Review Article

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Uveal Tumors in Ocular Oncology: Epidemiology, Molecular Genetics, Diagnostic Advances and Contemporary Management

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ABSTRACT

Uveal tumors represent the most common primary intraocular neoplasms in adults and constitute a significant component of ocular oncology practice. Among these tumors, uveal melanoma is the most frequent malignant intraocular tumor arising from melanocytes located within the iris, ciliary body, and choroid. Despite advances in diagnostic imaging, molecular classification, and treatment modalities, metastatic disease remains the leading cause of mortality in affected patients. The liver is the predominant site of metastasis and accounts for nearly 90% of metastatic cases [1–3]. Recent advances in molecular oncology have significantly improved understanding of the pathogenesis of uveal melanoma, particularly the identification of driver mutations in GNAQ and GNA11 genes and prognostic biomarkers such as BAP1, SF3B1, and EIF1AX [4–7]. Imaging modalities including ultrasonography, optical coherence tomography (OCT), and optical coherence tomography angiography (OCTA) have improved early detection and monitoring of uveal tumors [8–10]. Current treatment strategies include plaque brachytherapy, proton beam radiotherapy, surgical management, and emerging systemic targeted therapies [11-13]. This review summarizes current knowledge on the epidemiology, molecular genetics, clinical presentation, diagnostic advances, and contemporary management of uveal tumors.

Keywords: Uveal Melanoma, Ocular Oncology, Choroidal Melanoma, İntraocular Tumors, Molecular Oncology

Introduction

Ocular oncology is a specialized subspecialty of ophthalmology that focuses on the diagnosis and management of tumors affecting the eye and ocular adnexa. Among intraocular malignancies in adults, tumors of the uveal tract are the most common primary neoplasms [1].

The uveal tract consists of three main anatomical components:

- Iris
- Ciliary body
- Choroid

These tissues contain melanocytes derived from neural crest cells capable of malignant transformation [2].Uveal melanoma represents approximately 85–90% of all primary intraocular malignancies in adults and remains the most common primary intraocular cancer in this population [3].The annual incidence of uveal melanoma is estimated to be approximately 5–7 cases per million individuals in Western countries, although significant geographic variations exist [4]. Despite advances in local tumor control, overall survival has remained relatively unchanged due to the high frequency of metastatic disease [5].Approximately 40–50% of patients eventually develop metastasis, most commonly involving the liver [6].

Epidemiology

The epidemiology of uveal melanoma varies widely among different populations and geographic regions.Higher incidence rates have been reported in Northern Europe and North America, whereas the disease is relatively uncommon in Asian and African populations [7].

Age represents a significant risk factor for the development of uveal melanoma. The median age at diagnosis is approximately 60 years, and the incidence increases progressively with age [8].Several epidemiological studies have also demonstrated a slight male predominance [9].Environmental risk factors remain poorly understood, and the association between ultraviolet radiation and uveal melanoma remains controversial [10].

Risk Factors

Several phenotypic, ocular, and genetic factors have been associated with an increased risk of uveal melanoma.

Phenotypic risk factors include:

- fair skin
- light iris color
- light hair color [11]

Ocular risk factors include:

- choroidal nevus

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- oculodermal melanocytosis
- dysplastic nevus syndrome [12]

Genetic predisposition also plays a crucial role. Germline mutations involving the BAP1 tumor suppressor gene have been associated with increased susceptibility to uveal melanoma [13].The major risk factors associated with uveal melanoma are summarized in Table 1.

Table 1: Risk factors associated with uveal melanoma

Category	Risk factor
Phenotypic	Fair skin
Phenotypic	Light iris color
Phenotypic	Light hair
Ocular	Choroidal nevus
Ocular	Oculodermal melanocytosis
Genetic	BAP1 mutation
Genetic	Familial melanoma syndromes

Classification of Uveal Tumors

Uveal tumors can be broadly categorized into benign and malignant lesions.Benign tumors include choroidal nevus, iris nevus, melanocytoma, circumscribed choroidal hemangioma, and choroidal osteoma [14].Malignant tumors include uveal melanoma, metastatic carcinoma, and primary intraocular lymphoma [15].Choroidal nevi occur in approximately 5–10% of the general population and are usually asymptomatic [16].

The main benign and malignant uveal tumors are summarized in Table 2.

Table 2: Classification of uveal tumors

Tumor type	Nature	Typical location	Clinical characteristics
Choroidal nevus	Benign	Choroid	Flat pigmented lesion
Iris nevus	Benign	Iris	Usually asymptomatic
Melanocytoma	Benign	Optic disc	Dark pigmented tumor
Choroidal hemangioma	Benign	Choroid	Orange-red lesion
Choroidal osteoma	Benign	Posterior pole	Calcified lesion
Uveal melanoma	Malignant	Choroid / ciliary body / iris	Pigmented dome-shaped tumor
Metastatic tumor	Malignant	Choroid	Cream-colored lesion

Molecular Pathogenesis

Advances in molecular oncology have significantly improved understanding of the pathogenesis of uveal melanoma. Approximately 80–90% of uveal melanomas harbor activating mutations in the GNAQ or GNA11 genes [17].These mutations activate downstream signaling pathways such as the MAPK pathway and promote tumor proliferation [18].

Chromosomal abnormalities also play an important role in tumor progression. Monosomy 3 is strongly associated with increased metastatic risk and poor prognosis [19].Additional mutations involving BAP1, SF3B1, and EIF1AX genes have been identified and are used for molecular prognostic classification [20].These biomarkers are summarized in Table 3.

Table 3: Prognostic molecular markers in uveal melanoma

Gene	Prognostic significance
BAP1	High metastatic risk
SF3B1	Intermediate prognosis
EIF1AX	Favorable prognosis
GNAQ	Early oncogenic mutation
GNA11	Early oncogenic mutation

Clinical Presentation

The clinical presentation of uveal melanoma depends largely on tumor size and location. Common symptoms include blurred vision, photopsia, floaters, and visual field defects [21].However, a substantial proportion of tumors remain asymptomatic and are detected during routine ophthalmologic examination [22].

Fundoscopic examination typically reveals a dome-shaped pigmented mass associated with orange lipofuscin pigment and subretinal fluid [23].

Diagnostic Imaging

Modern ocular imaging plays a critical role in the diagnosis and monitoring of uveal tumors.B-scan ultrasonography remains the gold standard imaging modality for diagnosing uveal melanoma and typically demonstrates a dome-shaped lesion with low internal reflectivity [24].

Optical coherence tomography (OCT) allows detailed visualization of retinal changes associated with choroidal tumors [25]. Optical coherence tomography angiography (OCTA) provides noninvasive evaluation of tumor microvasculature [26]. Fine needle aspiration biopsy is increasingly used to obtain tumor samples for cytologic diagnosis and molecular testing [27].

Treatment Strategies

Management of uveal melanoma depends on tumor size, location, and metastatic risk. Plaque brachytherapy using radioactive isotopes such as iodine-125 or ruthenium-106 remains the most widely used treatment for medium-sized tumors [28].

Proton beam radiotherapy provides highly precise radiation delivery and is particularly useful for tumors located near critical structures such as the optic nerve [29]. Enucleation is typically reserved for large tumors or eyes with painful complications such as neovascular glaucoma [30].

Metastatic Disease

Metastasis remains the major cause of mortality in patients with uveal melanoma.Approximately half of all patients eventually develop metastatic disease [31].

The liver represents the most common site of metastasis, accounting for approximately 90% of metastatic cases [32].

Median survival following the diagnosis of liver metastasis ranges between 6 and 12 months [33].

Emerging Therapies

Recent therapeutic advances include targeted therapies and immunotherapies.Checkpoint inhibitors such as anti-PD-1 and anti-CTLA-4 antibodies have demonstrated limited efficacy in uveal melanoma compared with cutaneous melanoma [34].

The bispecific T-cell receptor fusion protein tebentafusp has demonstrated improved survival in patients with metastatic uveal melanoma [35].Additional targeted therapies involving MEK and PKC signaling pathways are currently under investigation [36].

Artificial Intelligence in Ocular Oncology

Artificial intelligence (AI) has emerged as an important tool in ocular oncology.Machine learning algorithms can assist in automated tumor detection, risk stratification, and prediction of metastatic potential [37–39].AI-based diagnostic systems may improve early detection and clinical decision-making in ocular oncology.

Future Perspectives

Future research in ocular oncology is increasingly focused on molecular diagnostics and personalized medicine.

Emerging technologies include:

- liquid biopsy
- circulating tumor DNA
- genomic profiling
- targeted molecular therapy [40-45]

These approaches may significantly improve prognostic stratification and individualized treatment strategies.

Conclusion

Uveal tumors represent a major focus of ocular oncology research, with uveal melanoma being the most common primary intraocular malignancy in adults. Advances in molecular genetics and imaging technologies have improved understanding of tumor biology and clinical management. However, metastatic disease remains the major determinant of patient survival. Continued research into molecular mechanisms and novel therapeutic strategies is essential for improving long-term outcomes in patients with uveal melanoma.

Conflict of Interest

The authors declare that they have no conflict of interest related to this manuscript.

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Ethical Approval

Not applicable for review articles.

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