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Utilizing non-histological serological markers in the prediction of recurrence and metastasis in head and neck melanoma

L. O. Kovtun

Odesa National Medical University

Odesa Regional Clinical Antitumor Center

Odesa (Ukraine)

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There is a need for the development of additional prognostic melanoma (e.g., head and neck melanoma) biomarkers to stratify melanoma patients and reliably identify high-risk subgroups with the aim of providing effective personalized therapy.

Biomarkers play an important role in the diagnosis and prognostic classification of various types of cancer and may be indicators of biological or pathological processes or responses to exposure or intervention, providing a physician with the data helpful for future decision making with regard to patient management.

The advent of novel treatments and modalities for treating various stages of the disease with a notable objective response-to-survival ratio gave us good reason, in this review, to emphasize non-histological serological biomarkers for the correction and improvement in the efficacy of treatment as well as the prognosis of survival in patients with head and neck melanoma.

Introduction

Melanoma incidence rates continue to rise, and primary head and neck melanomas (HNM) account for roughly 18-22% of all malignant melanoma diagnoses, although this region accounts for only 9% of the total surface area of the skin [1].

HNM are high-risk lesions because of the anatomy-related features such as active vascularization at and lymph outflow from head and neck sites, which makes a multidisciplinary approach to these patients essential.

The casual factors influencing the development of HNM can be divided into epidemiological (the gender, age, Fitzpatrick skin type, history of sunburns and chronic exposure to sun light) and clinical (the presence of freckles, lentigo, actinic keratosis, congenital melanocytic nevi larger than 20 cm in diameter ("giant nevi"), family history of melanoma, history of several primary melanomas, and xeroderma pigmentosum (an autosomal recessive disorder)). Prognosis is poorer with increased age, in male patients and truncal head and neck tumors compared to melanomas on limbs [2, 3].

In a study by Shaw and Fay (2011) [4], the most common site of HNM was the skin of face (52%), followed by scalp (19%), neck (17%), ear (9%), and mucosal lesions (3%). Primary melanomas of the eyelid skin are rare and account for < 7% of the HNM [5]. In the 2018 WHO Classification of skin tumors (4th edition), melanoma is classified based on the likely pathogenesis and the degree of its association with sun-exposure. For melanomas arising on sun-exposed skin, further classification is based on the degree of cumulative sun damage (CSD) as assessed by the degree of solar elastosis on biopsy specimen [6].

Typical mactoscopic features, as summarized in the ABCD rule, include Asymmetry of the lesion, irregular Borders, variability in Colors and Diameter larger than 5 mm. The clinical diagnosis of melanoma is based on: (1) total body visual site examination for the detection of lesions displaying one or more of the ABCDE criteria; (2) intra-individual comparative analysis, which is searching for the lesion that is not alike the others in the same patient (ugly duckling sign); and (3) assessment of the evolution of lesions in case there is available documentation [7]. Ulceration and a nodular component might develop with the evolution of the tumor. In terms of history of the lesion, melanoma is almost always growing and changing

shape and/or colors. The sensitivity of clinical diagnosis by experienced dermatologists is difficult to assess but is estimated to be around 70% [8, 9].

Less frequently, melanoma might be hypo- or amelanotic, rendering its recognition particularly challenging. Nodular melanoma may lack the aforementioned diagnostic features. In this case the EFG rule, standing for Elevated, Firm and Growing, is relevant to prompting excision of a potentially aggressive melanoma [9].

Dermatoscopy should always be used in the clinical diagnosis of skin tumors. It addition, it should be applied on all lesions and not only in clinically suspicious ones. This is because dermatoscopy has the potential to uncover the morphologic asymmetry of melanoma before it becomes clinically recognizable and reveal clues that are strongly suggestive of melanoma. Training in dermatoscopy is mandatory since the technique becomes more beneficial with increasing experience. A meta-analysis of 22 studies showed that when experts employed dermatoscopy, they achieved an increase in diagnostic accuracy over the clinical diagnosis alone in questionable lesions, reaching a sensitivity of 89% and a specificity of 79% [10].

Subtypes of invasive melanoma have been traditionally distinguished into four major clinicopathological subtypes: superficial spreading melanoma (SSM), nodular melanoma (NM), lentigo maligna melanoma (LMM) and acral lentiginous melanoma (ALM). The three first of these can occur on the head and neck.

SSM is the most common subtype of HNM and begins with an intraepidermal horizontal or radial growth phase, appearing first as a macular lesion. In addition, SSM is often associated with nevi and is often seen in younger patients.

ND is the second most common subtype of HNM and begins with a vertical growth phase [11].

LMM is characterized by a long radial growth phase. It is an in situ melanoma arising on chronically sun-exposed skin (often the face and the necki) and presents as a slowly growing patch. In addition, it is characterized by a lentiginous proliferation of atypical melanocytes at the dermo-epidermal junction and confluence, and commonly follows hair follicles [12].

The prototypical dermatoscopic progression model for LMM on the face includes four sequential patterns that are annular-granular pattern, asymmetrically pigmented follicular openings, rhomboidal structures [13, 14], whilst the importance of additional features such as increased vascular network and red rhomboidal structures have been linked to the development of tumor-induced neovascularization [15].

Desmoplastic melanoma (DM) and mucosal melanoma are rare subtypes.

DM commonly presents in conjunction with existing melanocytic lesions and can more frequently be amelanotic, which makes their diagnosis difficult. Desmoplastic/amelanotic melanomas tend to be characterized by infrequent metastasis with a higher local recurrence rate, as well as more frequent perineural involvement. DM commonly develops in the dermis and can present as ill-defined scar-like lesions; it is composed of population of low to moderate density spindle cells, with individual cells separated from each other by collagen fibers of fibrous stroma [16]. Amelanotypic melanoma lacks most of the aforementioned dermatoscopic criteria and is characterized by a polymorphic vascular pattern and white shiny streals/lines [17-20].

Head and neck mucosal melanoma primarily manifests in the mucosa of nasal cavity and paranasal sinus, followed by the oral cavity and and nasopharynx. It is dermatoscopically characterized by multiple colors, including various combinations of brown, black, red, white and gray [21]. This rare type of lesion has a poor prognosis. Since it develops in clinically occult sites, late diagnosis is common, which requires a more radical treatment and contributes to worse prognosis.

Melanomas can metastasize either by the lymphatic or the hematogenous route. About two thirds of metastases are originally confined to the drainage area of regional lymph nodes. Regional metastases can appear as:

• Satellite metastases (defined as up to 2 cm from the primary tumor)

• In-transit metastases (located in the skin between 2 cm from the site of primary tumor and the first draining lymph node).

• Micro-metastases in the regional lymph nodes identified via sentinel lymph node biopsy [22, 23]. In contrast to macrometastases, micrometastases are clinically recognizable neither by palpation, nor by imaging techniques.

Distant metastases have a very poor prognosis in untreated patients, although there is considerable variation depending on progression of the tumor, which can be clinically defined by the number of organs involved, presence of brain metastases, and serum levels of lactate dehydrogenase (LDH). The gold standard for the diagnosis of melanoma is biopsy followed by histopathological analysis. An initial biopsy allows us to determine the stage of melanoma. The American Joint Committee on Cancer (AJCC) staging system, which is based on evaluations of the primary tumor, regional lymphatics, and sites of metastasis, is widely used for the categorization of cutaneous melanoma and prognostication purposes. There are marked differences in melanoma-specific survival for the different tumor/node/metastasis (TNM) stages. The eighth edition of the AJCC staging system combines several well-established prognostic factors for melanoma, including the Breslow thickness, mitotic rate, presence of ulceration, extent of metastasis, and serum LDH level [24]. At present, genetic tests can facilitate the diagnosis and staging of melanoma. Further paramount advances in melanoma treatment include recently emerged immune checkpoint inhibitors (ICPi) which improve survival in late-stage melanoma. Pennock and colleagues (2012) [25] state that their study of patient responses to ipilimumab,

a novel immunopotentiator for metastatic melanoma, showed (1) difficulties with the prognosis of this response and (2) insufficiency of the conventional treatment response criteria for the prognosis for therapeutic benefit, because the benefits differ from patient to patient.

Therefore, research on potential biomarkers indicating patient response to therapy and prognostic biomarkers for survival in malignant HNM may be beneficial for developing individual follow-up methods to be used in the course of treatment for and during regular check-ups of patients with this condition.

In recent years, important developments in molecular analyses, genomics, and cancer biology technologies have led to the discovery of numerous new cancer biomarkers.

Biomarker is a parameter that can be measured accurately and reproducibly and may indicate the health status or death of a patient.

In other words, it is an objective index that reflects the events taking place in the cell or body at a certain point.

Cancer biomarkers can be classified into three categories: diagnostic, prognostic, or predictive. Diagnostic biomarkers are used to identify and confirm cancer occurrence and can facilitate early detection of recurrence. Prognostic biomarkers are used to predict the likely course and probable outcomes of the disease. Lastly, predictive biomarkers are used to evaluate the possible response from a specific treatment. Importantly, prognostic biomarkers can also aid in the stratification of patients into optimal treatment strategies, and predictive biomarkers can be helpful for the implementation of personalized therapy.

The first and historically best-recognized category of nonhistological prognostic biomarkers of cutaneous melanoma are the serologic tumor biomarkers.

In the United States, Canada, Europe, Australia and New Zeland, serum LDH level is assessed at the initial visit of a patient with early melanoma and at subsequent follow-up visits. An elevated serum LDH level is an independent prognostic factor for poor prognosis and may be used for melanoma staging. The national melanoma guidelines in Germany and Switzerland recommend measuring serum S100 calcium-binding protein B (S100B), levels in high-risk melanoma patients at follow-up in order to facilitate early detection of relapse. In addition, the national melanoma guidelines in Germany recommend measuring melanoma inhibitory activity (MIA) at the initial visit of a patient with suspected early melanoma and at subsequent follow-up visits. A high-serum MIA concentration at diagnosis correlates with an elevated risk of recurrence [26-28].

Therefore, serum biomarkers offer a convenient and potentially widely adopted method for assessing for the presence of residual disease and its extent [29]. The most studied serological prognostic markers are as follows: S100B, MIA, hepatocyte growth factor (HGF), eosinophil cationic protein (ECP), serum indoleamine 2,3-dioxygenase (IDO), decreased vitamin D level, and decreased serum LDH. These serological prognostic markers are reviewed briefly below.

S100 calcium-binding protein B (S100B)

The proposed utility of S100B as a prognostic biomarker of melanoma can be traced to its widely studied role in melanoma progression. This protein is secreted from malignant melanocytes into the blood, where its concentration can be measured. S100B is a member of the EF-hand family of calcium-binding proteins responsible for many cell processes, including cell-cycle progression and differentiation. Elevated serum S100B correlates with poor patient survival and a higher risk of relapse [30, 31].

In cutaneous malignant melanoma, the serum concentration of S100B has been shown to be correlated with the clinical stage, and the sensitivity for S100 was found to be 1.3%, 8.7% and 73.9% in patients with stage I/II, III and IV, respectively ($p < 0.05$) [32].

Krähn and colleagues (2001) [33] have found that S100B may be superior to LDH and MIA as a prognostic factor for overall and long-term survival in metastatic melanoma. The national melanoma guidelines in Germany and Switzerland recommend measuring serum S100B levels in high-risk melanoma patients at follow-up in order to facilitate early detection of relapse. However, such guidelines have not been adopted in the United States and other countries because there are data suggestive of a limited prognostic value for serum S100B to advanced melanoma [27, 34]. Given that an elevated serum S100B level is rarely seen in early melanoma, the biomarker should not be utilized for screening HNM, but it can be utilized for the detection of melanoma relapse and progression. Tarhini and colleagues [35] reported that a changing S100B from low at baseline to high on follow-up seemed to be associated with the worst relapse-free survival and overall survival in patients with high-risk resected melanoma.

Melanoma inhibitory activity (MIA)

MIA is a small protein secreted by melanoma tumor cells and interacting with proteins of the extracellular matrix (ECM). MIA overexpression promotes metastatic behavior of malignant melanoma cells, which makes it a potential prognostic marker for a patient with the disease [36].

MIA promotes the spread of metastatic cells over the entire body since the protein enables melanoma cells to detach from some of their ECM contacts. In individuals with melanoma, MIA binds to other proteins on or near the surface of healthy cells. This binding supports tumor cells as they invade healthy tissues in the body. Neoplastic melanocytes specifically change their attachment to components of the ECM and basement membranes to enhance their metastatic capability. In addition, MIA decreases the growth of new tumor cells in the body, making it harder for the immune system to defend the body against melanoma cells.

MIA levels increased in 5.6% of individuals with early-stage melanoma and up to 89.5% of people with late-stage melanoma. Moreover, a preoperative serum MIA concentration of 9.4 ng/mL or higher in patients with localized cutaneous malignant melanoma represents an alarm signal [37]! Therefore these patients should be monitored at shorter time intervals and thoroughly investigated in more detail in order to identify potential metastases.

We believe that quantitative measurements of serum MIA may be utilized for the detection of both clinically significant and insignificant metastatic HNM as well as for monitoring of the therapy for changes in the patient's condition [38, 39].

Hepatocyte growth factor (HGF)

HGF is a fibroblast-derived protein that affects the growth, motility and differentiation of epithelial cells. As early as the early 1990s, it has been demonstrated that HGF stimulates melanoma growth [40, 41].

HGF, an angiogenetic factor, is a heparin-binding growth factor. It is secreted by fibroblasts and is mitogenic for epithelial and endothelial cells and also melanocytes. Therefore, HGF creates a microenvironment through interaction between cancerous cells and adjacent stroma, increasing the further development and invasiveness of cancer.

HGF is a cytokine involved in multiple biological processes and facilitates melano-ma tumor genesis and tumor progression via its activation of the mitogen-activated protein linase (MAPK) pathway [42, 43].

HGF showed a significant prognostic association with progression-free survival (PFS) and overall survival (OS) in advanced metastatic melanoma patients. Specifically, lower serum HGF levels were correlated with better PFS and OS [44].

Therefore, HGF monitoring may contribute to the optimization of the treatment process and improved survival prognosis, enabling a more personalized approach to treating patients with HNM.

Eosinophil cationic protein (ECP)

ECP is a primary protein in the granule matrix of eosinophils, and it is released during eosinophil degranulation [45]. Eosinophils have potential mechanisms of antitumor action and enable wide variations in biochemical parameters, leading to either antitumor or protumor effects. Kruckel and colleagues [45] found that lower serum ECP levels (<12.2 ng/mL) were associated with longer OS in patients with metastatic melanoma. ECP is utilized as an early prognostic marker in metastatic melanoma because it mediates anticancer effects such as tissue remodeling and cytotoxis activity.

Patients with lower ECP levels showed a statistically significant longer OS than patients with higher ECP levels. Patients who exhibited an increase in eosinophils upon immunotherapy were shown to survive longer [46].

Therefore, tumor eosinophilia may help a clinician to manage a patient with HNM, depending on whether it developed due to systemic cancer-associated inflammation or was directly caused by the treatment.

Serum indoleamine 2,3-dioxygenase (IDO)

IDO is an intracellular enzyme and is rate-limiting during tryptophan catabolism to kynurenine, facilitating the development of some types of cancer, e.g., melanoma [47].

This enzyme helps cancer cells to produce kynurenine, an amino acid capable of contributing to tumor growth and spread. Overexpression of IDO in tumor cells and antigen presenting cells causes depletion of tryptophan and accumulation of kynurenine, a catabolite of tryptophan, in the local microenvironment of the tumor, resulting in immunosuppression via the induction of allergy and apoptosis of T-cells, and inhibition of T-cell differentiation [48-51]. It is worth of note that the enzyme ensures immune system protection against threats in a healthy individual.

Rubel and colleagues [52] showed that the level of IDO expression in primary human melanoma cells significantly correlates with Breslow thickness. They concluded that their results suggested that IDO induction within melanoma cells may directly reflect tumor progression, whereas IDO in antigen-presenting cells may determine immune surveillance with impact on local and systemic tolerance.

Moreover, the level of melanoma cell expression was strongly correlated to well-known prognostic histopathologic parameters such as ulceration, mitotic rate, lymphangioninvasion, microsatellitosis and tumor-infiltrating lymphocytes [53].

Therefore, IDO has an important immunoregulatory role in melanoma (particularly, HNM). In melanoma, serum IDO levels are significantly associated with disease stage, relapses and overall survival. These results indicate IDO could be a useful prognostic marker for HNM.

Decreased serum vitamin D level

Serum vitamin D level has a strong impact on the survival prognosis in melanoma. The biologically active metabolite of vitamin D, 1,25-dihydroxyvitamin D(3) (1,25(OH)(2)D(3)) is a secosteroid whose genomic mechanism of action is similar to that of other steroid hormones [54, 55]. Lombardo and colleagues [56] recognize a deficiency status of vitamin D as a possible predisposing factor for the development of melanoma. The hypothesis is supported by the deficit of the known anti-proliferative and antiangiogenics effect attributable to calcitriol, which would have an antitumor action [56].

A case control study showed higher vitamin D levels in serum of healthy controls than in patients at the time of melanoma diagnosis. A multivariate model revealed a negative association between vitamin D sufficiency and melanoma [57]. Subsequent studies confirmed that a lower vitamin D level was related to greater progression of melanoma (Breslow thickness, Clark level), the

presences of poor prognostic markers (ulceration, higher mitotic index), shorter overall survival and increased risk for melanoma-specific death [58-62]. However, some investigators [63] did not observe such relationships and found only longer disease-free survival for patients with higher vitamin D levels.

Given the above, it can be concluded that the activation of vitamin D receptors by 1,25(OH)2D regulates multiple cellular processes involved in carcinogenesis and cancer progression. Patients with aggressive skin cancer were found to have a shorter overall survival if they had vitamin D deficiency and the more severe the deficiency, the shorter the overall survival. A lower vitamin D level is also associated with the pathological parameters of melanoma, e.g., tumor thickness (the depth of tumor penetration into the skin), and can facilitate melanoma cell growth. On the contrary, a higher vitamin D level is associated with a reduced rate of melanoma progression and improved survival. Therefore, serum vitamin D measurements may be helpful in predicting the survival of patients with HNM, and in improving the efficacy of some anti-cancer treatment modalities.

Decreased serum LDH level

Despite emerging data on the prognostic significance of several serum markers discussed above, LDH remains the only widely adopted prognostic serum marker for melanoma that has been validated for metastatic disease [64]. However, there are also false-positive values through hemolysis, hepatocellular injuries like hepatitis, myocardial infarction, muscle diseases, and other infectious diseases with high amounts of necrotic cells [65]. Moreover, LDH is non-specific for melanoma and elevated levels are also found in many other benign and malignant diseases.

LDH is an enzyme catalyzing the conversion of pyruvate to lactate. This reaction is essential when oxidative phosphorylation is disrupted, for instance, in anaerobic conditions and in hypoxia, and the latter is quite common in fast growing tumors with high consumption of nutrients and oxygen [66]. In the AJCC staging system, serum LDH is the only serum biomarker that was accepted as a strong prognostic parameter in clinical routine for melanoma, classifying those patients with elevated serum levels in Stage IV M1C [64, 65]. In a meta-analysis of 76 studies on the prognostic role of LDH in solid tumors, including 12 melanoma studies from 1998 to 2014, Petrelli and colleagues confirmed that high serum LDH concentration is associated with lower overall survival in melanoma patients [67]. In a study by Kelderman and colleagues [68], baseline serum lactate dehydrogenase (LDH) was demonstrated to be the strongest predictive factor for overall survival in metastatic melanoma patients treated with immunotherapy. The suitability of serum LDH as a predictive factor was also demonstrated for therapy with further immunomodulatory drugs, anti-programmed death receptor-1 (anti-PD-1) antibodies pembrolizumab and nivolumab. It has been documented that anti-PD-1-treated patients with a relative reduction of serum LDH compared with their baseline LDH achieved partial remission. On the other hand, patients with an increased serum LDH level compared with the baseline LDH showed progressive disease [69, 70]. Therefore, it can be concluded that serum LDH is a useful marker not only at baseline but also during treatment in patients treated with immunomodulating medications in advanced HNM.

Conclusion

Prognostic biomarkers are important additional tools for assessing HNM mortality risk in various clinicopathological stages of the disease. The universally adopted AJCC staging system integrates histological and clinical findings and categorizes melanoma patients into subgroups with distinctly different outcomes. However, because the current AJCC staging system is population-based and was developed to aid clinical trials, it is not suitable for accurately predicting individual risk. The current staging approach initially categorizes most patients who ultimately succumb to the disease at the time of diagnosis as low risk. Therefore, better prognostic tools are needed to identify individuals at increased risk of HNM progression and metastasis, with the goal of providing earlier personalized treatment. Serological prognostic markers (S100B, MIA, S100B, MIA, HGF, ECP, IDO, decreased vitamin D level, and decreased serum LDH) offer a potential for predicting the risk of progression to metastasis, resistance to treatment, and relapse in HNM. The insufficient sensitivity, specificity and accuracy of serological biomarkers for melanoma are the key limitations for their clinical applications. This becomes especially important, given the heterogeneity of malignant melanoma. That is why we believe that further research is warranted to establish a combination of serological biomarkers with improved sensitivity, specificity and accuracy, which would enable early disease detection and staging, therapeutic monitoring and prognosis in melanoma.

References

1. Licata G, Scharf C, Ronchi A,PelleroneS, Argenziano G, VerolinoP,et al. Diagnosis and Management of Melanoma of the Scalp: A Review of the Literature. Clin Cosmet Investig Dermatol. 2021;14:1435-47.
2. Green AC, Baade P, Coory M,Aitken JF, Smithers M. Population-based 20-year survival among people diagnosed with thin melanomas in Queensland, Australia. J Clin Oncol. 2012;30:1462-67.
3. Joosse A, Collette S, Suciu S,Nijsten T, Lejeune F, Kleeberg UR, et al.Superior outcome of women with stage I/II cutaneous melanoma: pooled analysis of four European Organisation for Research and Treatment of Cancer phase III trials. J Clin Oncol. 2012;30:2240-47.
4. Shaw JHF, Fay M. Management of head and neck melanoma. In: Morton R, editor. Treatment of metastatic melanoma. London: Intech Open; 2011. Chapter 3, p. 29-50. Available from: https://www.intechopen.com/chapters/21336 DOI: 10.5772/19876.

5. Malignant Melanoma of the Eyelid. EyeWiki [Internet]. 2023 [cited 2024 May 29]. Available from: https://eyewiki.aao.org/Main_Page
6. Melanocytic tumour classification and the pathway concept of melanoma pathogenesis. In: WHO Classification of Skin Tumours. 4th ed. France: International Agency for Research on Cancer; 2018;66-71.
7. Garbe C, Amaral T, Peris K, et al. European consensus-based interdisciplinary guideline formelanoma. Part 1: diagnostics: update 2022. Eur J Cancer. 2022;170:236–255.
8. Gachon J, Beaulieu P, Sei JF, Gouvernet J, Claudel JP, Lemaitre M,et al. First prospective study of the recognition process of melanoma in dermatological practice. Arch Dermatol. 2005;141:434-8.
9. Chamberlain AJ, Fritschi L, Kelly JW. Nodular melanoma: patients' perceptions of presenting features and implications for earlier detection. J Am Acad Dermatol. 2003;48:694-701.
10. Kittler H, Pehamberger H, Wolff K, Binder M. Diagnostic accuracy of dermoscopy. Lancet Oncol. 2002;3:159-65.
11. Howard MD, Wee E, Wolfe R, McLean CA, Kelly JW, Pan Y. Anatomic location of primary melanoma: survival differences and sun exposure. J Am Acad Dermatol. 2019;81(2):500-9.
12. King R, Page RN, Googe PB, Mihm MC Jr. Lentiginous melanoma: a histologic pattern of melanoma to be distinguished from lentiginous nevus. Mod Pathol. 2005;18(10):1397-401.
13. Stolz W, Schiffner R, Burgdorf WH. Dermatoscopy for facial pigmented skin lesions. Clin Dermatol. 2002;20:276-8.
14. Schiffner R, Schiffner-Rohe J, Vogt T, Landthaler M, Wlotzke U, Cognetta AB, et al.Improvement of early recognition of lentigo maligna using dermatoscopy. J Am Acad Dermatol. 2000;42:25-32.
15. Pralong P, Bathelier E, Dalle S,Poulalhon N, Debarbieux S, Thomas L.Dermoscopy of lentigo maligna melanoma: report of 125 cases. Br J Dermatol. 2012;167:280-7.
16. Chen LL, Jaimes N, Barker CA, Busam KJ, Marghoob AA. Desmoplastic melanoma: a review. J Am Acad Dermatol. 2013;68(5):825-33.
17. Kittler H, Guitera P, Riedl E,Avramidis M, Teban L, Fiebiger M, et al. Identification of clinically featureless incipient melanoma using sequential dermoscopy imaging. Arch Dermatol. 2006;142:1113-9.
18. Menzies SW, Kreusch J, Byth K, Pizzichetta MA, Marghoob A, Braun R, et al.Dermoscopic evaluation of amelanotic and hypomelanotic melanoma. Arch Dermatol. 2008;144:1120-7.
19. Moloney FJ, Menzies SW. Key points in the dermoscopic diagnosis of hypomelanotic melanoma and nodular melanoma. JAMA Dermatol. 2011;38:10-15.
20. Pizzichetta MA, Stanganelli I, Bono R,Soyer HP, Magi S, Canzonieri V, et al.Dermoscopic features of difficult melanoma. Dermatol Surg. 2007;33:91-99.
21. Blum A, Simionescu O, Argenziano G, Braun R, Cabo H, Eichhorn A, et al. Dermoscopy of pigmented lesions of the mucosa and the mucocutaneous junction: results of a multicenter study by the International Dermoscopy Society (IDS). Arch Dermatol. 2011;147:1181-7.
22. Morton DL, Wen DR, Wong JH, Economou JS, Cagle LA, Storm FK, et al.Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg. 1992;127:392-9.
23. Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Elashoff R, Essner R, et al.Sentinel-node biopsy or nodal observation in melanoma. N Engl J Med. 2006;355:1307-17.
24. Gershenwald JE, Scolyer RA. Melanoma staging: American Joint Committee on Cancer (AJCC) 8th edition and beyond. Ann Surg Oncol. 2018;25:2105-10.
25. Pennock GK, Waterfield W, Wolchok JD. Patient responses to ipilimumab, a novel immunopotentiator for metastatic melanoma: how different are these from conventional treatment responses? Am J Clin Oncol. 2012;35(6):606-611.
26. Ding L, Gosh A, Lee DJ,Emri G, Huss WJ, Bogner PN,et al. Prognostic biomarkers of cutaneous melanoma. J Photodermatol Photoimmunol Photomed. 2022;38(5):418-434.
27. Zissimopoulos A, Karpouzis A, Karaitianos I, Baziotis N, Tselios I.Serum levels of S-100b protein after four years follow-up of patients with melanoma. Hell J Nucl Med. 2006;9:204-207.
28. Kruijff S, Hoekstra HJ. The current status of S-100B as a biomarker in melanoma. Eur J Surg Oncol. 2012;38:281-285.
29. Perkins GL, Slater ED, Sanders GK, Prichard JG. Serum tumor markers. Am Fam Physician. 2003;68(6):1075-82.
30. Hauschild A, Engel G, Brenner W, Gläser R, Mönig H, Henze E, Christophers E. S100B protein detection in serum is a significant prognostic factor in metastatic melanoma. Oncology. 1999;56(4):338-344.
31. Tarhini AA, Stuckert J, Lee S, Sander C, Kirkwood JM. Prognostic significance of serum S100B protein in high-risk surgically resected melanoma patients participating in Intergroup Trial ECOG 1694. J Clin Oncol. 2009;27(1):38-44.
32. Guo HB, Stoffel-Wagner B, Bierwirth T, Mezger J, Klingmüller D. Clinical significance of serum S100 in metastatic malignant melanoma. Eur J Cancer. 1995;31A:1898-1902.
33. Krähn G, Kaskel P, Sander S, Waizenhöfer PJ, Wortmann S, Leiter U, Peter RU. S100 beta is a more reliable tumor marker in peripheral blood for patients with newly occurred melanoma metastases compared with MIA, albumin and lactate-dehydrogenase. Anticancer Res. 2001;21(2B):1311-16.
34. Trotter SC, Sroa N, Winkelmann RR, Olencki T, Bechtel M.A global review of melanoma follow-up guidelines. J Clin Aesthet Dermatol. 2013;6(9):18-26.
35. Tarhini AA, Stuckert J, Lee S, Sander C, Kirkwood JM. Prognostic significance of serum S100B protein in high-risk surgically resected melanoma patients participating in Intergroup Trial ECOG 1694. J Clin Oncol. 2009;27(1):38–44.
36. Stahlecker J, Gauger A, Bosserhoff A, Büttner R, Ring J, Hein R. MIA as a reliable tumor marker in the serum of patients with malignant melanoma. Anticancer Res. 2000;20(6D):5041-44.
37. Sandru A, Panaitescu E, Voinea S, Bolovan M, Stanciu A, Cinca S, et al. Prognostic value of melanoma inhibitory activity protein in localized cutaneous malignant melanoma. J Skin Cancer Cancer [Internet]. 2014 Jun [cited 2024 Apr 30];2014. Available from: https://www.hindawi.com/journals/jsc/2014/843214/
38. Bosserhoff AK, Dreau D, Hein R, Landthaler M, Holder WD, Buettner R. Melanoma inhibitory activity (MIA), a serological marker of malignant melanoma. Recent Results Cancer Res. 2001;158:158–168.
39. Max N, Keilholz U. Minimal residual disease in melanoma. Semin Surg Oncol. 2001;20(4):319-328.

40. Kan M., Zhang G., Zarnegar R., Michalopoulos G., Myoken Y., McKeehan W.L., Stevens J.L. Hepatocyte growth factor/ hepatopoietin A stimulates the growth of rat kidney proximal tubule epithelial cells (RPTE), rat nonparenchymal liver cells, human melanoma cells, mouse keratinocytes and stimulates anchorage-independent growth of SV-40 transformed RPTE. Biochem. Biophys. Res. Commun. 1991;174:331–337.
41. Halaban R., Rubin J.S., Funasaka Y., Cobb M., Boulton T., Faletto D., Rosen E., Chan A., Yoko K., White W., et al. Met and hepatocyte growth factor/scatter factor signal transduction in normal melanocytes and melanoma cells. Oncogene. 1992;7:2195–2206.
42. Matsumoto K, Nakamura T. Hepatocyte growth factor and the Met system as a mediator of tumor-stromal interactions. Int J Cancer. 2006;119:477–483.
43. Bradbury J. A two-pronged approach to the clinical use of HGF. Lancet. 1998;351:272.
44. Hugel R, Muendlein A, Volbeding L,Drexel H, Richtig E, Wehkamp U, et al. Serum levels of hepatocyte growth factor as a potential tumor marker in patients with malignant melanoma. Melanoma Res. 2016;6(4):354–360.
45. Kruckel A, Moreira A, Frohlich W, Schuler G, Heinzerling L. Eosinophil-cationic protein - a novel liquid prognostic biomarker in melanoma. BMC Cancer. 2019;19(1):207.
46. Moreira A, Leisgang W, Schuler G, Heinzerling L. Eosinophilic count as a biomarker for prognosis of melanoma patients and its importance in the response to immunotherapy. Immunotherapy. 2017;9(2):115–121.
47. Routy JP, Routy B, Graziani GM, Mehraj V. The kynurenine pathway is a double-edged sword in immune-privileged sites and in cancer: implications for immunotherapy. Int J Tryptophan Res. 2016;9:67–77.
48. Munn DH, Mellor AL. Indoleamine 2,3 dioxygenase and metabolic control of immune responses. Trends Immunol. 2013;34(3):137–143.
49. Solvay M, Holfelder P, Klaessens S, Pilotte L, Stroobant V, Lamy J, et al. Tryptophan depletion sensitizes the AHR pathway by increasing AHR expression and GCN2/LAT1-mediated kynurenine uptake, and potentiates induction of regulatory T lymphocytes. J Immunother Cancer [Internet]. 2023Jun [cited 2024 Apr 30];11(6). Available from:https://pubmed.ncbi.nlm.nih.gov/37344101/
50. Minhas PS, Liu L, Moon PK,, Joshi AU, Dove C, Mhatre S, et al. Macrophage de novo NAD(+) synthesis specifies immune function in aging and inflammation. Nat Immunol. 2019;20(1):50–63.
51. Munn DH, Sharma MD, Baban B,Harding HP, Zhang Y, Ron D, et al. GCN2 kinase in T cells mediates proliferative arrest and anergy induction in response to indoleamine 2,3-dioxygenase. Immunity. 2005;22(5):633–42.
52. Rubel F, Kern JS, Technau-Hafsi K,Uhrich S, Thoma K, Häcker G,et al. Indoleamine 2,3-Dioxygenase Expression in Primary Cutaneous Melanoma Correlates with Breslow Thickness and Is of Significant Prognostic Value for Progression-Free Survival. J Invest Dermatol. 2018;138(3):679–87.
53. Rose C. Diagnostics of malignant melanoma of the skin: Recommendations of the current S3 guidelines on histology and molecular pathology. Pathologe. 2017;38:49–61.
54. Bikle DD. Vitamin D: An ancient hormone. Exp Dermatol. 2011;20(1):7–13.
55. Tuckey RC, Cheng CYS, Slominski AT. The serum vitamin D metabolome: What we know and what is still to discover. J Steroid Biochem Mol Biol. 2019;186:4–21.
56. Lombardo M, Vigezzi A, Ietto G,Franchi C, Iori V, Masci F, et al. Role of vitamin D serum levels in prevention of primary and recurrent melanoma. Sci Rep [Internet]. 2021March [cited 2024 Apr 30];11(1). Available from: https://www.nature.com/articles/s41598-021-85294-3
57. Cattaruzza MS, Pisani D, Fidanza L,Gandini S, Marmo G, Narcisi A, et al. 25-hydroxyvitamin D serum levels and melanoma risk: A case-control study and evidence synthesis of clinical epidemiological studies. Eur J Cancer Prev. 2019;28(3):203–11.
58. 5Newton-Bishop JA, Davies JR, Latheef F,Randerson-Moor J, Chan M, Gascoyne J, et al. 25-hydroxyvitamin D2/D3 levels and factors associated with systemic inflammation and melanoma survival in the Leeds melanoma cohort. Int J Cancer. 2015;136(12):2890–99.
59. Wyatt C, Lucas RM, Hurst CKimlin MG. Vitamin D deficiency at melanoma diagnosis is associated with higher Breslow thickness. PLoS One [Internet]. 2015 May [cited 2024 Apr 30];10(5). Available from:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4430535/
60. Bade B, Zdebik A, Wagenpfeil S,Graber S, Geisel J, Vogt T,et al. Low serum 25-hydroxyvitamin D concentrations are associated with increased risk for melanoma and unfavorable prognosis. PLoS One [Internet]. 2014 Dec [cited 2024 Apr 30];9(12). Available from:https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0112863
61. Lim A, Shayan R, Varigos G. High serum vitamin D level correlates with better prognostic indicators in primary melanoma: A pilot study. Australas J Dermatol. 2018;59(3):182–7.
62. Saiag P, Aegerter P, Vitoux D,Lebbe C, Wolkenstein P, Dupin N, et al. Prognostic value of 25-hydroxyvitamin D3 levels at diagnosis and during follow-up in melanoma patients. J Natl Cancer Inst [Internet]. 2015Sep [cited 2024 Apr 30];107(12). Available from: https://academic.oup.com/jnci/article/107/12/djv264/2457724?login=false
63. Lipplaa A, Fernandes R, Marshall A,Lorigan P, Dunn J, Myers KA, et al. 25-Hydroxyvitamin D serum levels in patients with high risk resected melanoma treated in an adjuvant bevacizumab trial. Br J Cancer. 2018;119(7):793–800.
64. Balch CM, Gershenwald JE, Soong SJ,Thompson JF, Atkins MB, Byrd DR, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009;27:6199–6206.
65. Vereecken P, Cornelis F, Van Baren N, Vandersleyen V, Baurain JF. A synopsis of serum biomarkers in cutaneous melanoma patients. Dermatol Res Pract Inst [Internet]. 2012Jan [cited 2024 Apr 30];2012. Available from:https://www.hindawi.com/journals/drp/2012/260643/
66. Alegre E, Sammamed M, Fernandez-Landazuri S, Zubiri L, Gonzalez A. Advances in clinical chemistry. 2015;69:47–89.
67. Petrelli F, Cabiddu M, Coinu A,Borgonovo K, Ghilardi M, Lonati V, et al. Prognostic role of lactate dehydrogenase in solid tumors: A systematic review and meta-analysis of 76 studies. Acta Oncol. 2015;54:961–970.
68. Kelderman S, Heemskerk B, van Tinteren H,van den Brom RR, Hospers GA, van den Eertwegh AJ, et al. Lactate dehydrogenase as a selection criterion for ipilimumab treatment in metastatic melanoma. Cancer Immunol Immunother. 2014;63:449–58.
69. Martens A, Wistuba-Hamprecht K, Geukes Foppen M,Yuan J, Postow MA, Wong P, et al. Baseline peripheral blood biomarkers associated with clinical outcome of advanced melanoma patients treated with ipilimumab. Clin Cancer Res. 2016;22:2908–18.

70. Diem S, Kasenda B, Spain L, Martin-Liberal J,Marconcini R, Gore M, et al. Serum lactate dehydrogenase as an early marker for outcome in patients treated with anti-PD-1 therapy in metastatic melanoma. Br J Cancer. 2016;114:256–61.

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Corresponding Author: *Larysa O. Kovtun, Cand Sc (Med), Department for Dermatology and Venerology, Odesa National Medical University, Odesa, Ukraine; Odesa Regional Clinical Antitumor Center, Odesa, Ukraine. E-mail: larysakovtun1972@gmail.com*

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Abbreviations: *ABCD: Asymmetry, Border irregularity, Color variegation, Diameter >6 mm; ECM, extracellular matrix; ECP, eosinophil cationic protein; EFG: Elevated, Firm, Growing; HGF, hepatocyte growth factor; IDC, International Disease Classification; IDO, serum indoleamine 2,3-dioxygenase; S100B, S100 calcium-binding protein B; LDH, lactate dehydrogenase; MAPK, mitogen-activated protein linase; MIA, melanoma inhibitory activity; OS, overall survival; PFS, progression-free survival.*