CHARACTERIZATION OF CUTANEOUS MELANOMA (CM): *a narrative review*

CARACTERIZAÇÃO DO MELANOMA CUTÂNEO (MC): uma revisão narrativa

Lairane Bridi Loss[1]; Juliana Casotti Santi[1]; Sarah Aparecida Fernandes Lima[1]; Mariana Santos Lorencini[1]; Sabrina Chaves Costa Ferri[1]; Rogério Pimentel Terra Junior[1]; Letícia Chiepe[1]; Luiza Daleprani Stanger[2]; Kelly Cristina Mota Braga Chiepe[3]; Orlando Chiarelli-Neto[3]*

[1] Medical Student at the University Center of Espírito Santo, Colatina, Espírito Santo, Brazil; [2] Farmacy Student at the University Center of Espírito Santo, Colatina, Espírito Santo, Brazil; [3] Faculty of Medicine, University Center of Espírito Santo, Colatina, Espírito Santo, Brazil

ABSTRACT

Melanoma is the most aggressive type of skin cancer due to its metastatic potential, and its incidence has increased considerably in recent decades. Sun exposure to ultraviolet A and B cause DNA damage, mutations and induction of the melanomas. The focus here is an updated review on melanoma. Through early diagnostic detection of the malignant lesion, it is possible to initiate therapy in an early and curative way, increasing survival with a subsequent decrease in the overall mortality rate. Surgeries are the first treatment option, but chemotherapy/radiotherapy have been alternative treatments for melanomas. Advances in immunotherapy and targeted therapy have changed treatment paradigms and improved the prognosis of late-stage disease.

Keywords: *Cancer; melanoma; melanin; diagnosis; treatments.*

1 INTRODUCTION

Cutaneous melanoma (CM), which originated from the mutation of melanocytes, represents one of the most aggressive forms of skin cancer and is responsible for 80% of the mortality associated with this type of cancer, mainly due to its high metastatic power (Gesbert; Larue, 2018; Leonardi *et al.,* 2018; Schadendorf *et al.,* 2018).

Unlike other solid tumors, CM mainly affects young and middle-aged individuals (mean age at diagnosis 57 years). The incidence increases after 25 years of age and continues until the age of 50, and then decreases, mainly in females. Women are more

Autor correspondente: orlandobqi@yahoo.com.br

frequent in the younger age groups, while males prevail after the age of 55 (Leonardi *et al.,* 2018; Dimitriou *et al.,* 2018*;* Dzwierzynski, 2021).

Exposure to ultraviolet (UV) rays without sun protection is one of the main risk factors for the development of CM. Indoor tanning, family and personal history of melanoma, melanocytic nevi, and certain phenotypic traits such as low phototype skin and hair color are also contributing factors. In addition to environmental causes, phenotypic and genetic characteristics have also been consistently associated with an increased incidence of CM, as a positive family history of melanoma is associated with a higher risk of the lesion at younger ages and in areas not exposed to the sun (Dimitriou *et al.,* 2018).

The main histological subtypes of melanoma are: superficial extensive, nodular, lentigo maligna, and acral lentiginous. Other less frequent forms are the amelanocytic, desmoplastic, spitzoid, soft tissue melanoma, malignant blue nevus, ocular and mucosal melanoma. Superficial extensive melanoma is the most common subtype, while acral lentiginous is the most aggressive among those presented (Schadendorf *et al.,* 2015; Carr; Smith; Wernberg, 2020).

Early diagnosis of CM is one of the main prognostic factors in the disease. As soon as a suspicious lesion is detected, the biopsy remains the first step to establish the definitive diagnosis. For localized forms, the surgical approach remains the therapeutic modality of choice, while systemic therapies are indicated for advanced stages of the disease (Swetter *et al.,* 2019). Here, the focus is a narrative review of all aspects of melanoma, including diagnosis, clinical characteristics and treatment.

2 EPIDEMIOLOGY

The incidence of melanoma has increased in the world, with a predominance of fair skinned individuals, with an estimated 325,000 new cases in 2020 (Saginala *et al.,* 2021). Women are more affected in younger age groups and men presented greater predominance after 55 years of age (Leonardi *et al.,* 2018). Its incidence is also related to ethnicity and country, with high rates in Australia, New Zealand, North America, and Western Europe. The incidence rate varies by sex, and it is currently the fifth most common cancer diagnosis in the US, accounting for 5.6% of all diagnoses with 106000 new cases estimated 2021 (Dimitriou *et al.,* 2018; Saginala *et al.,* 2021; Strashiloy;

Yordanov, 2021). Overall mortality rates in recent years have remained stable (Nader Marta *et al.,* 2020).

3 ETIOLOGY

Several etiological factors are related to the development of CM, some with a genetic interface, others influenced by the environment in which the patient is inserted (Strashiloy; Yordanov, 2021). Mutation in the CDKN2A gene being the most common among patients with hereditary melanoma (Strashiloy; Yordanov, 2021). The main risk factor associated with the development of melanoma is exposure to UV radiation, either through natural sun exposure or artificial tanning systems. UVA irradiation penetrates deeper into the skin, generating indirect DNA damage, such as cyclobutane pyrimidine dimers [CPDs] or 6-4 photoproducts [6-4PPs] (Saginala *et al.,* 2021) and UVB causes double strand breakage (Dzwierzynski, 2021; Saginala *et al.,* 2021). Transversion mutations (A →T) are also frequent in the BRAF gene of melanoma cells, commonly responsible for cell differentiation and growth (Meyskens; Farmer Jr; Anton-Culver *et al.*, 2004; Saginala *et al.,* 2021). Immunosuppressive conditions may also be related to DNA damage and mutations, as immunosuppression does not allow effective protection of the organism (Saginala *et al.,* 2021; Strashiloy; Yordanov, 2021).

There are six skin phototypes, with subtypes I and II being the most sensitive to UV exposure. Such subtypes refer to individuals with fair skin, blond or red hair, with a tendency to have lower resistance to UVB rays and are subject to a higher risk of developing CM (Strashiloy; Yordanov, 2021). Dark-skinned individuals synthesize eumelanin in greater proportion than fair-skinned people, being considered more protective against UV radiation than pheomelanin (Saginala *et al.,* 2021). Pigmented nevi are benign growths of melanocytes, they may remain unchanged during life or be related to the development of melanoma, being considered markers of increased risk for melanoma (Saginala *et al.,* 2021; Strashiloy; Yordanov, 2021). Several research groups are actively investigating visible light (VL) effects on skin. In addition to increasing pigmentation, VL has caused melanin photosensitization, generating singlet oxygen ($^1O_2$), 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) and cell death (Assis *et al.,* 2021; Mahmoud *et al.,* 2010; Zastrow *et al.,* 2009*;* Setlow *et al.,* 1993; Tonolli; Baptista; Chiarelli-Neto, 2021; Tonolli *et al*, 2020; Chen *et al.,* 2019; Chen *et al*., 2021). In an animal model, the green light (532 nm) reduced the growth of melanoma in mice

(Haussmann *et al.,* 2022). These findings show the duality of melanin photosensitization and its particularities in melanocytes and melanomas (Figure 1).

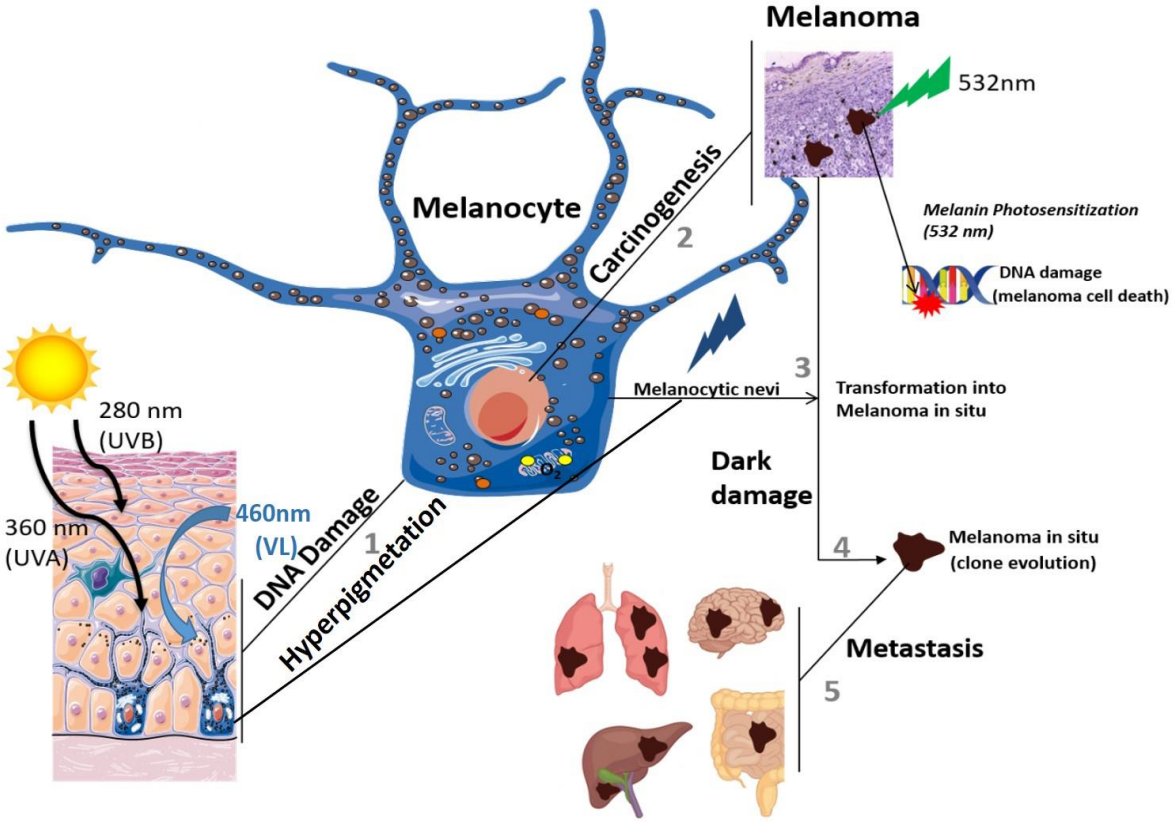

Figure 1: Pathophysiology of melanoma
Note: Excessive exposure to Ultraviolet irradiation (UVR) and Visible Light (VL), associated with the individual's intrinsic genetic factors, hyperpigmentation, triggers DNA damage (1) to melanocytes, generating carcinogenesis at that location (2). At this moment, normal nevi are transformed into melanocytic nevi (3). With these developments and after a while, melanocytic nevi turn into melanoma in situ (3). In addition, there is another way in which the individual's internal damage (dark damage) transforms normal nevi into melanoma in situ (4). From this stage, the melanoma can metastasize (5) to other sites, such as the lung, brain, intestine and liver. Melanoma irradiated at 532 nm suffers melanin photosensitization, cell damage and decrease in tumor size.
Fonte: Haussmann *et al.,* 2022.

4 PATHOPHYSIOLOGY

Melanoma may start from the association of genetic factors with exacerbated UV exposure without sun protection, which results in mutagenic defects in the DNA of melanocytes. After the accumulation of genetic defects, a hyperplastic transformation of normal melanocytes into melanocytic nevi occurs (Eddy; Shah; Chen, 2021). Over time, these nevi transform into melanoma *in situ* and are affected by several mutations at different points in the cell cycle, which culminates in the transformation into primary melanoma, with the ability to migrate to other tissue sites, a process called metastasis (Davis; Shalin; Tackett, 2019; Eddy; Shah; Chen, 2021; Haussmann *et al.,* 2022).

Melanomas go through two phases of growth: radial and vertical. In the radial growth phase, the lesion grows horizontally within the epidermis. In the vertical, growth occurs in a vertical format with subsequent invasion of other tissue layers. However, for the described steps to occur, as well as the process of metastasis formation, malignant melanomas need the association of endogenous and exogenous factors, such as hereditary factors and intense UV and VL exposure without the use of sunscreen (Schadendorf *et al.,* 2015; Schadendorf *et al.,* 2018).

There are different types of mutations that determine the emergence or not of CM. As for those of hereditary origin, the alteration is in the CDKN2A gene (cyclin-dependent kinase inhibitor 2A), a condition in which patients are more likely to have benign nevi (Schadendorf *et al.,* 2015; Schadendorf *et al.,* 2018). Changes in the BRAF gene pathway also determine the appearance of benign nevi, whereas in TERT (reverse transcriptase telomerase promoter) *in situ melanomas* and median lesions occur, and with the PTEN pathway (phosphatase and tensin homolog) and TP53, are related to metastatic melanomas (Schadendorf *et al.,* 2015; Schadendorf *et al.,* 2018; Davis; Shalin; Tackett, 2019; Eddy; Shah; Chen, 2021). Thus, it is emphasized that for the development of the disease to occur, it is necessary to have a combination of extrinsic and intrinsic factors (Schadendorf *et al.,* 2018).

Also noteworthy is the existence of other signaling pathways related to the induction of carcinogenesis by UV rays, namely the kinases ERK (protein kinases regulated by extracellular stimuli), JNK (c-Jun N-terminal kinase), and p38 (Davis; Shalin; Tackett, 2019, Eddy; Shah; Chen, 2021). These pathways are important for the future understanding of targeted therapies for carcinomas related to UV exposure (Davis; Shalin; Tackett, 2019). On the other hand, not all pathways are attributed to solar radiation damage, which corroborates this is that the MAP kinase pathway, the most important pathway for the understanding of melanoma and therapeutic purposes, is not related to UV damage (Leonardi *et al.,* 2018; Schadendorf *et al.,* 2018).

Regarding the metastasis phase, tumor cells initially migrate from the skin to the lymph nodes, a process in which changes in their characteristics occur through the epithelial mesenchymal transition to facilitate invasion at other tissue sites. In addition, specific biomarkers facilitate malignant transformation, such as the microphthalmia-associated transcription factor (MITF), which allows the survival of tumor cells as well

as their expansion in other parts of the body (Davis; Shalin; Tackett, 2019; Eddy; Shah; Chen, 2021).

5 CLINICAL CHARACTERIZATIONS

5.1 CUTANEOUS MELANOMA (CM)

In CM, the lesions are clinically characterized as typical, in the form of a macula or nodule, asymmetrical lesion, with irregular edges, color variation, diameter >0.5 cm, and with evolution in size. The findings described make up the so-called ABCDE of identification of melanoma, details that help to suspect malignancy of the lesion (Kibbi; Kluger; Choi, 2017; Situm *et al.,* 2014; Hartman; Lin, 2019). CM can appear in any area of the body, including previously healthy skin or through an already pigmented lesion. Furthermore, they are classified into four main subtypes: superficial extensive, nodular, lentigo maligna, and acral lentiginous, the subtypes being subject to variations according to the literature used (Kibbi; Kluger; Choi, 2017; Situm *et al.,* 2014).

5.2 SUPERFICIAL EXTENSIVE MELANOMA (SEM)

The most common subtype of melanoma is SEM, which accounts for up to 70% of all cases. Generally, the most affected age is between 30 and 50 years, mainly in individuals who have phototype I or II. The most common place to appear is in the trunk of men and the lower limbs of women (Kibbi; Kluger; Choi, 2017; Situm *et al.,* 2014). It has the characteristic of affecting the superficial layer of the skin, starting as a horizontal lesion, and therefore allows the patient to remain with the lesion for a while without being diagnosed without progressing into a deeper organ lesion. At dermoscopy, the lesion presents asymmetry in shape, the color is usually black or light brown and with the presence of a blue-white veil, if the lesion is in the vertical growth phase, it will be rough in the papillary form and may or may not be ulcerated (Kibbi; Kluger; Choi, 2017).

5.3 NODULAR MELANOMA (NM)

NM represents the second most common type of melanoma, accounting for about 15-30% of cases. The most frequent lesion sites are the trunk, neck, and head. NM cases tend to be diagnosed in more advanced stages due to vertical lesion

infiltration, being a more aggressive subtype than SEM. Initially, the lesion appears as a nodule or papule, asymmetrical with very sharp edges, often with black or blue pigmentation, with or without ulceration (Situm *et al.,* 2014; Hartman; Lin, 2019; Martínez-Piva *et al.,* 2021).

At the dermoscopy, a blue-white veil is also observed, with white streaks and irregular linear or dotted vessels, and even being of small diameter, it can reach high depths (Kibbi; Kluger; Choi, 2017; Situm *et al.,* 2014).

5.4 MALIGNANT LENTIGO MELANOMA (MLM)

Less common than the other subtypes, MLM accounts for 5-15% of all melanoma cases. It is usually more prevalent in elderly people over 65 years of age in places of cumulative photo exposure to UV radiation, especially on the face in the nose and cheeks region (Kibbi; Kluger; Choi, 2017; Situm *et al.,* 2014). The precursor lesion of MLM is called melanoma *in situ*. At dermoscopy, it presents with less pigmentation and the margins are not as well defined as in the previous subtypes. It has a slow growth of approximately 30 years, initially horizontally, and then becomes invasive. Areas with nodules and infiltrations are a strong indicator of progression (Situm *et al.,* 2014; Martínez-Piva *et al.,* 2021).

5.5 ACRAL LENTIGINOUS MELANOMA (ALM)

ALM accounts for less than 5% of all types, but is the most common subtype in individuals of Asian and African descent, around 50% and 70% respectively. The main characteristic of ALM is its occurrence in glabrous skin, areas of skin that do not have hair, such as the palms of the hands and soles of the feet, fingers, and nail apparatus. On dermatological examination, ALM starts as a black or brown macule, asymmetrical and with irregular edges, reaching up to 3 cm (Kibbi; Kluger; Choi, 2017; Situm *et al.,* 2014). The etiology is not so clear, it has a poor prognosis and is often associated with areas of physical stress that receive repetitive movements and minor trauma, which is why the diagnosis is delayed. Diagnosis can be facilitated if the lesion presents with Hutchinson's sign, and pigmented nail fold (Situm *et al.,* 2014; Dicaprio; Abousayed; Kambam, 2020; Martínez-Piva *et al.,* 2021).

5.6 OTHER SUBTYPES

Several other types of melanoma are not necessarily CM, among them Amelanotic Melanoma (AM), which can be present as a variant in any subtype of melanoma, although rare. Due to the pink color of the lesion, the diagnosis is commonly delayed, paying attention to the failures of previous treatments and dermoscopy, which if performed correctly, it is possible to observe irregular pigmentation in the lesion with atypical vascularization (Situm *et al.,* 2014).

Mucosal Melanoma (MM) occurs in any mucosal region. It is a low-prevalence subtype and presents unknown risks. Due to difficult visualization and lesion detection, diagnosis is difficult. The MM has a lentiginous growth pattern, destroys the mucosa, and is often associated with pain and bleeding due to the fragility of the sites (Martínez-Piva *et al.,* 2021).

The incidence of Uveal Melanomas (UM) is also lower compared to CM. The uveal components are iris, ciliary body, and choroid, it is related to younger ages as in young people and children with a considerable genetic component, more specifically to the BAP1 gene. The main symptoms are visual and approximately 50% of UM cases develop distant metastases (Kibbi; Kluger; Choi, 2017).

6 DIAGNOSIS

Melanoma-type skin cancers can be easily identified by the patient in a body self-examination. Increasingly, lesions are being identified in the early stages, but the presence of nevi and benign lesions makes diagnosis difficult. Clinical diagnosis is still ideal and is performed through a thorough evaluation of the entire body surface, after a complete anamnesis, seeking possible risk factors. The use of the dermatoscope, a device that enlarges the lesion for better visualization of colors and typical patterns that would not be possible to see with the naked eye, has improved the accuracy of the diagnosis and has reduced the need for unnecessary biopsies (Schadendorf *et al.,* 2015; Kibbi; Kluger; Choi, 2017).

For individuals who have a high number of nevi, whole body photography can be used as a complemente, making it possible to compare between consultations and identify new nevi or possible malignant lesions. To differentiate CM from common nevi and other lesions, the ABCDE rule and the “ugly duckling” sign are used, a method in which neighboring lesions are compared (Figure 2). Patients have a specific profile

and the lesion that appears to be different from the others should be suspected (Situm *et al.,* 2014; Schadendorf *et al.,* 2015).

The definitive diagnosis of CM is through skin biopsy (gold standard method) through 3 techniques, cauterization, puncture, or excision along with a 2 mm margin. The last method is preferable. The histopathological examination of the CM shows atypical melanoma cells in the epidermis or dermis (Hartman; Lin, 2019).

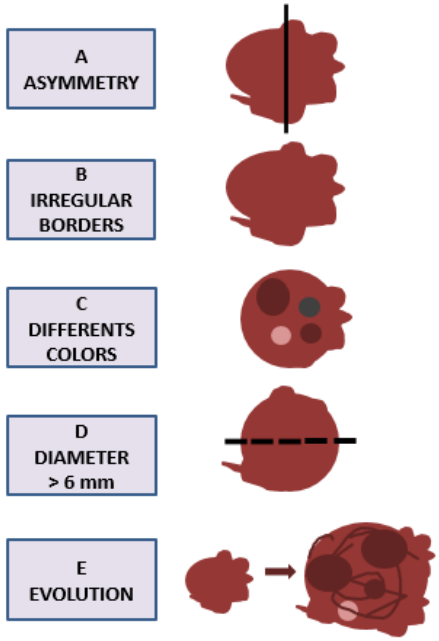

Figure 2: The figure demonstrates in a practical way the identification of lesions with suspicious characteristics for the diagnosis of melanoma, using the ABCDE rule.
Source: own authorship.

6.1 HISTOLOGICAL CLASSIFICATION

Melanoma is classified histopathologically using different scales. Based on this, therapeutic options based on histological classification and the calculation of the risk of tissue invasion are discussed. The classification is established according to tumor thickness (T stage and Breslow index), lymph node involvement (N stage), and presence of metastasis (M stage). Most CM is diagnosed before lymph node or distant metastases (N0 and M0 stage) (Davis; Shalin; Tackett, 2019; Tonolli; Baptista; Chiarelli-Neto, 2021). The Breslow index, based on tumor thickness, is the most relevant histological criterion to assess the prognosis of melanoma, capable of helping to determine the surgical parameters, in the selection of patients for sentinel lymph node biopsy and the preoperative need for studies by the image. (Schadendorf *et al.,* 2015; Davis; Shalin; Tackett, 2019; Shelley *et al.,* 2019; Martínez-Piva *et al.,* 2021).

Through the tumor-node-metastasis (TNM) staging system, melanoma-like skin cancer can be staged into local disease (stage I-II), node-positive disease (stage III), and advanced/metastatic disease (stage IV). Current staging uses the 8th edition of the American Joint Committee on Cancer - AJCC (Jenkins; Fisher, 2021).

Tumor thickness and depth described using the Breslow scale, presence/absence of ulceration, mitotic rate, presence/absence of microsatellites/transit lesions, the burden of lymph node disease, and presence/absence of distant metastases are the main clinical characteristics to assign a staging and/or recurrence risk assessment (Shelley *et al.,* 2019; Martínez-Piva *et al.,* 2021; Jenkins; Fisher, 2021).

The detection of thin melanomas (< 1 mm of tumor thickness) reflects cases in which the diagnosis was made early. The incidence of thick melanomas (with Breslow thickness ≥ 2 mm) determines a later diagnosis, and as the index increases, the worse the prognosis. In developed countries, most CM is diagnosed with thickness < 1 mm and the proportion of all primary tumors that will metastasize is 10 to 15% (Schadendorf *et al.,* 2015; Shelley *et al.,* 2019; Martínez-Piva *et al.,* 2021).

The AJCC melanoma classification was updated to the eighth edition in 2027. Histopathologically, mitotic counts are no longer relevant for staging, and tumor depth is now rounded to tenths of a millimeter. Patient survival prediction, particularly in low-risk stages of melanoma, has been improved. Different histological subtypes of melanoma can also be distinguished, including superficial spreading, nodular, acral lentiginous, and lentigo malignant melanoma (Schadendorf *et al.,* 2015; Schadendorf *et al.,* 2018, Elder *et al.,* 2020).

6.2 DIFFERENTIAL DIAGNOSIS

Due to the various types of CM, there is a similarity with several other skin lesions depending on the location and characteristics of the lesion (Abbas; Miller; Bhawan, 2014). SEM has similar characteristics to seborrheic keratosis and basal cell carcinoma (BCC) and the atypical nevus or common benign nevus. NM clinically resembles blue nevi, BCC, dermatofibromas, and variegated papules. MLM has an analogy with lesions caused by sun exposure, such as pigmented actinic keratosis and solar lentigo. The differential diagnosis of ALM is mainly made with acral nevi (Mitra; Bishop; Guadagnolo, 2020; Raigani; Cohen; Boland, 2017; Falk Delgado; Zommorodi;

Falk Delgado, 2019). In addition, the lesions can also be confused with other tumors, Bowen's disease, corneal hemorrhage, and even some forms of tattoos (Falk Delgado; Zommorodi; Falk Delgado, 2019).

6.3 TREATMENT

Tumor staging using the TNM system and classification of tumor thickness by Breslow depth is mandatory in the context of melanoma-type cancer since certain tumor types and the presence or absence of distant metastases determine different approaches to therapy. In the initial presentation, most of the localized tumors are classified in stages I and II, by the TNM system (Abbas; Miller; Bhawan, 2014; Jenkins; Fisher, 2021).

In the early stages, CM can be successfully treated with surgery alone, with high survival rates. However, after metastasis develops, survival rates drop significantly. Early diagnosis is essential to ensure a better prognosis for patients (Abbas; Miller; Bhawan, 2014; Mitra; Bishop; Guadagnolo, 2020).

6.4 NON-PHARMACOLOGICAL TREATMENT

In cases of lesion suggestive of CM, an excisional skin biopsy is indicated to obtain complete histological information, such as mitosis rate, ulceration, and Breslow depth, which influence preoperative staging and provide information for the need for biopsy of the sentinel lymph node (Abbas; Miller; Bhawan, 2014). The indicated follow-up is wide local excision, with safety margins. Therapeutic lymphadenectomy is recommended in cases of patients with radiologically or clinically positive lymph nodes (Abbas; Miller; Bhawan, 2014; Raigani; Cohen; Boland, 2017; Falk Delgado; Zommorodi; Falk Delgado, 2019). A surgical excision margin of 1-2 cm is indicated for invasive melanoma, depending on tumor thickness. Sentinel lymph node biopsy may be considered in cases of tumor thickness of 0.8 to 1.0 mm or Breslow less than 0.8 mm with ulceration (Falk Delgado; Zommorodi; Falk Delgado ,2019).

Previously, the therapy of choice for melanoma patients with nodal disease involved complete lymph node dissection plus adjuvant radiotherapy for high-risk features (Abbas; Miller; Bhawan, 2014; Mitra; Bishop; Guadagnolo, 2020). However, with the use of new, effective, and often well-tolerated systemic therapies, such as immune checkpoint inhibitors and targeted inhibitors of the MAPK pathway,

radiotherapy has fallen into disuse, due to a lack of evidence proving its efficacy and superiority over other modalities of its use (Mitra; Bishop; Guadagnolo, 2020; Takahashi; Nagasawa, 2020).

On the other hand, our research group has investigated melanin photosensitization in tumors with a focus on the generation of reactive oxygen species (ROS) and tumor cell death (Fig 1). Photobiomodulation upon green light (532 nm) has opened a window of preclinical investigation for the treatment of melanoma.

6.5 PHARMACOLOGICAL TREATMENT

New targeted and immunologic therapies have been approved for treating melanoma. Among the targeted ones, are Vemurafenib, a BRAF inhibitor, Cobimetinib, a MEK inhibitor, and the combination of Dabrafenib + trametinib, which act as BRAF and MEK inhibitors. Other important associations to be highlighted are Vemurafenib + Cobimetinib, and also Encorafenib + Binimetinib, which have a joint inhibitory action of BRAF and MEK (Abbas; Miller; Bhawan, 2014).

Regarding immunobiological, the main mechanism of action comes from the inhibition of immunological checkpoints. Immunotherapy acts on the activation and regulation of the immune system, mainly by inhibiting PD-1 and cytotoxic T lymphocyte antigen 4 (CTLA-4) (Zeng *et al.,* 2021). Among the immunobiological, emphasis should be given to Ipilimumab, a CTLA-4 inhibitor, Pembrolizumab, and Nivolumab, anti-PD-1. Furthermore, the association between Ipilimumab and Nivolumab may be indicated in some cases (Abbas; Miller; Bhawan, 2014).

In metastatic melanoma, surgical excision of the lesion has low success rates, so adjuvant therapy with immunobiological that acts by blocking PD-1 and/or CTLA-4 is indicated (Raigani; Cohen; Boland, 2017). Adjuvant drug therapy is relatively indicated for patients with stage III and IV melanoma after complete surgical resection (Raigani; Cohen; Boland, 2017).

7 PROGNOSIS

Tumor thickness (Breslow), mitotic rate, and ulceration have been considered the most important prognostic indicators among the histopathological criteria. However, there are cases of thin primary melanomas that have developed metastases despite complete excision. Given this, an accurate assessment of melanoma

progression is critical, and the development of molecular biomarkers that identify high-risk melanoma in its early stages is necessary (Jenkins; Fisher, 2021; Raigani; Cohen; Boland, 2017).

7.1 PREVENTION

The prevention of CM is based on the modification of risk factors associated with the development of the disease and can be divided into primary and secondary (Alberg, *et al.,* 2020; Tripp *et al*., 2016). In primary prevention, limiting exposure to ultraviolet (UVR) and visible light (VL) is the main protective factor to be highlighted, with the use of appropriate protective clothing, the use of sunscreen with a high protection factor, and mainly, avoiding sun exposure between 10 (am) - 16 (pm) (Falk Delgado; Zommorodi; Falk Delgado, 2019). Also, limiting indoor tanning sessions is of great importance, especially for teenagers and young adults. As for secondary prevention, medical screening using dermoscopy in suspicious lesions and the individual assessment of skin lesions are some of the main examples (Linos; Katz; Colditz, 2016).

7.2 PSYCHOSOCIAL ASPECTS

In addition to clinical features, melanoma-like skin cancer may be associated with symptoms related to Generalized Anxiety Disorder and Major Depressive Episodes, such as sadness, anhedonia, weight loss, insomnia or hypersomnia, agitation, daily fatigue or loss of energy, feelings of uselessness, difficulty in reasoning and concentration, thoughts, plans or attempts at self-extermination. Anxiety is frequent, being seen in almost all melanoma patients. It is a feeling of anguish caused by the anticipation of an undefined tragedy or danger, not grounded in logic (Vojvodic *et al.,* 2019).

In a longitudinal study of 675 patients with a recent diagnosis of melanoma, they found that 14% of participants had melanoma-related anxiety or depression and 20% were affected by depressive or anxious symptoms, these unrelated to the diagnosis (Beesley *et al.,* 2020). Of the 272 participants who reported symptoms related to other causes, 34% were seeing a psychologist or psychiatrist or taking antidepressant medication (Beesley *et al.,* 2020).

8 CONCLUSION

The incidence of different types of melanomas has increased around the world and extrinsic factors (such as solar radiation) cause DNA damage, mutations and induction of melanomas. Therefore, it is important to use sunscreen to prevent melanoma cancer. Surgeries have been the first treatment option, but chemotherapy/radiotherapy, blocking tumor signaling pathways by monoclonal antibodies have been alternative treatments for melanomas.

ACKNOWLEDGMENT

Espírito Santo Research and Innovation Support Foundation (FAPES, grant # 03/2021) and Centro Universitário do Espírito Santo (UNESC, PIBICT 2023).

INTEREST CONFLICTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. All authors read and approved the final manuscript.

ETHICS APPROVAL

All articles cited in this review produced by our research group were approved by the animal ethics committee (CEUA-UNESC - Brazil). Also, all authors do not present ethical conflicts.

REFERENCES

ABBAS, O., MILLER, D. D., & BHAWAN, J. Cutaneous malignant melanoma: update on diagnostic and prognostic biomarkers. **The American Journal of Dermatopathology**, v.36, n.5, p.363–379, 2014.

ALBERG, A. J. *et al.* American society of clinical oncology policy statement on skin cancer prevention. **JCO Oncology Practice**, v.16, n.8, p. 490–499, 2020.

ASSIS, L. V, M., *et al*. How does the skin sense sun light? An integrative view of light sensing molecules. **Journal of Photochemistry and Photobiology C: Photochemistry Reviews**, v. 47, p. 1-17, 2021.

BEESLEY, V. L. *et al.* Anxiety and depression after diagnosis of high-risk primary cutaneous melanoma: a 4-year longitudinal study. **Journal of Cancer Survivorship: Research and Practice**, v.14, n.5, p.712–719, 2020.

CARR, S., SMITH, C., WERNBERG, J. Epidemiology and Risk Factors of Melanoma. **The Surgical Clinics of North America**, v. 100, n. 1, p. 1–12, 2020.

CHEN, Z.; LI, W.; HU, X.; LIU, M. Irradiance plays a significant role in photobio modulation of B16F10 melanoma cells by increasing reactive oxygen species and inhibiting mitochondrial function. **Biomedical Optics Express**, v. 11, n. 1, p. 27–39, 2019.

CHEN, Z., *et al*. Comparative transcriptome analysis of gene expression patterns on B16F10 melanoma cells under Photobiomodulation of different light modes. **Journal of Photochemistry and Photobiology. B, Biology**, v. 216, 112127, 2021.

DAVIS, L. E., SHALIN, S. C., & TACKETT, A. J. Current state of melanoma diagnosis and treatment. **Cancer Biology and Therapy**, v. 20 n. 11, p. 1366–1379, 2019.

DICAPRIO, M. R., ABOUSAYED, M. M., & KAMBAM, M. Orthopaedic Manifestations of Melanoma and Their Management. **The Journal of the American Academy of Orthopaedic Surgeons**, v.28, n 13, p. e540–e549, 2020.

DIMITRIOU, F., *et al.* The World of melanoma: epidemiologic, genetic, and anatomic differences of melanoma across the globe. **Current Oncology Reports**, v. 20, n. 11, p. 1-9, 2018.

DZWIERZYNSKI, W. W. Melanoma risk factors and prevention. **Clinics in Plastic Surgery**, n. 48, v. 4, p. 543–550, 2021.

EDDY, K., SHAH, R., CHEN, S. Decoding Melanoma Development and Progression: Identification of Therapeutic Vulnerabilities. **Frontiers in oncology**, v. 10, 626129, 2021.

ELDER, D. E. *et al*. The 2018 World health organization classification of cutaneous, mucosal, and uveal melanoma: detailed analysis of 9 distinct subtypes defined by their evolutionary pathway. **Archives of Pathology & Laboratory Medicine**, v.144, n.4, p.500–522, 2020.

FALK DELGADO, A., ZOMMORODI, S., & FALK DELGADO, A. Sentinel Lymph Node Biopsy and Complete Lymph Node Dissection for Melanoma. **Current oncology reports**, v.21, n.6, p, 54, 2019.

GESBERT, F.; LARUE, L. Cutaneous melanoma: from rationalized models to patients care. **Medecine sciences: M/S**, v. 34, n. 5, p. 407–416, 2018.

HARTMAN, R. I.; LIN, J. Y. Cutaneous Melanoma-A Review in Detection, Staging, and Management. **Hematology/oncology Clinics of North America**, v. 33 n. 1, p. 25–38, 2019.

HAUSSMANN, P.B. *et al.* Melanin photosensitization by green light reduces melanoma tumor size. **Journal of Photochemistry and Photobiology**, v. 9, p. 1-9, 2022.

JENKINS, R. W., & FISHER, D. E. Treatment of Advanced Melanoma in 2020 and Beyond. **The Journal of Investigative Dermatology**, v.141, n.1, p.23–31, 2021.

KIBBI, N.; KLUGER, H.; CHOI, J. N. Melanoma: Clinical Presentations. **Cancer Treatment and Research**, v.167, p.107–129, 2016.

LEONARDI, G. C. *et al.* Cutaneous melanoma: From pathogenesis to therapy (Review). **International Journal of Oncology**, v. 52, n. 4, p. 1071–1080, 2018. doi: 10.3892/ijo.2018.4287

LINOS, E., KATZ, K. A., & COLDITZ, G. A. Skin Cancer-The Importance of Prevention. **JAMA Internal Medicine**, v.176, n.10, p.1435–1436, 2016.

MAHMOUD, B. H., *et al*. Impact of long-wavelength UVA and visible light on melano competent skin. **The Journal of investigative Dermatology**, v. 130, n. 8, p. 2092–2097, 2010.

MARTÍNEZ-PIVA, M. M. *et al*. Dermoscopy as a Tool for Estimating Breslow Thickness in Melanoma. **Actas Dermo-sifiliograficas**, v.112, n. 5, p. 434–440, 2021.

MEYSKENS, F. L.; FARMER JR, P. J.; ANTON-CULVER, H. Etiologic pathogenesis of melanoma: a unifying hypothesis for the missing attributable risk. **Clinical Cancer Research: an Official Journal of the American Association for Cancer Research**, v. 10, n. 8, p. 2581–2583, 2004.

MITRA, D., BISHOP, A., & GUADAGNOLO, B. A. Adjuvant Nodal Radiation Therapy for Melanoma in the Era of Immunotherapy. **International Journal of Radiation Oncology, Biology, Physics**, v.108, n.1, p.164–169, 2020.

NADER MARTA, G., *et al.* Trends in Melanoma Mortality in Brazil: A Registry-Based Study. **JCO Global Oncology**, v. 6, p. 1766–1771. DOI: 10.1200/GO.20.00426

RAIGANI, S., COHEN, S., & BOLAND, G. M. The Role of Surgery for Melanoma in an Era of Effective Systemic Therapy. **Current Oncology Reports**, v.19, n.3, p.17, 2017.

SAGINALA, K., *et al.* Epidemiology of Melanoma. **Medical Sciences**, v. 9, n. 4, 63, 2021.

SCHADENDORF, D., *et al.* Melanoma. **Nature reviews**, v. 1, n. 15003, 2015.

SCHADENDORF, D. *et al.* Melanoma. **The Lancet**, v. 392, n. 10151, p. 971–984, 2018.

SETLOW, R. B., GRIST, E., THOMPSON, K., WOODHEAD, A. D. Wavelengths effective in induction of malignant melanoma. **Proceedings of the National Academy of Sciences of the United States of America**, v. 90, n. 14, p. 6666–6670, 1993.

SHELLEY, A. J.; DOUBOVA, M.; LANGLEY, A. R.; BEECKER, J. Timing of Clinical Detection and Biopsy in Invasive Melanoma and Breslow Depth: A Chart Review. **Journal of Cutaneous Medicine and Surgery**, v. 23, n. 2, p. 229–230, 2019.

SITUM, M., BULJAN, M., KOLIĆ, M., & VUČIĆ, M. Melanoma--clinical, dermatoscopical, and histopathological morphological characteristics. **Acta Dermato Venerologica Croatica: ADC**, v. 22 n. 1, p. 1–12, 2014.

STRASHILOY, S.; YORDANOV, A. Aetiology and pathogenesis of cutaneous melanoma: current concepts and advances. **International Journal of Molecular Sciences**, n. 22, v. 12, 6395, 2021.

SWETTER, S. M., *et al.* Guidelines of care for the management of primary cutaneous melanoma. **Journal of the American Academy of Dermatology**, v. 80, n. 1, p. 208–250, 2019.

TAKAHASHI, J.; NAGASAWA, S. Immunostimulatory effects of radiotherapy for local and systemic control of melanoma: a review. **International Journal of Molecular Sciences**, v. 21, n. 23, p. 9324, 2020.

TONOLLI, P.N., BAPTISTA, M.S., CHIARELLI-NETO, O. Melanin, lipofuscin and the effects of visible light in the skin. **Journal of Photochemistry and Photobiology**, v. 7, p. 1-5, 2021.

TONOLLI, P.N*. et al.* Lipofuscin in keratinocytes: Production, properties, and consequences of the photosensitization with visible light. **Free Radical Biology and Medicine,** v. 160, p. 277-292, 2020.

TRIPP, M. K. *et al*. State of the science on prevention and screening to reduce melanoma incidence and mortality: The time is now. **CA: A Cancer Journal for Clinicians**, v. 66, n.6, p.460–480, 2016.

VOJVODIC, A., *et al.* Psychological Impact of Melanoma, How to Detect, Support and Help. **Open Access Macedonian Journal of Medical Sciences,** v.7, n.18, p.3043–3045, 2019.

ZASTROW, L. *et al.* Detection and Identification of Free Radicals Generated by UV and Visible Light in Ex Vivo Human Skin. **International Journal of Cosmetic Science**, v. 31, n. 5, p. 402-404, 2009.

ZENG, H., LIU, F., ZHOU, H., & ZENG, C. Individualized Treatment Strategy for Cutaneous Melanoma: Where Are We Now and Where Are We Going? **Frontiers in oncology**, v. 11, p.775100, 2021.