The Use of Intravitreal Anti-VEGF and Triamcinolone in the Treatment of Radiation Papillopathy

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Keywords

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Abstract

Background/Aims: To evaluate a treatment regimen for radiation papillopathy. **Methods:** This is a prospective non-comparative interventional case series of patients who developed radiation papillopathy after plaque brachytherapy for uveal melanoma. Treatment consisted of intravitreal bevacizumab (IVB) (1.25 mg in 0.05 mL) at the time of diagnosis, and 1 week later, intravitreal triamcinolone (IVK) (2.00 mg in 0.05 mL). One month later, patients again received both IVB and IVK. Patients were then switched to monotherapy with monthly IVB until the papillopathy resolved. **Results:** Eleven patients developed radiation papillopathy, with 9 receiving treatment. On multivariate analysis, total radiation dose to the optic nerve was the only significant predictor of papillopathy ($p = 0.005$). Four of nine patients presented with a significant decline in visual acuity (VA) at the time of diagnosis of papillopathy. In all 4, significant improvement was documented following treatment. Five patients did not present with a decrease in VA, and in this group, 80% remained stable with treatment. **Conclusions:** In this series, patients who

had a precipitous drop in VA at the time of diagnosis of radiation papillopathy returned to baseline VA following this treatment algorithm. This protocol was effective at maintaining stability of VA in 80% of those who developed papillopathy but did not present with an acute drop in VA.

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Introduction

Uveal melanoma is the most common primary intra-ocular malignancy in adults, for which many treatment modalities including proton beam radiotherapy, stereotactic radiosurgery, enucleation, and plaque radiotherapy have been used [1]. As equivalent survival of patients treated with enucleation versus plaque brachytherapy has been documented for medium-sized tumors [2], the latter has become the most commonly used treatment. Although plaque radiotherapy allows for globe retention in the majority of patients, complications including cataract formation, retinopathy, maculopathy, and papillopathy occur frequently [3].

Radiation papillopathy typically manifests months to years after radiation exposure [4], with an incidence ranging from 13 to 61% at 5 years, and from 22 to 77% at 10

years [3, 5]. This wide range of reported incidence is likely due to the fact that some studies evaluated patients with macular choroidal melanomas receiving plaque radiotherapy [5], whereas others only enrolled those with juxtapapillary lesions [3]. Although data is sparse, the majority of patients who develop this complication experience severe vision loss [4]. Previously described risk factors associated with the development of radiation papillopathy include distance to the optic disc <2 mm, dose to optic disc >5,904 cGy, larger plaque size, and longer duration of radiotherapy [3, 5].

A number of case reports and relatively small case series have evaluated various treatments for radiation papillopathy, including hyperbaric oxygen [6], intravitreal triamcinolone (IVK) [7], and intravitreal anti-vascular endothelial growth factor (VEGF) [8, 9]. These studies demonstrated that improvement by ≥ 2 Snellen lines could be obtained in 21 to 33% of cases, yet a significant proportion (22 to 36%) continued to worsen by ≥ 2 Snellen lines.

The combination of intravitreal anti-VEGF and corticosteroids has previously been described for other ischemic retinal microangiopathies, including diabetic macular edema. While some studies have not seen a benefit with combination therapy, others have reported earlier improvement, the need for fewer injections, and a longer-lasting effect when combining corticosteroids with anti-VEGF agents compared to monotherapy with anti-VEGF alone in cases of diabetic macular edema [10–13]. The potentially synergistic effects of combination therapy prompted us to investigate this algorithm in the context of radiation papillopathy. Herein, we present our experience with a protocol for the treatment of acute radiation papillopathy that combines both intravitreal bevacizumab and IVK.

Methods

Radiation papillopathy was diagnosed on the basis of examination findings including the development of clinically apparent unilateral optic disc edema, hemorrhage, and peripapillary exudation. A significant improvement or worsening in visual acuity (VA) was defined as a change of ≥ 2 Snellen lines. The patient's best corrected VA was obtained using a standard Snellen chart viewed from a distance of 6 m. If the patient's VA was less than 20/20, then a pinhole was utilized to minimize the influence of uncorrected refractive error. The same methodology was used in a standardized fashion for all patients at all visits. This VA measurement was converted to logarithm of the minimum angle of resolution (logMAR) units for statistical analysis [14]. Every patient had OCT assessment of the fovea, and color photos of the optic nerve, fovea, and tumor were taken at every visit.

Univariate and multivariate Cox proportional hazard models were utilized to evaluate for significant predictors of papillopathy. An exploratory analysis was performed to identify thresholds of increased risk for developing papillopathy. Those whose vision (a) declined from baseline (defined as VA recorded at the clinic visit prior to the development of papillopathy) by ≥ 2 Snellen VA lines or (b) had vision which was $\leq 20/40$ at the time of diagnosis of papillopathy were offered treatment with IVK and bevacizumab. One out of the eleven patients with papillopathy was excluded as his vision was excellent at the time of diagnosis of papillopathy (20/30) and he was therefore not offered treatment. Subsequently, ten of eleven patients met our inclusion criteria and were offered treatment; however, one patient decided not to pursue injections. The remaining 9 patients proceeded with our combined treatment algorithm, involving an intravitreal injection of bevacizumab (1.25 mg in 0.05 mL) at the time of diagnosis, followed by an intravitreal injection of triamcinolone (2.00 mg in 0.05 mL) 1 week later. All patients had repeat injections of intravitreal bevacizumab and triamcinolone at the 1-month follow-up. Patients were then switched to monotherapy with monthly bevacizumab until the optic nerve swelling resolved clinically (mean time to resolution of optic nerve swelling of 6.75 ± 2.60 months).

The nine patients receiving treatment were then subdivided into two groups: Group 1 consisted of those who had an acute decline in vision of ≥ 2 lines at the time of diagnosis of papillopathy compared to the prior visit (4/9 patients, 44.4%), and Group 2 consisted of patients who had no significant change in VA upon diagnosis of papillopathy when compared to the previous visit (5/9 patients, 55.5%). This subdivision was necessary to ensure accurate interpretation of response to treatment: in patients whose poor vision was not primarily attributable to papillopathy (as indicated by no drop in VA at the time of presentation of papillopathy), it would follow that even successful treatment of papillopathy would not alter their visual function. In this group, successful treatment would be defined as no worsening in their VA since prior research has demonstrated that severe visual loss typically occurs with follow-up [4]. Notably, a thorough ophthalmic examination was performed at each visit to reliably exclude an alternative explanation for the patients' decline in vision unrelated to papillopathy, such as the development of cataract or radiation maculopathy. The clinician's interpretation as to the primary cause of the vision loss was utilized as the "gold standard."

All tumors received a treatment dose of 70 Gy to the tumor apex using a dose calculation that accounted for plaque material heterogeneities, as per the joint recommendation of the American Association of Physicists in Medicine and the American Brachytherapy Society [15]. Additional parameters of radiotherapy delivered, including total apex dose, apex dose rate, and dose to the optic disc, center of lens, and fovea were recorded. Baseline demographic information, including gender, age, date of brachytherapy, date of development of papillopathy, and date of resolution was recorded. Tumor-specific variables, including size and proximity to the optic disc and fovea, were also noted. VA was noted at four time points: (a) prior to plaque radiotherapy, (b) 3 months prior to the development of radiation papillopathy (the visit preceding diagnosis of papillopathy), (c) VA on the clinic visit where papillopathy was noted, and (d) VA following resolution of optic disc swelling. The resolution of optic disc swelling was chosen as the final VA time point in order to limit any bias from multifactorial visual decline (e.g., cataract) occurring after the resolution of papillopathy.

Table 1. Clinical features of ten patients who developed radiation papillopathy following plaque brachytherapy with I¹²⁵ for choroidal melanoma treated with either combination anti-VEGF and intravitreal triamcinolone or observation

Study number	Age, years ^a	Gender	Interval between plaque to development of papillopathy, months	Radiation dose to optic nerve, Gy	Distance to optic nerve, mm	Snellen (logMAR) visual acuity prior to papillopathy ^b	Drop in visual acuity at the time of papillopathy ^c	Received treatment
1	43	Male	18	75.6	1.5	20/150 (0.88)	No	Yes
2	52	Female	28	115	0	20/30 (0.18)	Yes	Yes
3	59	Female	14	31.9	7	20/60 (0.48)	Yes	Yes
4	70	Female	15	49.7	3	20/50 (0.40)	No	Yes
5	49	Male	16	80.0	2	20/40 (0.30)	Yes	Yes
6	63	Female	8	127.1	0	Hand motion (3.00)	No	Yes
7	39	Male	14	33.4	3	20/400 (1.30)	No	Yes
8	65	Female	19	107.2	0	20/100 (0.70)	No	Yes
9	78	Male	19	34.3	6	20/30 (0.18)	No	No
10	74	Male	20	38.3	5.5	20/70 (0.54)	No	No
11	76	Female	19	72.2	0.7	20/30 (0.18)	Yes	Yes

^a Age at time of development of papillopathy. ^b Visual acuity prior to papillopathy is defined as that which was recorded at the clinic visit immediately prior to the development of papillopathy. ^c Drop in visual acuity is defined as loss of ≥ 2 Snellen visual acuity lines at the time of diagnosis of radiation papillopathy.

Results

A consecutive case series of 201 brachytherapy patients were followed for a mean ($\pm$ SD) of $1,041 \pm 541$ days (2.9 ± 1.5 years) from plaque implantation. Eleven patients (5.5%) developed radiation papillopathy noted at a mean of 537 ± 153 days (1.5 ± 0.4 years) from the date of plaque implantation (Table 1). The eleven patients who developed radiation papillopathy have been followed for a statistically significantly longer period of time ($1,438 \pm 442$ days; 3.9 ± 1.2 years) following plaque insertion, compared to the remaining 190 patients who have not developed radiation papillopathy ($1,018 \pm 538$ days; 2.8 ± 1.5 years) ($p = 0.01$). There was no difference in the mean age at time of plaque implantation between those who developed radiation papillopathy compared to those who did not (60.5 ± 13.4 years and 60.6 ± 14.9 years, respectively, $p = 0.98$).

Forty tumors (19.9%) were ≤ 1 mm from the optic nerve (juxtapapillary subgroup) and 66 tumors (32.8%) were ≤ 2 mm from the optic nerve (peripapillary subgroup). Of the 40 patients in the juxtapapillary subgroup, 4 patients (10.0%) developed radiation papillopathy and of the 66 patients in the peripapillary group, 5 patients (7.6%) developed radiation papillopathy. Of the remaining 135 patients with lesions > 2 mm from the optic nerve, 6 patients (4.4%) developed radiation papillopathy.

On univariate Cox proportional hazard analysis, super 9 plaque configuration, a plaque commonly used in jux-

Table 2. Percentage of eyes that developed papillopathy of those receiving a specified range of radiation dose to the optic nerve

Radiation dose to optic nerve	Percentage of eyes developing papillopathy
< 30 Gy	0.0%
30–60 Gy	5.1%
60–90 Gy	10.7%
> 90 Gy	14.8%

tapapillary lesions ($p = 0.02$), was found to be a statistically predictor of radiation papillopathy. Other statistically significant predictors included distance to optic disc ($p = 0.04$), dose to fovea ($p = 0.06$), and radiation dose to optic nerve ($p = 0.005$). Multivariate analysis revealed that total radiation dose to the optic nerve ($p = 0.03$) was the only variable that remained statistically significant. No patient receiving a dose of < 32 Gy to the optic nerve developed radiation papillopathy, and as the amount of radiation delivered to the optic nerve increased, so did the proportion of patients who developed papillopathy (Table 2).

Of the nine patients who received our treatment algorithm, the mean pre-plaque Snellen VA was 20/29 (logMAR 0.17 ± 0.29). Mean VA 3 months prior to the development of papillopathy was 20/138 (logMAR 0.84 ± 0.88),

Table 3. Visual acuity of eleven patients who developed papillopathy

Patient number	logMAR (Snellen) VA 3 months prior to papillopathy	logMAR (Snellen) VA when papillopathy was diagnosed	logMAR (Snellen) VA post-treatment and resolution of papillopathy
Group 1			
2	0.18 (20/30)	1.30 (20/400)	0.40 (20/50)
3	0.48 (20/60)	0.88 (20/150)	0.30 (20/40)
5	0.18 (20/30)	1.00 (20/200)	0.70 (20/100)
11	0.18 (20/30)	0.54 (20/70)	0.18 (20/30)
Group 2			
1	0.88 (20/150)	0.70 (20/100)	0.87 (20/150)
4	0.40 (20/50)	0.30 (20/40)	0.40 (20/50)
6	3.00 (hand motion)	3.00 (hand motion)	3.00 (hand motion)
7	1.30 (20/400)	1.30 (20/400)	1.30 (20/400)
8	0.70 (20/100)	0.60 (20/80)	0.88 (20/150)
Group 3			
9	0.54 (20/70)	0.40 (20/50)	0.48 (20/60)
10	0.18 (20/30)	0.18 (20/30)	0.30 (20/40)

Group 1: Patients with an acute decline in visual acuity at the time of diagnosis who had an excellent visual recovery. Group 2: Patients who had no significant change in visual acuity upon development of papillopathy. Group 3: Patients who did not receive treatment.

and at the time of diagnosis of radiation papillopathy it was 20/234 (logMAR 1.07 ± 0.80). Four of nine patients had an acute decline in their VA at the time of diagnosis of radiation papillopathy compared to their VA recorded from the visit 3 months prior (Table 3, Group 1). Clinically, it was felt that only these four patients developed a measurable decrease in their VA directly attributable to the development of papillopathy. This subgroup of patients had a mean Snellen VA of 20/36 (logMAR 0.26 ± 0.15) 3 months prior to diagnosis, 20/170 (logMAR 0.93 ± 0.31) at the time of diagnosis, and 20/50 (logMAR 0.40 ± 0.22) following treatment and resolution. Five of the nine patients, who presented with radiation papillopathy and VA $\leq 20/40$ did not demonstrate a drop in their VA at the time of presentation of the papillopathy (Table 3, Group 2). Four of the five Group 2 patients demonstrated stability, and one of the five worsened. Two patients were not treated; one because their VA was too good to qualify (20/30) and the other declined treatment (Table 3, Group 3). Both of the patients who were not treated demonstrated mild worsening of their VA over time.

Clinically visible swelling of the nerve resolved at a mean of 6.75 ± 2.60 months after diagnosis of papillopathy. Two of the nine patients developed a steroid response with elevated intraocular pressure to the high 20s. Both of these cases were successfully managed with topical glaucoma medications. No other complications occurred.

Discussion

The development of radiation papillopathy is a potentially devastating complication from the treatment of intraocular tumors with radiation. In a study evaluating the natural history of radiation papillopathy following proton beam irradiation of peripapillary melanomas, Kim et al. [4] reported that 5 years after the onset of papillopathy, only 45% retained VA of counting fingers or better.

While radiation papillopathy following plaque brachytherapy is less common than with other radiation modalities, such as stereotactic radiation [16], its incidence has been reported to vary between 22 and 77% at 5–10 years [3, 5]. The incidence of radiation papillopathy in our study was lower, both overall (5.5%) and within the subset of 40 patients with juxtapapillary tumors ≤ 1 mm from the optic nerve (10.0%). However, these numbers cannot be compared directly, as our mean follow-up time of $1,041 \pm 541$ days (2.9 ± 1.5 years) was shorter than both of these studies.

Although multiple variables on univariate Cox proportional hazard analysis were related to the development of papillopathy, total radiation dose to the optic nerve was the only independent significant predictor on multivariate analysis. Below a radiation dose of 32 Gy to the optic nerve, no cases of papillopathy were noted (Table 3).

Table 4. Comparison of interventional case series using monotherapy (with either triamcinolone or bevacizumab) versus combination therapy

Visual acuity	Shields et al. [7] (triamcinolone)	Finger and Chin [9] (bevacizumab)	Roelofs et al. [present paper] (combined Rx)
Improvement	33%	21%	44%
Stable	44%	43%	44%
Worsening	22%	36%	11%

Improvement = increase in visual acuity by ≥ 2 Snellen visual acuity lines. Stable = maintenance of visual acuity within 1 Snellen line. Worsening = decline in visual acuity by ≥ 2 Snellen visual acuity lines.

While the benefits of anti-VEGF and corticosteroids in the treatment of radiation maculopathy [17–20], retinopathy [21, 22], and iris neovascularization [23] following treatment of uveal melanoma with radiation have been documented, the literature clarifying the optimal treatment regimen for radiation papillopathy is sparse. Finger [8] previously reported the successful use of bevacizumab in a case report of radiation papillopathy in which this intervention was well tolerated, reduced angiographic leakage from the optic disc, and improved vision. Following this case, Finger and Chin [9] published a prospective interventional case series consisting of 14 patients with radiation optic neuropathy. They found that with intravitreal bevacizumab, 21% of patients demonstrated improvement, 43% remained stable, and 36% worsened despite treatment. Shields et al. [7] reported the use of IVK in a prospective, single-center case series of 9 patients and found that VA improved by ≥ 2 Snellen lines in 33% of patients, was stable in 44%, and worsened by ≥ 2 Snellen lines in 22%. Overall, in our study, of the treated patients 44% improved, 44% were stable, and 11% worsened (Table 4).

In the four patients with visual loss directly attributable to the development of radiation papillopathy (those that presented with a significant decline in VA at the time of diagnosis of papillopathy), significant visual improvement was seen in all cases following treatment, with a return to pre-papillopathy VA. In those who did not have a significant change in VA at the time papillopathy was noted, 80% demonstrated stability (± 1 Snellen line). Since no measurable VA loss could be directly attributed to the development of papillopathy in this subgroup, we feel that stabilization of VA for these patients should be considered a successful outcome (Table 5).

Table 5. Response to treatment for patients who lost vision from papillopathy versus those who did not

Patients who lost vision from papillopathy ($n = 4$)	
Improvement	100%
Stable	0%
Worsening	0%
Patients who did not lose vision from papillopathy ($n = 5$)	
Improvement	0%
Stable	80%
Worsening	20%

Improvement = increase in visual acuity by ≥ 2 Snellen visual acuity lines. Stable = maintenance of visual acuity within 1 Snellen line. Worsening = decline in visual acuity by ≥ 2 Snellen visual acuity lines.

Combination therapy with either posterior sub-Tenon’s or intravitreal injection of triamcinolone in combination with intravitreal anti-VEGF agents has been used in other ischemic retinal diseases [10–13, 24]. The effects of combining corticosteroids with anti-VEGF agents are thought to be both additive and complimentary. Corticosteroids block non-VEGF-dependent inflammatory pathways, including the arachidonic acid pathway [25]. In vivo studies have confirmed that in addition to their anti-inflammatory effects, corticosteroids also inhibit the secretion of angiogenic mediators from retinal microvascular pericytes [26]. Some have found that when corticosteroids are used in combination with anti-VEGF agents for macular edema, visual improvement is seen earlier [12] and fewer or less frequent anti-VEGF injections may be required over time [24, 27]. To the best of our knowledge, this is the first report evaluating the effect of combined therapy with IVK and bevacizumab for the treatment of radiation papillopathy.

The main limitations of this study are its small sample size, lack of a control group and unavailable visual field data. However, it is the second largest interventional case series evaluating VA outcomes following treatment of radiation papillopathy. In addition, this is a difficult group of patients to study given that visual decline post-brachytherapy is often multifactorial and may not be solely due to radiation papillopathy in all patients. Yet the results we have provided are representative of the real-world results that would be seen in the setting of multifactorial visual loss encountered by clinicians following these patients. Larger studies with appropriate control groups and long-term follow-up will be needed to clarify the optimal treatment protocol for radiation papillopathy.

Summary

Patients who presented with decreased VA directly attributable to radiation papillopathy improved to pre-papillopathy VA levels following treatment with intravitreal bevacizumab and triamcinolone. Of those patients with no measurable vision loss attributable to papillopathy, the majority (80%) remained stable following treatment.

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Statement of Ethics

Ethics approval was obtained from the Health Research Ethics Board for Alberta – Cancer Committee.

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