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Review

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Cutaneous Malignant Melanoma: A Review of Early Diagnosis and Management

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Abstract

Cutaneous melanoma (CM) is a malignant tumor formed from pigment-producing cells called melanocytes. It is one of the most aggressive and fatal forms of skin malignancy. In the last decades, CM's incidence has gradually risen, with 351,880 new cases in 2015. Since the 1960s, its incidence has increased steadily, in 2019, with approximately 96,000 new cases. A greater understanding of early diagnosis and management of CM is urgently needed because of the high mortality rates due to metastatic melanoma. Timely detection of melanoma is crucial for successful treatment, but diagnosis with histopathology may also pose a significant challenge to this objective. Early diagnosis and management are essential and contribute to better survival rates of the patient. To better control this malignancy, such information is expected to be particularly useful in the early detection of possible metastatic lesions and the development of new therapeutic approaches. This article reviews the available information on the early diagnosis and management of CM and discusses such information's potential in facilitating the future prospective.

Keywords: Cutaneous melanoma; Malignant melanoma; Early diagnosis; Management; Mortality; Tumor

Introduction

One of the most aggressive cancers seen in humans is cutaneous melanoma (CM), a tumor formed from melanocytes. Melanocytes originate from the neural crest located along with the choroidal layer of the eye, mucosal surfaces and meninges in the hair follicles and basal epidermis [1]. The incidence of CM continues to rise globally, becoming one of the most common cancers seen in young adults. CM accounts for 3% of all skin cancers, but 65% of skin cancer deaths are caused. However, in patients with incipient melanoma, early detection and appropriate treatment of the tumor results in a cure rate of over 90% [2]. CM can occur anywhere on the skin's surface, but its position in a specific section of the body seems to be affected by the sex and age of the patient. In the neck and head region, about 20% of all tumors have a poorer prognosis than CM at other locations [3].

The development of CM is the product of the interaction between host and environmental factors, as with all cancers [4]. Ultraviolet radiation (UV) is the most widely recognized environmental risk factor for CM growth from different sources such as sun and tanning beds. Individuals with lighter skin and hair tone have low melanin levels and are at increased risk of melanoma development. Additionally, the sunburns accumulated since adolescence in individuals are also at high risk. Moreover, the quantity of moles on an individual's body expands the risk of CM [5]. A positive family history of CM is also at an increased risk due to sun exposure habits and/or inherited genetic mutations. *CDKN2A* gene on chromosome 9 in a mutated form in individuals is believed to be at high risk for melanoma development. Studies reported that 70% of CM cells had affected the *CDKN2A* gene due to somatic mutations. Under normal circumstances, in cancer suppression, this gene's product plays an important role; this controls the growth of tumor cells; but if this gene mutates, the action of the tumor suppressor is lost and cancer cells can develop uncontrollably [5]. The survival of patients with malignant melanoma is closely associated with early detection. There is no risk of death for melanoma limited to the epidermis (*in situ*), and there is little chance of metastatic spread from a thin melanoma lesion. Although several factors influence survival, in some studies, tumor thickness is the most important factor [6]. With fundamental behavioral changes, melanoma can be practically preventable. Therefore, even with the emergence of modern methods for the treatment of advanced diseases, in this new century, the focus on prevention in professional and public education and the early identification and management of this tumor is becoming increasingly important. The current review discusses the advancement in approaches towards diagnosis, staging, specific biomarkers associated with melanoma and management strategies with these backgrounds.

Epidemiology

CM causes mortality in more than 90% of skin diseases. In a report by the Canadian Cancer Society, about 1,250 Canadians died in 2017 and 7,200 individuals were diagnosed with melanoma. Worldwide, CM has continued to show rates of rising

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Table 1. Classification of Cutaneous Melanoma According to TNM

Melanoma stage	Description
0 (*in situ*)	Only the outer or top layer of skin cancer cells.
IA	The tumor is > 0.8 mm but < 1 mm with possible ulceration or without ulceration; the tumor is 0.8 mm thick or less.
IB	The tumor, without ulceration, is > 1 mm but < 2 mm thick.
IIA	The tumor is > 2 mm thick but < 4 mm thick without ulceration or with ulceration, the tumor is > 1 mm thick but < 2 mm thick.
IIB	The tumor is > 2 mm thick with ulceration but < 4 mm thick, or the tumor is > 4 mm thick without ulceration.
IIC	With ulceration, the tumor is more than 4 mm thick.
III	The spread of cancer to one or more lymph nodes close to the initial disease site.
IV	Cancer, also called metastatic melanoma, has spread to other body areas, such as the liver and lungs.

TNM: tumor-node-metastases.

incidence. It is currently predicted that one in 34 males and one in 53 women will be diagnosed with melanoma during their lives [5]. The overall frequency of CM has been expanding yearly at a quicker rate than other cancer types. It is ranked the 15th among the most common cancers worldwide with a growing incidence. The incidence rate of CM differs significantly among countries, and this variation in incidences is attributed to variations in sunlight exposure and differences in the phenotype of skin [5]. The three countries with the highest occurrence rate of CM are European countries, such as Denmark, Sweden and the Netherlands; and the incidence of CM is positively associated with the age group of above 75 years [7, 8].

Staging, Subtypes and Pathogenesis

According to the classification of tumor-node-metastases (TNM), the five stages of CM (0 - IV) were shown in Table 1 [5]. The five disease stages of CM were defined using the following terms: early, locoregional and metastatic. Cancer that has persisted in the primary site and within the skin is called early stages (stages 0 - IIC). Cancer has spread to the skin or lymph nodes (LNs) or lymph vessel areas refer to a locoregional. The cancer is in stage IIII if such a spread has occurred. Cancer that has spread to other body parts and other organs is called "metastatic". In such cases, stage IV of the disease will be considered. Patients diagnosed through biopsy with shallow lesions (4.0 mm) are correlated with elevated risk for the metastatic stage. If metastasis occurs, patients are given a diagnosis of stage III or IV. The LNs are the most probable noncontiguous regions where CM spreads. Sentinel lymph nodes (SLNs) are specifically crucial because they are the first nodes identified in the area where the primary CM is located [5, 9].

A good indicator of recurrence and survival in patients with CM is the absence or presence of CM cells in the SLN. The common areas for CM metastasis are the subcutaneous tissues and skin. With 10% of patients developing pulmonary metastasis in the disease, lungs and pleura are the first most common visceral metastasis sites in CM. Another such place for the metastatic spread in CM cases is the brain [5, 9].

In 10-20% of cases with metastatic CMM, hepatic metastases are found. Skeletal metastasis is uncommonly diagnosed compared to other sites but is still diagnosed in 11-17% of CM cases. The gastrointestinal spread is diagnosed in later-stage disease, close to skeletal metastasis, with the small intestine being the frequent site. In contrast with men whose CM is found on the trunk, head or neck, women are most commonly diagnosed with CM on an extremity, which is the crucial explanation for improved overall prognosis. Increased age is associated with a more unsatisfactory outcome. An excellent prognostic factor is the degree of LN involvement, i.e., a favorable prognosis is inversely proportional to an increased number of nodes and metastasis. A higher mortality rate than spread confined to different locations is often associated with pulmonary, hepatic and brain metastasis. It is necessary to identify the exact location of metastasis, as it determines options for treatment [5].

Amelanotic, desmoplastic, acral lentiginous, nodular, lentigo maligna and superficial spreading are the subtypes of melanoma [10]. The superficial spreading subtype is most commonly found in approximately 70% of melanomas. The lentigo maligna subtype is less commonly diagnosed; it progresses slowly and seems to be found in areas exposed to sunlight (face, head). The absence of a radial growth phase, robust vertical invasion, and variable presentation define nodular melanomas. In cases with darker skin tone, acral lentiginous melanomas are also associated and are usually found in the subungual spaces, hands and soles. In elderly patients, desmoplastic melanomas are sporadic and are usually observed. Amelanotic melanomas, the most complex diagnostic subtype, have no pigmentation and are very rarely diagnosed [9]. The response rate to treatment decreases to approximately 5-20% after melanoma spreads or metastasizes from its origin into other cutaneous or subcutaneous tissues, and the 10-year survival rate is only around 10% [11]. It was challenging to treat metastatic melanoma, showing low cure and survival rates following surgical resection and radiation therapy. Cancer cells have distinctive molecular properties at the cellular level that allow for apoptosis avoidance, infinite growth potential without the need for growth factors, angiogenesis and metastasis. Identifying the specific molecular changes that allow the growth and survival advantage of melanoma cells over others can enable more successful targeted therapies to be developed to improve the prognosis of melanoma patients [12].

Early Diagnosis and Its Current Trends

For the effectiveness of treatment, early detection of lesions is essential. Diagnosis is considered early when, during the stage of radial development, the time in which the neoplastic cells are confined to the epidermis is detected. This is important for lower morbidity-related treatment, a greater chance of cure, and mortality reduction [13]. The melanoma clinical diagnosis is based on morphological criteria analysis and is thus subjective and can be challenging for dermatologists and general practitioners. It is performed by visual examination, aided by lesion dermoscopy. A diagnostic excision is recommended when a lesion is clinically suspected of having melanoma. Skin biopsy remains the initial step to set up an authoritative finding of CM, though different molecular and imaging techniques are also known. For a lesion that is clinically indicative of CM, a complete excision biopsy should be performed, including the entire lesion with negative margins; notice that the lesion is not histologically cut around the deep margin [14-16]. This can be accomplished using a restricted fringe edge of 1 - 3 mm around the skin lesion concerned [14]. A partial biopsy can wrongly stage CM, which may affect the planning of treatment [14, 17-19]. Previously the diagnosis of skin cancer was done by bleeding ulceration, dermoscopy, computer analysis *in vivo* diagnosis procedures etc. Recently, there has been great interest in developing artificial intelligence (AI)-enabled computer-aided diagnostics solutions for the diagnosis of skin cancer [20, 21].

A SLN biopsy is routinely performed in cases having tumors more than 1 mm thickness. Excisional biopsy in various forms such as elliptical, punch, and saucerization is performed; amongst which saucerization being the most common as it is more convenient and time-saving. Saucerization with a superficial shave biopsy should not be confused that is only used when suspected of invasive melanoma. Superficial shave biopsies might misjudge Breslow thickness, ultimately mislabeling CM's stage and are thus not encouraged for diagnosis of CM [19, 22]. Complete excisional biopsy is difficult to perform in challenging areas, including acral/face surfaces. Under such circumstances, shave, punch or elliptical/fusiform incisional biopsy should be performed [23].

Incisional/partial biopsies have not yet been shown to impact patient outcomes adversely due to the transfer of melanoma cells into blood vessels or cutaneous lymphatics. Incisional vs. excisional biopsy types rarely affect disease recurrence rates or SLN, nor does it result in metastasis [18, 24]. For a suspicious nail lesion (e.g., diffuse pigmentation, melanonychia striata, or amelanotic changes), after the nail matrix is sampled, a biopsy is carried out. Since nail anatomy is complex and melanoma occurs in the nail matrix, professional practitioners better evaluate and sample suspected nail lesions. Prebiopsy photos are of significant help to pathologic/clinical connection and help to forestall medical procedure at an incorrect site if further therapy is required. Due to availability, noninvasive approaches such as optical coherence tomography, gene expression analysis, electrical impedance spectroscopy and reflectance confocal microscopy are more useful [25-27]. To further label melanocytic lesions as malignant or benign, noninvasive genomic methods such as adhesive patch biopsy are also used to predict the need for biopsy testing. The selection of these noninvasive techniques ultimately depends upon clinical utility, the cost versus advantage, and contending methodologies [19]. Several principles and mechanisms are involved in the non-biopsy diagnosis of skin cancer such as optical based, thermography, photodynamic based, sonography and electrical bioimpedance. The optical based mechanism involved, the light is passed inside the tissues of the skin as the light is scattered into the tissues. The change in the property of the reflected light is used for diagnosis. The photodynamic based mechanism involved to detect the presence of tumor cells, a photosensitive marker is introduced into the particular area. The diagnosis of skin cancer performed using sound waves is called sonography. Thermal imaging is based on the phenomenon of electromagnetic radiation being produced by any object with a temperature above absolute zero. Photodynamic based mechanism used to detect the presence of tumor cells into the particular area [20, 28].

Despite the significance of early detection to prevent melanoma mortality, little is understood about how patients with the disease will be detected [29]. The probability of melanoma death is causally linked to Breslow's primary lesion thickness, and there is a strong association between the thickness of the tumor and the delay in reporting the lesion as suspicious [30]. Therefore, in predicting the outcome, it is vital to minimize the diagnostic delay, considering the patient's identification and the search for assistance and the doctor's diagnosis and proper evaluation. There are multifactorial reasons for delays in diagnosing patients with signs and symptoms of melanoma, including a lack of regular skin examination by patients and physicians, and a lack of population awareness of the disease. A study by Xavier et al [31] (2016) reported that the patient's critical delay factor was connected. Although there is some difference in other studies, our average delay of 5 months was comparable to patient-related delays of around 2 to 9.8 months previously published [30, 32, 33]. Although the study by Richard et al [34], recorded an average delay of 2 months, the author states that this period is awfully long for this population, as at this time several campaigns were carried out in France. Several studies reported that the patient's delay was demonstrated in Table 2 [30-32, 35-40].

Clinical Characteristics

Patients history

During regular skin examination, melanoma lesions are usually detected unintentionally [41]. Occasionally, persistent scratching, bleeding, or crusting of a pigmented lesion may alert patients to the presence of a related nodule. Nevertheless, most melanomas are symptomless and can only induce those mentioned above local inflammatory symptoms after growth progression has occurred [42].

Once a diagnosis is suspected, the past should include questions related to locations of possible metastasis. New-onset back pain, changes in bowel habits, dyspnea, shortness of

Table 2. Various Studies Reported the Patient's Delay of Diagnosis

		Mean delay, month	< 1 month	1 - 3 month	3 - 6 month	6 - 12 month	> 12 month	No delay
Basnet et al, 2018 [35]	National Cancer Data Base (NCDB) (n = 313,329)	-	59.05%	31.89%	-	9.05%	-	-
Xavier et al, 2016 [31]	Brazil (n = 211)	5	16.6%, (n = 35)	17.1%, (n = 36)	11.8%, (n = 25)	8.1%, (n = 17)	18%, (n = 38)	28.4%, (n = 60)
Tyler et al, 2005 [32]	Canada (n = 176)	4.7	50%, (n = 88)		19.3%, (n = 34)		51.1%, (n = 9)	19.9%, (n = 35)
Betti et al, 2003 [30]	Italy (n = 216)	6.1	-	-	-	-	-	26.6%, (n = 57)
Richarde et al, 1999 [36]	France (n = 590)	2	23.10%, (n = 136)	17.60%, (n = 104)	13.40%, (n = 79)	8.50%, (n = 50)	8.30%, (n = 49)	29.2%, (n = 172)
Rampen et al, 1989 [37]	The Netherlands (n = 284)	-	6.7%, (n = 19)	16.9%, (n = 48)	15.8%, (n = 45)	16.9%, (n = 48)	33.6%, (n = 95)	10.3%, (n = 29)
Doherty er al, 1986 [38]	Scotland (n = 25)	-	16%, (n = 20)		50.4%, (n = 55)		33.6%, (n = 42)	
Krige et al, 1991 [39]	South Africa (n = 250)	9.8	16.8%, (n = 42)	18%, (n = 45)	22%, (n = 55)	15.2%, (n = 38)	16.4%, (n = 41)	11.6%, (n = 29)
Schmid-Wendtner et al, 2002 [40]	Germany (n = 233)	-	15.5%, (n = 36)	16.7%, (n = 39)	14.6%, (n = 34)	11.6%, (n = 27)	29.20%, (n = 68)	12.4%, (n = 29)

breath, hemoptysis, coughing, vision changes, headaches, seizures and other systemic symptoms (weight loss, night sweats, chills, fever) can be possible indications of metastatic spread [43].

Histologic confirmation

Routine histologic examination by the receiving department of pathology requires diagnostic confirmation [9]. In an attempt to distinguish benign from malignant melanoma diseases, microscopic observations, including amplified cellularity, cytologic atypia, and it is essential to note the number of dermal mitotic figures.

Formal reporting of Breslow thickness (mm), deep margin status, peripheral margin status, dermal mitotic rate, histologic subtype and the absence and presence of histologic ulceration, pure desmoplasia, neurotropism, vertical growth phase, angiolymphatic invasion, cellular regression, tumor-infiltrating lymphocytes and microsatellitosis is recommended by established guidelines [43].

Disease Types and Prognostic Factors

Amelanotic, desmoplastic, acral lentiginous, nodular, lentigo maligna, superficial spreading are the main histologic subtypes of melanoma [10]. Stage 0 is known as *in situ* melanoma, which occurs when microscopically observed tumor cells have not reached the epidermis [44]. The most common form is the superficial spreading subtype and occurs from an existing nevus, comprising approximately 70% of melanomas recorded. The subtype of lentigo maligna is less prevalent, usually shows gradual development, and mostly occurs in sun-exposed areas. In patients with darker skin pigmentation, Acral lentiginous melanomas have a higher occurrence and occur commonly in subungual spaces, hands and soles. In terms of diagnosis, amelanotic melanomas are the most complicated subtype, have a distinctive pigmentation absence and are considered uncommon [9].

Diagnostic Tools Used for the Early Detection of CM

The diagnostic tools play a significant role in the early identification of the CM. Several diagnostics tools are used for the early detection of CM were listed in Table 3. Category I instruments including total body photography, sequential digital dermoscopy and dermoscopy are available for patient screening in the everyday clinical routine, meaning that several (if not all) lesions may be checked for a reasonable period. Diagnosis has remained a significant challenge in the face of advancements in diagnostic aids such as dermoscopy, and better methods of precisely diagnosing melanoma are required. Studies have shown that the precise diagnosis of melanoma is challenging even for expert dermoscopists, with one study showing 71% biopsy sensitivity for melanomas below 6 mm, especially in small diameter lesions [45].

Table 3. Categories of Noninvasive Detectors for Melanoma

Category	Explanation	Devices
Category-I devices	For large-scale screening purposes	Dermoscopy Sequential digital dermoscopy Total body photography
Category-II devices	Evaluation of a few preselected, atypical lesions	Computer-aided multispectral digital analysis Electrical impedance spectroscopy Raman spectroscopy
Category-III devices	For evaluations by qualified experts of preselected lesions in specialist clinics	Reflectance confocal microscopy Multiphoton tomography
Category-IV devices	Experimental development stage, appropriate for the evaluation of a few preselected lesions	Stepwise two-photon-laser spectroscopy Quantitative dynamic infrared imaging

Other Technologies

Thermal imaging

Compared to normal healthy tissue, the melanoma lesions have more significant metabolic activity, like many other cancers. To evaluate lesions with infrared imaging, using dynamic thermal imaging, this property could be exploited. Early results indicate that melanoma and healthy tissue have detectable temperature differences.

Due to the skin must be cooled to emphasize temperature variations, this approach is presently technically tricky as the sophisticated motion control is important when capturing a thermal image to compensate for the patient's movement [46].

Tissue elastography

Real-time tissue elastography is an early research technique focused on the premise that milder, normal tissue deforms more quickly than more rigid, malignant tissue. By applying light pressure manually to an ultrasonic transducer, the lesions are measured with simultaneous ultrasonic imaging [46].

Fiber diffraction

In all mammals, irrespective of age or species, the alpha keratins in hair and nail proteins create a distinctive X-ray fiber diffraction pattern. Like melanoma, some cancers have been shown to cause observable changes in the macromolecules' molecular patterns in nails, skin and hair in recent studies [46].

Noninvasive genomic detection

An adhesive tape put on suspected lesions to noninvasively sample cells from the stratum corneum is used to collect epidermal genetic information. Using real-time polymerase chain reaction (PCR), cell-isolated RNA is amplified and then hybridized with U133 plus 2.0 GeneChip human genome Affymetrix [47].

Biomarkers Associated With CM

The recognizable proof of biomarkers that can anticipate persistent advantages towards therapy is a focal objective of disease research. *B-RAF* proto-oncogene (BRAF) mutations are a standard disease marker in response to RAF inhibitors. After a variable timeframe, these cases develop disease progression and show primary resistance to inhibitors of BRAF. Many researchers have discussed the acquired genetic mutations' role, which affects the signaling pathways and induces resistance to both targeted therapy and chemotherapy in CM [48]. Currently, detecting the mechanisms responsible

for BRAF and mitogen-activated protein kinase (MEK) inhibitor resistance is not a concern for clinicians; however, it would be more useful to establish noninvasive strategies for determining a tumor's mutation status [49]. A newly developed liquid biopsy helps identify circulating cell-free DNA (cfDNA) derived from melanoma in plasma and serves as a useful blood-based biomarker to detect melanoma's status. Several studies indicate that BRAF kinase inhibitors' response is predicted by *BRAF*-mutated melanoma detection by cfDNA before initiation of treatment. Progression-free survival and lower response rate were found to be correlated with cases with elevated basal cfDNA levels [49, 50]. cfDNA is a predictive tumor burden biomarker, and a rise in cfDNA levels during treatment indicates disease progression and resistance to inhibitor acquisition. Outstandingly, cfDNA helps to mutation detection responsible for resistance to targeted BRAF therapies and can direct us to follow-up treatment strategies in the future [49, 50]. The low overall response rate (ORR) has immune checkpoint inhibitors. It was found that programmed cell death protein 1 (PD1) immunohistochemistry assays done on tumor specimens are not markers of choice to determine PD1 inhibitor treatment response due to the heterogeneity in clinical trials [51]. Many other predictive biomarkers are still under investigation. Recently, specific gut microbiota compositions have been found to drive differing responses to immune checkpoint inhibitors in humans [52, 53]. Several genetic and immunohistochemical markers associated with the diagnosis of CM were summarized in Table 4 [54-79]. This shows that the composition of human gut microbiota modulation could improve the response of immunotherapy. Bioinformatics has yielded promising outcomes in identifying complex biological interactions in different pathways, having a specific role in the immune system. The metabolic, biochemical, and immune-mediated interactions are limited by the computational models and illustrate how they could be involved in melanoma progression [1, 80]. Therefore, computational methods may also promote the detection of new therapeutic targets and shorten drug discovery [81].

Management

Mostly, patients who are newly diagnosed with melanoma are at the primitive stage. For these cases, excision is the treatment of choice, and it is the ultimate remedy [82]. Some cases relapse with the disseminated disease; however, 10% of melanoma cases are diagnosed at an advanced stage and are already metastatic. Amongst cases with stage IV tumors, one-third percent have brain involvement at the time of diagnosis are at a lower likelihood of sustaining the treatment response [83]. For such cases, revolutionization in therapeutic agents occurred since 2011. These agents are BRAF and MEK inhibitors and immune checkpoint inhibitors such as cytotoxic T lymphocyte-associated antigen 4antibodies (CTLA4) and PD1 antibodies. PD1 and CTLA4 antibodies (such as pembrolizumab, ipilimumab, and nivolumab), along with specific BRAF inhibitors (dabrafenib and vemurafenib) alone and/or blended with MEK inhibitors (cobimetinib and trametinib), have the promising outcome [84-90]. Immunotherapy and kinase inhibitors are considered promising therapy, while chemotherapy is considered a second-line treatment option [51]. Several treatment modalities for melanoma metastases were shown in Table 5, and the grades of recommendation were shown in Table 6 [91].

PD1 and CTLA4 antibodies as therapeutic agents offer low response rates with a durable response [85, 89, 90]. In *BRAF*-mutated melanoma, BRAF inhibitors, along with MEK inhibitors, are used as a therapy. The blend has prompted high reaction rates (70%) with a quick response rate, along with an advantage of progression-free survival for 1 year [87, 92]. In some *BRAF*-mutated melanoma cases, where BRAF inhibitor resistance has risen, nivolumab and pembrolizumab have shown to be effective [1, 92, 93].

The aberrant expression of normal testicular proteins has become common knowledge in neoplastically transformed cells over the last decade. A novel family of immunogenic proteins is the cancer testis antigens (CTAs). The genes *LAGE*, *GAGE*, *BAGE*, *MAGE* and *NY-ESO-1* code for antigens that autologous, cytolytic CD8 (+) T lymphocytes recognize in different neoplastically transformed cells. One of the most immunogenic antigens ever isolated is the newly identified CTA, NY-ESO-1, which induces spontaneous host immune responses in 50% of patients with NY-ESO-1-expressing neoplasms [94]. In most cancer forms, NY-ESO-1 is a well-known CTA with re-expression. Recently used NY-ESO-1 in clinical trials was demonstrated in Table 7.

Future Prospective

Several diagnostic tools, dermoscopy, sequential digital dermoscopy and total body photography are available to identify CM. However, detection has remained a significant challenge amid advancements in diagnostic aids such as dermoscopy, and improved methods of accurately diagnosing melanoma are required. The recent diagnostic tools, including melanoma sniffing dogs, electrical impedance spectroscopy and noninvasive genomic detection, will help detect skin cancer. The combination of PD1/CTLA4with targeted therapy must be considered an experimental approach in recent clinical trials. Interferon-α treatment might be offered to patients with stage II and III melanoma as an adjuvant treatment, as these treatments increase infection-free survival time but disappoint due to toxicity. The consideration of patient attributes (such as lactate dehydrogenase and other biochemical parameters) with toxicity profile, along with comorbidities, and individual patient inclinations are focal components to be considered for cutting edge treatment strategy. Vital cooperation of patients in randomized clinical trials will be of great importance.

Despite potentially promising progress in the treatment of advanced malignant melanoma, prevention and early detection remain the primary priorities in the fight against this disease as we reach the new century. We may minimize the incidence and mortality of malignant melanoma with increased clinical education, public knowledge, patient education, and scientific advancement. As the incidence continues

Table 4. Genetic and Immunohistochemical Markers and Their Diagnostic Methods of Cutaneous Melanoma

Method/marker	Method description	Reference
Comparative genomic hybridization (CGH)	Accurate quantification of DNA copy number variations over a wide dynamic range with detection of single-copy deletions and duplications FFPE	[54]
Analyses of allelic imbalance (AI)	Detects the presence of deletions or gains of specific alleles Uses PCR amplification of microsatellite polymorphic markers followed by gel electrophoresis Performed on DNA from formalin-fixed paraffin-embedded tissues (FFPE) tissues	[55]
Multiplex ligation-dependent probe amplification (MLPA)	Measures the copy number of up to 45 nucleic acid sequences in one single reaction Performed on DNA extracted from routinely processed	[56]
Fluorescence *in situ* hybridization (FISH)	Utilizes a fluorescent probe or group of probes to search for preselected genomic abnormalities in tumors	[57]
Immunohistochemical markers		
S100A6	Part of the family of S100 proteins	[58]
PCNA	A 36-kDa protein that is a cofactor of DNA polymerase d (expressed in all phases of cell cycle proliferation) Proliferation marker	[59, 60]
Ki-67	Proliferation marker	[61, 62]
FLIP	Immune modulatory marker	[63]
CD40	Immune modulatory marker-B-cell marker; also a tumor suppressor	[64]
CD26	Immune modulatory marker, an adenosine deaminase receptor	[65]
Cancer/testis antigens	Immune modulatory marker Proteins that are aberrantly expressed in many types of malignancies	[66]
Skp2	Cell cycle-related/anti-apoptosis markers F-box protein which aids the formation of a more massive protein complex that degrades p27	[67]
Retinoblastoma protein (RB)	Cell cycle-related/anti-apoptosis markers	[68, 69]
P53	Cell cycle-related/anti-apoptosis markers	[69, 70]
P21	Cell cycle-related/anti-apoptosis markers	[6, 70]
P16	Cell cycle-related/anti-apoptosis markers	[61, 72, 73]
HDM2	Cell cycle-related/anti-apoptosis markers 90-kDa zinc finger protein that binds to p53 transcription activation domain inhibiting its function and targeting it for degradation by proteasomes	[74]
GADD	Cell cycle-related/anti-apoptosis markers Control transcription factors associated with cell cycle arrest, apoptosis, and cellular differentiation	[75]
Cyclin D3	Cell cycle-related/anti-apoptosis markers	[71]
Cyclin B	Cell cycle-related/anti-apoptosis markers	[70, 71]
Cyclin A	Cell cycle-related/anti-apoptosis markers	[70, 71]
Cdk2	Cell cycle-related/anti-apoptosis markers	[76]
Bcl-2	Cell cycle-related/anti-apoptosis markers	[77]
Trk-A	Signaling molecule Nerve growth factor receptor tyrosine kinase involved in activation of major oncogenic signaling pathways in melanoma, including the Ras/MAPK and phosphatidylinositol-3 kinase pathways	[78]
PTEN	Signaling molecule	[71, 79]

Table 5. Treatment Modalities for Melanoma Metastases

Metastases localization, number (pathological stage)	Treatment modalities	Grade of recommendation
Painful bone metastases (pTxNxM1a-1c)	Radiotherapy	B
	Bone-modifying agents	C
	Consider clinical trial participation	
Multiple metastases (pTxNxM1a-1c)	Systemic therapy	A
	Consider clinical trial participation	
Solitary lung, liver, kidney and other metastases (pTxNxM1)	Systemic therapy	A
	Surgical removal	C
	Stereotactic irradiation	C
	Consider clinical trial participation	
Solitary CNS metastases (pTxNxM3)	Stereotactic irradiation	B
	Systemic treatment	B
	Neurosurgical removal	C
	Consider clinical trial participation	
Locoregional LNs (pTxN1bN2b, N2c, 3)	Complete surgical removal followed by adjuvant therapy	A
	Irradiation in case of incomplete resection	C
	Consider trial participation	
Loco regional LNs (pTxN1a, 2a, N3a)	Consider adjuvant therapy	A
	Consider trial participation	B
Multiple ITMs (> 5; pTXN2cM0)	T-VEC	B
	Systemic therapy	C
	Perfusion of the extremity	C
	Electro chemotherapy	D
Few ITMs (pTXN2cM0)	Surgical removal	C
	T-VEC	C
	Irradiation, electrochemotherapy	D

CNS: central nervous system; LNs: lymph nodes; ITMs: in-transit metastases; T-VEC: talimogene laherparepvec.

to increase, a multidisciplinary strategy using those concerned' best expertise is our best defense against this potentially deadly neoplasm.

Conclusions

The incidence of CM continues to increase globally, and efficient clinical management strategies are necessary to meet this increasing demand. This current review provided valuable information regarding the early diagnosis and management of CM. While the best standard of treatment for melanoma patients is a multidisciplinary approach, surgery remains the best choice for most localized cases. According to rules defined by clinical trials, the disease can be cured by early detection, state of the art biopsy, and sizeable local excision. Eventually, the management of CM depends on the individual patient staging and their response to the therapy.

Table 6. Grades of Recommendation [91]

Grades	Recommendation
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended.
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended.
C	Insufficient evidence for efficacy or benefit does not outweigh the risks or disadvantages (adverse events, costs), optional.
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended.
E	Strong evidence against efficacy or for adverse outcome, never recommended.

Table 7. NY-ESO-1 Vaccine, Adoptive T Cell Therapy and Combinatorial Immune-Based Interventions Currently in Clinical Trial

ID	National clinical trial (NCT) number	Type	Interventions	Conditions	Status
GCO 14-0780	NCT02334735	Vaccines	Multi peptide (NY-ESO-1 and Melan-A/ MART-1) - pulsed DC vaccine	Melanoma	Recruiting
IMDZ-C131	NCT02387125	Vaccines	CMB305 (peptide-pulsed DC vaccine LV305 + G305 recombinant NY-ESO-1 protein vaccine)/TLR4 agonist (G100)	Melanoma	Recruiting
ID-LV305-2013-001	NCT02122861	Vaccines	DC lentiviral vector vaccine (LV305)	Melanoma	Active, not recruiting
NCI-2014-00898/CITN-07- FLT3L/U01CA154967	NCT02129075	Vaccines	DEC-205/NY-ESO-1 fusion protein vaccine (CDX-1401) + recombinant Flt3 ligand (CDX-301)	Stage II - IV melanoma	Active, not recruiting
ADP 01611	NCT01350401	Adoptive T cell therapy	NY-ESO-1c259-T cells	Metastatic melanoma	Active, not recruiting
MAT-02/2012-000450-63	NCT01946373	Combinatorial immune-based intervention	Peptide-pulsed DC vaccine/TILs	Melanoma	Recruiting
MCC-15400/NCI-P-7997/ CA209-006/007/10-15526-99-01	NCT01176461	Combinatorial immune-based intervention	Multi peptide vaccine (MART-1, NY-ESO-1, gp100209-217, gp100280-288/ PD-1 inhibitor) (nivolumab)	Melanoma	Active, not recruiting
MCC-15651/NCI-8316	NCT01176474	Combinatorial immune-based intervention	NY-ESO-1157-165/gp100280-288 vaccine/ PD-1 inhibitor (nivolumab)/PD-1 inhibitor (nivolumab)/CTLA-4 inhibitor (ipilimumab)	Stage III - IV melanoma	Active, not recruiting

NY-ESO-1: New York esophageal squamous cell carcinoma 1; DC: dendritic cell; PD-1: programmed cell death protein-1.

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Conflict of Interest

None to declare.

Data Availability

The author declares that data supporting the findings of this study are available within the article.

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