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AJCC 8th Edition (2017) versus AJCC 7th Edition (2010) in thin melanoma staging

Minireview

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In comparison with the 7th Edition, the 8th Edition of the American Joint Committee on Cancer (AJCC) staging system no longer considers mitotic count in a or b T1 categorization for melanoma, but it adopts a sub-stratification based on Breslow's depth. Today, the death burden of thin melanoma is still severe, despite attempts for early screening. We believe that bio-histological implementation can explain this evidence. It is generally accepted that melanoma progression includes two subsequent phases: radial growth phases (RGP) and vertical growth phase (VGP). If left untreated, RGP is able to move towards VGP. In this second phase, melanoma grows as a malignant, mitotically active, tumor with invasive and metastatic capacity. Our experience shows that thin melanoma has three bio-histological subtypes: non-tumorigenic micro-invasive RGP without significant regression; micro-invasive RGP with regression of uncertain tumorigenic potential at diagnosis due to the extensive presence (>75%) of regression which can contain a VGP clone and micro-invasive tumorigenic VGP. Therefore, we support the conclusion that the diagnosis in melanoma is correlated with the type of growth phase inside it.

Key words: melanoma, thin melanoma, radial growth phase (RGP), vertical growth phase (VGP), regression, biopsy, histology, American Joint Committee on Cancer (AJCC)

2010 AJCC 7th Edition

Thin melanomas, as defined in the 7th Edition of the American Joint Committee on Cancer (AJCC) staging system for melanoma, are micro-invasive lesions with Breslow's depth ≤1 mm [1]. They represent approximately 70% of cutaneous melanomas [2]; the 10-year specific survival for thin melanomas ranges from 97% to 82% and it is correlated with Breslow's depth, mitoses and ulceration [3]. In the 7th Edition of the AJCC staging system, T1 was classified in two well-known subcategories: T1a without ulceration and mitoses <1/mm^2 and T1b with ulceration or mitoses ≥1/mm^2 [1]. An approximately 10% risk of occult metastases in the sentinel lymph node (SLN) was expected in thin melanomas with a mitotic rate ≥1 mm^2 and a Breslow's depth ≥0.76 mm [4]. Therefore, the Committee of the 7th Edition suggested that these parameters were important in the choice to perform SLN biopsy in patients with T1b melanoma [4]. Evidence-based guidelines of the American Society of Clinical Oncology, in conjunction with the Society of Surgical Oncology [5], recommend that SLN biopsy should be considered, as routine procedure, in thin melanomas with high-risk features (elevated mitotic index and ulceration). This was because the criteria of the 7th Edition of the AJCC staging system would have caused an increase in the number of patients to be submitted to SLN biopsy, without a corresponding increase in the positive rate of SLN biopsy [5]. Therefore, reconsideration of the mitotic criterion for T1b classification and of recommendations to perform SLN biopsy for pT1b melanoma has been advanced [6].

2017 AJCC 8th Edition

The 8th Edition of the AJCC staging system has introduced a new classification for thin melanoma, subdividing it into: T1a ≤0.8 mm without ulceration and T1b ≤0.8 mm with ulceration or 0.8–1.0 mm with or without ulceration (Table 1). Tumor mitotic rate has been removed as staging criterion for thin melanoma, because, sub-stratifying tumors using as cut-point 0.8 mm, it is emerged a strongest association with outcome than utilizing the presence or absence of mitoses [7]. However, tumor mitotic rate remains a very important prognostic factor for all patients affected by T1–T4 primary melanoma [7]. In the new manual, the mitogenicity continues to be evaluated with the so-called "hot-spot" method, in which the area with the highest number of mitoses is first identified and, then, the number of mitoses per square millimeter in that area is counted. By this method, a tumor with a single mitosis in the "hot-spot" has a mitotic rate equal to 1, with two mitoses 2, with three mitoses 3 and so on.

Table 1. Malignant melanoma of the skin can be subdivided by Breslow depth in thin melanoma (≤1 mm) or thick melanoma (>1 mm).

THIN MELANOMA	THICK MELANOMA
BRESLOW THICKNESS ≤1 mm	BRESLOW THICKNESS >1 mm
a: without ulceration at any thickness and thin melanoma thickness <0.8 mm	
b: without ulceration and thin melanoma thickness >0.8 mm ≤1 mm	
b: with ulceration at any thickness of thin or thick melanoma	

According to the 8th Edition of the American Joint Committee on Cancer (AJCC) staging system, a and b specifications are assigned based on ulceration and thickness which replaces the mitotic count for square millimeters.

2017 & beyond: bio-histological implementations

We support the controversial opinions regarding the prognostic value of tumor mitotic rate and depth in thin melanoma, and related SLN biopsy recommendations may be solved by bio-histological implementation based on the tumor progression phases [8, 9]. Melanoma progression reflects two subsequent phases (Figure 1): the radial growth phase (RGP) and the vertical growth phase (VGP).

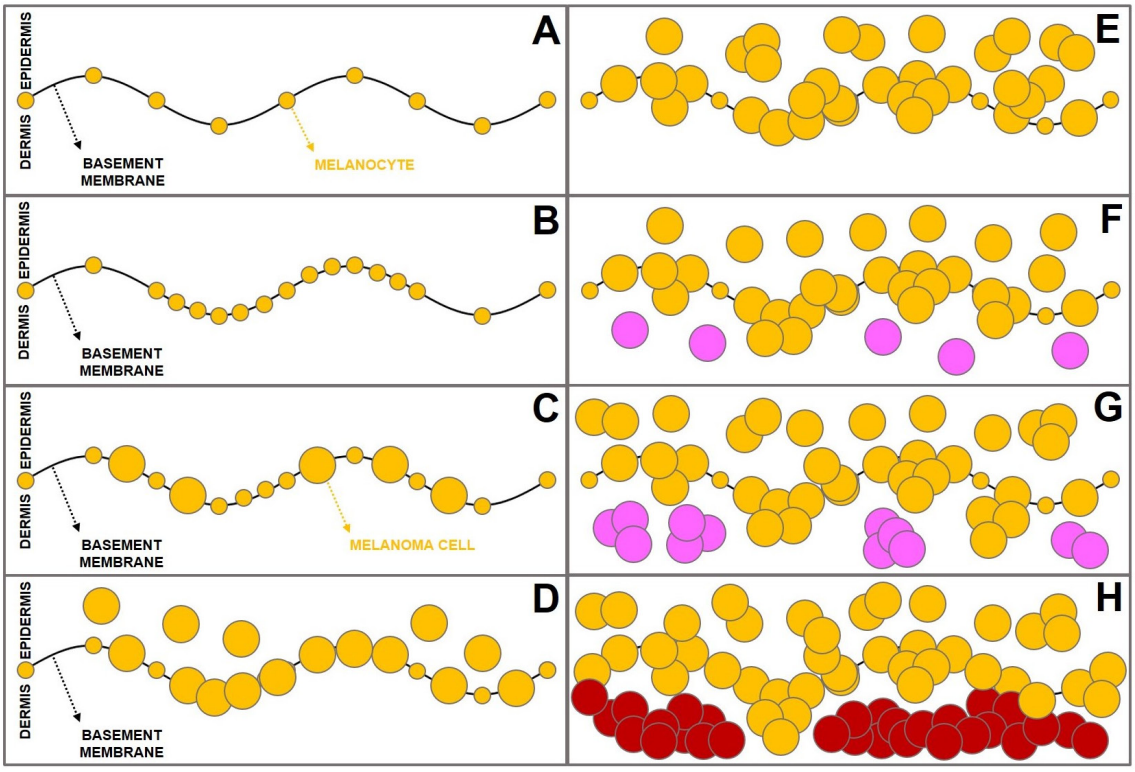

Figure 1. Schematic representation of the progression from normal skin to primary invasive malignant melanoma. A) normal skin with melanocytes (smaller yellow bullets) regularly distributed at the base (black line) of the epidermis; B) epidermis with basal hyperplastic melanocytes, arranged in a closer manner; C) epidermis with basal melanoma cells (larger yellow bullets); D) intra-epidermal radial growth phase (RGP) with lentiginous pattern (single melanoma cells are depicted in yellow only within the epidermis); E) intra-epidermal RGP with pagetoid pattern (small clusters of melanoma cells are depicted in yellow only within the epidermis); F) micro-invasive RGP with lentiginous pattern (single melanoma cells are depicted in pink even inside the papillary dermis); G) micro-invasive RGP with pagetoid pattern (small clusters of melanoma cells are depicted in pink even inside the papillary dermis); H) invasive (micro-invasive if ≤ 1 mm in depth) vertical growth phase (large clusters of melanoma cells are depicted in red even inside the papillary dermis and beyond).

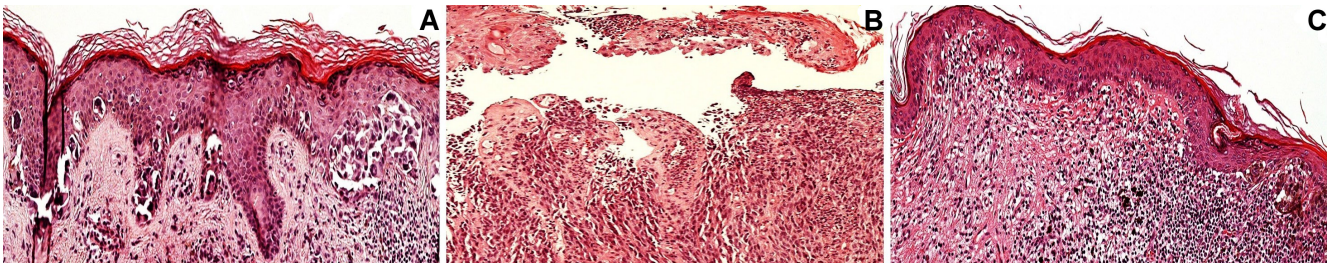

Figure 2. Histological exemplification of a non-tumorigenic intra-epidermal radial growth phase (RGP) with pagetoid pattern (A, H&E, ×10) and of a micro-invasive tumorigenic vertical growth phase (VGP) with epidermal ulceration (B, H&E, ×10): when extensive regression in thin melanoma is encountered (C, H&E, ×10), a regressed VGP clone cannot be excluded. Therefore, a statement of uncertain tumorigenic potential at diagnosis is recommended in these cases.

Radial growth phase (RGP). RGP is the first progression phase of melanoma and, at the beginning, it consists of malignant cells which proliferate in the epidermis (Figure 2). In this intra-epidermal (*in situ*) step, the transformed melanocytes are confined above the basement membrane [10]. The proliferative pattern can be pagetoid (superficial spreading melanoma) or lentiginous (acral lentiginous melanoma, lentigo maligna melanoma). The intra-epidermal malignant cells express relatively high levels of the proliferative antigen Ki-67 [11]. The capacity to migrate into the dermis is considered a form of micro-invasion of these cells across the basement membrane. Over time, RGP can invade the superficial papillary dermis (Clark's levels II or III) in the absence of tumorigenic nodule or papule (Figure 1). When it occurs, single cells or small nests are present in the sub-epidermal space, but these nests are invariably smaller than the junctional ones, and the Ki-67 index is very low compared to the transformed epidermal melanocytes [10]. This entity is defined non-tumorigenic micro-invasive RGP with lack of metastatic potential, if devoid of significant regression [10]; the absence of dermal mitoses is an absolute criterion. In the dermis, melanoma cells may either undergo apoptosis and disappear, or proliferate and evolve in VGP; therefore, micro-invasive RGP has the properties for persistence, local recurrence or progression to VGP [10]. Consequently, the complete removal of the lesion is necessary. The Breslow's depth is generally <0.8 mm and the histological examination must be very accurate to exclude a VGP focus. SLN biopsy is not recommended in the management of micro-invasive RGP without significant regression [12, 13]. In contrast, the presence of extensive regression (greater than 75% of tumor volume) can be associated with metastatic behavior [14]. It is likely that this regression incorporated malignant cells able to metastasize prior to its occurrence (Figure 2). For this reason, we believe that micro-invasive RGP with extensive regression should be considered of uncertain tumorigenic potential [15–19], and SLN biopsy is prudentially indicated [20, 21].

Vertical growth phase (VGP). VGP is the second phase of melanoma evolution when, after a period of indolent but progressive growth as an RGP plaque, it acquires the power of tumorigenic dermal invasion in one or more areas [10]. It is associated with a statistical chance for distant metastasis even in thin melanomas, where an "early VGP", defined as a nodule of at least 25–50 cells in the papillary dermis [14], can be encountered. The cells are larger than any of the overlying theques at the dermal-epidermal junction or within the epidermis [10]. The VGP of thin melanoma is accompanied by tumorigenicity and mitogenicity which correlate with metastatic potential [10].

Therefore, a bioptic specimen of thin melanoma must be always examined with serial sections in order to exclude the presence of an underling VGP. The SLN biopsy is necessary at any T stage that a VGP clone has been detected [22].

In conclusion, thin melanoma causes a high death toll despite excellent prognosis [23]. Certainly, the prognosis worsens with depth starting at 0.51 mm, and the outcome in the T1 stage is not explained simply by ulceration [23, 24]. From this framework, it emerges that the death burden of thin melanoma is still severe, despite attempts for early screening [23]. We believe that a novel sub-typing of thin melanoma can explain this evidence [25–27]. In our opinion, the T1 stage of the 7th and 8th Editions of the AJCC staging system includes three bio-histological variants of thin melanoma: 1) the non-tumorigenic micro-invasive RGP without significant regression; 2) the micro-invasive RGP with regression >75% of uncertain tumorigenic potential at diagnosis due to the extensive presence of regression which could contain a VGP clone and 3) the micro-invasive tumorigenic VGP. In our experience [8–10], the prognosis for thin melanoma is correlated with the type of growth phase, which must be always accompanied by the micro-staging attributes (Breslow's depth, Clark's level, mitotic count, ulceration, satellitosis, tumor-infiltrating lymphocytes, lympho-vascular and perineural invasion) [28–30]. The growth phase type, well-ascertained by serial sectioning, should be always present in the histological report of thin melanoma and taken into account in the studies of thin melanoma survival.

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