Review

The prognostic significance of the clinical and histological parameters in primary cutaneous melanoma patients

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Abstract

Cutaneous melanoma is the most aggressive form of skin cancer and its incidence is unfortunately increasing. In the last decades, a progressive increase of new cases of diagnosed thin melanoma has been noted. This may be due to earlier detection, better surveillance, improved diagnostic criteria or increased exposure to sunlight. Despite the fact that Breslow tumor thickness has the strongest proven prognostic significance, there are still thin melanomas that metastasize and thick melanomas with favorable evolution. Therefore, the identification of strong predictive factors for survival is mandatory, particularly for patients with thin melanoma.

Keywords: melanoma, thin melanoma, prognosis, survival rate, predictive factors

Introduction

Over time, there has been a significant decrease in median tumor thickness, such as from 1.8 mm in 1976 to 0.5 mm in 2000, as well as an increase of the incidence in cases of thin cutaneous melanoma (Breslow thickness ≤1 mm), from 39% in 1976 to 65.5% in 2000 [1]. Nowadays it represents approximately 70% of all diagnosed skin melanomas [2] and accounts for 25% of all melanoma deaths [3].

Fortunately, in most cases with thin cutaneous melanomas, surgical excision is curative and these patients have a favorable overall prognosis. Five percent of patients with this subtype of melanoma have a risk of metastasis and even death within 10 years [4]; the overall survival rate for this group at 10-year follow-up is approximately 4.5-8% [5]. Therefore, the identification of strong predictive factors for metastasis and survival is mandatory, particularly for patients with thin melanoma.

Numerous studies have shown that no parameter (serological, molecular, histological or immunohistochemical) alone has an accurate predictive value for the evolution of melanoma. Thus, a combination of new factors is needed to identify patients at high risk of metastasis, which would further benefit from a more aggressive treatment plan.

The histopathological reports bring plenty of information about the prognosis of melanoma patients thus contributing to a better management and follow-up of these patients. Over time, many studies have shown that the main parameters that are associated with poor prognosis are the older age, male gender, localization of the primary tumor at the axial or head or neck level, increased Breslow and Clark indices, vertical growth phase, ulceration, increased mitotic rate, tumor regression and the absence of inflammatory infiltrate [6–9].

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Age

Most studies have shown that with age, the risk of unfavorable outcome of patients diagnosed with melanoma increases. The main reason for this is that as age increases, the thickness of the tumor grows and the risk of ulceration and regression of the tumor is higher [10]. This happens because elderly patients are less concerned about skin changes that occur over time and tend to practice self-examination less often than young people [11].

Several studies have shown that old age is an independent predictor of survival in melanoma patients [1,12].

Cutaneous melanoma in children is rare, especially before puberty. It represents 1.2% of all forms of cancer by the age of 15 years and 7% between 15 and 19 years [7]. In a study of 354 patients aged up to 18 years with cutaneous melanoma, 80% were diagnosed over the age of 14 years [13]. A large epidemiological study found that the mortality rate in cutaneous melanoma patients was 8 to 18 times higher in adolescent patients, with age between 15 to 19 years, compared to younger ones [14].

In addition to age, studies have shown that the main factors that associate a decrease in overall survival in children and adolescents with melanoma are the high number of melanocytic nevi, innate immunodeficiency, increased Breslow tumor thickness and increased Clark level [7]. It has been observed that patients with more than 100 nevi have a 34 times higher risk of developing melanoma than those with few nevi [15]. In addition, innate immunodeficiency confers a 3-6 times higher risk for melanoma [7].

Interestingly, besides all these prognostic factors, some studies have shown that the prognosis of children with melanoma who had positive SLNB (SLNB - sentinel lymph node biopsy) was better than in adults [16]. Some authors believe this is due to changes in the density of lymphatic flow related to age and in the immune system which is able to better fight malignant cells [7,17].

Gender

Numerous studies have shown that in patients with cutaneous melanoma, males have a worse prognosis compared to females. Multivariate analysis in a study of 5093 patients showed a favorable predictive role in females in terms of prognosis [18].

Several factors have been incriminated to influence the better outcome in women, namely the location of the primary tumor, hormonal and endocrine factors, the prevalence of smoking. Most studies have shown that survival rates in women at 5 and 10-year follow-up are 10-20% higher up to 65 years. After this age this advantage is lost [11,18].

Although the role of estrogens was initially invoked, this hypothesis was excluded since it has been found that melanoma does not have estrogen receptors and does not respond to anti-estrogen therapy [11,19].

The location of the primary tumor is an important factor in the protective role of female sex as it has been observed that the most common locations in women are the limbs. In a study conducted in Sweden on six national registries that included 12,533 patients, women presented with 53.5% extremity and 30.2% trunk melanomas, while men had 25.2% extremity and 56.7% trunk melanomas [20]. It has been observed that in men the locations of the tumor at the level of the head and neck and the axial locations are more frequent [21]. These are associated with a poorer prognosis.

In addition, the thickness of the tumor seems to be another important factor, as women tend to have thinner melanomas than men [22], perhaps they have a higher addressability to doctors.

However, the protective role of female sex remains controversial. For example, another study showed that in case of thin melanomas with tumor thickness less than 1 mm, sex was not an important predictive factor [23].

Location of the primary tumor

Many studies have shown a poorer prognosis for axial and head or neck lesions than for extremities. A retrospective cohort study of 51,704 patients using United States cancer registries compared the prognosis of patients with head or neck lesions to melanoma patients with other primary tumor sites. Among the conclusions of the study was that 5-year overall survival was 83.1% in patients with melanoma on the scalp or neck compared to 92.1% in those with other locations. Also the 10-year overall survival for scalp or neck melanoma was 76.2% compared to 88.7% in melanoma patients with other location. In addition, they observed that the risk of death in patients with melanoma on the head or neck was about twice higher than in patients with other locations of the primary tumor [24].

One reason why trunk melanoma has a worse prognosis than those of the extremities is perhaps the difference in lymphatic drainage; axial tumors can drain to the mediastinal or para-aortic lymph nodes but also to inguinal or axillary areas [25].

Breslow tumor thickness

The maximum thickness of the tumor is measured from the granular layer or from the base of the ulceration, if the tumor is ulcerated, to the deepest area of invasion. It was first defined as having prognostic significance by pathologist Alexander Breslow in 1970 [26].

Despite the fact that Breslow index has proven to have a high prognostic significance in numerous clinical trials, there are still cases of thin melanomas that metastasize and thick melanomas with good evolution and long-term survival. Therefore, for thin melanomas,

identifying other factors that could provide information about the prognosis of the disease is essential.

A large German study conducted on 12,728 patients found that tumor thickness, age at the time of diagnosis, gender, subtype and location of the tumor are independent prognostic factors. Among these, tumor thickness has the strongest significance [1].

Moreover, a Swedish study with more than 15 years of follow-up data, conducted on 13,026 patients with stage T1 melanoma, showed that tumor thickness, Clark level of invasion and ulceration confer an independent prognostic value and that the prognostic role of the Breslow index decreases when the tumor is ulcerated [27].

Clark's level

Since 1969 Clark and his collaborators had found a link between level of tumor invasion and prognosis of patients with cutaneous melanoma. Clark's classification includes five stages according to the histological penetration depths of the tumor cell, as follows: level I – involves only epidermis and corresponds to melanoma in situ, level II – invasion of papillary dermis, level III – invasion up to the interface between the papillary and the reticular dermis, level IV – invasion of reticular dermis and level V – invasion of subcutaneous tissue. Clark and his collaborators showed a median survival time of 6.83 years for the patients with level II of invasion and 3.5 years for the level V [28].

Many studies have shown an inverse correlation between the depth of tumor invasion and patient survival [29–31].

Some studies have shown that the prognostic significance of Clark index is not as strong compared to Breslow thickness [26,32] and others have shown that it is an independent prognostic factor only for thin melanomas (≤1 mm) [6,33,34].

The 6th (2001) American Joint Committee on Cancer (AJCC) melanoma staging guidelines used Clark level of invasion and ulceration in addition to tumor Breslow thickness to subdivide thin melanoma as T1a or T1b [35].

In the 7th edition (2009) of the AJCC classification, Clark level has been replaced by mitotic rate for stratification of primary tumors in the T1 stage [36]. Thereafter, an increase in the number of T1a melanoma cases was observed [37,38]. This modification led to changes in the clinical approach with a different use of the sentinel lymph node biopsy (SLNB) [38]. Current National Comprehensive Cancer Network Guidelines recommend performing SLNB in patients with tumor thickness between 0.76 and 1 mm if they associate either ulceration or 1 or more mitoses per mm^2 [5].

Radial and vertical growth phase

Gimotty et al. demonstrated by multivariate analysis that the vertical growth phase confers an important predictive significance for the risk of metastasis at 10-year follow-up and carries a 42 times higher risk of metastasis than the radial growth phase tumors [22].

Ulceration

Ulceration is defined as the epithelial disruption over its entire thickness and appears to be due to tumor ischemia that occurs with rapid tumor growth [39]. This suggests that ulceration is more likely to occur in more aggressive tumors [6].

Many studies have shown by multivariate analysis that the presence of tumor ulceration correlates with decreased overall survival [33,39] but also with the risk of relapse of melanoma patients [5,40].

It has been observed that the presence and prognostic role of ulceration is influenced by tumor thickness and that its incidence increases with a higher Breslow index. One study found a 12.5% incidence of ulceration in melanomas with tumor thickness less than 0.75 mm and 72.5% in melanomas thicker than 4 mm [41].

Mitotic tumor rate

Numerous investigators have shown the prognostic value of mitotic tumor rate in patients with cutaneous melanoma. Several studies have proven that the mitotic rate has an independent prognostic value and also it is the most important prognostic factor for survival after Breslow tumor thickness [3,36,42].

Barnhill and colleagues have shown that a mitotic index of 1-6 mitoses/mm^2 increases the risk of mortality at 5 years by 8 times whereas a mitotic rate of more than 6 mitoses/mm^2 increases the mortality at 5 years by 11 times [43].

In 2009 the AJCC included the mitotic rate in the melanoma TNM staging system for its independent predictive value of survival to subclassify T stage into T1a and T1b [37].

However, in the current (8th) edition of AJCC staging system, the mitotic rate was removed from the staging criteria because it was concluded that the use of 0.8 mm cut point for stratification of T1 tumors is more strongly associated with the prognosis of the disease. However, that should be further calculated and recorded in the histological reports (Table I) [44].

Caldarella and colleagues showed that the most significant correlation with survival was at least 1 mitosis/mm^2 [38].

In a recent retrospective study, investigators revealed that mitotic rate is the strongest predictor of survival after positive sentinel lymph node biopsy [2]. Another large study concluded that mitotic rate is an independent predictor for survival [45].

Table I. The 8th Edition of the American Joint Committee of Cancer (AJCC) Melanoma Staging System.

T category	Tumor thickness	Ulceration
Tx -The thickness of the primary tumor cannot be assessed	Not applicable	Not applicable
T0 - No evidence of primary tumor	Not applicable	Not applicable
Tis - Melanoma in situ	Not applicable	Not applicable
T1	≤ 1.0 mm	Unknown / unspecified
T1a	< 0.8 mm	No ulceration
T1b	< 0.8 mm	With ulceration
	0.8 -1 mm	With / without ulceration
T2	1-2 mm	Unknown / unspecified
T2a	1-2 mm	Without ulceration
T2b		With ulceration
T3	2-4 mm	Unknown / unspecified
T3a	2-4 mm	Without ulceration
T3b		With ulceration
T4	> 4 mm	Unknown / unspecified
T4a	> 4 mm	Without ulceration
T4b		With ulceration
N category	**The number of affected regional lymph nodes**	
Nx	Lymph nodes cannot be evaluated	
N0	No regional metastases detected	
N1	Single lymph node metastases or transit / satellite metastases without lymph node metastasis	
N2	Metastases in two or three nodes or metastases in transit / satellites with metastasis in one node	
N3	Metastases in four or more lymph nodes or transit metastases / satellites with metastasis in two or more nodes or any number of lymph node metastases with / without transit / satellite metastases	
M category	**Anatomical location**	
M0	No distant metastases detected	
M1	Distant metastasis detected	

Regression

Histological regression can be found in 10 to 35% of melanomas [11] and is defined as the replacement of tumor cells with fibrous tissue, inflammatory cells, neoformation vessels and melanophages. It is considered to be the result of the interaction between the tumor cells and the host's immune system via TILs (TILs - tumor infiltrating lymphocytes) [6,39,46,47].

Some authors believe that thin melanomas that showed regression and had a poor prognosis were initially thick melanomas and had a significant regression area in the past [48].

Clark and coworkers thought that regression gives a poor prognosis, especially in thin melanomas in which the primary lesion regresses by more than 75% [11,49]. It has long been considered a negative prognostic factor due to the assumption that it could affect the correct assessment of Breslow's tumor thickness [36,50]. More recently, histological regression has been associated with a favorable prognosis. Two meta-analyses showed that tumor regression was associated with a low risk of lymph node metastases [51] and a favorable prognosis [52,53].

This may be due to the fact that histologic regression is correlated with an early activation of the immune system. Despite this, there are no data in the literature to demonstrate the predictive role of immunotherapy response. However, it has been shown that there are similarities between the immune infiltrate from tumor regression and vitiligo-like reaction produced by immunotherapy and target therapy [53].

In a recent study of thin melanomas, the authors showed low expression of CEACAM1 (CEACAM1-carcinoembryonic antigen-related cell adhesion molecule 1) in the tumor regression area. CEACAM1 is a key molecule that is associated with increased invasion and tumor progression in melanoma. This could strengthen the hypothesis that histological regression is rather a favorable prognostic factor in melanoma [54].

Tumor-infiltrating lymphocytes (TILs)

Nowadays, the role of the host immune response against the development of melanoma is much more

debated and it is believed that TILs have a key role in this process [55]. Several studies have shown that the absence of TILs has an independent predictive role for the occurrence of lymph node or regional metastases.

For example, a study of 887 patients who underwent sentinel lymph node mapping showed that the absence of TILs was an independent predictive factor, in addition to tumor thickness, ulceration, and male sex. The absence of tumor infiltrate gives a 26.2% probability of developing lymph node metastases compared to a 3.9% probability of positive SLNB for melanomas with brisk infiltrate [56].

Other factors with prognostic significance for melanoma patients are microscopic satellites [11], tumor lymphangiogenesis [57], vascular invasion, angiotropism, neurotropism, cellular atypia or the association with melanocytic nevus. The presence of microscopic satellites seems to suggest the existence of lymphatic metastases. [11]. Some authors consider that tumor lymphangiogenesis is the strongest predictor for SLNB positivity. It might have even greater prognostic value than tumor thickness [57].

Conclusions

Biological behavior and prognostic factors for primary cutaneous melanomas are still debatable. We reviewed in this article some important clinical and histological parameters with prognostic value in melanoma patients. These factors are conventional and are found in histopathology reports. Breslow tumor thickness remains the strongest prognostic factor for melanoma in general. However, for thin melanomas, other morphological, biological or molecular parameters with a predictive role on survival are needed. Currently, only Clark invasion index and ulceration have proven their prognostic value in this type of melanoma.

More studies are needed to analyze the prognostic role for other parameters such as tumor regression, tumor mitotic rate or tumor-infiltrating lymphocytes activity. Representing most of the melanomas, optimization of diagnosis and staging of thin melanomas has become particularly challenging at present.

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