

METASTATIC EYE CANCER AS A PROGNOSTIC FACTOR FOR PATIENT SURVIVAL: A REVIEW ARTICLE

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The eye is a rare organ of metastatic disease spreading. Secondary eye tumor can be diagnosed in all structures of the eye from ocular adnexa to uvea, and optic disc.

Metastatic eye tumors originate from different primary tumor lesions such as: melanoma, squamous cellular carcinoma, lymphoid tissue tumors, breast, lungs, gastrointestinal tract, prostate, kidney, bladder. Some of these primary tumors are specific to the place of metastatic lesions. Symptoms and clinical manifestation vary according to the involvement of different structure. The diagnosis of metastatic eye tumor is connected to the poor prognosis. The treatment depends on the primary tumor lesions, part of the eye that is involved, and stage of the disease. Novel immunological, biological, and radiotherapy techniques give promising results in treatment.

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Key words: metastatic cancer, eye, prognosis, treatment

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Introduction

The eye is a rare organ in which metastatic processes occur. Only 8-10% of all metastases are eye metastases (1). About 80% of affected persons present with a single tumor in only one eye (1). The other 20% have bilateral, multiple tumors or both (1, 2). Metastatic tumor to the eye may be in the ocular adnexal structures: the eyelid, lacrimal gland, conjunctiva (1, 3). Intrabulbar secondary tumors are detected in the uveal tract: the iris, the ciliary body, and the choroid (4-8). The optic disc can also be a site of secondary metastatic tumors (1, 9).

No consensus has yet been reached on a treatment strategy. Complex treatments are not recommended due to limited survival expectancy.

The most commonly used treatment is external beam radiation therapy (ERBT), most often more advanced radiation techniques due to less unwanted evacuees such as stereotaxic body radiotherapy (SBRT) and carbon ion beam radiotherapy (CIRT) are proposed (10-12). Systemic therapies targeting oncogenic drivers or immunotherapy lead to regression of choroidal metastases and improvement of visual symptoms (13-16). Transpupillary thermotherapy (TTT), enucleation and the intravitreal use of anti-VEGF factors also give a big hope for effective therapy of those conditions (1, 2, 17, 18). The aim of our study was to present the literature findings of metastatic tumors to the eye adnexa and intrabulbar tumors, prognostic factor for survival of these patients and possible treatment. The author performed a search of studies indexed in MEDLINE PubMed database using terms: metastatic cancer, eye, prognostic factor, treatment and gave the illustration of their own cases. Relevant articles were extracted and reviewed.

Eyelid

The eyelids are characterized by their complex structure, and by rich and varied pathology. They are supplied with blood through two arches which are formed by anastomoses of the lateral palpebral arteries and medial palpebral arteries. The lateral palpebral arteries and medial palpebral arteries are branches of the lacrimal artery and ophthalmic artery. The skin is thin and has more pigment cells. The skin of the eyelid contains the greatest concentration of sebaceous glands found anywhere in the body.

Metastatic cancer of the eyelid is rare, and in multiple case series accounts for < 1% of malignant eyelid lesions (3). These patients have multiple ocular or extraocular metastatic sites. The most common is basal cell carcinoma (80.4%), than the squamous cell carcinoma (7%), melanoma (5.1%), and sebaceous carcinoma (3.3%) (3, 19-21). However, of the small number of metastases to the eyelids, breast carcinoma represents the most common one (3, 21, 22). Other distant primary tumors may originate from renal, medullary thyroid carcinoma, lung adenocarcinoma, prostate and salivary gland adenocarcinoma (19, 20, 22). The most common location is upper lid in 40% and the less common is the inner angle with 10% of all diagnosed metastatic eyelid tumors (3). Eyelid metastasis usually appears in patients with a known systemic cancer. But, it can be the first symptom of systemic cancer or the first sign of metastasis from a known malignant neoplasm (1). The management of eyelid metastases depends on the clinical features of the tumor itself: shape, location and also primary site and presence of other metastatic lesions (Figure 1a) (1, 3). Therapy includes excisional biopsy, EBRT, systemic chemotherapy/immunotherapy, and observation (1, 3, 10). A small, solitary nodular lesion can be managed with excisional biopsy (Figure 1a). Survival from diagnosis can vary between 12 and 40 months, and it mostly depends on systemic primary tumor and number of lesions (Table 1) (1, 3). Multiple eyelid metastasis as well as metastatic lesions in other organs presented at the same time are connected to the poor prognosis.

Lacrimal gland

The lacrimal gland and lacrimal drainage system are rare places of secondary metastatic lesions. About 26-50% of all malignant tumors of lacrimal gland are metastatic (1, 23). Surrounding structures

such as the mucosa of nasal cavity and paranasal structures during their evolution propagate to the lacrimal drainage system. In the present literature, there are case presentations of renal tumor, hepatocellular and breast tumors with metastatic progression to the lacrimal gland (1, 23, 24). Lymphoproliferative tumor can also be diagnosed in the lacrimal gland during the progression of lymphoma, or as one of the first symptoms of lymphopoietic disorders. Lymphoproliferative lesions are softer, and mold to the globe bilaterally (23). These lesions involve both the orbital and palpebral portions of the lacrimal gland. Treatment of primary tumor is the treatment option for metastatic lesions. CIRT for head and neck cancer has already been proven a promising treatment, particularly for patients with radioresistant tumors (12, 25).

Prognosis of this tumor depends on primary tumor lesion and is usually poor. In the current literature, the time of survival is not precise, and it is based on few cases (Table 1).

Conjunctiva

Metastatic lesions of the conjunctiva are not common. They are typically characterized by the presence of tumor malignant cells under epithelium while the epithelium itself stays intact (4, 5, 26). At the time of diagnosis, patients usually have distant and disseminated metastatic lesions in other organs and die within the period of one year of diagnosing conjunctival involvement (Table 1) (26).

In the present literature, colon carcinoma and cutis melanoma are described as case presentations (4, 5, 26). In the presence of lymphoid nodular structures in conjunctiva in patients with lymphoid tumors, surgical treatment is not recommended (Figure 1b) (26). Radiotherapy and different protocol for lymphoid tumors should be used (Table 1) (1, 25).

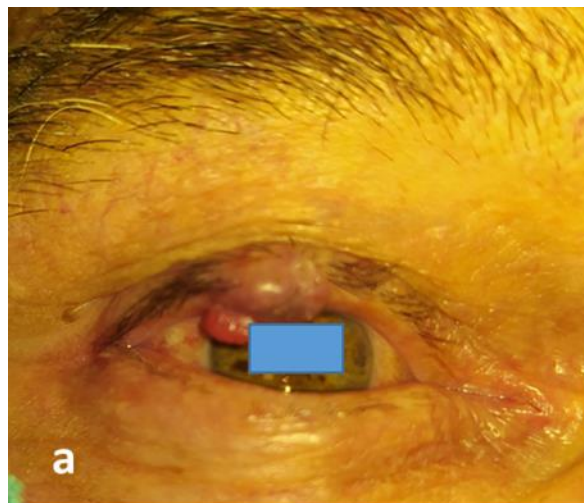


Figure 1a. Metastatic squamous cell carcinoma starting from the skin to the upper eyelid in a 78-year-old patient. Macroscopically consisted of cystic, vascular, and slightly pigmented area. Treatment included surgical excision, 3 mm area, with local reconstruction.



Figure 1b. Metastatic lymphoid tumor in the tarsal and bulbar conjunctiva, a 19-year-old male patient with previously diagnosed lymphoid disorder was referred to ophthalmologist for consultations. Systemic treatment of primary disease and incisional biopsy were proposed

Table 1. Primary tumor site, recommended therapy and survival in patients with metastatic cancer to the different eye structures

Site of secondary metastasis	Primary organ	Recommended therapy*	Survival (in months)
Eyelid	Basal cell carcinoma (80.4%), Squamous cell carcinoma (7%), Melanoma (5.1%), Sebaceous carcinoma (3.3%), Breast (case reports)	Surgical excision EBRT Immunological	12-40
Conjunctiva	Cutaneous melanoma, Colon, Lymphoid, Breast (case reports)	Surgical excision** BRAF inhibitors CIRT	12
Lacrimal gland	Breast, Renal tumor, Hepatocellular Lymphoproliferative	CIRT	24-50
Corpus vitreum (cavity)	Cutaneous melanoma (eyelid, sacral back)	PPV PRP EBRT Episcleral plaque radiation therapy Enucleation	5-14
Uvea	Breast (37%-40%), Lung (26%), Kidney (4%), Gastrointestinal (GI) tract (4%), Cutaneous melanoma (2%), Lung carcinoid (2%), Prostate (2%), Thyroid (1%), Pancreas (1%), Endometrial carcinoma in one patient (1.4%), Acute myeloid leukemia in one patient (1.4%), Unknown (16%)	PPV PRP TTT SBRT Biological therapy (eg. anti VEGF, epidermal GF receptor tyrosine kinase inhibitors, ect.) Immunological	60 (in 23%)
Optic disc	Breast (40%), Lung (27%), Intestine (3%), Kidney (3%), Prostate (3%), Unknown	EBRT	About 13

*systemic therapy according to primary tumor; ** not recommended in lymphoid metastatic lesions abbreviations: EBRT-external beam radiation therapy, CIRT-carbon ion beam radiotherapy, PPV-Pars Plana Vitrectomy, PRP-Pan Retinal Photocoagulation, TTT-Trans pupillary thermotherapy SBRT-stereotaxic body radiation therapy

Corpus vitreum cavity

Metastatic lesions of the vitreous are extremely rare. They may manifest as vitreous cells or they may be associated with one or more discrete intraocular masses (1, 27, 28). Further, they can present with pigmented or nonpigmented cellular clumps, such as in case of cutaneous metastatic melanoma (27-31).

The route by which metastatic melanoma cells gain access to the vitreous cavity is unknown (28, 31-33). Review of the present literature shows that vitreous metastasis may be associated with retinal, ciliary body, optic disc, and iris involvement but rarely with choroidal involvement (31, 34). This fact points out that vitreous cells may be derived from the tissues that directly surround the vitreous cavity (34). The management of vitreous melanoma is difficult. In the case of symptomatic intraocular metastatic lesions, external beam or episcleral plaque radiation therapy is the proposed treatment (Table 1) (1, 10, 28, 31, 34). Asymptomatic lesions in patients with systemic therapy should be observed. Enucleation is reserved for the case of blind, painful eye (1, 34).

The mean survival time of patients vary from 5 to 14 months (Table 1). Patients with ocular metastases from cutaneous melanoma generally have a poor prognosis (27-31).

Uvea

The uvea is the most common place of secondary eye tumor, especially the choroid (1, 2). This fact is due to the rich vascularization of uveal tissue itself. According to the literature, 66-71% of patients presented with knowledge of their primary cancer (6-8). The primary tumor originated in the breast (37%-40%), lung (26%), kidney (4%), gastrointestinal tract (GIT) (4%), cutaneous melanoma (2%), lung carcinoid (2%), prostate (2%), thyroid (1%), pancreas (1%), and unknown (16%) (35-40).

Individual choroidal lesions typically appear as relatively thin, amelanotic, round or oval choroidal masses (Figure 2a) (36-38). They are unifocal and unilateral in 80% of cases, multifocal, bilateral or both in 20% of cases (Figure 2a) (2, 41-46). Choroidal metastatic lesions commonly include the involvement of the optic disc and vitreous cavity (Figure 2b) (1, 2, 6, 47).

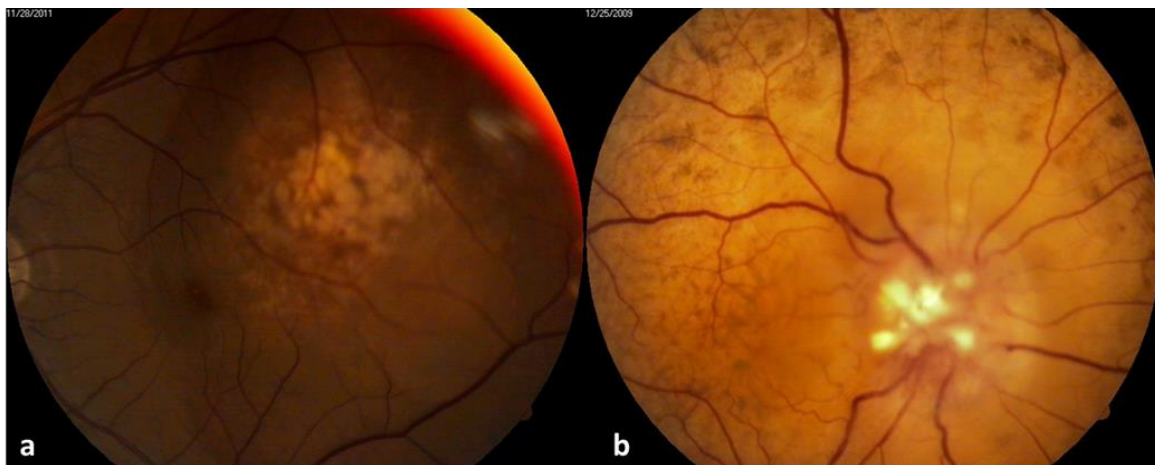


Figure 2a. Metastatic choroidal lesion in a 42-year-old man with low visual acuity, metamorphopsia, visual field defect. Choroidal metastatic lesions diagnosed as unilateral. Lung carcinoma as a primary tumor lesion diagnosed later. Treated by systemic therapy.

Figure 2b. Metastatic choroidal lesion with optic disc involvement in a 45-years-old woman with low visual acuity, metamorphopsia, visual field defect. Choroidal metastatic lesions were bilateral. Breast carcinoma as primary tumor lesion diagnosed previously. Treated by surgical (mastectomy) and systemic therapy (hormonal).

Systemic hormonal therapy like tamoxifen given for the primary breast and other systemic metastases may cause regression of choroidal metastasis, thereby avoiding ocular radiotherapy (39,40). In the cases where chemotherapy and systemic hormonal therapy did not give results, EBRT or plaque radiotherapy and proton beam irradiation were recommended (48). More sparing irradiation treatments such as SRBT proved to be a valuable

alternative for metastatic tumors to the choroid (48).

Some biological agents, like anti-VEGF, give good results in treatment of choroidal metastatic lesions (13, 18, 19). The treatment with epidermal growth factor receptor tyrosine kinase inhibitors in patients with metastatic choroidal lesions and in patients with epidermal growth factor receptor-mutant non-small cell lung cancer gives promising results (16). Overall, life expectancy prognosis of uveal

metastatic lesions is very poor with a 5-year survival in 23%, the worst survival is with pancreatic metastasis, whereas the best survival is with lung carcinoma metastasis (Table 1) (49).

Optic disc

The optic disc is a site of metastatic tumors in about 5% of all intraocular metastasis (1, 9). The close criteria are needed for differentiation of metastatic lesions of the optic head from other causes of optic disc edema. The most common primary tumor was breast cancer (40%), lung cancer (27%), intestine cancer, kidney cancer and prostate cancer (3%) (50-52). Visual acuity varied from preserved

to light perception. Better visual acuity was observed in patients with smaller tumors and more eccentric location on the optic disc. The ophthalmoscopic features of the optic metastasis showed: a diffuse protrusion of the optic disc (84%), the color of the tumor tissue was white (52%) or yellow (32%) (Figure 2c) (9). Venous stasis was noted in 64%, without a complete retinal vein obstruction (9). Juxtapapillary component was present in 74% (Figure 2c) (9). Optic disc involvement was typical for adulthood. Patients usually received different treatment protocols based on primary tumor lesion (Table 1) (1, 9). The systemic prognosis was usually poor (Table 1).



Figure 2c. . Metastatic optic disc tumor in a 42-year-old woman with low visual acuity, metamorphopsia, visual field defect. Breast carcinoma as a primary tumor lesion diagnosed previously.

Conclusion

Metastatic lesions of the eye are rare. They can be present in almost all structures of the eye. The most common site of secondary deposits is the choroid. Breast cancer is the most frequent primary tumor lesion. Sometimes the primary tumor lesion remains unknown. The treatment depends on the

type of primary tumor, systemic involvement and structure of the eye that is involved. Chemotherapy, radiotherapy, and some new treatment options such as immunotherapy and biological therapy are used.

Despite early diagnosis and new treatment options, the systemic prognosis remains poor.

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METASTATSKI TUMORI OKA KAO PROGNOСТИČKI FAKTOR DUŽINE PREŽIVLJAVANJA BOLESNIKA: PREGLED LITERATURE

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Oko je organ koji retko zahvata metastatsko širenje maligne bolesti. Sekundarni tumori oka mogu se dijagnostikovati u bilo kom delu oka, počevši od pomoćnih organa oka do sudovnjače i optičkog diska.

Metastatski tumori oka vode poreklo od primarnih tumora, kao što su: melanom, skvamocelularni karcinom, tumori limfoidnog tkiva, dojke, pluća, digestivnog trakta, prostate, bubrega i mokraćne bešike. Neki od primarnih malignih tumora daju tipično mesto metastaziranja u oku. Simptomi i kliničke manifestacije variraju u zavisnosti od zahvaćenog dela oka. Prisustvo metastaza u oku najčešće je povezano sa lošom prognozom. Terapijski pristup zavisi od primarnog tumora, dela oka u kome je sekundarni metastatski tumor dijagnostikovao, odnosno stadijuma bolesti. Novi imunološki i biološki lekovi i nove radioterapijske tehnike daju, za sada, ohrabrujuće rezultate.

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Ključne reči: metastatski tumor, oko, prognoza, terapija