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Research Article

Causes, symptoms, diagnosis and treatment of melanoma

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ABSTRACT

Melanoma is potentially the most dangerous form of skin tumor with a 90% fatality rate. The diagnosis of melanoma can be made clinically and should always be confirmed by dermatoscopy. If a melanoma is detected, a histopathological examination is required. Sequential digital dermatoscopy and full-body photography can be used in at-risk individuals to detect the development of melanoma at an earlier stage. In addition, confocal reflection microscopy can increase the information content of clinical diagnostics in special cases. Classification of melanomas is carried out according to the AJCC version. Thin melanomas up to 0.8 mm thick tumors do not require further diagnosis. Starting from stage IB, it is recommended to examine the lymph nodes using ultrasound, but no additional imaging studies are performed.

From stage I, it is recommended to examine the entire body using CT or PET-CT in combination with MRI of the brain. Starting from stage III and higher, mutation testing is recommended, especially for the BRAF V600 mutation. It is important to provide structured follow-up to detect relapses and secondary primary melanomas as early as possible.

Keywords: melanoma, causes, diagnosis, treatment.

INTRODUCTION

Melanoma is a malignant tumor that arises from melanocytes and primarily affects the skin. Melanoma can occur in the eyes (the vasculature of the eyeball, conjunctiva, and ciliated body), in the meninges, and on various mucous surfaces. Although melanomas are usually highly pigmented, they can also be amelanotic. Even small tumors can have a tendency to metastasize, which leads to a relatively poor prognosis.

Epidemiology and etiology of the incidence of melanoma is increasing worldwide in white populations, especially where people with light skin color are exposed to excessive sun exposure [14]. In Europe, the incidence rate is<10-25 new cases of melanoma per 100,000 inhabitants; in the US, it is 20-30 per 100,000; and in Australia, where there is a very high incidence; it is 50-60 per 100,000.

In recent years, there has been an increase in the incidence of diseases in people over 60 years of age and especially in men in some parts of Europe, but the incidence of this continent continues to increase at all ages and according to projections it will continue to increase for several decades [15].

The most common phenotypic risk factor is skin prone to sunburn, and inherited variants of the melanocortin-1 receptor (MC1R) are the most important base genotype. Inheritance of melanoma in most cases occurs in people with lower risk susceptibility genes, but 5-10% of cases of melanoma occur in families prone to melanoma that carry high susceptibility genes for this disease [10]. The most important exogenous factor is exposure to ultraviolet radiation, especially intermittent high sun exposure [22].

RESULTS

Dermic melanoma is classified as a local melanoma when it is located inside the epidermis, or invasive when atypical melanocytes gradually penetrate the dermis. Subtypes of invasive melanoma differ in clinical and histopathological features into four main histological subtypes: surface spreading melanoma (SSM) (41%), followed by nodular melanoma (NM) (16%), lentigo malignant melanoma (LMM) (2.7% - 14%), and Lentin melanoma in Acral (ALM) (1-5% in the non-Hispanic white population and higher rates in the Asian or African American population) [16].

SSM begins with an intraepidermal horizontal or radial growth phase, appearing first as a spot that slowly turns into a plaque, often with multiple colors and pale areas of regression. A characteristic histological feature is the presence of an epidermal lateral component with a

pagidoid spread of clear malignant melanocytes throughout the epidermis. Secondary nodular areas that represent the vertical phase of tumor growth may develop in the future.

NM, in contrast, is a predominantly nodular, exophytic brown-black, often eroded or bleeding tumor characterized by a predominant aggressive vertical growth phase. Early diagnosis of this type of melanoma is quite difficult [14].

LMM is defined as the invasive development of a slow-growing malignant lentigo tumor. LMM is a special subtype located mainly on sun-damaged faces of elderly people [14]. LMM is characterized by histologically purulent proliferation of atypical melanocytes in the dermoepidermal junction, fusion, formation of nests in the dermis, and peripollicular localization of melanocytes.

ALM has a typically subungal or palmoplantar (Volar) localization. In the initial intraepidermal phase (which may be prolonged), irregular, poorly defined pigmentation is observed; later, the nodular area reflects the nature of invasive growth.

In the updated WHO classification of skin tumors (4th edition, 2018), melanoma is classified based on the concept of pathogenesis of melanoma and its relationship to sun-exposed skin (table 1) [19]. For melanomas that occur in skin exposed to the sun, further classification is based on the degree of cumulative sun damage (CSD), estimated by the degree of solar elastosis during biopsy. Melanomas that occur in skin exposed to the sun include low CSD melanoma (SSM and a subset of NM) and melanoma in skin exposed to constant sun exposure (LMM, desmoplastic melanoma and a subset of NM).

Melanomas that occur in areas protected from the sun or without known etiological associations with UV exposure include Spitz melanoma, Acral melanoma, mucosal melanoma (genital, oral, sinonasal), melanoma that occurs in congenital nevus, melanoma that occurs in blue nevus, uveal melanoma, nodular, and nevoid [11].

Table 1: Classification of melanomas, including epidemiological, clinical, pathological, and general genomic features Adapted from [19]

Type of UV exposure / CSD	Subtype of melanoma	The affected genes
Melanoma with low CSD	SSM	BRAF V600 E / K or NRAS CDKN2A TP53 SWI / SNF TERT
Melanoma with high CSD	LMM Desmoplastic melanoma	NF1, NRAS, BRAF, KIT CDKN2A TP53 SWI / SNF TERT
Low or zero UV exposure (or variable / occasional)	Spitz's melanoma	HRAS, ROS1, NTRK1, NTRK3, ALK, RET, MET, BRAF, CDKN2A, TERT
	Acral melanoma	NRAS, KIT, NF1, SPRED1, BRAF, CCND1, ALK, ROS1, RET, NTRK1, CDKN2A, CDK4, TP53, SWI / SNF, TERT
	Melanoma of the mucosa (genital, oral, sinonasal)	
	Uveal melanoma	GNAQ, GNA11, CYSLTR2, PLCB4, BAP1,SF3B1, EIF1AX
	Melanoma that occurs with a congenital nevus	NRAS
	Melanoma that occurs in the blue nevus	GNAQ, GNA11, CYSLTR2, BAP1, SF3B1, EIF1AX

*CSD = The cumulative damage from the sun

About 90% of melanomas are diagnosed as primary tumors without any signs of metastasis. The specific 10-year survival rate for such tumors is 95-75%. The most important histological prognostic factors of primary melanoma without metastases, reflected in recent studies, are:

– the vertical thickness of the tumor (Breslow depth) is measured on a histological sample using an optical micrometer scale and is defined as the histological depth of the tumor from the granular layer of the epidermis to the deepest point of invasion;

– presence of histologically recognized ulceration. Melanoma ulceration is defined as a combination of the following features: a full thickness epidermal defect (including the absence of the stratum corneum and basal membrane), evidence of a host response (i.e. deposition of fibrin, neutrophils), and thinning, erasure, or reactive hyperplasia of the surrounding epidermis[17];

– mitosis frequency (number of mitoses / mm2) appears as an independent predictor in several population studies.

Melanomas can metastasize either by lymphatic or hematogenic pathways. Approximately two-thirds of metastases are initially confined to the drainage area of regional lymph nodes. Regional metastases can manifest as:

- satellite metastases (defined as up to 2 cm from the primary tumor);
- metastases in the path (located in the skin between 2 cm from the site of the primary tumor and the first draining lymph node);
- micrometastases in regional lymph nodes are detected using a sentinel lymph node biopsy [18]. Unlike macrometastasis, micrometastasis is not clinically recognized by palpation or imaging methods.

Metastases in regional lymph nodes are clinically or radiologically recognizable.

10-year survival was observed for 30-50% of patients with satellite and transit metastases, for 69-75% of patients with micrometastases in the lymph nodes, and for 40-60% of patients with clinically expressed regional metastases in the lymph nodes [19].

In most cases, the clinical manifestation of melanoma varies depending on the subtype of melanoma. Typical signs are asymmetry of the lesion, irregular borders, color variability, a diameter of 5 mm or more, nodule growth, and regression within the lesion. The sensitivity of a clinical diagnosis by experienced dermatologists is difficult to assess, but it is estimated to be about 70% [12].

The dermatologist's clinical diagnosis is based on a combination of 3 analyses of any pigmented lesion:

- visual analysis of each lesion separately, which usually excludes non-melanocytic lesions, although melanomas can rarely mimic pigmented seborrheic keratoses. The naked eye examination evaluates the presence of so-called criteria A (asymmetry), B (irregular borders), C (non-uniform color) and D (diameter ≥ 5 mm), which indicate suspicious melanocytic lesions (ABCD rule);
- intra-individual comparative analysis that looks for a lesion that is not similar to others in the same patient [10];
- a chronological analysis of changes that looks for a rapid and recent change in a given pigmented lesion (e-like evolution), at least when it can be confirmed by the patient or documented by comparison with previous photos. Papular or nodular lesions may not have clinical diagnostic signs. In these cases, the EFG rule for Elevated Firm and Growing is relevant to speed up the removal of potentially aggressive melanoma [10].

Dermatoscopy should be used to clarify the differential diagnosis of pigmented lesions. In general, a dermatoscopic examination should be performed. However, if it is not available without significant delay due to lack of access to a dermatologist, the final diagnosis and removal should not be delayed. To apply this technique requires training and experience. A meta-analysis of 22 studies showed that when specialists used dermatoscopy, they achieved an increase in diagnostic accuracy compared only with the clinical diagnosis for doubtful lesions, reaching a sensitivity of 89% and specificity of 79% [10].

Characteristic features for the diagnosis of melanoma, also called melanoma-specific criteria, include an atypical pigment network, irregular brown-black dots / globules, streaks, and pigmentation with multiple colors asymmetrically distributed. Additional criteria, such as blue-whitish turbidity and polymorphic vessels, are common for invasive melanoma [8,11,15].

Amelanotic and faceless melanoma may present a diagnostic problem, although suspicion should arise when a polymorphic vascular pattern is observed or when lesions do not show any well-known melanocytic or non-melanocytic characteristics of dermatoscopic features [18]. This requires urgent removal of any growing skin damage suspected of being a skin tumor, even if it looks more like a squamous cell than a melanoma.

The prototype model of dermatoscopic progression for LMM on the face includes four consecutive patterns, which are a ring-granular pattern, hyperpigmented follicular openings, rhomboid structures, and atypical pseudosets [18], while the importance of additional functions

such as enlarged vascular network and red rhomboid structures have been associated with the development of tumor neovascularization [16].

Finally, a parallel ridge and irregular diffuse pigmentation are the main dermatoscopic signs of early and invasive Acral melanoma, respectively [18].

Dermatoscopy should be applied to all lesions, not just those that are clinically suspicious. This is due to the fact that Dermoscopy can reveal the natural asymmetry of melanoma, before it becomes clinically recognizable.

The differential diagnosis of melanoma includes other pigmented melanocytic lesions (congenital, atypical, and common melanocytic ulcers), non-melanocytic pigmented lesions (seborrheic keratosis, actinic lentigo, hemangioma , dermatofibroma, and pigmented basal cell carcinoma), and other non-pigmented tumors, basal cell carcinoma, and squamous cell carcinoma).

Whenever a suspicious skin lesion is removed, a histological examination is required. Difficulties in the clinical diagnosis of melanoma can be also held at the histological level. The sample should be entrusted to a dermatologist who has experience in interpreting pigmented lesions. The histopathological report should include the following information [21];

1. Diagnosis and clinical pathologic type (SSM, NM, LMM, ALM); when there is uncertainty about malignancy, this should be clearly indicated in the report conclusion.
2. Thickness of the tumor in mm (Breslow depth).
3. Presence or absence of ulceration.
4. The number of mitoses per mm 2 (in hot spots).
5. Microsatellites (if present), defined as any intermittent nest of intra-lymphatic metastatic cells> 0.05 mm in diameter, clearly separated by normal dermis or subcutaneous fat from the invasive component of the tumor at a distance of at least 0.3 mm.

In addition to these necessary histological features, additional information may be provided, including:

– growth phase (horizontal or vertical);
– whether or not there is a set regression;
– presence or absence of tumor-infiltrating lymphocytes (TIL), preferably using the terms "brisk", "not brisk" or "absent";
- lymphatic embolism;
- vascular or perineural lesion.

In some cases, when the histological diagnosis is unclear, immunohistochemical spots may be useful (for example, protein S-100, Melan-A, HMB45, and SOX10 are to confirm the melanocytic nature of the tumor, HMB45 is as an additional sign of malignancy when there is an inverted positive gradient, MIB-1 is as a marker of proliferation).

Monitoring the diagnosis of melanoma has the following goals:

1. Detection of a relapse of the disease (local, remote) at the earliest stage.
2. Offering psychosocial support.
3. Providing prevention education for the patient and their first-degree relatives.
4. Provide patient and family training in skin self-analysis to promote early detection of melanoma.
5. Administration and monitoring of adjuvant therapy, where necessary.
6. Improvement of early detection of secondary (melanoma) and non-melanoma skin cancer; [11].
7. Recognition and treatment of skin side effects associated with adjuvant or palliative treatment [13].

The main treatment for melanoma is surgical removal [3]. Excisional biopsy with a minimal clinical margin (1-3 mm) is preferable both to give the dermatopathologist / pathologist the optimal sample, and to assess the fields for removing residual tumors.

A post-incision biopsy should not be performed if a biopsy is technically possible. Such procedures may lead to a diagnostic error due to sampling and may compromise the analysis of architectural features or the assessment of the Breslow thickness. In some cases, they are necessary to confirm the diagnosis, for example, when we are talking about a large malignant lentigo tumor on the face or Acral melanoma. Large studies have not found evidence that a post-incision biopsy worsens the prognosis compared to an immediate full excision biopsy [16,19,23].

Recommendations for removing melanoma are presented in Table 2.

Table 2: Recommendations for removing melanoma

Primary exeresis	Recommendations
GCP	If melanoma is suspected, the entire histological examination should be completely removed with a narrow (1-3 mm) edge. A post-incision biopsy can be performed for large injuries, such as facial lesions (such as lentigo maligna), Acral and genital lesions
GCP	If melanoma cannot be ruled out, destructive blind treatment such as laser, cryotherapy or topical medications should not be performed.

Removing safety boundaries remains the standard of treatment for patients with melanoma. Despite the fact that there is a slight deviation between the recommendations, fields with a width of more than 2 cm are not recommended even in the case of thick primary tumors. The recommendations in the next section correspond to those in the United States, Great Britain, and Australia. In invasive melanomas, the depth of removal should include subcutaneous tissue. Final surgical removal should be performed primarily within 4-6 weeks after diagnosis. Recommendations for the limit of removal of melanoma are presented in table 3.

Table 3: Recommendations regarding the limits of melanoma removal

The safety limits for secondary removal of (re-removal)	Evidence-based recommendation
GCP	In the case of primary melanoma, subsequent removal should be performed to minimize the risk of local relapses. The following safety indicators for peripheral surgical fields * should be taken into account: the surface thickness of the tumor is 0.5 cm <2 mm: 1 cm and the thickness of the tumor is> 2 mm: 2 cm. Large excisions are not recommended.
GCP	Narrower margins for repeated removal can be exclusively considered for specific anatomical locations to preserve function and allow reconstruction, especially in the area of facial, Acral and genital lesions

For skin metastases, depending on the number, size, and location, various options include surgery or other destructive treatments such as cryotherapy, laser therapy, electrochemotherapy, as well as systemic treatments with targeted thermal (TT) or immunotherapy (IT), intravenous / local immunotherapy such as talimogen laherparepvec [7], IL-2 or imiquimod, and RT. Isolated limb perfusion with tumor necrosis factor melphalan is an invasive technique that has only palliative value [17].

Radiation therapy (RT) of the primary tumor is rarely indicated. However, in patients where surgery will lead to serious disorders, RT can be used for therapeutic purposes. This often refers to lentigo's malignant melanoma [19].

Melanoma has a pronounced tendency to metastasize to the brain. Strategies for systemic treatment of brain metastases with a high response rate combined with a short response time to treatment using combined immunotherapy [17] or targeted therapy (melanoma with BRAF mutation) should lead to new considerations regarding the planning of optimal treatment for patients with melanoma with brain metastases.

Adjuvant therapy is offered to patients without signs of macroscopic metastases, but with a high risk of microscopic metastases. In published studies, adjuvant therapy is mainly used in patients with tumors with a thickness of more than 1.5 mm or according to the criteria of the American Joint Committee on Cancer (AJCC), in patients with fully resected stage II-IV melanoma.

The main indications for systemic therapy are inoperable regional metastases and distant metastases (stage IV). From the long list of available cytostatic drugs, only a few were able to cause tumor reactions, but almost no long-term reactions that affect survival. However, new target compounds and immunotherapy drugs have been shown to significantly prolong survival [18]. Two main goals of systemic therapy:

- prolonging progression-free survival (PFS) and OS with acceptable drug toxicity;
- reducing the tumor load or specific symptoms associated with the tumor to improve the quality of life.

Chemotherapy was the only available systemic treatment before targeted therapy and immune control modulators became available. Currently, chemotherapy can be considered as a last-line treatment in patients with immunotherapy resistance and - where applicable-targeted therapy. However, single-drug and combination chemotherapy may still play a role in countries where new and more effective drugs are still unavailable and / or not being reimbursed.

A number of drugs with comparable effectiveness are used for systemic chemotherapy of common melanoma. Chemotherapy can lead to tumor regression and a reduction in tumor-related symptoms, but none of the regimens has shown a survival advantage over symptoms.

CONCLUSION

Thus, there is currently insufficient data to establish a comprehensive treatment algorithm for stage IV melanoma. However, some general principles can be applied.

Treatment of patients with metastatic melanoma should be discussed in multidisciplinary tumor

control bodies with representation from several cancer specialties.

Mutational testing of tumor tissue (at least searching for BRAF mutations) is a prerequisite for treatment decisions and should be performed primarily in metastatic tumor tissue from stage IIIB AJCC and onwards.

PD-1 blockade, either as monotherapy or in combination with CTLA-4 blockade, should be considered a good first-line treatment option in all patients with inoperable metastatic melanoma, regardless of the BRAF tumor status.

Chemotherapy can be considered in patients with a good working condition who are resistant to targeted therapy and immune checkpoint modulators.

REFERENCES

1. Howick J CI, Glasziou P, Greenhalgh T, Heneghan C, LiberatiA, et al. . In: Group OLoEW, editor The Oxford levels of evi-dence 2: Oxford center for evidence-based medicinehttps://wwwcebmnet/indexaspx?oZ5653 [Accessed 23 April 2019].
2. Pflugfelder A, Kochs C, Blum A, Capellaro M, Czeschik C,Dettenborn T, et al. Malignant melanoma S3-guideline diag-nosis, therapy and follow-up of melanoma. J German SocietyDermatol 2013;11(Suppl. 6). 1e116, 1e26.
3. Onkologie L. Leitlinienprogramm Onkologie (Deutsche Krebs-gesellschaft, Deutsche Krebshilfe, AWMF): diagnostik, Therapieund Nachsorge des Melanoms, Langversion 3.1, 2018. 2018.AWMFRegisternummer:032/024OL,http://www.leitlinienprogramm-onkologie.de/leitlinien/melanom/[Accessed5 November 2019].
4. Eggermont AM, Spatz A, Robert C. Cutaneous melanoma.Lancet 2014;383:816e27.
5. Garbe C, Peris K, Hauschild A, Saiag P, Middleton M, Spatz A,et al. Diagnosis and treatment of melanoma: Europeanconsensus-based interdisciplinary guideline. Eur J Cancer 2010;46:270e83.
6. Dummer R, Guggenheim M, Arnold AW, Braun R, vonMoos R. Updated Swiss guidelines for the treatment and follow-up of cutaneous melanoma. Swiss Med Wkly 2011;141:w13320.
7. Marsden JR, Newton-Bishop JA, Burrows L, Cook M,Corrie PG, Cox NH, et al. Revised U.K. guidelines for themanagement of cutaneous melanoma 2010. Br J Dermatol 2010;163:238e56.
8. Saiag P, Bosquet L, Guillot B, Verola O, Avril MF, Bailly C,et al. Management of adult patients with cutaneous melanomawithout distant metastasis. 2005 update of the French Standards,Options and Recommendations guidelines. Summary report.Eur J Dermatol 2007;17:325e31.
9. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S,Coebergh JW, Comber H, et al. Cancer incidence and mortalitypatterns in Europe: estimates for 40 countries in 2012. Eur JCancer 2013;49:1374e403.
10. Leiter U, Garbe C. Epidemiology of melanoma and non-melanoma skin cancerethe role of sunlight. Adv Exp Med Biol2008;624:89e103.[14]Garbe C, Leiter U. Melanoma epidemiology and trends. ClinDermatol 2009;27:3e9.
11. Whiteman DC, Green AC, Olsen CM. The growing burden ofinvasive melanoma: projections of incidence rates and numbersof new cases in six susceptible populations to 2031. J InvestigDermatol 2016;136:1161e71.
12. Bauer J, Garbe C. Acquired melanocytic nevi as risk factor formelanoma development. A comprehensive review of epidemio-logical data. Pigment Cell Res 2003;16:297e306.
13. Grob JJ, Gouvernet J, Aymar D, Mostaque A, Romano MH,Collet AM, et al. Count of benign melanocytic nevi as a majorindicator of risk for nonfamilial nodular and superficialspreading melanoma. Cancer 1990;66:387e95.
14. Holly EA, Kelly JW, Shpall SN, Chiu SH. Number of melano-cytic nevi as a major risk factor for malignant melanoma. J AmAcad Dermatol 1987;17:459e68.
15. Bishop JN, Harland M, Randerson-Moor J, Bishop DT.Management of familial melanoma. Lancet Oncol 2007;8:46e54.
16. Curtin JA, Fridlyand J, Kageshita T, Patel HN, Busam KJ,Kutzner H, et al. Distinct sets of genetic alterations in mela-noma. N Engl J Med 2005;353:2135e47.
17. Curtin JA, Busam K, Pinkel D, Bastian BC. Somatic activationof KIT in distinct subtypes of melanoma. J Clin Oncol 2006;24:4340e6.
18. Tsao H, Atkins MB, Sober AJ. Management of cutaneousmelanoma. N Engl J Med 2004;351:998e1012.
19. Minini R, Rohrmann S, Braun R, Korol D, Dehler S. Incidencetrends and clinical-pathological characteristics of invasive cuta-neous melanoma from 1980 to 2010 in the Canton of Zurich,Switzerland. Melanoma Res 2017;27:145e51.
20. Matas-Nadal C, Malvehy J, Ferreres JR, Boada A, Bodet D,Segura S, et al. Increasing incidence of lentigo maligna andlentigo maligna melanoma in Catalonia. Int J Dermatol 2019;58(5):577e81.
21. Teramoto Y, Keim U, Gesierich A, Schuler G, Fiedler E,Tuting T, et al. Acral lentiginous melanoma: a skin cancer withunfavorable prognostic features. A study of the German centralmalignant melanoma registry (CMMR) in 2050 patients. Br JDermatol 2018;178:443e51.
22. Clark Jr WH, From L, Bernardino EA, Mihm MC. The histo-genesis and biologic behavior of primary human malignantmelanomas of the skin. Cancer Res 1969;29:705e27.

23. Elder D, Barnhill RL, Bastian BC, Cook MG, de laFouchardiere A, Gerami P, et al. Melanocytic tumour classifi-cation and the pathway concept of melanoma pathogenesis. In:Elder DM, Scolyer D, Willemze RA, editors. WHO classificationof skin tumours. 4th ed. France: International Agency forResearch on Cancer (IARC); 2018. p. 66e71.
24. Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV,Ross MI, et al. Melanoma staging: evidence-based changes in theAmerican Joint Committee on Cancer eighth edition cancerstaging manual. Cancer J Clin 2017;67:472e92.
25. Dessinioti C, Geller AC, Stergiopoulou A, Swetter SM, Baltas E,Mayer JE, et al. Association of skin examination behaviors andthinner nodular vs superficial spreading melanoma at diagnosis.JAMA Dermatol 2018;154:544e53.
26. Lattanzi M, Lee Y, Simpson D, Moran U, Darvishian F,Kim RH, et al. Primary melanoma histologic subtype: impact onsurvival and response to therapy. J Natl Cancer Inst 2019;111:180e8.
27. Scolyer RA, Barnhill RL, Bastian BC, Busam KJ,McCarthy SW. Desmoplastic melanoma. In: Elder DM,Scolyer D, Willemze RA, editors. WHO classification of skintumours. 4th ed. France: International Agency for Research onCancer (IARC); 2018. p. 105e7.
28. Jones Jr DV, Ajani JA, Blackburn R, Daugherty K, Levin B,Patt YZ, et al. Phase II study of didemnin B in advanced colo-rectal cancer. Investig New Drugs 1992;10:211e3.
29. Gong HZ, Zheng HY, Li J. Amelanotic melanoma. MelanomaRes 2019;29:221e30.
30. Wee E, Wolfe R, McLean C, Kelly JW, Pan Y. Clinicallyamelanotic or hypomelanotic melanoma: anatomic distribu-tion, risk factors, and survival. J Am Acad Dermatol 2018;79:645e651 e4.

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PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7