INTRODUCTION

Retinoblastoma is the most common intraocular tumor of childhood and accounts for 11% of all cancers that occur during the first year of life (1). Because treatments for retinoblastoma cure over 90% of patients, organ and vision preservation and the minimization of late treatment side-effects are important secondary treatment goals. Retinoblastoma had been treated by external beam radiotherapy (EBR), and for many years this was the accepted treatment standard (2-7). However, greater knowledge of radiation induced morbilities and of secondary tumor risks after radiation therapy (8, 9) have encouraged the use of primary chemotherapy plus conservative focal therapy over the past decade.

Despite the recent trend toward chemoreduction (10-13), radiotherapy remains an excellent means of preserving vision in children (aged >1 yr) with retinoblastoma, because the tumor is radiosensitive and routinely responds to radiotherapy. Moreover, technologic advances made in the radiation oncology enable more precise targeting for tumor, avoiding healthy tissues, and the risks of secondary nonocular cancer reduced. Brachytherapy (14-16) has been used for selected cases in expert hospitals, and stereactic conformal radiotherapy (17-19), and proton therapy (20, 21) could also be considered components in the modern radiotherapy armamentarium for retinoblastoma. However, available clinical data for stereactic conformal therapy and proton therapy is limited.

The Korea Cancer Center Hospital (KCCH) has considerable experience of treating retinoblastoma in Korea, and thus, we retrospectively reviewed our experiences of treating retinoblastoma patients with EBR, as initial treatment, to determine its long-term effect on subsequent tumor control and complications. A total of 32 eyes in 25 patients that underwent EBR for retinoblastoma were reviewed retrospectively. The patients consisted of 21 boys and 4 girls of median age at treatment of 7.1 months. Radiation doses ranged from 35 to 59.4 Gy. The 10-yr ocular and patient survivals were 75.4% and 92.3%, respectively. Nine of the 32 eyes progressed; 7 of these were enucleated and 2 were salvaged by focal treatment. According to the Reese-Ellsworth classification, 4 of 5 eyes of Group II, 13 of 16 Group III eyes, 2 of 4 Group IV eyes, and 5 of 7 Group V eyes were retained, and of the 32 eyes, 13 had visual acuity better than 20/200. Eleven patients experienced a radiation-induced complication. No patient developed a second malignancy during follow-up. Despite the limited number of patients enrolled, EBR may provide a mean of preserving eyeball and vision for some advanced lesions.

Key Words : Retinoblastoma; External Beam Radiotherapy; Complication

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MATERIALS AND METHODS

Patients and tumor characteristics

The medical records of all patients diagnosed as retinoblastoma who received EBR as an initial treatment at the KCCH between July 1987 and June 1998, were reviewed. A total of 36 eyes in 29 patients with intraocular retino-
blastosma underwent EBR as an initial treatment. Of these, 4 patients were excluded due to a short follow-up duration (<3 yr). Patient details and data concerning tumor features, treatment parameters, and complications were collected by chart review.

The characteristics of patients and tumors are described in Table 1. Briefly, the study subjects were 21 boys and 4 girls of median age at treatment commencement of 7.1 months (range 7 weeks to 65 months). Twenty-one presented with bilateral involvement and 4 with unilateral disease. The most frequent presenting finding was leukocoria in 16 patients (64%) followed by strabismus in 6 (24%). For the 21 patients with bilateral involvement, 28 eyes received external beam radiation, and 14 eyes were enucleated due to advanced disease without visual potential before EBR. Of the 32 eyes treated, 0 were of Reese-Ellsworth (RE) Group I, 5 were Group II, 16 were Group III, 4 were Group IV, and 7 were Group V (5 in RE Group Va and 2 in RE Group Vb). All of two eyes in Group Vb had a localized vitreous seeding pattern.

Table 1. Demographic data for retinoblastoma patients

| Pt | Irradiated eye | RE | Dose (Gy) | Clinical course | Visual acuity | OS (mon) | Complications |
|----|----------------|----|-----------|---------------|--------------|----------|---------------|
| 1  | Od (Bil)       | 2a | 37.4      | LP (+)        | 80           |          |               |
|    | Os (Bil)       | 3a | 50.0      | 20/250        | 80           |          |               |
| 2  | Od (Bil)       | 3a | 38.0      | Phthisis → enucleation | Enucleation | 74        | Cataract, phthisis |
|    | Os (Bil)       | 4a | 38.0      | LR            | Enucleation  | 35        |               |
| 3  | Od (Bil)       | 2a | 43.0      | LP (+)        | 116          |          |               |
|    | Os (Bil)       | 3a | 43.0      | 20/20         | 116          |          |               |
| 4  | Os (Bil)       | 2a | 46.0      | 20/20         | 140          |          | Cataract      |
|    | Od (Bil)       | 3a | 44.0      | LR            | Enucleation  | 16        |               |
| 5  | Od (Bil)       | 3a | 48.0      | 20/1000       | 150          |          |               |
|    | Os (Bil)       | 3a | 49.0      | 20/15         | 150          |          |               |
| 6  | Od (Bil)       | 5a | 50.0      | LR            | Enucleation  | 8         |               |
|    | Os (Bil)       | 5b | 50.0      | 20/25         | 104          |          |               |
| 7  | Od (Bil)       | 5a | 59.4      | 20/1000       | 153          |          |               |
|    | Os (Bil)       | 5a | 50.0      | LR            | Enucleation  | 10        |               |
| 8  | Os (Un)        | 2b | 35.0      | LR            | Enucleation  | 13        | RD, VH, facial asymmetry |
| 9  | Os (Bil)       | 4a | 38.0      | LR            | Enucleation  | 34        | Cataract      |
| 10 | Os (Bil)       | 3a | 38.0      | 20/25         | 127          |          | Cataract      |
| 11 | Os (Un)        | 3a | 38.0      | 20/500        | 117          |          |               |
| 12 | Os (Bil)       | 3a | 38.0      | 20/25         | 131          |          | RD            |
| 13 | Os (Bil)       | 3a | 41.0      | LR → laser    | 20/60        | 64        |               |
| 14 | Os (Bil)       | 3a | 41.0      | 20/25         | 96           |          |               |
| 15 | Od (Bil)       | 4a | 41.6      | LR → cryotherapy | 20/1000     | 148       | Cataract, RD, VH |
| 16 | Os (Bil)       | 2a | 41.6      | 20/100        | 105          |          |               |
| 17 | Od (Bil)       | 3a | 41.6      | 20/150        | 136          |          | Cataract      |
| 18 | Os (Bil)       | 5b | 45.0      | 20/25         | 71           |          |               |
| 19 | Os (Bil)       | 4a | 46.0      | 20/20         | 78           |          |               |
| 20 | Od (Un)        | 3a | 46.0      | LR            | Enucleation  | 37        |               |
| 21 | Od (Bil)       | 3a | 46.8      | HM (+)        | 85           |          | Cataract      |
| 22 | Od (Bil)       | 5a | 48.0      | 20/500        | 150          |          | Cataract      |
| 23 | Os (Bil)       | 3a | 48.0      | 20/100        | 55           |          |               |
| 24 | Os (Bil)       | 3a | 48.0      | 20/500        | 132          |          |               |
| 25 | Os (Un)        | 5a | 56.0      | LP (+)        | 78           |          | Cataract, RD, microophthalmia |

Pt, patient; RE, reese-ellsworth classification; OS, oculus survival; Od, oculus dexter; Os, oculus sinister; Bil, bilateral; LP, light perception; LR, local recurrence; Un, unilateral; RD, retinal detachment; VH, vitreous hemorrhage; HM, hand motion.
scopic tumors. Twenty-two patients received cyclophosphamide plus vincristine with or without doxorubicin at various doses and cycle numbers.

Additional cryotherapy or laser therapy was administered after EBR when tumor progression was detected. Enucleation was performed in cases with definite tumor progression after additional treatment or due to a severe complication.

Evaluations and statistics

Evaluations were performed at each follow-up to determine tumor sizes and visual acuities, and to detect new lesions and complications, such as, retinopathy, cataract, neovascular glaucoma, and midfacial hypoplasia. In addition, we analyzed prognostic factors, such as, gender, age, and the RE classification according to ocular survival using the log-rank test. In addition, the relationship between RE classification and visual acuity was analyzed using the t-test. The Kaplan-Meier method was used to estimate overall and ocular survivals. Overall survival was calculated from EBR commencement to final follow-up or death, whereas ocular survival was calculated from EBR commencement to time of enucleation or final follow-up with an intact eye.

RESULTS

Median follow up was 150 months (range 55-249 months), and the 10-yr ocular and overall survival rates were 75.4% and 92.3%, respectively (Fig. 1). Two patients died after involvement of the central nervous system.

Nine of the 32 eyes developed new lesions or reactivation of previous lesions. Of these, 7 eyes were enucleated and 2 were salvaged by cryotherapy and laser treatment (Table 1). One additional enucleation was performed due to phthisis bulbi (patient No. 2 in Table 1). Therefore, ocular preservation was achieved in 24 of the 32 (75.4%) eyes. According to RE classification, 4 of 5 eyes were retained in Group II, 13 of 16 in Group III, 2 of 4 in Group IV, and 5 of 7 in Group V. Vision was preserved in 24 (75%) out of 32 treated eyes. Of the preserved 24 eyes, 9 (37.5%) had a visual acuity better than 20/40; 5 (20.8%) had an acuity worse than 20/40 but better than 20/200, and 10 (41.7%) had vision worse than 20/200. All the patients with visual acuity less than 20/200 presented with the involvement of the posterior pole, and showed macular degeneration following treatment.

Records showed that 11 patients experienced a radiation-induced complication; 6 had cataracts alone, 1 had retinal detachment alone and 4 had one more complications (Table 1). Nine cataracts were recorded and removed when necessary, and vision restoration or improvement was achieved in all cases. The median time to cataract development was 5 yr and 9 months (range 13 to 125 months). Serous retinal detachment was detected in 3 eyes; 2 were transient and reattached after 3 months and 6 months respectively. One patient developed vitreous hemorrhage and underwent enucleation. Midfacial hypoplasia occurred to some degree in all patients. Typically, deforming hypoplasia was recorded in 2 patients. Fig. 2 shows typical hypoplasia in a treated eye by CT and photography. No patient developed a second malignancy during follow-up.

An age of less than 13 months was found to be a significantly favorable factor of ocular survival by univariate analysis, but this was not confirmed by multivariate analysis. No
other prognostic factor was identified during this study (Table 2), and in particular, no significant relationship was found between RE classification and visual acuity.

**DISCUSSION**

EBR has a valuable role in the treatment of retinoblastoma, but radiation-induced secondary tumors jeopardize the role played by EBR in retinoblastoma. Large-scale cohort studies performed to quantify cancer risks in retinoblastoma treated by radiotherapy (9) have found that radiotherapy contributed significantly to the risks of developing brain, nasal cavity, and eye and orbit cancers. Notably, the risk of cancer of the nasal cavity increased by 1,364-fold in hereditary retinoblastoma treated by EBR. External beam radiation is usually favored for the treatment of bilateral retinoblastoma, which is almost always hereditary, and thus, all possible efforts should be made to reduce the risk of secondary malignancies after radiotherapy.

Various EBR techniques have been developed to reduce radiation dose to the lens. A review of EBR technology revealed that the lateral field is usually used because it requires lower lens doses (2-7). In most cases, radiation-induced cataract is not an obstacle to the vision preservation. However, reductions in doses administered to the orbital cavity, optic nerve, or cranial bone appear to be more important. Recently, more meticulous techniques, such as, intensity modulated radiation therapy (IMRT) and stereotactic hypofractionated radiation therapy, have been introduced, which administer lower doses of radiation to critical organs. Reisner et al. (7) compared several EBR techniques, that is, electron beam, the lateral 2 field and anterior-lateral 2 field techniques, and IMRT, and found that IMRT had an advantage over the other techniques, because it allowed greater dose reductions to the orbit and lacrimal gland, while maintaining therapeutic doses to the ora serrata retinae and vitreous. Recently, Sahgal et al. (18) reported that stereotactic fractionated radiation therapy for localized tumor masses can achieve markedly lower doses to surrounding critical normal tissues than conventional radiation therapy. Furthermore, proton therapy (20, 21) is also likely to reduce cranial bone radiation dose due to the radiation quality of the Bragg peak. However, few clinical trials have been performed and clinical data is scarce.

Brachytherapy (14-16) was introduced in the 1920’s to treat ocular tumors and reduce the exposure to normal tissue around tumors, and has been further developed in terms of new radioisotopes, implant designs, and techniques of placement. Table 3 details the ocular survival and cataract incidence rates of conventional radiation therapy techniques and

| Table 2. Prognostic factors by univariate analysis |
|-------------------------------|-----------------|-----------------|-------|
| Prognostic factors | No. of cases | Ocular survival (%) | P value |
| Gender | | | |
| Male | 25 | 75.3 | 0.7 |
| Female | 7 | 71.4 | |
| Age (mon) | | | |
| <13 | 17 | 94.1 | 0.008 |
| ≥13 | 15 | 52.5 | 0.2 |
| RE | | | |
| 2-3 | 21 | 80.0 | |
| 4-5 | 11 | 63.6 | |
| RT dose (Gy) | | | |
| <41 | 8 | 50.0 | 0.08 |
| ≥41 | 24 | 83.3 | |

RE, Reese-Ellsworth classification; RT, radiotherapy.

| Table 3. Review of retinoblastoma treated by EBR or plaque brachytherapy |
|------------|---------------------|---------------------|---------------|
| Method of radiation | Series | Year | No. of eyes | Method | Dose (Gy)/ Fraction No. or dose | Ocular survival (%) | Incidences of cataract (%) |
| EBR | Schipper (3) | 1983 | 54 | Oblique 6 MV photon enhanced dynamic wedge | 45/15 fraction | 81 | 33 |
| Hernandez (24) | 1996 | 34 | Ant & lateral 4 MeV photon field, no lens shielding | 34.5-49.5/1.5-2.0 Gy | 73 | 41 |
| Blach (25) | 1996 | 113 | Lat collimated 6 MV photon field | 42-46/21-23 fraction | 84 (LC) | 22 |
| Phillips (2) | 2003 | 47 | Ant lens-sparing electron beam | 38-50/15-20 fraction | 38 (LC) | |
| Present series | 2006 | 32 | Single and two field technique | 35-55/1.6-2.0 Gy | 74 | 28 |
| Brachytherapy | Shields (14) | 2001 | 208 | Lat or ant & lateral 6 MV photon field | 40 to tumor apex | 79 | 31 |
| Merchant (22) | 2004 | 25 | I-125(178), 106-Ru(7) Co-60(17), I-192(6) | 44 (35-47.6) to tumor apex | 60 (crude) | NA |
| Shields (16) | 2006 | 84 | I-125 | 40 to tumor apex & 2 mm | 95 | 43 |
| Schueler (15) | 2006 | 175 | I-125, 106-Ru | 50 to 70 to tumor apex | 87 | 17 |
| Abouzeid (23) | 2008 | 41 | I-125, 106-Ru | 50 to tumor apex | 76 (crude) | 10 |

LC, local control; NA, not assessed; MV, megavoltage; MeV, megavoltage electron.
brachytherapy; it is worth noting that the radiation doses, fraction numbers, and beam delivery techniques used at different institutes over the last 20 yr has varied considerably. The literature review revealed that ocular survival ranged from 38% to 84% (median 73%) for EBR, but from 60% to 95% (median 79%) for brachytherapy. Furthermore, radiation-induced cataract was found to be the most common complication of radiation therapy; the incidence of cataract ranged from 22% to 41% (median 28%) for EBR and from 10% to 43% (median 17%) for brachytherapy. However, it should be noted that because retinoblastoma is rarely encountered in infants, skilled treatment is required to obtain good outcomes after EBR and brachytherapy.

In the present study, we analyzed patient and ocular survival, and long-term treatment toxicities. Our results, in terms of ocular survival and the incidence of cataract, compare well with those of other EBR series (22-25). Long-term follow-up findings revealed that late radiation effects were milder than expected, and that favorable visual outcome had been maintained. Furthermore, ocular survival analysis by RE classification, despite the limitations imposed by small patient numbers, showed that involved eyes with an RE classification of 4 or 5 achieved 64% ocular survival, which indicates that radiation therapy should be considered before enucleation as primary or secondly treatment for even advanced retinoblastoma.

In conclusion, our long-term results show that EBR has an important role to play in the avoidance of enucleation in retinoblastoma with small lesions or advanced lesions with vitreous seeding. Furthermore, non-conventional radiation therapies as brachytherapy, stereotactic radiotherapy, IMRT, and proton therapy, are likely to reduce complication rates. Additional research is required to establish new indications for the various radiation therapy techniques available for the treatment of retinoblastoma.

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