The Results of Pars Plana Vitrectomy in the Treatment of Intraocular Retinoblastoma: A Retrospective Study and Literature Review

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Abstract
Purpose: To assess the efficacy and safety of pars plana vitrectomy (PPV) as a treatment for intraocular retinoblastoma (RB) patients. Methods: Twenty-eight RB patients who had PPV were recruited in this retrospective case study, using the digital wide-angle retinal imaging device to record and assess disease condition. Results: The mean value of follow-up time was 79.4 months from diagnosis and 73.1 months from PPV. Up to the end of the follow-up time after PPV, the 5-year survival rate was 96.4%. Ultimately, 35.7% patients underwent enucleation of the eyeball. Among patients with salvaged eyes, 50% had no light perception vision. During the postoperative follow-up time, 14.3% of patients required no further antitumor treatment, and the remaining patients still need to continue to receive systemic or local antitumor treatment, such as chemotherapy, arterial interventional therapy, laser treatment, cryotherapy, and so on. The complication after PPV include cataracts (46.4%), iris adhesion (7.1%), emulsification of the silicone oil (17.9%), band degeneration of the cornea (10.7%), glaucoma (3.6%), and retinal neovascularization (3.6%). Conclusion: According to our observations, we recommend that the utmost care should be taken when considering PPV for the treatment of activated RB. When weighing the risk of tumor recurrence and metastasis, PPV is not suitable for routine treatment. It is necessary to fully grasp the operative indications and strictly observe operation specifications, which includes close postoperative follow-up.

Keywords
pars plana vitrectomy, retinoblastoma, survival rate, eye salvaged rate, visual acuity, complications

Abbreviations
BDC, band degeneration of cornea; CF, counting fingers vision; CHEMOTX, chemotherapy; CRTX, cryotherapy; ENCL, enucleation; ERG, electroretinogram; HM, hand movement vision; IIRC, International Intraocular Retinoblastoma Classification; IT, arterial intervention therapy; IVC, intravitreal chemotherapy; LP, light perception vision; LT, laser treatment; NLP, no light perception vision; PPV, pars plana vitrectomy; RB, retinoblastoma; VA, visual acuity

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Introduction
Retinoblastoma (RB) is the most common primary intraocular malignant tumor in infants and young children, threatening both the children’s eyesight and life. The survival rate of RB patients varies greatly around the world. Early diagnosis, intervention, and personalized treatment are the main strategies to improve the survival rate of RB patients in clinics. At present, the goal of RB treatment has shifted from saving the patient’s life to improving their quality of life through preserving the eyeball and visual function as much as possible. The personalized treatment is usually designed and implemented based on the clinical stage. In children with early stage RB, local treatment...
treatment combined with systemic chemotherapy are usually used, and the affected eyeball can be preserved most often as expected in clinics. However, in patients with advanced stage RB, due to the large tumor size and invaded optic nerve, retention of the affected eyeball could be a main disadvantage to prevent systemic metastasis. Therefore, the removal of the affected eyeball is usually considered as the first-line treatment inevitably. Although systemic chemotherapy can improve the rate of eye retention in RB children, it has little effect on cases of drug resistance and localized vitreous seeds. Due to the lack of blood supply in vitreous body and the obstruction of blood-retina barrier, chemotherapeutic agents are barely to reach the target site and effective concentrations in the vitreous cavity. The intraarterial chemotherapy can be considered as an alternative to increase the concentration of chemotherapeutic agents in the eye, however, the effective rate for the patients with vitreous seeds was only 64% to 67%. Intravitreal chemotherapy was firstly reported by Kaneko and Suzuki in 2003 for the treatment of vitreous seeding, but there are 2 major drawbacks to this approach. Firstly, the chemotherapeutic agent has dose-dependent toxicity to the retina. Melphalan is the most common used agent for intravitreal chemotherapy. It was reported that low doses of melphalan had little effect on the vitreous seeding, and the repeated low dose injections can significantly increase the risk of drug resistance and metastasis of extraocular tumor. However, increasing the dose of melphalan is associated with the toxic effect on the retina. There were significant correlates with reduction in electroretinogram (ERG) amplitudes with an estimated 5.3 μV decrease for every intravitreal melphalan injection of 25 to 30 μg. In addition, intravitreal chemotherapy can also cause retinopathy, referred to as salt and pepper retinopathy, presents as an abrupt, irreversible chorioretinopathy. The incidence of such complications can be as high as 43%. The second most frequently injected agent is topotecan. Topotecan is usually considered as a second-line treatment when Melphalan alone failed to control the progression of tumor. Secondly, intravitreal chemotherapy has no effect in patients with active retinal tumors. For these reasons, the intravitreal chemotherapy has some considerable limitations. Intravitreal chemotherapy combined with intraarterial chemotherapy or systemic chemotherapy can increase resistance to chemotherapy drugs. In clinics, pars plana vitrectomy (PPV) is commonly used for the treatment of vitreous hemorrhage, retinal detachment, endophthalmitis, and other eye diseases. With the development of surgical techniques, many surgeons have been trying to introduce PPV as a new approach to preserve the eyeball of RB children, especially for the treatment of the patients who are resistant to chemotherapeutic agents or the tumors with vitreous seeds. Despite these factors, the feasibility of this kind of treatment has been controversial.

In this study, we retrospectively analyzed the medical records from the RB patients who had PPV and follow-up review after surgery in Renmin Hospital of Wuhan University. During long-term follow-up, the analysis of surgical safety and postoperative complications was conducted to assess the efficacy and safety of PPV in the treatment of intraocular RB.

Materials and Methods

Materials

This is a retrospective study that involved 28 children (15 male and 13 female) with RB who underwent PPV and postoperative follow-up in Renmin Hospital of Wuhan University from July, 2011 to July, 2020. As a routine preoperative systemic chemotherapy, all the children were administered 2 to 13 cycles of treatment with carboplatin, etoposide/teniposide, and vincristine to control the progression of disease and minimize the tumor size, and meanwhile, the localized vitreous seeds or active retinal lesions still could be observed. This study was approved by the Ethics Committee of Renmin Hospital of Wuhan University (Approval Number: WDRY2020-K047), and followed the tenets set forth in the Declaration of Helsinki. Regarding the operation consent, all the guardians of children had been informed the possible risks and complications before the surgery, and signed the written consent form as expected.

Methods

Before vitrectomy, systemic chemotherapy was conducted to control the progression of disease and minimize the tumor size. Combination therapy, such as laser treatment, cryotherapy, and arterial intervention therapy were also needed if necessary. The PPV operations were performed by the same surgeon and medical team, who are experienced and professional in this area. The specific surgical procedure can be referred to the relevant literature. Standard 23G or 25G PPV with silicone oil tamponade was performed. About 5 μg/ml melphalan was added to the irrigation fluid. All the tumor tissue was removed completely without any residual. For the retinal lesions, a local retinectomy including tumor should be performed. If tumor was closed to the macula, both tumor and macula would be removed accordingly. And meanwhile, preserving the optic disc was usually the first priority although the tumor was very closed to it in some cases. For this reason, the tumor or peripheral tumor would be removed along the edge of the optic disc, and then initiated the following treatments to clear the remaining tumor cells. Additionally, a well-designed follow-up should be implemented strictly as scheduled after vitrectomy. As soon as any sign of recurrence or metastasis was observed, the eyeball enucleation should be performed straight away to control the progression of disease. The vitreous hemorrhage during the operation should be managed immediately to reduce the delay of the examination of fundus as much as possible. To confirm the diagnosis, the intraoperative biopsy of the resection of vitreous or retinal lesions is compulsory for each patient. After the local tumor resection, retinal photocoagulation or cryotherapy was performed if necessary. When the procedure of PPV was finished, 0.2 ml melphalan (5 μg, 25 μg/ml) was injected into subconjunctiva around the surgical entry points. In addition, cryotherapy was taken on the entry points. Melphalan injection was repeated 2 to 4 times in the follow-up examinations.
RB children attended the postoperative follow-up regularly as scheduled. Both eyes were examined by an experienced ophthalmologist with a digital wide-angle retinal imaging device (RetCam II, Clarity Medical Systems) under sevofoflurane inhalation anesthesia. Before the fundus examination, 0.5% tropicamide phenylephrine eye drops (Santen Pharmaceutical Co.) were instilled into the both eyes once every 15 min for 1 h to dilate the pupillary. The eyelids were opened using a child speculum (MR-O208 T, Suzhou Mingren Medical Equipment, Co., Ltd). The 130 diopter camera lens was placed on the cornea after instilling carbomer eye drops (Bausch & Lomb) onto the cornea. The RB patients were classified on the basis of International Intraocular Retinoblastoma Classification, according to the literature.10

Statistical Analysis
Prism 8 (GraphPad Software, Inc.) was used for analyses. The age distribution was a nonnormal distribution confirmed by the Shapiro Wilk test, represented by the median number.

Results
Clinical Information
There were 28 RB children, of which 15 (53.6%) were males and 13 (46.4%) were females. Of the 28, 18 were unilateral RB patients (64.3%) and 10 were bilateral RB patients (35.7%). The age of RB onset ranged from 2 months to 6 years and 2 months, with a median of 10.5 months. There were 22 children (78.6%) diagnosed with RB under the age of 3 years, and 6 children (21.4%) diagnosed at more than 3 years. The age of receiving PPV ranged from 3 months to 6 years and 6 months, with a median of 1 year and 9 months. There were 21 children (75%) who were under 3 years old at the time of receiving PPV, and 7 children (25%) who were older than 3 years. When receiving PPV, 2 patients (7.1%) were in stage B, 22 patients (78.6%) were in stage D, and 4 patients (14.3%) were in stage E. Up to the end of July, 2020, the follow-up time from diagnosis was 56 to 108 months, with an average value of 79.4 months. The follow-up time from PPV was 54 to 88 months, with an average value of 73.1 months (Table 1). The details of pre and post of operative treatment were listed in Table 1.

Antitumor Treatment After PPV
During the postoperative follow-up time, 4 patients (14.3%, Patient No. 4, 13, 15, and 17) required no further antitumor treatment (Figure 1). There were 23 patients (82.1%) who received systemic chemotherapy with carboplatin, etoposide or teniposide, and vincristine due to a suspicious new lesion, or the treatment of the other eye appeared to be urgent during the follow-up, 9 of whom received 1 cycle (Figure 2), 5 of whom received 2 cycles, 6 of whom received 3 cycles, 2 of whom received 4 cycles, and 1 of whom received 5 cycles (Patient No. 25). There were 2 patients (7.1%) who received arterial interventional therapy (Patient No. 7 and 21). In total, 5 patients (17.9%) received local treatment, including laser treatment (5 eyes, 17.9%) and cryotherapy (3 eyes, 10.7%). Patient No. 7 received PPV 2 times, but ended up with the enucleation of eyeball (Figure 3).

Complications After PPV
All children included in this study had silicone oil infusion. In the process of postoperative follow-up, silicone oil can be removed when the tumor has no sign of recurrence for more than half a year. No patients included in this study developed hypotony. Up to the end of the follow-up time after PPV, there were 18 eyes salvaged. All of these 18 patients with salvaged eyes had oil removed, and none of them developed retinal detachment. During the postoperative follow-up time, 13 patients (46.4%) developed cataracts and 12 patients underwent cataract surgery. When the cataract affects the fundus examination, and the tumor was stable for at least half a year without any sign of recurrence and metastasis, the cataract extraction can be performed. There were 2 patients (7.1%) who developed iris adhesion. Five patients (17.9%) developed emulsification of the silicone oil, which needed to be removed in advance. Of all the patients, 3 (10.7%) developed band degeneration of the cornea (Patient No. 12, No. 24, and No. 17). Patient No. 12 and No. 24 had developed wide range of corneal lesions that affected the fundus examination. Therefore, the progression of disease could not be examined and tracked properly. For this reason, the Patient No. 12 and No. 24 underwent the eyeballs enucleation to prevent the risk of recurrence, metastasis and complications. Patient No. 17 had a small area of corneal lesion, and fundus examination could be performed properly through the nonlesion area. There was 1 patient (Patient No. 26) who developed glaucoma and 1 patient (Patient No. 3) had retinal neovascularization of the affected eye, which was in stable condition during follow-up (Figure 4). Additionally, the postoperative complications among the patients with different stages appeared to be similar.

The Outcome of the Disease
Up to the end of the follow-up time after PPV, 1 patient (3.6%) died of tumor recurrence and brain metastases (Patient No. 6). The 5-year survival rate was 96.4%. There were 10 eyes (35.7%) that ultimately received enucleation because of uncontrollled tumors and the potential for distant metastases (Patient No. 6, 7, 10, 11, 12, 24, 25, 26, 27, and 28), and 18 eyes (64.3%) were salvaged. All the isolated eyeballs were examined histopathologically and confirmed RB diagnosis. Among the 18 patients with salvaged eyes, only 1 patient (5.6%) (Patient No. 5) had visual acuity of 20/80. There were 9 patients (50%) who had no light perception vision and 4 patients (22.2%) who did have light perception vision caused by the loss of a large retina and severe damage to the macular area. In all, there
| No. | Eyes   | Stage | Treatment before PPV | Treatment after PPV | Complications of PPV | Ending | VA after PPV |
|-----|--------|-------|----------------------|---------------------|----------------------|--------|-------------|
| 1   | Left   | D     | CHEMOTX              | CHEMOTX             | /                    | Stable | NLP         |
| 2   | Right  | D     | CHEMOTX; IT          | CHEMOTX             | Cataract of right eye| Stable | NLP         |
| 3   | Binoculars (R,C) (L,B) | D     | CHEMOTX; LT on right eye; PPV on left eye | CHEMOTX | Retinal neovascularization on left eye | Stable | NLP         |
| 4   | Right  | D     | CHEMOTX; IT          | /                   | Cataract of right eye| Stable | LP          |
| 5   | Binoculars (R,E) (L,B) | CHEMOTX; ENCL of right eyeball; LT and PPV on left eye | CHEMOTX | Emulsification of the silicone oil | Stable | 20/80       |
| 6   | Left   | D     | CHEMOTX; IT          | CHEMOTX             | /                    | ENCL of left eyeball; Died of recurrence and metastases | ENCL of right eyeball |
| 7   | Right  | D     | CHEMOTX              | CHEMOTX; IT         | Cataract of right eye| ENCL of right eyeball | /           |
| 8   | Right  | D     | CHEMOTX              | CHEMOTX             | Cataract of right eye| ENCL of right eyeball | /           |
| 9   | Right  | D     | CHEMOTX; LT and CRTX on right eye | CHEMOTX | Cataract of right eye| Stable | NLP         |
| 10  | Binoculars (R,D) (L,E) | CHEMOTX; IT; IVC; LT on right eye; PPV on left eye | LT on right eye; CHEMOTX | / | ENCL of left eyeball | /           |
| 11  | Binoculars (R,D) (L,E) | CHEMOTX; LT and PPV on right eye | CHEMOTX | Cataract of right eye | ENCL of right eyeball | /           |
| 12  | Binoculars (R,C) (L,B) | CHEMOTX; PPV on left eye | LT and CRTX on right eye; CRTX | BDC | ENCL of left eyeball | /           |
| 13  | Left   | D     | CHEMOTX              | /                   | Cataract of right eye| Stable | NLP         |
| 14  | Binoculars (R,B) (L,D) | CHEMOTX; IVC PPV on left eye | CHEMOTX; LT on right eye | CHEMOTX | Cataract of right eye; Iris adhesion | Stable | NLP         |
| 15  | Left   | D     | CHEMOTX; IT          | /                   | Cataract of left eye; Emulsification of the silicone oil | Stable | HM          |
| 16  | Left   | D     | CHEMOTX              | CHEMOTX; LT and CRTX on left eye | Cataract of left eye | Stable | HM          |
| 17  | Left   | D     | CHEMOTX; IT          | /                   | Cataract of left eye; BDC | Stable | NLP         |
| 18  | Left   | D     | CHEMOTX              | CHEMOTX             | Cataract of left eye | Stable | LP          |
| 19  | Right  | D     | CHEMOTX              | CHEMOTX             | Emulsification of the silicone oil | Stable | CF          |
| 20  | Right  | D     | CHEMOTX              | CHEMOTX             | /                    | Stable | NLP         |
| 21  | Right  | D     | CHEMOTX; IT; IVC     | CHEMOTX; IT         | Emulsification of the silicone oil | Stable | LP          |
| 22  | Binoculars (R,B) (L,D) | CHEMOTX; LT on both eyes; PPV on left eye | CHEMOTX | / | Stable | CF          |
| 23  | Binoculars (R,D) (L,D) | CHEMOTX; ENCL of right eyeball; PPV on left eye | LT and CRTX on left eye | Cataract of left eye | Stable | LP          |
| 24  | Left   | D     | CHEMOTX              | CHEMOTX             | BDC                  | ENCL of left eyeball | /           |
| 25  | Binoculars (R,D) (L,B) | CHEMOTX; LT on left eye; PPV on right eye | CHEMOTX | / | ENCL of right eyeball | /           |
| 26  | Binoculars (R,E) | CHEMOTX | ENCL of right eyeball | / | ENCL of right eyeball | /           |

(continued)
were 2 patients (11.1%) who had hand movement vision, and 2 patients (11.1%) who had counting fingers vision.

In this analysis, for patients with different lesion stages, the milder the lesion, the better the prognosis. The 2 patients who were diagnosed with stage B disease and received PPV had a better prognosis for visual acuity, one of 20/80 (Patient No. 5) and one of counting fingers vision (Patient No. 22). They underwent the vitrectomy inevitably because they had developed resistant to the chemotherapy agents. There were 4 patients who were diagnosed with stage E disease and underwent PPV had to receive enucleation in the end. Patient No.27, who underwent vitrectomy at 3 months old, was the youngest patient in this study. She was diagnosed with the stage E lesions in her right eye at the first visit. The doctor suggested the enucleation of the eyeball, however, the parents refused this management plan straight away. They were expecting a treatment that can at least preserve the appearance of the effected eyeball, although they no longer held out any hope of preserving the visual acuity. For this reason, the systemic chemotherapy was initiated to stabilize the condition, and then the treatment of vitrectomy was introduced into the management plan afterwards. A further postoperative systemic chemotherapy was continued due to the progression of RB. However, the patient eventually had to undergo the eyeball enucleation because of the RB recurrence. There were 22 patients who were diagnosed with stage D disease and received PPV, 6 of whom underwent enucleation (27.3%) and 9 of whom had no light perception vision (40.9%).

Patient No. 6 had tumor recurrence 9 months after PPV (Figure 5). The magnetic resonance imaging results showed thickening of the optic nerve in the orbital segment (Figure 5G). The patient received enucleation of the left eyeball as well as the removal of 2.5 cm of the optic nerve with the eyeball (Figure 5H). When the eyeball was removed,
the optic nerve was found to adhere to the dura and surrounding tissues of the orbital apex. The excised segment of the optic nerve was thickened and dark. Pathologic findings showed tumor cell infiltration in the optic nerve stump. This patient died 1 year later due to brain metastasis following the enucleation.

Figure 3. The fundus image of Patient No. 7. (A) The fundus image of the patient at the first diagnosis. There were huge tumors in the fundus hiding the optic disc, which was diagnosed as RB stage D. (B) The fundus image of the patient after 3 cycles of chemotherapy. The tumor shrank in size and there was hemorrhage on the lesion below the optic disc. The patient underwent PPV. (C) The fundus image of the patient 2 months after PPV. There were tumor growers with seeds under the retina (yellow arrow). The patient received PPV for the second time. (D) The fundus image of the patient 1 month after the second PPV. The tumors were all cleared, and no residual or new lesions were found. (E) The fundus image of the patient 3 months after the second PPV. No new lesions were found in the eye, but there was a cataract. The patient underwent cataract surgery. (F) The fundus image of the patient at 6 months after the second PPV and 3 months after cataract surgery. There were old scars in the fundus. No new lesions were found in the eye. (G) The fundus image of the patient 7 months after the second PPV and 4 months after cataract surgery. There was tumor recurrence with hemorrhage in the superior nasal retina (yellow arrow). The patient underwent enucleation of the right eyeball. (H) The image after enucleation. There was no tumor residue or recurrence in the orbit.

Discussion

At present, the survival rate of RB is greater than 80% in some developing countries and even 100% in developed countries.11 Apart from saving patients’ lives, a number of medical teams have been trying to improve their life quality as much as possible by keeping the eyeball intact and visual function after surgery. As a new approach for the treatment of RB that has been approved for clinical trials in some hospitals, PPV has attracted increasing attention and caused a lot of debates among professionals.

In the year 2000, Shields et al. published the first article regarding the PPV in eyes with RB, however, these case studies were unsuspected prior to surgery and 11 patients with RB were misdiagnosed.12 The medical team initiated the enucleation of the eyes and antitumor treatments shortly as soon as the RB were diagnosed during or after the operation of PPV. One patient died 2 years later, although 10 patients had no metastasis or orbital recurrence during the follow-up time. As the outcome of intervention, the authors concluded that the eye surgery was not recommended in children with suspected RB.12 Kaliki et al. retrospectively analyzed the cases of 14 patients with unsuspected RB who had intraocular surgery. The authors reported that 57% of patients died during the follow-up period due to the progression of disease despite receiving the enucleation or antitumor treatment.13 Shen et al. also studied 2 children with unsuspected RB who were treated with PPV and ultimately died due to the systemic metastasis of the tumors.14 Honavar et al. researched 12 cases of RB patients who had PPV. During the follow-up period, 4 patients
had tumor recurrence, 2 patients had systemic metastasis, and 7 patients had to undergo the eyeball enucleation. The medical research team believed that, for some reasons, the PPV treatment was associated with a high risk of the RB recurrence and the systemic metastasis of tumor, and thereby cause the eyeball extraction inevitably.\textsuperscript{15} Ohshima et al. performed PPV for a patient with RB, who had to undergo eye enucleation 4 months later due to the intraocular tumor recurrence.\textsuperscript{16}

There were only 3 studies that had positive results regarding the PPV for RB patients. Ji et al. reported a successful trial of vitrectomy in the treatment of localized vitreous seeds in an RB patient with pretreated and single eye. During the surgery, the localized vitreous seeds were removed first by vitreous cutter with dry vitrectomy technique without irrigation. After the 26 months’ follow-up, there was no RB recurrence or metastasis observed.\textsuperscript{17} Additionally, Yarovoy et al. reported a case study of a pretreated RB child who had only 1 eye left and received treatment with PPV with melphalan irrigation for vitreous hemorrhage with suspected viable RB. After 34 months’ follow-up, there was no sign of tumor recurrence or dissemination.\textsuperscript{18} Furthermore, Zhao et al. performed a planned PPV with melphalan irrigation in the treatment of 21 children with RB who had only 1 remaining eye.\textsuperscript{9} The postoperative follow-up period continued for 1.6 to 4.3 years (mean 3.3 years). The affected eyeballs of 18 cases (86%) were successfully preserved by the PPV surgery. Five children need no more treatment, and 11 children still need systemic or intravitreal chemotherapy as adjuvant treatments. However, due to the tumor recurrence, 2 patients had to undergo the enucleation of the eyeball inevitably, and 2 patients had to receive further PPV treatment for another 1 or 2 times, and one of them died eventually after 3 times’ PPVs due to the repeated recurrence.\textsuperscript{9}

In our follow-up study, 9 eyes had to receive the treatment of enucleation, and 1 child died due to the tumor recurrence. The 5-year survival rate and the eye retention rate was 96.4% and 67.9%, respectively. Compared with intraarterial chemotherapy, which had an eye retention rate of about 64% to 67%,\textsuperscript{4} PPV was not superior by our findings. Among 18 patients with salvaged eyes, 9 patients had no light perception vision, and only 1 patient had visual acuity greater than 20/200. Hence, the PPV did not improve the eye retention rate or vision acuity as expected based on our findings. However, the results were not as optimistic as those of Ji,\textsuperscript{17} Yarovoy,\textsuperscript{18} and Zhao.\textsuperscript{9} In our study, all patients who were diagnosed with stage E disease had to undergo enucleation of the eyeball even after PPV. Also, 68.2% of patients who were diagnosed with stage D eventually lost their vision permanently. However, the eye retention rate and vision retention rate were not as optimistic as those determined by Zhao, either.\textsuperscript{9} We thought one possible reason might be that our study had a longer follow-up time than other studies. In addition, the stage and location of tumors seem to closely correlate with the prognosis of disease, for example, the prognosis of stage B was better than stage E, and the patients with tumors that were not at a location of macular and optic disc generally had better prognosis of visual acuity. In our case studies, the patient No.22 was diagnosed with stage B disease and had to undergo the treatment of PPV due to the tumor was located in the macular area. As a consequence, the child eventually only had a vision to count fingers properly. In contrast, the Patient No. 5, who also diagnosed with stage B disease and received the treatment of PPV, had better visual function due to the tumor was located in the inferior nasal retina and avoided the area of macular and optic disc.

In addition, the high incidence rate of complications following vitrectomy in children should be paid attention to. In our study, 13 patients (46.4%) developed cataracts, 2 patients (7.1%) developed iris adhesion, and 3 patients (10.7%) developed corneal banded degeneration. These complications may not only cause the advanced visual impairment of children, but also complicate the clinical management of disease. In some cases, the repeated surgical interventions appeared to increase the risk of metastasize of tumor cells.

A number of other studies regarding the PPV in RB patients were also reviewed, however, these research articles focused on the management of the ocular complications such as retinal detachment, vitreous hemorrhage, vitreous turbidity, and other conditions after chemotherapy or radiotherapy.\textsuperscript{19–23} However, based on these studies, the prognosis of the regressed patients under the treatment of PPV appeared to be much better than the patient with uncontrolled tumors. The literatures also summarized some advices to improve the outcome of PPV for RB patients: (1) Retinal tumors should be stabilized for a long enough time before surgery. The longer the tumor is under controlled, the better the outcome of the PPV with lower risk of recurrence and metastasis.\textsuperscript{24} (2) The localized vitreous seeds should be removed firstly and entirely using a vitreous cutter with the dry vitrectomy technique.\textsuperscript{16,17} (3) An appropriate cut rate and low negative pressure is crucial to the outcome of PPV.\textsuperscript{17} (4) Routine injection of chemotherapy agents should be delivered into the vitreous cavity and subconjunctiva around the sclerotomies.\textsuperscript{25,26} (5) An appropriate follow-up schedule should be well designed and implemented strictly as planned. In the event of tumor recurrence or metastasis, the enucleation of eyeball should be performed as soon as possible.

This study has some limitations which could affect the results to varying degrees, for example, the number of cases was small, no control group was involved, and the follow-up time was varied. Because the sample size was small in this study and the pathological degree of the RB might be inconsistent, it is hard to make such a conclusion as optimal number of courses of the preoperative chemotherapy. Also, for the same reason, it is not statistically significant in comparing which treatment is more effective at preventing recurrence or metastasis after vitrectomy. More controlled studies on large sample are needed to make conclusions regarding these points. However, as far as we know, our study involved the largest sample size and the longest observation period among all relevant case studies regarding the application of PPV in RB treatment.
Conclusion

Based on this retrospective study, some key points should be well discussed when considering the PPV for the treatment of active RB. PPV should not be recommended as a routine treatment due to the risk of recurrence, metastasis, and postoperative complications. However, on top of the intravitreal injection of chemotherapeutic agents, PPV can be considered for the patient with limited localized vitreous seeds, especially when the conventional treatment alone is not sufficient to achieve the desired therapeutic effect. And meanwhile, to improve the safety, effectiveness, and outcome of PPV surgery, the strict operative indications and operation procedure should be followed. Furthermore, a well-designed follow-up should be implemented strictly as scheduled to prevent any unexpected postoperative incidence.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Authors' Note

This study was approved by the Ethics Committee of Renmin Hospital of Wuhan University (Approval Number: WDRY2020-K047), and followed the tenets set forth in the Declaration of Helsinki. Regarding the operation consent, all the legal guardians of children had been informed the possible risks and complications before the surgery, and signed the written consent form as expected.

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