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NOVELTIES IN DERMATOLOGY

Primary Cutaneous Melanoma: Prognostic Factors Not Included in the Classification of the American Joint Committee on Cancer

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Abstract Skin histopathology reports of melanoma routinely include important prognostic information used in the staging system of the American Joint Committee on Cancer (AJCC). This information, which influences disease management, includes tumor depth, presence of ulceration, number of mitotic figures, and presence or absence of microsatellites. However, numerous studies have found many other factors that are not included in the AJCC classification but that are nevertheless of prognostic significance. We discuss these factors in this paper.

PALABRAS CLAVE
Melanoma;
Pronóstico;
Histología

Factores pronósticos en el melanoma cutáneo primario no incluidos en la clasificación de la *American Joint Committee on Cancer* (AJCC)

Resumen
En un informe rutinario dermatopatológico sobre un melanoma se recoge una significativa información pronóstica para el manejo de estos pacientes y que actualmente es empleada en la estadificación de la *American Joint Committee on Cancer* como el grosor tumoral, la presencia de ulceración, el número de mitosis y la presencia o no de microsatelitosis. Sin embargo, existen múltiples factores que si bien no están incluidos en esta clasificación, han demostrado tener un impacto pronóstico en diversos estudios y que son objeto del presente texto.

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The most recent version of the melanoma staging system of the American Joint Committee on Cancer (AJCC)[1] is probably the best among the currently available tumor classification systems. The committee's work is based on information for over 50 000 patients with melanoma treated at large referral hospitals on 3 continents.

However, in spite of considerable efforts to identify prognostic factors for localized cutaneous melanoma (stages I and II) in recent decades, the AJCC's most recently published system names only tumor depth, ulceration, and mitotic index—this last only considered for T1 (thin) melanomas—as being useful for predicting survival curves in this large database of cases.

Further research on additional predictors is still needed if we are to adequately explain the behavior of melanoma tumors and, therefore, survival curves. In this review we discuss the various prognostic factors that can be recorded when reporting the dermatopathologic features of a melanoma as well as clinical factors that have been shown to be statistically significant predictors of prognosis in studies to date.

Gender

The incidence of melanoma has been higher in women in most series of white patients but has risen faster in men in recent decades.[2,3]

Numerous epidemiologic studies have demonstrated that in primary melanoma females have a clear advantage in terms of survival.[4-6] Although a role for estrogen was therefore initially suggested, this hypothesis was ruled out by research showing that these tumors lack estrogen receptors and fail to respond to antiestrogen drugs.[7,8] The favorable effect of female gender on survival can also be seen in internal organ tumors, such as pulmonary, colorectal, gastric, and esophageal carcinoma, and as well as in soft tissue sarcoma.[9] In the case of melanoma, gender differences in survival may be attributable to additional factors, such as depth or location. Women tend to have thinner melanomas[10,11] that are more often located on the limbs, whereas in men tumors more often develop on the trunk, a site associated with a poorer prognosis. Five- and 10-year survival rates are generally 10% to 20% higher for women in most studies.[12,13] This advantage may be lost after the age of 65 years.[14]

Location

The location of a primary melanoma has been shown to be an independent predictor of survival,[15] which is usually longer for patients with tumors on the extremities (with the exception of hands or feet) than for patients with axial tumors.[15] Localized melanoma on an arm or a leg has been associated with a 90% survival rate at 10 years (vs 70% for localized axial melanomas).[16] The melanoma sites usually associated with a poor prognosis may be remembered by means of the acronym BANS, referring to the back, arm (posterior surface), neck (posterior), and scalp.[17] The survival prognosis for patients with BANS lesions is worst when the site is the scalp, followed by the neck, the back, and the arms.[18]

Studies of more specific areas show that patients with localized melanomas on the forearm or anterior aspect of the upper arm have a better prognosis than those with tumors on the hands or back of the arm.[19] The prognosis is also worse when tumors appear on the middle or lower part of the back or on the mammary and supramammary regions.[20]

One reason why melanoma tumors on the trunk have a worse prognosis than those on the extremities may be differences in lymphatic drainage in these locations. An axial tumor can drain toward mediastinal or paraortic lymph nodes[21] in addition to the axillary or inguinal nodes; axial tumors would thus have a more systemic pattern of dissemination than would tumors on the extremities, explaining why the latter are associated with more encouraging survival curves.[22,23]

Age

Older age has been repeatedly linked to a more aggressive melanoma phenotype, mainly deeper tumors with ulceration.[24-27] Some studies have shown age to be an independent predictor affecting overall survival.[28]

That a more aggressive phenotype is found in older age groups may be explained by various factors. Older patients are less concerned with changes they may observe in their skin, and they perform self-examination less often than younger persons.[29] Finally, nodular melanoma tumors are more common in older patients and this phenotype—in contrast with superficial spreading or lentigo maligna melanomas—is not associated with the presentation of early signs and symptoms of disease.[30]

In the largest study of survival to take age groups into consideration, in which patients were censured if lost to follow-up or dead from other causes, patients aged under 40 years had a 10-year survival rate of 77%. The rate decreased with each decade of life: 10-year survival was 69%, 63% and 56% for patients in the sixth, seventh, and eighth decades of life, respectively. In the group of patients over the age of 80 years, the rate was 43%.

The worsening of prognosis with age has also been explained in terms of immune system aging,[32] as DNA repair becomes compromised and the ability to respond to tumor formation is reduced. However, this process is poorly understood at this time.[33]

Age at first appearance of a tumor also seems to be relevant in pediatric melanoma. One study found that 5-year disease-free survival was higher in children under the age of 10 years (90%) than in those who were older (47%).[34] As the difference could not be attributed to lesion thickness, it may be that tumors behave differently in children and adults. However, these findings must be interpreted with great caution, given that the figures were based on only 33 cases.

Histologic Type

For 40 years melanomas have been grouped into 4 main types based on clinical and pathologic features. The 3 types initially described were superficial spreading, lentigo maligna, and nodular melanomas.[35] A fourth type, acral lentiginous melanoma, was added some years later.[36,37] Classification is based on whether or not the tumor has displayed a radial growth phase (absent in the nodular type). When such a phase has been confirmed, further differentiation is based on the intraepidermal component of the tumor, which may display a growth pattern that is pagetoid (superficial spreading melanoma) or lentiginous (lentigo maligna and acral lentiginous melanomas).

These variants have been associated with manner of sun exposure based on BRAF or N-RAS expression in skin tumors on areas that receive intermittent sun exposure.[38] Acral lentiginous melanomas, on the other hand, have been associated with greater c-KIT expression.[39]

One suggestion, supported by dermatoscopic findings, has been that these histologic subtypes had their origin in stem cells of the follicle (lentigo maligna melanoma), dermis (nodular melanoma), or epidermal basal layer (superficial spreading melanoma).[40]

This hypothesis has drawn criticism, however: overlapping classification is fairly common when traditional histologic and pathologic features are taken into account and such information adds little prognostic value beyond the predictive ability of melanoma location; as a result these terms are now little used.[41,42] Melanoma classifications based on cellular changes that have greater predictive power and therapeutic relevance seem more likely to prosper in the future.[43]

Among the less common variants, desmoplastic melanoma, which consists of spindle cells in a fibrotic stroma, should be mentioned. Some studies have named 2 subtypes of desmoplastic melanoma: a "pure" type that is entirely desmoplastic and a "mixed" type in which more conventional melanoma structures can be seen in the tumor.[44] Evidence suggests that the prognosis is better for the pure type.[45] At the time of diagnosis, desmoplastic melanomas are usually 3-fold thicker than other types, with inconsistent effects on survival; some authors have reported longer survival for patients with desmoplastic tumors in comparison with more common melanomas of comparable thickness[46] while others have found that survival is similar after adjusting for thickness.[47]

Small series of rare histologic types have been reported. One is animal-type melanoma, which is characterized by intense brown or black coloring. This tumor might arise at any location, including mucosal tissues, and while it has a tendency to regional metastasis it is less capable of systemic spread.[48] Other variants (eg, nevoid, spitzoid, angiotropic, or malignant blue nevus melanomas) are so rare that nothing can be inferred about prognosis.[49]

Tumor Progression Phase

Two tumor progression phases, a radial growth phase and a vertical phase, have been described. A melanoma in the radial growth phase has remained within the epidermis (melanoma in situ) or has isolated tumor cells or nests of cells that have reached the papillary dermis but that are smaller than those in the epidermis; tumors considered to be in this phase always lack evidence of mitotic activity (Figure 1). The vertical growth phase, on the other hand, is characterized by the presence of mitotic figures or nests of tumor cells in the dermis that are larger than those in the epidermis.[50] Clark and coworkers[15] at first suggested that prognosis is worse when tumors are growing vertically than when they are in the radial growth phase, which was associated with nearly 100% survival. However, later studies of survival using multivariable analytic methods were unable to demonstrate that tumor progression phase is an independent predictor.[51]

As melanomas in the radial growth phase do not show evidence of metastasis to the sentinal node, however, this factor might still be considered an exclusion criterion for selective sentinal node biopsy.[52] Vertical-phase progression, on the other hand, is a risk factor for sentinal node dissemination even of thin tumors (<1 mm). This increased risk has been associated with a higher mitotic rate and, to a lesser extent, male gender.[53]

Histologic Regression

Even though histologic regression may be observed in 10% to 35% of melanomas, there is probably less agreement about this traditional prognostic factor than about any other in terms of both the description of a finding of regression and its predictive value.[54]

Histologic regression involves a reduction in or disappearance of the dermal portion of the tumor and its replacement by fibrosis; melanophage accumulation is observed, with a proliferation of blood vessels that are usually arranged perpendicular to the epidermis (Figure 2).[55]

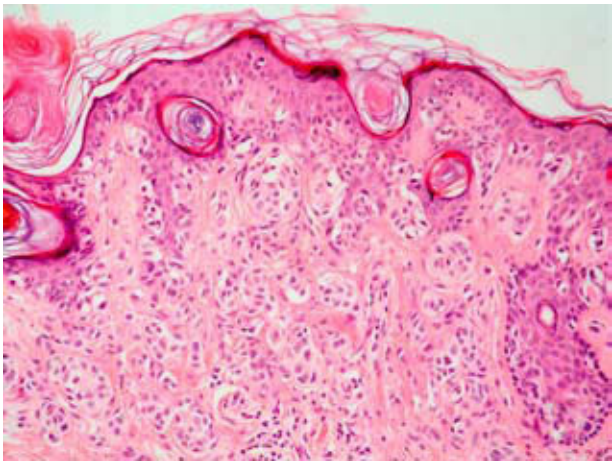

Figure 1 Radial growth of a melanoma. Observe that nests of tumor cells are smaller in the dermis than in the epidermis and that no mitotic figures are present (hematoxylin-eosin, original magnification ×200).

Regression has traditionally been thought to be an indicator of poor prognosis,[15] especially when thin melanomas show more than a 75% reduction in size.[56] In a study of over 9500 patients, that degree of regression (>75%) was present in all cases of thin melanoma (<0.8 mm) that had metastasized to regional lymph nodes.[57] Poor prognosis has also been associated with regression of 50% of the tumor or more,[58] though some authors have not observed this association.[59,60]

Inflammatory Infiltrate

The immune system is thought to play a key role in controlling the growth of a melanoma. The presence of inflammatory infiltrates, specifically tumor-infiltrating lymphocytes (TIL) has been thought to indicate the host's immune response to the tumor, yet the immune system's role and the predictive value of such infiltrates are still much debated.

For Clark and coworkers,[15] TIL are inflammatory cells that appear around or infiltrate the area of vertical growth. Intense lymphocytic infiltration is defined as that which affects the entire infiltrative part of the tumor or is found at the deep margin of the vertical phase of progression (Figure 3). Less intense infiltration would be more localized. In the lowest level of intensity, TIL may be absent or, if present, they do not invade the tumor. In the initial study by Clark's group, in patients whose tumors had entered the vertical growth phase, the 8-year survival rate was 88% for cases with intense TIL, 75% with less intense TIL, and 59% for those with the lowest level of intensity. Similar studies followed,[61] and 1 group even reported 5-year survival to be 100% for patients with intense TIL (10-year survival, 93%).[62] Other authors, however, have not observed that the presence of an inflammatory infiltrate favors survival. A study by Barnhill and coworkers[51] of 548 patients found 5-year survival to be 86% for patients with TIL and 91% for patients without TIL. Those authors, however, included tumors in both radial and vertical growth phases, and only 25% of the patients had tumors more than 1.7 mm thick. Discrepancies might be partly attributable to differences in study populations. For example, while 25% of the patients included by Barnhill and coworkers had tumors exceeding 1.7 mm in size, such tumors accounted for 82% of the population of Clemente and coworkers[61] and 74% of the population studied by Turthill and coworkers.[62]

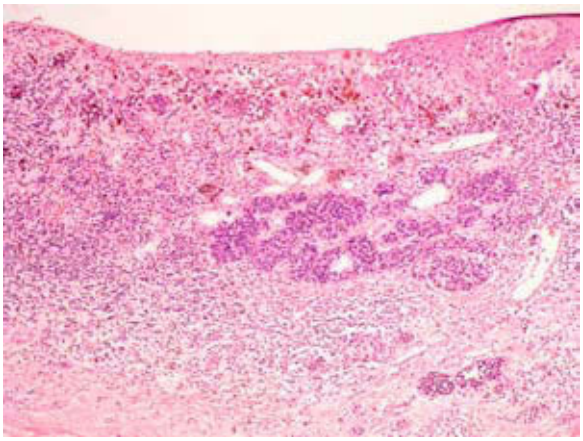

Figure 3 Intense inflammatory infiltrate invading the tumor (hematoxylin-eosin, original magnification ×100).

The absence of TIL has been shown to be an independent predictor of metastasis to the sentinal lymph node and of regional recurrence, but evidence does not suggest that survival will be shorter than in cases in which TIL are present.[63]

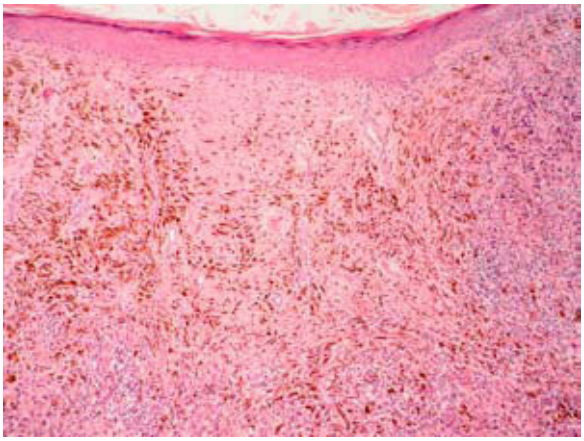

Figure 2 Melanoma regression with fibrotic replacement, intense melanophage accumulation, and vascular proliferation in a direction perpendicular to the epidermis (hematoxylin-eosin, original magnification ×100).

Microscopic Satellite Metastasis (Microsatellites)

First described by Day and colleagues[64] in 1981, microscopic satellites are melanoma cell nests measuring more than 0.05 mm that are clearly separated from the tumor mass by a layer of collagen or subcutaneous fat at least 0.3 mm wide (Figure 4).

Although the TNM classification of the AJCC[1] puts microsatellitosis in the cN2 category, indicating stage III disease and therefore outside the scope of this review, we note that the guideline authors based their decision on the results of several studies showing that survival is similar to that of patients with macroscopic satellite lesions.[65-67] Furthermore, this classification of a tumor is partly the result of an assumption that microsatellites are a step on the way to the development of lymphatic metastasis.

Tumor Lymphangiogenesis

We now have evidence that melanoma can induce the formation of new lymph vessels and that lymphangiogenesis is associated with a higher incidence of metastasis to the

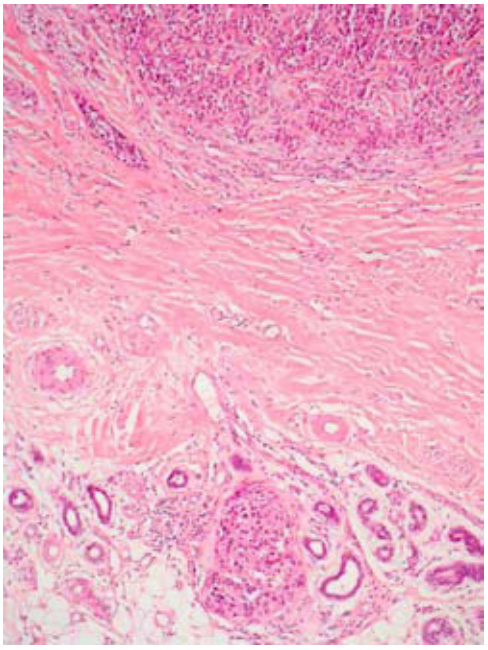

Figure 4 Microscopic satellites. A nest of tumor cells measuring more than 0.05 mm can be seen at the bottom of the figure. The distance between the nest and the tumor above it exceeds 0.3 mm (hematoxylin-eosin, original magnification ×40).

sentinal lymph node and a shorter period of disease-free survival. Therefore, lymphangiogenesis may prove to be a prognostic factor at some point in the future.

Vascular endothelial growth factor (VEGF) C, released by melanoma cells and by tumor-associated macrophages, is probably the most important lymphangiogenic factor, not only in melanoma but also in many other cancers,[68] acting alongside other growth factors such as VEGF-D and VEGF-A.[69,70]

Most cutaneous melanomas initially metastasize to regional lymph nodes,[22,23] and tumor-induced lymphangiogenesis plays an active role in such regional spread. The process develops through formation of a premetastatic niche induced by VEGF expression by the primary melanoma,[69] and the extension of lymphangiogenesis in the primary tumor has been correlated with a finding of metastasis to the sentinal lymph node at the time of surgery.[72] Multivariable analysis has in fact confirmed tumor lymphangiogenesis to be the strongest predictor of sentinal lymph node positivity, with a predictive value even greater than tumor thickness.[72] Negative correlations of lymphangiogenesis with both disease-free survival and overall survival have also been reported.[73]

Vascular Invasion

Clear identification of melanoma cells within the lumen of blood vessels is the criterion for vascular invasion, an independent predictor of poor prognosis.[74,75] The frequency of vascular invasion increases with thickness and is unusual in tumors less than 1.5 mm thick.[75]

A condition of "uncertain" vascular invasion, in which cells are found immediately adjacent to but not invading the endothelium of a vessel, has also been described.[75] The reported prognosis in such cases is similar to that reported for cases in which there is an unequivocal finding of vascular invasion; the slightly higher recurrence rate in cases of "uncertain" invasion suggests that this is in fact an early step in the progression of the melanoma.[75]

The use of immunohistochemical markers to study vascular invasion does not appear to increase the diagnostic yield in comparison with hematoxylin-eosin staining.[75,76]

Another concept is angiotropism. Just as melanoma cells can migrate along the edges of such structures as nerves or cutaneous adnexa, they may also follow a perivascular course along blood vessels. Angiotropism has been seen to mainly affect small vessels at the border of the melanoma and has been hypothesized to be a newly identified mechanism of extravascular metastasis,[77] as this finding is more common than vascular invasion. Local recurrence and in-transit metastasis have been associated with angiotropism.[78]

Neurotropism

Neoplastic infiltration of nerve fibers by a tumor spreading along a nerve is the definition of neurotropism (Figure 5). A finding of neurotropism points to a diagnosis of desmoplastic neurotropic melanoma, given that nondesmoplastic neurotropic melanoma is extremely rare.[79]

In a study of 190 patients diagnosed with desmoplastic melanoma, 90 of whom had the neurotropic variant, no significant differences in survival were observed in association with either type in comparison with other cutaneous melanomas, but local recurrence of desmoplastic neurotropic melanoma was more frequent.[80] Lower recurrence rates, however, were reported based on a more recent study,[81] a discrepancy possibly attributable to differences in surgical margins between the 2 studies.

Cellular Atypia

Few studies have looked at the prognostic value of cellular atypia (Figure 6). One study of 669 patients found the 10-year survival rate for those with melanoma tumors with marked atypia was 40%, whereas the rate was 60% for moderate atypia and 80% for slight atypia.[82] In a report of a series of 12 cases, 11 tumors with severe cellular atypia metastasized.[83]

Association With Melanocytic Nevus

A nevus is identified during histologic examination of a melanoma in approximately 25% of cases. In a classic study of 557 patients published by Friedman and colleagues nearly

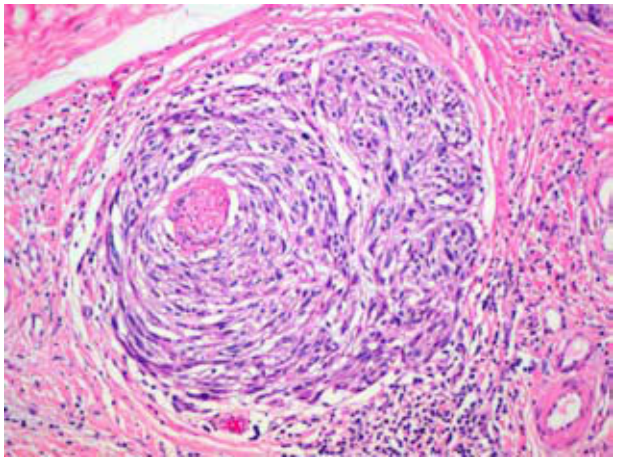

Figure 5 Neurotropism. Note the invasion of a dermal nerve by tumor cells (hematoxylin-eosin, original magnification ×100).

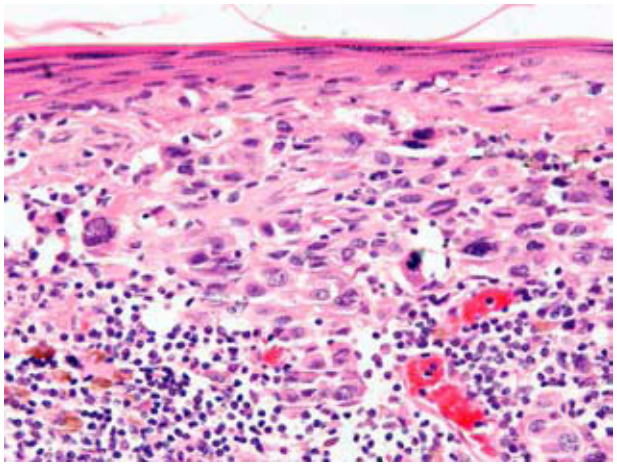

Figure 7 Marked cell atypia in the presence of mitotic figures (hematoxylin-eosin, original magnification ×200).

3 decades ago, the presence of a nevus conferred a benefit in terms of disease-free survival at 5 years (91% survival vs 78%). A more recent study showed that a prior finding of a nevus correlated with a lower rate of metastasis,[84] although the association has not been confirmed by other studies.[85-87] Nonetheless, the risk of finding a second such tumor is 9-fold higher for patients with a history of a melanoma arising from a nevus.[88]

Cell Type

A considerable variety of cell types may be found in melanoma, yet studies have not looked systematically at the prognostic value of this factor. Epithelioid melanomas are generally more likely to metastasize, whereas a finding of fusiform or spindle cells generally suggests a better prognosis.

A study of small cell melanomas (Figure 7) found this cell type, and also ulceration, to be significant independent predictors of metastasis to the sentinal node.[89]

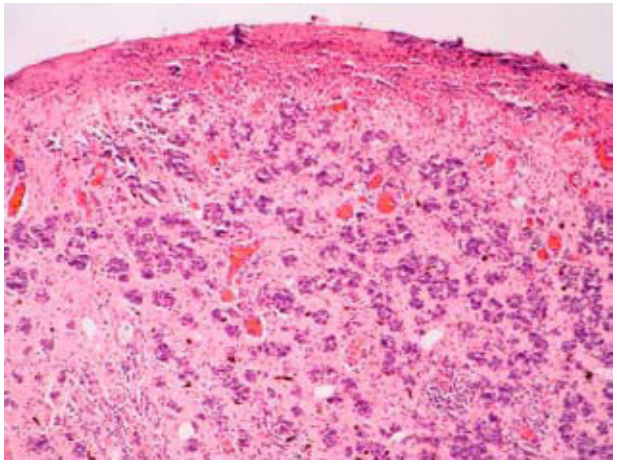

Figure 6 Small-cell melanoma, showing compact nests of tumor cells with hyperchromatic nuclei and scant cytoplasm (hematoxylin-eosin, original magnification ×100).

Paratumoral Epidermal Hyperplasia

Paratumoral epidermal hyperplasia, which refers to changes in the epidermis adjacent to the melanoma, is assessed as the difference between the deepest paratumoral epidermal penetration and the thickness of the normal epidermis; such hyperplasia has been shown to have a protective effect in thick melanomas, particularly if the hyperplasia exceeds 1 mm.[84]

Melanoma Growth Rate

The melanoma growth rate is the increase in tumor volume per unit of time. As the real volume of a melanoma cannot usually be determined, however, in 2002 Grob and coworkers[90] proposed an index that uses tumor thickness (Breslow depth or thickness) as a surrogate for volume. The unit of time used to calculate this index is the time the patient reports as elapsed since appearance of the lesion in de novo cases, or time elapsed since changes were observed in a prior melanocytic lesion. Change is expressed in millimeters per month. Later, this index was found to correlate with more aggressive melanoma phenotypes (eg, nodular melanoma), higher mitotic rate, presence of ulceration, and amelanosis as well as older age and male sex.[91] A growth rate exceeding 0.4 (ie, growth of 0.4 mm/mo) has recently been shown to predict a poor outcome.[92]

In conclusion, risk groups in the most recent AJCC melanoma staging system are based on only 3 factors: tumor thickness, ulceration, and number of mitotic figures. However, much more information than that can be gathered during histology of the primary tumor and, if considered in conjunction with various clinical features, such information may help to explain outcome differences in patients with identically staged tumors. Therefore, pathology reports should reflect as much information as possible about such prognostic variables, as they may facilitate case management and follow-up in the future.

Conflict of Interest

The authors declare that they have no conflict of interest.

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