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REVIEW

Cutaneous Melanoma in the Elderly: Review of a Growing Problem☆

N. Iglesias-Pena,[a] S. Paradela,[a] A. Tejera-Vaquerizo,[b,*] A. Boada,[c] E. Fonseca[a]

[a] *Servicio de Dermatología, Complejo Hospitalario Universitario de A Coruña, A Coruña, España*
[b] *Servicio de Dermatología, Instituto Dermatológico GlobalDerm, Palma del Río, Córdoba, España*
[c] *Servicio de Dermatología, Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, Barcelona, España*

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Abstract Cutaneous melanoma (CM) causes more deaths than any other skin tumor, and incidence and mortality rates have risen in recent years, especially in patients of advanced age. There are differences in the biological behavior of CM tumors in the elderly as well as differential management of the disease, evidently influenced by such factors as limited life expectancy, the high incidence of concomitant conditions in older patients, and issues of quality of life unrelated to CM itself. We review relevant current literature on the epidemiology, etiology, pathogenesis, and immunology of CM as well as research on the clinical features, prevention, and management of these tumors in the elderly.

PALABRAS CLAVE
Melanoma;
Anciano;
Pronóstico;
Cirugía;
Ganglio centinela;
Revisión;

Melanoma cutáneo en el anciano: revisión de un problema creciente

Resumen El melanoma cutáneo (MC) es el tumor cutáneo que más muertes provoca, con un aumento importante de la incidencia y la mortalidad en las últimas décadas, especialmente en el paciente anciano. Existen evidencias del diferente comportamiento biológico, así como de las diferencias en el manejo del MC en este subgrupo de pacientes con respecto al resto de otras franjas de edad, evidentemente condicionadas por unas limitadas expectativas de

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* Corresponding author.
E-mail address: antoniotejera@aedv.es (A. Tejera-Vaquerizo).

Servicio de salud para el anciano

supervivencia y calidad de vida ajenas al melanoma y una elevada incidencia de comorbilidades. El presente artículo revisa los datos actuales más relevantes de la epidemiología, etiopatogenia e inmunología, clínica, prevención y manejo del MC en el anciano.

Introduction

The Spanish population, like other populations in the Western world, is getting older. Old age is associated with a higher incidence of melanoma and a higher disease-related mortality.[1] Improvement in screening and treatment of melanoma in elderly patients is therefore essential.[2] Moreover, the biological behavior of cutaneous melanoma is different in elderly individuals. This may lead to differences in the management and treatment of this group, for which life expectancy and quality of life are limited by causes unrelated to melanoma and a high incidence of comorbidities. This review will focus on the most relevant aspects of epidemiology, pathogenesis and immune system, clinical characteristics, surgical management, and systemic treatment of cutaneous melanoma in elderly patients.

Materials and Methods

A literature review was undertaken in Pubmed, EMBASE, and Scholar Google. The search terms used were (''elderly'' OR ''older age'' OR ''aged'' OR ''aged 80 and over'') AND ''cutaneous melanoma,'' adding different terms according to the subsection under study (Table 1 of the supplementary material). The reference lists of the selected articles were also reviewed to identify additional relevant articles.

Epidemiology

Advanced Age and Frequency of Melanoma

The largest epidemiological registry in existence, the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER), reported in 2015 an incidence of melanoma of 14.4 cases/100 000 inhabitants for patients under 65 years of age, 101.7/100 000 inhabitants for those over 65 years, and 114.7 cases/100 000 inhabitants for those over 75 years (Fig. 1),[3] with a larger yearly percentage increase in men over 65 years.[4]

In Spain, a recent meta-analysis by Tejera-Vaquerizo et al.[5] reported a raw overall incidence of 8.82 (95% confidence interval [CI], 7.59-10.04)/100 000 person-years, with differences between studies conducted several decades ago (3-4/100 000 person-years) and those conducted from the 1990s onwards, with rates greater than 7/100 000 person-years, reflecting the possible increase in melanoma incidence.

Advanced Age and Melanoma Prognosis

Elderly patients are more likely to die from melanoma than young ones,[6] with an annual increase in incidence rate of 1.7% (Fig. 2).[4] Although melanomas in elderly individuals account for 40% of such tumors diagnosed, they are cause of 60.2% of melanoma-related deaths.[7]

In Spain, the ARIADNA Interactive Epidemiology Information System, managed by the Instituto de Salud Carlos III,[8] shows an increase in mortality for men and women, both in terms of raw rates and those adjusted to the world population (Fig. 3).[9]

The SEER data suggest that the raw incidence of melanoma is significantly greater in patients aged over 60 years and that mortality is higher than in other age groups. The age group with highest percentage of deaths due to melanoma corresponds to patients between 75 and 84 years.[10] A study that analyzed 3 different cohorts, including the SEER cohort, with more than 300 000 patients, found that age is a predictor of worse melanoma-specific survival (MSS).[11]

In a multicenter study, which analyzed more than 7000 patients with cutaneous melanoma, age was identified as an independent prognostic factor in patients with stage I-III disease.[12] In elderly patients, melanoma was more frequently located on the head and neck, and had a greater thickness, mitotic rate, and ulceration. In patients with regional lymph node involvement (stage III), age was still an important prognostic factor when variables such as number of positive sentinel lymph nodes, tumor burden, and ulceration of the primary tumor were included. Moreover, a progressive decrease in overall survival at 5 years was observed, such that survival in patients aged 60-70 years was 20% greater than those aged 80-90 years.

In a retrospective study of 4785 patients, increased age and male sex was associated with greater tumor thickness and ulceration. MSS at 10 years was 10% lower in patients over 65 years.[13] The fact that advanced age was maintained as an independent factor of poor prognosis after adjusting for histological characteristics of the tumor, socioeconomic level, and comorbidity suggest that the differences observed in overall survival do not depend solely on delayed diagnosis (Table 1).[14]

Lymphatic System in Elderly Patients With Cutaneous Melanoma

Baltch et al.[16] observed that sentinel lymph node involvement occurred less frequently in elderly patients, even in cases with more aggressive phenotypes. This observation has also been made in other studies.[24–28] It is believed that atrophy of cutaneous lymphatic vessels may contribute to a decrease in immune response and explain the low rate of positive sentinel lymph node dissection.[14] Conway et al.[29] demonstrated that lymphatic function, as measured by radiocolloid transit to and uptake within the sentinel

Table 1 Studies With Multivariate Analyses That Included Age as a Prognostic Factor in Cutaneous Melanoma.

Reference	Stage/N/Type of Sample/Country	Measurement of Age as Prognostic Factor	Method of Outcome Assessment	Other Independent Prognostic Factors
Kemeny et al.[15]	All stages/N = 23 341/population/US	m ≤ 45 vs f ≤ 45, HR: 1.9 (1.6-2.3), *P* < .0001 f ≥ 55 vs m ≤ 45, HR: 2.8 (2.3-3.3), *P* < .0001 m ≥ 55 vs f ≤ 45, HR: 3.6 (3.0-4.2), *P* < .0001	Cox/DFS	S, H, A
Balch et al.[16]	I, II /N = 13 581/hospital/international	Decades of increasing age, RR: 1.1 (1.07-1.13), *P* < .00001	Cox/DFS	T, U, A, G, C
Azzola et al.[17]	I, II/N = 3661/hospital/Australia	Decades of increasing age, RR: 1.15 (1.07-1.2), *P* < .0001	Cox/DFS	T, U, A, G, IM
Leiter et al.[18]	Breslow ≤ 1 mm/N = 11 927/hospital/Germany, Austria, Switzerland	> 50 vs ≤ 60, HR: 1.6 (1.1-1.2), *P* = .0075	Cox/DFS	T, H, A
Lindholm et al.[19]	I, II/N = 6191/population/Sweden	≥ 70 vs < 50,HR: 1.59 (1.23-2.06), *P* = .0005	Cox/DFS	T, U, A, G, C, H, DM
Caracò et al.[20]	I, II referred for SLNB/N = 399/hospital/Italy	> 50 vs < 50, OR: 1.95 (1.13-3.39), *P* = .01	Cox/DFS	T, U, G, SLNB
Reyes-Ortiz et al.[21]	All/N = 23 068/population/US	70-74 vs 65-69, HR: 1.15 (1.01-1.3), *P* = .04 75-79 vs 65-69, HR: 1.24 (1.08-1.3), *P* = .001 ≥ 80 vs 65-69, HR: 1.48 (1.3-1.68), *P* < .001	Cox/DFS	T, A, G, S, H, income, civil status, race, year of diagnosis, comorbidities
Downing et al.[22]	All/N = 3127/population/United Kingdom	Increasing age in years, HR: 1.04 (1.04-1.05), *P*: n.a.	Cox/DFS	T, A, G, H, socioeconomic status
Lasithiotakis et al.[13]	I, II, IIIA/N = 4785/population/Germany	Increasing age in years, HR: 1.01 (1.003-1.013), *P* = .005	Cox/DFS	T, U, A, G, H, C, SLNB, year of diagnosis
De Vries et al.[23]	All/N = 10 538/population/Netherlands	65-74 vs < 45, RER: 1.37 (1.15-1.64), *P* = n.a. 75-84 vs < 45, RER: 2.2 (1.8-2.7) ≥ 85 vs < 45, RER: 2.18 (1.39-3.4)	Multivariate model/DFS	T, A, G, H, N, geographic region

Abbreviations: A, anatomic site; C, Clark level; Cox, Cox proportional risks survival analysis; DFS, disease-free survival; G, sex; H, histologic subtype; HR, hazard ratio (95% confidence interval); f, female; m, male; M, presence of distant metastasis; N, presence of lymph node metastasis; n.a. not available; RER, relative excess risk (95% CI); RR, relative risk; S, stage; SLNB, sentinel lymph node biopsy; T, Breslow tumor thickness; U, ulceration.
Adapted from Lasithiotakis et al.[14]

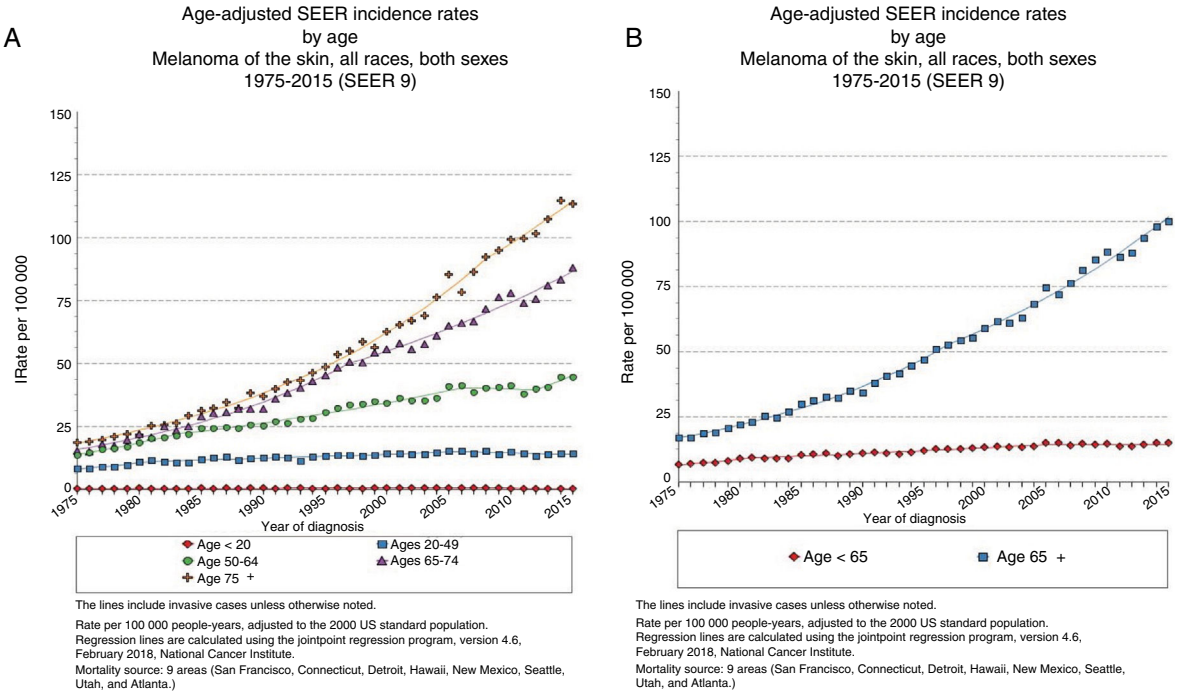

Figure 1 Age-adjusted melanoma incidence in the Surveillance, Epidemiology and End Results (SEER) Program, National Cancer Institute.

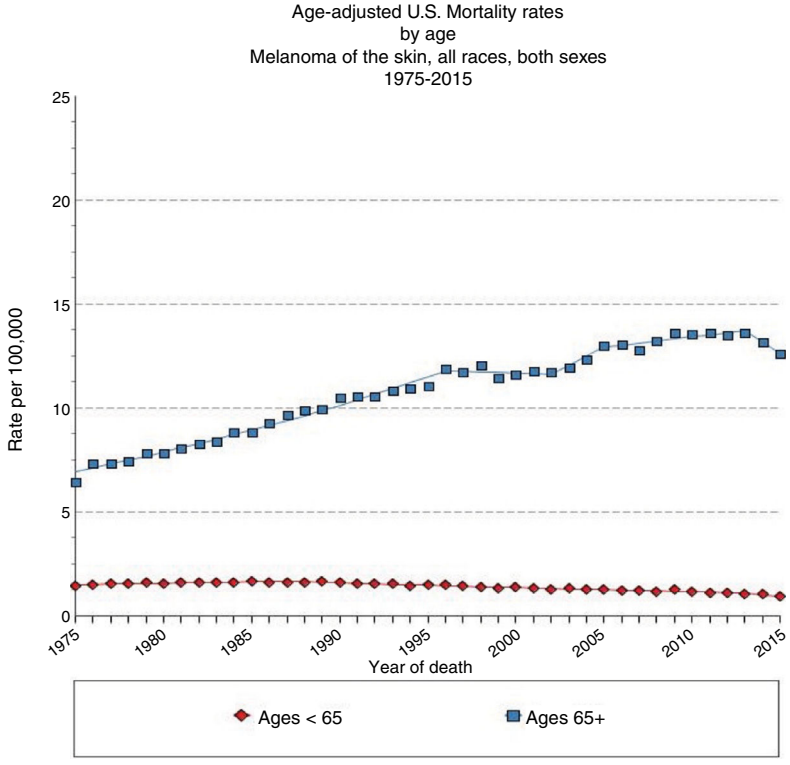

Figure 2 Registry of age-adjusted melanoma mortality in the Surveillance, Epidemiology and End Results (SEER) Program, National Cancer Institute.

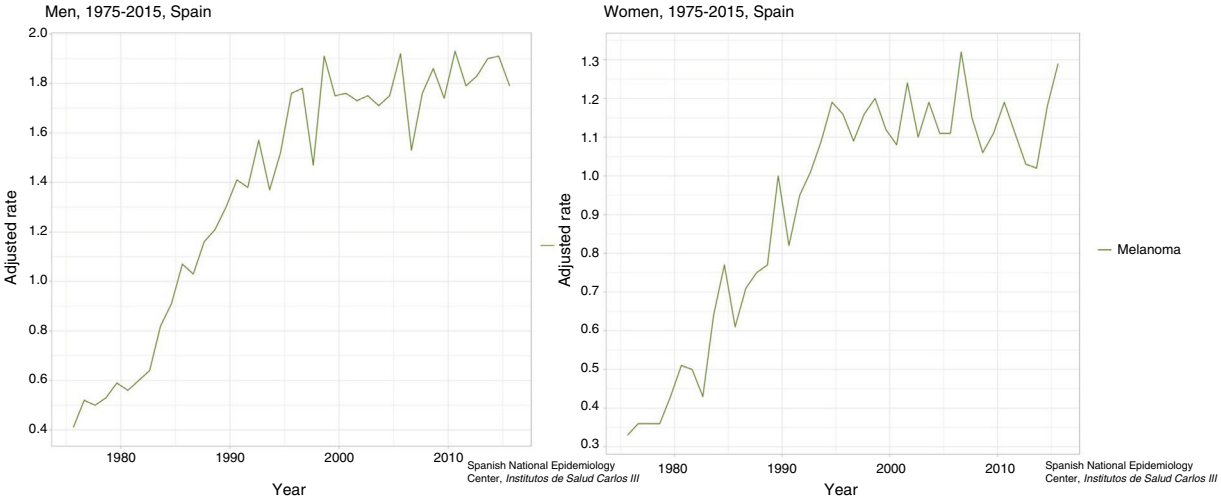

Figure 3 Mortality due to melanoma in Spain by sex (data from the ARIADNA Interactive Epidemiological Information System, dependent on the *Instituto de Salud Carlos III*).

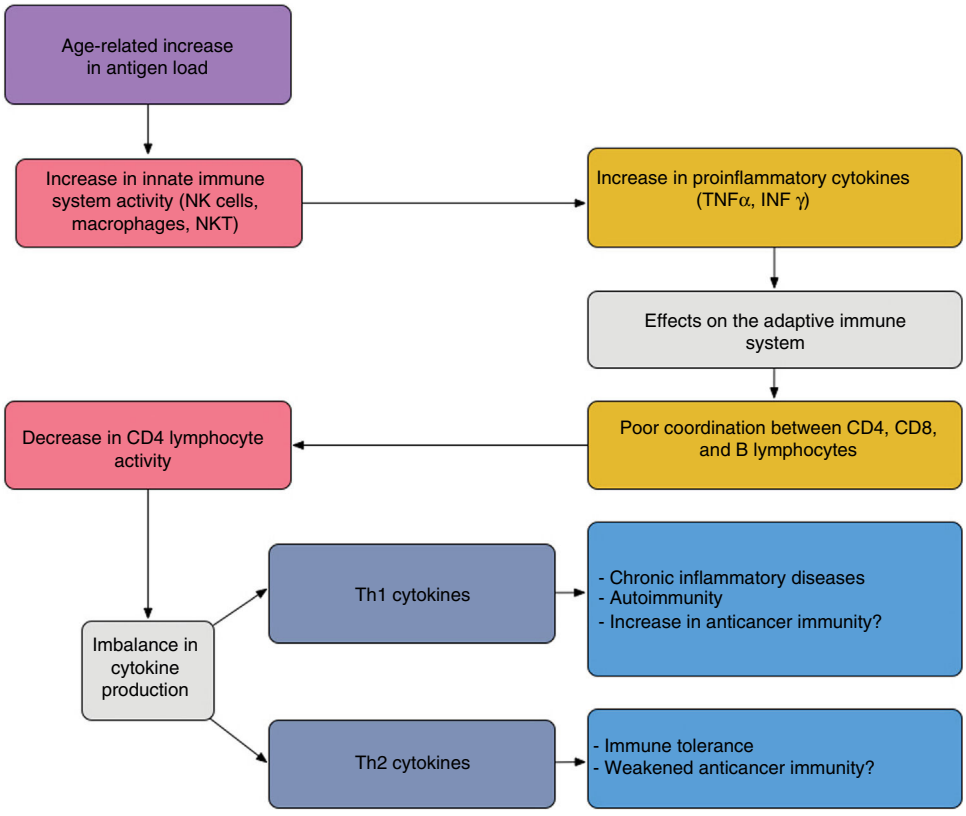

Figure 4 Proposed interaction between the innate and adaptive immune system in elderly patients; the age-related increase in antigen load leads to overstimulation of the innate immune system thereby increasing proinflammatory cytokines. This has an impact on the acquired immune system, giving rise to poor coordination between CD4, CD8, and B lymphocytes, and an imbalance between Th1 and Th2 cytokine production. The activity of cytotoxic T lymphocytes under Th1 conditions favors autoimmunity and chronic inflammatory diseases; under Th2 conditions, immune tolerance is favored.
Adapted from Hegde et al.[33]

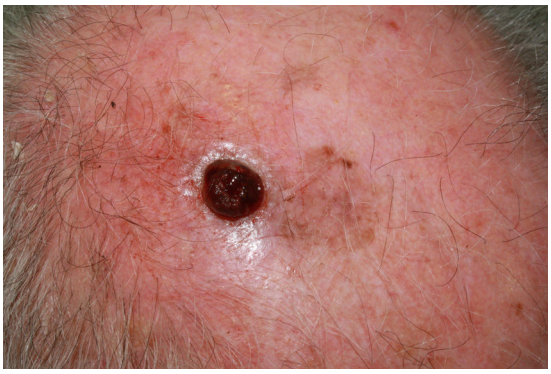

Figure 5 Ulcerated, fast-growing nodular amelanotic melanoma of 4 months standing on the left temple of an 87-year-old man, with a Breslow thickness of 7 mm and 8 mitoses per mm.[2]

lymph node, decreased with age. Some authors concluded that this lymphatic dysfunction might have an impact on metastatic spread, with predominance of hematogenous dissemination.[30]

Role of the Immune System in Elderly Patients With Cutaneous Melanoma

With age, immune system function changes, resulting in a different response to infections and tumors, with decreased defense against infections and tumors.[31,32] Tumor infiltrating lymphocytes (TIL), a marker of host immune response, are considered an indicator of good prognosis. Weiss et al.[11] observed that the intensity of TIL in the primary tumor was positively correlated with MSS and that this effect appeared to be greater in patients aged more than 45 years.

In elderly patients, imbalances between the effector and regulatory components of immune response are present; this state is known as immunosenescence[32] and arises because of chronic antigen stimulation and oxidative stress during the lifetime of the individual.[33] The increase in proinflammatory lymphokines due to chronic antigen stimulation leads to an increase in Th1 response and tumor cell death. This effect is amplified when tumor antigens are generated by cell death caused by chemotherapy (Fig. 4).

Clinical Aspects of Melanoma in Elderly Individuals

Although the same clinical presentation of cutaneous melanoma occurs in elderly patients and their younger counterparts, melanomas in elderly patients are diagnosed in more advanced stages. This can be explained by multiple factors.

Superficial-spreading melanoma is the most common histological subtype, but in elderly patients, thicker and more ulcerated tumors tend to be diagnosed compared with younger patients, due to the higher proportion of nodular clinicopathologic subtypes.[34,35]

Furthermore, in elderly patients, there is a higher proportion of fast-growing melanomas,[36,37] many of which are nodular and amelanotic.[38] This hinders early diagnosis, as the lesions do not follow the classic clinical description of asymmetry, borders, color, and diameter (ABCD rule). Thus, there are suggestions to add the term *E* to this classic diagnostic mnemonic, which refers not only to the elevation of the lesion but also to *evolving* lesions during follow-up.[39] Other authors propose adding the acronym EFG[34] (elevated, firm, and growing) to help identify these lesions (Figs. 5 and 6).

Clinically, these nodular lesions have been described in dermoscopy as typical multiple and irregular peripheral dots and globules, with blue-white veil, homogeneous blue pigmentation, more than 5 colors, and black color.[40] Often, these melanomas are completely amelanotic on clinical examination. To assist with diagnosis, dermoscopy has been reported to feature the presence of milky-red areas and an atypical vascular pattern, but these are criteria that at times are insufficient for diagnosis of nodular amelanotic melanoma (Fig. 7).[41] The fast-growing variant appears to be more likely to present with the above findings simultaneously.[42]

In elderly patients, the lentigo maligna melanoma histological subtype is more common, with a predilection for the head and neck.[43] The dermoscopic criteria described for diagnosis include presence of grey dots, isobar sign (circle-within-a-circle structure), pigmented rhomboidal structures, target-like patterns, follicular occlusion, and grey-white scar-like areas.[44] Lentigo maligna lesions on the cheeks occur more frequently in women whereas lesions on the nose and scalp are more frequent in men. But the most notable difference with respect to age is that in the eldest patients, lentigo maligna lesions are located on areas with lesions of chronic sun damage, unlike the case in younger individuals, who do not show such an extent of skin damage.[44]

Another characteristic described recently is the low frequency of association of melanoma with nevus, whether common or atypical.[45]

Possible Causes of Delayed Diagnosis in Elderly Patients

In addition to the characteristic phenotypic features of melanoma in elderly patients described above, there are other possible causes for the delay in melanoma diagnosis (Table 2) and these may contribute to the increased thickness of melanomas observed in this population.

In the case of site, there are some relevant characteristics. One of these is that melanoma may present in anatomical sites with low visibility. Thus, a Dutch epidemiological study reported a greater propensity, almost double, for melanoma to present on the trunk in men compared with women, and this may contribute to a greater thickness.[23] The scalp is also a more frequent site in this risk group of elderly men, with the same characteristics as the more aggressive phenotype.[53]

There are a series of demographic factors related to a longer delay in diagnosis. The fact that elderly patients have lower income has been independently associated with diagnosis of thicker melanoma.[21,46,47,54]

Marital status has also been associated with thickness of melanomas. Thus, patients who are single, separated, or widowed, with predominance for males, have thicker melanomas compared with married ones. It seems that the

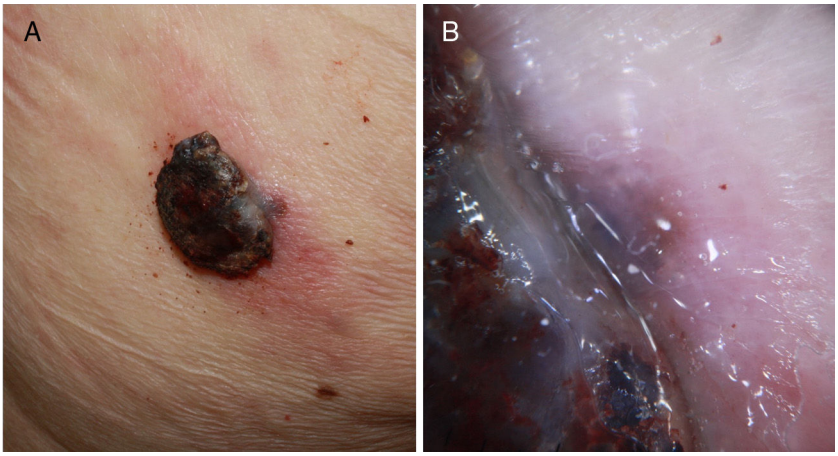

Figure 6 A, Fast-growing nodular melanoma of 3 months standing in the right scapular region on a prior flat lesion of several years standing. The Breslow thickness was 4 mm, the lesion was not ulcerated, and there were 5 mitoses per mm.[2] Presence of perilesional in situ melanoma in the histopathological study. B, Detail of the lesion base where pigmentation is observed, corresponding to the in situ component of the prior lesion.

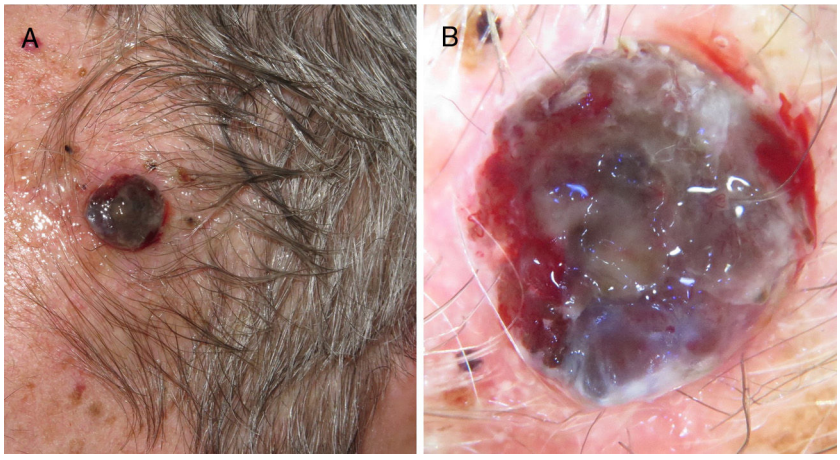

Figure 7 Ulcerated, fast-growing nodular melanoma on the left temple with a Breslow thickness of 4 mm and 10 mitoses por mm.[2] B, Dermoscopy of the lesion in which several colors and small milky areas are observed with atypical vascularization.

partner contributes to recognition of suspected lesions that would otherwise not be noticed.[47]

Among the patient-dependent causes, elderly patients are less likely to participate in prevention campaigns,[50] or conduct whole-body skin self-examinations.[49]

Finally, possible causes related to quality of health care have also been described as a possible reason for delay in diagnosis. Data are contradictory in terms of frequency of whole-body skin examinations by the primary care physician. Some studies have reported that fewer whole-body skin examinations are performed in older patients than younger ones,[51,54] whereas another study of the population in Queensland, Australia, did not observe this difference.[55] Moreover, up to a third of the population over 50 years of age had had a partial skin examination in the past year.

Surgical Locoregional Management of Melanoma in Elderly Patients

Treatment of the Primary Lesion

Primary excision of melanoma is considered a minor surgical procedure that can generally be performed under local anesthetic.[56] However, elderly patients are often not considered candidates for surgical treatment, resulting in lower rate of excision of suspected pigmented lesions and failure to comply with recommendations for tumor management.[6]

Thus, Marks et al.[57] showed that the ratio between nevus and melanoma in excised pigmented lesions was 27:2 in patients between 21 and 40 years of age, and 1:4 in those aged over 60 years.

There is also a greater tendency to perform incisional biopsy in large pigmented lesions that are often found on

Table 2 Causes of Delay in Diagnosis of Melanoma in Elderly Patients.

Cause of Delay	Remarks
Aspects pertaining to melanoma	
Increased frequency of fast-growing melanoma	Increase in nodular subtypes[34] which do not follow the classic ABCD rule and which are hypomelanotic or amelanotic[38]
Increased frequency of lentigo maligna melanoma	Very slow-growing lesions on photoaged skin[44]
Site	More frequent location of melanomas in elderly patients in areas difficult to observe, particularly in men[23]
Aspects pertaining to the patient	
Low socioeconomic status	Low income has been associated with thicker melanomas[21,46,47]
Marital status	Single, separated, or widowed patients have thicker melanomas than married patients[47]
Level of education	The stage on diagnosis bears an inverse relationship with level of education of the patient[46,48]
Whole-body skin self-examination and participation in screening campaigns	Less frequent in elderly patients[49,50]
Aspects pertaining to the physician	
Whole-body skin examination	Elderly patients undergo fewer routine whole-body skin examinations[51]
Level of training of the physician	Longer delay when the lesion is seen by a primary care physician than by a dermatologist[52]

Adapted from Lasithiotakis et al.[14]

elderly patients, but this technique complicates histopathological study and should be avoided, unless, as for other age groups, diagnosis is uncertain and excisional biopsy requires complex reconstruction.[58]

Finally, elderly patients have a higher proportion of head and neck melanoma,[59,60] with a functional and esthetic impact on complex areas, such as the nose and eyelids. The tendency to reduce the surgical margin, along with the difficulty in establishing margins for lentiginous lesions, which are more frequent in elderly individuals, is responsible for a higher proportion of peritumoral resections or resections with inadequate margins.[14] Although this does not have an impact on overall survial,[61] it could be significant for determining the risk of local recurrence.

On analyzing more than 18 000 patients with melanoma in the SEER,[62] it was found that in patients aged 65 years or more, excision with inadequate margins was more frequent than in those under 65 years (risk ratio, 1.37), and this difference was even greater for those aged 75 years or more (risk ratio, 2.38). In a retrospective study conducted in France, in which variations in treatment of patients with stage I-III melanoma were assessed, it was found that the factors associated with excision with inadequate margins as defined by the recommendations of the clinical guidelines were age greater than 60 years, greater tumor thickness, and site on the head and neck.[63] These latter 2 factors are, furthermore, more frequent in elderly patients.

Selective Sentinel Lymph Node Biopsy

With regards SLNB, although a previous study suggested that age did not influence whether one was performed,[63] other studies have found that the procedure is indicated less frequently in patients aged 75 years or more,[59,64,65] regardless of their comorbidities.

Moreno-Ramírez et al.[66] showed that the main deciding factor for performing SLNB was Breslow thickness, such that 71.6% of patients with tumors with a thickness of 1.01-4.00 mm underwent SLNB. In this group, the Karnofsky performance status and age were the most significant deciding factors in patients with tumors thicker than 4 mm, while age was the most relevant determinant for lack of indication of SLNB, performed in 64.1% of patients under 70 years of age and only in 8.7% of those over 70 years.

Unlike for excision of the primary tumor, SLNB may require spinal or general anesthesia, and so, in these cases, the procedure is associated with anesthetic risk. This risk can be calculated with general comorbidity scales or more specific scales, such as the American Society of Anesthesiologists Physical Status System classification system.[67] These patients require a preoperative study (that includes analysis with coagulation, plain chest X-ray, and electrocardiogram); detailed knowledge of the patient's general clinical condition, cardiorespiratory function, and usual medications; meticulous surgical planning; intraoperative monitoring; and appropriate postoperative follow-up.[56,67] The most important clinical trial of SLNB in melanoma, the Multicenter Selective Lymphadenectomy Trial-I (MSLT-I), excluded patients over 75 years of age[68]; however, other studies have shown the undoubted prognostic value of this test in elderly individuals and its feasibility in patients with a reasonable life expectancy.[69]

Table 3 Staging and Treatment of Cutaneous Melanoma in Elderly Patients.

Intervention	Remarks	Level of Evidence and Strength of Recommendation (USPSTF)
Primary excision	Same recommendation as for other age groups LMM requires adequate margins to be established around the lesion, ideally through Mohs micrographic surgery	III A
SLNB	Staging, no therapeutic benefit. Lower rate of positive findings (lower sensitivity, rate of micrometastasis, or lymphatic spread?) Assess anesthetic risk	II-2 B
Lymphadenectomy	Morbidity (lymphedema, nerve damage, surgical wound complications) No impact on survival demonstrated. Palliative treatment if clinically relevant lymph node metastasis	III C
Adjuvant treatment	Little information available on benefit-risk Favorable response to immunotherapy due to imbalance in immune system	III I
Intraarterial chemotherapy via hyperthermic isolated limb perfusion	Assess in locally advanced melanoma (unresectable, in transit metastasis)	III-2 B
Treatment of metastatic melanoma (immunotherapy, targeted therapy)	Same therapeutic approach as in young patients Assess prior geriatric assessment	III B

Levels of evidence (USPSTF): II, at least one randomized, controlled clinical trial with appropriate design; II-1, well-designed, controlled clinical trials, but not randomized; II-2, well designed cohort studies or case-control studies, preferably multicenter; II-3, multiple series compared over time, with or without intervention, and surprising results in uncontrolled studies; III opinions based on clinical experience, descriptive studies, clinical observations, or expert committee reports.
Strength of Recommendation: A, extremely recommended (good evidence that the measure is effective and that the benefits easily outweigh the harms); B, recommended (at least moderate evidence that the measure is effective and that the benefits outweigh the harms); C, not recommended or unadvised (at least moderate evidence that the measure is effective but the benefits are similar to the harms and cannot justify a general recommendation); D, unadvised (at least moderate evidence that the measure is ineffective or that the harms exceed the benefits); I, insufficient evidence, of poor or contradictory quality, and the balance between benefits and harms cannot be determined.
Abbreviations: LMM, lentigo maligna melanoma; SLNB, selective sentinel lymph node biopsy; USPSTF, United States Preventive Services Task Force
Adpated from Lasithiotakis et al.[14]

Lymphadenectomy

Lymphadenectomy after positive SLNB (immediate complete lymphadenectomy [ICL]) is also indicated less frequently in elderly patients.[70,71] Moreover, age greater than 75 years has been identified as a predictive factor for not complying with the recommendations in terms of performing ICL, with a lower mean number of lymph nodes dissected during the procedure in older patients.[71]

Some authors consider that this lower level of intervention in elderly patients is a possible explanation for the greater mortality observed in this age group.[1] However, the lower frequency of metastasis in SLNB and the results of the Multicenter Selective Lymphadenectomy Trial-II (MSLT-II),[72] which show a lack of survival benefit in patients with positive SLNB and ICL (compared with observation and therapeutic lymph node dissection once the patient develops identifiable lymph node metastasis), would not support a possible association between undertreatment and mortality. In any case, of note is that the age range established as an inclusion criterion in the MSLT-II was 18 to 75 years. Although the consistency of the results of the trial suggest that they could be extrapolated to elderly patients, we still lack high quality evidence to support ICL in these patients. Confirmation of the regional control observed in patients treated with ICL in the MSLT-II would, moreover, have been of great interest to guide decisions in elderly patients.[1]

Treatment of Advanced Locoregional and Metastatic Disease

Advanced Locoregional Disease

Several studies have shown that the efficacy of intraarterial chemotherapy with melphalan (with or without tumor necrosis factor alfa or actinomycin) administered by

hyperthermic isolated limb perfusion in the treatment of locally advanced malignant melanoma (unresectable lesions, with in-transit metastasis) was similar in patients aged 75 years or more than in younger patients.[73–76] Moreover, perioperative mortality does not increase with increasing age and most events were of locoregional toxicity.

Systemic Treatment

The elderly population has certain characteristics (greater presence of other diseases, several concomitant pharmacological treatments with the potential for drug-drug interactions, possibility of cognitive decline, and general state of the patient) that make it particularly important to assess the benefit-risk of each treatment.[77] There is evidence that geriatric assessment prior to an oncological therapeutic plan could help achieve more satisfactory outcomes in terms of survival, quality of life, functional status, and risk of hospitalization in elderly patients with cancer.[78]

Before 2010, treatment of metastatic melanoma was limited to classic chemotherapy with dacarbazine or the use of high-dose interleukin 2. Both treatments had low efficacy and a high toxicity that limited their use in elderly patients.[14] In 2010, the results of the first clinical trials with vemurafenib and ipilimumab were published, and treatment of advanced melanoma entered a new era. Information on the usefulness of these new therapies in elderly patients is derived mainly from subgroup analyses of this population who participated in the clinical trials, with the associated limitations of such an approach.

Therapeutic Target

The clinical utility of treatment with BRAF inhibitors (vemurafenib and dabrafenib) alone or, as currently employed, in combination with MEK inhibitors (cobimetinib or trametinib) is limited to melanomas carrying the BRAF kinase mutation. Several studies suggest that the frequency of appearance of BRAF mutations is inversely correlated with age.[79,80] In an Australian cohort of more than 300 patients with metastatic melanoma, all patients under 30 years of age had the BRAF mutation, whereas only 25% of those over 70 years did.[80] Interestingly, in elderly patients, the proportion of individuals with the most frequent BRAF mutation, V600E, decreases whereas other less common BRAF mutations, such as the V600K BRAF mutation, increase in frequency.

Although the low number of elderly patients recruited to clinical trials is a global problem in oncology,[81] in trials involving this therapeutic target, the decrease in BRAF mutation frequency with age has surely also contributed to their underrepresentation.

Currently, the regimen most widely used for this therapeutic target is a combination of a BRAF inhibitor with a MEK inhibitor, as this not only offers greater efficacy but also limits adverse cutaneous effects. In the analysis by age subgroups, no differences in efficacy were observed.[82,83]

With regards the safety of these treatments in the elderly population, it seems that the overall frequency of adverse effects is similar to the younger population. However, the most severe adverse effects (grade III-IV), as well as the risk of withdrawing treatment, are greater in the elderly population.[84]

Immunotherapy

Ipilimumab, a CTLA-4 inhibitor, was the first immunotherapy agent to be approved for metastatic melanoma. A response rate of 10% to 15% was achieved with its use.[85] Subsequently, in 2015, anti-PD-1 agents (nivolumab and pembrolizumab) became available, with better efficacy and safety profiles than ipilimumab. Anti-PD-1 agents in monotherapy can achieve response rates of between 33% and 40%.[86] The combination of ipilimumab with an anti-PD-1 agent is the most effective immunotherapy regimen, with a response rate of 61%, although this combination is the one that generated greatest toxicity.[87]

There is currently some debate as to whether the elderly population is particularly sensitive to immunotherapy. While some studies have found differences between the efficacy of immunotherapy in different age groups,[88] others have even pointed to a better response, particularly for anti-PD1 agents in elderly patients. In a recent retrospective cohort study, in which all patients treated with new immunotherapy agents in the Hospital of Lyon, France, were reviewed, the authors reported longer disease-free survival in patients aged over 65 years compared with those under 65 years.[89] Another recent multicenter study found that the risk of progression under treatment with pembrolizumab decreased by 13% for every decade of life of the patient on starting treatment.[90] The mechanisms that might explain this possible benefit are not yet understood, but they focus on the potential of immunotherapy for reverting changes in the immune system that arise during old age.[91]

Given the particular mechanism of action of immunotherapy, deterioration in the function of several organs —characteristic of aging —is of greater relevance. For example, there is no contraindication for use of immunotherapy in patients with renal or heart failure. Nevertheless, it is of vital importance that patients and their caregivers are aware of potential unwanted effects of immunotherapy, particularly those such as asthenia and arthralgia, which could be attributed to aging. The best option for minimizing immunotherapy toxicity is one centered on diagnosis and early management of adverse effects. Toxicity associated with immunotherapy does not appear to increase with increasing age.[85,89,90]

In Spain, the only approved adjuvant for high-risk melanoma is high-dose interferon alfa-2b. Given the substantial toxicity and limited benefit, this treatment is not usually used in elderly patients.[92]

Currently, treatment of metastatic disease with targeted therapy and immunotherapy is thought to have a comparable effect on overall survival in elderly patients, without a substantial increase in toxicity in elderly patients.[93] Nevertheless, it is necessary to perform studies in every-day clinical practice in elderly patients treated with these new drugs, given that these patients, who are increasingly numerous, are excluded from clinical trials.

Table 3 shows the level of evidence for each therapeutic procedure in patients with melanoma.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.adengl.2019.05.012.

References

1. Moreno-Ramírez D, Fernández-Orland A, Ferrándiz L. Disección ganglionar en el paciente de edad avanzada con melanoma. Piel. 2018;33:1–4, http://dx.doi.org/10.1016/j.piel.2017.07.017.
2. Lange JR, Kang S, Balch CM. Melanoma in the older patient: Measuring frailty as an index of survival. Ann Surg Oncol. 2011;18:3531–2, http://dx.doi.org/10.1245/s10434-011-2015-6.
3. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, et al. (Eds). SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017. DOI: 10.1016/j.carbpol.2013.11.026.
4. Linos E, Swetter SM, Cockburn MG, Colditz GA, Clarke CA. Increasing burden of melanoma in the United States. J Invest Dermatol. 2009;129:1666–74, http://dx.doi.org/10.1038/jid.2008.423.
5. Tejera-Vaquerizo A, Descalzo-Gallego MA, Otero-Rivas MM, Posada-García C, Rodríguez-Pazos L, Pastushenko I, et al. Incidencia y mortalidad del cáncer cutáneo en España: revisión sistemática y metaanálisis. Actas Dermosifiliogr. 2016;107:318–28, http://dx.doi.org/10.1016/j.ad.2015.12.008.
6. Tsai S, Balch C, Lange J. Epidemiology and treatment of melanoma in elderly patients. Nat Rev Clin Oncol. 2010;7:148–52, http://dx.doi.org/10.1038/nrclinonc.2010.1.
7. Garcovich S, Colloca G, Sollena P, Andrea B, Balducci L, Cho WC, et al. Skin cancer epidemics in the elderly as an emerging issue in geriatric oncology. Aging Dis. 2017;8:643, http://dx.doi.org/10.14336/AD. 2017.0503.
8. Instituto de Salud Carlos III. Servicio interactivo de información epidemiológica (Ariadna) [accessed 26 Jun 2018]. Available from: http://ariadna.cne.isciii.es.
9. Tejera-Vaquerizo A. Incidence and mortality of skin cancer in Spain. Piel. 2018;33:341–3, http://dx.doi.org/10.1016/j.piel.2017.09.004.
10. Surveillance, Epidemiology, and End Results (SEER). Program Cancer Statistics Review, 1975–2015, National Cancer Institute [Internet]. Melanoma of the skin - Cancer Stat Fact [Accessed 16 Sept 2018]. doi: 10.1083/jcb.144.6.1219.
11. Weiss SA, Han J, Darvishian F, Tchack J, Han SW, Malecek K, et al. Impact of aging on host immune response and survival in melanoma: An analysis of 3 patient cohorts. J Transl Med. 2016;14, http://dx.doi.org/10.1186/s12967-016-1026-2.
12. Balch CM, Soong SJ, Gershenwald JE, Thompson JF, Coit DG, Atkins MB, et al. Age as a prognostic factor in patients with localized melanoma and regional metastases. Ann Surg Oncol. 2013;20:3961–8, http://dx.doi.org/10.1245/s10434-013-3100-9.
13. Lasithiotakis K, Leiter U, Meier F, Eigentler T, Metzler G, Moehrle M, et al. Age and gender are significant independent predictors of survival in primary cutaneous melanoma. Cancer. 2008;112:1795–804, http://dx.doi.org/10.1002/cncr.23359.
14. Lasithiotakis KG, Petrakis IE, Garbe C. Cutaneous melanoma in the elderly: Epidemiology, prognosis and treatment. Melanoma Res. 2010;20:1, http://dx.doi.org/10.1097/CMR.0b013e328335a8dd.
15. Kemeny MM, Busch E, Stewart AK, Menck HR. Superior survival of young women with malignant melanoma. Am J Surg. 1998;175:437–45, http://dx.doi.org/10.1016/S0002-9610(98)00070-1.
16. Balch CM, Soong SJ, Gershenwald JE, Thompson JF, Reintgen DS, Cascinelli N, et al. Prognostic factors analysis of 17,600 melanoma patients: Validation of the American Joint Committee on Cancer melanoma staging system. J Clin Oncol. 2001;19:3622–34, http://dx.doi.org/10.1200/JCO.16.3622 200119.
17. Azzola MF, Shaw HM, Thompson JF, Soong SJ, Scolyer RA, Watson GF, et al. Tumor mitotic rate is a more powerful prognostic indicator than ulceration in patients with primary cutaneous melanoma: An analysis of 3661 patients from a single center. Cancer. 2003;97:1488–98, http://dx.doi.org/10.1002/cncr.11196.
18. Leiter U, Buettner PG, Eigentler TK, Garbe C. Prognostic factors of thin cutaneous melanoma: An analysis of the Central Malignant Melanoma Registry of the German Dermatological society. J Clin Oncol. 2004;22:3660–7, http://dx.doi.org/10.1200/JCO.2004.03.074.
19. Lindholm C, Andersson R, Dufmats M, Hansson J, Ingvar C, Moller T, et al. Invasive cutaneous malignant melanoma in Sweden, 1990-1999: A prospective, population-based study of survival and prognostic factors. Cancer. 2004;101:2067–78, http://dx.doi.org/10.1002/cncr.20602.
20. Caracò C, Marone U, Celentano E, Botti G, Mozzillo N. Impact of false-negative sentinel lymph node biopsy on survival in patients with cutaneous melanoma. Ann Surg Oncol. 2007;14:2662–7, http://dx.doi.org/10.1245/s10434-007-9433-5.
21. Reyes-Ortiz CA, Goodwin JS, Freeman JL, Kuo YF. Socioeconomic status and survival in older patients with melanoma. J Am Geriatr Soc. 2006;54:1758–64, http://dx.doi.org/10.1111/j.1532-5415.2006.00943.x.
22. Downing A, Newton-Bishop JA, Forman D. Recent trends in cutaneous malignant melanoma in the Yorkshire region of England; incidence, mortality and survival in relation to stage of disease, 1993-2003. Br J Cancer. 2006;95:91–5, http://dx.doi.org/10.1038/sj.bjc.6603216.
23. De Vries E, Nijsten TEC, Visser O, Bastiaannet E, van Hattem S, Janssen-Heijnen ML, et al. Superior survival of females among 10 538 Dutch melanoma patients is independent of Breslow thickness, histologic type and tumor site. Ann Oncol. 2008;19:583–9, http://dx.doi.org/10.1093/annonc/mdm498.
24. Chao C, Martin RCG, Ross MI, Reintgen DS, Edwards MJ, Noyes RD, et al. Correlation between prognostic factors and increasing age in melanoma. Ann Surg Oncol. 2004;11:259–64, http://dx.doi.org/10.1245/ASO.2004.04.015.
25. Paek SC, Griffith KA, Johnson TM, Sondak VK, Wong SL, Chang AE, et al. The impact of factors beyond breslow depth on predicting sentinel lymph node positivity in melanoma. Cancer. 2007;109:100–8, http://dx.doi.org/10.1002/cncr.22382.
26. Muller MGS, van Leeuwen PAM, de Lange-de Klerk ESM, van Diest PJ, Pijpers R, Ferwerda CC, et al. The sentinel lymph node status is an important factor for predicting clinical outcome in patients with stage II or III cutaneous melanoma. Cancer. 2001;91:2401–8, http://dx.doi.org/10.1002/1097-0142(20010615)91:12<2401AID-CNCR1274>3.0.CO;2-I.
27. Sondak VK, Taylor JM, Sabel MS. Mitotic rate and younger age are predictors of sentinel lymph node positivity: lessons learned from the generation of a probabilistic model. Ann Surg Oncol. 2004;11:247–58.
28. Tejera-Vaquerizo A, Martín-Cuevas P, Gallego E, Herrera-Acosta E, Traves V, Herrera-Ceballos E, et al. Factores predictivos del estado del ganglio centinela en el melanoma cutáneo: análisis mediante un árbol

de clasificación y regresión. Actas Dermosifiliogr. 2015;106:208–18, http://dx.doi.org/10.1016/j.ad.2014.10.012.
29. Conway WC, Faries MB, Nicholl MB, Terando AM, Glass EC, Sim, et al. Age-related lymphatic dysfunction in melanoma patients. Ann Surg Oncol. 2009;16:1548–52, http://dx.doi.org/10.1245/s10434-009-0420-x.
30. Balch CM, Thompson JF, Gershenwald JE, Soong SJ, Ding S, McMasters KM, et al. Age as a predictor of sentinel node metástasis among patients with localized melanoma: An inverse correlation of melanoma mortality and incidence of sentinel node metástasis among young and old patients. Ann Surg Oncol. 2014;21:1075–81, http://dx.doi.org/10.1245/s10434-013-3464-x.
31. Sunderkötter C, Kalden H, Luger TA. Aging and the skin immune system. Arch Dermatol. 1997;10:1256–62, http://dx.doi.org/10.1001/archderm.1997.03890460078009.
32. Fulop T, Kotb R, Fortin CF, Pawelec G, de Angelis F, Larbi A. Potential role of immunosenescence in cancer development. Ann N Y Acad Sci. 2010;1197:158–65, http://dx.doi.org/10.1111/j.1749-6632.2009.05370.x.
33. Hegde UP, Chakraborty N, Mukherji B, Grant Kels JM. Metastatic melanoma in the older patient: Immunologic insights and treatment outcomes. Expert Rev Pharmacoeconomics Outcomes Res. 2011;11:185–93, http://dx.doi.org/10.1586/erp.11.14.
34. Chamberlain AJ, Fritschi L, Giles GG, Dowling JP, Kelly JW. Nodular type and older age as the most significant associations of thick melanoma in Victoria, Australia. Arch Dermatol. 2002;138:609–14, http://dx.doi.org/10.1001/archderm.138.5.609.
35. Rees MJ, Liao H, Spillane J, Speakman D, McCormac C, Donahoe S, et al. Melanoma in the very elderly, management in patients 85 years of age and over. J Geriatr Oncol. 2018;9:488–93, http://dx.doi.org/10.1016/j.jgo.2018.01 001.
36. Tejera-Vaquerizo A, Barrera-Vigo MV, López-Navarro N, Herrera-Ceballos E. Growth rate as a prognostic factor in localized invasive cutaneous melanoma. J Eur Acad Dermatology Venereol. 2010;24:147–54, http://dx.doi.org/10.1111/j.1468-3083.2009.03367.x.
37. Martorell-Calatayud A, Nagore E, Botella-Estrada R, Scherer D, Requena C, Serra-Guilén C, et al. Defining fast-growing melanomas: Reappraisal of epidemiological, clinical, and histological features. Melanoma Res. 2011;21:131–8, http://dx.doi.org/10.1097/CMR.0b013e328342f312.
38. Liu W, Dowling JP, Murray WK, McArthur GA, Thompson JF, Wolfe R, et al. Rate of growth in melanomas: Characteristics and associations of rapidly growing melanomas. Arch Dermatol. 2006;142:1551–8, http://dx.doi.org/10.1001/archderm.142.12.1551.
39. Abbasi NR, Shaw HM, Rigel DS, Friedman RJ, McCarthy WH, Osman I, et al. Early diagnosis of cutaneous melanoma: Revisiting the ABCD criteria. J Am Med Assoc. 2004;292:2771–6, http://dx.doi.org/10.1001/jama.292.22.2771.
40. Menzies SW, Moloney FJ, Byth K, Avramidis M, Argenziano G, Zalaudek I, et al. Dermoscopic evaluation of nodular melanoma. JAMA Dermatology. 2013;149:699–709, http://dx.doi.org/10.1001/jamadermatol.2013.2466.
41. Pizzichetta MA, Talamini R, Stanganelli I, Puddu P, Bono R, Argenziano G, et al. Amelanotic/hypomelanotic melanoma: Clinical and dermoscopic features. Br J Dermatol. 2004;150:1117–24, http://dx.doi.org/10.1111/j.1365-2133.2004.05928.x.
42. Tejera-Vaquerizo A, Arias-Santiago S, Nagore E, Martín-Cuevas P, Orgaz-Molina J, Traves V, et al. Defining the dermoscopic characteristics of fast-growing cutaneous melanomas. Melanoma Res. 2014;25:269–72, http://dx.doi.org/10.1097/CMR. 0000000000000157.
43. Samaniego E, Redondo P. Lentigo maligno. Actas Dermosifiliogr. 2013;104:757–75, http://dx.doi.org/10.1016/j.ad.2012.05.006.
44. Tiodorovic-Zivkovic D, Argenziano G, Lallas A, Thomas L, Ignjatovic A, Rabinovitz H, et al. Age, gender, and topography influence the clinical and dermoscopic appearance of lentigo maligna. J Am Acad Dermatol. 2015;72:801–8, http://dx.doi.org/10.1016/j.jaad.2015.01.030.
45. Martin-Gorgojo A, Requena C, Garcia-Casado Z, Traves V, Kumar R, Nagore E. Dysplastic vs common naevus-associated vs de novo melanomas: An observational retrospective study of 1,021 patients. Acta Derm Venereol. 2018;98:556–62, http://dx.doi.org/10.2340/00015555-2908.
46. Ibfelt EH, Steding-Jessen M, Dalton SO, Lundstrøm SL, Osler M, Hölmich LR. Influence of socioeconomic factors and region of residence on cancer stage of malignant melanoma: A Danish nationwide population-based study. Clin Epidemiol. 2018;10:799–807, http://dx.doi.org/10.2147/CLEP.S 57 1603.
47. Sharon CE, Sinnamon AJ, Ming ME, Chu EY, Fraker DL, Karakousis GC. Association of marital status with T stage at presentation and management of early-stage melanoma. JAMA Dermatology. 2018;154:574–80, http://dx.doi.org/10.1001/jamadermatol.2018.0233.
48. Pollitt RA, Swetter SM, Johnson TM, Patil P, Geller AC. Examining the pathways linking lower socioeconomic status and advanced melanoma. Cancer. 2012;118:4004–13, http://dx.doi.org/10.1002/cncr.26706.
49. Aitken JF, Janda M, Lowe JB, Firman DW, Lowe JB, Youl PH, et al. Prevalence of whole-body skin self-examination in a population at high risk for skin cancer (Australia). Cancer Causes Control. 2004;15:453–63, http://dx.doi.org/10.1023/B:CACO.0000036451.39128.f6.
50. Geller AC, Sober AJ, Zhang Z, Brooks DR, Miller DR, Halpern A, et al. Strategies for improving melanoma education and screening for men age $\geq$ 50 years: Findings from the American Academy of Dermatology National Skin Cancer Screening Program. Cancer. 2002;95:1554–61, http://dx.doi.org/10.1002/cncr.10855.
51. Swetter SM, Pollitt RA, Johnson TM, Brooks DR, Geller AC. Behavioral determinants of successful early melanoma detection: Role of self and physician skin examination. Cancer. 2012;118:3725–34, http://dx.doi.org/10.1002/cncr.26707.
52. Richard MA, Grob JJ, Avril MF, Delaunay M, Gouvernet J, Wolkenstein P, et al. Delays in diagnosis and melanoma prognosis (I): The role of patients. Int J Cancer. 2000;89:271–9, http://dx.doi.org/10.1002/1097-0215(20000520)893<271::AID-IJC10>3.0.CO;2-7.
53. Xie C, Pan Y, McLean C, Mar V, Wolfe R, Kelly JW. Scalp melanoma: Distinctive high risk clinical and histological features. Australas J Dermatol. 2017;58:181–8, http://dx.doi.org/10.1111/ajd.12437.
54. Youl PH, Baade PD, Parekh S, English D, Elwood M, Aitken JF. Association between melanoma thickness, clinical skin examination and socioeconomic status: Results of a large population-based study. Int J Cancer. 2011;128:2158–65, http://dx.doi.org/10.1002/ijc.25540.
55. Zhao CL, Chen H, He SH, Dai YC. Radulotubus resupinatus gen. et sp. nov. with a poroid hymenophore in Pterulaceae (Agaricales Basidiomycota). Nov Hedwigia. 2016;103(1-2):265–78, http://dx.doi.org/10.1127/nova_hedwigia/2016/0350.
56. Testori A, Stanganelli I, della Grazia L, Mahadavan L. Diagnosis of melanoma in the elderly and surgical implications. Surg Oncol. 2004;13:211–21, http://dx.doi.org/10.1016/j.suronc.2004.09.002.
57. Marks R, Jolley D, McCormack C, Dorevitch AP. Who removes pigmented skin lesions? J Am Acad Dermatol. 1997;36(5 I):721–6, http://dx.doi.org/10.1016/S0190-9622(97)80324-6.

58. Xu X, Elder DE. A practical approach to selected problematic melanocytic lesions. Am J Clin Pathol. 2004;121 Suppl:S3–32, http://dx.doi.org/10.1309/YP99JBAUDXVEPVPG.
59. Ciocan D, Barbe C, Aubin F, Granel-Brocard F, Lipsker D, Velten M, et al. Distinctive features of melanoma and its management in elderly patients: A population-based study in France. JAMA Dermatology. 2013;149:1150–7, http://dx.doi.org/10.1001/jamadermatol.2013.706.
60. Macdonald JB, Dueck AC, Gray RJ, Wasif N, Swanson DL. Malignant melanoma in the elderly: Different regional disease and poorer prognosis. J Cancer. 2011;2:538–43, http://dx.doi.org/10.7150/jca.2.538.
61. Golger A, Young DS, Ghazarian D, Neligan PC. Epidemiological features and prognostic factors of cutaneous head and neck melanoma: A population-based study. Arch Otolaryngol - Head Neck Surg. 2007;133:442–7, http://dx.doi.org/10.1001/archotol.133.5.442.
62. Cormier JN, Xing Y, Ding M, Lee JE, Mansfield PF, Gershenwald JE, et al. Population-based assessment of surgical treatment trends for patients with melanoma in the era of sentinel lymph node biopsy. J Clin Oncol. 2005;23:6054–62, http://dx.doi.org/10.1200/JCO.2005.21.360.
63. Grange F, Vitry F, Granel-Brocard F, Lipsker D, Aubin F, Hédelin G, et al. Variations in management of stage I to stage III cutaneous melanoma: A population-based study of clinical practices in France. Arch Dermatol. 2008;144:629–36, http://dx.doi.org/10.1001/archderm.144.5.629.
64. Sabel MS, Kozminski D, Griffith K, Chang AE, Johnson TM, Wong S. Sentinel lymph node biopsy use among melanoma patients 75 years of age and older. Ann Surg Oncol. 2015;22:2112–9, http://dx.doi.org/10.1245/s10434-015-4539-7.
65. Lange JR, Bilimoria KY, Balch CM. Health care system and socioeconomic factors associated with variance in use of sentinel lymph node biopsy for melanoma in the United States. J Clin Oncol. 2009;27:1857–63, http://dx.doi.org/10.1200/JCO.2008.18.7567.
66. Moreno-Ramírez D, Tejera-Vaquerizo A, Mendonça FI, Ojeda-Vila T, Ferrándiz L. Making decisions on sentinel lymph node biopsy for malignant melanoma: Prioritization of determinants using a decision tree. J Eur Acad Dermatology Venereol. 2017;31:e247–9, http://dx.doi.org/10.1111/jdv.14019.
67. Testori A, Soteldo J, Sances D, Mahadavan L. Cutaneous melanoma in the elderly. Melanoma Res. 2009;19:125–34, http://dx.doi.org/10.1097/CMR.0b013e328329fe95.
68. Morton DL, Cochran AJ, Thompson JF, Elashoff R, Essner R, Glass EC, et al. Sentinel node biopsy for early-stage melanoma: Accuracy and morbidity in MSLT-I, an international multicenter trial. Ann Surg. 2005;242:302–13, doi 110.1097/01.sla.0000181092.50141.fa.
69. Koskivuo I, Hernberg M, Vihinen P, Virolainen S, Talve L, Seppänen M, et al. Sentinel lymph node biopsy and survival in elderly patients with cutaneous melanoma. Br J Surg. 2011;98:1400–7, http://dx.doi.org/10.1002/bjs.7565.
70. Shah DR, Yang AD, Maverakis E, Martinez SR. Age-related disparities in use of completion lymphadenectomy for melanoma sentinel lymph node metástasis. J Surg Res. 2013;185:240–4, http://dx.doi.org/10.1016/j.jss.2013.05.090.
71. Bilimoria KY, Balch CM, Bentrem DJ, Talamonti MS, Ko CY, Lange JR, et al. Complete lymph node dissection for sentinel node-positive melanoma: Assessment of practice patterns in the United States. Ann Surg Oncol. 2008;15:1566–76, http://dx.doi.org/10.1245/s10434-008-9885-2.
72. Faries MB, Thompson JF, Cochran AJ, Andtbacka RH, Mozzillo N, Zager JS, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. N Engl J Med. 2017;376:2211–22, http://dx.doi.org/10.1056/NEJMoa1613210.
73. Smith HG, Wilkinson MJ, Smith MJF, Strauss DC, Hayes AJ. The effect of age on outcomes after isolated limb perfusion for advanced extremity malignancies. Eur J Cancer. 2018;100:46–54, http://dx.doi.org/10.1016/j.ejca.2018.04.014.
74. Kroon HM, Coventry BJ, Giles MH, Henderson MA, Speakman D, Wall M, et al. Safety and efficacy of isolated limb infusion chemotherapy for advanced locoregional melanoma in elderly patients: An Australian multicenter study. Ann Surg Oncol. 2017;24:3245–51, http://dx.doi.org/10.1245/s10434-017-6046-5.
75. Noorda EM, Vrouenraets BC, Nieweg OE, van Geel AN, Eggermont AMM, Kroon BBR. Safety and efficacy of isolated limb perfusion in elderly melanoma patients. Ann Surg Oncol. 2002;9:968–74, http://dx.doi.org/10.1245/ASO.2002.05.011.
76. Madu MF, Deken MM, van der Hage JA, Jóźwiak K, Wouters MWJM, van Akkooi ACJ. Isolated limb perfusion for melanoma is safe and effective in elderly patients. Ann Surg Oncol. 2017;24:1997–2005, http://dx.doi.org/10.1245/s10434-017-5803-9.
77. Orloff M. Melanoma immunotherapy in the elderly. Curr Oncol Rep. 2018;20:1–6, http://dx.doi.org/10.1007/s11912-018-0656-3.
78. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen MLG, Extermann M, et al. International society of geriatric oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol. 2014;32:2595–603, http://dx.doi.org/10.1200/JCO.2013.54.8347.
79. Liu W, Kelly JW, Trivett M, Murray WK, Dowling JP, Wolfe R, et al. Distinct clinical and pathological features are associated with the BRAFT1799A(V600E) mutation in primary melanoma. J Invest Dermatol. 2007;127:900–5, http://dx.doi.org/10.1038/sj.jid.5700632.
80. Menzies AM, Haydu LE, Visintin L, Carlino MS, Howle JR, Thompson JF, et al. Distinguishing clinicopathologic features of patients with V600E and V600K BRAF-mutant metastatic melanoma. Clin Cancer Res. 2012;18:3242–9, http://dx.doi.org/10.1158/1078-0432.CCR-12-0052.
81. Scher KS, Hurria A, Hope C. Under-representation of older adults in cancer registration trials: Known problem, little progress. J Clin Oncol. 2012;30:2036–8.
82. Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015;372:30–9, http://dx.doi.org/10.1056/NEJMoa1412690.
83. Larkin J, Ascierto PA, Dréno B, Atkinson V, Liszkay G, Maio M, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med. 2014;371:1867–76, http://dx.doi.org/10.1056/NEJMoa1408868.
84. Larkin J, del Vecchio M, Ascierto PA, Krajsova I, Schachter J, Neyns B, et al. Vemurafenib in patients with BRAFV600mutated metastatic melanoma: An open-label, multicentre, safety study. Lancet Oncol. 2014;15:436–44, http://dx.doi.org/10.1016/S1470-2045(14)70051-8.
85. Robert C, Thomas L, Bondarenko I, O'Day S, Jeffrey W, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med. 2011;364:2517–26, http://dx.doi.org/10.1056/NEJMoa1104621.
86. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372:320–30, http://dx.doi.org/10.1056/NEJMoa1412082.
87. Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med. 2015;372:2006–17, http://dx.doi.org/10.1056/NEJMoa1414428.

88. Betof AS, Nipp RD, Giobbie Hurder A, Johnpulle RAN, Rubin K, Rubinstein SM, et al. Impact of age on outcomes with immunotherapy for patients with melanoma. Oncologist. 2017;22:963–71, http://dx.doi.org/10.1634/theoncologist.2016-0450.
89. Perier-Muzet M, Gatt E, Péron J, Falandry C, Amini-Adlé M, Thomas L, et al. Association of immunotherapy with overall survival in elderly patients with melanoma. JAMA Dermatology. 2018;154:82–7, http://dx.doi.org/10.1001/jamadermatol.2017.4584.
90. Kugel CH, Douglass SM, Webster MR, Kaur A, Liu Q, Yin X, et al. Age correlates with response to anti-PD1 reflecting age-related differences in intratumoral effector and regulatory T-cell populations. Clin Cancer Res. 2018;24:1–11, http://dx.doi.org/10.1158/1078-0432.CCR-18-1116.
91. Hurez V, Padrón A, Svatek RS, Curiel TJ. Considerations for successful cancer immunotherapy in aged hosts. Exp Gerontol. 2018;107:27–36, http://dx.doi.org/10.1016/j.exger.2017.10.002.
92. Fleming NH, Tian J, Vega-Saenz De Miera E, Gold H, Darvishian F, Pavlick AC, et al. Impact of age on the management of primary melanoma patients. Oncol. 2013;85:173–81, http://dx.doi.org/10.1159/000351499.
93. Bastiaannet E, Battisti N, Loh KP, de Glas N, Soto-Perez-de-Celis E, Baldini C et al. Immunotherapy and targeted therapies in older patients with advanced melanoma. Young International Society of Geriatric Oncology review paper. J Geriatr Oncol. 2018 (Epub ahead of print).