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Purpose

To reveal differences or advantages in regards to different treatment options after proton beam therapy for uveal melanoma.

Design

Retrospective, comparative, interventional case series.

Methods

All patients receiving intravitreal treatment between January 2011 and July 2014 for radiation maculopathy after proton beam therapy were included. Excluded were all patients who required re-irradiation, vitrectomies or tumor resections, those whose treatment was performed for potentially other reasons, such as radiation induced optic neuropathy, or where visual outcome was influenced by tumor growth under the macula or macular ischemia. Minimum follow-up was 12 months after last injection.

Results

Of 78 patients 38 (48.7%) received bevacizumab-injections, 35 (44.9%) triamcinolone acetonide-injections, and 5 (6.4%) a dexamethasone-implant. In the bevacizumab group visual acuity improved in 11 patients (28.9%) by 0.25 logMAR (0.1-0.4 logMAR) and remained stable in 24 patients (63.2%) 4 weeks after injection. In the triamcinolone group visual acuity showed improved outcomes in 10 patients (28.6%) by 0.25 logMAR (0.1-0.4 logMAR) and stability in function in 20 patients (57.1%). Four weeks after dexamethasone implantation visual acuity remained stable in 4 patients (80%). No differences amongst the groups were detected regarding functional outcome or reduction in central foveal thickness.

Conclusions

This study showed that antiangiogenic or corticosteroid intravitreal treatment led to reduced central foveal thickness and visual improvement in some patients without showing differences or advantages. Therefore a patients-specific treatment choice can be recommended.

Antiangiogenic or corticosteroid treatment in patients with radiation maculopathy after proton beam therapy for uveal melanoma

Anti-VEGFs versus corticosteroids for radiation maculopathy

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Introduction:

Ever since the COMS-Study, priority has been given to eye preserving irradiation modalities.[1] Due to adequate local tumor control and subsequent eye retention rates, visual outcome has become an area of great interest.[2,3,4] Visual outcome is often compromised due to complications resulting from irradiation. Such complications are irradiation retinopathy, maculopathy, and/or optic neuropathy. To date, a common consensus concerning the best treatment for radiation maculopathy has not been reached yet. Studies reporting about intravitreal injections, either with corticosteroids after brachytherapy, or with anti-vascular endothelial growth factor (anti-VEGFs) agents after external beam and brachytherapy treatment, all showed promising results in reducing foveal thickness and improving visual acuity.[5-13] This study will reveal, retrospectively, if there are differences or advantages in regards to different treatment options after proton beam therapy for choroidal or ciliary-body melanoma.

Methods:

Inclusion and exclusion criteria

The retrospective, comparative, interventional case series was approved by the institutional review board of the Charité-Universitätsmedizin Berlin, Berlin, Germany, and was performed in accordance with the tenets of the Declaration of Helsinki. A total of 134 charts of patients presenting with uveal melanoma receiving intravitreal treatment between January 2011 and July 2014 were reviewed. Inclusion criteria consisted of the diagnosis of choroidal or ciliary-body melanoma treated with primary proton beam therapy, the occurrence of proton beam-associated radiation maculopathy with verified macular edema in optical coherence tomography (OCT), an intravitreal treatment with only one drug for radiation maculopathy, and a minimal follow-up of 12 months after last injection. All included patients had underwent proton beam therapy with a dose of 60 Cobalt Gray Equivalent in total (Cobalt Gray Equivalent: 1 Cobalt Gray Equivalent = 1.1 Gray, taking a radio biological effectiveness of 1.1 into account), given in 4 fractions of 15 Cobalt Gray Equivalent at 4 sequential days.[14]

Excluded were all patients who required re-irradiation, vitrectomies or tumor resections. Further excluded were those of whom received intravitreal treatment combined with other surgical procedures or where the etiology of macular edema could not be clarified due to potential influence of previous surgeries, diabetes or age related macular degeneration. Furthermore, those whose treatment was performed for potentially other reasons, such as radiation induced optic neuropathy, or where visual outcome was influenced by tumor growth under the macula or macular ischemia (defined as >180° enlargement of the foveal arcade) was identified in fluorescein angiography at the time of detecting radiation maculopathy.

Main outcome measures:

Main outcome measures were defined as differences in applied drugs regarding changes in central foveal thickness on optical coherence tomography (OCT) using Spectralis (Heidelberg Engineering; Heidelberg, Germany) and visual outcome. Best-corrected-visual acuity (BCVA), central foveal thickness on OCT, and when available, fluorescein angiography (Heidelberg Engineering; Heildelberg, Germany), were evaluated at initial diagnosis of radiation maculopathy. Besides information of central foveal thickness in micrometer (µm), macular edema was furthermore classified in resolved, reduced (reduction of more than 10 µm in central foveal thickness), stable, and increased (increase of more than 10 µm in central foveal thickness).

Secondary outcome measures reported in subgroup analysis:

Secondary outcome measures were defined as changes or differences regarding enlargement of the foveal avascular zone. Due to inconsistently performed fluorescein angiographies at baseline visits, we included only those patients whom underwent, at minimum two fluorescein angiographies, before treatment and during further follow-up, for subgroup analysis. Furthermore, patients with inconsistent intravitreal therapy were excluded from the study and analyzed separately in another subgroup analysis.

Statistical methods

Statistical analysis was performed using SPSS 20.0 (SPSS, Inc, Chicago, Illinois, USA). The Kolmogorov–Smirnov test and the Shapiro Wilk Test were used for testing

normality. To detect potential initial differences amongst the three groups, a Kruskal-Wallis-Test was performed. Per analysis of covariance (ANCOVA), the influence of radiation doses to fovea and optic disc on functional outcome, OCT and fluorescein angiography changes was tested. A Wilcoxon-Mann-Whitney test was used to find differences in not normally distributed variables. A Fisher's exact test was used to detect interrelationships between the clinical grading of macular edema on OCT according to treatment groups, the =χ2 test, and factorial ANOVA were used to assess statistically significant differences between groups. Interrelationships between variables were assessed by calculating correlation coefficients according to Spearman/Pearson. Visual acuity is described as logMAR. In relation to the MARAN protocol, light perception (LP) was added as 2.1 logMAR, hand motion (HM) as 2.0 logMAR and counting fingers (CF) as 1.9 logMAR.[15]

Results:

Patient demographics:

In total, 78 patients were included for analyzing the main outcome measures of visual acuity and central foveal thickness. Of these patients, 38 (48.7%) received 1.25 mg in 0.05 ml bevacizumab injections, 35 (44.9%) received 4 mg in 0.1 ml triamcinolone acetonide injections, and 5 received (6.4%) a dexamethasone implant. Mean patient age was 59 years (34-74 years), 61 years (27-81 years), and 69 years (60-77 years) in patients treated with bevacizumab, triamcinolone acetonide, or dexamethasone, respectively. Median tumor thickness was 3.1 mm (1.2-14.1 mm), 3.5 mm (1.4-11.6 mm), and 2.9 mm (2.3-4.4 mm) in the bevacizumab, triamcinolone acetonide, and dexamethasone group, respectively. Median largest basal diameter was 10.0 mm (4.3-20.8 mm) in the bevacizumab group, 10.3 mm (5.8-21.9 mm) in the triamcinolone acetonide group, and 11.3 mm (7.6-12.3 mm) in the dexamethasone group. Tumor volume was 141 mm^3 (9-2535 mm^3), 158 mm^3 (25-1735 mm^3), and 139 mm^3 (72-236 mm^3), median distance to fovea was 0.9 mm (0-11.0 mm), 2.1 mm (0-12.0 mm), and 1.6 mm (0-3.7 mm), and distance to optic disc was 2.6 mm (0-11.0 mm), 1.5 mm (0-14.7 mm), and 2.3 mm (0-2.7 mm) in patients receiving bevacizumab, triamcinolone acetonide, or dexamethasone implant, respectively.

Kruskal-Wallis-Test revealed no statistically significant differences between the groups in age ($\chi2(2) = 3.551$, $p = 0.169$), tumor thickness ($\chi2(2) = 0.274$, $p = 0.872$), largest basal diameter ($\chi2(2) = 1.156$, $p = 0.561$), volume ($\chi2(2) = 0.537$, $p = 0.765$), distance to fovea ($\chi2(2) = 4.095$, $p = 0.129$), distance to optic disc ($\chi2(2) = 2.531$, $p = 0.282$), initial visual acuity ($\chi2(2) = 4.993$, $p = 0.82$), and central foveal thickness before injection ($\chi2(2) = 0.673$, $p = 0.769$). Therefore groups were defined to be homogenous and comparable. (Table 1)

Follow-up and important intervals:

In all patients (n=78), the median observation period from the time of proton beam therapy to final follow-up visit was 49 months (18.1-120.0 months). Radiation maculopathy with increased central foveal thickness on OCT occurred on average 16.6 months (4.6- 69.3 months) following proton beam therapy. The symptom/treatment-interval was defined as interval between detection of radiation maculopathy and first injection and was on average 4.5 weeks (0.5-10 weeks).

Visual acuity according to group and further limiting complication as optic neuropathy:

Bevacizumab-group:

On average, 2 injections (1-11 injections) were administered and median time between initial detection of macular edema and first intravitreal injection was 5 weeks (0.5-8 weeks). Median initial visual acuity was 0.1 logMAR (0-1.3 logMAR) before proton beam therapy. Median visual acuity at time of diagnosis of radiation maculopathy was 0.5 logMAR (0-1.5 logMAR). Furthermore, median visual acuity before injection was 0.8 logMAR (0-2.0 logMAR) and 0.7 logMAR (0.1-2.0) 4 weeks following last injection. Final visual outcome was 1.0 logMAR (0.1-2.0 logMAR) with 10 patients (26.3%) maintaining visual acuity of 0.5 logMAR or better.

Visual acuity improved in 11 patients (28.9%) on average by 0.25 logMAR (0.1-0.4 logMAR), remained stable in 24 patients (63.2%) and decreased in 3

patients (7.9%) by 0.1 logMAR (0.1-0.3 logMAR) upon visual acuity assessment 4 weeks after last injection. When measured at last follow-up, compared with values before injection, median visual outcomes showed long-term improvement in 6 patients (15.8%) by 0.2 (0.05-0.3 logMAR), stability in 13 patients (34.2%), and deterioration in 19 patients (50%) by 0.3 (0.1-0.5 logMAR).

Radiation optic neuropathy affecting long-term visual outcome:

Twelve patients (31.6%) developed radiation optic neuropathy 18 months (2-35 months) after last injection. Long-term visual outcome was slightly affected however without any statistically significant difference. While patients without optic neuropathy presented with final visual outcomes of 1.0 logMAR (0.3-2.0 logMAR), patients with radiation optic neuropathy showed poorer outcomes with 1.1 logMAR (0.1-1.9 logMAR).

Triamcinolone-acetonide-group:

Triamcinolone acetonide was administered on average, as a single dose (range: 1-3 injections) and median symptom/treatment-interval, the time between first detection of macular edema and first intravitreal injection, was 4 weeks (0.5-9.5 weeks). Patients presented with median visual acuity of 0.2 logMAR (0-0.7 logMAR) before proton beam therapy, with 0.6 logMAR (0-1.5 logMAR) upon diagnosis of radiation maculopathy, with 0.8 logMAR (0.1-2.0 logMAR) before injection, with 0.8 logMAR (0.1-2.0 logMAR) four weeks after last injection, and finally with 1.0 logMAR (0.2-2.1 logMAR) at last follow-up. Final visual acuity of 0.5 logMAR or better was sustained in 9 patients (25.7%).

Visual acuity showed improved outcomes in 10 patients (28.6%) by 0.25 logMAR (0.1-0.4 logMAR) measured 4 weeks after last injection and in 7 patients (20%) by 0.1 logMAR (0.05-0.4 logMAR) at last follow-up compared with visual acuity before injection. Stability in function was achieved in 20 (57.1%) and 6 (17.1%) patients after injection and at last follow-up, respectively. Decreased vision was detected in 5 patients (14.3%) by 0.1 logMAR (0.05-0.3) 4 weeks after last injection and in 19 patients (54.3%) by 0.3 (0.1-0.8 logMAR) at last follow-up visit.

Radiation optic neuropathy affecting long-term visual outcome:

Radiation optic neuropathy occurred in 15 patients after 6 months (2-24 months). Patients with radiation optic neuropathy also showed decreased final visual outcome with 1.2 logMAR (0.2-2.1 logMAR) compared to 1.0 logMAR (0.2-1.7logMAR) without optic neuropathy. There was no statistically significant difference detected.

Dexamethasone implant-group:

The dexamethasone implant was injected on average once (1-2 injections) after a median symptom/treatment-interval of 4 weeks (2-10 weeks). Patents who received a dexamethasone implant had visual acuity of 0.2 logMAR (0-0.3 logMAR) before proton beam therapy. Median visual acuity, at time of radiation maculopathy diagnosis was 0.5 logMAR (0-1.3 logMAR). Median visual acuity before and after intravitreal injection was 0.8 logMAR (0.2-1.3 logMAR). Final visual acuity was 1.0 logMAR (0.4-2.0 logMAR) in one patient (25%) in whom visual acuity of 0.5 logMAR or better was maintained.

Four weeks after implantation, visual acuity remained stable in 4 patients (80%) and decreased in one patient (20%) by 0.2 logMAR compared with visual acuities before implantation. Comparing last follow-up visual acuity with visual acuity

before implantation, one patient (20%) remained stable whereas visual acuity decreased in 4 patients (80%) by 0.2 logMAR (0.1-0.3 logMAR).

Radiation optic neuropathy affecting long-term visual outcome:

One patient developed radiation optic neuropathy 2 months after injection exhibiting a final visual acuity of 0.7 logMAR.

(Figure 1, Figure 2)

Optical coherence tomography:

Analysis of OCT scans showed a significant reduction ($p< 0.05$) in foveal thickness in each of the three groups comparing central foveal thickness in µm at date of radiation maculopathy diagnosis with central foveal thickness 4 weeks after intravitreal treatment. After bevacizumab injection, a decrease was observed from 479 µm (248-1123 µm) to 362 µm (134-836 µm) ($p=0.01$). Furthermore, after triamcinolone acetonide administration, a decrease was detected from 454 µm (156-957 µm) to 314 µm (138-940 µm) ($p=0.034$), and after dexamethasone implant injection from 440 µm (226-589 µm) to 265 µm (142-534 µm) ($p=0.049$). There was no statistically significant difference amongst the groups according to intravitreal treatment.

Of 78 patients, 25 (32.1%) showed completely resolved macular edema 4 weeks after last injection, 31 showed (41.0%) reduced macular edema, 11 with (14.1%) stable macular edema, and finally 10 patients (12.8%) exhibiting increased macular edema. Final visual acuities were statistically significant better in patients who presented with resolved macular edema than with reduced, stable, or increased macular edema. (Bevacizumab group: $p= 0.046$, triamcinolone acetonide group: $p=0.05$).

(Table 2 and 3)

Large (>1mm by 200µm) cysts were detected, remarkably often, in patients with poorer response to treatment. Of 10 patients who presented with increased macular edema, 5 had developed large cysts on OCT before treatment. Amongst the 11 patients with stable macular edema, 2 presented with large cysts before injection. In patients who had resolved or reduced macular edema these cysts were not detected.

Influence of symptom/treatment-interval

All 78 patients showed a strong correlation between a short symptom/treatment-interval and change of visual acuity comparing visual acuity before and 4 weeks after intravitreal treatment ($rho= -0.661$, $p< 0.0001$). A Spearman correlation revealed a Spearman´s $rho = -0.676$, $p < 0.0001$ in the bevacizumab group, a Spearman´s $rho = -0.672$, $p < 0.0001$ in the triamcinolone acetonide group, and a Spearman´s $rho = -0.707$, $p= 0.182$ in the dexamethasone implant group.
(Figure 3)

Affection of irradiation doses on visual outcome or change in central foveal thickness on OCT

Final visual acuity was statistical significantly affected by irradiation doses on fovea and optic disc ($p<0.001$ and $p=0.028$). No statistically significant influence by irradiation doses on fovea or optic disc was detected concerning changes in visual acuity or central foveal thickness or clinical classification of macular edema (ranging from resolved to increased).

Comparison between different intravitreal agents:

As previously mentioned, groups were defined to be homogenous and therefore comparable.
Visual acuities and values of central foveal thickness were not normally distributed and therefore a Kruskal- Wallis-Test was performed. Regarding visual acuity it revealed no statistically significant differences between the groups at diagnosis of radiation maculopathy (p=0.530), before injection (p=0.780), four weeks after last injection (p=0.871), and at last follow-up (p=0.792).
Concerning the decrease in central foveal thickness no statistically significant difference between the groups was detected (p=0.757). Furthermore, a Fishers exact test revealed no statistically significant differences between the clinical classification of macular edema (from resolved to increased macular edema) according to treatment group (p=0.879). Thus there was no statistically significant difference between the three groups, neither in functional nor anatomical outcome.

Subgroup analysis:
Forty patients underwent fluorescein angiography at the time of diagnosing radiation maculopathy. Of these, 8 (20%) exhibited slight vascular rarefication, which reached from 10°-170° of the foveal arcade. Of 32 patients with no signs of macular ischemia, 15 (47%) patients underwent fluorescein angiography during follow-up (4-24 weeks after last injection). Of 8 patients with minimal vessel rarefication, 4 (50%) underwent fluorescence angiography 4-24 weeks after last injection during follow-up.

Patients with no ischemic signs:

Data regarding foveal perfusion, allowing for a direct comparison between pre- and post-injection periods, were therefore available for 15 patients (19.2%). Of these 15 patients, 10 (67%) underwent bevacizumab-treatment, 4 (27%) triamcinolone acetonide injections, and 1 (6%) received a dexamethasone implant. Macular ischemia developed in 1 patient after bevacizumab injections with an enlargement of the foveal arcade of 150°. This patient had receive d 4 injections of bevacizumab. Fluorescein angiography was performed 8 weeks after last injection due to a lacking response.

Patients with pre-existing vessel rarefication:

Of 4 analyzable patients, 2 were treated with bevacizumab, 1 with triamcinolone acetonide, and 1 with a dexamethasone implant. Macular ischemia increased in 2 patients from 20° to 120° and from 170° to 360° who received bevacizumab injections. These patients had received, at minimum, 4 injections of bevacizumab (4-8 injections). Fluorescein angiography was performed 8 and 6 weeks after last injection, respectively.
No correlation between foveal irradiation doses and occurrence or enlargement of macular ischemia was found.

(Figure 4)

Patients with switched intravitreal treatment according to changes in OCT

As aforementioned in exclusion criteria, all patients with inconsistent treatment were excluded from the study which was applicable for 6 patients. In these patients, treatment was changed either from bevacizumab to triamcinolone acetonide in 2 patients or vice versa in 4 patients. All patients did not respond to the first injection and therefore treatment was switched. Irrespective of approach, all patients responded after secondary injection. Both patients receiving secondary bevacizumab injections presented with completely resolved macular edema. Of the patients treated with triamcinolone acetonide secondarily, 2 exhibited completely resolved macular edema and 2 with a reduced foveal thickness.

Discussion:

Radiation retinopathy presents primarily with endothelial damage secondary to increased permeability and coagulation activity with subsequent vascular occlusions thereby disrupting microcirculation. Clinical manifestations include teleangiectasia, microaneurysms, retinal edema or exudation from insufficient capillary beds.[16,17] The pathophysiology is analogous to diabetic retinopathy both being occlusive vasculopathies. Besides elevated VEGF levels due to retinal ischemia, an increased activation and invasion of microglia cells and macrophages after irradiation has been found.[18,19] Therefore the effect of intravitreal injections of corticosteroids and antiangiogenic agents is not surprising. Uncontrolled studies have been proven to reduce macular thickness with varying visual outcome.[5,10]

This study showed that visual improvement or stability was achieved in 80% (dexamethasone), 85.6% (triamcinolone), and 92.1% (bevacizumab) of patients 4 weeks after last injection versus 20% (dexamethasone), 37.1% (triamcinolone), and 50% (bevacizumab) at last follow-up (average 49 months). Visual acuity of 0.5 logMAR or better was achieved in 25.0 % (dexamethasone), 37.1% (triamcinolone), and 26.3% (bevacizumab) of patients at last follow-up. We did not find any statistically significant difference between different treatment options. It has to be kept in mind that the dexamethasone group consisted of only 5 patients, all of whom exhibited good results on OCT. However a larger cohort would have to be examined in order to increase the statistical significance. Mashayekhi et al reported in their findings, that 86% of patients had maintained or improved visual acuity after 4-6 months after 4 injections of bevacizumab. These results are in accordance with our findings at 4 weeks status post injection. They assumed that visual outcome was perhaps limited due to undetected macular ischemia.[9] In our study we could only report on 40 patients with fluorescein angiographies at the time of diagnosis of radiation maculopathy and only 15 of them had follow-up fluorescein angiography. Therefore higher rates of macular ischemia are conceivable. In our subgroup analysis we looked at any enlargement of the avascular foveal arcade and all patients that developed an enlargement or new foveal ischemia were treated with bevacizumab injections. However, drawing conclusions about any correlation is not justified at the present moment but cannot be ruled out. In the case that miniscule vessel rarefication was seen before injection, we would probably prefer corticosteroid injections in those special cases. Recently, very promising results published by Finger et al, demonstrated that 80% of patients treated with continuous injections of anti-VEGF, remained in their 2 lines of initial visual acuity, after a mean follow-up of 38 months.[20] These results are supported by Shah et al. who achieved visual acuity of 20/50 (0.4 logMAR) in 51% of patients after 54 months, emphasizing early and direct treatment with multiple anti-VEGF injections after macular edema occurrence.[8] In our patients, we showed that time delay was a limiting factor regarding visual outcome. The first striking decrease in function occurred between before proton beam therapy (0.1 logMAR) and detection of radiation maculopathy (0.5 logMAR). It raises the question, if the symptom/treatment interval was extended, as the time between occurrence of macular edema and patient´s presentation in our department was unknown. Furthermore, the secondary decrease in function occurred between detection of radiation maculopathy, which is equal to the date intravitreal treatment was indicated (0.5 logMAR) and visual acuity before injection (0.8 logMAR). The average symptom/treatment-interval of 4.5 weeks was obviously too long. This underlines the importance of closer patient follow-ups. In patients already presenting with large (>1mm by 200µm) cysts on OCT that may also imply chronicity,

inefficient treatment can be avoided.

We furthermore detected a good response to secondary triamcinolone acetonide or bevacizumab in non-responding patients first treated with bevacizumab or triamcinolone acetonide, respectively. As reported by Bakri et al. non responders may profit from a switch in treatment. Patients not responding or having developed a resistance to anti-vegf treatment showed good responses after the treatment was changed to or supported with triamcinolone acetonide.[10,12]

In conclusion our study revealed similar outcomes concerning changes in central foveal thickness and visual acuity after antiangiogenic or corticosteroid intravitreal treatment in patients with radiation maculopathy. Therefore an individual patient-specific treatment with anti-VEGFs or corticosteroid agents can be recommended. A prospective randomized study including frequent OCT imaging and fluorescein angiographies would be required for final conclusion.

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c: Other Acknowledgments: Dr. Ulrich Gauger, medical statistician Berlin, Germany, performed statistical analysis.

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Figure Captions:

Figure 1. Visual change at last follow-up according to different treatment options. Final visual acuity minus visual acuity before injection according to three intravitreal treatment groups for macular edema related to radiation retinopathy after proton beam therapy for uveal melanoma.

Figure 2. Change in vision 4 weeks following intravitreal injections according to different intravitreal agents. Visual acuity 4 weeks after injection minus visual acuity before injection according to three intravitreal treatment groups for radiation maculopathy after proton beam therapy for uveal melanoma.

Figure 3. Change in vision according to symptom/treatment-interval. Change in visual acuity (visual acuity after intravitreal injection minus visual acuity before intravitreal injection) for radiation maculopathy after proton beam treatment in uveal melanoma according to time between symptoms and treatment. Composite image of 4 different scattergrams, Top left displays visual change in logMAR according to symptom/treatment-interval of all patients irrespective of applied intravitreal agent. Top right displays visual change in logMAR according to symptom/treatment-interval of patients treated with dexamethasone implant, bottom left shows visual change in logMAR according to symptom/treatment-interval of patients treated with bevacizumab and bottom right shows visual change in logMAR according to symptom/treatment-interval of patients receiving triamcinolone acetonide injections.

Figure 4. Composite image of two different fluorescein angiographies of the right eye after proton beam therapy for choroidal melanoma. Proton beam therapy was performed in May 2012 for a 12 mm prominent choroidal melanoma, located at the temporal inferior arcade. Top left to top right shows early to late phase in fluorescein angiography performed in August 2013 exhibiting slight vascular rarefication. Bottom left to bottom right shows the same patient undergoing fluorescein angiography in April 2014 after 8 injections of bevacizumab. Compared to August 2013 an enlargement of the foveal avascular zone is visible.

	Bevacizumab	Triamcinolone acetonide	Dexamethasone implant	P Value (Kruskal-Wallis-Test)
N=78	38 (48.7%)	35 (44.9%)	5 (6.4%)	
Mean age in years (range)	59 (34-74)	61 (27-81)	69 (60-77)	0.169
Median tumor thickness in mm (range)	3.1 (1.2-14.1)	3.5 (1.4-11.6)	2.9 (2.3-4.4)	0.872
Median largest basal diameter in mm (range)	10.0 (4.3-20.8)	10.3 (5.8-21.9)	11.3 (7.6-12.3)	0.561
Median tumor volume in mm^3 (range)	141 (9-2535)	158 (25-1735)	139 (72-236)	0.765
Median distance to fovea in mm (range)	0.9 (0-11.0)	2.1 (0-12.0)	1.6 (0-3.7)	0.129
Median distance to optic disc in mm (range)	2.6 (0-11.0)	1.5 (0-14.7)	2.3 (0-2.7)	0.282
Median initial visual acuity in logMAR (range)	0.1 (0-1.3)	0.2 (0-0.7)	0.2 (0-0.3)	0.82
Median visual acuity before injection in logMAR (range)	0.8 (0-2.0)	0.8 (0.1-2.0)	0.8 (0.2-1.3)	0.780
Median visual acuity at 4 weeks after injection in logMAR (range)	0.7 (0.1-2.0)	0.8 (0.1-2.0)	0.8 (0.2-1.3)	0.871
Median central foveal thickness in µm before injection (range)	479 (248-1123)	454 (156-957)	440 (226-589)	0.769
Median central foveal thickness in µm at 4 weeks after injection (range)	362 (134-836)	314 (138-940)	265 (142-534)	0.757

Table 1. Patient´s characteristics as age, tumor thickness, largest basal diameter, tumor volume, distance to optic disk and fovea, and furthermore median visual acuity

and central foveal thickness before injection and 4 weeks after injection according to treatment option for radiation maculopathy. Kruskal-Wallis-Test revealed no statistically significant differences between the groups in age ($\chi2(2) = 3.551$, $p = 0.169$), tumor thickness ($\chi2(2) = 0.274$, $p = 0.872$), largest basal diameter ($\chi2(2) = 1.156$, $p = 0.561$), volume ($\chi2(2) = 0.537$, $p = 0.765$), distance to fovea ($\chi2(2) = 4.095$, $p = 0.129$), distance to optic disc ($\chi2(2) = 2.531$, $p = 0.282$), initial visual acuity ($\chi2(2) = 4.993$, $p = 0.82$), and central foveal thickness before injection ($\chi2(2) = 0.673$, $p = 0.769$). Furthermore during follow-up as well, no statistically significant differences were found concerning change in visual acuity and change in central foveal thickness.

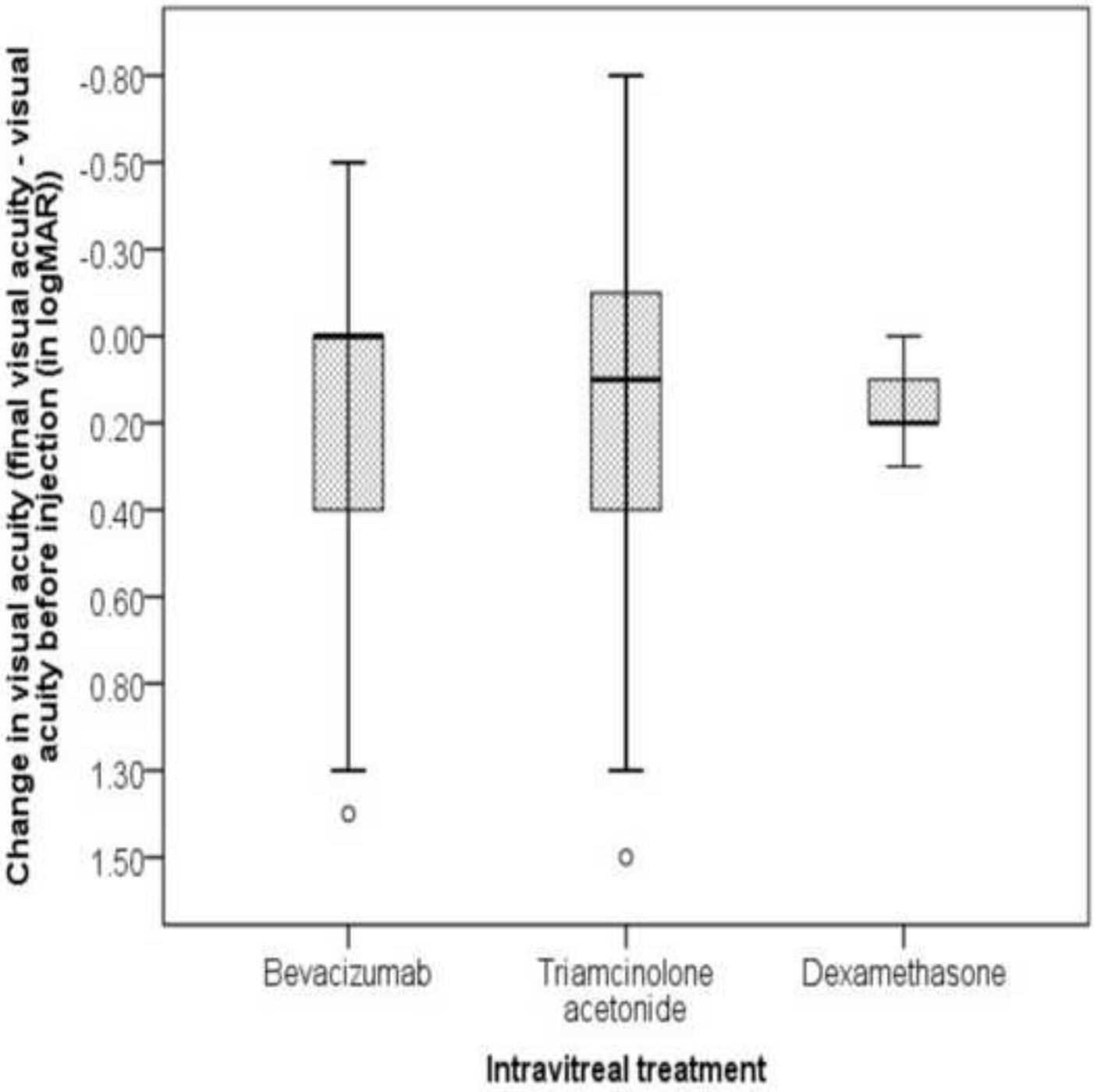
			Bevacizumab	Triamcinolone acetonide	Dexamethasone implant	Total
Macular edema	Resolved	N	11	12	2	25
		%	28.9%	34.3%	40.0%	32.1%
	Reduced	N	15	14	3	32
		%	39.5%	40.0%	60.0%	41.0%
	Stable	N	5	6	0	11
		%	13.2%	17.2%	0,0%	14.1%
	Increased	N	7	3	0	10
		%	18.4%	8.5%	0,0%	12.8%

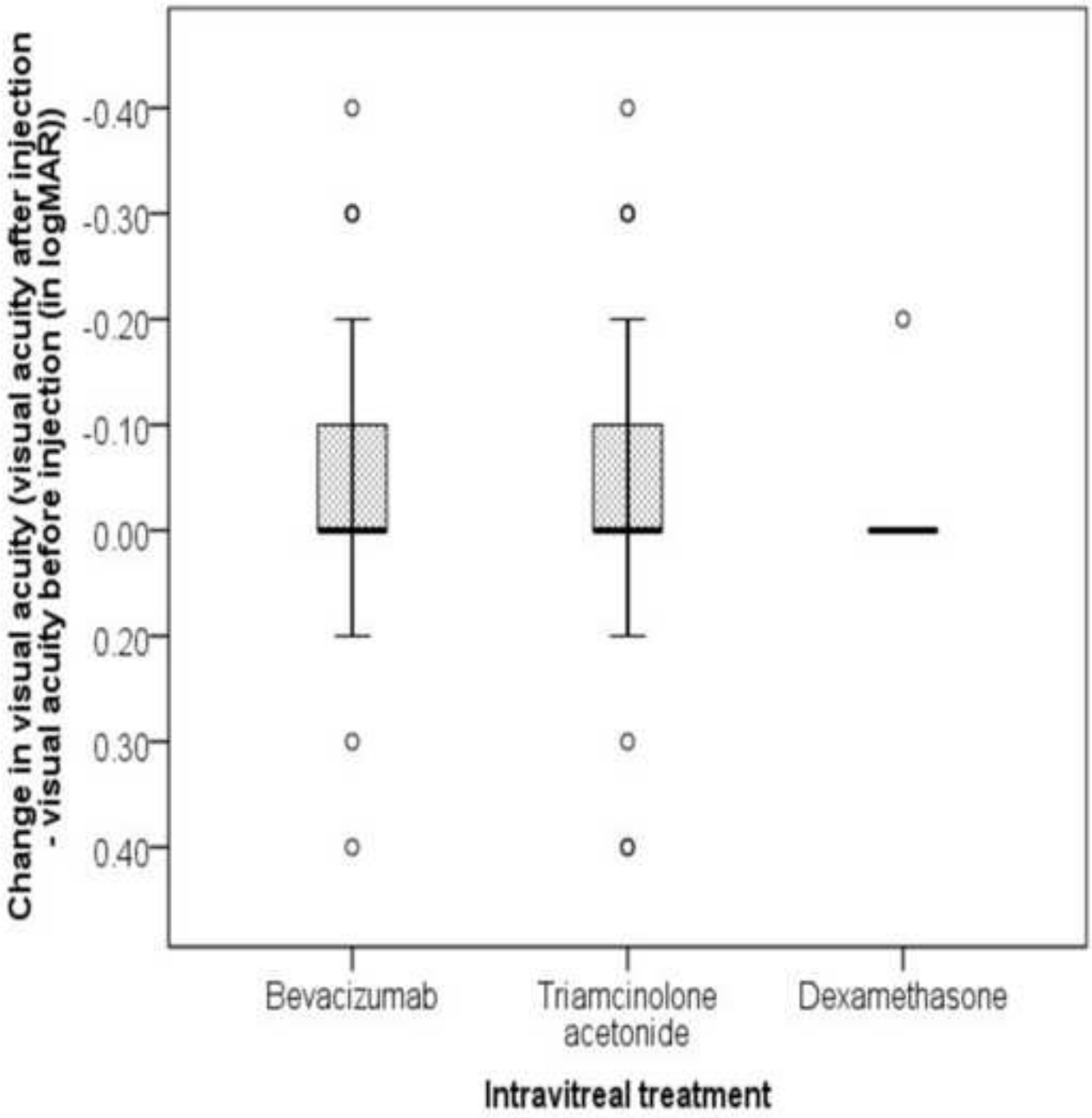
Table 2: Clinical graduation performed by OCT ranging from resolved to increased macular edema in patients treated with different intravitreal treatment for radiation maculopathy after proton beam therapy in uveal melanoma. Fishers exact test revealed no statistically significant differences between the clinical classification of macular edema (from resolved to increased macular edema) according to treatment group (p=0.879).

			Bevacizumab	Triamcinolone acetonide	Dexamethasone implant
Macular edema	Resolved	N	11	12	2
		VA preinj.	0.5 (0-1.4)	0.65 (0.3-1.3)	0.85 (0.4-1.3)
		VA 4 weeks	0.4 (0-1.4)	0.5 (0.2-1.0)	0.75 (0.2-1.3)
		Final VA	0.5 (0.1-1.9)[a]	0.75 (0.2-2.0)[b]	1.0 (0.7-1.3)[c]
	Reduced	N	15	14	3
		VA preinj	0.8 (0.3-1.3)	1.0 (0.1-2.0)	0.8(0.2-1.0)
		VA 4 weeks	0.7 (0.3-1.3)	1.0 (0.1-1.9)	0.8 (0.2-1.0)
		Final VA	1.0 (0.3-1.3)	1.0 (0.3-1.6)	1.0 (0.3-1.0)
	Stable	N	5	6	0
		VA preinj.	1.3 (0.8-2.0)	1.1 (0.6-1.5)	
		VA 4 weeks	1.3 (0.8-2.0)	1.1 (0.8-1.7)	
		Final VA	1.5 (0.7-2.0)	1.25 (1.0-1.7)	
	Increased	N	7	3	0
		VA preinj.	0.5 (0.3-1.5)	0.6 (0.4-2.0)	
		VA 4 weeks	0.8 (0.5-1.5)	1.0 (0.4-2.0)	
		Final VA	1.3 (0.5-1.5)	1.3 (0.4-2.1)	

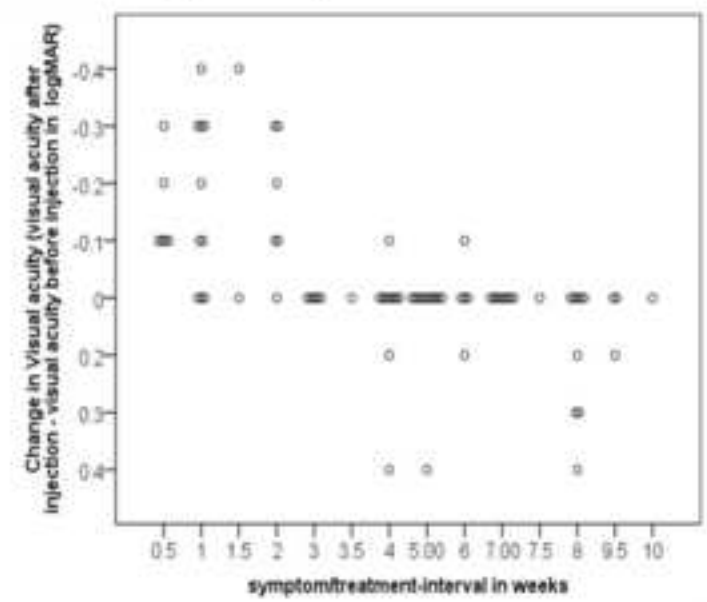
Table 3: Visual outcome according to grade of macular edema in patients treated with intravitreal treatment for radiation maculopathy after proton beam therapy in uveal melanoma. Median visual acuity and range in logMAR before injection (VA preinj.), at 4 weeks (VA 4 weeks), and at last follow-up (Final VA) are displayed according to resolved, reduced, stable, or increased macular edema. Best functional outcome was detected in patients with completely resolved edema.

[a] P=0.046
[b] P=0.05
[c] P=0.067 (no statistical significance)

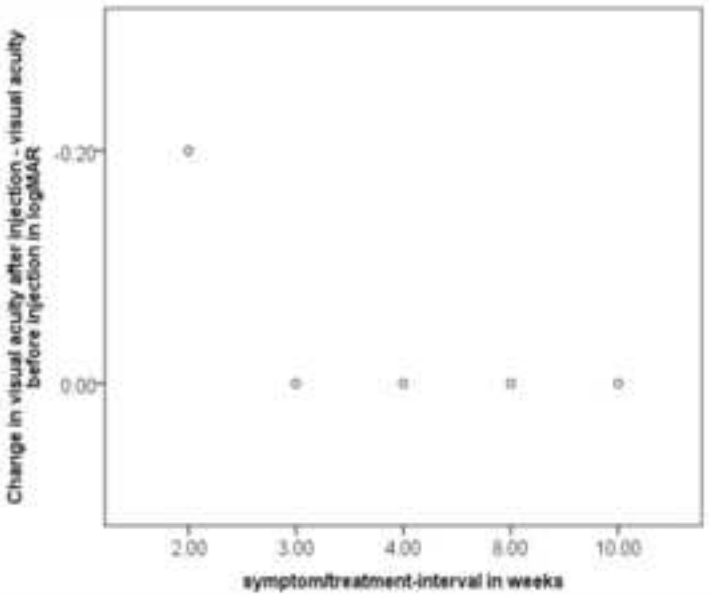

Change in visual acuity (final visual acuity - visual acuity before injection (in logMAR))
-0.80
-0.50
-0.30
0.00
0.20
0.40
0.60
0.80
1.30
1.50
Bevacizumab
Triamcinolone acetonide
Dexamethasone
Intravitreal treatment


Change in visual acuity (visual acuity after injection - visual acuity before injection (in logMAR))
-0.40
-0.30
-0.20
-0.10
0.00
0.20
0.30
0.40
Bevacizumab
Triamcinolone acetonide
Dexamethasone
Intravitreal treatment

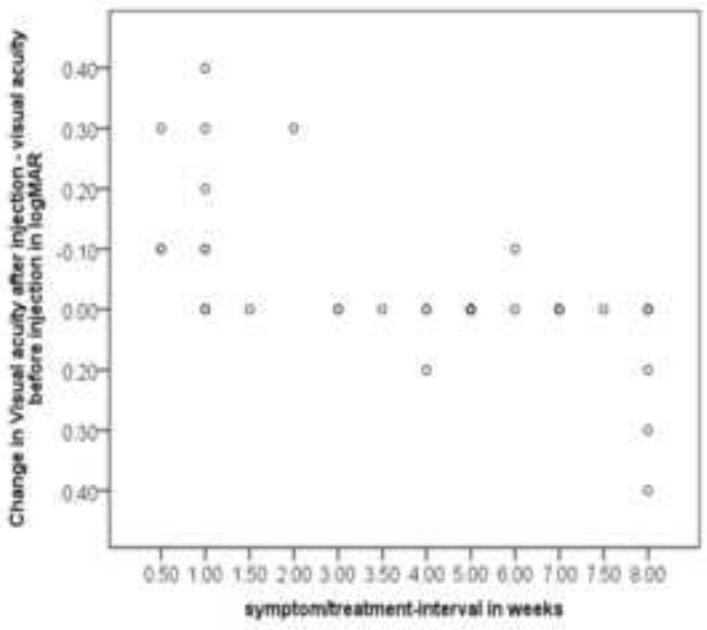
All patients irrespective of intravitreal treatment



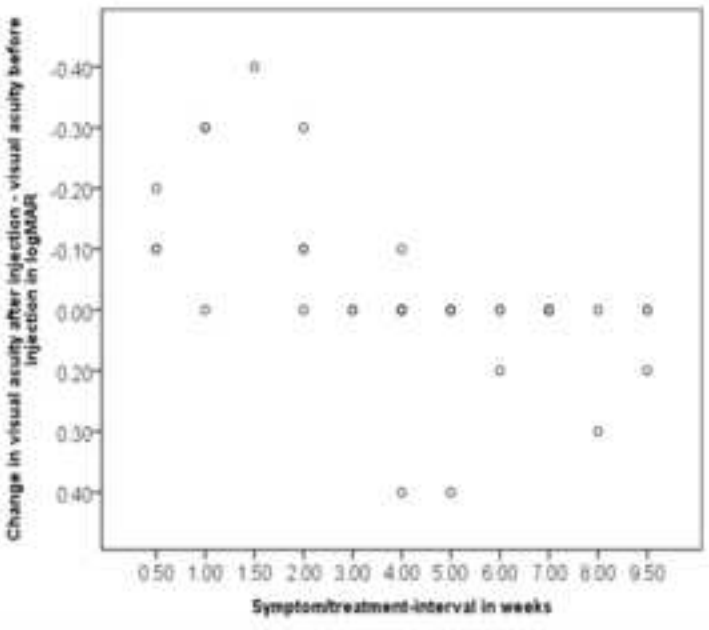
Dexamethasone implant

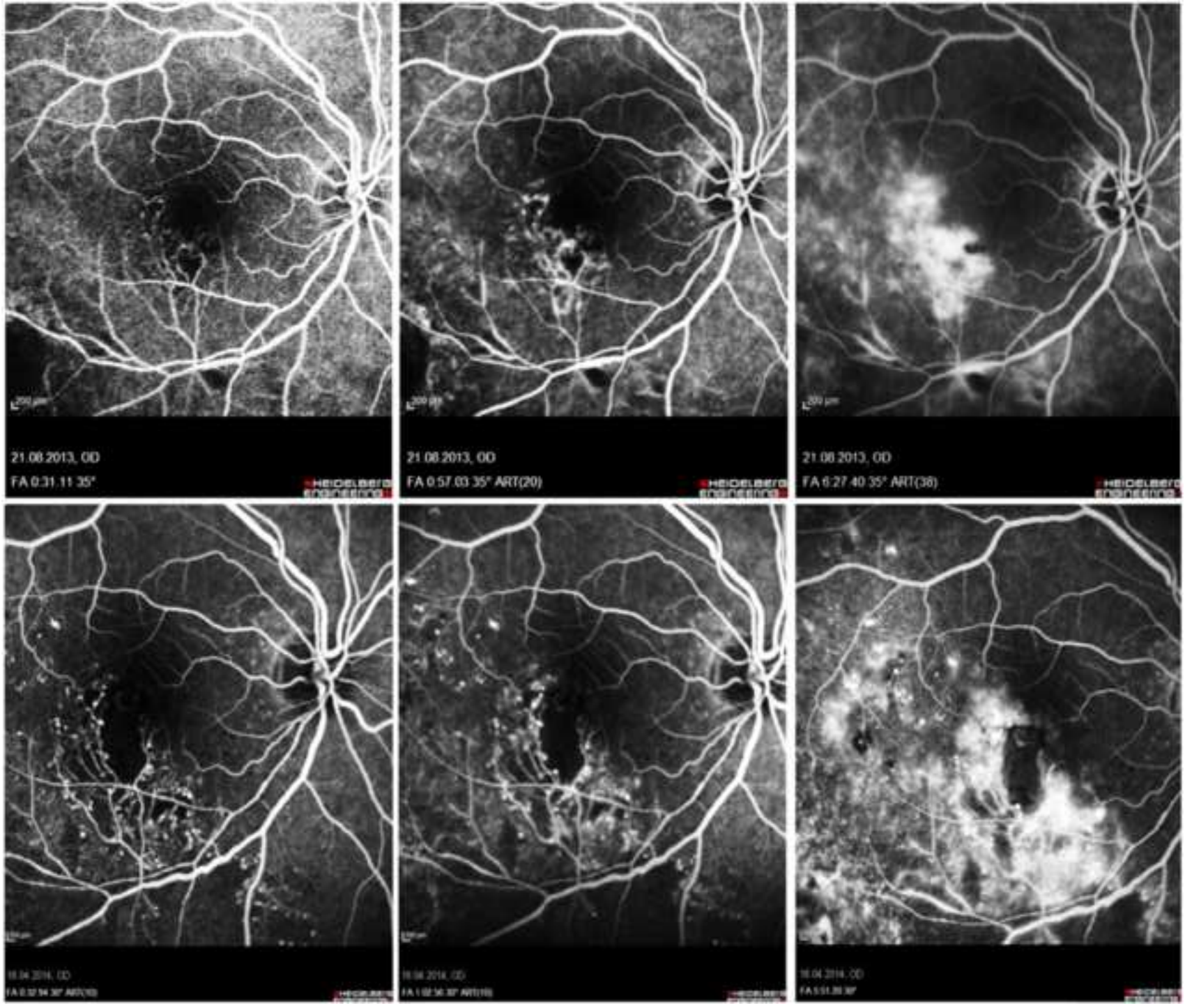


Bevacizumab



Triamcinolone acetonide

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