

# A long follow-up of a patient with bilateral retinoblastoma who underwent globe-preserving therapy and had metastasis after 72mo

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## Dear Editor,

I am Dr. Yi Zhang, from the Department of Pediatrics, Beijing Tongren Hospital, Capital Medical University, Beijing, China. I would like to describe the metastasis in the left parotid and cervical lymph nodes of a patient with bilateral retinoblastoma 72mo after the initial successful globe-preserving therapies, which included chemotherapy, laser photocoagulation, and cryotherapy. After the secondary chemotherapy and enucleation, the recurrent tumor regressed, the right eye's vision was normal throughout the follow-up period.

Retinoblastoma is the most common intraocular malignancy in children, and its etiology has been elucidated as the mutation of the *RBI* gene, approximately one-third of these tumors are bilateral retinoblastoma, which are more hereditary and usually found in younger children<sup>[1-2]</sup>. Traditionally, extraocular retinoblastoma was treated with radiotherapy and surgery; in recent years, a great progress has been made in the treatment techniques such as systematic chemotherapy, interventional therapy, and autologous peripheral blood stem cell transplantation, which have greatly improved the survival rate of patients with orbital extension and distant metastasis, leading to a tremendous decrease in the frequency of primary enucleation<sup>[3-4]</sup>; nevertheless, enough attention should be paid

to the recurrence and metastasis of the retinoblastoma under the setting of globe-preserving therapy.

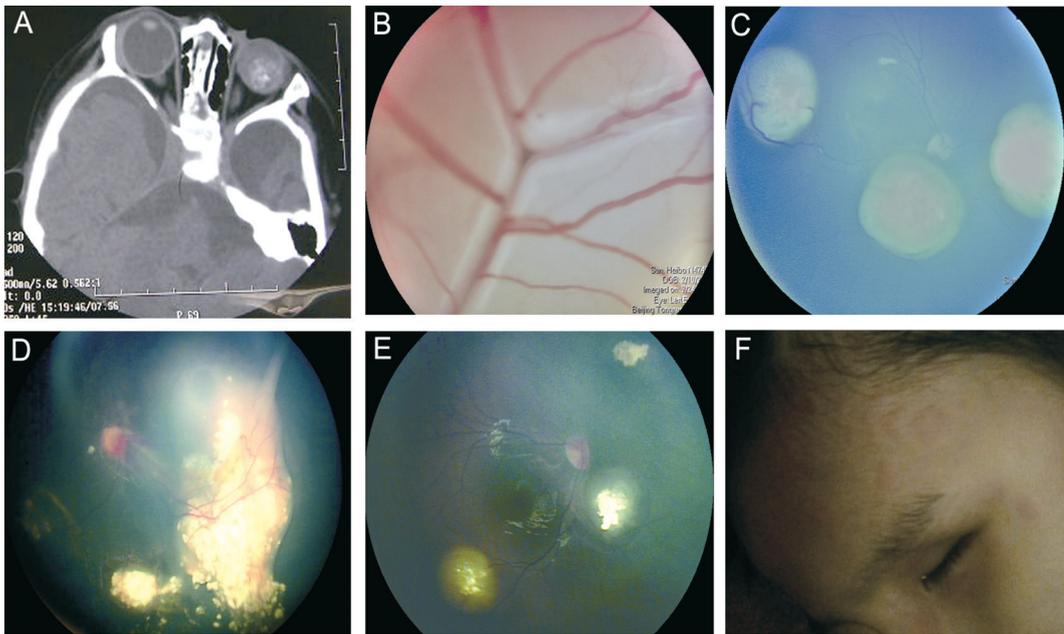
A 7.5-month-old boy presented with a white pupillary reflex in his left eye for 3mo. Ultrasonography indicated a mass occupation under the retina. Thereafter, orbital computed tomography (CT) scan was performed, and results revealed soft tissue mass radiographic shadows in the vitreous bodies of both eyes (greater in the left), patchy calcification could be found in the lesions (Figure 1A). The maximal sectional area of the left eye is about 1.8×1.4-cm<sup>2</sup>. Subsequently, with a suspicion of retinoblastoma, funduscopy examination was performed. Results of the left eye showed a large mass with rich blood supply and total retinal detachment; and three smaller masses in the fundus of the right eye, beside the nasal, under the temporal bone and nose, respectively (Figure 1B, 1C). According to the International Intraocular Retinoblastoma Classification (IIRC)<sup>[5]</sup>, the left eye is classified as D, and the right eye is C of the intraocular stage. The boy's father has bilateral retinoblastoma, whereas his brother is normal, and genetic test revealed a point mutation of his *RBI* gene located on the chromosome 13.

After a diagnosis of retinoblastoma was made, the patient was started on a protocol consisting of a seven-cycle chemotherapy with carboplatin, vincristine, and teniposide/etoposide (regimen refer to Table 1), as well as laser photocoagulation and/or cryotherapy, which was performed under the funduscopy (under general anesthesia) before each cycle of the chemotherapy.

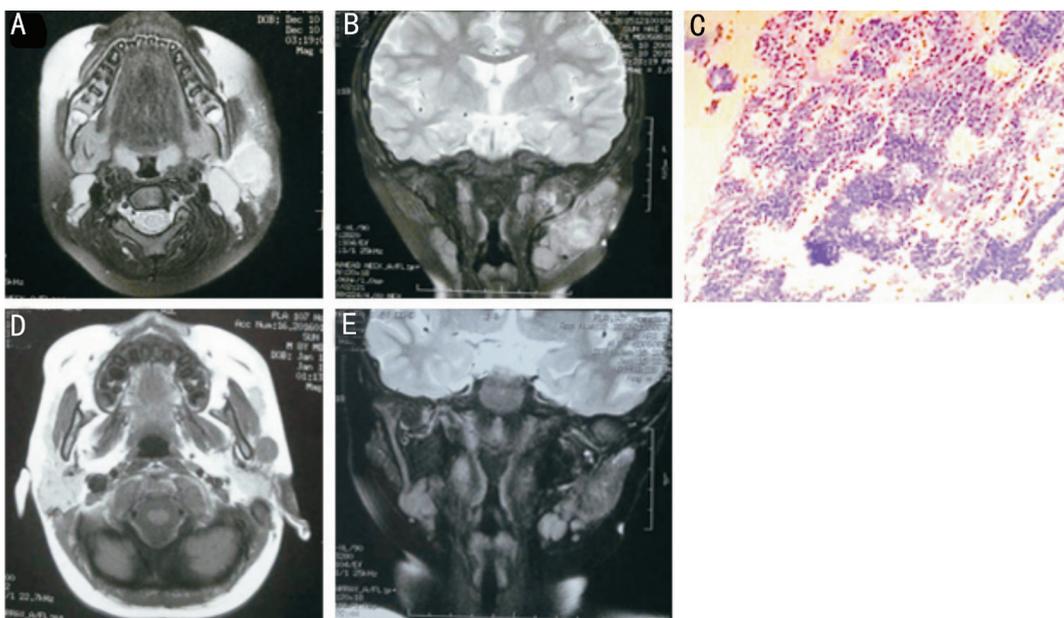
**Table 1 The protocol of the chemotherapy performed after the diagnosis of retinoblastoma**

Cycle No.	Weight (kg)	Day 1 CBP (mg)	Day 2	
			VM-26/VP-16 (mg)	VCR (mg)
1	9	260	75	0.6
2	9	280	70	0.6
3	9	290	80	0.6
4	9	290	85	0.6
5	9	300	85	0.6
6	10.5	330	<sup>1</sup> 70	0.6
7	10.5	330	<sup>1</sup> 80	0.6

<sup>1</sup>VP-16. CBP: Carboplatin; VM-26: Teniposide; VP-16: Etoposide; VCR: Vincristine.



**Figure 1** Images before and after the initial comprehensive therapy A: Images of primary orbital computed tomography scan; B, C: Fundoscopy images of the left and right eyes before the first comprehensive treatment, respectively; D, E: Fundoscopy images of the left and right eyes after the first comprehensive treatment, respectively; F: The left eye 6mo after the therapy.



**Figure 2** Images after a follow-up of 72mo A, B: Head-and-neck magnetic resonance imaging revealed a mass of the left parotid, and multiple cervical lymph node enlargement; C: Hematoxylin and eosin staining of the lesions; D, E: Head-and-neck magnetic resonance imaging revealed a significant reduction of the mass after two cycles of chemotherapy.

For the left eye, laser photocoagulation and cryotherapy were adopted, and the right, laser photocoagulation was mainly used after the tumor regression. After the seven-cycle comprehensive chemotherapy, the left-eye tumor was stabilized and mostly calcificated, and the right eye showed type 3 regression which is the mixture of type 1 (calcification) and type 2 (fish flesh lesion) regression (Figures 1D, 1E). Follow-up was made at an interval of 2-3mo for 4 times, 6mo for 4 times, and 1y afterwards in our hospital, fundus and orbital CT examinations were performed at each time. After 6mo of follow-up, the left eye atrophied (Figure 1F), the right-

eye tumor was stably calcificated and the visual acuity was normal.

In September 2015, 72mo after the initial seven-cycle comprehensive chemotherapy, a swelling appeared before the left ear of the patient and kept growing, and was treated as lymphadenitis; however, remission was not achieved. On December 17, 2015, head-and-neck magnetic resonance imaging (MRI) revealed the mass of the left parotid, as well as multiple cervical lymph node enlargements, indicating the possibility of lymphoma (Figures 2A, 2B). The suspicion of retinoblastoma recurrence was supported by the aspiration

biopsy histopathology results including hematoxylin and eosin staining (Figure 2C) and immunohistochemistry, which showed CD56 (+), CD99 (-), chromogranin A ( $\pm$ ), neuron-specific enolase ( $\pm$ ), synaptophysin (+), and a 90% positive rate of Ki67 staining. The patient was then admitted to our hospital on December 22, 2015 and underwent chemotherapy: carboplatin, 300 mg/m<sup>2</sup> for days 1 and 2; plus etoposide, 200 mg/m<sup>2</sup> for days 2 to 4. After two cycles the mass was reduced by more than 50% (Figures 2D, 2E), and following that, on January 27, 2016, surgeries including mass resection of the left parotid, facial nerve dissection, and lymphadenectomy were successfully performed. Left-eye enucleation was performed on March 23, 2016. Pathological findings showed the formation of vascular nets, tumor invasion reaching the iris, ciliary body and lamina cribrosa within the atrophied eyeball, and necrosis was observed in most parts of the tumor. According to the International Staging of Retinoblastoma, the patient was classified as Stage IV-a2. A significant remission was achieved after the comprehensive treatment.

In the present case, the patient's symptoms were typical and were verified by constitutional *RBI* mutations. The chemotherapy regimen was made and carried out according to the status of the patients' left eye, as its condition is worse; meanwhile, focal treatments including the laser photocoagulation and cryotherapy were used in combination with chemotherapy, based on the specific situations. After the initial treatment, tumors in both eyes significantly regressed and were calcified, the right eye's vision was saved, though the left eye's vision was relatively poor. The outcomes indicated that chemotherapy combined with focal treatments is effective in saving the life of patients with intraocular retinoblastoma, and even the affected eye's vision. Impressively, after a long follow-up of 72mo, recurrence manifested by the metastasis of the parotid region and cervical lymph node was observed in the present case. Brain metastasis happens usually through the optic nerve to the cerebrospinal fluid (CSF), then the meninges and ependymal were affected; however, in the present case, the CSF cytology and biochemistry examinations showed negative results, therefore, we speculate that the metastasis is probably through the lymphatic pathway. It was reported that, once distal metastasis occurred, the prognosis is poor<sup>[6]</sup>, whereas in the present case, after regular chemotherapy and surgery, regression or metastasis was not observed till the last follow-up. The reported case suggests that, for those infants with heritable bilateral retinoblastoma, attention should be paid to the long-

term recurrence after successful conservative globe-preserving therapy. Regarding the present case, a close follow-up plan was made for this patient, we suggested a re-examination every 3 to 6mo till 14 years old, and even in the annual follow-up period, the patient was still closely monitored at the local hospital. The present report is instructive especially in the current medical environment, as over the past decade, there has been a significant decrease in enucleation for retinoblastoma patients due to the development of more effective conservative treatment options. The present report also indicates that, in order to reduce the incidence of recurrence, for those patients undergoing globe-preserving therapy, enucleation should be timely performed on the atrophied eye(s), considering the possible presence of residual tumors<sup>[7-9]</sup>. Tailored and timely management consisting of multidisciplinary approaches might save the patients' life, the affected eye(s), and even the vision.

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**Conflicts of Interest:** Zhang Y, None; Huang DS, None; Zhang WL, None; Wang YZ, None; Zhou Y, None; Zhang PW, None; Han T, None; Ma JM, None; Shi JT, None; Ge X, None.

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