

# Role of Anti-Vascular Endothelial Growth Factor Agents in the Treatment of Uveal Metastases

Georges Sukkarieh<sup>1\*</sup>, Tarek Rustom<sup>1</sup>, Amine Al Soueidy<sup>1</sup>, Hampig Raphael Kourie<sup>2</sup> and Joelle Antoun<sup>1</sup>

<sup>1</sup>Ophthalmology Department, Hôtel-Dieu de France Hospital, Faculty of Medicine, Saint Joseph University, Lebanon

<sup>2</sup>Hematology-Oncology Department, Hôtel-Dieu de France Hospital, Faculty of Medicine, Saint Joseph University of Beirut, Lebanon

\*Corresponding author: Georges Sukkarieh, Ophthalmology Department, Hôtel-Dieu de France Hospital, Faculty of Medicine, Saint Joseph University, Beirut, Lebanon

## ARTICLE INFO

**Received:** 📅 August 17, 2023

**Published:** 📅 September 11, 2023

**Citation:** Georges Sukkarieh, Tarek Rustom, Amine Al Soueidy, Hampig Raphael Kourie and Joelle Antoun. Role of Anti-Vascular Endothelial Growth Factor Agents in the Treatment of Uveal Metastases. Biomed J Sci & Tech Res 52(5)-2023. BJSTR. MS.ID.008310.

## ABSTRACT

**Introduction:** Anti-vascular endothelial growth factor agents (Anti-VEGF) have been recently used, locally and systemically, in the treatment of uveal metastases. The aim of this review is to summarize the available data concerning response of uveal metastases to intraocular and/or systemic anti-VEGF agents.

**Methods:** An exhaustive PubMed database search for articles describing the treatment of iris or choroidal metastasis (CM) with anti-VEGF agents was done.

**Results:** In total, 48 case reports and case series describing anti-VEGF use in iris and choroidal metastases (CM) were collected. Thirty-two out of 43 cases of CM treated by intravitreal anti-VEGF injections had a positive response. Four out of 6 cases of CM secondary to non-small cell lung carcinoma responded well to systemic anti-VEGF. Iris metastases regressed in the 12 reported cases of iris metastases treated by intraocular anti-VEGF. No reported cases were found concerning the treatment of iris metastases with systemic anti-VEGF molecules.

**Conclusion:** Anti-VEGF intraocular injections seem to be a valid alternative for the palliative management of patients with iris or choroidal metastases by promptly reducing pain, improving visual acuity and reducing tumor size thus ameliorating the patient's quality of life.

**Keywords:** Choroidal Metastases; Intravitreal Anti-VEGF Injection; Iris Metastases; Systemic Anti-VEGF; Uveal Metastases

**Abbreviations:** CM: Choroidal Metastases; Anti-VEGF: Anti-Vascular Endothelial Growth Factor Agents; IM: Iris Metastases; NSCLC: Non-Small Cell Lung Carcinoma; SCLC: Small Cell Lung Carcinoma

## Introduction

Anti-vascular endothelial growth factor agents (Anti-VEGF) have been used, locally and systemically, in the treatment of uveal metastases. The objective of this article is to review the available data concerning the intraocular and/or systemic anti-VEGF agents treatment of uveal metastases.

## Methods

A database search was performed on PubMed, using the keywords "choroidal metastasis", "choroidal metastases", "iris metas-

tasis" and "iris metastases" in combination with the terms: "bevacizumab", "ranibizumab", "aflibercept" and "intravitreal injection". All published articles up until 30 March 2021, describing the treatment of iris or choroidal metastases (CM) were included. In total, 48 case reports and/or case series were collected: 27 articles of anti-VEGF IVI for CM, 9 articles of systemic anti-VEGF use for CM and 12 articles of anti-VEGF IVI for iris metastases (IM). The main findings of the 48 articles are presented in the Table 1. The following text summarizes main features of anti-VEGF IVI role in treating ocular metastases.

## Results

### Intravitreal Anti-VEGF for Choroidal Metastases

**Anti VEGF-IVI in Lung Cancer CM:** 17 cases of CM secondary to lung cancer were found (12 of non-small cell lung carcinoma (NSCLC) and 5 of small cell lung carcinoma (SCLC)). Among patients with CM from NSCLC, visual acuity improved in 8 cases, decreased in 1 case, was not reported in 2 cases, and in 1 case of bilateral CM visual acuity remained stable in 1 eye and decreased in the other. Concerning SCLC, visual acuity improved in 4 cases and worsened in 1 case. Among all patients with lung carcinoma that benefited from anti-VEGF IVI, improvement of visual acuity was reported as early as 1-2 weeks after IVI injection in 3 cases [1-3].

**Anti-VEGF IVI in Breast Cancer:** In total 13 cases of CM secondary to breast cancer were treated with IVIs. Visual acuity improved in 8 cases, deteriorated in 4, and one case with bilateral disease had improvement in an eye and deterioration in the other. Visual acuity improved as early as 3 weeks in some cases [4-6].

**Anti-VEGF IVI in Other Tumors:** 5 cases presenting with colorectal carcinoma were treated by anti-VEGF injections. Two cases presented improvement, while two cases presented a deterioration. One patient with bilateral CM presented a regression of tumor with stable visual acuity in an eye, and progression of disease in the other eye [7]. Details of all reported cases of CM treated by Anti-VEGF can be found in Table 1.

**Table 1:** Studies using intravitreal anti-VEGF for the treatment of choroidal metastases.

Authors	Number of patients Age Sex	Primary lesion	Treatment of cancer	Concomitant treatment	Number of injections (dosing in mg)	BCVA pre-injection	BCVA post-injection	SRF evolution (OCT)	Tumor response	Follow-up period (months)	Ocular complications
Amselem, et al. [5]	1 57 years Female	Breast carcinoma ER negative	Eight cycles: oxaliplatin + vinorelbine	None	1 Bevacizumab IVI (4mg)	10/200	20/60	Decrease	Regression (3 weeks after IVI)	3 weeks	None
Kuo, et al. [20]	1 65 years Female	Colorectal adenocarcinoma of the sigmoid colon  (immunohistochemical staining for VEGF was demonstrated)	Surgical excision + CT: fluorouracil, leucovorin calcium, and oxaliplatin for 6 months  Radiotherapy for brain metastasis	None	3 Bevacizumab IVI (1.25 mg in 0.05 mL) at monthly intervals	Hand Motion	20/40 five days after 1 <sup>st</sup> IVI  20/30 at 5 months follow-up	Decrease	Regression 50% at one month follow-up  - Complete regression at 5 months follow-up	5	None
Kim, et al. [21]	1 57 years Female	Adenocarcinoma of the lung	CT: Docetaxel and cisplatin	Oral erlotinib (150 mg) daily 9 weeks after first IVI	3 Bevacizumab IVI (2.5 mg) at 6 weeks interval	20/200	20/40 after 3 <sup>rd</sup> IVI	Decrease	Complete regression	4	None
Fabrini, et al. [22]	1 (both eyes) 57 years Male	Thyroid carcinoma with solid and papillary areas of oxyfil cell-type	Total thyroidectomy, parathyroidectomy, bilateral cervical lymphadenectomy  + adjuvant radio-metabolic treatment with I-131.	CT: Anthracycline	1 Bevacizumab IVI (NR)	20/25	20/20 (at 5 months)	Decrease	Stable	20	Vitreous hemorrhage at 20 months
				LE: episcleral 106-Ru plaque brachytherapy	1 Bevacizumab IVI (NR)	20/70	20/40 (at 5 months)	Decrease	Regression	20	None

Lin, et al. [23]	1 (both eyes) 43 years Male	Colon adenocarcinoma	CT: oxaliplatin, fluorouracil, Calcium folinat Ebewee		4 Bevacizumab IVI (4mg)	RE: 20/20	20/20	NR	Regression	NR	None
				4 Bevacizumab IVI (4mg)	LE: 20/400	Hand Motion	NR	Progression	NR	None	
Yao, et al. [24]	1 50 years Female	Brest carcinoma ER negative Her 2 negative PR weakly positive	Modified radical mastectomy + axillary lymph nodes dissection + Adjuvant CT: cyclophosphamide, doxorubicin and 5-fluorouracil.	CT: paclitaxel and gemcitabine	1 Bevacizumab IVI (2.5mg in 0.1mL)	20/400 : CF	20/30	Decrease	Regression (6 months after IVI)	24	None
de la Barquera Cordero, et al. [25]	1 50 years Female	Non-small cell lung cancer	Carboplatin, paclitaxel and systemic bevacizumab for 8 months	NR	5 Bevacizumab IVI (2.5mg) every 1.4 months	20/40	20/20	Decrease	Complete regression	10	None
Mansour, et al. [26]	1 49 years Female	Breast ductal carcinoma ER+ PR+ Her 2-	CT: cisplatin, capecitabine, gemcitabine, paclitaxel and tamoxifen + Radiotherapy	CT	9 Bevacizumab IVI (2.5mg) (At 0, 4, 6, 7, 10, 13, 16, 19, 22 months)	20/20 Before first IVI	20/40 after last IVI	Stable	Regression withing 2 weeks of first IVI	22	None
Lai, et al. [27]	1 73 years Male	Adenocarcinoma of lung	CT: vinorelbine + cisplatin	CT: Erlotinib, pemetrexed, and docetaxel	2 Bevacizumab IVI (2.5mg)	10/200	20/60 two weeks after first IVI and remained stable	Decrease	Regression	4	None
D'Antonio, et al. [28]	1 34 years Female	Invasive papillary lung adenocarcinoma	NR	Gemcitabine + cisplatin + systemic Bevacizumab (after IVI)	2 Bevacizumab IVI (1.25mg)	NR	NR	Decrease	Complete regression	20	None
Singh, et al.[29]	1 42 years Female	Large cell carcinoma of the lung	None	4 three weekly cycles of Paclitaxel + Cisplatin	7 Bevacizumab IVI (1.25mg in 0.05mL) at monthly intervals	2/60	3/60	Resolution after 6 months	Regression after 6 months	9	None
	1 53 years Man	Lung adenocarcinoma	None	Three weekly cycles of Pemetrexed + Cisplatin	3 Bevacizumab IVI (1.25mg in 0.05mL) at monthly intervals	Hand motion	NR	NR	Progression	NR	None

Detorakis, et al. [30]	1	Small-cell lung carcinoma	None	CT	3 Ranibizumab IVI (0.5mg) at monthly intervals	20/80	20/32	Resolution	Regression	9	None
	1	Nasopharyngeal cancer	Previous radiotherapy	None	3 Ranibizumab IVI (0.5mg) at monthly intervals	CF	NR	NR	Regression	9	None
Zako, et al. [31]	1 51 years Female	Ductal breast carcinoma ER+	Mastectomy + 5-deoxy-5-fluorouridine + tamoxifen	Tamoxifen + cyclophosphamide hydrate	1 Bevacizumab IVI after 9 months of tamoxifen + cyclophosphamide	20/60	20/400	Regression three weeks after injection	CM regressed after CT  Optic disk metastasis remained	Patient switched to letrozole 2 years later because of recurrence of SRF	None
Arevalo, et al. [32]	1 47 years Female	Breast carcinoma	Radical mastectomy + CT + Radiotherapy	ICG mediated thrombosis + CT	1 Bevacizumab IVI (4mg in 0.16ml)	CF	20/400 at 3 weeks after IVI 20/100 at 4 months	Resolution	Regression	4	None
	1 (both eyes) 70 years Female	Breast carcinoma	Radical mastectomy + CT + Radiotherapy	ICG mediated thrombosis + CT	1 Bevacizumab IVI (4mg in 0.16ml)	20/25	Unchanged at 5 weeks 20/40 at 7 months	Resolution	Regression	7	None
						Hand motion	Unchanged at 5 weeks CF at 7 months				
Kim, et al. [33]	5 eyes of 4 patients 54 years	NR	NR	CT started after the injections	2.6 Bevacizumab IVI (2.5mg)	Mean: 20/100	Mean: 20/25	Resolution at 2.8 months	Regression	15	None
Kuo, et al. [34]	1 57 years Female	Ovarian serous cystadenocarcinoma	None	None	1 Bevacizumab IVI (1.25mg in 0.05 ml)	Hand motion	Hand motion after 20 days	No decrease	No regression	None	None
Bhattacharyya, et al. [35]	1 54 years Male	Small-cell lung cancer	NR	CT: Cisplatin + Etoposide EBRT 30 Gy in 10 fractions over 2 weeks	5 Bevacizumab IVI (2.5mg) at monthly intervals	20/200	20/60	NR	NR	6	None

Maturu, et al. [36]	Case 1: 60 years Female	Adenocarcinoma of the lung	NR	CT: Pemetrexed + Cisplatin + Zoledronate + oral Gefitinib	4 Bevacizumab IVI (1.25mg in 0.05 mL) every 4 weeks	CF at 1 meter	20/60	Decrease	Regression	4	None
	Case 2: 49 years Male	Small-cell lung cancer	NR	CT: Cisplatin + Irinotecan	3 Bevacizumab IVI (1.25mg in 0.05 mL) every 4 weeks	RE: 20/20 LE: 20/60	RE: 20/80 LE: 20/120	Increase	Progression	3	Exudative retinal detachment
Fenicia, et al. [37]	3 patients Case 1: 39 years Female	Breast carcinoma	Mastectomy + CT	Tamoxifen	2 Bevacizumab IVI (1.25mg) One month apart	20/50	At 2 weeks 20/25 At 6 months 20/20	Decrease	Regression	6	None
	Case 2: 36 years Female	Invasive papillary lung adenocarcinoma	CT: Gemcitabine + Cisplatin	After IVI results: carboplatin, taxol and intravenous bevacizumab	2 Bevacizumab IVI (1.25mg) One month apart	CF	At 2 weeks 20/25 At 9 months 20/25	Decrease	Regression	9	None
	Case 3: 54 years Female	Breast carcinoma	Multiple cycles of CT, including Docetaxel	NR	4 Bevacizumab IVI (1.25mg) at monthly intervals	20/25	At 1 month 20/20 At 12 months 20/20	Decrease	Regression	12	None
Augustine, et al. [38]	1 72 years Female	Ductal breast carcinoma	Resection + postoperative radiotherapy + Tamoxifen + 3 cycles of Fluorouracil+ epirubicine + Cyclophosphamide + 9 weekly doses of paclitaxel +letrozole	CT: 3 cycles of paclitaxel + gemcitabine before IVI switched to Capecitabine + Trastuzumab	4 Bevacizumab IVI (1.25mg) at monthly intervals	20/50	20/30 after third injection 20/25 after 5 months	Resolution after 4 months	Regression after 4 months	8	None
asui, et al. [39]	1 68 years Male	Non-small cell lung cancer	NR	CT: carboplatin, pemetrexed, bevacizumab (15 mg/kg)	1 Bevacizumab IVI (1.25mg)	20/50	NR (but improved visual symptoms)	Decrease	Regression (27 days after systemic CT, 7 days after IVI)	2	None

Maudgil, et al. [40]	1 80 years Male	Caecum adenocarcinoma	Hemicolec-tomy and partial hepatoctomy	None	1 Bevacizumab IVI (1.25mg/0.05mL)	20/200	Hand motion	Increase	Progression (3 weeks after IVI) Then regression after systemic CT	2	None
	1 61 years Female	Adenocarcinoma of the lung	NR	NR	3 Bevacizumab IVI (1.25mg/0.05mL) at monthly intervals	20/60	20/120	NR	Progression (1 month after last IVI dose) Requiring EBRT	4	Extraocular extension
	1 43 years Female	Breast carcinoma	Wide local excision, axillary clearance, and chemoradiotherapy + Hormone replacement therapy for metastasis (bone, lung, lymph nodes)	PDT (3 spots, 7.2 mm, 83 s, 600 mW/cm <sup>2</sup> ) with good tumor regression at 6 weeks	3 Bevacizumab IVI (1.25mg/0.05mL) at monthly intervals	20/70	20/200	NR	Progression then regression after EBRT	3	None
	1 62 years Female	Breast carcinoma	Local excision and chemo-radiotherapy	CT : induced regression over 6 months Edge recurrence 10 months later : no immediate response to EBRT	3 Bevacizumab IVI (1.25mg/0.05mL) at monthly intervals	20/60	20/200	NR	Regression	4	None
	1 57 years Female	Caecum adenocarcinoma	CT + bowel and liver resection	NR	3 Bevacizumab IVI (1.25mg/0.05mL) at monthly intervals	CF	Hand motion	NR	Progression requiring EBRT	3	None

Lin and Tsai [41]	3 patients 5 eyes: Case 1: 47 years Male	Small-cell lung cancer	NR	TTT one session to both eyes + Gefitinib 250 mg daily for 3 months	3 Bevacizumab IVI (4mg/0.16mL) Weekly in both eyes	RE: 20/30 LE: 20/25	20/20 at 3 months 20/20 at 3 months	Decrease	Regression Regression	6	None
	Case 2: 34 years Female	Breast carcinoma	NR	TTT one session to both eyes + Cetuximab	3 Bevacizumab IVI (4mg/0.16mL) Weekly in both eyes	RE: 20/40 LE: 20/20	20/20 at 3 months 20/20 at 3 months	Decrease	Regression Regression	6	None
	Case 3: 40 years Male	Small-cell lung cancer	NR	TTT one session + Gefitinib 250 mg daily for 3 months	3 Bevacizumab IVI (4mg/0.16mL) Weekly	LE: 20/1000	10/100 at 3 months	Decrease	Regression	6	None
Nadiminti, et al. [42]	1 (both eyes) 38 years Female	Ductal carcinoma of the breast ER+ PR+ HER2-	Mastectomy + axillary node dissection, + 4 cycles of docetaxel, cyclophosphamide + adjuvant radiation	EBRT after the 2 injections + CT: Gemcitabine + Denosumab	2 Bevacizumab IVI (1.25 mg) in each eye at monthly intervals	20/30 20/40	20/20 20/30	NR	Regression Regression	4	None
Boss, et al. [43]	1 68 years Female	Rectal adenocarcinoma with KRAS mutation	Pelvic radiation + CT including 5-fluorouracil and FOLFOX, FOLFIRI and systemic Bevacizumab + perineal and abdominal resection of sigmoid rectum and anus + experimental medication KTN3379	None	3 Bevacizumab IVI (1.25mg) at monthly intervals	20/70	NR	Decrease after first injection Increase after third injection	Regression after first injection Increase after third injection	NR	None
Menoux, et al. [44]	1 (both eyes) 58 years Female	Lung adenocarcinoma	5 cycles of carboplatin + paclitaxel	EBRT: Brain + choroid 30 Gy in 2 weeks	1 Ranibizumab + 4 Aflibercept IVI at monthly intervals 4 Aflibercept IVI at monthly intervals	20/200 20/40	CF 20/40	NR	Regression Regression	8	Neovascular complication
Karimi, et al. [45]	1 16 years Male	Lung bronchial carcinoid	Systemic octreotide	PDT (83 s; 50 J/cm)	3 Bevacizumab IVI (1.25mg) at monthly intervals	20/32	20/25 at 6 weeks	Decrease	Regression	6	None

Note: BCVA: Best corrected visual acuity; CF: Counting fingers; CM: Choroidal metastasis; CT: chemotherapy; EBRT: External beam radiotherapy; ER: Estrogen receptor; FOLFIRI: Folinic acid, Fluorouracil, Irinotecan FOLFOX: Folinic acid, Fluorouracil, Oxaliplatin; Gy: Gray; HER 2: Human epidermal growth factor receptor 2; I-131: Iodine-131; ICG: Indocyanin green; IVI: Intravitreal injection; KRAS: Kirsten rat sarcoma viral oncogene homolog; LE: Left eye; NR: not reported; NSCLC: Non-small cell lung cancer; OCT: Optical coherence tomography; PDT: Photodynamic Therapy; PR: Progesterone receptor; RE: Right eye; Ru-106: Ruthenium -106; SRF: Subretinal fluid; TTT: Transpupillary thermotherapy; VEGF: Vascular endothelial growth factor.

### Systemic Anti-VEGF for Choroidal Metastases

Systemic anti-VEGF treatment of choroidal metastasis was reported 9 times (Table 2). No cases of iris metastases treated by systemic Anti-VEGF agents were found. Improvement of VA was reported in 4

cases and stability of VA at 20/20 in 1 case. No response was found in 1 case, and response was not reported in 3 cases. The positive response to systemic anti-VEGF remained stable for a follow-up of 18 weeks to 20 months [8-11].

**Table 2:** Studies using systemic bevacizumab for the treatment of choroidal metastases.

Authors	Primary lesion	Previous treatment	Local therapy	Chemotherapy	VA evolution	SRF evolution	Tumor response	Follow-up period	Complications
George, et al. [46]	Large cell lung carcinoma	None	No	7 cycles (3 weekly) of Carboplatin + gemcitabine + bevacizumab	Improved	Present and decreased	Disappearance after cycle 3	Stable through 21 weeks	None
D'antonio, et al. [28]	Lung adenocarcinoma	Gemcitabine + cisplatin + 2 IVI bevacizumab after which CM, SRF and vision improved	None	Six cycles of	NR	NR	NR	Vision, SRF and CM remained stable for 20 months	None
				Gemcitabine + Cisplatin + 18 doses of bevacizumab used as maintenance therapy					
Singh, et al. [29]	Lung adenocarcinoma with liver, adrenal and bone metastasis	4 three weekly cycles of: pemetrexed (500 mg/m <sup>2</sup> ) + cisplatin (60 mg/m <sup>2</sup> ) + 3 IVI bevacizumab (1.25 mg in 0.05 mL every 4 weeks) that failed	Eye EBRT (30 Gy in 10 fractions)  Additional 2 doses of IVI bevacizumab	Ten 3 weekly cycles:  Docetaxel (75 mg/m <sup>2</sup> ) + carboplatin (AUC <sup>^</sup> of 5.0 mg/mL per min) + bevacizumab at a dose of (7.5 mg/kg)	Improved from hand motion to 6/24 after 5 cycles of bevacizumab	Disappeared	Regressed after five cycles of bevacizumab	Stable through 30 weeks	Death after 16 months from cancer progression
Besic, et al. [47]	Follicular thyroid carcinoma with lung and bone metastasis	NR	Radiotherapy	Other chemotherapy including bevacizumab	NR	NR	NR	NR	NR
Lu, et al. [48]	Lung adenocarcinoma, no EGFR, KRAS or ALK mutation with bone and hepatic metastasis	None	None	Six cycles of Carboplatin + Pemetrexed + Bevacizumab with Pemetrexed + Bevacizumab maintenance	No response	NR	No response	Changed to crizotinib after 1 year because of no response	NR
Kourie, et al. [49]	Lung adenocarcinoma	None	None	Three weekly cycles of docetaxel + cisplatin + bevacizumab (10mg/kg)	Remained stable at 20/20	Disappeared after 4 cycles	Disappeared after 4 cycles	Stable after 6 cycles	None



Khawaja, et al. [50]	Rectal adenocarcinoma with lung, adrenal gland, and bone metastasis	CT: capecitabine + radiotherapy + laparoscopic resection	Radiation therapy to the eye (3500 cGy over 14 fractions)	Two weekly cycles: 5FU+ Leucovorin + oxalyplatin + bevacizumab	Improved	NR	Disappeared	8 months	None
Makabe, et al. [51]	Lung adenocarcinoma metastatic to paraaortic lymph nodes and adrenal gland	Gefitinib for EGFR mutation that was ineffective	None	6 four weekly cycles Carboplatin (AUC 5) + Pemetrexed (500 mg/m <sup>2</sup> ) + Bevacizumab (15 mg/mg)	Improved from HM to 20/200 after 2 cycles	NR	Disappeared after 2 cycles	Stable through 16 months	None
Hattori, et al. [52]	Breast cancer with axillary lymph node, liver, lung metastasis	Surgery	None	Paclitaxel + bevacizumab	NR	NR	Disappeared	NR	NR

Note: 5 FU: 5-Fluorouracil; ALK: Anaplastic lymphoma kinase; AUC: Area under the curve ; CM: Choroidal metastasis; EGFR: Epidermal growth factor receptor; HM: Hand motion; IVI: Intravitreal injection; KRAS: Kirsten rat sarcoma viral oncogene homolog; NR: Not reported; SRF: Subretinal fluid; VA: Visual acuity.

### Intravitreal Anti-VEGF for Iris Metastases

12 reported cases of iris metastasis treated by intraocular injections of anti-VEGF agents were found. All cases were unilateral except one case reported by Zhou et al. which was bilateral [12]. Anti-VEGF injections were given for secondary glaucoma with pain and reduced vision in 10 cases, reduced vision with no secondary glaucoma in 1 case [13] and for an asymptomatic iris metastasis in 1 case [14]. Cases with secondary glaucoma showed a decrease in IOP, pain and iris neovessels. Visual acuity improved in 6 cases, worsened in 1 case and was not reported in 5 cases.

## Discussion

### Intravitreal Anti-VEGF for Choroidal Metastases

Intravitreal Anti-VEGF agents are effective because of their anti-angiogenic effect, knowing that metastases rely on VEGF to develop their own blood supply [15,16]. This review shows that anti-VEGF IVI appear to be effective in treating choroidal metastasis since regression of choroidal metastases was reported in 32 of the 43 cases. Concomitant chemotherapy was used in 28 out of the 42 cases reported, that can overestimate the true response to the anti-VEGF injections but the fast recovery of visual acuity can be attributed to the effect of anti-VEGF.

### Systemic Anti-VEGF for Choroidal Metastases

Response to systemic bevacizumab is probably due to its antiangiogenic effects since intravenous administration delivers the drug directly to the highly vascularized choroid. However, firm conclusions cannot be drawn because of the limited reported cases, where, moreover, multiple other systemic and/or local therapies were used.

### Intravitreal Anti-VEGF for Iris Metastases

On our search of literature 12 reported cases of iris metastasis treated by intraocular injections of anti-VEGF agents were found and are detailed in Table 3. Iris metastases are markers of poor prognosis with a life expectancy of 10 months [17,18]. Hence, the main goal of the treatment is the improvement of the quality of life [17]. Many therapeutic options have been proposed for IM with multiple side effects and/or complications [17,18]. Taking into account all these considerations and since intravitreal anti-VEGF injections were able to show improvement in all 12 reported cases, anti-VEGF IVI seems to be a valid option for the treatment of iris metastasis. Intravitreal injection seems more adequate than intracameral injections because of the longer half-life of the molecules in the vitreous [19-62].

**Table 3:** Studies using intravitreal anti-VEGF injections for the treatment of iris metastases.

Authors	Primary lesion	Previous treatment	Concomitant treatment	Number of injections (dosing in mg)	VA pre-injection	VA post-injection	IOP pre-injection	IOP post-injection	Tumor response	Fol-low-up	Complications
Schell, et al. [53]	Non-small cell lung cancer with brain metastasis	Paclitaxel Bevacizumab Carboplatin Temozolomide Chest radiotherapy Whole brain radiotherapy	None	1 Intracameral bevacizumab injection (1.25 mg in 0.05 mL)	20/70	NR	Secondary glaucoma with: 22 mm Hg	Normal 2 weeks after IVI	Disappeared 2 weeks after IVI	Stable 2 months after with no IOP lowering drops	None
Nakashima, et al. [54]	Small-cell lung cancer with adrenal gland, abdominal lymph node and brain metastasis	Cisplatin Etoposide Amrubicin Whole brain radiotherapy	None	1 IVI bevacizumab (1.25 mg)	20/300	NR	Secondary glaucoma with: 36 mm Hg	18 mmhg 2 weeks after IVI with regression of INV	Regressed 2 weeks after IVI	Stable 3 months after on one IOP lowering drop	None
Yokouchi, et al. [55]	Large-cell neuroendocrine lung cancer with adrenal gland, abdominal lymph node, and bone metastasis	Chemotherapy Whole brain radiotherapy	None	Three monthly IVI bevacizumab (1.25 mg in 0.05 ml)	20/40	20/20	Secondary glaucoma with: 36 mm Hg	Normal 2 weeks after first IVI with regression of INV	Disappeared 4 months after first IVI	Stable 6 months after with no IOP lowering drops	None
Dhakal, et al. [56]	Eso-phageal adenocarcinoma	Surgery for resection of the primary cancer + chemotherapy	Stereotactic body radiation therapy	2 monthly IVI bevacizumab	20/100	20/30 6 months after SBRT + Injections	Normal	Normal	Disappeared 2 months after SBRT + IVI	Stable 6 months after with no IOP lowering drops	Anterior uveitis after SBRT

Zhou, et al. [57]	Multiple myeloma	Autologous stem cell transplantation	None	2 monthly IVI bevacizumab	LE : NR	LE : 20/50 2 weeks after the second injection	Secondary glaucoma with: 36 mm Hg	20 mmHg 1 week after first IVI with regression of INV 2 weeks after second IVI	Regression 1 month after first IVI	Stable 8 months after with no IOP lowering drops	None
		Bortezomib Cyclophosphamide Epirubicin Thalidomide	Same as previous treatment	1 IVI bevacizumab		RE : Hand motion	RE : Hand motion	Secondary glaucoma with high IOP	30 mmhg with no pain 2 weeks after IVI	Disappeared 4 months after IVI	Stable 4 months after
Makri, et al. [58]	Non-small cell lung cancer	None	None	2 monthly IVI ranibizumab	Hand motion	20/100 2 weeks after first injection	Secondary glaucoma with 47 mmHg	20-28 mmhg 2 weeks after first IVI with regression of INV	Regressed 2 weeks after first IVI	Stable 1 month after on one glaucoma drops	None
Seidman, et al. [59]	Breast cancer with liver, lung and brain metastasis	Whole brain radiotherapy Carboplatin Anastrozole	None	3 monthly IVI bevacizumab (1.25mg in 0.05ml)	20/32	20/50	Secondary glaucoma with 39 mmHg	16 mmHg 1 month after first IVI with regression of INV	Regressed 1 month after first IVI	Stable 1 month after	None
Akinci, et al. [60]	Breast cancer with bone marrow, lung and brain metastasis	Radical mastectomy + radiotherapy Abemaciclib Fulvestrant.	Pablociclib + Letrozole 3 month after first injection for new abdominal metastasis	3 monthly IVI bevacizumab followed after 3 months by 2 IVI bevacizumab given 3 months apart (1.25mg)	20/20	NR	16 mmHg	NR	Regressed one month after first IVI; disappeared 5 months after first IVI	Stable 12 months after	None
Vale, et al. [61]	Breast cancer	Radical mastectomy Chemotherapy	Chemotherapy 1 week after injection for lung, adrenal glands, liver and bones metastasis	1 IVI bevacizumab (1.25mg)	CF at 2 feet	20/80 1 week after injection	Secondary glaucoma with IOP 30mmHg	15 mmHg 1 week after IVI	Regression 8 weeks after IVI	Stable 8 months after on 2 glaucoma drops	None
Hidaka, et al. [62]	Small-cell lung cancer	Carboplatin Etoposide Amrubicin	Brain radiotherapy for brain metastasis	1 IVI bevacizumab (1.25mg)	NR	LP	Secondary glaucoma with IOP > 30 mmHg	30 mmHg with disappearance of INV	Regression 1 month after IVI	NR	None

Aydin, et al. [63]	Biliary tract adenocarcinoma with lung and bone metastasis	5-FU Irinotecan	5 FU + Irinotecan	3 monthly IVI bevacizumab (1.25 mg/0.05 ml)	20/50	20/20 after third injection	Secondary glaucoma with IOP 34 mmHg	20 mmHg after first IVI	Tumor completely disappeared after third IVI	Stable with glaucoma drops	Anterior chamber inflammation after first injection that recovered swiftly
Raval, et al. [64]	Squamous cell carcinoma of the lung	None	Systemic CT	1 IVI bevacizumab (1.25 mg in 0.05 mL)	20/40	20/30 1 month after injection	Secondary glaucoma with 22 mmHg	16 mmHg 1 month after IVI with reduced pain	Regression of tumor 1 month after IVI	NR	None

Note: CT: Chemotherapy; IOP: Intraocular pressure; VA: Visual acuity; IVI: Intravitreal injection; LE: Left eye; LP: Light perception; 5-FU: 5-Fluorouracil; NR: not reported; INV: Iris neovessels; RE: Right eye; SBRT: Stereotactic external-beam radiation therapy.

## Limitations

First limitation of this review is that all acquired data are based on case reports. The second limitation is that cases that showed response to Anti-VEGF agents are more likely to be published.

## Conclusion

Anti-VEGF intraocular injections seem to be a valid alternative for the palliative management of patients with iris or choroidal metastases by promptly reducing pain, improving visual acuity and reducing tumor size thus ameliorating the patient's quality of life.

## Declarations of Interest

None.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## References

- Yasui H, Sato K, Takeyama Y, Nishihara H, Maeda M, et al. (2015) Effective Treatment with Intravitreal Injection of Bevacizumab for Exudative Retinal Detachment Secondary to Choroidal Metastasis of Non-Small Cell Lung Carcinoma. *Am J Case Rep* 16: 728-732.
- Fenicia V, Abdolrahimzadeh S, Mannino G, Verrilli S, Balestrieri M, et al. (2014) Intravitreal bevacizumab in the successful management of choroidal metastases secondary to lung and breast cancer unresponsive to systemic therapy: a case series. *Eye* 28(7): 888-891.
- Lai CL, Fan KS, Lee YH, Chen HC, Fan WH (2012) Intravitreal administration of bevacizumab in the treatment of choroidal metastasis in a patient with erlotinib-failed pulmonary adenocarcinoma. *Lung Cancer* 76(3): 496-498.
- Mansour AM, Alameddine R (2012) Intravitreal bevacizumab for consecutive multiple choroidal breast metastatic lesions. *Case Reports*.
- Amselem L, Cervera E, Díaz-Llopis M, Montero J, Garcia-Pous M, et al. (2007) Intravitreal bevacizumab (Avastin) for choroidal metastasis secondary to breast carcinoma: short-term follow-up. *Eye* 21(4): 566-567.
- Arevalo JF, Espinoza JV (2012) Indocyanine Green Mediated Photothrombosis and High Dose Intravitreal Bevacizumab as Adjuvant Therapy for Isolated Choroidal Metastasis from Breast Cancer. *J Ophthalmic Vis Res* 7(4): 332-340.
- Kuo IC, Haller JA, Maffrand R, Sambuelli RH, Reviglio VE (2008) Regression of a subfoveal choroidal metastasis of colorectal carcinoma after intravitreal bevacizumab treatment. *Arch Ophthalmol* 126(9): 1311-1313.
- Makabe K, Kurishima K, Shiozawa T, Miyazaki K, Ohara G, et al. (2016) Treatment of choroid metastasis from lung adenocarcinoma with bevacizumab-containing chemotherapy: A case report. *Exp Ther Med* 11(1): 239-242.
- Singh N, Kulkarni P, Aggarwal AN, Mittal BR, Gupta N, et al. (2012) Choroidal metastasis as a presenting manifestation of lung cancer: a report of 3 cases and systematic review of the literature. *Medicine (Baltimore)* 91(4):179-194.
- D'Antonio C, Viterbo A, Romiti A, Enrici MM, Lauro S, et al. (2012) Complete regression of a non-small cell lung cancer choroidal metastasis with intravitreal bevacizumab. *J Thorac Oncol* 7(2): 468-469.
- Lu S, Azada MC, Ou SHI (2015) Choroidal metastasis response to crizotinib in a ROS1-rearranged NSCLC patient. *Lung Cancer* 87(2): 207-209.
- Zhou Q, Liang J, Lu H (2013) Intravitreal bevacizumab for ocular metastasis of multiple myeloma. *Optom Vis Sci* 90(9): e236-240.
- Dhakal S, Lema GMC, Diloreto DA, Katz AW (2012) Esophageal metastasis to the iris effectively palliated using stereotactic body radiation therapy and adjuvant intravitreal chemotherapy: case report and literature review. *Case Rep Oncol* 5(3): 639-643.
- Akinci GE, Hondur AM, Tezel TH (2019) Management of Metastatic Breast Carcinoma of Iris with Intraocular Bevacizumab Injections. *Retin Cases Brief Rep* 13(3): 220-223.
- Nishida N, Yano H, Nishida T, Kamura T, Kojiro M (2006) Angiogenesis in cancer. *Vasc Health Risk Manag* 2(3): 213-219.
- Boyd SR, Tan D, Bunce C, Gittos A, Neale MH, et al. (2002) Vascular endothelial growth factor is elevated in ocular fluids of eyes harbouring uveal melanoma: identification of a potential therapeutic window. *Br J Ophthalmol* 86(4): 448-452.
- Shields JA, Shields CL, Kiratli H, de Potter P (1995) Metastatic tumors to the iris in 40 patients. *Am J Ophthalmol* 119(4): 422-430.

18. Shields CL, Kaliki S, Crabtree GS, Peshtani A, Morton S, et al. (1995) Iris metastasis from systemic cancer in 104 patients: the 2014 Jerry A. Shields Lecture. *Cornea* 34(1): 42-48.
19. Radcliffe NM, Finger PT (2009) Eye cancer related glaucoma: current concepts. *Surv Ophthalmol* 54(1): 47-73.
20. Kuo IC, Haller JA, Maffrand R, Sambuelli RH, Reviglio VE (2008) Regression of a subfoveal choroidal metastasis of colorectal carcinoma after intravitreal bevacizumab treatment. *Arch Ophthalmol* 126(9): 1311-1313.
21. Kim SW, Kim MJ, Huh K, Oh J (2009) Complete regression of choroidal metastasis secondary to non-small-cell lung cancer with intravitreal bevacizumab and oral erlotinib combination therapy. *Ophthalmologica* 223(6): 411-413.
22. Fabrini MG, Genovesi-Ebert F, Perrone F, De Liguoro M, Giovannetti C, et al. (2009) A multimodal approach to the treatment of bilateral choroidal metastases from thyroid carcinoma. *Rare Tumors* 1(1): e4.
23. Lin CJ, Li KH, Hwang JF, Chen SN (2010) The effect of intravitreal bevacizumab treatment on choroidal metastasis of colon adenocarcinoma—case report. *Eye* 24(6): 1102-1103.
24. Yao HY, Horng CT, Chen JT, Tsai ML (2010) Regression of choroidal metastasis secondary to breast carcinoma with adjuvant intravitreal injection of bevacizumab. *Acta Ophthalmol* 88(7): e282-e283.
25. de la Barquera Cordero AS, Hidalgo RAC (2010) Intravitreal bevacizumab for choroidal metastasis of lung carcinoma; a case report. *J Ophthalmic Vis Res* 5(4): 265-268.
26. Mansour AM, Alameddine R (2012) Intravitreal bevacizumab for consecutive multiple choroidal breast metastatic lesions. *BMJ Case Rep*.
27. Lai CL, Fan KS, Lee YH, Chen HC, Fan WH (2012) Intravitreal administration of bevacizumab in the treatment of choroidal metastasis in a patient with erlotinib-failed pulmonary adenocarcinoma. *Lung Cancer* 76(3): 496-498.
28. Detorakis Efstathios T, Agorogiannis George, Drakonaki Eleni E, Tsilimbaris Miltiadis K, Pallikaris Ioannis G (2012) Successful Management of Choroidal Metastasis with Intravitreal Ranibizumab Injections. *Ophthalmic Surgery, Lasers and Imaging Retina* 43(6): e47-e51.
29. Zako M, Takeyama M, Naito E, Mizumoto K, Iwaki M (2012) Choroidal and optic disc metastases from breast cancer and their response to combination pharmacotherapy with tamoxifen, cyclophosphamide hydrate, letrozole, and bevacizumab. *J Ocul Pharmacol Ther* 28(1): 89-93.
30. Arevalo JF, Espinoza JV (2012) Indocyanine green mediated photothrombosis and high dose intravitreal bevacizumab as adjuvant therapy for isolated choroidal metastasis from breast cancer. *J Ophthalmic Vis Res* 7(4): 332-340.
31. Kim M, Kim CH, Koh HJ, Lee SC, Kim SS (2014) Intravitreal bevacizumab for the treatment of choroidal metastasis. *Acta Ophthalmol* 92(1): e80-e82.
32. Kuo IC, Sambuelli RH, Bono J, Smith RJ, Reviglio VE (2013) Progression of choroidal metastasis of ovarian serous cystadenocarcinoma after intravitreal bevacizumab treatment. *Rare Tumors* 5(1): e5.
33. Bhattacharyya T, Kapoor R, Bahl A, Yadav BS, Singh U, et al. (2013) Carcinoma lung presenting with choroidal metastasis as initial presentation: a rarity. *J Cancer Res Ther* 9(3): 504-506.
34. Maturu VN, Singh N, Bansal P, Rai Mittal B, Gupta N, et al. (2014) Combination of intravitreal bevacizumab and systemic therapy for choroidal metastases from lung cancer: report of two cases and a systematic review of literature. *Med Oncol* 31(4): 901.
35. Fenicia V, Abdolrahimzadeh S, Mannino G, Verrilli S, Balestrieri M, et al. (2014) Intravitreal bevacizumab in the successful management of choroidal metastases secondary to lung and breast cancer unresponsive to systemic therapy: a case series. *Eye (Lond)* 28(7): 888-891.
36. Augustine H, Munro M, Adatia F, Webster M, Fielden M (2014) Treatment of ocular metastasis with anti-VEGF: a literature review and case report. *Can J Ophthalmol* 49(5): 458-463.
37. Yasui H, Sato K, Takeyama Y, Nishihara H, Maeda M, et al. (2015) Effective Treatment with Intravitreal Injection of Bevacizumab for Exudative Retinal Detachment Secondary to Choroidal Metastasis of Non-Small Cell Lung Carcinoma. *Am J Case Rep* 16: 728-732.
38. Maudgil A, Sears KS, Rundle PA, Rennie IG, Salvi SM (2015) Failure of intravitreal bevacizumab in the treatment of choroidal metastasis. *Eye (Lond)* 29(5): 707-711.
39. Lin CJ, Tsai YY (2015) The effect of intravitreal bevacizumab and transpupillary thermotherapy on choroidal metastases and literature review. *Indian J Ophthalmol* 63(1): 37-41.
40. Nadiminti K, Leone JP (2016) Intraocular bevacizumab in the treatment of choroidal metastases from breast cancer. *BMJ Case Rep*.
41. Boss JD, Lieu P, Tewari A (2016) Effect of treatment of rectal cancer metastasis with intravitreal bevacizumab (Avastin) in patient with subretinal fluid and macular oedema: short-term follow-up. *BMJ Case Rep*.
42. Menoux I, Guihard S, Antoni D, Bijon JC, Noël G (2017) [Choroidal metastasis from a lung adenocarcinoma treated by intravitreal injection of anti-VEGF and external beam radiotherapy: A case report]. *Cancer Radiother* 21(2): 130-133.
43. Karimi S, Arabi A, Shahraki T (2020) Intravitreal Bevacizumab (Avastin) as an Adjuvant Therapy for Choroidal Carcinoid Metastasis. *J Curr Ophthalmol* 32(4): 420-422.
44. George B, Wirostko WJ, Connor TB, Choong NW (2009) Complete and durable response of choroid metastasis from non-small cell lung cancer with systemic bevacizumab and chemotherapy. *J Thorac Oncol* 4(5): 661-662.
45. Besic N, Luznik Z (2013) Choroidal and orbital metastases from thyroid cancer. *Thyroid* 23(5): 543-551.
46. Lu S, Azada MC, Ou SHI (2015) Choroidal metastasis response to crizotinib in a ROS1-rearranged NSCLC patient. *Lung Cancer* 87(2): 207-209.
47. Kourie HR, Antoun J, Schakal A, Nasr E, Sahyoun M, et al. (2015) Complete Disappearance of Choroidal Metastasis from Lung Adenocarcinoma Treated with Bevacizumab and Chemotherapy. *Case Rep Ophthalmol Med*.
48. Khawaja MR, Minturn JT, Spittler AJ, Chiorean EG (2015) Ocular metastasis of colorectal cancer: An uncommon presentation of a common malignancy. *Hematol Oncol Stem Cell Ther* 8(4): 176-180.
49. Makabe K, Kurishima K, Shiozawa T, Miyazaki K, Ohara G, et al. (2016) Treatment of choroid metastasis from lung adenocarcinoma with bevacizumab-containing chemotherapy: A case report. *Exp Ther Med* 11(1): 239-242.
50. Hattori M, Shirahane K, Sakai M, Sassa Y, Nishihara Y, et al. (2020) [Combination Therapy of Bevacizumab plus Paclitaxel Was Effective for a Metastatic Choroidal Tumor Secondary to Breast Cancer in a Patient with Ocular Symptoms]. *Gan To Kagaku Ryoho* 47(8): 1221-1214.
51. Schell JC, Koenig SB, Bastin K, Wirostko WJ (2011) Intracameral bevacizumab administered for non-small cell lung cancer metastasis to iris. *Clin Pract* 1(2): e39.
52. Nakashima C, Keino H, Watanabe T, Taki W, Okada AA (2011) Intravitreal bevacizumab for iris metastasis of small-cell lung carcinoma with neovascular glaucoma. *Jpn J Ophthalmol* 55(1): 80-81.

53. Yokouchi H, Kitahashi M, Oshitari T, Yamamoto S (2013) Intravitreal bevacizumab for iris tumor metastasized from large cell neuroendocrine carcinoma of lung. *Graefes Arch Clin Exp Ophthalmol* 251(9): 2243-2245.
54. Dhakal S, Lema GMC, Diloreto DA, Katz AW (2012) Esophageal metastasis to the iris effectively palliated using stereotactic body radiation therapy and adjuvant intravitreal chemotherapy: case report and literature review. *Case Rep Oncol* 5(3): 639-643.
55. Zhou Q, Liang J, Lu H (2013) Intravitreal bevacizumab for ocular metastasis of multiple myeloma. *Optom Vis Sci* 90(9): e236-240.
56. Makri OE, Psachoulia C, Exarchou A, Georgakopoulos CD (2016) Intravitreal Ranibizumab as Palliative Therapy for Iris Metastasis Complicated With Refractory Secondary Glaucoma. *J Glaucoma* 25(1): e53-e55.
57. Seidman CJ, Finger PT, Silverman JS, Oratz R (2017) Intravitreal Bevacizumab in the Management of Breast Cancer Iris Metastasis. *Retinal Cases and Brief Reports* 11(1): 47-50.
58. Akinci GE, Hondur AM, Tezel TH (2019) Management of Metastatic Breast Carcinoma of Iris with Intraocular Bevacizumab Injections. *Retin Cases Brief Rep* 13(3): 220-223.
59. Vale S, Montalvo L, Baez E, Oliver AL (2018) Intravitreal bevacizumab as therapy for refractory neovascular glaucoma secondary to iris metastasis of breast carcinoma. *Am J Ophthalmol Case Rep* 9: 45-47.
60. Hidaka T, Chuman H, Nao-I N (2018) A Case Report of Intravitreal Bevacizumab for Iris Metastasis of Small Cell Lung Carcinoma with Neovascular Glaucoma. *Case Rep Ophthalmol* 9(2): 401-404.
61. Aydin R, Tezel TH (2018) Use of Intravitreal Bevacizumab for the Treatment of Secondary Glaucoma Caused by Metastatic Iris Tumor. *J Glaucoma* 27(6): e113-e116.
62. Raval V, Saldanha M, Mittal R, Das T (2019) Intravitreal bevacizumab in treatment of iris metastasis from primary lung carcinoma. *BMJ Case Rep* 12(9).

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2023.52.008310

Georges Sukkarieh. Biomed J Sci & Tech Res



This work is licensed under Creative Commons Attribution 4.0 License

Submission Link: <https://biomedres.us/submit-manuscript.php>



#### Assets of Publishing with us

- Global archiving of articles
- Immediate, unrestricted online access
- Rigorous Peer Review Process
- Authors Retain Copyrights
- Unique DOI for all articles

<https://biomedres.us/>