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Bilateral retinoblastoma: Long-term follow-up results from a single institution

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= Abstract =

Purpose : The authors aimed to analyze the long-term effects of treatments, especially external beam radiotherapy (EBRT), in bilateral retinoblastoma patients.

Methods : This retrospective study analyzed the medical records of 22 bilateral retinoblastoma patients who were registered between October, 1987 and October, 1998 and followed-up for more than 10 years. They were treated by enucleation, EBRT, and systemic chemotherapy. Age at diagnosis, sex, delay prior to treatment, Reese-Ellsworth (RE) classification, and the local treatment modalities were analyzed in relation to recurrence-free survival (RFS) and complications.

Results : Median age at diagnosis was 7.0 months (range 1.7-31.6 months). Leukocoria was the most common presenting feature. Two patients had a familial history. The RE classifications of the 44 eyes were group II in 4, III in 14, IV in 4, and V in 22. At the end of a median follow-up period of 141 months (range 55-218 months), 20 patients were alive. The 10-year ocular survival rate of the 44 eyes was 56.8±7.5%. The 10-year RFS and ocular survival rate of the 29 eyes treated by combined EBRT and chemotherapy were 75.9% and 86.2%, respectively. Treatment delay (>3 months) was found to be related to higher risk of recurrence. Complications after EBRT were cataract, retinal detachment, phthisis bulbi, and facial asymmetry. No patient developed a second malignancy during the follow-up period.

Conclusion : Early detection and prompt treatment can increase ocular survival rates. In addition, careful attention should be paid to possible long-term sequelae in these patients. (Korean J Pediatr 2009;52:674-679)

Key Words : Bilateral retinoblastoma, Long-term effects, Treatment

Introduction

The survival of retinoblastoma patients has greatly improved over the past decades, and interestingly, this was achieved without collaborative trials or randomized studies[1, 2]. The incidence of retinoblastoma is low, and currently, represents much less than 1% of all human malignancies[1]. Therefore, progress made in the treatment of retinoblastoma has been achieved by developing new treatments and by retrospective analysis[1, 3-5]. In Korea, approximately 16-17 unilateral and 8-9 bilateral retinoblastoma cases are newly diagnosed annually[6, 7].

The treatment of bilateral retinoblastoma is challenging. The preservations of eyes and visual acuity are problematic, and a younger age at diagnosis limits the choice of treatment options and places patients at higher risk of developing treatment-related toxicities. Furthermore, the germ-line mutation, which underlies the pathogenesis of bilateral retinoblastoma, increases the risk secondary malignancies[8, 9]. In keeping with the progress made in ophthalmic oncology, chemoreduction plus focal therapy is replacing the classical treatment modalities, that is, enucleation or external beam radiotherapy (EBRT)[4, 10-12]. Although treatment approaches are being developed to minimize sequelae, few reports have

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been issued regarding the long-term outcomes of the traditional treatment modalities that had been undertaken in our country.

In this retrospective study, we aimed to evaluate the treatment outcomes of bilateral retinoblastoma patients and focused on the long-term effects of EBRT and systemic chemotherapy[3, 13, 14]. Also relations between recurrence rates and Reese-Ellsworth classifications, ages at diagnosis, and treatment modalities were analyzed.

Materials and methods

1. Selection of Patients and Clinical Characteristics

From October 1987 to October 1998, a total of 132 retinoblastoma patients were registered at our institution. In the present study, we retrospectively reviewed 22 selected patients who met the following criteria: (1) Bilateral retinoblastoma; (2) no history of previous treatment; (3) surgery at our institution; (5) the receipt of EBRT at our institution, and (7) event-free patients who had more than 10-years follow up to evaluate the long-term effects of treatment.

Of the 132 cases, 36 (27.3%) patients had bilateral retinoblastoma. Patients were excluded in this study for the following reasons: refusal to treat (n=2) and referral to other institutions (n=5) and follow-up duration less than 10 years (n=7). Therefore, the final study population consisted of 22 patients.

The median age at first presentation was 3.7 months (range, 1-31.6 months). Presenting features were; leukocoria (n=10), strabismus (n=7), orbital swelling (n=2), and others (n=3). Seventeen (77.3%) patients were males and 5 (22.7%) were females. Median age at treatment was 10.3 months (range, 1.7-31.6 months). Two cases had a relevant family history. The RE classifications[3] of the 44 eyes were; group II in 4 eyes (9.1%), group III in 14 (31.8%), group IV in 4 (9.1%), and group V in 22 (50.0%). All cases were bilateral intraocular diseases and did not have any evidence of distant metastasis. Informed consent was acquired from legal guardians.

2. Diagnosis, Treatment and Follow-up

Diagnosis of retinoblastoma was made based on the typical ophthalmologic and radiographic findings, and was confirmed pathologically using the surgical specimens of the enucleated eyes.

The initial treatments were chosen according to the RE classification and chance of preserving visual acuity. Usually RE group V tumors and eyes considered unlikely to preserve vision were treated by enucleation, and eyes with lesser involvements (RE group IV or less) or eyes considered likely to preserve vision were treated by external beam radiation (EBRT) and chemotherapy. However, when both eyes were RE group V, EBRT and chemotherapy were attempted. The EBRT techniques used followed guidelines described in the radiotherapy literature, that is, a daily fraction size of 1.8-2.0 Gy to a mean total dose of 46 Gy (range, 24-60 Gy)[5, 15]. Twenty-two patients received chemotherapy. Chemotherapeutic regimens varied according to treatment era; doses and schedules are summarized in Table 1. Patients eyes were followed up by performing fundoscopic examinations monthly and examinations under general anesthesia every 2 months. Recurrent tumors, vitreous and subretinal seeds identified during follow-up were treated by cryotherapy or laser photocoagulation.

Long-term effects of treatment were meticulously checked

Table 1. Chemotherapy Regimens for Bilateral Retinoblastoma

Regimen (Number of patients)	Agents and dose	Schedule
CV (n=7)	Cyclophosphamide (30 mg/kg, day 0) Vincristine (0.05 mg/kg, day 0)	q 3 wk×20
CVA (n=2)	Cyclophosphamide (20*-30† mg/kg, day 0) Vincristine (0.05 mg/kg, day 0) Doxorubicin‡ (2 mg/kg, day 0)	q 3 wk×20 (*×8, †×12, ‡×8)
CARBOPEV (n=11)	Carboplatin (200 mg/m^2, day 0-2) VP-16 (150 mg/m^2, day 0-2) Vincristine (1.5 mg/m^2, day 0,7,14)	q 4 wk×9
CARBOPEVD (n=2)	Carboplatin (400 mg/m^2, day 0) VP-16 (100-150 mg/m^2, day 2-3) Vincristine (1.5 mg/m^2, day 0) Actinomycin-D (1.0 mg/m^2, day 2),	q 4 wk×9

in the course of 10-year follow-up period. In the affected eyes, functional as well as cosmetic effects, i.e., preservation of useful vision, orbital hypoplasia, cataract, retinal detachment, vitreous or anterior chamber hemorrhage and phthisis bulbi were concerns. And development of secondary malignancy at- or outside the previously irradiated filed was another concern.

3. Statistical Analysis

Clinical data were analyzed with respect to outcome, which included disease recurrence and ocular survival. The variables analyzed were; age at diagnosis, sex, delay prior to treatment, RE classification and the local treatment modalities used (EBRT vs. enucleation). Chi-square tests were used to find relations between clinical and outcome variables. Continuous variables were analyzed by grouping them into discrete categories. The Kaplan-Meier product limit method was used to estimate ocular, overall, and event-free survival (EFS). Event was defined as relapse after initial response and the development of new tumors. Relations between clinical variables and survival were sought using the log-rank test. All calculations were performed using SPSS version 11.5 software (SPSS Inc, Chicago, IL, USA), and P values of <0.05 were considered significant.

Results

1. Tumor control and Recurrences

Fifteen eyes (34.1%) were enucleated. All RE group II to IV tumors (n=22) underwent EBRT and chemotherapy. EBRT and chemotherapy were tried as a first line treatment for some RE group V tumors to avoid enucleation, that is, for 4 eyes in 2 patients and for 3 eyes in 3 patients after enucleation of contralateral group V eyes (Table 2).

Of the 29 eyes initially treated with EBRT and chemotherapy, 5 eyes developed new tumor or 2 eyes developed orbital recurrence. Initial RE group and choice of chemotherapy were not found to influence the event-free survival rate. Treatment delay (>3 months) was associated with higher event rates (P=0.04). New tumors or orbital recurrences were managed using various treatments, i.e., cryotherapy (n=1), radiation+chemotherapy (n=2), radiotherapy (n=2), and enucleation (n=2). Enucleation was undertaken when tumors were too large to be controlled by other local treatments or when the attainment of useful vision could not be expected. In 2 patients, recurrent tumors progressed despite treatment and these patients eventually succumbed to the disease.

2. Overall survival of patients and Ocular survival

After a median follow-up of 141 months (range, 55-218 months), 20 patients remained alive (90.7%). The 2 patients who died of retinoblastoma were lost to follow-up for more than a year and at re-presentation they were found to have developed orbital recurrence with tumor spread to the brain and metastasis to bone and bone marrow. Chemotherapy and radiation therapy failed to halt progression in these two patients.

The 10-year ocular survival rates of the entire 44 eyes were 56.8±7.5% (Fig. 1). Because of the different treatment strategies used, ocular survival rates of the 44 eyes varied by RE group. In detail, survival rates by group were; 100% for group II, 92.9% for group III, 75.0% for group IV and 22.7% for group V (P<0.001). In terms of the 29 eyes that were treated with EBRT and chemotherapy, 10-year recurrence-free and ocular survival rates were 75.9% and 86.2%, respectively (Fig. 2).

3. Vision Preservation, Late Effects of Treatment

Visual acuity information was available for 19 of the 20 patients that survived to the last follow-up. These data represent the most recent visual acuity that was recorded for each patient. Eight patients (42%) attained a visual acuity better than or equal to 20/40. Five patients (26%) achieved a visual acuity worse than 20/40 and better than 20/200. Six patients had a visual acuity worse than 20/200 and one patients visual acuity was unknown.

Eye complications after EBRT were; cataract, retinal detachment, phthisis bulbi, and others. Facial asymmetry or hypoplasia of the orbital area occurred to some degree in patients who underwent EBRT. However, no standard scale exists to record facial asymmetry and, in our analysis, 1

Table 2. Local Control of Treated Eyes

Stages (n=44)	Enucleated	Retained		
		EBRT only	EBRT and cryotherapy	EBRT and laser
II (n=4)		4		
III (n=14)		10	3	1
IV (n=4)		3	1	
V (n=22)	15	7		

Abbreviation : EBRT, external beam radiotherapy

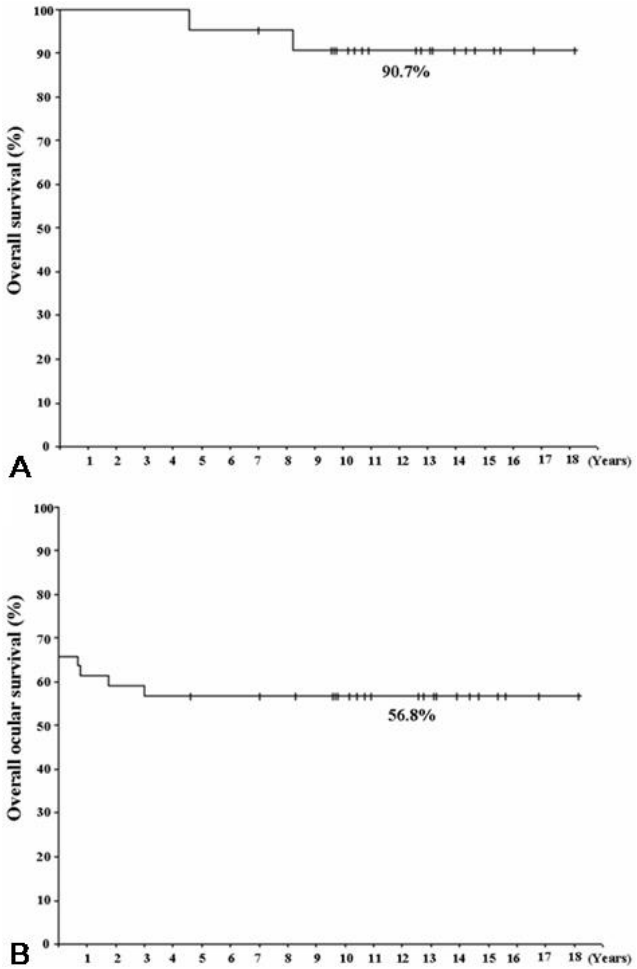

Fig. 1. Kaplan-Meier survival plot. (A) Overall survival of 22 patients, (B) Ocular survival of the 44 eyes.

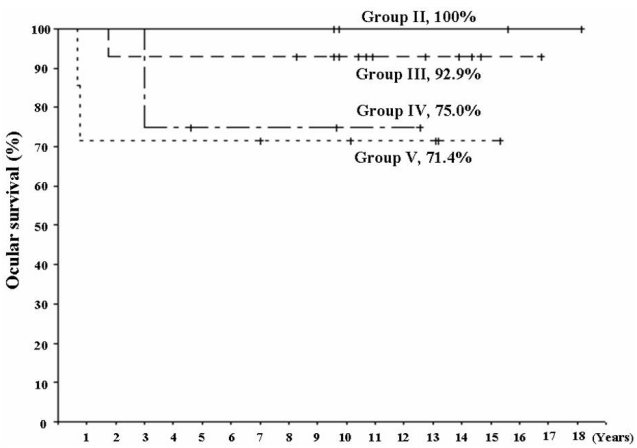

Fig. 2. Ocular survival of the 29 eyes treated with external beam radiotherapy and chemotherapy. Survival was plotted according to the Reese-Ellsworth classifications.

Table 3. Late Effects of External Beam Radiotherapy

Complication	Number of patients (%)
Orbital	
Cataract	6 (20.7)
Retinal detachment	3 (10.3)
Phthisis bulbi	2 (6.9)
Orbital hypoplasia	1 (3.4)
Vitreous hemorrhage	1 (3.4)
Anterior chamber hemorrhage	1 (3.4)
Secondary malignancy	0 (0)

patient who had more severe asymmetry than the expected were recorded as having facial asymmetry or hypoplasia. None of our patients developed a second new malignancy during follow up (Table 3).

Discussion

In this retrospective analysis of bilateral retinoblastoma, treatment delay was found to be associated with a higher recurrence rate. Cataract was the most frequently encountered complication after EBRT, and no patient had developed a secondary malignancy during the 12-year follow-up period. Based on these findings, we speculate that early detection and prompt treatment are probably necessary to increase ocular survival rates. In addition, careful attention should be paid to the detection of possible long-term sequel in these patients.

Our study has several limitations. First, the number of cases was small and the median follow-up duration of 12 years was not long enough to detect secondary malignancies. Collaborative studies and follow-up over a longer period are necessary to assess genetic impact on the development of secondary malignancies. Second, local treatment modalities were not homogeneous, especially in group V. However, this heterogeneity provided us with an opportunity to compare enucleation and systemic chemotherapy in controlling tumors of group V eyes.

Our study also shows that a treatment delay of more than 3 months is related to a higher recurrence rate. On the other hand, age at diagnosis was not found to be associated with outcome. During this era of chemoreduction, there is a need to define tumor characteristics associated with outcome. We initially believed that a younger age might be related to a higher risk of developing new tumor or recurrence. During the initial 3 months of life body weight doubles[16], and thus, we presumed that tumors encountered during this period

would be highly aggressive. When patients were divided into two groups using an age of 3 months as a cut off and compared in terms of outcome, it was found that a younger age was not associated with a more advanced RE grouping, although it tended to be associated with recurrence. We also found that treatment delay was associated with a higher risk of recurrence and of inferior ocular survival. In 13 cases treatment was delayed, due to a delayed diagnosis in 9 or a refusal to undergo treatment due to the fear of losing an eye (n=4). We propose that a routine eye examination be added to infant health examinations to facilitate early detection and prompt treatment[17].

In addition, we found that 70% of RE group V eyes were saved by EBRT and systemic chemotherapy. According to the landmark paper by Reese, bilateral retinoblastoma should be managed by enucleation of the more involved eye and irradiation of the other eye[3]. As a result of the increased incidence of second tumors among irradiated patients and cosmetic problems of enucleation, current attention has focused on chemoreduction plus focal therapies, such as, transpupillary thermotherapy, laser photocoagulation or cryotherapy[4, 10, 18]. However, control of recurrence remains an issue, especially in RE group V eyes. Previous studies have found that 50% of group V eyes were eventually enucleated after repeated recurrences[20]. At our institution, some RE group V eyes were treated by EBRT and systemic chemotherapy first, rather than by enucleation. According to the RE classification, group V eyes are not good candidates for EBRT. Nevertheless, we attempted systemic chemotherapy and EBRT hoping that the former would control tumors located on the anterior side of the eyeball and that the latter would control the tumors located on the posterior side. Although development of new tumor and recurrence were still the problems, 70% of group V eyes were saved. The results of our cases cannot be directly compared with those of the chemoreduction and focal therapy, since we have applied EBRT and our results might have been influenced by selection bias.

Complications arising after treating retinoblastoma have become major issues[21]. The adoption of the multidisciplinary approach has increased survival in retinoblastoma to 90-95 %, and thus, the proper management of long-term survivors is crucia[12, 22]. Patients treated their bilateral retinoblastoma present two issues. First, the preservation of useful vision and cosmetic problems are major concerns[20, 23, 24]. In the present study, 65% of 20 patients who survived bilateral retinoblastoma had visual acuity better than 20/200. Although various orbital complications were encountered after EBRT, visual acuity was not compromised in these patients. The second concern is the development of secondary malignancy [9, 25]. The occurrence of sarcoma in radiated areas has been reported, and a strong causal relationship between EBRT and sarcoma development has been suggested[9, 21, 25]. Radiation dose and patient age during radiotherapy were also related to the development of secondary malignancies[1, 25]. Therefore, chemoreduction treatments were developed to avoid EBRT. Nevertheless, the Rb gene defect that underlies the pathogenesis of bilateral retinoblastoma also contributes to the development of secondary malignancy[8, 9]. For example, although the majority of retinoblastoma cases were unilateral, 98% of secondary malignancies occurred in bilateral cases[9]. Furthermore, the occurrence of secondary acute myelogenous leukemia has also been reported, and has been putatively linked with exposure to etoposide-based chemotherapy[9, 25]. In our cohort, after 12 years of follow-up, none of our 22 bilateral cases developed a secondary malignancy. All these patients underwent EBRT and systemic chemotherapy simultaneously. Furthermore, 11 cases received EBRT before the age of 1 and 13 patients received chemotherapy containing etoposide. However, because these patients are at higher risk, a more meticulous follow-up procedure is being considered.

한 글 요 약

단일기관의 장기추적 결과

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목 적 : 양측성 망막모세포종 환자들의 치료 후 장기후유증을 분석하고자 하였다.

방 법 : 1987년 10월부터 1998년 10월까지 원자력병원에서 치료를 받고 10년 이상 장기추적관찰 중인 양측성 망막모세포종 환자 22명의 의무기록을 분석하였다. 진단시 연령, 치료지연, Reese-Ellsworth (RE) 분류, 국소치료방법 등의 임상 변수와 생존율, 안구합병증을 포함한 장기후유증의 발생과의 관계를 알아보았다.

결 과 : 진단 시 정중 연령은 7.0 개월로(범위, 1.7-31.6개월), 백색동공으로 내원한 경우가 가장 많았다. 44개 안구의 RE 분류는 각각 group II (n=4), III (n=14), IV (n=4), V (n=22)이었다. 추적관찰 141개월째인 현재 20명이 생존하여 있으며, 10년 안구생존율은 56.8±7.5%이었다. 임상변수 중, 3개월 이상의 치료지

연이 재발과 관련이 있었다. 방사선 치료 후 백내장, 망막박리, 안구로, 안면비대칭 등의 합병증이 관찰되었으며 현재까지 이차성 종양의 발생은 없었다.

결 론 : 안구생존율을 향상시키기 위해서는 종양을 조기에 발견하도록 노력하고 진단즉시 치료를 시작해야 할 것이다. 이와 더불어 장기적인 후유증의 발생여부에 대해서도 세심한 추적관찰이 필요하다.

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