Low-Energy Stereotactic Radiotherapy for Treatment of Exudative Age-Related Macular Degeneration in a Treat-and-Extend Regimen

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BACKGROUND AND OBJECTIVE: To evaluate the effectiveness and safety of low-energy stereotactic radiotherapy (SRT) combined with anti-vascular endothelial growth factor (VEGF) treatment following a treat-and-extend regimen (TER) in wet age-related macular degeneration (AMD).

PATIENTS AND METHODS: Before/after SRT, the authors compared retrospective consecutive case series of 50 patients requiring frequent anti-VEGF treatment (every 4 or 6 weeks) in wet AMD, treated with a single session of SRT and TER (same manner pre/post-SRT). Outcomes were visual acuity (VA), recurrence-free interval, and central retinal thickness (CRT).

RESULTS: After SRT, CRT was reduced from baseline (407.3 µm ± 153.2 µm) to 12 months (320.2 µm ± 112.1 µm; \( P < .001 \)), with statistical significance from month 2 onward. VA was stable for 12 months (64.0 letters ± 15.1 letters vs. 63.6 letters ± 16.2 letters). The mean recurrence-free interval increased from 4.24 weeks ± 0.66 weeks to 7.52 weeks ± 3.05 weeks at 12 months (\( P < .001 \)). No severe side effects were observed.

CONCLUSION: Low-energy SRT, combined with anti-VEGF TER, was associated with reduced injection frequency and preserved VA during 12 months of follow-up.

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries in people aged older than 50 years. Increased life expectancy, combined with the impact of risk factors such as arteriosclerosis, obesity, and smoking, means that the expected incidence will increase around two-fold by the year 2020. About one-tenth of those with AMD have the neovascular or “wet” form of the disease. The standard of care for wet AMD involves intravitreal injections of drugs that target vascular endothelial growth factor (VEGF), and the introduction of these therapies in 2006 has led to a marked improvement in prognosis. However, the treatment usually entails ongoing center-based visits and multiple intravitreal injections, which leads to a considerable burden for the patient.

Since the 1990s, radiotherapy, which offers the chance of a single treatment, has been used to treat wet AMD. Unfortunately, the clinical results have been conflicting, most likely explained by different technique, precision, dose, and fractionation concepts used. Motivated by clinical results from trials on vascular diseases with high single doses and the development of a device specifically designed for ophthalmic use, interest in high-precision radiation therapy (RT) as a single RT-treatment (radiosurgery) for AMD has been renewed. The IRay System (during this study Oraya Therapeutics, Newark, CA; now Zeiss, Oberkochen, Germany) uses low-voltage X-rays to generate three highly collimated radiation beams that pass through the...
inferior pars plana and overlap at the macula.\textsuperscript{16} During this procedure, the eye is immobilized using a suction-coupled contact lens.\textsuperscript{16} The safety and efficacy of low-voltage, external beam, stereotactic radiotherapy (SRT) was determined in The IRay in Conjunction with Anti-VEGF Treatment for Patients with Wet AMD (INTREPID) randomized, controlled trial.\textsuperscript{17,18} At 2 years, a single dose of SRT reduced significantly the number of intravitreal injections compared with sham treatment.\textsuperscript{17} This 2-year safety analysis suggested that SRT might induce microvascular change, but in only 1% of eyes this possibly affected vision.\textsuperscript{17} As a subgroup analysis of INTREPID results showed, SRT is most effective in terms of reducing injection frequency (55% less ranibizumab [Lucentis; Genentech, South San Francisco, CA] injections) for neovascular AMD lesions that are leaking actively at the time of treatment (macular volume greater than the median value of 7.4 mm\textsuperscript{3}) and are no larger than 4 mm (ie, the beam diameter).\textsuperscript{19} Further, this subgroup showed a mean visual acuity (VA) change that was statistically significantly superior to sham and a greater reduction in mean central subfield thickness.\textsuperscript{19}

This current study reports the 12-month outcomes of a treat-and-extend regimen (TER) in combination with a low-energy SRT in the treatment of wet AMD in a routine clinical setting in Switzerland. To the best of our knowledge, this is the largest published analysis of real-life data obtained from eyes treated with the IRay System.

\section*{PATIENTS AND METHODS}

\subsection*{Patient Selection and Treatment Regimens}

Results of a retrospective, consecutive case series of eyes that received a single-session SRT treatment between August 2013 and November 2014 due to persistent choroidal neovascularization (CNV) activity, defined as persisting intra- or subretinal fluid on optical coherence therapy (OCT), despite four weekly anti-VEGF-injections or necessity for frequent injection treatments (every 4 or 6 weeks) following a TER in wet AMD are reported. Only those patients who, before as well as after SRT, were followed at Vista Klinik Binningen, Switzerland, and completed follow-up of 12 months were included in the retrospective efficiency analysis.

The anti-VEGF TER used prior to SRT was continued in the same manner and with the same anti-VEGF drug during the follow-up. In TER, anti-VEGF injections were given at each visit. If no signs of retinal fluid were observed according to the defined OCT parameters and no new hemorrhage was visible, treatment intervals were sequentially lengthened by 2 weeks, from a starting interval of 4 weeks.

![Figure 1. Central retinal thickness in µm during 12 months of follow-up. The values are significantly different compared with baseline from month 2 onwards ($P < .05$).](image-url)
to a maximum of 12 weeks. Extensions in treatment intervals continued until signs of exudation or new hemorrhage recurred. If sub- or intraretinal fluid was persistent, but stable for three consecutive visits, the treatment interval was extended providing that OCT findings remained completely stable without any other signs of disease activity (eg, hemorrhage). In the case of OCT-observed instability or new CNV activity (hemorrhage), treatment intervals were shortened by 4 weeks to a minimum of 4 weeks.

Intravitreal injections of 0.5 mg ranibizumab or 2 mg aflibercept (Eylea; Regeneron, Tarrytown, NY), respectively, were performed according to standard procedures. VA was measured as best-corrected VA (BCVA) using Snellen charts and transferred into ETDRS letter score. OCT analysis was performed with a Spectralis SD-OCT system (Heidelberg Engineering, Heidelberg, Germany), using the following parameters: horizontal volume scan, 19 sections; macular star, six sections; and horizontal follow-up 6 mm scan. Both qualitative assessments (sub- or intraretinal fluid in any scan; volume and macular star scans) and quantitative assessments (central retinal thickness [CRT] as thickness in the central Early Treatment Diabetic Retinopathy Study [ETDRS] subfield of the volume scan) were performed. Inner segment/outer segment (IS/OS) and external limiting membrane (ELM) disruption, respectively, were evaluated as the mean of the horizontal and vertical scans and graded as: 0 (no disruption in 1 mm center), 1 (mild disruption less than one-fourth within 1 mm center), 2 (one-fourth to three-fourths disruption within 1 mm center), and 3 (more than three-fourths disruption within 1 mm center).

Inclusion criteria were: patients receiving treatment with ranibizumab or aflibercept for a minimum of 6 months prior to SRT, persistent CNV activity despite four weekly anti-VEGF-injections or necessity for frequent injection treatments in the course (every 4 or 6 weeks), AMD lesion present within a 4 mm diameter centered of the fovea, and ocular axial length greater than 20 mm but less than 26 mm.

Exclusion criteria were: patients with fewer than 12 months of TER follow-up after SRT, patients without TER follow-up before SRT, BCVA of less than 10/200, advanced fibrosis of the lesion, advanced pigment epithelium-atrophy zones, and inability to sit quietly with a slightly bowed head for approximately 30 to 60 minutes (about 20 minutes in a fixed position on the system’s chin rest).

SRT was performed using the IRay System. This novel, noninvasive system comprises a precision-controlled X-ray tube, a patient interface, an eye-
The system has been described in full previously. Currently, the device is CE certificated for use in Europe but does not have marketing authorization in the U.S.

After topical anesthesia of the eye’s surface, the head was positioned for proper alignment with the robotic X-ray delivery system. The I-Guide Eye Stabilization unit was placed (this also serves as the stereotactic frame of reference for the robot), the eye and robot were co-aligned, treatment planning confirmed, standard operating procedure authorization given, and then delivery of radiotherapy was administered. The dose was delivered via three different entry angles within one session through the inferior pars plana of the affected eye. The sequential beams converge on the retina, delivering a 16 Gy dose to an area 4 mm in diameter, centered on the fovea. Although the total treatment time (not including local anesthesia, preparation of the device, calculations, etc.) is typically between 30 and 60 minutes, the radiation delivery time is only between 4 and 5 minutes as delivery is usually interrupted for several times during the procedure (repositioning, realignment).

All patients were treated at the EyeRAD Center in the Vista Klinik, Binningen, Switzerland. The study followed the tenets of the Declaration of Helsinki, and approval was received from the local ethics approval board (Ethikkommission Nordwestschweiz – EKNZ; EKNZ No. 2015-251). A general consent regarding retrospective analyses of data obtained at the Vista Klinik was signed by the patients.

Data Analysis

Data are presented as mean or percentage ± standard deviation (SD). Differences between baseline and follow-up visits were tested for statistical significance using paired t-tests. P values (two-sided) were considered significant if P was less than .05. All statistical analyses were performed using SPSS version 27.0 for Windows (SPSS, Chicago, IL).
RESULTS

Baseline Characteristics

Between August 2013 and November 2014, 68 lesions were treated by SRT at Vista Klinik-EyeRAD SWISS Medical Center, Switzerland. Of these, 15 patients had been referred for SRT treatment by ophthalmologists from elsewhere in Switzerland or abroad. These patients were pretreated and continued treatment after SRT according to different treatment regimens at their place of residence. The remaining 53 patients were pretreated and continued treatment/follow-up after SRT at Vista Klinik Binningen, Switzerland. One patient died during the 12-month follow-up period due to causes that were unrelated to SRT; one was lost for follow-up; one had a BCVA before and after treatment of less than 10/200 and therefore could not be evaluated regarding all efficiency parameters. Therefore, 50 lesions from 50 patients were available for analysis. The following characteristics refer to the point of time of SRT (“baseline” = baseline of post SRT phase). Mean age was 78.24 years ± 6.69 years, and 31 (62%) patients were female. They had a long history of anti-VEGF treatment (37.64 months ± 21.44 months, range: 7 months to 84 months; number of anti-VEGF treatments: 26.12 ± 12.44, range: 8 to 56), with the majority (60%) receiving aflibercept (40% ranibizumab) at baseline.

Efficacy as Measured by Spectral-Domain Optical Coherence Tomography

Following SRT, a significant reduction in CRT was seen from baseline to 12 months (407.3 ± 153.2 µm to 320.2 ± 112.1 µm; \( P < .001 \)), which showed to be significant from month 2 onward, with the most impressive reduction between month 3 and month 9 (Figure 1) [\( P \) values [compared to baseline] month 1: \( P = .435 \), month 2: \( P = .009 \), month 3: \( P = .01 \), month 6: \( P < .001 \), month 9: \( P < .001 \)]. After month 9 it continues to decrease, albeit less rapidly (Figure 1). In addition, there was a reduction in optical coherence tomography (OCT)-morphologic activity CNV signs in terms of macular fluid. Being continuously treated with TER, at baseline we found seven lesions (14%) without intra-or subretinal fluid, 25 lesions (50%) with only subretinal fluid, eight lesions (16%) with only intraretinal fluid and 10 (20%) with both sub- and intraretinal fluid, whereas at 12 months, a significant reduction (Chi-square test Pearson 20.61, \( P = .015 \)) in these morphologic activity CNV signs in SD-OCT was seen (33 [66%] without fluid, 10 [20%] with only subretinal fluid, six [12%] with only intraretinal fluid, and one [2%] with sub- and intraretinal fluid). The mean IS/OS disruption score remained stable from baseline to 12 months (2.52 ± 0.68, 2.44 ± 0.73; \( P = .103 \)); the same was found for the ELM disruption score (1.80 ± 0.97, 1.82 ± 1.02, \( P = .844 \)). Severe IS/OS disruption at baseline (score >2) correlated with lower baseline VA (56.4 letters ± 20.7 letters versus 68.3 letters ± 8.5 letters; \( P = .006 \)) and predicted less VA gain at 12 months (-4.4 letters ± 11.1 letters versus 1.9 letters ± 5.9 letters; \( P = .011 \)).

Visual Acuity

Corrected VA was stable during a 12-month period after SRT, with no significant change: baseline ETDRS score, 64.0 letters ± 15.1 letters; 1 month, 63.9 letters ± 14.5 letters; 2 months, 64.6 letters ± 14.0 letters; 3 months, 63.7 letters ± 14.6 letters; 6 months, 63.8 letters ± 15.6 letters; 9, 62.4 letters ± 16.4 letters; 12 months, 63.6 letters ± 16.2 letters (\( P = .908, P = .459, P = .733, P = .811, P = .203, \) and \( P = .744, \) respectively). At baseline, 27 (54%) eyes were phakic whereas 23 (46%) were pseudophakic. During the 12-month follow-up, cataract surgery was performed in four eyes (at months 7, 10, 10, and 11, respectively). In one of these eyes, VA did not improve after removal of cataract (pre- and post-cataract surgery VA: 35 letters), one eye gained two lines, the remaining two eyes gained three or more lines after cataract surgery. Further, five eyes experienced progression of cataract during the 12-month follow-up without receiving cataract surgery during that time. Of these, one eye experienced VA loss of fewer than five letters, two eyes experienced a loss of five or more but fewer than 10 letters, one eye experienced a loss of 10 or more but fewer than 15 letters, and one eye lost 15 letters or more. No case of cataract progression was directly attributed to radiation therapy, but rather to the natural course of cataract development in the elderly, especially in patients with long-term high frequent intravitreal treatments.

Treatment Intervals

The mean maximum recurrence-free anti-VEGF interval during the last 6 months of TER prior SRT was 4.24 weeks ± 0.66 weeks (baseline). After SRT, the mean maximum recurrence-free anti-VEGF interval was significantly increased to 4.76 weeks ± 1.25 weeks at 3 months, 5.66 weeks ± 2.08 weeks at 6 months, 6.62 weeks ± 2.78 weeks at 9 months, and 7.52 weeks ± 3.05 weeks at 12 months (\( P < .001 \) for all compared to mean maximum recurrence-free interval prior SRT). Eleven patients (22%) reached
an increase already after 3 months, followed by 22 patients (44%) at 6 months, 27 patients (54%) at 9 months, and 34 patients (68%) at 12 months. Figure 2 shows the distribution of treatment intervals at baseline and 12 months.

Safety
The most common immediate effect of the therapy in almost all patients was a slight corneal discomfort due to the application of the I-Guide Eye Stabilization unit. This typically resolved within a few hours. All patients received topical surface lubricants. No other and no long-lasting effects could be detected during the treatment or during the 12 months’ follow-up of the patients. In particular, there were no signs of retinal side effects or of side effects relating to the lens, which is the most sensitive structure of the eye to X-ray.

Case Illustration
Figure 3 describes outcomes for three patients in whom SRT was used.

DISCUSSION
The first-year outcomes for SRT for treatment of wet AMD in a TER showed a significant reduction in CRT, stable VA, and a significant increase in the interval between injections combined with a reduction of OCT-morphologic CNV activity signs in terms of macular fluid. Good morphologic results with radiotherapy have also been previously reported in AMD and other indications including non-AMD CNV. For example, in a 12-month phase 1 study in patients with neovascular AMD, noninvasive, low-voltage X-ray irradiation, combined with ranibizumab rescue therapy as needed, showed a VA-stabilizing effect and reduction in retinal thickness combined with a good safety profile.

In contrast to other radiotherapy trials, VA in this study did not improve. This is most probably due to optimized anti-VEGF therapy administered before and after SRT as well as high mean baseline IS/OS and ELM disruption scores, reflecting the progressed structural outer retinal damage due to progressed wet AMD. TER offers maximum CNV control, avoiding large recurrences like in a pro re nata (PRN) regimen. SRT in maximally anti-VEGF-controlled lesions has not previously been carried out. However, this is important, and it ensures a real SRT effect is seen rather than an effect that is overlapped by the anti-VEGF effect on active wet AMD. If SRT was performed in treatment-naïve lesions, the SRT effect might be overlapped by the anti-VEGF loading-phase improvement; if it was performed during a recurrence within a PRN schema, the SRT effect might be overlapped by the anti-VEGF effect on the recurrence. In our real-life analysis, VA was stable during the course of 12 months in these anti-VEGF-pretreated eyes, whereas several big real-world studies like the one of the United Kingdom Age-Related Macular Degeneration Electronic Medical Records Users Group showed VA tends to reduce over time after the loading phase in chronic, active AMD under anti-VEGF treatment (VA loss of 0.03 logMAR units and 0.05 logMAR units/year in first and second treated eyes, respectively). There was only a very low number of eyes that needed cataract surgery during the follow-up, which could have influenced VA in a positive manner. Conversely, there was a quite similar number of eyes with progression of cataract that could have influenced VA in a negative manner. Therefore, we cannot assume that these few cases influenced the VA outcome significantly. Cataracts are unlikely to be a side effect of SRT as they were pre-existing, the entrance angles of the radiation portals spare the lens and the follow-up time is too short for cataract as a late effect of SRT with such low, scattered doses to the lens. Furthermore, the incidence of cataract (progression) is in the range for elderly people who had received long-term anti-VEGF treatment.

Increasing the recurrence-free treatment interval from 4.24 weeks ± 0.66 weeks at baseline to 7.52 weeks ± 3.05 weeks at 12 months and reaching an at least 2-week-step increase in 68% of patients at 12 months means not only a reduction in the frequency of anti-VEGF treatments, but also in follow-up examinations, etc. Thus, there is a reduced burden for patients and doctors combined with a reduction of costs for health insurance, especially as wet AMD is a disease with need for long-term treatment with increasing costs for anti-VEGF treatment. The follow-up period in the analysis was too short to allow for assessments of safety outcomes. However, in the INTREPID study, safety outcomes were promising, with the numbers of adverse events similar in the SRT and ranibizumab and sham and ranibizumab arms at 1 and 2 years.

Comparison of results of SRT and other radiation treatments for AMD, like epimacular brachytherapy (EMB), is difficult as the radiation procedures are very different. In the CABERNET trial, EMB did not meet the superiority/noninferiority end points regarding vision gain/loss. Also, the results of the MERLOT trial did not support the use of EMB for chronic, active, neovascular AMD. The differences between SRT and EMB might be explained by
the lack of vitrectomy in SRT (which reduces drug half-life), eye tracking (SRT) versus surgeon positioning (EMB), and the exponential decline in dose with EMB device.

Additionally, there is a controversial discussion about the optimal amount of a thinning of the retinal and choroidal thickness, either by anti-VEGF treatment or by radiation therapy, to achieve a best morphological recovery of the outer retinal layers. The morphological modifications seen in both arms of the INTREPID study have been very similar: both treatments decreased choroidal and retinal thickness, sharing similar morphological effects, but it is not known if the therapies act independently or synergistically. Furthermore, it is not known if a further choroidal thinning may even worsen the visual capacity of the patients. Regarding long term efficacy, a too-intensive SRT might even decrease the VA by causing a strong fibrotic layer, decreasing the nutritional retinal support, or further atrophy of retinal or choroidal layers. These effects need to be evaluated in long term follow-ups, in addition to other options like a further reduction of radiation dose (ie, to 12 Gy) or an earlier indication with a very focused SRT to a reduced volume might be investigated.

Limitations of our real-life analysis are its retrospective nature, lack of a control group, and an inadequate follow-up duration for assessment of long-term safety concerns. These aspects need to be evaluated in a prospective trial, and the currently ongoing STAR study might answer these questions. As we did not follow patients without anti-VEGF treatment after SRT within our analysis, it is not possible to distinguish between the “SRT-only” drying effect or the possibility of anti-VEGF-facilitating effects of SRT. Concerning safety outcomes in terms of microvascular abnormalities, the follow-up period in the analysis was too short to allow for assessments, and these changes may not be detected on clinical examination. They could be better visualized using fluorescein angiography. However, in the INTREPID 2-year safety analysis, this possibly affected vision in only 1% of eyes. The advantages of our analysis are that these findings are from a real-life setting (to the best of our knowledge this is the largest real-life evaluation with the iRay System published in this context). Compared to the smaller case series of Ranjbar et al., the data pre- and post-SRT were consistently documented/followed up in a population that was maximally anti-VEGF controlled within a strict TER. As the pre-SRT period was well-documented, a comparison to this period was possible.

In this current study of wet AMD, SRT applied using an anti-VEGF TER appears to present an advantageous option for a combination treatment with anti-VEGF therapy to reduce CNV activity in terms of macular fluid and therefore the injection frequency and furthermore, the associated burden to patients and healthcare professionals over the long-term in patients with AMD.

REFERENCES


