

Mucosal Melanoma: Epidemiology, Molecular Biology, Clinical Features, and Current Treatment StrategiesAhmet Gokhan Saritas¹, Ugur Topal²¹Department of General Surgery, Cukurova University Faculty of Medicine, Adana, Turkiye²Department of General Surgery, Cukurova University Faculty of Medicine, Adana, Turkiye

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Abstract:

Mucosal melanoma is a rare and aggressive subtype of melanoma arising from melanocytes located in mucosal surfaces, accounting for approximately 1% of all melanomas. Unlike cutaneous melanoma, mucosal melanoma demonstrates distinct epidemiological, molecular, and clinical characteristics, often leading to delayed diagnosis and poor prognosis. The pathogenesis is driven by unique molecular alterations, including frequent mutations in KIT, NRAS, and structural chromosomal aberrations, whereas BRAF mutations are less common. Clinically, mucosal melanomas present with nonspecific symptoms depending on anatomical location, most commonly affecting the head and neck, anorectal, and female genital tracts. Surgical resection remains the cornerstone of treatment when feasible; however, high recurrence rates necessitate multimodal approaches. Advances in immunotherapy and targeted therapy have improved outcomes, although response rates remain lower compared to cutaneous melanoma. This review provides a comprehensive overview of the epidemiology, molecular biology, clinical features, and current treatment strategies of mucosal melanoma, highlighting emerging therapeutic approaches and future directions.

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Introduction

Mucosal melanoma (MM) represents a rare and biologically distinct subtype of melanoma arising from melanocytes located within mucosal membranes of the respiratory, gastrointestinal, and genitourinary tracts. Unlike cutaneous melanoma, which has been extensively studied and is strongly associated with ultraviolet (UV) radiation exposure, mucosal melanoma lacks a clearly defined environmental risk factor, making its pathogenesis less well understood [1]. This fundamental difference contributes to challenges in prevention, early detection, and therapeutic targeting.

The rarity of MM, accounting for approximately 1% of all melanomas, has historically limited large-scale prospective studies, resulting in a reliance on retrospective analyses and small cohort studies [2]. Despite its low incidence, mucosal melanoma is associated with disproportionately high mortality rates due to its aggressive biological behavior and tendency for late-stage diagnosis. The anatomical locations where MM arises are often concealed, leading to delayed clinical recognition and advanced disease at presentation.

Another critical distinction is the unique molecular landscape of mucosal melanoma. Compared to cutaneous melanoma, which frequently harbors

BRAF mutations, MM is characterized by a higher prevalence of KIT mutations, NRAS alterations, and complex chromosomal aberrations [3]. These molecular differences not only influence tumor biology but also have significant implications for therapeutic strategies.

Clinically, mucosal melanoma presents heterogeneously depending on the anatomical site involved. Symptoms are often nonspecific, including bleeding, obstruction, or pain, which can easily be misattributed to benign conditions. As a result, diagnosis is frequently delayed, and patients often present with locally advanced or metastatic disease [4].

Given these challenges, there is a growing need for a comprehensive understanding of mucosal melanoma, integrating epidemiological data, molecular insights, clinical characteristics, and evolving treatment strategies. This review aims to provide an updated and in-depth synthesis of current knowledge on mucosal melanoma, with a particular focus on its unique biological features and emerging therapeutic approaches.

Epidemiology: Mucosal melanoma is an uncommon malignancy, representing approximately

1% of all melanoma cases but contributing significantly to melanoma-related mortality [5]. Its incidence has remained relatively stable over time, unlike cutaneous melanoma, which has shown a steady increase globally. This stability suggests that environmental factors such as UV radiation, which play a major role in cutaneous melanoma, are less relevant in the pathogenesis of MM.

The disease predominantly affects older individuals, with a median age at diagnosis ranging between 60 and 70 years [6]. There is no strong overall gender predilection; however, site-specific differences exist. For example, melanomas of the female genital tract are naturally more prevalent in women, while head and neck mucosal melanomas show a slight male predominance in some series.

Anatomically, mucosal melanoma most commonly arises in three major regions:

- Head and neck (particularly sinonasal and oral cavities)
- Anorectal region
- Female genital tract

Among these, head and neck mucosal melanomas account for approximately 50–55% of cases, followed by anorectal (20–25%) and vulvovaginal melanomas (15–20%) [7]. Each site has distinct clinical and prognostic implications.

Geographically, some studies have reported a relatively higher proportion of mucosal melanoma cases among Asian populations compared to Caucasian populations, although the absolute incidence remains low [8]. This observation suggests possible genetic or environmental modifiers, although definitive explanations remain lacking.

Prognosis in mucosal melanoma is generally poor. Five-year overall survival rates range from 10% to 30%, significantly lower than those observed in cutaneous melanoma [9]. Survival outcomes vary depending on anatomical site, stage at diagnosis, and resectability. Head and neck melanomas tend to have slightly better outcomes compared to anorectal and vulvovaginal melanomas, although all subtypes are associated with high recurrence rates.

Importantly, mucosal melanoma is characterized by a high rate of local recurrence and early distant metastasis, particularly to the lungs, liver, and brain. These patterns further contribute to the overall poor prognosis and highlight the need for improved systemic therapies.

Molecular Biology and Pathogenesis: The molecular landscape of mucosal melanoma differs significantly from that of cutaneous melanoma, reflecting its distinct pathogenesis and clinical behavior. One of the defining features of MM is the relatively low tumor mutational burden compared to

UV-induced cutaneous melanoma, but a higher prevalence of structural genomic alterations [10].

Genetic Alterations: Unlike cutaneous melanoma, where BRAF mutations (particularly V600E) are present in approximately 50% of cases, mucosal melanoma demonstrates a much lower frequency of BRAF mutations, typically below 10% [11]. Instead, KIT mutations are among the most characteristic alterations, observed in approximately 15–25% of mucosal melanomas [12]. These mutations often occur in exons 11 and 13 and are particularly enriched in melanomas of the anorectal and vulvovaginal regions.

NRAS mutations are present in approximately 15–20% of cases and contribute to activation of downstream signaling pathways such as MAPK and PI3K/AKT [13]. Additionally, amplifications in genes such as CDK4 and CCND1 have been reported, indicating dysregulation of cell cycle control mechanisms.

Chromosomal Instability: A hallmark of mucosal melanoma is extensive chromosomal instability, characterized by copy number variations and structural rearrangements rather than point mutations [14]. This genomic complexity contributes to tumor heterogeneity and therapeutic resistance.

Signaling Pathways

Key oncogenic pathways implicated include:

- MAPK pathway activation (via NRAS, KIT)
- PI3K/AKT pathway activation
- Cell cycle dysregulation (CDK4/6 axis)

These pathways drive tumor proliferation, survival, invasion, and resistance to therapy.

Tumor Microenvironment: The tumor microenvironment in mucosal melanoma is distinct, often characterized by lower immune infiltration compared to cutaneous melanoma [15]. This may partly explain the reduced responsiveness to immunotherapy. Additionally, expression of immune checkpoint molecules such as PD-L1 varies widely, contributing to heterogeneous treatment responses.

Clinical Features: The clinical presentation of mucosal melanoma is highly variable and depends on the anatomical site of origin. A common feature across all sites is the nonspecific nature of symptoms, which frequently leads to delayed diagnosis.

Head and Neck Melanoma: Sinonasal melanomas often present with symptoms such as nasal obstruction, epistaxis, facial pain, or anosmia [16]. Oral melanomas may appear as pigmented or amelanotic lesions on the palate or gingiva. Due to

their location, these tumors are often advanced at diagnosis.

Anorectal Melanoma: Patients typically present with rectal bleeding, pain, tenesmus, or changes in bowel habits [17]. These symptoms are frequently mistaken for benign conditions such as hemorrhoids, leading to diagnostic delays.

Genitourinary Melanoma: Vulvar and vaginal melanomas may present with bleeding, discharge, or a visible mass [18]. These tumors are often aggressive and associated with poor outcomes.

Metastatic Disease: At diagnosis, a significant proportion of patients already have regional or distant metastases. Common metastatic sites include the lungs, liver, and brain.

Diagnostic Approach: Diagnosis of mucosal melanoma requires a comprehensive and multidisciplinary approach that integrates histopathological evaluation, immunohistochemistry, advanced imaging modalities, and molecular profiling. Due to its rarity, anatomical concealment, and nonspecific clinical presentation, mucosal melanoma is frequently diagnosed at an advanced stage, making accurate and timely diagnostic strategies critically important.

Histologically, mucosal melanoma demonstrates considerable morphological heterogeneity, which can complicate diagnosis. Tumors may present with epithelioid, spindle cell, plasmacytoid, or mixed cellular patterns, often accompanied by marked cytologic atypia and high mitotic activity. In some cases, particularly in amelanotic variants, the absence of melanin pigment can obscure the diagnosis and lead to confusion with poorly differentiated carcinomas, sarcomas, or lymphomas. Additional histopathological features such as ulceration, necrosis, lymphovascular invasion, and perineural infiltration may be present and are associated with more aggressive behavior.

Immunohistochemical analysis plays a pivotal role in confirming the melanocytic origin of the tumor. Among the commonly used markers, S100 protein is highly sensitive but lacks specificity, whereas HMB-45 and Melan-A (MART-1) offer greater specificity for melanocytic differentiation. More recently, SOX10 has emerged as a highly reliable marker with both high sensitivity and specificity, particularly useful in diagnostically challenging or amelanotic cases. The combined use of multiple immunohistochemical markers is often necessary to establish a definitive diagnosis and to distinguish mucosal melanoma from other malignancies [19].

Radiological imaging is essential for both initial staging and treatment planning. Computed tomography (CT) provides valuable information regarding regional and distant metastases,

particularly in the lungs and liver. Magnetic resonance imaging (MRI) is superior for evaluating local tumor extent, especially in anatomically complex regions such as the head and neck or pelvic cavity, due to its excellent soft tissue resolution. Functional imaging with positron emission tomography combined with computed tomography (PET/CT) has become increasingly important, as it allows for the detection of metabolically active lesions and occult metastases that may not be visible on conventional imaging. PET/CT is also widely used in assessing treatment response and in the surveillance of disease recurrence, providing both anatomical and functional information [20].

In addition to conventional diagnostic tools, molecular testing has gained significant importance in the management of mucosal melanoma. Identification of actionable mutations, particularly in genes such as KIT, NRAS, and less frequently BRAF, has direct therapeutic implications. KIT mutations, in particular, may render tumors susceptible to tyrosine kinase inhibitors, making their detection clinically relevant. Furthermore, molecular profiling contributes to a better understanding of tumor biology and may help stratify patients for targeted therapies or clinical trials. As precision oncology continues to evolve, the integration of molecular diagnostics into routine clinical practice is expected to further refine diagnostic accuracy and guide individualized treatment strategies.

Overall, the diagnostic evaluation of mucosal melanoma requires a high index of clinical suspicion and a coordinated approach combining pathology, radiology, and molecular biology to ensure accurate diagnosis, appropriate staging, and optimal treatment planning.

Treatment Strategies (Expanded Version):

Management of mucosal melanoma remains highly challenging due to its aggressive biological behavior, anatomical complexity, and limited responsiveness to conventional therapies. Optimal treatment requires a multidisciplinary approach involving surgical oncologists, medical oncologists, radiation oncologists, pathologists, and radiologists. Treatment decisions are influenced by tumor location, stage at diagnosis, resectability, and molecular characteristics. Despite advances in systemic therapies, outcomes remain inferior compared to cutaneous melanoma, underscoring the need for tailored therapeutic strategies.

Surgery: Surgical resection with negative margins remains the cornerstone of treatment for patients with localized mucosal melanoma [21]. The primary objective of surgery is to achieve complete tumor removal (R0 resection), which is associated with improved local control and survival outcomes. However, due to the anatomical complexity of

mucosal sites—particularly in the head and neck region, anorectal area, and female genital tract—achieving wide surgical margins is often technically challenging or functionally debilitating.

In head and neck mucosal melanoma, extensive resections may compromise critical structures such as the orbit, cranial nerves, or airway, necessitating a balance between oncologic control and preservation of function. Similarly, in anorectal melanoma, the choice between wide local excision and more radical procedures such as abdominoperineal resection remains controversial, as more aggressive surgery has not consistently demonstrated a survival advantage. Increasingly, organ-preserving approaches are favored when feasible, given the high likelihood of systemic disease progression.

Sentinel lymph node biopsy has a limited and controversial role in mucosal melanoma compared to cutaneous melanoma, largely due to differences in lymphatic drainage patterns and the high incidence of hematogenous spread. Nevertheless, regional lymph node involvement remains an important prognostic factor and may influence staging and adjuvant treatment decisions.

Despite complete surgical resection, recurrence rates remain high, highlighting the need for effective adjuvant therapies.

Radiotherapy: Radiotherapy plays an important role in the multimodal management of mucosal melanoma, particularly in the adjuvant and palliative settings [22]. Although mucosal melanomas have historically been considered relatively radioresistant, advances in radiotherapy techniques have improved their effectiveness in achieving local disease control.

Adjuvant radiotherapy is commonly recommended in patients with high-risk features, including positive or close surgical margins, perineural invasion, or locally advanced disease. In head and neck mucosal melanoma, radiotherapy has been shown to significantly reduce local recurrence rates, although its impact on overall survival remains limited.

In cases of unresectable disease, radiotherapy may serve as a definitive treatment modality, providing symptom relief and local tumor control. Additionally, stereotactic body radiotherapy (SBRT) and other advanced techniques allow for precise delivery of high-dose radiation while minimizing damage to surrounding tissues.

Radiotherapy is also frequently used in the palliative setting to manage symptoms such as pain, bleeding, or obstruction in patients with advanced disease. Emerging evidence suggests that radiotherapy may enhance the efficacy of immunotherapy through immunomodulatory effects, including the so-called

“abscopal effect,” although this remains an area of ongoing research.

Immunotherapy: The advent of immune checkpoint inhibitors has revolutionized the treatment landscape of melanoma, including mucosal melanoma. Agents targeting programmed death-1 (PD-1) receptors, such as nivolumab and pembrolizumab, as well as cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) inhibitors such as ipilimumab, have demonstrated clinical benefit [23].

However, compared to cutaneous melanoma, mucosal melanoma exhibits lower response rates to immunotherapy, typically ranging from 15% to 30%. Several factors may contribute to this reduced efficacy, including a lower tumor mutational burden, distinct tumor microenvironment, and decreased immunogenicity.

Combination immunotherapy, particularly the use of anti-PD-1 plus anti-CTLA-4 agents, has shown improved response rates compared to monotherapy, albeit at the cost of increased toxicity. These regimens may be considered in selected patients with good performance status.

Biomarkers such as PD-L1 expression and tumor mutational burden have been investigated as predictors of response, but their role in mucosal melanoma remains less clearly defined than in cutaneous melanoma. Ongoing studies aim to identify more reliable predictive markers to optimize patient selection.

Despite its limitations, immunotherapy remains a cornerstone of systemic treatment, particularly in advanced or metastatic disease.

Targeted Therapy: Targeted therapy plays a role in a subset of mucosal melanoma patients with specific actionable mutations. Among these, KIT mutations are the most clinically relevant and are found in approximately 15–25% of cases [24]. These mutations are more common in anorectal and vulvovaginal melanomas.

Tyrosine kinase inhibitors such as imatinib have demonstrated efficacy in KIT-mutant mucosal melanoma, leading to tumor regression in selected patients. Other agents, including nilotinib and dasatinib, have also been explored, particularly in cases of resistance or intolerance to imatinib.

However, the overall effectiveness of targeted therapy is limited by several factors:

- Heterogeneity of KIT mutations
- Development of secondary resistance
- Short duration of response

In contrast to cutaneous melanoma, BRAF mutations are relatively rare in mucosal melanoma, limiting the applicability of BRAF inhibitors. NRAS-mutant melanomas lack effective targeted

therapies, although MEK inhibitors have shown modest activity.

Given these limitations, molecular testing remains essential to identify patients who may benefit from targeted therapy, even though this represents a minority of cases.

Combination Therapy: Combination therapeutic strategies are increasingly being explored to overcome the limitations of single-modality treatments and to improve clinical outcomes in mucosal melanoma [25]. These approaches aim to exploit synergistic effects between different treatment modalities.

Dual immunotherapy, combining anti-PD-1 and anti-CTLA-4 agents, has demonstrated higher response rates compared to monotherapy, although toxicity remains a significant concern. Careful patient selection and management of immune-related adverse events are essential.

Another promising strategy involves combining immunotherapy with targeted therapy, particularly in patients with actionable mutations. Additionally, the integration of radiotherapy with immunotherapy is being investigated, based on the potential for radiation to enhance tumor antigen presentation and stimulate systemic immune responses.

Neoadjuvant approaches are also gaining attention, with early evidence suggesting that preoperative immunotherapy may improve resectability and induce durable immune responses.

Furthermore, ongoing clinical trials are evaluating novel agents, including:

- LAG-3 inhibitors
- Tumor-infiltrating lymphocyte (TIL) therapy
- Personalized cancer vaccines

These emerging strategies hold promise for improving outcomes in this difficult-to-treat malignancy.

Prognosis: The prognosis of mucosal melanoma remains significantly poorer than that of cutaneous melanoma despite recent advances in surgical techniques, systemic therapies, and immunotherapy. This unfavorable outcome is primarily attributed to delayed diagnosis, aggressive tumor biology, and limited responsiveness to currently available treatment modalities [26]. Due to its anatomical location and nonspecific clinical presentation, mucosal melanoma is frequently diagnosed at an advanced stage, often with regional or distant metastases already present at the time of initial evaluation.

Survival outcomes vary depending on tumor site, stage at diagnosis, and the feasibility of complete surgical resection. Overall, the reported 5-year survival rates range between 10% and 30%,

markedly lower than those observed in cutaneous melanoma. Median overall survival in advanced-stage disease is often limited to approximately 12–24 months, reflecting the aggressive nature of the disease.

Several clinicopathological factors have been identified as important prognostic indicators. Advanced tumor stage at diagnosis remains the most significant determinant of survival. Regional lymph node involvement and the presence of distant metastases are associated with markedly reduced survival rates. Histopathological features such as high mitotic index, tumor thickness, ulceration, lymphovascular invasion, and perineural invasion further correlate with poor prognosis. In addition, amelanotic variants, which are often more difficult to diagnose, tend to present at more advanced stages and may be associated with worse outcomes.

The anatomical site of the tumor also plays a critical role in prognosis. Head and neck mucosal melanomas tend to have slightly better outcomes compared to anorectal and vulvovaginal melanomas, although survival remains poor across all subtypes. Anorectal melanoma, in particular, is associated with a high rate of early hematogenous dissemination and poor long-term survival.

Recurrence is a major clinical challenge in mucosal melanoma. Even after complete surgical resection with negative margins, local recurrence rates are high, and distant metastases frequently develop. The most common sites of metastasis include the lungs, liver, and brain. The propensity for early systemic spread underscores the need for effective adjuvant and systemic therapies.

Follow-up strategies are therefore critical in the management of these patients. Intensive surveillance is generally recommended, particularly during the first two to three years after treatment, when the risk of recurrence is highest. Imaging modalities such as CT, MRI, and PET/CT are commonly used for monitoring, allowing for early detection of recurrence and timely intervention.

Despite advances in immunotherapy and targeted therapy, long-term survival improvements remain modest. This highlights the urgent need for better prognostic models and more effective treatment strategies tailored to the unique biology of mucosal melanoma.

Future Directions: Future research in mucosal melanoma is focused on improving therapeutic outcomes through a deeper understanding of tumor biology and the development of more effective, personalized treatment strategies. Given the distinct molecular and immunological characteristics of mucosal melanoma, there is a growing recognition that treatment approaches successful in cutaneous

melanoma may not be directly applicable to this subtype.

One of the most promising areas of research is the advancement of personalized medicine. Comprehensive molecular profiling of tumors is increasingly being used to identify actionable mutations and guide targeted therapies. The identification of alterations in genes such as KIT, NRAS, and others provides opportunities for individualized treatment approaches. As next-generation sequencing technologies become more widely available, their integration into routine clinical practice is expected to enhance patient stratification and optimize therapeutic decision-making.

The identification of predictive biomarkers represents another critical area of investigation. Currently, reliable biomarkers for predicting response to immunotherapy or targeted therapy in mucosal melanoma are lacking. While markers such as PD-L1 expression and tumor mutational burden have shown some predictive value in other malignancies, their role in mucosal melanoma remains unclear. Ongoing research aims to identify novel biomarkers that can better predict treatment response and guide therapy selection.

Advances in immunotherapy continue to play a central role in future treatment strategies. Novel immune checkpoint inhibitors targeting additional pathways, such as LAG-3 and TIM-3, are being investigated in clinical trials. Combination immunotherapy approaches, including dual checkpoint blockade and combinations with other treatment modalities, are also being explored to overcome resistance and improve response rates.

Targeting the tumor microenvironment is another emerging strategy. Mucosal melanomas often exhibit an immunosuppressive microenvironment, characterized by low immune cell infiltration and altered cytokine profiles. Therapeutic approaches aimed at modulating the tumor microenvironment, enhancing immune infiltration, and reversing immune suppression are under active investigation.

In addition, adoptive cell therapies, including tumor-infiltrating lymphocyte (TIL) therapy, and personalized cancer vaccines are gaining attention as potential treatment options. These approaches aim to harness the patient's own immune system to generate a more effective and durable anti-tumor response.

The integration of radiotherapy with immunotherapy represents another promising area, based on the potential synergistic effects of radiation-induced antigen release and immune activation. Similarly, neoadjuvant treatment strategies are being explored to improve surgical

outcomes and induce systemic immune responses at earlier stages of disease.

Overall, advances in genomic profiling, immunotherapy, and translational research are expected to play a key role in improving survival outcomes for patients with mucosal melanoma. However, given the rarity of the disease, collaborative multicenter studies and clinical trials will be essential to generate high-quality evidence and accelerate progress in this field [27].

Conclusion

Mucosal melanoma is a rare but highly aggressive malignancy that differs fundamentally from cutaneous melanoma in terms of its epidemiology, molecular landscape, clinical presentation, and therapeutic responsiveness. Its biological heterogeneity, combined with the absence of well-defined environmental risk factors, contributes to significant challenges in early diagnosis and effective management. As a result, most patients present with advanced-stage disease, which is a major determinant of the poor overall prognosis associated with this entity.

Despite notable advances in surgical techniques, radiotherapy, immunotherapy, and targeted therapies, clinical outcomes for mucosal melanoma remain suboptimal. Surgical resection continues to be the primary treatment modality for localized disease; however, high rates of local recurrence and early distant metastasis limit its long-term effectiveness. Similarly, although immune checkpoint inhibitors have transformed the treatment landscape of melanoma, their efficacy in mucosal melanoma is comparatively limited, likely due to its lower tumor mutational burden and distinct tumor microenvironment.

The unique molecular profile of mucosal melanoma, characterized by alterations such as KIT and NRAS mutations and extensive chromosomal instability, underscores the need for tailored therapeutic approaches. Current evidence suggests that a "one-size-fits-all" strategy is insufficient, and that individualized treatment plans based on molecular and clinical characteristics are essential for improving patient outcomes.

Future progress in the management of mucosal melanoma will depend on several key factors. These include the integration of comprehensive molecular profiling into routine clinical practice, the identification of reliable predictive biomarkers, and the development of more effective combination therapies. In addition, emerging treatment modalities such as adoptive cell therapy, novel immune checkpoint inhibitors, and tumor microenvironment-targeting strategies hold promise for overcoming current therapeutic limitations.

Given the rarity of the disease, collaborative efforts across institutions and the establishment of large, multicenter clinical trials are crucial to advancing knowledge and improving evidence-based treatment strategies. Furthermore, increased awareness among clinicians may facilitate earlier diagnosis and more timely intervention, potentially improving outcomes.

In conclusion, mucosal melanoma remains a formidable clinical challenge. A deeper understanding of its unique biological behavior, coupled with continued innovation in therapeutic strategies, is essential to achieve meaningful improvements in survival and quality of life for affected patients.

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