin used in a single case; µg=Microgram; HM=Hand motions; LP=light perception

patients (7 years) was 2%.[20] Since the publication of that report 33 years ago, survival has improved conclusively.[21]

More recently, we and others have employed IAC for moderate to advanced RB, particularly in patients with unilateral disease.[9-14,21,22] In a cohort of 70 eyes with RB managed with IAC in patients of all ages; we achieved complete tumor control with globe salvage in 72% of those treated primarily and 62% of those treated secondarily (after the failure of other treatments).[13] In that series, none of the patients developed metastatic disease or had a serious adverse event such as cerebrovascular accident, despite catheterization of the internal carotid artery. An international collaborative effort from six major RB centers, including ours, evaluating 1177 eyes of 1139 patients with RB managed with IAC found metastatic disease and death in three patients (<1%), all treated in South America and with difficulty in follow-up.[22] This compelling evidence provides the support that IAC can adequately control RB with little risk for metastasis and death.

In this analysis, we evaluated a unique subset of patients older than the age of 5 years to explore if IAC provided adequate control for this older cohort. At a median of 14 months follow-up, we found compelling evidence that IAC was safe and effective for these patients, with the need for additional EBRT in no case, enucleation in 5 cases, and metastasis and death in no case. The patients in this series had advanced RB with ICRB group D (n = 9) or E (n = 4) as is typical in older patients presenting with RB.

Further, comparison of this older cohort managed in the IAC era (2008-2018) versus a similar cohort managed in the prechemotherapy era (<1994) revealed significant reduction in the need for enucleation (P value <0.001) and EBRT or enucleation ($P < 0.001$). Moreover, comparison of those in the IAC era to those in the IVC era (1994-2007), revealed significant reduction in EBRT ($P = 0.02$) and EBRT or enucleation ($P = 0.03$), and similar prevention of metastasis ($P > 0.99$) and death ($P > 0.99$). Both of these comparisons support our observations that IAC is more effective than IVC or older methods in avoiding EBRT and/or enucleation, without risking tumor-related metastasis.

There are limitations to our analysis as we realize that these older patients are from published cohorts at different eras, and staging and treatment strategies have evolved over time. In addition, our evaluation of RB in older children during the IAC era included only those selected for IAC, while there were others who were managed with enucleation, deemed not suitable for IAC. Furthermore, our comparison of IAC to IVC for unilateral RB included all ages and might not be directly comparable to our older children described herein.

Table 3: Summary of demographics, treatment, and outcomes in 13 older patients (>5 years) with retinoblastoma treated with intra-arterial chemotherapy (IAC)

Case No.	Findings at the time of IAC				IAC characteristics				IVT characteristics	Outcomes			
	Age (year)/sex/ laterality	ICRB Group	Visual Acuity	Prior treatment	Total number of IAC cycles	Cumulative Melphalan dose (mg)	Cumulative Topotecan dose (mg)	Cumulative Carboplatin dose (mg)	Total number of IVT injections	Enucleation	Metastasis/ Death	Total follow up (mo)	Visual acuity at last follow up
1	5.2/F/uni	D	20/20	None	3	15	2	0	6	Yes	No	13.9	Enuc
2	5.2/F/bi	D	20/50	IVC	2	10	2	0	6	No	No	5.0	NA
3	5.8/F/uni	D	LP	None	3	15	3	0	0	No	No	11.3	20/200
4	5.8/M/bi	D	20/100	IVC/plaque	7	45	1	0	3	Yes	No	74.5	Enuc*
5	5.9/F/uni	D	20/60	None	6	27	3	0	6	Yes	No	15.0	Enuc
6	6.1/M/bi	E	20/100	IVC	4	20	0	120	0	Yes	No	22.7	Enuc
7	6.8/F/uni	E	20/100	None	4	20	4	0	6	No	No	17.1	20/400
8	7.2/M/uni	E	20/200	IVC/IVT	2	10	2	0	6	No	No	12.9	20/400
9	8.6/M/uni	D	CF	None	3	20	3	0	4	No	No	39.9	20/30
10	9.6/F/uni	D	LP	None	3	15	0	0	0	No	No	1.9	HM
11	9.9/M/uni	E	LP	None	4	20	0	0	0	Yes	No	10.3	Enuc
12	23.1/M/uni	D	20/70	None	3	15	3	0	4	No	No	8.1	20/30
13	32.3/M/uni	D	20/70	EBRT	3	22.5	2	0	4	No	No	71.0	20/400

*Received plaque after initiation of IAC, prior to enucleation; IAC=intraarterial chemotherapy; IVT=intravitreal chemotherapy; Uni=unilateral; Bi=bilateral; ICRB=international classification of retinoblastoma; mg=milligram; mo=month; LP=light perception; HM=hand motions; F and F=fix and follow; EBRT=external beam radiotherapy; IVC=intravenous chemotherapy (systemic chemotherapy); Plaque=radioactive iodine brachytherapy; NA=not available; Enuc=enucleation

Table 4: Outcomes of retinoblastoma management in older children (>5 years) in the intra-arterial chemotherapy (IAC) era (2008-2018) vs. the prechemotherapy era (<1994)

Outcome	Prechemotherapy era* <1994 *n*=26	IAC era 2008-2018 *n*=13	*P*
Need for EBRT, no. (%)			0.07
EBRT	7 (27%)	0 (0%)	
No EBRT	19 (73%)	13 (100%)	
Need for enucleation, no. (%)			<0.001
Enucleation	24 (92%)	5 (38%)	
No enucleation	2 (8%)	8 (62%)	
Need for EBRT or Enucleation, no. (%)			<0.001
EBRT or Enucleation	26 (100)	5 (38%)	
No EBRT or Enucleation	0 (0)	8 (62%)	
Development of Metastasis, no. (%)			0.28
Metastasis	4 (15%)	0 (0%)	
No Metastasis	22 (85%)	13 (100%)	
Development of Death, no. (%)			0.28
Death	4 (15%)	0 (0%)	
No Death	22 (85%)	13 (100%)	

*Data from Shields CI, Shields JA, Shah P. Retinoblastoma in older children. Ophthalmology1991;98 (3):395-399; EBRT=External beam radiotherapy

Table 5: Outcomes of retinoblastoma management in older children (>5 years) in the intra-arterial chemotherapy (IAC) era (2008-2018) vs. the intravenous chemotherapy (IVC) era (1994-2007)

Outcome	IVC era* 1994-2007 *n*=12	IAC era 2008-2018 *n*=10†	*P*
Need for EBRT, no. (%)			0.02
EBRT	6 (50%)	0 (0%)	
No EBRT	6 (50%)	0 (0%)	
Need for enucleation, no. (%)			0.23
Enucleation	7 (58%)	3 (30%)	
No enucleation	5 (42%)	7 (70%)	
Need for EBRT or Enucleation, no. (%)			0.03
EBRT or Enucleation	10 (83%)	3 (30%)	
No EBRT or Enucleation	2 (17%)	7 (70%)	
Development of Metastasis, no. (%)			>0.99
Metastasis	0 (0%)	0 (0%)	
No Metastasis	12 (100%)	10 (100%)	
Development of Death, no. (%)			>0.99
Death	0 (0%)	0 (0%)	
No Death	0 (100%)	10 (100%)	

*Twelve patients with Reese-Ellsworth group V retinoblastoma. Data from Shields CL, Honavar SG, Meadows AT, *et al*. Chemoreduction for unilateral retinoblastoma. *Arch Ophthalmol* 2002;120 (12):1653-1658; †Only the 10 cases of unilateral RB from this series were used in this comparison; EBRT=External beam radiotherapy

However, it has been shown that RB in older children tends to be more advanced with greater risk for metastasis and death.[20] The globe salvage and survival rates in this study cannot be attributed solely to IAC, as IVT and prior therapies are equally contributory. In addition, longer follow-up regarding metastasis and death is preferred and our study is limited by a relatively short follow-up interval.

Conclusion

In summary, we present 13 cases of RB in older children treated with IAC and with ultimate globe salvage in 62% and with no evidence of metastasis or death. Despite most eyes having advanced disease, IAC was safe and effective. Furthermore, comparisons to similar cohorts treated in the prechemotherapy and IVC eras suggested a reduction in need for additional EBRT and/or enucleation. We advise that selected older children with RB could be managed successfully with IAC.

Acknowledgements

We would like to acknowledge Kunal Malik for his help in creating the spreadsheet used for data collection.

Financial support and sponsorship

Support provided by the Eye Tumor Research Foundation, Philadelphia, PA (CLS). The funders had no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, or in the preparation, review or approval of the manuscript. All authors have met the criteria for inclusion and the manuscript has been read and approved by all authors. Carol Shields, M.D. has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. No conflicting relationship exists for any author.

Conflicts of interest

There are no conflicts of interest.

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