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Nine cases of recurrence and metastasis of retinoblastoma with stable primary tumors

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Abstract

Purpose: To investigate the clinical characteristics, treatment, and outcomes of metastatic and recurrent retinoblastoma in patients with stable primary tumors. Methods: Clinical data were reviewed for nine patients (two boys and seven girls; median age, 23 months) with stable primary tumors who exhibited metastatic and recurrent retinoblastoma. All patients were treated in the Pediatrics Department of our hospital in the past 5 years. The clinical characteristics, treatment methods, and patient prognoses were recorded. Results: Of the nine patients, three had binocular disease and six had monocular disease (n=12 eyes in this study). The median interval between the end of initial treatment and onset of recurrence was 12 months (range, 3–96 months). Of the nine patients, primary tumors were proved to be stable, seven had bone metastasis, five had lymph node metastasis, two had parotid gland involvement, and three had bone marrow infiltration. At the end of the study period, one patient was lost to follow-up, one patient died, seven patients were alive and three of them were in complete remission and survived disease-free until the end of follow-up. In December 2020, the median overall survival after onset was 32.0 months (range, 18–155 months); the median overall survival after recurrence was 18.0 months (range, 5–34 months). Conclusions: Recurrent and metastatic retinoblastomas are uncommon and easily misdiagnosed at an early stage in patients with stable primary tumors. These cancers can be effectively treated using systemic intravenous chemotherapy combined with surgery, radiotherapy, and hematopoietic stem cell transplantation.

Introduction

Retinoblastoma (RB) is the most common primary eye cancer in children and the second most common intraocular cancer worldwide; it comprises approximately 4% of all malignant tumors in children [**1**] . Patient prognosis depends on early diagnosis and timely treatment**[2].** There are substantial differences in global mortality: up to 40% and 70% in Asia and Africa, respectively, compared with 3%–5% in Europe, Canada, and the United States. Factors associated with the loss of life in patients with RB include delayed diagnosis, difficulty in arranging evaluation by an eye cancer specialist, limitations regarding ophthalmic pathology and genetic testing, and socioeconomic considerations **[3]** . Current treatment methods include systemic chemotherapy, local treatment, surgical treatment, and radiotherapy. In recent years, explorations of novel RB treatment methods have led to an individualized treatment approach. Previous treatment of RB was intended to improve the survival rate; current treatment focuses on eye and vision preservation, while improving the quality of life for affected patients. RB recurrence and metastasis are important issues in RB treatment; extraocular dissemination and metastasis greatly affect patient survival and prognosis. This study investigated RB recurrence involving a stable primary tumor without intracranial and ocular involvement, but with distant metastasis and recurrence. This type of RB is uncommon and easily misdiagnosed, thus requiring vigilance among clinicians.

Methods

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This retrospective study included patients with RB who were diagnosed and treated in the Department of Pediatrics Beijing Tongren Hospital from January 2016 to December 2020. All included patients exhibited recurrence, defined (in accordance with previous literature[**4**]) as progression in tumor size/reappearance or new lesion within 3 months after completion of primary therapy plus adjuvant therapy. Complete systemic examinations were performed during the diagnosis of RB recurrence, including bone puncture, lumbar puncture, lymph node ultrasound, fundus photography examination, eye/head Magnetic Resonance Imaging(MRI), and bone scan or positron-emission tomography/computed tomography(PET/CT). Patients were excluded if they exhibited intraocular or intracranial spread; only patients with recurrence and distant metastasis were included.

The following clinical data were collected for statistical analysis: age at first onset, sex, clinical signs at onset, tumor laterality, family history, tumor stage, treatment after onset, pathology in enucleated eyes, age at recurrence, interval between end of initial treatment and onset of recurrence, interval from the appearance of symptoms to diagnosis after recurrence, neuron-specific enolase(NSE) level at recurrence, metastasis location after recurrence, treatment after recurrence, survival after RB onset, and disease-free survival after recurrence.

In this study, the guardians of participating children provided written informed consent for treatment. This study protocol was approved by the hospital's medical ethics committee[TRECKY2021-096].

Results

In total, nine cases (two boys and seven girls; age at onset, 6–34 months; median age at onset, 23 months) met the criteria above(Table-1). All patients had no family history of RB. Of the nine patients, three had binocular disease and six had monocular disease (n=12 eyes in this study). Using the International Intraocular Retinoblastoma Classification, the disease stages were E in eight eyes, D in one eye, C in two eyes, and B in one eye. Eight patients had white pupils at disease onset, and two patients had eye pain. In the treatment of the original disease, three cases with monocular stage E disease underwent primary enucleation alone, while five case underwent comprehensive treatment includes eye enucleation, intravenous chemotherapy, intra-arterial chemotherapy, photocoagulation; one case achieved disease control after photocoagulation and intra-arterial chemotherapy. Pathological analyses of tissue from patients who underwent eye enucleation revealed undifferentiated RB in three cases, invasion of the anterior segment and extensive choroidal invasion in one case, lamina and optic nerve invasion in one case, and no pathological high-risk factors in three cases. Notably, the pathology reports were missing for two patients.

The median age at recurrence was 40 months (range, 16–132 months). The median interval between the end of initial treatment and onset of recurrence was 12 months (range, 3–96 months)(Table-2). At the diagnosis of recurrence, two patients were undergoing regular follow-up and craniofacial bone metastases were found by ocular MRI. Furthermore, one patient presented with a temporal mass, two patients presented with limb pain, two patients had traumatic onset, and two patients were misdiagnosed with lymphadenitis and mumps, respectively. Although timely diagnosis was achieved in the re-examined patients and the patient with temporal masses, the remaining patients had various delays in diagnosis and treatment. Among the six patients with delay in diagnosis and treatment, the median time was 2.5 months (range, 1–7 months). Among the nine cases (table-1), bone metastasis (7/9), lymph node metastasis (5/9), parotid gland (2/9), and bone marrow infiltration (3/9) were present. Among the seven patients with bone metastases, six had multiple bone metastases. The serum NSE level at relapse was 17.8–370.0 ng/dl. However, in subsequent follow-up, two patients with a low serum NSE level exhibited a late increase (Table-2; No. 1, 5). In four patients who underwent histological biopsy of the metastatic site, pathological examination revealed blue-stained small round cells; three of these patients underwent immunohistochemical analysis. The results were positive for synaptophysin (3/3), NSE (2/2), and CgA (2/3); the results were negative for CD99 (0/3), S-100 (0/3), FLI-1 (0/2), and TdT (0/1), consistent with RB metastasis (Figue-1). One case did not undergo immunohistochemical analysis.

All patients received systemic intravenous chemotherapy. Commonly used chemotherapy drugs were vin-

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cristine (V), cyclophosphamide (C), platinum (cisplatin [DDP]/carboplatin [CBP]), and etoposide (E); The commonly used chemotherapy regimens were "CEV", "CCEV" and "PCEV". Other treatments include local radiotherapy, surgery, autologous stem cell rescue (ASCT)(table-2),and intrathecal chemotherapy in cases with a risk of central nervous system metastasis. At the end of the study period, one patient was lost to follow-up, four patients were undergoing treatment, three patients were in complete remission and survived disease-free until the end of follow-up, one patient died. Among the two patients with both parotid gland and lymph node metastasis, one (No. 2) had partial remission (PR) after 3 months of treatment and was then lost to follow-up, and the other (No. 1) patient (Figue-2), whose target VEGFR-2 was found to be highly expressed on examination, received individualized chemotherapy+ parotid gland and lymph node dissection+ local radiotherapy+ bevacizumab injection after disease recurrence and progression related to irregular treatment after remission. Six patients received systemic intravenous chemotherapy, of which two received local radiotherapy, and one patient (Systemic chemotherapy alone did not achieve complete remission) with multiple bone metastases and bone marrow infiltration combined with ASCT. All of them achieved complete remission (CR) after treatment (Figue-3). However, one patient (No.5) developed ocular involvement at 8 months after recurrence, and the eyeball was enucleated; another patient (No. 6) progressed after remission and died after giving up treatment. The remaining patient (No. 3) had not been reviewed at the end of the follow-up. In December 2020, the median overall survival after onset was 32.0 months (range, 18–155 months); the median overall survival after recurrence was 18.0 months (range, 5–34 months). In the three patients, the mean disease-free survival was 11.0 months (range, 5–13 months).

Discussion

RB relapse is an important issue that requires close monitoring during post-treatment follow-up. Most RB relapse occurs within 3 years after treatment **[5]** . However, late recurrence has been reported up to 11 years after initial treatment **[6]** . The incidence of new tumors after all types of treatment ranges from 6% to 45%. The recurrence site is usually in the eye; recurrence has been reported in the retina, vitreous, and subretinal areas **[7]** . It is suggested that after the patient has achieved complete remission, the tumor should be monitored frequently until the patient reaches the age of 7 years; the follow-up interval can then be extended for patients with stable disease **[6]** .In our study, the mean interval between initial treatment and relapse was 28 months; most patients exhibited relapse within 3 years, which is consistent with the findings in previous reports. Since patients with RB cells usually undergo fundus examination and eye imaging during the follow-up period, ocular recurrence is easier to detect early during the follow-up period; this allows timely diagnosis and treatment. In our study, ocular symptoms were absent in recurrence cases and the interval between recurrence and the primary tumor was long in some cases (up to 8 years); therefore, most patients had various degrees of diagnosis and treatment delays. Lymph node and parotid gland metastasis are often initially diagnosed as lymphadenitis and mumps. After anti-infective treatment fails, the diagnosis is finally confirmed by histopathology. Distant bone metastases usually begin with trauma and limb pain; they are often diagnosed by imaging and histological examinations after protracted and unhealing disease. Therefore, the onset of lymphadenopathy, mumps, limb pain, or trauma in patients with a history of RB should be regarded as an indication for systematic examination to exclude metastases.

RB patients, especially patients with binocular and RB gene mutations, should undergo close monitoring of second primary malignancies (SPM)**[4]** . SPMs are important factors associated with death in RB survivors who have undergone external beam radiation therapy and chemotherapy (especially involving alkylating agents)**[8-10]** . Based on this, RB recurrence and metastasis without involvement of the eye both require careful assessment to distinguish them from other tumors. The common site of RB metastasis is intracranial area **[11]** , followed by bone, and metastasize to the parotid gland and submandibular lymph nodes through the lymphatic vessels has been reported **[12]** . Previous studies have investigated the pathological characteristics of metastatic RB. The diagnostic immunohistochemical markers include CRX and synaptophysin; these can also be combined with RB1 gene mutation or deletion and MYCN proliferation **[13]** . In addition, studies have also confirmed that NSE and synaptophysin are useful markers for the diagnosis of RB **[14]** . In our study, four cases with metastatic lesions underwent pathological examination, which confirmed RB metastasis. One case developed ocular involvement at 8 months after recurrence; pathological analysis of

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the enucleated eye confirmed the diagnosis of RB. In addition, bone marrow cytology and increased serum NSE level are important considerations when distinguishing RB metastasis and recurrence from SPM. Overall, RB recurrence and metastasis, especially when they are not accompanied by ocular lesion recurrence, require careful assessment to clearly differentiate them from SPM. Further clarification can be achieved on the basis of medical history, clinical symptoms, imaging examinations, bone marrow cytology, serum NSE level monitoring, and pathological biopsies of metastases. We suggest that in patients with potential RB metastasis, timely pathological examinations should be performed when possible to confirm the diagnosis and identify secondary tumors.

Generally, the treatment of metastatic RB involves high-dose systemic chemotherapy and radiotherapy. Patients with intracranial lesions require combined treatment with intrathecal chemotherapy; patients with systemic metastases may receive hematopoietic stem cell transplantation (HSCT). There is increasing evidence that high-dose chemotherapy with HSCT is associated with improved survival for patients who exhibit distant metastatic RB without CNS involvement **[15]** . In our study, all patients underwent systemic intravenous chemotherapy; three patients also received local radiotherapy, one patient also underwent parotid gland and lymph node dissection, and one patient also underwent ASCT. Five cases achieved CR, one cases achieved PR, one case died, one case lost to follow-up, one additional case was undergoing treatment. These findings suggest that systemic intravenous chemotherapy is effective for metastatic RB; moreover, focal lesions (e.g., parotid gland and cervical lymph node involvement) can undergo combined treatment with surgery and radiotherapy, consistent with previous reports **[12, 16]** . One patient who was failed to achieve complete remission by chemotherapy alone, underwent ASCT after systemic chemotherapy; the tumor achieved CR and the patient's condition was stable, suggesting that metastatic RB may benefit from chemotherapy combined with HSCT. However, because of the small number of cases in this study, additional studies with more cases are needed to confirm our findings.

Conclusion

We reported nine cases of RB recurrence with stable primary tumors; regardless of primary ocular tumor recurrence, there is a possibility of tumor recurrence in another location (e.g., bone, lymph node, parotid gland, or bone marrow) during RB follow-up. These forms of recurrence are often misdiagnosed as lymphadenitis, mumps, or trauma; the tumor can recur several years later. We recommend that patients with recurrence undergo complete examinations (e.g., serum NSE level, lumbar/bone marrow puncture, ultrasound/CT/MRI/bone scan, or PET/CT if possible) to assess their general condition. For cases with recurrence and metastasis, pathological examination of the metastatic site is ideal for confirming the diagnosis and identifying the secondary tumor. Systemic chemotherapy has an effect on most patients, and it can be combined with surgery, radiotherapy and HSCT according to each patient's manifestation of disease. For complex cases, individualized treatment can be considered; molecular targeted drugs may be beneficial to the treatment of patients with RB.

For various reasons, our patients did not undergo RB gene detection; however, there was no family history of RB in our patients and most data were retrospectively reviewed in this study. Because of lacking ocular symptoms, it is easily misdiagnosed, leading to delays in early diagnosis and treatment; and must be differentiated from secondary tumors. Thus, it requires vigilance among clinicians. During follow-up for patients with RB, ophthalmologists should carefully assess the potential for ocular recurrence, as well as the potential for distant metastasis and recurrence. During a pediatric examination of patients with a history of RB, the presence of lymph node and parotid gland swelling, limb pain, or trauma should be regarded as potential risk factors for tumor recurrence and metastasis, despite long-term remission of the primary tumor.

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The raw/processed data required to reproduce these findings cannot be shared at this time as the data also forms part of an ongoing study.

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References

[1] Wei WB, Zhou N. Attach importance to standardized treatment of retinoblastoma to improve its treatment outcome. *Chin J Ocul Fundus Dis* . 2020 Jun; 36(06):413-418.

[2] Tomar AS, Finger PT, Gallie B, et al. Global Retinoblastoma Treatment Outcomes: Association with National Income Level.*Ophthalmology* . 2021 May;128(5):740-753.

[3] Tomar A S, Finger P T, Gallie B, et al. A Multicenter, International Collaborative Study for American Joint Committee on Cancer Staging of Retinoblastoma: Part I: Metastasis-Associated Mortality.*Ophthalmology* . 2020 Dec;127(12):1719-1732.

[4] Singh U, Katoch D, Kaur S, et al. Retinoblastoma: A Sixteen-Year Review of the Presentation, Treatment, and Outcome from a Tertiary Care Institute in Northern India. *Ocul Oncol Pathol* . 2017 Dec;4(1):23-32.

[5] Shah SU, Shields CL, Lally SE, et al. Hydroxyapatite orbital implant in children following enucleation: analysis of 531 sockets.*Ophthalmic Plast Reconstr Surg* . 2015 Mar-Apr;31(2):108-14.

[6] Ancona-Lezama D, Dalvin LA , Shields CL . Modern treatment of retinoblastoma: A 2020 review. *Indian J Ophthalmol* . 2020 Nov;68(11):2356-2365.

[7] Berry JL, Kogachi K, Murphree AL, et al. A Review of Recurrent Retinoblastoma: Children's Hospital Los Angeles Classification and Treatment Guidelines. *Int Ophthalmol Clin* . 2019 Spring;59(2):65-75.

[8] Temming P, Arendt M, Viehmann A, et al. How Eye-Preserving Therapy Affects Long-Term Overall Survival in Heritable Retinoblastoma Survivors. *J Clin Oncol* . 2016 Sep 10;34(26):3183-8.

[9] Temming P, Arendt M, Viehmann A, et al. Incidence of second cancers after radiotherapy and systemic chemotherapy in heritable retinoblastoma survivors: A report from the German reference center.*Pediatr Blood Cancer* . 2017 Jan; 64(1):71-80.

[10] Shinohara ET, Dewees T, Perkins SM. Subsequent malignancies and their effect on survival in patients with retinoblastoma. *Pediatr Blood Cancer* . 2014 Jan;61(1):116-9.

[11] Ebata K, Mizutani H, Kaneda T, et al. Metastatic retinoblastoma to the orofacial region. *J Oral Maxillofac Surg* . 1991 Oct;49(10):1120-3.

[12] Wang P, Li YJ, Zhang SB, et al. Metastatic retinoblastoma of the parotid and submandibular glands: a rare case report. *BMC Ophthalmol* . 2017 Dec 2;17(1):229.

[13] Meredith DM, Charville GW, Fletcher CDM, et al. Distantly Metastatic Retinoblastoma to Soft Tissue and Bone: A Challenging Diagnosis Highlighting the Utility of CRX. *Am J Surg Pathol* . 2021 Jun 1;45(6):820-824.

[14] López López JC, Fernández Alonso N, Cuevas Álvarez J, et al. Immunohistochemical assay for neuron-specific enolase, synaptophysin, and RB-associated protein as a diagnostic aid in advanced retinoblastomas. *Clin Ophthalmol.* 2018 Jun 28;12:1171-1179.

[15] Dunkel IJ, Khakoo Y, Kernan NA, et al. Intensive multimodality therapy for patients with stage 4a metastatic retinoblastoma.*Pediatr Blood Cancer* . 2010 Jul 15;55(1):55-9.

[16] Purkayastha A, Sharma N, Pathak A, et al. An extremely rare case of metastatic retinoblastoma of parotids presenting as a massive swelling in a child. *Transl Pediatr* . 2016 Apr;5(2):90-4.

Figure 1. Pathology of lymph node metastases

Hematoxylin and eosin staining,Original magnification for all images: 10 x 20.Microscopic observation showed small round blue stained cell nest arrangement (F). Immunohistochemistry showed CgA+(A), Syn+ (D),

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S-100-(C), Ki-67 40%+(B). Tumor emboli in the vascular vessel were visible, Syn+ (E).HE: Hematoxylin and eosin.

Figure 2: CASE-1 after irregular treatment progression

Figure 2-A: Multiple nodules in the right parotid gland area, parapharyngeal space, posterior neck and pretracheal space in PET-CT. Some of them were enlarged and fused into clusters with increased metabolism, which was considered as malignant lymph node metastasis;

Figure 2-B MRI showed multiple nodules in the right parapharyngeal space, parotid gland area, posterior neck and anterior tracheal space, with partial fusion, showing equal T1 and slightly longer T2 signals, which were significantly enhanced after enhancement; Figure 2-C MRI review after 3 cycles of chemotherapy: the original lesion was moderately enhanced, with a smaller range and increased necrosis; Figure 2-D MRI reexamination after cervical lymph node dissection + radiotherapy and chemotherapy, the original lesions only showed multiple spotty short T2 signal shadows in a small area, while the enhanced scan showed slightly uneven enhancement.

Figure 3: Bone scan image of a patient with bone metastases

A1-2: Before treatment: Concentrated area of radioactive distribution can be seen in the sphenoid bone, the right ethmoid bone, the right maxilla and the right femur; B1-2: Under treatment: Concentrated area of radioactive distribution in the right periorbital bone and proximal right femur;C1-2: Post-treatment review: No obvious abnormalities in the whole body bone scan.

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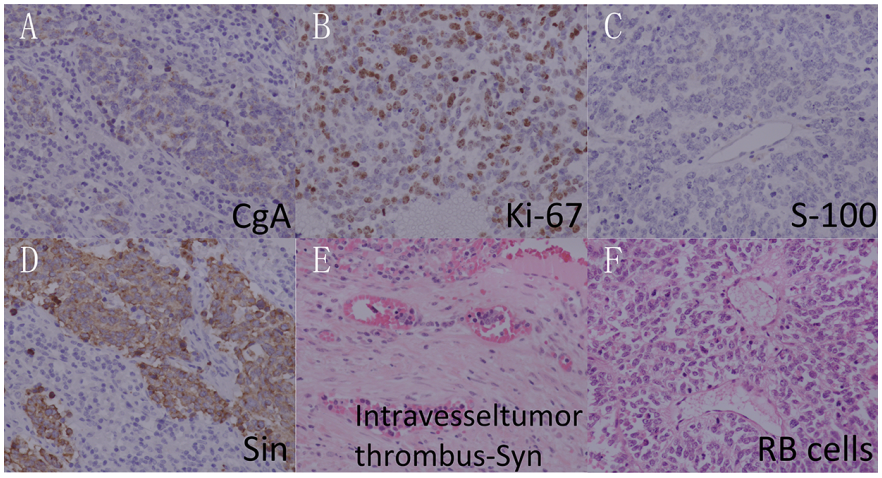

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