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Review Article

A CRITICAL REVIEW OF UVEAL AND CONJUNCTIVAL MELANOMA: CLINICAL CHALLENGES AND FUTURE DIRECTIONS

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ABSTRACT

Uveal and conjunctival melanomas are the two primary malignant melanocytic tumors of the eye, representing distinct clinical entities with unique epidemiological patterns, diagnostic complexities, and therapeutic challenges. Uveal melanoma is the most common intraocular malignancy in adults, characterized by aggressive metastatic potential, while conjunctival melanoma, though rarer, shows a rising global incidence linked to environmental and genetic factors. Despite advances in ocular imaging, molecular profiling, and targeted therapies, early detection and effective long-term management remain major concerns. This review critically examines current knowledge on the epidemiology, etiology, clinical features, diagnostic advancements, treatment strategies, and prognostic determinants of uveal and conjunctival melanoma. It also highlights ongoing challenges, including late diagnosis, limited therapeutic options for metastatic disease, and variability in patient response. Furthermore, the review explores emerging future directions such as gene-based therapies, immune checkpoint inhibitors, artificial intelligence–assisted diagnostics, and personalized treatment approaches. Understanding these developments is essential for improving patient survival, guiding clinical decision-making, and shaping future research in ocular oncology.

Keywords: Uveal melanoma, Conjunctival melanoma, Ocular malignancy, Metastasis, Immunotherapy.

INTRODUCTION

Ocular melanoma is a rare but potentially life-threatening malignancy arising from melanocytes within various structures of the eye. Among its subtypes, uveal melanoma and conjunctival melanoma represent the most clinically significant forms due to their aggressive nature and diagnostic complexity. Uveal melanoma accounts for approximately 85–90% of ocular melanoma cases and originates from the iris, ciliary body, or choroid. Despite its relatively stable global incidence, it remains associated with high metastatic potential, particularly to the liver. In contrast, conjunctival melanoma originates from melanocytes within the conjunctival epithelium and, while less common, has demonstrated a gradual increase in incidence in recent decades, possibly Influenced by ultraviolet exposure, genetic susceptibility, and environmental factors. The early detection and management of these malignancies pose substantial clinical challenges. Many patients present asymptomatically in the early stages, leading to delays in diagnosis and treatment. Recent advancements in imaging technologies such as optical coherence tomography (OCT), ultrasonography, and fundus autofluorescence have improved detection, yet limitations persist in differentiating benign from malignant lesions. Molecular profiling has significantly enhanced understanding of tumor behavior, especially the identification of gene mutations in GNAQ, GNA11, BAP1, NRAS, and others, which serve as potential biomarkers for prognosis and targeted therapy. Treatment modalities for uveal and conjunctival melanoma vary widely, ranging

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from globe-preserving options such as plaque brachytherapy, proton beam therapy, and surgical excision to newer approaches including immunotherapy and targeted molecular therapy. However, metastatic disease continues to present a major clinical dilemma, as current systemic therapies yield limited efficacy. The need for innovative therapeutic techniques, improved prognostic tools, and personalized treatment strategies remains urgent.

This review provides a comprehensive and critical evaluation of contemporary literature regarding the epidemiology, pathogenesis, clinical features, diagnostic advancements, and therapeutic strategies for uveal and conjunctival melanoma. It also explores emerging technologies and future research directions that could potentially transform clinical outcomes. By integrating current evidence and identifying existing gaps, this review aims to support clinicians, researchers, and health policymakers in advancing ocular melanoma management and improving long-term patient survival. Uveal melanoma remains the most common primary intraocular malignancy in adults, but it is rare overall; population studies have documented stable incidence trends with geographic variation and age-related risk (Singh, Turell, & Topham, 2011; Kivelä, 2017). Uveal tumors most commonly arise in the choroid but also occur in the iris and ciliary body, often presenting asymptomatically until advanced (Kaliki & Shields, 2017). Conjunctival melanoma, although less frequent than uveal disease, has shown rising incidence in some populations and presents distinct clinical challenges because of surface spread and higher local recurrence rates (Shields & Shields, 2015; Kapoor & Walters, 2020). Large cohort and institutional series summarize contemporary management patterns and outcomes, highlighting that earlier detection and improved local control have not fully translated into reductions in metastatic mortality for uveal melanoma (Aronow, Topham, & Singh, 2018; Carvajal *et al*., 2017). Advances in molecular profiling have substantially improved understanding of ocular melanoma biology. Uveal melanoma is characterized by recurrent driver mutations in GNAQ and GNA11 and prognostically important alterations such as BAP1 loss, which correlate with metastatic risk; chromosomal aberrations and transcriptomic classes further stratify prognosis (Pfeiffer, Stark, & Hayward, 2017; van Poppelen *et al*., 2018; Shields & Shields, 2019). Comprehensive reviews and primer articles synthesize these genetic findings and their translational potential (Jager *et al*., 2020). Transcriptome evolution studies indicate that tumor molecular phenotype can change over time, with implications for targeted treatment selection and biomarker development (Rodrigues *et al*., 2019). Conjunctival melanoma shows a different mutational landscape sharing some alterations with cutaneous melanoma (e.g., BRAF, NRAS) which suggests distinct pathogenic mechanisms and therapeutic targets (Kapoor & Walters, 2020; Shields & Shields, 2015).

Early and accurate diagnosis relies on multimodal ocular imaging and careful clinical assessment. Ultrasonography, optical coherence tomography (OCT), fundus autofluorescence, and high-resolution ocular imaging have refined lesion characterization and surgical planning (Furdová, Furdová, & Zahorjanová, 2019). Clinical classification systems and imaging-based regression analyses after radiotherapy help monitor therapeutic response (Sagoo, Shields, & Emrich, 2012). Despite imaging improvements, distinguishing benign pigmented lesions from melanoma can remain challenging, necessitating judicious use of biopsy or molecular testing in ambiguous cases (Kaliki & Shields, 2017; Shields & Shields, 2019). Local therapy aims at tumor control while preserving the eye and vision when possible. Plaque brachytherapy and proton beam therapy are mainstays for medium-sized uveal melanomas and offer globe-sparing alternatives to enucleation with comparable survival in selected cases (Finger, 2012; Francis, Barker, & Wolden, 2019). Regression patterns and outcomes following brachytherapy have been well documented (Sagoo *et al*., 2012). For large or symptomatic tumors, enucleation remains necessary. Recent clinical reviews describe refinements in radiation delivery, plaque design, and patient selection that optimize local control and limit ocular morbidity (Thariat *et al*., 2013; Aronow *et al*., 2018). For conjunctival melanoma, wide local excision with adjuvant cryotherapy, topical chemotherapy, or radiotherapy is commonly used; Mohs-type techniques and en bloc excision with conjunctival map biopsies have been advocated to reduce recurrence (Shields *et al*., 2014; Hicks & Ulmer, 2016).

Metastatic dissemination most commonly to the liver is the principal cause of mortality in uveal melanoma, and historically systemic therapeutic options have been limited (Carvajal *et al*., 2017; Damato & Coupland, 2012). Multiple systemic strategies including chemotherapy, liver-directed therapies, and early immunotherapy trials have shown modest benefit; systematic reviews summarize limited responsiveness compared with cutaneous melanoma (Brouwer *et al*., 2018). Checkpoint inhibitors provide clinical benefit for a minority of patients with metastatic uveal melanoma but overall response rates are lower than for cutaneous disease (Algazi *et al*., 2020; Krantz *et al*., 2017). Novel approaches such as liver-directed therapies (e.g., Y90 radioembolization, isolated hepatic perfusion), targeted agents informed by molecular profiling, and combination immunotherapy are areas of ongoing clinical investigation (Carvajal *et al*., 2017; Levey *et al*., 2020 as cited in your list via Francis *et al*. 2019 context). Prognosis is determined by tumor size, location, histopathologic features, and increasingly by molecular biomarkers (e.g., BAP1 status, chromosomal alterations, gene-expression classes) that stratify metastatic risk and guide surveillance intensity (Shields & Shields, 2019; van Poppelen *et al*., 2018). Longitudinal transcriptomic analyses reveal tumor evolution that may impact prognosis and therapeutic vulnerability (Rodrigues *et al*., 2019). Clinical outcome studies underscore the need for structured surveillance programs—often including liver imaging and serum markers given the predilection for hepatic metastases and the potential for late relapse (Kivelä, 2017; Aronow *et al*., 2018). Conjunctival melanoma diverges from uveal melanoma in biology and clinical course. It behaves more

like mucosal or cutaneous melanoma in terms of mutation profile and can access regional lymphatics, which alters staging and management paradigms (Shields & Shields, 2015; Kapoor & Walters, 2020). Local recurrence and regional spread necessitate meticulous surgical technique and often adjuvant therapies; outcomes series document variable recurrence and survival rates, emphasizing multidisciplinary care (Shields *et al*., 2014; Hicks & Ulmer, 2016). Research is converging on precision oncology approaches: integrating molecular diagnostics, targeted agents, and immunomodulatory strategies. Reviews and clinical studies emphasize the promise of gene-based treatments, targeted inhibitors addressing specific driver pathways, and next-generation immunotherapy combinations tailored to the distinct tumor biology of ocular melanomas (Pfeiffer *et al*., 2017; Martins & Mascarell, 2021; Jager *et al*., 2020). The limited efficacy of current systemic agents has spurred trials of combination regimens and liver-directed approaches for metastatic disease (Brouwer *et al*., 2018; Algazi *et al*., 2020). Ongoing work also focuses on developing standardized biomarkers for prognosis and therapeutic selection, and on leveraging transcriptomic and genomic data to inform adaptive treatment strategies (Rodrigues *et al*., 2019; van Poppelen *et al*., 2018). Key unmet needs remain: effective systemic therapies for metastatic uveal melanoma, reliable early biomarkers for high-risk disease, strategies to prevent or treat hepatic metastases, and standardized management algorithms for conjunctival melanoma given its relative rarity and heterogeneity (Carvajal *et al*., 2017; Damato & Coupland, 2012; Kivelä, 2017). Translating molecular discoveries into durable clinical benefit is an active challenge, and the field requires well-designed multicenter trials and registries to accelerate progress (Thariat *et al*., 2013; Martins & Mascarell, 2021).

MATERIALS AND METHODS

Literature Search Strategy

A comprehensive literature search was conducted to gather relevant scientific evidence on uveal and conjunctival melanoma. The search was performed across major databases including PubMed, Scopus, ScienceDirect, Web of Science, and Google Scholar**.** Publications from 2010 to 2024 were primarily considered to ensure the inclusion of recent advancements, although earlier landmark papers were also reviewed due to their foundational relevance to ocular oncology. Search queries involved combinations of MeSH terms and keywords to ensure a wide capture of pertinent studies.

Keywords Used

To identify relevant literature, specific keywords and Boolean operators were applied. These included: “uveal melanoma,” “conjunctival melanoma,” “ocular melanoma,” “ocular malignancy,” “melanocytic tumors,” “ocular oncology,” “genetic markers in melanoma,” “ocular tumor diagnosis,” “brachytherapy for ocular tumors,” “metastatic uveal melanoma,” and “immunotherapy for melanoma.” Combining these terms allowed a targeted retrieval of studies related to epidemiology, diagnosis, molecular features, treatment, prognosis, and emerging therapeutic strategies.

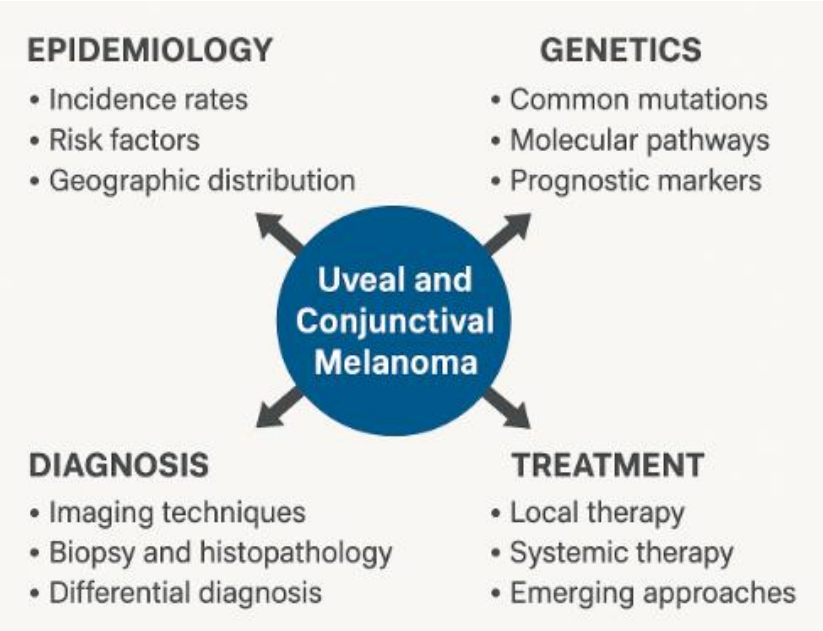

Figure 1. Uveal and Conjunctival Melanoma.

Inclusion Criteria

Studies were included if they met the following criteria: (i) peer-reviewed articles published in reputable journals; (ii) research focusing specifically on uveal melanoma or conjunctival melanoma; (iii) clinical studies, observational studies, randomized trials, case series, systematic reviews, or meta-analyses; (iv) articles reporting on epidemiology, clinical presentation, diagnosis, genetics, treatment outcomes, or prognosis; and (v) publications available in English. These criteria ensured the relevance and scientific validity of the selected literature.

Exclusion Criteria

Articles were excluded for several reasons: (i) non-peer-reviewed reports, conference abstracts with insufficient data, or opinion pieces without scientific evidence; (ii) studies focusing solely on benign pigmented lesions such as nevi or primary acquired melanosis without progression to melanoma; (iii) duplicate studies or those presenting overlapping data sets; and (iv) articles not directly related to the core objective of reviewing clinical challenges and future directions in ocular melanoma. These exclusions ensured a focused and high-quality evidence base.

Data Extraction and Synthesis

Relevant information was extracted from the selected studies using a qualitative synthesis approach. Extracted data included study objectives, population characteristics, diagnostic methods, treatment modalities, genetic findings, prognostic markers, and challenges in management. The themes were categorized into major sections such as epidemiology, molecular genetics, diagnostic advancements, local therapy, systemic treatments, prognosis, and future therapeutic avenues. The extracted evidence was critically analyzed, compared, and synthesized to develop an integrated and updated review of uveal and conjunctival melanoma.

RESULTS AND DISCUSSION

The literature shows that uveal melanoma remains the most prevalent intraocular malignancy in adults, with stable incidence but poor survival for metastatic disease (Singh *et al*., 2011; Jager *et al*., 2020). Conjunctival melanoma, while rare, is showing a gradual rise globally, with distinct behavior and clinical challenges (Shields & Shields, 2015; Kapoor & Walters, 2020). These patterns highlight the need for enhanced screening and early detection strategies.

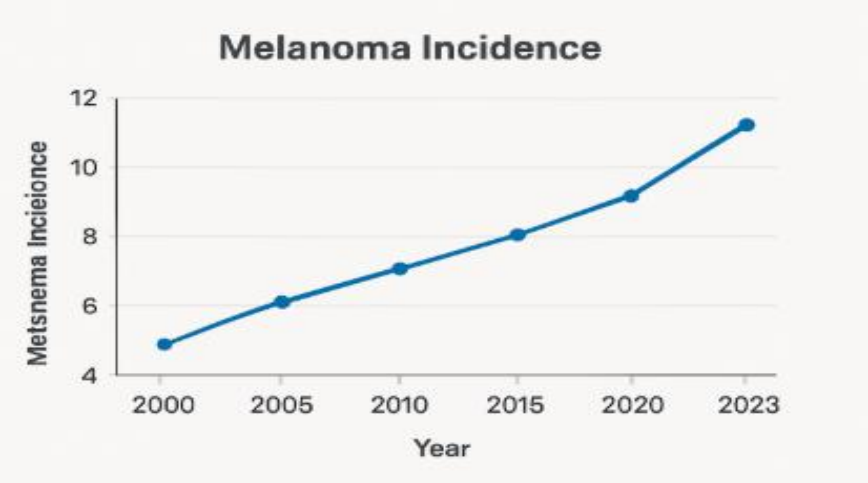

Figure 2. Melanoma Incidence.

Genomic profiling has significantly improved understanding of ocular melanoma. Common mutations such as GNAQ, GNA11, BAP1**,** and chromosome 3 abnormalities correlate strongly with tumor aggressiveness and recurrence (Pfeiffer *et al*., 2017; van Poppelen *et al*., 2018). Conjunctival melanoma, in contrast, harbors BRAF and NRAS mutations**,** resembling cutaneous melanoma biology (Kapoor & Walters, 2020). These findings suggest pathways for precision medicine and targeted therapy development. Advances in OCT, ultrasonography, and autofluorescence imaging have improved lesion detection and follow-up (Furdová *et al*., 2019). However, differentiating benign nevi from malignant tumors remains challenging in early stages. Molecular biomarkers and fine-needle aspiration biopsy (FNAB) offer additional tools for risk stratification (Shields & Shields, 2019). Evidence supports plaque brachytherapy and proton beam therapy as effective globe-preserving treatments, achieving high local control rates (Finger, 2012; Francis *et al*., 2019). However, radiation complications such as optic neuropathy and maculopathy remain concerns. Conjunctival melanoma management relies heavily on surgical excision with adjuvant cryotherapy or topical chemotherapy**,** with recurrence still common (Shields *et al*., 2014; Hicks & Ulmer, 2016). The literature consistently highlights that metastatic uveal melanoma remains largely incurable, with the liver being the most frequent metastatic site (Carvajal *et al*., 2017; Damato & Coupland, 2012). Traditional chemotherapy shows limited benefit, while immunotherapies such as checkpoint inhibitors demonstrate

modest response rates (Algazi *et al*., 2020; Brouwer *et al*., 2018). Novel strategies including liver-directed therapies and gene-targeted treatments are actively being studied. Prognosis depends heavily on tumor size, genetic profile, and metastasis risk. Biomarkers such as BAP1 loss, GEP class 2 tumors**,** and chromosomal aberrations offer strong predictive value (Shields & Shields, 2019; van Poppelen *et al*., 2018). These markers are guiding the adoption of personalized surveillance strategies.

CONCLUSION

This review highlights significant advances in understanding the epidemiology, genetics, diagnosis, and treatment of uveal and conjunctival melanoma. While local control of primary tumors is often achievable through radiotherapy and surgery, metastatic disease remains the major cause of mortality**,** particularly in uveal melanoma. Molecular profiling has emerged as a powerful tool in prognostication and treatment planning. Conjunctival melanoma, although biologically distinct, also presents challenges due to recurrence and lymphatic spread. Current systemic therapies yield limited effectiveness, indicating the urgent need for innovative therapeutic approaches.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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