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CUTANEOUS MELANOMA – DIAGNOSIS, TREATMENT, AND THE  
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## CUTANEOUS MELANOMA – DIAGNOSIS, TREATMENT, AND THE POTENTIAL IMPACT OF PHYSICAL ACTIVITY

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## ABSTRACT

Malignant melanoma is one of the most aggressive forms of skin cancer, with its incidence steadily increasing worldwide. Although it accounts for a minority of skin cancer cases, it is responsible for the majority of skin cancer-related deaths. This review discusses the epidemiology, clinical characteristics, and histopathological features of the main melanoma subtypes, including superficial spreading melanoma (SSM), nodular melanoma (NM), lentigo maligna melanoma (LMM), and acral lentiginous melanoma (ALM). Particular attention is given to current diagnostic strategies, ranging from the gold standard of histopathological examination to emerging non-invasive techniques such as dermoscopy, reflectance confocal microscopy (RCM), optical coherence tomography (OCT), high-frequency ultrasound (HFUS), and the novel tape stripping method. These approaches have improved early detection and the accurate assessment of tumor margins, supporting more personalized therapeutic planning. Treatment remains primarily surgical in early-stage melanoma, while advanced cases increasingly benefit from immunotherapy and targeted therapies, which have significantly improved survival outcomes. Additionally, this article explores the potential association between physical activity and melanoma risk, emphasizing that outdoor activity may increase susceptibility due to greater ultraviolet (UV) exposure. Prevention strategies, including public education and effective photoprotection, remain essential in mitigating disease burden. In conclusion, despite significant advances in diagnosis and therapy, malignant melanoma continues to pose major clinical and public health challenges, underscoring the importance of early detection, prevention, and ongoing research.

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## KEYWORDS

Malignant Melanoma, Skin, Cancer, Physical Activity

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## CITATION

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## Introduction

Malignant melanoma is a type of skin cancer whose development is primarily associated with excessive exposure to ultraviolet (UV) radiation [1] and genetic predispositions [2]. Although it accounts for a small percentage of all malignant skin tumors, it is the leading cause of death within this group of diseases [1]. The likelihood of developing melanoma increases with age, and the risk is approximately 1.5 times higher in men than in women [3]. Over the past 25 years, the incidence of malignant melanoma has risen in the United Kingdom, although mortality rates have remained relatively stable. The five-year survival rate depends on the stage of the cancer and ranges from 20% to 95%. A higher risk of developing the disease is observed among individuals of white ethnicity and those with numerous skin moles [4]. Globally, approximately 160,000 new cases of melanoma are diagnosed each year, with around 48,000 deaths reported [5]. In some countries, the incidence is increasing at a rate of about 3% annually. Considering the rising incidence and high treatment costs, melanoma poses a significant challenge for healthcare systems [6]. The most common types of malignant melanoma are superficial spreading melanoma (SSM) and nodular melanoma (NM). These subtypes primarily affect individuals of white ethnicity and together account for over 80% of all melanoma cases [1].

Other less frequent subtypes include lentigo maligna melanoma (LMM) and acral lentiginous melanoma (ALM) [7].

## Superficial Spreading Melanoma (SSM)

Superficial spreading melanoma is the most common subtype of this cancer. It is characterized by typical features of melanoma, such as asymmetry, irregular borders, varied pigmentation, and an increasing lesion size. This type of melanoma exhibits a prolonged radial growth phase, with proliferation confined to the epidermal layer and no signs of invasion into the deeper layers of the skin [7].

### **Nodular Melanoma**

Nodular melanoma most commonly develops in areas of the skin that are frequently exposed to sunlight, such as the head and neck. Histopathologically, it is characterized by vertical tumor growth only, without a preceding radial growth phase. It has a rapid growth rate and typically reaches a significant depth of invasion (according to the Breslow scale) by the time of diagnosis. This subtype accounts for approximately 15–20% of all primary melanoma cases but is responsible for up to 40% of deaths caused by this cancer [7].

### **Lentigo Maligna Melanoma (LMM)**

Lentigo maligna melanoma (LMM) is a slow-growing type of melanoma that most commonly appears on sun-damaged skin, particularly in the head and neck region of older individuals. Due to its clinical and histopathological resemblance to benign lesions, LMM is often misdiagnosed for many years, which can lead to an increased risk of morbidity and mortality [8].

### **Acral Lentiginous Melanoma (ALM)**

Acral lentiginous melanoma (ALM) is a type of melanoma that develops on the skin of the hands and feet, including the palmar and plantar surfaces, fingers and toes, as well as the nail apparatus [9].

### **Prognosis**

The prognosis for patients with early-stage malignant melanoma (stages I–II), clinically limited to the primary skin lesion, primarily depends on the depth of dermal invasion and the presence of ulceration. In stage III, when the cancer involves regional lymph nodes, the predicted survival rate worsens with an increasing number of affected lymph nodes [10].

### **Diagnostics**

The standard diagnostic method for suspected malignant melanoma (MM) is surgical excision of the lesion, followed by histopathological analysis, which is considered the gold standard for diagnosing this cancer [11]. Technological advancements have contributed to the growing popularity of non-invasive diagnostic methods in dermatology, such as reflectance confocal microscopy (RCM), optical coherence tomography (OCT), and high-frequency ultrasound (HFUS). Jung and colleagues demonstrated that RCM, OCT, and HFUS can assist in assessing tumor margins and monitoring therapeutic response. In turn, research by Schuetzenberger and collaborators showed that HFUS offers greater depth of penetration, enabling imaging of deeper skin structures and potentially revealing areas where residual melanoma may be present [12].

### **Dermoscopy**

Dermoscopy is a non-invasive diagnostic method that uses a handheld magnifying device and lighting—often polarized—to minimize light reflection and provide better visualization of structures just beneath the skin's surface. When performed by trained specialists, dermoscopy offers higher sensitivity and specificity in the evaluation and classification of skin lesions compared to standard visual examination without magnification [13].

### **Reflectance Confocal Microscopy (RCM)**

Reflectance Confocal Microscopy (RCM) can aid in the diagnosis of skin cancers that may be suitable for non-surgical treatments, potentially eliminating the need for diagnostic biopsy—particularly in patients with suspected basal cell carcinoma (BCC) [14]. The use of preoperative in vivo mapping with RCM is gaining importance, as it allows for the detection of subclinical foci of lentigo maligna (LM) that may extend beyond the standard surgically recommended margins [15].

### **Optical Coherence Tomography (OCT)**

Optical Coherence Tomography (OCT) is a modern imaging technique used for the non-invasive diagnosis of skin conditions [16]. It is a microscopic imaging method that uses near-infrared light to generate magnified images of skin lesions. When combined with clinical examination, dermoscopy, or both in cases of suspected skin cancer, OCT can provide additional valuable diagnostic information compared to other imaging techniques [17].

### High-Frequency Ultrasound (HFUS)

Ultrasonography is a non-invasive imaging method based on the analysis of sound waves reflected from body structures. At lower frequencies, it enables visualization of deep internal organs. In contrast, high-frequency ultrasound (HFUS), which uses probes with frequencies of 20 MHz or higher, has limited penetration depth but provides high-resolution images of tissues located near the skin surface. When combined with clinical and/or dermoscopic assessment in suspected cases of skin cancer, HFUS can offer additional valuable diagnostic data, surpassing some other imaging techniques in this regard [18].

### Differential Diagnosis

Skin tumors can be either benign or malignant, and each type may present with a distinct clinical appearance. Due to the wide variability in symptom presentation, differential diagnosis should consider all skin lesions appearing as macules, pigmented spots, papules, plaques, or nodules. In rare cases, they may also manifest as vesicles, bullae, or pustules.

The differential process should include vascular, infectious, neoplastic (including cutaneous metastases from internal organs), inflammatory, post-traumatic, metabolic, mechanical, allergic, autoimmune, and iatrogenic conditions [19].

Characteristic conditions that help distinguish them from true skin cancer include:

- Psoriasis
- Atopic dermatitis
- Tinea corporis or other fungal skin infections
- Acne vulgaris
- Skin warts
- Lupus erythematosus
- Actinic keratosis
- Metastatic skin cancers
- Sebaceous gland hyperplasia
- Skin nevi
- Benign melanocytic lesions
- Dysplastic nevi [19]

### Detection of Cutaneous Melanoma – Tape Stripping Method

The tape stripping (TS) method was previously used in the diagnosis of other skin diseases such as atopic dermatitis and psoriasis [3]. Recently, its application has been extended to pigmented lesions as a new non-invasive technique supporting the diagnosis of malignant melanoma (MM). Studies have identified a variety of biomarkers—including RNA, cells, and lipids—that may have diagnostic value. MM-affected skin shows a distinct RNA expression profile compared to healthy skin and benign nevi, which can be utilized for melanoma detection [19].

In clinical practice, an adhesive patch is directly applied to the pigmented lesion, which has been previously marked with a surgical marker or dark pen. Upon rapid removal, corneocytes from the stratum corneum adhere to the patch and are subsequently analyzed. This process can be repeated multiple times using a new patch on the same lesion. If specific RNA molecules are detected above a defined threshold, the test result is considered positive (TS+); the absence of key RNA markers—particularly those known to be down-regulated in melanoma—may also indicate MM and result in a positive finding.

It is important to note that this method is less effective for lesions located on mucous membranes, palms, soles, nail units, or in the presence of bleeding or serous exudate. Each year, a substantial number of pigmented skin lesions suspected of melanoma are excised, only to be found non-malignant upon histopathological examination. These unnecessary excisions place a significant burden on dermatologists, surgeons, laboratory staff, and pathologists [11].

### Diagnosis of Cutaneous Melanoma

The diagnosis of melanoma is based on the histopathological evaluation of tissue samples at the cellular level by a pathologist, with the interpretation of morphological features often being subjective. The complexity of histopathological assessment contributes to significant inter-observer variability, which may be attributed to the wide diversity of histologic patterns. As a result, up to 17% of cases are reclassified during expert panel reviews, either as false positives or false negatives [20].

### **Treatment of Cutaneous Melanoma**

The choice of treatment for melanoma largely depends on the stage of the disease at the time of diagnosis. In early-stage cases, the standard approach involves wide local excision of the skin lesion, often complemented by sentinel lymph node biopsy in tumors classified as moderate- or high-risk [2]. Surgical excision has remained the standard treatment for skin cancers for many years. However, the decision to proceed with surgery depends on various factors, including the presence of comorbidities, the anatomical location of the lesion, and potential intolerance to repeated surgical interventions. In some situations, topical treatment may be a more appropriate alternative. This approach enables higher drug concentrations directly at the tumor site while reducing the risk of systemic side effects [21].

In more advanced cases, it may be necessary to remove regional lymph nodes and introduce systemic therapies such as immune checkpoint inhibitors or targeted therapies. In certain situations, palliative radiotherapy may also be considered. The introduction of novel therapeutic strategies, particularly in immunotherapy and targeted treatment, has significantly improved the prognosis for patients with advanced disease. This highlights the crucial role of ongoing scientific research and participation in clinical trials [2].

### **Surgical Treatment of Cutaneous Melanoma**

Mohs micrographic surgery and staged surgical excisions are key treatment methods for melanoma, allowing for precise histological evaluation and accurate visualization of peripheral margins. Careful preoperative assessment is essential for proper surgical planning and ensuring effective removal of the malignant lesion [12].

### **Mohs Micrographic Surgery Techniques**

Mohs micrographic surgery (MMS) is indicated for the treatment of malignant skin tumors that carry a high risk of recurrence, incomplete excision, or in cases where preserving as much healthy tissue as possible is critical. Guidelines on the appropriate use of MMS serve as a decision-support tool for dermatologists, helping them determine the suitability of this method for treating specific tumors based on individual patient characteristics, lesion location, and tumor profile [22]. In anatomically and functionally critical areas such as the face, neck, hands, feet, and anterior lower legs, MMS is recommended for melanoma in situ (MMIS) and all thin melanomas with a Breslow depth of less than 0.8 mm. Additionally, for the head and neck region, all superficial spreading and lentigo maligna histologic subtypes with a Breslow depth under 0.8 mm should be treated using MMS. Intraoperative immunostaining for the MART-1 antigen, recognized by T cells, is also recommended due to its high sensitivity [23].

### **The Relationship Between Physical Activity and the Risk of Cutaneous Melanoma**

Data suggest a potential association between physical activity and the risk of cutaneous melanoma, which may depend on the level of exposure to ultraviolet (UV) radiation. Most case-control studies have accounted for individual factors such as sun sensitivity or personal sun exposure, whereas none of the analyzed cohort studies considered these variables. In two cohort studies, UV exposure was assessed ecologically—based on geographic region and levels of UV radiation. One of these studies demonstrated a statistically significant positive association between physical activity and melanoma risk in areas with high sun exposure, while in regions with lower UV levels, the association was positive but not statistically significant. In the second study, which included only regions with low UV exposure, a similarly non-significant positive association was observed. These findings suggest that physical activity performed outdoors, especially under high sunlight conditions, may increase the risk of melanoma due to greater exposure to UV radiation [24].

### **Conclusions**

Malignant melanoma remains one of the most aggressive forms of skin cancer, with a steadily increasing global incidence. Despite representing a minority of skin cancer cases, it is responsible for the majority of deaths in this group. Early diagnosis and accurate classification of melanoma subtypes—such as superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, and acral lentiginous melanoma—are crucial for effective treatment and improved prognosis.

Recent advances in non-invasive diagnostic techniques, including dermoscopy, reflectance confocal microscopy (RCM), optical coherence tomography (OCT), and high-frequency ultrasound (HFUS), have significantly enhanced the accuracy of melanoma detection and the assessment of tumor margins. The emerging tape stripping method offers further potential as a non-invasive diagnostic tool, especially in



distinguishing malignant from benign pigmented lesions. However, histopathological examination remains the gold standard for definitive diagnosis.

Treatment strategies continue to evolve, with surgical excision remaining the cornerstone of early-stage melanoma management. In more advanced cases, targeted therapies and immunotherapy have dramatically improved survival rates, underscoring the importance of personalized treatment plans and continued research.

An emerging area of interest is the relationship between lifestyle factors—particularly physical activity—and melanoma risk. While physical activity is generally considered beneficial to overall health, evidence suggests that outdoor physical activity may increase the risk of melanoma, especially in regions with high ultraviolet (UV) radiation exposure. These findings highlight the need for increased awareness and preventive strategies, such as appropriate sun protection, particularly among physically active individuals.

Given the growing incidence and complex nature of melanoma, ongoing research, early detection, public education, and the refinement of treatment methods are essential to improving patient outcomes and reducing the burden on healthcare systems.

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