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Long-term Results of Radiotherapy for Subfoveal Choroidal Neovascularization (CNV) in Age-related Macular Degeneration (ARMD)

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Purpose: We performed this prospective randomized study to evaluate the efficacy and the complications of radiotherapy for Subfoveal CNV in ARMD and to compare the treatment results at two dosages (14.4 Gy and 19.8 Gy).

Materials and Methods: 60 eyes of 55 patients were enrolled, and randomized into 14.4 Gy (31 eyes) or 19.8 Gy (29 eyes) groups. CT was used to plan the radiotherapy. All patients received radiotherapy with a 1.8 Gy daily dose using 4 MV photon. We categorized treatment results as improved, stable, or deteriorated based on visual acuity changes of more than 2 lines on the ETDRS chart.

Results: Median follow-up period was 33.5 months. At 12 months, visual acuity improved in 9 (16.7%), stable in 41 (75.9%), and aggravated in 4 (7.4%) of 54 evaluated eyes. At 24 months, 49 eyes (81.7%) were evaluated. Visual acuity improved in 6 (12.2%), was stable in 33 (67.4%), and deteriorated in 10 (20.4%). At 36 months, 37 eyes were evaluated. Six (16.2%) eyes were improved, 21 (56.8%) stable, and 10 (27.0%) deteriorated. No significant difference in response was observed between the 14.4 Gy and 19.8 Gy groups (Mantel-Haenszel χ^2=0.4756). The proportion of eyes with a vision of 20/100≤increased from 28.3% initially to 32.7% after 24 months of radiotherapy. There were no severe acute or chronic complications.

Conclusion: External beam radiotherapy with doses of 14.4 or 19.8 Gy may be an effective treatment for subfoveal CNV in ARMD. No dose-response relationships with respect to treatment response or toxicity were observed between the 14.4 Gy and 19.8 Gy groups.

Key Words: Subfoveal choroidal neovascularization, Radiotherapy

Introduction

Age-related macular degeneration (ARMD) is a leading cause of blindness in the elderly. The natural course of visual acuity in untreated ARMD is highly variable. In the non-exudative "dry" form, which accounts for approximately 85% of ARMD, drusen and atrophic changes predominate, and in most cases, the process is self-limiting and causes no dramatic visual deterioration. However, the "wet" exudative form is characterized by the formation of choroidal neovascularization (CNV) beneath the retinal Bruch's membrane, and the natural history of eyes with CNV is poor. Visual acuity deteriorates to 20/200 or worse in approximately 70% of affected eyes within 18 months, and about 90% of legal blindness can be attributed to the wet form of ARMD.[1] CNV is classified as classic or occult based on fluorescein angiogram (FAG) findings. "Classic" CNV is a well-circumscribed lesion of early hyper-fluorescence on FAG and progressive leakage in the late phase. Subretinal hemorrhage and marginal lipid deposits may also occur. By contrast, if the neovascular membrane is poorly demarcated or even invisible, the CNV is referred to as occult, which accounts for about 60~70% of CNVs. The spontaneous worsening of visual acuity is usually quicker in classic CNV than in occult CNV.[2]

Despite the serious visual outcome, therapeutic options in cases of choroidal neovascularization (CNV) are scarce. The

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efficacy of laser photocoagulation has been confirmed, however, only a small subset (10~15%) of patients with well-demarcated exudative macular degeneration is suitable candidates. Management is difficult and controversial especially when CNV involves the fovea. In cases of subfoveal CNV, laser photocoagulation results in a significant and immediate drop in visual acuity, and sometimes, results in the destruction of the overlying retina and visual loss.[3~5] So many attempts have been made to identify new effective treatment modalities, e.g., photodynamic therapy, pharmacological intervention, and surgical treatment. However, the success of these therapies is limited, and some are currently under investigation.

Radiotherapy for ARMD was occasionally used at some European Institutes in the 1960s. The rationale for using ionizing radiation is based on its proven efficacy on various neovascular structures such as arteriovenous malformations and hemangiomas. But, because of the lack of sound systematic investigations, radiotherapy did not become common practice for ARMD.

We performed this prospective randomized trial to evaluate the long-term effectiveness of radiotherapy and to compare the dose-response relationships to 14.4 Gy vs. 19.8 Gy in subfoveal or juxtafoveal CNV in ARMD.

Materials and Methods

Sixty eyes of 55 patients treated for age-related CNV at the Department of Radiation Oncology, Seoul National University Hospital from June 1997 to August 2000 were enrolled in this study. Eyes were randomized into 14.4 Gy (A, 31 eyes) and 19.8 Gy (B, 29 eyes) groups.

Eligibility criteria included recent visual acuity aggravation within the 6 month period prior to treatment, a subfoveal or juxtafoveal CNV, and age >50 years. Patients with advanced cataract or other definite causes of CNV were excluded.

Before radiotherapy, baseline ocular examinations were performed, namely, anterior chamber and fundoscopic examination, tonometry, fluorescein angiography, indocyanin green test, visual field, and visual acuity test using the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart.

CT based planning was performed for radiotherapy. 100% dose was prescribed to cover the posterior retina including the fovea and the optic disc. All patients were treated with a single lateral or lateral-oblique port using a 4 MV photon beam. A half beam was used to reduce radiation dose to the ipsilateral lens and contralateral eye. A field size of 3×6 cm^2 was most commonly used. A total dose of 14.4 Gy or 19.8 Gy was given in 1.8 Gy daily fractions, 5 times per week.

After radiotherapy, ocular examinations same as baseline examination were planned to all the enrolled patients monthly for 3 months, and then 6 monthly. But because of the low compliance to the fluorescein angiography, indocyanin green test or visual field examination, ocular examinations including anterior chamber and fundoscopic examination and visual acuity assessment using the ETDRS protocol were only accessible to all the patients. According to visual acuity changes of more than 2 lines on the ETDRS chart, we determined treatment response as improved, stable, or deteriorated. Impact on quality of life was evaluated by a loss of reading ability. A value of 0.2 (20/100) on the ETDRS scale was chosen as the lower limit. We excluded fluorescein angiography for the evaluation of treatment response because it had not been done as initially scheduled in many patients.

To ascertain the statistical significance of changes in visual acuity at the two dosages (14.4 Gy and 19.8 Gy), we used the Chi-square test in the SAS 8.0 Windows package.

Results

Median patient age was 62 years, and male patients predominated (male : female=38 : 22). The median duration of visual acuity decrement before radiotherapy was 5 months. In 55 eyes, the choroidal neovascular membrane involved the fovea center, and in 5 eyes was in a juxtafovea location. Before radiotherapy, a subretinal hemorrhage was observed in 30 eyes, and classic CNV was observed in 57 eyes (Table 1).

The period of follow-up was 3~61 months (median; 33.5). At twelve months after radiotherapy, visual acuity improved in 9 (16.7%) eyes, was stable in 41 (75.9%), and deteriorated in 4 (7.4%) of the 54 evaluated eyes. After 24 months, 49 eyes were evaluated. Visual acuity was improved in 6 (12.2%), stable in 33 (67.4%), and deteriorated in 10 (20.4%) eyes. No significant difference in radiotherapy response as evaluated by visual acuity was observed between the two treatment groups (Mantel-Haenszel χ^2=0.4756) (Table 2).

The proportion of eyes having a vision of 20/100≤ was

Table 1. Patient Characteristics

		Group A (14.4 Gy)	Group B (19.8 Gy)
Number of eyes		31	29
Age	Year	49~75 (Median; 63)	53~75 (Median; 61)
Sex	Male : Female	22 : 9	16 : 13
F/U period	Months	4~60 (Median; 33)	3~61 (Median; 34)
Both eye involvement		2	5
Previous laser photocoagulation		7	2
Ant. chamber exam	Cataract	10	3
	Nucleosclerosis	1	4
	Pseudophakia	2	0
Foveal involvement	Yes : No	28 : 3	27 : 2
Initial SRH*	Yes : No	12 : 19	18 : 11
Initial symptom	V/A† decrease only	4	4
	Metamorphopsia	18	17
	Scotoma	22	20
	Metachromopsia	3	2
	Blurred vision	0	1
	Photophobia	1	5
	Other	1 (pain)	1 (lightening)
Systemic disease	Hypertension (HT)	3	5
	Diabetes mellitus (DM)	4	1
	HT+DM	2	0
	Ischemic heart disease	0	3

*subretinal hemorrhage, †visual acuity

Table 2. Visual Acuity Changes after Radiotherapy by ETDRS* Chart

	Group A (14.4 Gy, 31)			Group B (19.8 Gy, 29)		
	No. of eyes/No. of evaluated eyes (%)			No. of eyes/No. of evaluated eyes (%)		
Months	Improved	Stable	Deteriorated	Improved	Stable	Deteriorated
3	5/31 (16.0%)	24/31 (77.4%)	2/31 (6.6%)	1/29 (3.4%)	26/29 (89.7%)	2/29 (6.9%)
6	5/30 (16.7%)	23/30 (76.7%)	2/30 (6.6%)	2/28 (7.1%)	22/28 (78.6%)	4/28 (14.3%)
12	4/28 (14.3%)	23/28 (82.1%)	1/28 (3.6%)	5/26 (19.2%)	18/26 (69.2%)	3/26 (11.6%)
24	3/24 (12.5%)	17/24 (70.8%)	4/24 (16.7%)	3/25 (12.0%)	16/25 (64.0%)	6/25 (24.0%)
36	1/18 (5.6%)	10/18 (55.6%)	7/18 (38.8%)	4/19 (21.1%)	11/19 (57.8%)	4/19 (21.1%)

Cochran-Mantel-Haenzel χ^2 test, p=0.4756†

A visual acuity change of more than 2 lines was considered as an improvement or as a deterioration.
*early treatment of diabetic retinopathy study (ETDRS) chart, †the p values of each months were all greater than 0.05

28.3% before radiotherapy, and this increased to 32.7% at 24 months after radiotherapy. Initially 7 (22.6%) patients in group A and 10 (34.5%) patients in group B had a vision of 20/100 ≤, and after 24 months there were 8 (33.3%) and 8 (32%) in groups A and B, respectively. All patients with a vision of 20/100≤ had a pretreatment vision of 20/100≤.

Central scotoma was the most commonly improved symptom. 17 (39.5%) of 43 eyes with central scotoma showed improvement, and in 2 eyes, central scotoma was completely resolved at 12 and 15 months after radiotherapy. Scotoma was aggravated in only 1 patient. Metamorphopsia improved in 10 (28.6%) of 35 eyes (Table 3).

After radiotherapy, a subretinal hemorrhage (SRH) occurred 15 times in 13 eyes (8 in the 14.4 Gy group, and 5 in the

Table 3. Symptom Changes after Radiotherapy

	A (14.4 Gy)	B (19.8 Gy)
Metamorphopsia	18	17
Improved	5* (27.8%)	5† (29.4%)
Stable	12 (66.7%)	12 (70.6%)
Aggravated	1 (5.5%)	0 (0%)
Scotoma	22	20
Improved	11‡ (50.0%)	6 (30.0%)
Stable	10 (45.5%)	14 (70.0%)
Aggravated	1 (4.5%)	0 (0%)

*completely disappeared in 2 patients, †completely disappeared in 1 patients at 3 months, ‡completely disappeared in 2 patients at 12 & 15 months, respectively

Table 4. Complications after Radiotherapy

	A (14.4 Gy, 31)	B (19.8 Gy, 29)
Acute*	1 (3.2%)	7 (24.0%)
Mild headache	0	1 (3.4%)
Nausea	0	2 (6.9%)
Increased lacrimation	0	2 (6.9%)
Conjunctivitis	0	1 (3.4%)
Dry eye	1 (3.2%)	1 (3.4%)
Chronic	0	0

*all acute complications were minimal and tolerable without medication

19.8 Gy group). Five eyes of those 13 had pretreatment SRH, and it was observed in 2 and 3 eyes in group A and B, respectively. In 4 eyes, SRH recurred (once in 3 eyes, twice in 1 eye). Recurrent SRH occurred at 1 eye in group A and in 3 eyes in group B. Seven of 15 SRHs occurred within 6 months of radiotherapy, 1 between 6 and 12 months, 6 between 12 and 24 months, and 1 SRH at 35 months.

There were no severe acute or chronic complications such as radiation keratitis, retinopathy, or cataract (Table 4).

Discussion

Low dose ocular irradiation has been shown to be generally effective and safe in the cases of benign disease such as choroidal hemangioma or thyroid ophthalmopathy. Based on these results, low dose radiotherapy had been used to treat CNV.

Ionizing radiation could affect CNV in at least three possible ways. First, it can cause stenosis and small capillary closure. Second, radiation exhibits an anti-angiogenesis effect on capillaries and reduces endothelial cell migration and new capillary formation. The suppression of angiogenesis by radiation is a complex process that involves several growth factors, regulatory genes, direct action on fibroblasts, growth arrest, and apoptosis.[6,7] Third, radiation can reduce inflammatory reactions, mainly by its effects on white blood cells.[8]

Debate about the efficacy of radiotherapy continues (Table 5,[9~15] 6[16~18]), and because of the lack of sound systematic investigation, radiotherapy has not become common practice for ARMD. Moreover, studies undertaken to evaluate the efficacy of radiotherapy have shortcomings. First, the radiation schedules used have been diverse, i.e., total doses have ranged from 8~24 Gy and fraction sizes from 1.8~8.0 Gy. Second, the treatment volumes of external beam radiotherapy also differ. For example, Chakravarthy et al. included over 50% of the choroid in the treatment field,[9] and Gripp et al., after CT based simulation, aligned the radiation portal to cover the posterior uvea of the involved eye.[19] Mandai et al. included the macula and optic disc in the clinical target volume,[20] and Bergink et al. irradiated a 1 cm^2 area of the choroid using a 16 MV photon beam.[10] At our institution, after a CT simulation, we use a single lateral port to cover the posterior uvea, including macula and optic disc, with a 100% isodose line. However, no treatment recommendations have been issued. Therefore, because CNV localization is difficult by CT, and low dose radiation is not associated any severe complication, we recommend that the posterior uvea, including macula and optic disc, be included in the treatment volume. Further controlled studies upon treatment volume, treatment failure sites, and on the efficacy of radiotherapy are required. Third, outcome measurements are critical for assessing the efficiency of treatment. It seems advisable to consider the proportion of patients above a functionally significant level of visual acuity. We used a threshold of 20/100 as the minimal visual acuity necessary for reading ability. Grouping is also critical in terms of assessing treatment success. Grouping a wide range of visual acuities together may erroneously suggest an effective therapy. Forth, because ARMD progresses with time, a follow-up period is crucial. Most studies are lacking in terms of patient numbers (i.e., <50) or adequate follow-up (i.e. 12 months). In addition, the separate evaluation of occult and classic CNV is mandatory, because the better natural

Table 5. Positive Treatment Results of Radiotherapy for ARMD

Author	Patient's number	F/U (Mos)	Total dose (Gy)/ Fraction size	Response criteria	Result (Stable/Improved)
Chakravarthy et al[9]	26	12	10~15/2~3	Any VA change	63% (14% at control)
Bergink et al[10]	40	12	8~24/6~8	VA change ≥2 lines	Better than natural course
Freier et al[11]	41	2~3	10~14.4/1.8~2	Subjective VA	93%
Brady et al[12]	278	2~3	10~20/1.8~2	Subjective VA	93%
Berson et al[13]	52	3~16 (7)	14~15/1.8	VA change ≥3 lines	79%
Donati et al[14]	28	6~9	16/4	VA change ≥3 lines	72%
Bergink et al[15]	74	12	24/6	VA change ≥3 lines	68% vs. 48%
This study	60*	34	14.4 or 19.8/1.8	VA change ≥3 lines	80% (2 yr), 73% (3 yr)

ARMD: age-related macular degeneration, VA: visual acuity, NS: not significant. *Eyes

Table 6. Negative Treatment Results of Radiotherapy for ARMD

Author	Patient's number	F/U (Mos)	Total dose (Gy)/ Fraction size	Response criteria	Result (Stable/Improved)
Tholen et al[16]	95*	12~24	10 or 36/2	Any VA change	No significant differences in VA decrease after 24 Mos.
Spaide et al[17]	91	12	10/2	VA change ≥3 lines	50% vs 62%
Holz et al[18]	205	12	16/2	Any VA change	Drop of VA 3.5 vs 3.7 (NS) 51% vs 53% lost ≥3 lines

VA: visual acuity, NS: not significant. *Eyes

course of predominantly occult CNV may be erroneously attributed to therapy. However, only a few studies have been stratified according to occult and classic CNV. In the present study, except for 3 patients, all patients had classic CNV and the resulting improvement in visual acuity was considerable compared with the natural course of the disease. Due to the weakness of published studies, it is important that the efficacy of radiotherapy should not be either over- or underestimated; better designed studies are needed.

In the present study, visual acuity was maintained in 79.6% of patients 24 months after radiotherapy. Compared with the natural course of the classic form of subfoveal CNV this was a considerable result. However, no dose-response relationship was observed for 14.4 Gy and 19.8 Gy and no remarkable radiotherapy related complications occurred. Reading ability was preserved only in patients who had reading ability before radiotherapy, which suggests that pretreatment visual acuity and treatment time based on disease process may affect radiotherapy response.

Recently, the effectiveness of low dose radiotherapy in CNV has been questioned by some studies, and its use is not recommended. But the results of the present study indicate that radiotherapy should not be abandoned and that it might be considered as a possible treatment option for CNV, especially, when located on the fovea or juxta-fovea. More studies are needed; especially studies on factors affecting radiation response, disease course, treatment volume, and possible chronic complications.

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국문초록

연령관련 황반하 맥락막 신생혈관증에서 방사선의 장기적 치료 결과

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목 적: 본 연구는 연령관련 황반변성 중 황반하 맥락막 신생혈관증에서 외부방사선치료의 효과 및 부작용의 확인 및 조사선량과의 관련성을 확인하기 위하여 시행되었다.

대상 및 방법: 55명의 환자에서 60안이 본 연구에 포함되었으며, 14.4 Gy군(31안)과 19.8 Gy군(29안)으로 무작위 배정되었다. 방사선치료는 CT를 이용하여 계획하였으며, 4 MV 광자선을 이용하여 1일 1.8 Gy를 조사하였다. 치료의 효과는 ETDRS 시력표에서 3줄 이상의 변화를 보일 경우 향상, 안정, 악화로 판정하였다.

결 과: 중간 추적관찰기간은 33.5개월이었다. 방사선치료 종료 12개월 후, 54안이 추적관찰 가능하였으며, 이 중 9안(16.7%)이 향상, 41안(75.9%)이 안정, 4안(7.4%)이 악화되었다. 24개월 및 36개월 후에는 각각 49안, 37안이 추적관찰 가능하였으며, 24개월에는 6안(12.2%)이 향상, 33안(67.4%)이 안정, 10안(20.4%)이 악화되었으며, 36개월에는 6안(16.2%)이 향상, 21안(56.8%)이 안정, 10안(27%)이 악화되었다. 두 선량 군간에 효과는 의미 있는 차이를 보이지 않았다(Mantel-Haenszel χ^2=0.4756). 20/100 이상의 시력을 지닌 환자의 비율은 방사선치료 전 28.3%에서 치료 24개월 후 32.7%로 증가하였다. 방사선치료와 연관된 심각한 급성 또는 만성합병증은 관찰되지 않았다.

결 론: 14.4 또는 19.8 Gy의 외부방사선조사는 연령관련 황반변성 중 황반하 맥락막 신생혈관증에 효과적인 치료법일 가능성을 지니며, 치료의 효과 및 부작용 면에서 두 선량 간에 의미 있는 차이는 관찰되지 않았다.

핵심용어: 황반하 맥락막 신생혈관증, 방사선치료