Malignant Tumors and Related Lesions of the Eyelids, Conjunctiva, Globe, and Orbit: A Literature Review

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ABSTRACT

Globally, eye disorders and complications increased during the past two decades for various reasons. Ocular cancer differs from other ocular diseases in that it is a principal reason for death and morbidity and threatens vision. Hence, this literature review aims to study malignant tumors and their associated lesions in the eyelid, conjunctiva, globe, and orbit. PubMed and EMBASE were used to search the available literature. This review examined 11 prior studies from 1987 to 2024, including 488 reported benign and malignant cases of tumors and their associated lesions in the eyelid, conjunctiva, globe, and orbit from nine countries. The clinical presentation ranged from pain to orbital extension. In most cases, tumors and their associated lesions were in the eyelid and conjunctiva. Surgical treatment was performed in most cases, and recurrence and metastasis were reported in some cases. BCC and SCC were the most common eyelid and conjunctiva malignancies, UM and retinoblastoma were the most common intraocular malignancies, and lymphoma and RMS were the predominant orbit malignancies. UV and sun exposure, genetic factors, age, and immunodeficiency play a critical role in malignant tumors and their associated lesions in the eyelid, conjunctiva, globe, and orbit. Follow-up is predominantly required due to metastases, mortality, and recurrence risk, which are associated with an aggressive prognosis. Regular screening is recommended for high-risk populations. More awareness campaigns are advised to enhance public awareness of modifiable risk factors.

Keywords: Malignant; Tumor; Eyelids; Conjunctiva; Globe; Orbit

INTRODUCTION

Globally, eye disorders and complications increased during the past two decades for various reasons[1-5]. Ocular cancer differs from other ocular diseases in that it is a principal reason for death and morbidity and threatens vision. Therefore, early detection and diagnosis of ocular cancer are critical[6], as this contributes to appropriate treatment and thus avoids associated death, eye damage, and/or vision loss[7]. Ocular cancer is often diagnosed through ophthalmic examinations performed by treating physicians and a detailed clinical history[8-10].

Ocular tumors are relatively uncommon and encompass malignant and benign tumors of the eyelid, conjunctiva, globe, and orbit. However, their management and even diagnosis pose a significant challenge for physicians[11]. Many of these cancers can be misdiagnosed, such as Merkel cell carcinoma (MCC), squamous cell carcinoma (SCC), and basal cell carcinoma (BCC)[12]; MCC can be misdiagnosed as lymphoma, sebaceous gland carcinoma, BCC, keratoacanthoma, chalazion, or cyst[13].

Despite the serious complications associated with ocular cancers, studies related to them are limited due to the rarity of cases[14]. Hence, this literature review aims to study malignant tumors and their associated lesions in the eyelid, conjunctiva, globe, and orbit.

Malignant tumors and their associated lesions in the eyelid, conjunctiva, globe, and orbit overview

There are wide range of types of malignant tumors and their associated lesions in the eyelid, conjunctiva, globe, and orbit; in the eyelid, the most common types are BCC, SCC, malignant melanoma (MM), MCC, and sebaceous cell carcinoma; in the conjunctiva: SCC, MM, and lymphoma; in the globe/intraocular: uveal melanoma (UM) and retinoblastoma (RMS); and in the orbit: lymphoma and RMS. Each type has a different clinical presentation, features, risk factors, and treatment options (Table 1).

BCC, basal cell carcinoma; UV, ultraviolet; IMQ, imiquimod; RT, radiotherapy or radiation therapy; MMS, Mohs micrographic surgery; SCC, squamous cell carcinoma; MM, malignant melanoma; chemo, chemotherapy; MCC, Merkel cell carcinoma; 5-FU, 5-fluorouracil; EBRT, external beam radiation therapy; UV, uveal melanoma; RMS, rhabdomyosarcoma.

EVIDENCE FROM THE LITERATURE

This review examined 11 prior studies from 1987 to 2024 [104-114], including 488 reported benign and malignant cases of tumors and their associated lesions in the eyelid, conjunctiva, globe, and orbit from Argentina, Italy, France, USA, Turkey, Nepal, Poland, India, and Japan. The age ranges from child to older, with most cases observed among 40 years old or above. The clinical presentation ranged from pain to orbital extension. In most cases, tumors and their associated lesions were in the eyelid and conjunctiva. Surgical treatment was performed in most cases, and recurrence and metastasis were reported in some cases. Follow-up is mandated (Table 2).

M, male; F, female; BCC, basal cell carcinoma; SCC, squamous cell carcinoma; IV, intravenous; NAC, neoadjuvant chemotherapy; 5-FU, 5-fluorouracil; MM, malignant melanoma; chemo, chemotherapy; RT, radiotherapy or radiation therapy; N/A, not available.

This study has limitations. The narrative literature review study design could have missed some of the relevant studies that are relevant to the topic. The review process and data extraction were performed by single

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Table 1. Overview of the most common malignant tumors and their associated lesions in the eyelid, conjunctiva, globe, and orbit.

Tumor/lesion	Clinical presentation	Features	Risk factors	Treatment option
Malignant tumors and their associated lesions in the eyelid				
BCC	Pink color, bleeding, ulceration, and pearly edge[15].	It is the most common type of eyelid malignancy in the world[16,17].	Excessive UV light exposure, cigarette smoking, male gender, and age[18,19].	IMQ, Vismodegib, RT, exenteration, and/or MMS[15].
	The size of the tumor is associated positively with age[15].	It rarely metastasizes, is locally invasive, and is significantly morbid[17].		
SCC	A new mass or growth, purple nodules, chalazion, wart, non-healing stye, excessive tearing, scarring, bleeding, eyelid discomfort, non-specific eyelid swelling, tarsal plate thickening, conjunctivitis, refractory blepharitis, loss of eyelashes, and/or skin ulcers[20].	It is easy to confuse BCC and SCC as they have considerably matched clinical characteristics[21].	Excessive UV light exposure, cigarette smoking, male gender, age, human papillomavirus infection, chemicals exposure (e.g. arsenic), a high fat diet, and fair skin[18-20].	Surgical removal, adjuvant RT, or definitive RT.
		It is highly invasive and may metastasize to hematologic and lymphatic, invade perineural, invade orbital, and destroy local tissue[22].		Surgical removal is the standard treatment[20].
MM	Irregular borders, bleeding, changes in color, ulceration, or irritation[23-27].	Tumor thickness and dermal depth affect metastasis and prognosis potential[24].	Excessive UV light exposure, cigarette smoking, male gender, age, skin types I to II on the Fitzpatrick scale, personal history of melanoma, presence of atypical moles, and excessive sun exposure[18,19,28-30].	Standard treatment includes wide surgical excision with adequate margins, metastasis evaluation, and follow-up. Other treatments include immunotherapy, chemo, cryotherapy, and RT[24].
MCC	It appears as a rapidly growing, aggressive mass lesion accompanied by loss of eyelashes (complete or partial[13,31-33]and soft tissue ulceration and destruction.	It is commonly misdiagnosed[31,34].	Psoralens and associated UV-A radiation, UV exposure in sun-exposed skin people, immunosuppressants, sun exposure, HIV infection, and polyomavirus infection[34-39].	Surgical resection, alternative therapy, RT, or chemo such as 5-FU, vincristine, doxorubicin, cyclophosphamide, and cisplatin[40-42].
		It has a high rate of local recurrence and metastasis (distant and early nodes) [13,31,32].		
Sebaceous cell carcinoma	A firm, painless eyelid subcutaneous nodule[43].	Highly prevalent among Asian populations[44].	Immunosuppression, prolonged diuretic use, systemic association (Muir-Torre syndrome[48-52]), previous radiation exposure, race, female sex, advanced age[53].	Surgery[47] [usually aggressive surgical operation due to delayed diagnosis][54,55].
		The prognosis is poor and worsens if there is a vascular or orbital invasion[45].		
		It has a difficult diagnosis and can metastasize[46,47].		
		The risk of death, metastasis, and recurrence increases due to delayed diagnosis[43].		
Malignant tumors and their associated lesions in the conjunctiva				

SCC	A gradual, painless white growth on the eye surface, foreign body sensation, irritation, photophobia, and eye redness[56].	It can lead to blindness, and in severe cases, it results in death[57].	Immunosuppression, allergic conjunctivitis, HIV infection, HPV infection, radiation exposure, and exposure to UV sunlight[57,62].	Surgical excision[63].
		Invasion and metastasis are rare[58-60].		Adjuvant therapies, such as RT, 5-FU, mitomycin C, and cryotherapy[57], are also used because using surgical treatment alone is linked with a high incidence of recurrence[64].
		Lesions predominantly occurred in the interpalpebral fissure[61].		
MM	Diffuse infiltration, nodule, plaque, or raised patch with varying shades of brown pigmentation[65], lighter in color if the lesion is recurrent[66].	The most common conjunctival malignancy after SCC[24,67].	Sun exposure[68] and age[24].	Surgical excision, followed by adjuvant therapies, such as topical mitomycin C and cryotherapy, because using surgical treatment alone is linked with a high recurrence risk[24].
		Highly mortal[68].		
		Highly metastasizes and recurrence[69].		
Lymphoma	A salmon-pink conjunctival mass[67,70-72].	The prognosis is good in general[76], but there is a risk of mortality even after years, so long-term follow-up is required[77].	Immune regulation drugs, genetic mutations, infectious etiologies (Chlamydia psittaci, Helicobacter pylori), immune dysfunction, autoimmune conditions, and immune deficiency[78-80].	Treatment options include observation, surgery, antibiotics, cryotherapy, monoclonal antibodies, interferon-a, brachytherapy, EBRT, and chemo. However, the most applied treatment is low-dose RT[76].
	Other uncommon symptoms include photophobia, eyelid swelling, pterygium, ectropion, tearing, discharge, pain, dryness, eyelid drooping, eyelid congestion, and eyelid swelling[73-75].			
Malignant tumors and their associated lesions in the globe/intraocular				
UM	Many experienced no symptoms or blurred vision[81].	In adults, it is considered the most prevalent primary intraocular malignancy[83].	Genetic mutations, oculodermal or ocular melanocytosis, presence of iris and cutaneous moles, and pigmentation factors (tendency to sunburn, fair skin tone, light irises)[24,86,87].	Local enucleation and excision, laser therapy, RT, or a combination of these treatments can achieve better results. However, no effective treatment options are available for metastases or advanced-stage cases[88].
	Other symptoms include blurred vision, pain, visible tumors, loss of field of vision, floaters, and photophobia[82].	High metastasize rate[84].		
		Life-threatening[85].		
Retinoblastoma	The most common clinical manifestations include a white reflex in the pupil (leukocoria) followed by strabismus[89-91].	In childhood, it is considered the most prevalent primary intraocular malignancy[92].	Gene mutations in hereditary cases[94].	Laser, cryotherapy, enucleation, RT, local or systemic ocular chemo, followed by or combined with cryotherapy or laser, and EBRT as a last resort[90].
		After UM, it is considered the most common intraocular malignancy[91].		
		The prognosis is excellent, and the survival rate is high[91].		
		Can metastasize[93].		
Malignant tumors and their associated lesions in the orbit				

Lymphoma	A painless, palpable mass. It may cause abnormal eye movement, diplopia, ptosis, or proptosis[95].	In adults aged 60 years or older, it is the most prevalent primary orbital tumor[96]. It is more common in Asia and Europe[95].	Immunosuppression and aging[95].	Surgery, RT, immunotherapy, and Chemo[95].
RMS	Subconjunctival mass, eyelid ptosis, and rapid, progressive, painless eye protrusion [97].	The most prevalent childhood primary orbital malignancy[98] and the most childhood diagnosed soft tissue sarcoma [99]. It progresses rapidly[100].	History of birth defects, fertility medications, premature birth, family history of RMS in a first-degree relative, parental medications, and fetal radiation exposure[101,102].	Chemo, surgery, and RT[103].

Table 2. Summary of 11 prior studies documented cases of tumors and their associated lesions in the eyelid, conjunctiva, globe, and orbit.

Study design	Country	Aim	M/F, Mean age or age (years)	Case(s) presentation	Tumor type(s)	Treatment	Outcome(s)	Authors, year
A case report	Argentina	Document a case of nodule at the limbus in a pigmented area since earlier boyhood.	M/ age:11	Right eye brown lesion.	MMs of the conjunctiva	Exenteration	After a few months, cervical lymphadenopathy developed, and then the disease had metastasized widely.	Croxatto et al., 1987 [104]
A case report	Italy	Document a rare case of malignant conjunctival with orbital extension.	M/ age: 53	A conjunctival tumor arising from left eye external bulbar conjunctiva.	Malignant conjunctival epibulbar fibrous histiocytoma with orbital extension	Orbital exenteration.	No recurrence traces were observed during follow-up, and the patient's health remained good.	Balestrazzi et al., 1991 [105]
A case report	France	Document a conjunctival tumor case.	Age: 9	Raspberry-colored conjunctival tumor. Xeroderma Pigmentosum.	Conjunctival epithelial carcinoma	Surgical treatment	Successfully treated.	Rouberol et al., 2001 [106]
A case report	USA	To describe a case with recurrent BCC and underscore the significance of follow-up after managing BCC.	M/ age: 58	Mucoid and bloody drainage from right eye.	Recurrent BCC destructing the globe and orbit	Extensive surgical removal, followed by skin grafting.	Aggressive recurrent BCC was due to lack of follow up. Because recurrence is possible, the patient should be closely monitored after treatment during the first year and then annually monitored.	Chew, 2007 [107]

A retrospective study	Turkey	Document treatment outcomes and histopathological and clinical characteristics of progressive conjunctival malignant tumors with orbital extension in all secondary orbital tumors.	10/11, mean age: 71.9 years	Globe displacement, pain, photophobia, mucous discharge, tearing, diplopia, incomitant strabismus, conjunctival mass, foreign-body sensation, and red eye.	19% MM of the conjunctiva	9.5% underwent wide excision with margins control and additional postoperative topical chemo.	No tumor recurrence or associated death was observed after a mean follow-up period of about 3 years. There were seven deaths from non-tumor-related reasons.	Gökmen Soysal and Ardiç, 2008 [108]
				57.1% right orbit involved.	81% SCC of the conjunctiva	9.5% with regional metastasis treated by RT to the neck and radical neck dissection.		
				42.9% left orbit involved.		90.5% needed exenteration.		
A retrospective study	Nepal	To determine the prevalence pattern of malignant tumors of eyelids.	15/22, mean age: 14–84	N/A	2.7% MM 5.4% basosquamous carcinoma 24.3% BCC 27% SCC 40.5% Sebaceous gland carcinoma	N/A	Sebaceous gland carcinoma is the most prevalent tumor in Bhairahwa, Nepal, potentially influenced by environmental and geographic factors. For practical treatment approaches, prompt diagnosis and consultations of lid lesions are essential for individuals over 40 years.	Kumar, 2010 [109]
A case report	Poland	Document a pigmented SCC of the palpebral conjunctiva case.	Age: 86	Eye pain.	SCC of the lower eyelid with orbital extension	Surgical removal, followed by RT.	N/A	Nina et al., 2013 [110]
A case report	India	Report a conjunctival SCC case with orbital invasion and without metastatic condition.	M/ age: 40	An orbital extension of conjunctival SCC	Conjunctival SCC with orbital extension	IV NAC: 5-FU and cisplatin, then eyelid-sparing orbital exenteration.	The patient was free of regional and local disease at a six-month follow-up.	Nair et al., 2015 [111]
A retrospective study	India	To investigate whether the extent of orbital tumor resection is affected by approach, disease, and location.	17/23, mean age: 40.89 ± 19 years	90% proptosis 75% visual blurring	Orbital tumors	Surgical treatment	The use of the frontotemporal-orbital approach with or without zygoma removal resulted in surgical success in 70% of patients.	Menon et al., 2021 [112]

A retrospective study	Japan	To investigate the epidemiology of the orbit and ocular adnexa tumors in Japan.	Total: 196/176, mean age: 62.9 ± 18.3 Benign: 115/106, mean age: 59.0 ± 17.9 Malignant: 81/70, mean age: 68.9 ± 17.0	N/A	Conjunctiva/ eyelids: 61.5% benign 38.5% malignant Orbit: 53.9% benign 46.1% malignant Malignant tumors of conjunctiva/ eyelids and orbit include retinoblastoma, carcinoma in situ, MM, SCC, BCC, sebaceous gland carcinoma, malignant lymphoma, and others	N/A	In Japan, malignant lymphoma is a principal malignant tumor.	Shimizu et al., 2021 [113]
A descriptive, observational, retrospective study	India	To represent their experience with orbital exenteration from 2017 to 2022.	4/8, mean age: 64.3	8.3% decreased vision 25% eyelid mass 33.3% ocular surface growth 33.3% protrusion of an eyeball	8.3% recurrent optic nerve schwannoma 8.3% choroidal melanoma 16.7% sebaceous gland carcinoma 25% BCC 41.7% invasive SCC The site of origin of tumor: 8.3% orbit 8.3% globe 41.7% eyelid 41.7% conjunctiva	Orbital exenteration.	After a mean follow-up period of approximately 8 months, 83.3% of patients were free from surgical margins, and 16.7% had positive surgical margins.	Patil et al., 2024 [114]

researcher; which might have limited precision compared to systematic review that involves multiple researchers and enhance the quality of data extraction and narrative synthesis.

CONCLUSIONS

BCC and SCC were the most common eyelid and conjunctiva malignancies, UM and retinoblastoma were the most common intraocular malignancies, and lymphoma and RMS were the predominant orbit malignancies. UV and sun exposure, genetic factors, age, and immunodeficiency play a critical role in malignant tumors and their associated lesions in the eyelid, conjunctiva, globe, and orbit. The treatment approach depends on tumor types and stages; however, surgical treatment is the dominant and adjuvant therapy frequently necessitated. Follow-up is predominantly required due to metastases, mortality, and recurrence risk, which are associated with an aggressive prognosis.

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