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Review Article

Melanoma Classification, Diagnosis and Management

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Abstract

Introduction: Evidence on melanoma from most countries demonstrate a fast elevation of the incidence rates of this malignancy, with this incidence rate becoming slower during the period between 1990 and 2000. The main environmental predisposing factor for developing melanoma that is highly modifiable is the exposure to ultraviolet rays due to its genotoxic actions.

Aim of Work: In this review, we will discuss melanoma classification, diagnosis and management.

Methodology: We did a systematic search for melanoma classification, diagnosis and management using PubMed search engine and Google Scholar search engine. All relevant studies were retrieved and discussed. We only included full articles.

Conclusion: Artificial ultraviolet exposure might have an important a role in malignant melanoma development. The main host predisposing factors for the development of malignant melanoma are the number of melanocytic nevi, the presence of familiar history and genetic predisposition. Despite that most melanoma patients have a localized disease at their diagnosis and are managed by performing surgical removal of the primary melanoma, many other patients develop metastatic disease. evidence on malignant melanoma from most countries have demonstrated a fast elevation of the incidence rates of this malignancy, with a slowing of the incidence rates during the period between 1990 and 2000.

Keywords: *Melanoma; Classification; Diagnosis and Management*

Introduction

This review article will discuss issues on melanoma including its epidemiology, predisposing factors, pathophysiology and diagnosis. Evidence on melanoma from most countries demonstrate a fast elevation of the incidence rates of this malignancy, with this incidence rate becoming slower during the period between 1990 and 2000. Male sex are estimated to be 1.5-times higher likely to have melanoma

when compared to female sex, whereas based on results from other studies, the different frequencies in both genders should be assessed in relation with the age of melanoma patients: the incidence of melanoma is higher in females than males until they are forty years old, while by seventy-five years of age, incidence rates are almost three-times as high in males when compared to females.

The main environmental predisposing factor for developing melanoma that is highly modifiable is the exposure to ultraviolet rays due to its genotoxic actions. Artificial ultraviolet exposure might have an important a role in malignant melanoma development. The main host predisposing factors for the development of malignant melanoma are the number of melanocytic nevi, the presence of familiar history and genetic predisposition. A patient who has a personal past history of malignant melanoma should be considered to be at a significantly higher risk for another later malignant melanoma. In fact, it is estimated that up to eight percent of patients who have a past history of malignant melanoma will later develop multiple other primary malignant melanomas.

In this review, we will discuss the most recent evidence regarding melanoma classification, diagnosis and management.

Methodology

We did a systematic search for melanoma classification, diagnosis and management using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: melanoma, classification, diagnosis and management.

Epidemiology

By the beginning of twenty-first century, malignant melanoma remains to be a possibly fatal cancer. At a time when incidence rates of several malignancy types are declining, malignant melanoma incidence rates continue to significantly increase [1]. Despite that most melanoma patients have a localized disease at their diagnosis and are managed by performing surgical removal of the primary melanoma, many other patients develop metastatic disease [2].

Incidence rates of malignant melanoma has been elevating around the world, causing a significant socio-economic dilemma. From being a relatively rare malignancy just last century, the mean lifetime risk for developing malignant melanoma has now become as high as one in every fifty individuals in many Western countries [3]. Starting from the 1960s, incidence rates of malignant melanoma have elevated among white individuals and, therefore, malignant melanoma has become one of the most common malignancies among fair-skinned individuals [4]. Malignant Melanoma is now considered as the fifth most frequent malignancy in males and the sixth most frequent malignancy in females in the US, where the incidence of malignant melanoma between the years 1973 to 2002 became 270 percent higher.

Nowadays, one in every sixty-three Americans are expected to develop malignant melanoma during their life [5]. It has been approximated by the U.S. Surveillance, epidemiology and End Result Program (SEER) that there are more than 793,000 males and females currently living in the US and have a past history of invasive melanoma (more than 385,000 males and 408,000 females) [6]. In the year 1973, the United States malignant melanoma incidence was estimated to be 6.8 per 100,000 and by the year 2003 to 2007, this incidence has grown to become about 20.1 per 100,000. Based on data that was collected during the period between 1998 and 2002, Mackie and colleagues demonstrated that the highest incidence rates of malignant melanoma around the world is present in Queensland (Australia), where there is an incidence that is equal to 55.8/105/per year for men and 41.1/105/per year for women. The incidence rates of this malignancy are also higher in New Zealand (34.8/105/per year and 31.4/105/per year for men and women, respectively). Recorded incidence varies for European countries and are found to be highest in Switzerland and the Scandinavian countries including Norway, Sweden and Denmark. Incidence of malignant melanoma in Europe is increased in the more affluent European countries, when compared to evidence from the Baltic states of Latvia, Estonia, Lithuania, Belarus and Serbia, despite that recent evidence has demonstrated an increase in the incidence of malignant melanoma in many East European areas [1].

Incidence rates of malignant melanoma in Italy have been found to be about five-to-seven cases per 100,000 person-years despite that Mediterranean populations are usually thought to have a relatively low risk for developing malignant melanoma. thus, in Europe there is a gradient in incidence rates of malignant melanoma with highest incidence rates of malignant melanoma being in the Northern European countries and lowest incidence rates of malignant melanoma being in the Southern European countries. This is possibly a result of higher protection against ultraviolet rays classical of highly pigmented skin (as individuals who reside in Southern countries) but it is also a result of the varying patterns of sun (chronic rather than intermittent in Southern European countries) [7].

In summary, evidence on malignant melanoma from most countries have demonstrated a fast elevation of the incidence rates of this malignancy, with a slowing of the incidence rates during the period between 1990 and 2000 [1]. In parallel with this increase in incidence rates, there has also been observed an increase in malignant melanoma incidence-based mortality, albeit to a relatively lower degree. In United States malignant melanoma mortality rates increased by about 1.4 percent every year during the period between 1977 and 1990. However, since the year 1990, it has demonstrated a relatively small declining trend and decreased by 0.3 percent per year during the period between 1990 and 2002 [5]. Based on date from Rigel., *et al.* between the years 2003 and 2007 the median age of death from malignant melanoma was estimated to be sixty-eight years [6]. There is a higher mortality rate of malignant melanoma in males when compared to females of the same age in United States [6]. In contrast to other solid malignancies, malignant melanoma mostly affects relatively young or middle-aged individuals. The median age at diagnosis of malignant melanoma is fifty-seven years and it was demonstrated that incidence rates of this malignancy increase linearly following the age of twenty-five years until the age of fifty years and then slows, specifically in women.

As for incidence rates of malignant melanoma in relation to gender, several studies demonstrate outcomes that are not always consistent. Based on results from Markovic., *et al.* men are estimated to be 1.5-times more likely to get malignant melanoma than women, whereas based on other studies, the different frequency in both genders should be assessed after taking age into consideration: incidence rates of malignant melanoma is considered to be higher in females when compared to males until they become forty years old, on the other hand, by the age of seventy-five, incidence rates are almost three-fold higher in males when compared to females (145.6 per 100,000 *vs.* 47.3 per 100,000, respectively) [6,7].

The distribution of favored sites of occurrence of malignant melanoma has been found to be gender-related: the most frequent sites are the back for males and the arms and legs for females [5]. Incidence rates of malignant melanoma can vary greatly also depending on ethnicity. The white race has an estimated ten-fold higher risk of acquiring cutaneous malignant melanoma when compared to black, Asian or Hispanic races. On the other hand, both white and black individuals have a similar predisposition of developing plantar malignant melanoma, while non-cutaneous melanomas (*like* mucosal) are more frequent among non-white individuals [8]. Based on the dates that were collected during the year 2007 by the SEER program in the United States, incidence rates of malignant melanoma among the white individuals was as high as 27.5 per 100,000 person-years, while among black individuals was about 1.1 per 100,000 person-years [6].

Risk factors

Currently, malignant melanoma is considered to be a multi-factorial medical condition that arises from the presence of a significant interaction between genetic predisposition and environmental exposures. The most important and possibly modifiable environmental predisposing factor that increases the risk of developing malignant melanoma is ultraviolet rays exposure, due to their genotoxic mechanisms. Elwood., *et al.* evaluated the association between malignant melanoma and sun exposure and concluded that intermittent exposure to sun rays seems to be the main determinant of risk for developing malignant melanoma [9]. A history of sunburn might be an indicator of the presence of intense intermittent sun rays exposure. In addition, a past history of sunburns in childhood is linked to the highest risk [9]. On the other hand, the chronic long-term continuous pattern of sun rays exposure is more linked to the development of actinic keratosis and non-melanomatous skin malignancies. Artificial ultraviolet exposure might have an important role in the development of malignant melanoma; in fact, the amount of artificial ultraviolet exposure happening in a classical tanning bed session is significantly high when compared to the normal exposure during everyday outdoor activities or even during normal sunbathing [10].

In addition, the psoralen–ultraviolet-A radiation photochemotherapy that is used in the management of psoriasis has also been linked to a higher risk of developing malignant melanoma [11]. The main host predisposing factors are the number of present melanocytic nevi, the presence of a familiar history and/or genetic susceptibility. Melanocytic nevi are known to be benign accumulations of melanocytes or nevus cells and might be either congenital or acquired. It is estimated that about twenty-five percent of malignant melanoma cases develop in conjunction with a pre-existing nevus [12]. In addition, the total count of nevi is strongly associated with the risk of developing later malignant melanoma and it varies based on the size, number and type of nevi. The results from a published meta-analysis emphasized that patients who had more than one hundred nevi show a seven-fold higher risk for developing malignant melanoma [13].

As for the size, bigger (more than five millimeters) and huge (more than twenty centimeters) nevi are positively correlated with a significantly elevated risk of developing malignant melanoma [14]. An atypical nevus is often known as being big, more than five millimeters, with having a flat component and has atypical characteristics including variable pigmentation, irregular asymmetric outlines and indistinct borders. Twenty-nine to forty-nine percent of non-familial malignant melanomas occur in the setting of a preexisting dysplastic nevus [15]. Not only atypical nevi are correlated with having a higher risk of developing malignant melanoma; the presence of even a single nevus with atypical characteristics increases the risk. The presence of 5 atypical nevi causes a 6-fold increase for malignant melanoma development [13].

Malignant melanomas, that develop in the presence of previous nevi, are often present on the trunk in younger individuals and belong to the superficial spreading subtype [16]. The presence of a family history of malignant melanoma leads to a significantly stronger risk for developing the disease. Taking into consideration that familial clustering of a medical condition is a marker of potential genetic etiologies, there has been an explosion in research directed at elucidating the genetic basis for malignant melanoma in the past twenty years. Tsao., *et al.* evaluated families who had inherited malignant melanoma showing the presence of an obvious pattern of autosomal dominant inheritance with several members of the family being affected. Mutations in cyclin-dependent kinase inhibitor 2A (*CDKN2A* or p16) were the most frequent genetic mutations detected among these families, while mutation in cyclin-dependent kinase 4 (*CDK4*), was a relatively rarer mutation [17]. Patients who had an underlying genetic susceptibility to develop malignant melanoma often demonstrated occurrence at a relatively younger age (younger than forty years old), several primary malignant melanomas or the presence of a past history of precursor lesions like dysplastic nevi and are highly likely to develop neoplasms that are superficially invasive and have a better outcome [18]. In addition, patients who have family cancer syndromes, including Li-Fraumeni cancer syndrome familial retinoblastoma, and/or Lynch syndrome type II, demonstrate significantly increasing predisposition of the development of malignant melanoma [5].

Certain phenotypic features including fair skin, red hair, light eyes, numerous freckles, sun sensitivity and/or the inability to tan, are known to increase the risk for developing malignant melanoma by about fifty percent [19]. Patients who belong to the lower photo-types usually acquire featureless melanomas or amelanotic melanomas which are usually challenging to discover. Therefore, it seems logical that they must be followed by a specialized dermatologist independent of the occurrence of any other predisposing factors [5].

Diagnosis

Early diagnosis of melanoma is still considered to be the most important factor that significantly decreases mortality rates. The prognosis of malignant melanoma is positively correlated with the depth of the tumor, that in turn becomes more with time. In fact, in malignant melanoma diagnosis, timely detection, recognition and fast management of the melanoma remain to be crucial. Malignant melanoma, when compared to other malignancies, has the advantage of the cutaneous location, that allows its early discovery through non-invasive approaches. However, pathological examination is still considered to be the gold standard for diagnosis.

Skin self-examination can have great potential as an easy, convenient way of screening for malignant melanoma and pre-cancerous lesions [20]. Prior to the 1980s, malignant melanomas were usually diagnosed by detecting clinically macroscopic characteristics; they were usually discovered in an late stage when they were already large, ulcerated and/or fungating [21].

The early detection of malignant melanoma is becoming an essential public health priority [22]. The challenge is present in detecting treatment modalities that improve the accuracy of skin self-examination for discovering lesions that show the highest possibility of being malignant. Since there is a necessity to inform clinicians and the public to detect malignant melanoma in its early clinical stages, the "ABCD" criteria were introduced in the year 1985. 'ABCD' is an acronym that stands for Asymmetry, Border Irregularity, Color Variegation, and Diameter that is more than six millimeters. Later the letter "E" was additionally added to stand for Evolving, which is specifically essential for the diagnosis of nodular malignant melanomas [23]. These criteria were meant to be an easy tool that can alert non-dermatologists healthcare providers in distinguishing between normal moles and cutaneous lesions that are most suspicious for the presence of an early malignant melanoma. They were not intended to provide a thorough template to recognize all melanomas, as a "good clinical eye" is still considered to be crucial in the assessment of the lesion. Using the ABCD(E) criteria, the sensitivity of self-skin examination can range between fifty-seven percent to ninety percent [24].

Other clinical modalities have been used to increase rates of early detection of malignant melanoma, including the Glasgow 7-point checklist, that has three major criteria points (size changes, shape changes, and color changes) and four minor criteria points (sensory changes, having a diameter of seven millimeters or greater; and the presence of inflammation, crusting and/or bleeding). The Glasgow 7-point checklist, due to its sophisticated nature, has been less widely used than the ABCD criteria. Another paradigm is the presence of the "ugly duckling" sign, which is dependent on the perception that a pigmented lesion "seems to be different from its other neighbors". This criterion for detecting suspected lesions has been demonstrated to be relatively sensitive for the detection of malignant melanoma lesions, even for non-dermatologists [25].

During the diagnosis of malignant melanoma cases, several assistive optical gadgets have become crucial. These gadgets include the use of high-resolution optical handheld gadget that have been designed to work as or dermatoscopes or dermoscopes or epiluminescent microscopes [5]. Dermoscopy is considered to be a non-invasive diagnostic modality to be used for *in vivo* screening of the skin; this medical gadget uses optic magnification to allow for visualization of morphological characteristics that are not normally visible to the eye. Dermoscopy has elevated the accuracy of malignant melanoma diagnosis since this modality shows early manifestations of the condition visible in the pigmented lesions long before visible clinical manifestations [26].

Some cases of malignant melanoma could not be detected neither with the naked eye nor with the use of the dermoscope. In these extreme cases, it may be is possible to create images that could be electronically captured, archived, retrieved and analyzed. In this method it becomes possible to detect minimal changes in the early stages of malignant melanoma. With this approach, it is possible to follow the dynamic evolution of the melanocytic naevi over time [5,26]. Reflectance confocal microscopy has also been demonstrated to be an important imaging modality to be used for the diagnosis of melanocytic lesions. Reflectance confocal microscopy allows non-invasive examination of native skin in real-time at a nearly histologic resolution. The reflectance confocal microscope emits a near-infrared, coherent laser beam by which the human skin is illuminated. Some of the most important advantages of this non-invasive imaging modality are: improving the accuracy of diagnosis, improving assessment of dermoscopic-histologic correlation, *in vivo* biopsy side selection, surgical margin evaluation and response control of conservative therapies in skin conditions [27].

Conclusion

Despite that most melanoma patients have a localized disease at their diagnosis and are managed by performing surgical removal of the primary melanoma, many other patients develop metastatic disease. evidence on malignant melanoma from most countries have demonstrated a fast elevation of the incidence rates of this malignancy, with a slowing of the incidence rates during the period between 1990 and 2000. malignant melanoma is considered to be a multi-factorial medical condition that arises from the presence of a significant interaction between genetic predisposition and environmental exposures. The most important and possibly modifiable environmental predisposing factor that increases the risk of developing malignant melanoma is ultraviolet rays exposure, due to their genotoxic mechanisms. Early diagnosis of melanoma is still considered to be the most important factor that significantly decreases mortality rates. The prognosis of malignant melanoma is positively correlated with the depth of the tumor, that in turn becomes more with time.

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