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CLINICAL INVESTIGATION

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External beam radiation in patients suffering from exudative age-related macular degeneration

A matched-pairs study and 1-year clinical follow-up

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Abstract ● Background: The aim of this prospective study was to ascertain whether external beam irradiation is effective in patients with subretinal neovascularization (SRN) due to age-related macular degeneration (AMD). ● Methods: All patients had subfoveal SRN due to AMD as verified by fluoresceinangiography. Two hundred and eighty-seven patient-eyes were treated by external beam irradiation (total dose of 16 Gy in 2-Gy fractions, 5 times a week) from January 1996. The analysis was restricted to those 73 patients with a minimum follow-up of 11 months. Eighteen patients with subfoveal SRN who refused treatment served as control group (CG). 18 patients of the treatment group (TG) were matched for visual acuity, refraction and extent of SRN. The statistical analysis was performed with the unpaired *t*-test. ● Results: The mean age of the CG was 73.9 years (range 66.9–81.3 years) and of the TG 75.6 years (range: 65.7–80.6 years). The median follow-up was 13.5 months (range 11.9–18.4 months) in the CG and 12.9 months (range 11–13.9 months) in the TG. The initial visual acuity (VA) was 20/80 in both groups. After 7 months the follow-up revealed median VA of 20/400 in the CG and 20/160 in the TG (P=0.0335). The final median VA was 20/400 in both groups, with a range from 20/40 to 20/1000 in the CG and from 20/63 to 20/500 in the TG (P=0.2433). The SRN doubled in size during this time in both groups. ● Conclusion: These results suggest that external beam irradiation applied in 2-Gy fractions 5 times a week slows down the visual loss in exudative AMD for a short time. Nevertheless, the patients' reading vision could not be saved in the long term.

Introduction

Subretinal neovascularization (SRN) is a leading cause of legal blindness in people over 50 years of age in the western world. This pathologic process leads to growth of blood vessels beneath the retina and the retinal pigment epithelium (RPE). As a consequence, exudates and other components of the blood accumulate in the retina [7, 9]. The resulting scar (fibrovascular tissue) destroys the macular retina and is a leading cause of severe irreversible loss of vision [7, 9, 20] in western countries. SRN can be idiopathic or associated with the presumed ocular histoplasmosis syndrome, high myopia or, more commonly, with age-related macular degeneration (AMD) [7, 27]. The prevalence of AMD increases with age, from 11% of persons between 65 and 74 years to 27.9% in those older than 75 years [7]. Although most patients suffer from the atrophic form of macular degeneration, in 10% of patients a rapidly evolving neovascularization develops [6, 23, 25, 27].

For several years laser photocoagulation has been used to destroy SRN [30–38]. The main disadvantage of laser photocoagulation is destruction of the overlying retina and consequently visual loss [30, 31, 49]. Patients with subfoveal membranes – the majority of cases – loose

three lines of vision, as noted after laser photocoagulation in the Macular Photocoagulation Study [34–36, 38].

In contrast, radiation therapy has been shown to induce regression of choroidal hemangiomas and stunt the growth of the neovascular component of ocular and cutaneous wounds without thermal damage [3, 11, 12, 15, 24]. Reinhold [41] showed that a single dose of 8.7 Gy on normal capillaries leads within hours to vasodilation, swelling and vacuolation of the cytoplasm of endothelium cells. A few weeks after irradiation loss of endothelial nuclei occurs, with a reduction in the number and length of the capillaries and occlusive changes [13, 41]. Radiation retinopathy is unlikely to occur in eyes exposed to 25 Gy irradiation or less when delivered in daily fractions less than or equal to 2 Gy. The risks of low-dose radiotherapy may be limited to cataract formation and transient keratoconjunctivitis with epiphora [10, 14, 39, 40].

Several studies and presentations on the irradiation of SRN published since 1993 have shown a benefit for the majority of patients [4, 13, 16]. The stabilization of the size of SRN and reduction of leakage were reported independently [4, 13]. The visual acuity had stabilized or improved in at least 60% of patients by 12 months after treatment [16]. The natural course of the visual acuity of patients with SRN is poor. In 70% of the affected eyes the visual acuity will be 20/200 or worse within 18 months [7], when the SRN is initially present within the foveal avascular zone.

In view of these reports and the increasing number of patients presenting at our clinic, we started to use radiation treatment for patients suffering from subfoveal neovascularization. We present our method of application, dose distributions, and clinical findings after radiotherapy for SRN.

Patients and methods

Patient selection and eligibility criteria

Beginning in January 1996, 287 consecutive patients with subfoveal neovascularization were treated with external beam radiotherapy. They were untreatable according to Macular Photocoagulation Study criteria or had refused laser therapy.

All lesions demonstrated evidence of SRN on fluorescein angiography. Such evidence included SRN, blood, and exudate, as well as retinal pigment epithelial and neurosensory retinal detachments. Classic subretinal neovascular lesions were characterized by well-demarcated areas of hyperfluorescence discerned on the early phases of a fluorescein angiogram, which progressed into the late phases.

Among the 287 patient-eyes in our series, we restricted the analysis to those with a minimum of 11 months of follow-up. Patients with diabetes, previous laser treatment, occult type of SRN, duration of symptoms (visual decrease, metamorphopsy) exceeding a month and visual acuity below 20/1000 were excluded. With these criteria, our analysis includes 73 patients (50 women, 23 men) with the classic type of SRN. Eighteen patients who refused treatment were followed up and matched with 18 treated patients for visual acuity, refraction, size of SRN, age and gender distribution. The matched pairs were analyzed with the unpaired *t*-test.

Clinical evaluation and diagnosis

At presentation, each patient underwent a complete eye examination. After standard nonmasked Early Treatment Diabetic Retinopathy Study refraction, pupillary, ocular motor, and slit-lamp examinations were performed. For calculation the visual acuity was expressed in logMAR (Table 1). A Goldmann tonometer was used to measure intraocular pressure. Ophthalmoscopy was performed with direct, indirect, and contact lens techniques as needed. The basal dimensions and presence of the SRN membranes were determined by ophthalmoscopy, fundus photography, and fluorescein angiography. The size of SRN was calculated relative to the optic nerve head of the same eye (Fig. 1). The angiography was done on the same day, before we mentioned the possibility of radiation therapy to the patient.

Radiation treatment planning

Within 10 days each patient suitable for radiotherapy was seen by the radiation oncologist. Treatment was initiated during the following 2 weeks. For all patients an individual aquaplastic head cast and mask fixation was prepared. Radiation was delivered with a linear accelerator using 5- to 6-MeV photons based on computerized treatment planning and simulation. The majority of patients had a lateral single beam portal angled 3–5 deg posteriorly, to spare the anterior bulbus and the contralateral eye. With CT-scan-based computerized treatment planning it was guaranteed that the target volume (posterior third of bulbus oculi) received a homogeneous dose, and the dose to the contralateral lens was limited to an average of 5–6% (Fig. 2). Usually field size was 3 cm×3 cm. The calculated total reference dose was 16 Gy, according to the criteria of the ICRU (International Criteria for Radiation Units) 50 report, divided into eight fractions of 2 Gy (5 fractions per week).

Every patient was seen once weekly by the radiation oncologist to determine subjective and objective reactions and possible side effects.

The first complete ophthalmologic follow-up examination was performed 6–8 weeks after the end of radiation therapy. There was evaluation of possible radiation side effects such as eyelid erythema, conjunctival injection, corneal epitheliopathy and cataract as well as measurements of visual acuity, standardized refraction, pu-

Table 1 Corresponding logMAR and ETDRS values

LogMAR	ETDRS
0.0	20/20
0.1	20/25
0.2	20/32
0.3	20/40
0.4	20/50
0.5	20/63
0.6	20/80
0.7	20/100
0.8	20/125
0.9	20/160
1.0	20/200
1.1	20/250
1.2	20/330
1.3	20/400
1.4	20/500
1.5	20/660
1.6	20/800
1.7	20/1000
1.8	Hand movement 20 cm
2.3	Intact light perception
2.6	Defective light perception
3.0	No light perception

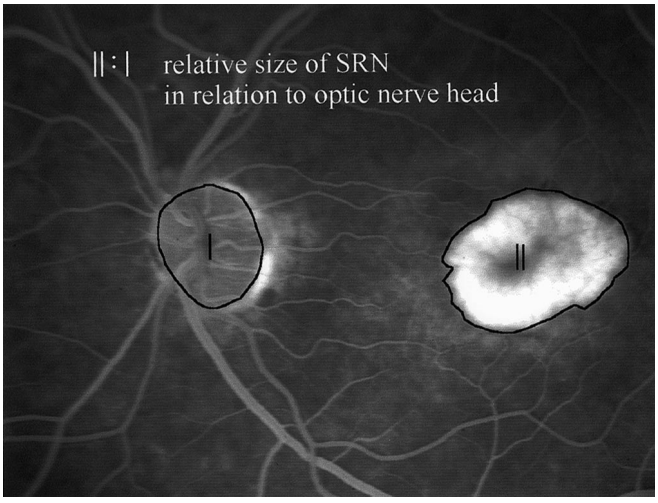

Fig. 1 Calculation of size of SRN relative to head of optic nerve using software Imagescape 4.45

pillary function, ocular motor function, slit-lamp examination, Goldman tonometry, ophthalmoscopy, fundus photography, and a control fluorescein angiography. Further follow-up visits every 3 months were recommended.

Results

The results of 73 patients with a median follow-up of 13.3 months (rnge 11–16.9 months) are presented. The median age was 74.3 years (range 52.2–88.8 years). The visual acuity dropped one line or more in 46 eyes (63%), 10 eyes (13.7%) remained unchanged and 17 eyes (23.3%) improved one line or more during the follow-up. The mean and median loss of visual lines are presented in Table 2, and Fig. 3 shows the development of visual acuity over time. The ophthalmic examination growth of the subretinal lesion showed in 71 eyes (97.3%); only 1 eye stabilized and 1 eye improved (Fig. 4).

Table 2 Lost of visual acuity at follow-up examination expressed in lines, in relation to the initial visual acuity

Months	2.1	4.5	7.6	10.5	13.3
Mean	0.019	0.096	1.73	2.68	2.90
Median	0	0	1	2	3

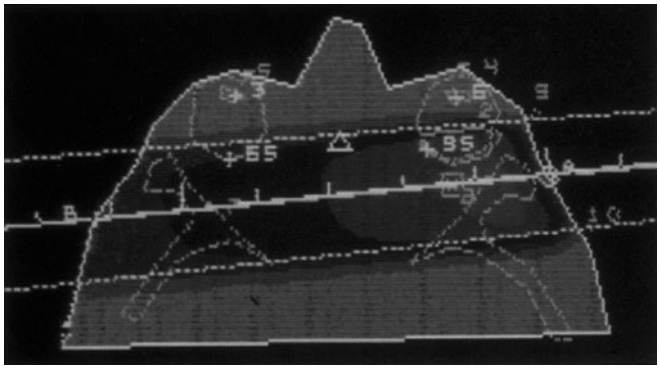

Fig. 2 CT simulation of irradiation. The numbers (e.g. 95) represent percentage of the total dose

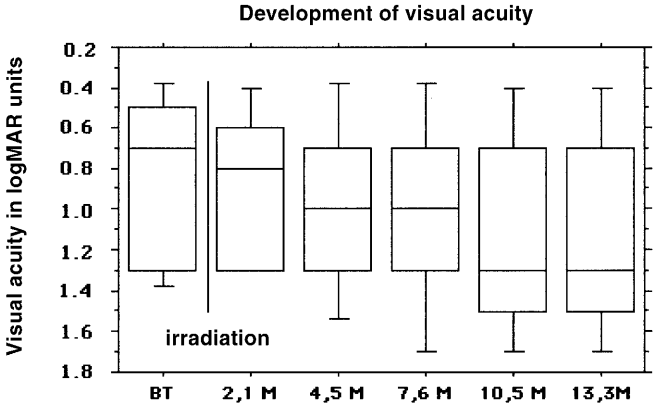

Fig. 3 LogMAR distribution of visual acuity over time in 73 eyes (*BT* before treatment, *M* months)

In the matched-pairs study, the two groups had equal gender distribution (13 women, 5 men), refraction, visual acuity (P=0.8368) and membrane size (P=0.9408) at recruitment. Sixteen (89%) out of 18 eyes of the patients who refused treatment showed a decrease of vision, one eye was stable, and one improved. The matched treated eyes lost vision in 16 cases (89%) and 2 eyes stabilized (Table 3, Fig. 5). The vision decrease was slower in the treatment group (visual acuity 20/160) than in the control group (20/250) over the first 7 months (P=0.0335). After 13 months the visual acuity was 1.2 logMAR (20/330 ETDRS) in the treatment group and 1.3 logMAR (20/400 ETDRS) in the control group (P=0.2433). The membrane

Table 3 Lost of visual acuity at follow-up examination, expressed in lines, in relation to the initial visual acuity (*CG* control group, *TG* treatment group)

	CG	TG	CG	TG	CG	TG	CG	TG	CG	TG
Months	1.83	1.81	4.38	4.25	7.13	7.33	9.67	9.83	13.31	13.48
Mean	0.094	0.056	0.294	0.144	0.475	0.228	0.561	0.422	0.7	0.561
Median	0	0	0.3	0.15	0.55	0.2	0.6	0.4	0.8	0.7

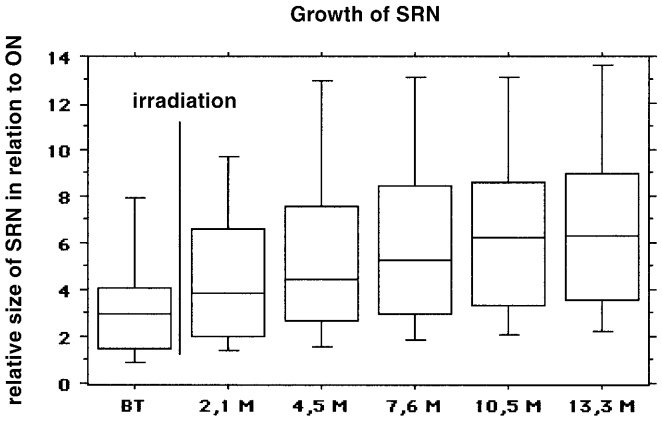

Fig. 4 Size of SRN over time in 73 eyes (*BT* before treatment, *M* months, *ON* optic nerve head)

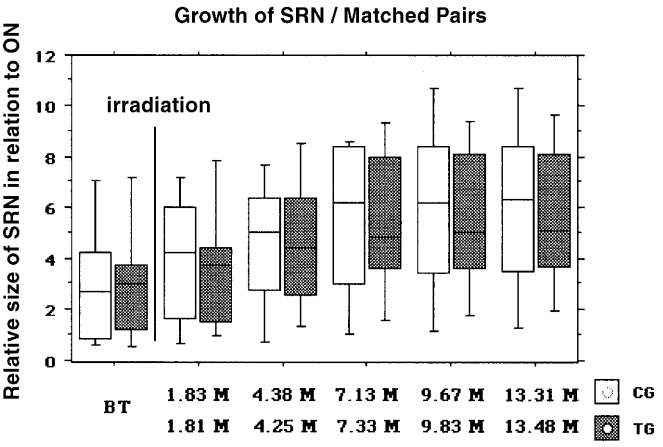

Fig. 6 Development of SRN size in the matched pairs study (*CG* control group, *TG* treatment group, *BT* before treatment, *M* months, *ON* optic nerve head)

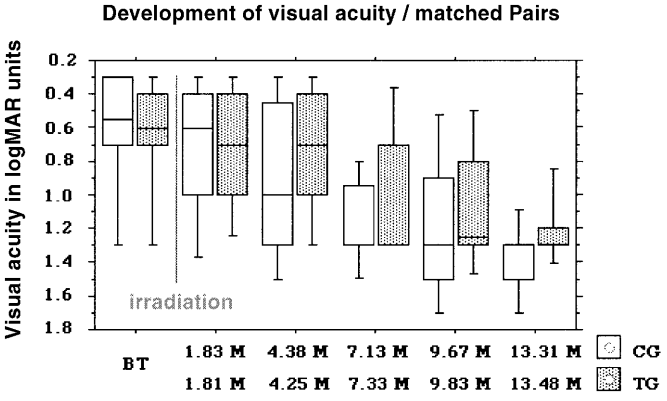

Fig. 5 Development of visual acuity in the matched pairs study (*CG* control group, *TG* treatment group, *BT* before treatment, *M* months)

doubled in size during the study period in both groups (Fig. 6). From the beginning of recruitment to the end of follow-up, no statistically significant difference was seen between the two groups in the growth of the subretinal membrane (P=0.8398).

There was no evidence of conjunctival and eyelid edema in patients receiving external beam radiotherapy. None of the patients complained of transient epiphora or ocular irritation.

Discussion

Subretinal neovascularization is a major challenge for an ophthalmologist today. The total number of patients with AMD, and thus of thus with the wet form, is increasing. This is related to the demographic development in western societies. Additionally, the patient of today is more demanding than 30 years ago. The disease itself has a poor outcome for visual acuity [8, 20, 25, 27]. After 21 months' follow-up an eye with a subfoveal SRN, and an initial visual acuity of 20/200 or better, shows in at least 70% of cases visual acuity of 20/200 or worse. Guyer et al. [20] reported that more than three quarters of eyes with a subfoveal choroidal neovascularization had lost at least four lines of visual acuity after 24 months' follow-up.

Laser photocoagulation, one treatment form, is recommended for classic subfoveal SRN by the Macular Photocoagulation Study Group, if the patient is willing to accept a large decrease in visual acuity immediately after treatment. After 3 years, treated patients had a lesser decrease in visual acuity from baseline. Fifty-one percent of the laser-treated eyes showed persistent or recurrent SRN 24 months after initial treatment without influence on the visual acuity [28]. Perifoveal laser photocoagulation has been proven effective in preservation of visual acuity in the short term, but this treatment resulted in a six-line decline of visual acuity after 42 month in 76% of patients [33]. Eyes treated with scattered photocoagulation of the macula had less visual loss from baseline but did not recover visual acuity of 20/100 or better [48].

The surgical approach, pars plana vitrectomy with subretinal membrane peeling [47] in combination with macular relocation according to Machemer [29, 43], is beneficial only for selected patients. It might be an option in the future combined with transplantation of retinal and/or iris pigment epithelium cells [1, 2, 19]. Today, this technique is still experimental and the subject of many in vitro or in vivo research projects.

Neovascularization is a complex process of cellular endothelial stimulation followed by growth, migration, and differentiation. This is promoted by platelet-derived endothelial cell growth factor, vascular endothelial-derived growth factor, basic fibroblast growth factor, and endothelial growth factor [5, 18, 21, 22, 42, 50]. These prod-

ucts of endothelial cells, macrophages, and supporting host tissues exert strong autocrine and paracrine actions on focal areas of neovascularization [21]. It is not clear which of these factors, or their regulatory genes, may be responsible for SRN. However, interruption of angiogenic pathways may inhibit the development and/or progression of SRN.

Low-dose radiotherapy has been shown to inhibit neovascularization, but there is controversy regarding the exact mechanism or factors that drive this effect [5, 50]. Sublethal doses of radiation that fall on the shoulder of the cell survival curve may affect the production of cytokines. Such threshold doses of radiotherapy induce growth arrest and DNA damage of genes. These damaged genes are thought to represent downstream effectors for cellular responses resulting in growth arrest and/or apoptosis [5, 18, 21, 22, 42, 50].

Thus, radiotherapy of SRN may affect angiogenesis directly (by directly destroying neovascular endothelial cells and cytokine-producing macrophages) and/or indirectly (through effects on regulatory genes within cells which produce endothelial-growth-regulating cytokines). In addition, low-dose radiotherapy inhibits fibroblast proliferation with subsequent scar formation [11, 12]. Therefore, radiotherapy also may inhibit the scar formation characteristic of end-stage exudative macular degeneration.

Because of the poor prognosis of subfoveal SRN, the limited treatment possibilities and the quite positive results of the presented preliminary studies, we started to treat subfoveal and neovascular membranes with low-dose external beam radiotherapy. Unlike laser photocoagulation, radiotherapy did not result in the destruction of the overlying retina, avoiding the acute visual loss associated with laser therapy [30, 31]. External beam radiotherapy delivered doses below levels known to cause retinopathy in healthy human eyes [10, 25, 39].

Although a higher proportion of normal structures received unnecessary radiation when 6-MV photons were used, the dose of these structures was low (generally less than 1000 cGy). The clinical significance of this dose to these structures may be negligible. This is because the 6-MV radiotherapy we used is not likely to cause persistent dry eye problems, and although minimal doses of radiation have been reported to cause cataract, we found that most of our patients either had lenticular opacities or were pseudophakic. Our short follow-up period and lack of a control group are obstacles to any proof of efficacy. However, we have not noted such a benefit for visual acuity, neither have we found any control of the growth of the subretinal membranes as noted by Bergink, Chakravarty, and Finger and their respective colleagues [4, 13, 16]. In our matched-pairs study [26] we found a temporary benefit for the treated patients. In the first 6 months after treatment the visual acuity did not decline as fact as in the untreated patients. Yet, we have noted no short-term complications that might preclude the clinical investigation of this treatment.

Therefore, our clinical experience with external beam radiotherapy has differed from that of Chakravarthy et al. [13], Bergink et al. [4], and Finger et al. [16]. Although this is not a long-term comparative study, we believe that external beam radiation as used in our patients (total dose of 16 Gy in 2-Gy fractions 5 times a week) is not an effective treatment for SRN [46]. Our results are supported by the recently published study by Stalmans et al. [45], who treated 111 patients using 20 Gy. However, we are now considering retreating patients after 6 months with 10 Gy to prolong the initial effect, slowing down the loss of visual function.

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