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# Ophthalmic artery chemosurgery for retinoblastoma: an initial 3-year experience from two major institutes in Egypt

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## Abstract

**Background:** Intra-arterial chemotherapy has shown promising results and improved the prognosis of retinoblastoma in the developed countries. Here, we aim to report our initial experience, in Egypt, in the treatment of all stages of naïve retinoblastoma with ophthalmic artery chemosurgery (OAC), using melphalan.

**Results:** The technique was successful in 23 out of 26 eyes. Overall, a total of 63 treatment sessions were performed. Ophthalmic artery catheterization was performed in 59 treatment sessions, whereas middle meningeal artery catheterization was performed in 4 treatment sessions. Adequate tumor control was achieved in 95.6%. Progression has developed in one eye after the third OAC session. The mean follow-up period was 18.5 months. Recurrence of the main tumor as well as vitreous and subretinal seeds was reported in one eye after 19-month duration. A globe salvage rate of 91.3% was attained. No metastasis was recorded, and all patients were alive within the stated follow-up period.

**Conclusion:** A high globe salvage rate along with metastasis free survival and mild complications were achieved. Therefore, our initial experience with OAC in primary retinoblastoma proved to be safe and effective.

**Keywords:** Developing countries, Retinoblastoma, Ophthalmic artery chemosurgery, Melphalan

## Background

Retinoblastoma is the most common pediatric intraocular neoplasm. It remains a significant health problem, particularly in the developing countries [1]. For both unilateral and bilateral diseases, enucleation used to be the main treatment strategy to cure patients and maintain their survival [2]. Yet, this was at the expense of the globe and vision salvage. In more advanced stages, external beam radiation was the alternative treatment procedure that provided globe salvage [3]. This was, however,

associated with a high rate of second cancer which, in most cases, might have been more fatal than the retinoblastoma [4]. Therefore, systemic intravenous chemotherapy was proposed to reduce the harmful effect of radiotherapy [5] and was frequently used in combination with other focal therapies such as laser or cryotherapy. Some major systemic complications, however, were associated with systemic chemotherapy such as acute myeloid leukemia and neutropenia [6]. Intra-arterial chemotherapy through the carotid artery was introduced early to save the globe and to minimize the radiation exposure and the systemic side effects [7]. The regimen has been modified afterward, to include selective ophthalmic artery infusion chemotherapy, which has been

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developed by the Japanese [8, 9]. Eventually, the super-selective ophthalmic artery chemotherapy, which is also known as ophthalmic artery chemosurgery (OAC), has introduced by Abramson et al. [10].

The use of OAC has been increased, gradually, to be the first choice of retinoblastoma treatment in the developed countries. Consequently, the enucleation rate has been reduced from 95 to about 10% [11] with the estimated survival rate of retinoblastoma exceeds 95% in the developed countries [12]. OAC was implemented, however, in a small percent of low- and middle-income countries [1]. Thus, the enucleation rate, in such regions, remains high and ranges from 50 to 87.6%, with estimated survival rate of retinoblastoma reaches about 60% in Asia and about 30% in Africa [12].

Here, we introduce our OAC experience in Egypt. Namely, we report our 3 years initial experience for the treatment of early and advanced naive retinoblastoma with OAC, in two major referral centers in Egypt.

## Methods

### Patients

A prospective study, included patients with newly diagnosed retinoblastoma undergoing OAC, was conducted from January 2016 till March 2019. The study was performed in collaboration between Assiut University Hospital and El-Sheikh Zayed Hospital after obtaining patients' written consents (from parents) and approval from the institutional ethics committees. Both hospitals represent tertiary referral centers, both in the south and north of Egypt. Patients were referred to our neuro-interventional suites for OAC after the discussion in the multidisciplinary meetings (including ophthalmologists, pediatric oncologists, diagnostic, and interventional neuro-radiologists). Three patients were referred to us from other Middle East areas (Yemen, Libya, and Sudan). Inclusion criteria included patients who received no prior treatment, the presence of unilateral or bilateral diseases, and any stage of the disease except patients with neovascular glaucoma and anterior chamber invasion. Exclusion criteria further included patients in which the disease can be totally controlled with focal therapy such as laser ablation, cryotherapy, and brachytherapy as well as patients with optic nerve involvement and those with orbital or metastatic diseases. In addition, patients who had abnormal coagulopathy renal or hepatic impairment were excluded. Therefore, a total number of 26 eyes, 19 patients (age ranges 2–48 months) were included in this study.

### Technique

OAC procedures were performed at the angiography suites under general anesthesia. Intravenous heparin (100 UI/kg) was administered as a systemic

anticoagulant. A femoral artery puncture was performed at the right side, and a four-French arterial sheath was inserted into the femoral artery. A four-French (vertebral) guide catheter, supported with a 0.035-inch hydrophilic (Terumo) guidewire was then placed through the sheath to reach the targeted internal carotid artery (ICA), under fluoroscopic guidance. Non-ionic iodine contrast media was injected, and serial angiograms were taken to visualize the cerebral and orbital vascular anatomy. A super-selective catheterization of the ophthalmic artery (OA) was then performed (Fig. 1) via a 1.5 French micro-catheter (Marathon, EV3-Medtronic, USA), supported by either 0.008 in. (Mirage, EV3-Medtronic, USA) or 0.012/0.014 in. (Traxcess, Microvention, USA) micro-guidewires, and contrast media was injected to confirm the appropriate catheter position and to detect the choroidal blush. If there was no adequate choroidal blush after OA catheterization or even if the OA was not well visualized after ICA catheterization, catheterization of the middle meningeal artery (MMA) through the external carotid artery (ECA) was achieved. In case of bilateral retinoblastoma, tandem technique, previously described by Abramson et al. [13] was performed.

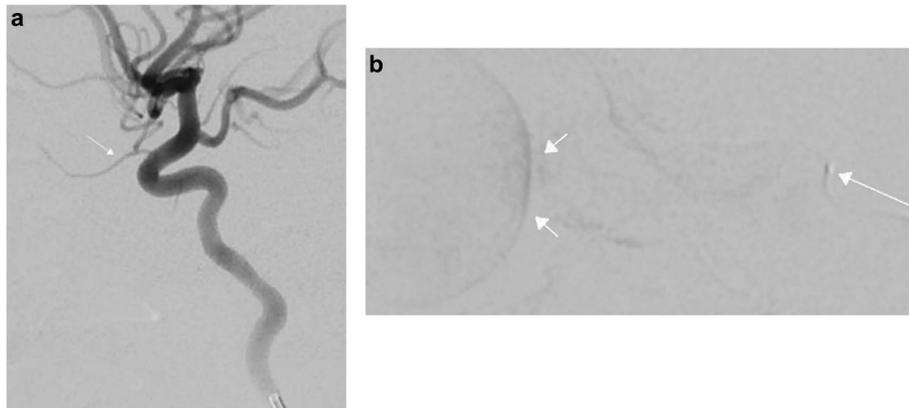
All patients in the current study received melphalan as a single chemotherapeutic drug for OAC. Preparation was performed only after the catheterization of OA. The dose was adjusted according to the age, size of the globe, and the territory infused. Body weight was, particularly, taken into consideration to estimate the toxic dose, < 0.48 mg/kg. Melphalan was diluted in 30 ml saline and infused via pulsatile injection, over 30 min, to insure homogenous delivery of the drug. After the infusion, an angiogram was taken to rule out complications related to the procedure such as vasospasm, vascular dissection, or embolism. The catheter and the sheath were then removed, and femoral artery hemostasis was obtained by manual compression at the puncture site. Patients were then awakened and kept under observation for 24 h.

### Sessions

Patients were scheduled to obtain repeated sessions, whenever required, in order to achieve adequate tumor control. Repeated sessions were performed in 3 to 4 weeks interval. At any stage, whenever the residual disease can be controlled by any adjuvant focal therapy, at the discretion of the ophthalmologist, the appropriate therapy was given.

### Response assessment

The response was recorded after the ophthalmological evaluation. Complete regression (CR) was assigned if there was no evidence of a viable tumor or any viable seeds. Partial regression (PR) was assigned whenever



**Fig. 1** **a** ICA angiogram with OA is shown (arrow). **b** Catheterization of the OA, with catheter tip noted inside its ostium (long arrow) and an adequate choroidal blush was obtained (two short arrows)

there was a reduction in the size of the tumor or in the percent of the viable seeds. Bad response was assigned when changes remain persistent after 2 sessions or if a progression in the tumor size and or seeds was recorded after any session.

#### Follow-up

Initially, onco-pediatric evaluation was performed within 7–10 days after each session, whereas ophthalmological evaluation was performed before the initial session and 3 weeks after each session. Follow-up was then continuous at 3 months interval (or earlier whenever required by the pediatric oncologist or the ophthalmologist).

Ophthalmological evaluation included external examination, ocular motility assessment, and complete fundus examination (using indirect ophthalmoscope, ultrasound and, whenever possible, Retcam). It aimed to assess the response of the tumor to the OAC, i.e., the tumor size, the presence and extent of the subretinal/vitreous seeds, distance of the tumor from the optic disc, and fovea as well as the associated retinal detachment. Additionally, it aimed to assess the recurrence as well as the ocular and periocular complications.

Onco-pediatric evaluation included the clinical assessment and the hematological investigation. It aimed to assess the general condition, toxicity from chemotherapy, systemic complications, and patient survival. MRI of the brain and orbit was performed every 6 months, or at shorter interval whenever required, to assess the extra-ocular extension, any associated pineal, or suprasellar diseases (trilateral or quadrilateral retinoblastomas) and to detect the metastasis.

Eventually, our analysis consisted of primary and secondary measures. The primary measures included evaluation of the success of the technique, the response to OAC sessions, and complications related to the

procedure, whereas the secondary measures included assessment of the recurrence, metastasis, and patient survival.

## Results

### The primary measures

#### Success of the technique and number of the sessions

OAC was successful in 23 out of 26 eyes. Catheterization of OA failed, however, in 3 eyes, due to the sharp angle along with the small ostium of OA, even after reshaping the tip of guidewire to fit the OA. In 2 out of those, it failed in the first session. Yet, in one eye, catheterization was successful in the first session but not in the second session. Therefore, 23 eyes of 16 patients were included in our analysis. Details of patients' characteristics are demonstrated in (Table 1).

The number of OAC sessions received by each eye ranged from 1 to 4, with four eyes underwent four OAC sessions, ten eyes underwent three sessions while eight eyes underwent 2 sessions, and only one eye underwent one session. Thus, a total of 63 sessions were ultimately performed. OA catheterization was performed in 59 sessions (shaping the tip of the guidewire to fit the sharp angle of OA was achieved in two eyes) (Fig. 2), while MAA catheterization was performed in 4 sessions (due to reflux of the contrast back to the ICA (Fig. 3) and due to non-visualized OA after ICA catheterization).

#### Response to OAC treatments

Adequate tumor control was achieved in 22 out of 23 eyes (95.66%). Fifteen eyes (65.2%) showed CR after the OAC treatments. Eight eyes (34.8%) showed PR after the OAC sessions and were amenable for adjuvant therapy, either laser ( $n = 6$ ) or plaque brachytherapy ( $n = 2$ ). On the other hand, (4.34%) one eye (stage D) showed a progression of the main solid tumor after the third session and enucleation was performed.

**Table 1** Characteristic of retinoblastoma patients received OAC treatments between January 2016 and March 2019

Features	Patient characteristics
Number of patients included in the final analysis	16 patients
Number of eyes	23 eyes
Age	Range (2–48 months) Mean age = 11.1 months
Sex	8 males, 8 females
Laterality	Unilateral, 9 patients Bilateral, 7 patients
Family history	Positive, 6 patients Negative, 10 patients
Stage of the disease according to the International Classification of Retinoblastoma	Stage B = 8 eyes (34.8%) Stage C = 7 eyes (30.5%) Stage D = 5 eyes (21.7%) Stage E = 3 eyes (13 %)
Follow-up period	Range (9–36 months) Mean = 18.5 months

**Complications**

The main ocular complications included ophthalmic artery stenosis ( $n = 4$ ) and localized chorioretinal atrophy ( $n = 3$ ). The periocular complications included temporary eyelid edema ( $n = 4$ ) and periorbital hyperemia ( $n = 2$ ). The systemic complications mainly included vomiting ( $n = 15$ ), transient neutropenia ( $n = 2$ ), but no one required a blood transfusion, and reduced tidal volume ( $n = 2$ ) that has been treated with intravenous epinephrine, after pausing catheterization. No

anaphylactoid reaction had been recorded and no major intracranial complications such as ischemic stroke, seizure, or any neurological deficits.

**The secondary measures**

The mean follow-up duration is equal to 18.5 months (ranges 9–36 months) with only one eye has been followed up for less than 12 months (9 months).

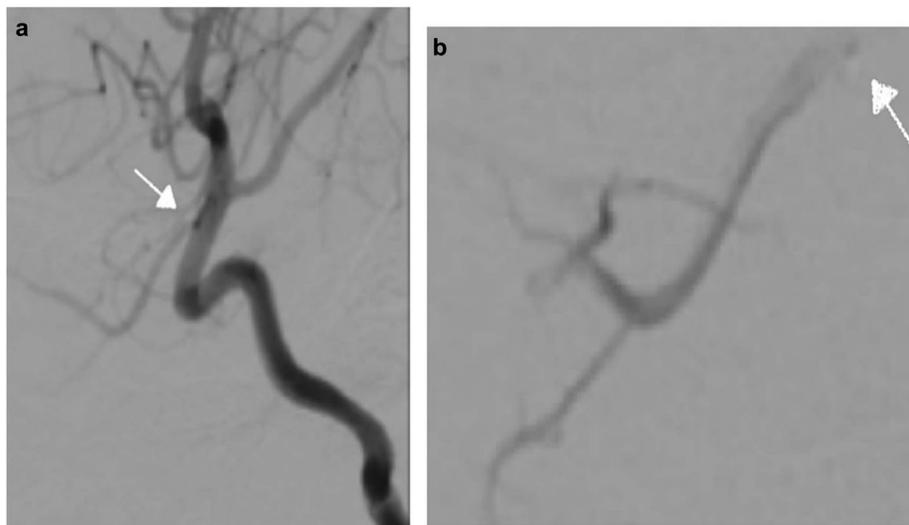
**Recurrence and globe salvage**

Only one eye (4.3%) showed orbital recurrence. A 4-year-old female with bilateral disease has developed the recurrence in the right eye (stage E, at time of presentation). The patient received four sessions of OAC treatments and later received laser ablation therapy, then showed a complete resolution. Yet, recurrence of the main solid tumor, with subretinal and vitreous seeds was recorded, during a follow-up duration of 19 months, and enucleation was then performed.

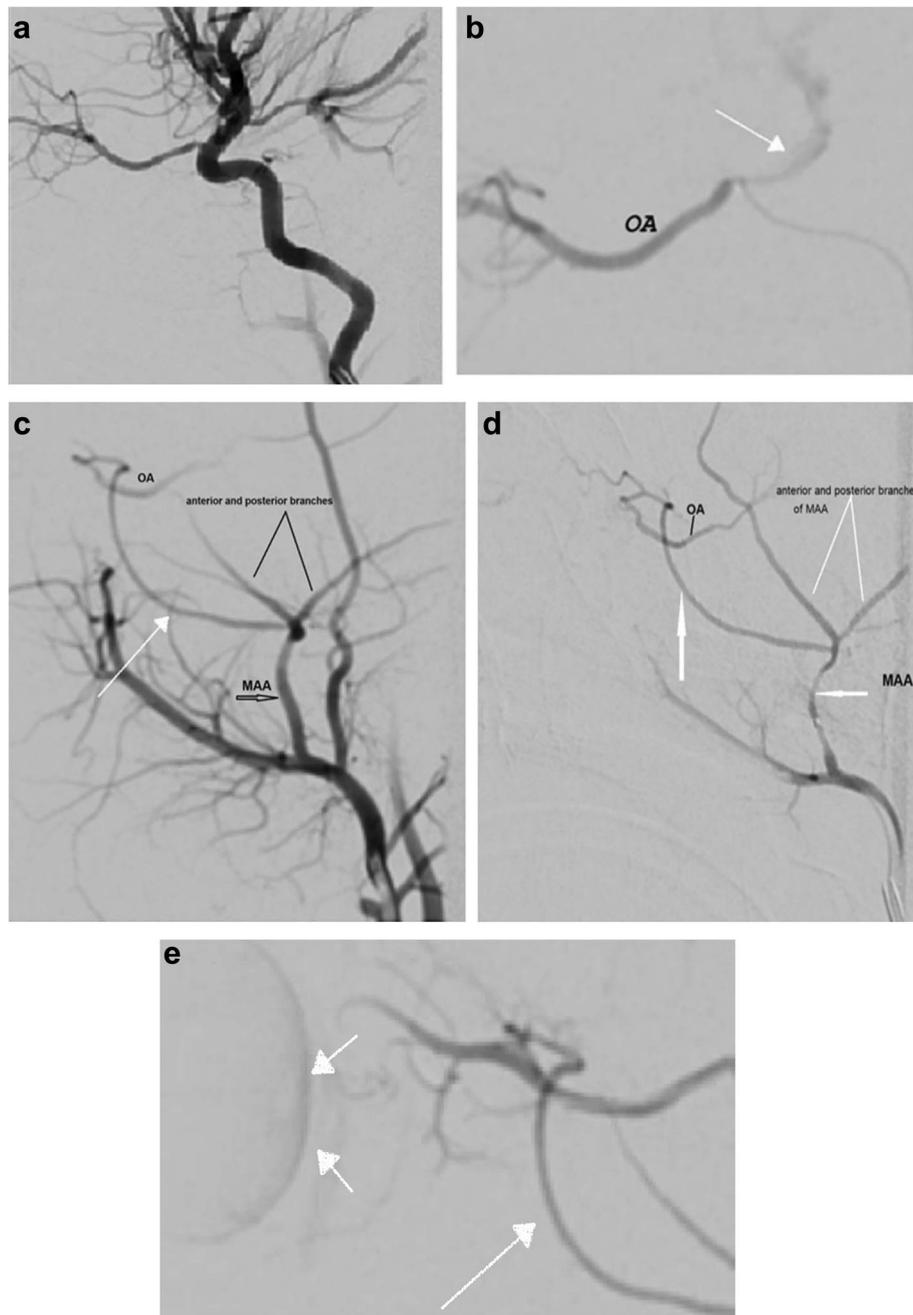
Overall, out of 23 eyes, two eyes underwent enucleation (In one eye, enucleation was performed after a recurrence of the main tumor, while in the other eye enucleation was performed due to progression of the disease even after the third OAC session). Therefore, the globe salvaged has been achieved in 91.3% of our population, during a mean follow-up duration of 18.5 months.

**Metastasis and patient survival**

No reported case of metastasis or death (100% metastasis free survival) during a mean follow-up period of 18.5 months.



**Fig. 2** a ICA angiogram with noted sharp angle of the OA (arrow). b Catheterization of the OA was successful after reshaping of the guidewire. The tip of the micro-catheter is noted inside the ostium (arrow)



**Fig. 3** **a** Angiogram of the ICA. **b** A reflux of the contrast back from the OA to ICA is noted (white arrow). **c** ECA angiogram was then performed and revealed an anastomotic branch between MMA and OA (white arrow). **d** MAA angiogram: the anastomosis between MAA and OA (long vertical arrow) is shown again. **e** Zoomed image, an adequate choroidal blush (two short arrows) was obtained, through the anastomotic branch (long arrow), after MAA catheterization

## Discussion

In the current study, we evaluated our initial experience in Egypt to implement OAC for the treatment of both unilateral and bilateral naive retinoblastoma patients. About 34.7% presented with advanced stage and the youngest patient was 2 months old. At such young age, OAC might be challenging. Therefore,

only few reports have included this age while applying OAC [14–16].

Catheterization was successful in 23 eyes out of 26, with a total of 63 sessions, in the current study. The main reason why the technique failed, in three of our cases, was the sharp angle of the OA which hindered the proper catheterization of its ostium. In such cases,

shaping the tip of the guidewire was performed to fit the OA ostium, as described previously [17, 18]. Despite being successful in two eyes of our cases, it failed in the other three eyes. Catheterization, however, was not further forced to avoid OA injury. An alternative approach to overcome the sharp angle of OA was by applying the temporary balloon occlusion technique to the ICA [8, 19]. Yet, we have not apply this maneuver to avoid the risk of thromboembolic complications and to avoid dilution of melphalan over a larger volume of the blood [17, 20]. Another difficulty we encountered here was the reflux of the contrast media back to the ICA. Such reflux usually occurs as a result of a hemodynamic flow imbalance with inversion of the blood flow through multiple collaterals between OA and the MMA [17]. The presence of the catheter inside the OA ostium has been thought to be a trigger factor for this hemodynamic disturbance with activation of the collaterals [17, 21]. Catheterization of the MMA via ECA approach, as previously proposed [17, 19], was successfully performed in such cases.

Initially, tumor control has been achieved in 95.6% of the treated eyes. While 65.2% revealed CR after OAC sessions, 34.8% revealed CR only after additional adjuvant therapy. We relied on melphalan as a single chemotherapeutic drug in treating our patients. It is the primary drug used in OAC and has been shown to be the most powerful one [10, 22]. Other studies have used both single and multiple drug regimen, e.g., carboplatin and topotecan in combination with melphalan [18, 19, 23–26]. Combined drug therapy was particularly employed in more advanced cases [23–25] or in tandem therapy [22].

In keeping with our data, Tuncer et al. revealed that, of those who had been treated only with melphalan during OAC, only one eye out of 17 retinoblastomas, with stage D, did not reveal CR [27]. Similarly, other studies achieved high rates of tumor control, even in advanced stages, when relied only on melphalan for OAC [28–30]. On the other hand, Thampi et al. achieved good tumor response only in less advanced stages but not in the more advanced retinoblastomas, when used melphalan as a single agent for OAC [31].

In the current study, only one eye (4.3%) developed a recurrence after 19 months. A tumor resistance to the chemotherapy has been recorded previously, particularly, when a single agent is used [27, 32]. Such a resistance might be a reason for the recurrence in our case. Contrast to our results, different studies revealed a higher rate of recurrence. Shield et al. reported a recurrence rate of 19%, after OAC in primary retinoblastomas, including all stages, within 24 months [33]. Furthermore, Tuncer et al, in a 4-year experience, reported a recurrence rate of 29% after OAC in group D

retinoblastomas, within the first year [27]. The relatively small sample size, particularly, with the small number of advanced retinoblastomas, in addition to the short follow-up duration, may explain our lower recurrence rate. Our results, however, are in agreement with other studies in which low recurrence rates were recorded after OAC, even in advanced cases [30, 34]. In fact, there were notable variations regarding the disease stage, the number of the eyes received treatment, as well as the follow-up period among the different studies which might, in part, contributed to these results discrepancy. In this context, in 10 years' experience study conducted by Francis et al. investigating the risk factors associated with recurrence after OAC, they found that in addition to using single chemotherapeutic agent, increase the number of chemotherapeutic agents used in combination, bridge therapy, as well as presence of vitreous seeds at the first visit, older age at the time of presentation, and longer interval between OAC sessions (more than 4 weeks) are all significantly associated with high recurrence rate. The latter was the only factor significantly associated with a high recurrence rate if OAC was accompanied by intravitreal chemotherapy injection. Furthermore, they revealed that eyes which did not develop recurrence in the first year had only 8% risk of recurrence by the 2nd year [32].

In the present study, enucleation was performed due to disease progression in one eye and due to recurrence of the disease in another eye. Eventually, we were able to attain a high globe salvage rate (91.3%). Such results are consistent with other studies [28, 35] in which high globe salvage rates were achieved, and further emphasizing the efficacy OAC in retinoblastoma.

Fortunately, none of our patients developed metastasis and all of them were alive within the stated follow-up period (mean = 18.5 months). In parallel with our data, other studies showed no metastasis developed after OAC [18, 27, 33, 36]. Others reported a low incidence of metastasis [11]. Nevertheless, different studies worldwide revealed that no patient has died from the metastatic disease after OAC [11, 30, 31].

The main ocular complications that we encountered in the current study were ophthalmic artery stenosis and chorioretinal atrophy. The ophthalmic artery narrowing was detected by fluoroscopy, in four eyes, in the late sessions and is likely caused by catheter injury or by the toxic effect of chemotherapy to the vascular endothelium. Localized chorioretinal atrophy was detected in three eyes after either the third or fourth session. It is most likely secondary to the toxic effect of the chemotherapy from earlier sessions, since it takes several months to progress. Previous studies also showed low rates of chorioretinal atrophy [27, 29, 33, 37]. In line with other studies [19, 27], other minor periorcular

complications such as lid edema and periorbital hyperemia have been reported in our study yet, they were resolved shortly afterward. A transient neutropenia, which is related to the chemotherapy toxicity, has been reported in our series yet, none of our patient required blood transfusion. In addition, reduced tidal volume was evident twice in the current study. Similarly, it has been shown previously in some patients during OAC [38, 39] and has been assumed to evolve secondary to catheter placing in the ICA or OA orifice [40]. In such cases, reduced tidal volume was managed by suspending the catheterization and elevating the airway pressure. Immediate intravenous epinephrine would aid to avoid further hemodynamic collapse [40].

One of our limitations was the lack of availability of other chemotherapeutic drugs during the time of our study. Thus, we relied only on melphalan even in the advanced stages or in tandem therapy. In our future OAC treatments, combined drug therapy will be included. The small sample size is another limitation of this study. Being an initial experience that is less accustomed by clinicians and parents may be the reason behind this.

## Conclusion

In summary, we were able to achieve a high rate of globe salvage with a minimal rate of complications and at the same time, 100% metastasis free survival was maintained. Therefore, our study provides promising results for treating both early and advanced stages of retinoblastoma, safely, in the developing countries, particularly in Egypt.

## Abbreviations

CR: Complete regression; ECA: External carotid artery; ICA: Internal carotid artery; OA: Ophthalmic artery; OAC: Ophthalmic artery chemosurgery; MAA: Middle meningeal artery; PR: Partial regression

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## Authors' contributions

EAA, MHO, FH, RKS, and HMI were responsible for the study conception, design, and data analysis. MHO, FH, HMI, and GY performed the procedures. RKS wrote the manuscript. MSA, MFR, KFR, EBK, and MAM were responsible for the clinical and ophthalmological examinations as well as for the follow-up. SAH, AMT, SME, RAH, and ASI were responsible for intra- and post-operative monitoring. All authors substantially revised the manuscript and approved the submission.

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## Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics approval and consent to participate

The study was approved by the institutional ethical committee (Faculty of Medicine, Assiut University Ethical Committee), and the committee's

reference number is not applicable. Written informed consent was obtained from all individual participants included in the study.

## Consent for publication

All patients included in this research gave written informed consent to publish the data contained within this study.

## Competing interests

The authors declare that they have no conflict of interest.

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