Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2012;21:27-31
doi: 10.2478/v10162-012-0008-1

Prognostic factors in patients with localized primary cutaneous melanoma

Liljana Mervic[1] ✉

Abstract

The clinical and histopathological characteristics that predict the outcomes of patients with melanoma have been studied for more than four decades. Increasingly more melanoma patients are being included in prospectively collected databases and our understanding of the biology of melanoma is improving. Therefore, the melanoma staging system is constantly being revised. The currently valid American Joint Committee on Cancer (AJCC) staging system for melanoma has been in place since early 2010 and is crucial for the determination of appropriate treatment, follow-up, and evaluating the risk of recurrence. Staging of a localized primary melanoma is based on the histopathological characteristics of the tumor: Breslow tumor thickness, mitotic rate, and presence or absence of ulceration. The Clark level of invasion is no longer recommended as a staging criterion. When mitotic rate is taken into consideration, it is no longer an independent prognostic factor. Other important and independent adverse predictors of primary cutaneous melanoma survival that are not part of the AJCC staging system are the age and sex of the patient and the anatomic location of the primary tumor. These factors, combined with the melanoma's histopathological features, could predict an individual patient's prognosis more precisely than the AJCC staging system currently in use.

Received: 11 December 2011 | **Returned for modification:** 7 February 2012 | **Accepted:** 27 February 2012

Introduction

Cutaneous melanoma is still a potentially fatal tumor that raises ongoing concern. Its incidence continues to increase in white populations worldwide. Moreover, its incidence is one of the most rapidly increasing ones in Caucasians (1). There are several possible reasons for the increasing melanoma incidence over the last four decades; however, the main reason proposed is differences in sun-exposure behavior; namely, more intensive exposure of white individuals' pale skin to natural sunlight (2). Despite constantly increasing incidence rates, mortality rates show different trends. The rise in mortality figures is much less than the rise in incidence (1). For the time being, early diagnosis is the most important factor for effective management of melanoma. It allows treatment to be undertaken at the point when the malignancy can be cured. Treatment of metastatic disease has only modest effectiveness for the time being (3).

The clinical and histopathological characteristics that predict the outcomes of patients with melanoma have been studied for more than four decades. The first multivariate analysis of prognostic factors was published in 1978 (4). Well-known factors leading to poorer prognosis for primary invasive melanoma survival are tumor thickness (with worse prognosis in thicker lesions), the presence of ulceration on histopathological examination, a high mitotic rate, anatomic site (trunk and/or facial lesions have worse prognosis than lesions on extremities), male sex, and age (with worse prognosis in older patients) (5).

Classification and staging of melanoma

Staging systems are clinically important because they allow patients to be categorized into groups that differ significantly from one another in terms of prognosis. In 1959, the American Joint Committee on Cancer (AJCC) was set up with the aim of formulating and publishing cancer classification and staging systems. Since then, the AJCC's Melanoma Staging Committee has been constantly revising the melanoma staging system. Clinical and histopathological features of the tumor that more precisely correlate with the biology of melanoma have been regularly incorporated. The Melanoma Staging Committee acts on behalf of major melanoma centers around the world. Based on experience and published data, changes to the tumor, node, and metastasis (TNM) criteria and groupings into stages have been regularly proposed. TNM categories are primarily determined by factors that strongly correlate with melanoma survival. Stage groupings therefore represent cohorts of patients that have similar disease outcomes, as determined by melanoma survival rates (6). Staging of a localized primary melanoma determined by the tumor's histopathological characteristics is crucial for appropriate treatment decisions, planning follow-up visits, and evaluation of recurrence risk. AJCC introduced the previous staging system for melanoma in 2002. It was built on data from more than 17,000 patients from 13 centers around the world specializing in melanoma treatment. It introduced some major changes and was widely adopted. The strongest predictors of survival in patients with stage I and II melanomas (localized tumor without evidence of metastasis) were Breslow tumor thickness and the presence or absence of ulceration. Clark level of invasion was an important predictor only for the group of patients with thin melanomas measuring 1 mm or less. The most significant predictors of survival in stage III disease, which represents patients with nodal metastases, were the total number of metastatic nodes, tumor burden (whether nodal metastases were clinically occult or clinically apparent), and primary tumor ulceration. The most powerful survival predictor in stage IV melanoma, which includes patients with metastatic disease, was the location of distant metastases (6).

The newest melanoma staging system from the recently published seventh edition of the AJCC Cancer Staging Manual has been in use since 2010 (7, 8). The updated criteria are based on evidence from more than 30,000 patients with stage I through III

[1]Department of Dermatovenereology, University Medical Centre Ljubljana, Zaloška cesta 2, SI-1000 Ljubljana, Slovenia. ✉ **Corresponding author: liljana.mervic@kclj.si**

melanoma as well as almost 8,000 patients with stage IV melanoma. Data were collected from 17 centers on three continents specializing in melanoma treatment. Not only was the sample size substantially expanded, but a new covariate was added into the survival analyses: the mitotic rate of the primary tumor. The use of melanoma thickness in TNM categorization has not changed, nor has the use of ulceration status. However, the mitotic rate of the primary tumor has been determined to be a powerful independent indicator of survival. Thus, for the first time, the mitotic rate has been incorporated into the AJCC staging classification for thin melanomas and is now valid as one of the three criteria for classification of stage T1b disease, replacing the Clark level of invasion. The Clark level is not an independent prognostic factor when mitotic rate is included in the calculation and thus it is no longer suggested as a staging criterion. T1a melanomas are characterized in the new classification as tumors that are no thicker than 1.0 mm, are not ulcerated, and have a mitotic rate of less than one mitosis/mm^2 (stage IA). T1b melanomas are now characterized as tumors that are thicker than 1.0 mm and either have at least one mitosis/mm^2 or evidence of tumor ulceration (stage IB). Staging of melanomas thicker than 1.0 mm has not changed since the previous version of the AJCC staging system. In stage IIA melanomas are classified as ulcerated tumors measuring from 1.01–2.0 mm or nonulcerated tumors with thickness from 2.01–4.0 mm. Stage IIB melanomas represent ulcerated tumors 2.01–4.0 mm thick or nonulcerated tumors that are thicker than 4.0 mm. Stage IIC melanomas are ulcerated tumors thicker than 4.0 mm (7). The sentinel node biopsy has become a standard procedure for detecting nodal metastases in patients with clinically uninvolved lymph nodes. The procedure identifies and removes the sentinel lymph node (the one that drains the area of the primary melanoma), which is then histologically analyzed. Clinically occult nodal metastases are therefore discovered in more melanoma patients. This procedure provides powerful prognostic information. The use of sentinel lymphadenectomy is recommended for patients with clinical stage IB or II melanoma with the aim of identifying occult stage III melanoma (9). What is new in the 2010 AJCC staging system is the inclusion of immunohistochemical staining for detection of micrometastases. Isolated tumor cells or tumor deposits larger than 0.1 mm detected histopathologically or immunohistochemically should be classified as stage III melanoma (7).

Important and independent predictors of primary cutaneous melanoma survival that are not currently in the AJCC staging system include the age and sex of the patient and the anatomic location of the primary tumor. These and other, still unknown factors in combination with the TNM criteria could predict an individual patient's prognosis more accurately than the AJCC staging system currently in use. A validated predictive model for localized primary melanoma, which was based on a very large data set, is available on the Internet. The prognostic factors included in this model are tumor thickness, ulceration, and level of invasion, as well as lesion site and patient age and sex. It is clinically useful and helps with treatment planning, predicting the outcome, and designing clinical trials (10). With increasing knowledge, our understanding of melanoma stage-specific prognostic features will further improve. Still unknown factors will probably refine the prognoses for individual patients.

Prognostic factors for localized primary melanoma survival

About 90% of melanomas are diagnosed as primary tumors without any evidence of metastasis (5). Data on more than 27,000 primary invasive melanoma patients (stages I and II) was prospectively collected in the 2008 AJCC Melanoma Staging Database. The 10-year survival rate for patients with thin, nonulcerated melanomas with less than 1 mitosis/mm^2 (stage IA) is 93%, but it falls to 39% for patients with thick and ulcerated primary tumors (stage IIC) (7). Three histopathological features of the primary melanoma—Breslow tumor thickness, mitotic rate, and presence or absence of ulceration—are currently the most important prognostic and staging factors. Therefore, a critical point for correct diagnosis and staging is the proper biopsy of a tumor. When melanoma is in question, the technique of choice is an excisional biopsy of the entire lesion, with a narrow margin of adjacent skin. For larger lesions an incisional biopsy can be justified. In addition to histopathological features, demographic or clinical factors such as age, sex, and anatomic site have also been associated with melanoma patient survival.

Breslow tumor thickness

The determination of tumor thickness was first introduced by Breslow in 1970. The distance from the upper part of the granular layer to the melanoma cell that is located the deepest was measured by micrometer (11). It was soon identified as the strongest prognostic feature for primary invasive melanoma. Based on Breslow's work, a clinically useful scheme was proposed. Patients with tumors thinner than 0.76 mm were designated low-risk patients because thin melanomas seldom metastasized. Low-intermediate risk patients were those with melanoma thickness from 0.76–1.5 mm, and high-intermediate risk were patients with tumors thicker than 1.5 mm but thinner than 4.0 mm. At very high risk for recurrence were patients with tumors thicker than 4.0 mm. In the population-based study, patients with melanomas thinner than 0.76 mm had 5-year survival of 97.9%, whereas the group of patients with tumor thickness of 0.76–1.69 mm had 91.7% 5-year survival. 72.8% of patients with melanomas ranging from 1.7–3.6 mm and 57.5% of patients with tumor thickness > 3.6 mm survived at least 5 years (12). Different breakpoints were set in other studies. The AJCC staging system selected the breakpoints of 1.0, 2.0, and 4.0 mm because there are no distinguishable thresholds as tumor thickness increases, and these breakpoints are generally more convenient (13). Tumors measuring 1.0 mm or less in thickness are defined as thin melanomas and are prognostically favorable. Tumors measuring more than 4.0 mm in thickness are defined as thick melanomas and are prognostically unfavorable. Studies showed a high correlation between increasing melanoma thicknesses and 10-year melanoma-specific survival (6, 7). In the study that was the foundation for the current AJCC melanoma staging system, 10-year survival in 11,841 patients with thin melanomas (1.0 mm or thinner) was 92%. Ten-year survival in 8,046 patients with melanomas measuring from 1.01–2.0 mm was 80%, and it was 63% in the 5,291 patients with tumors measuring from 2.01–4.0 mm. Ten-year survival in the 2,461 patients with thick melanomas (thicker than 4.0 mm) was 50% (7). The fact that tu-

mor thickness is the most important prognostic factor of survival at the primary tumor stage is now well accepted (7, 13).

Ulceration

The negative association of primary melanoma ulceration with worse disease outcome has been studied thoroughly (6, 7, 14, 15). The definition of ulceration is a loss of the epithelium continuity in full thickness with several features of host response (16). In the population-based study, 5-year survival in patients with ulceration was 66.2%, compared to 91.6% in patients with nonulcerated tumors (12). The presence or absence of primary melanoma ulceration was the second most powerful survival predictor in the analysis for the 2002 AJCC staging system and the third most powerful survival predictor in the analysis for the currently valid 2010 AJCC staging system (6, 7). Thicker tumors are more commonly ulcerated. The incidence of melanoma ulceration in thin melanomas was only 6% and thick melanomas were ulcerated in 63% of cases (6). However, melanoma ulceration is a factor that predicts the disease outcome independently of tumor thickness. Patients with ulcerated melanomas had a twofold higher estimated risk of dying due to melanoma compared to those with nonulcerated tumors. Interestingly, the presence of ulceration diminishes survival rates to the same level as for the patients with nonulcerated melanomas of the next, larger thickness group. Five-year survival in the case of 2.01–4.0 mm thick and nonulcerated melanoma was 79%, similar to the 82% rate for a 1.01–2.0 mm thick and ulcerated melanoma. Therefore, both were included in stage IIA (7).

Mitotic rate

The mitotic rate is a measure of proliferation of the primary tumor. It can easily be quantitatively assessed during the histopathological examination. When it is analyzed in the vertical growth phase it is among the strongest factors predicting survival. Mitoses in the epidermal component are of no prognostic value (17). Therefore, the present agreement is to report on the dermal mitotic rate in the vertical growth-phase tumor as the number of mitoses/mm^2. First, the area of the tumor with the greatest mitotic activity or the "hot spot" is identified. Then mitoses over an area of at least 1 mm^2 are counted (18). Sometimes mitoses are sparse and no "hot spot" can be found. In this case an area of 1 mm^2 around a representative mitosis is assessed and the result is expressed as the number of mitoses/mm^2. If the invasive component of the tumor is smaller than 1 mm^2, the mitotic rate is either at least 1/mm^2 or 0/mm^2 (9). Many researchers have found the mitotic rate to be highly predictive of survival (12, 19–20). Survival times decline as the mitotic rate increases, especially in thin melanomas (7). In a population-based study, 5-year survival for patients with mitotic rates of 0 mitoses/mm^2 was 98.7% and 85.1% for those with mitotic rates from 0.1–6.0 mitoses/mm^2. Patients with mitotic rates of more than 6 mitoses/mm^2 had 5-year survival of 68.2%. In this study mitotic rate and tumor thickness were the only two independent factors predicting survival (12). Similarly, in a recently published study 10-year survival ranged from 93% for patients whose tumors had 0 mitosis/mm^2 to 48% for those with 20 mitoses/mm^2 or more. In the same study, 10,233 patients with localized primary melanoma were included in the multivariate analysis. The mitotic rate was determined as the strongest prognostic factor after tumor thickness among the independent predictors of melanoma-specific survival (20). As with tumor thickness, there is a correlation between mitotic rates and adverse outcomes in melanoma. As the mitotic rate increases survival tends to decrease. At least 1 mitosis/mm^2 is the threshold at which the most significant correlation with outcome was detected (7). Tumor thickness, mitotic rate, and ulceration were the most powerful factors predicting survival in a multivariate analysis of 4,861 patients with thin melanomas. In the same study, when mitotic rate and ulceration were included in the hazard rates calculation, the Clark level of invasion lost its statistical significance. The 10-year survival rate for nonulcerated thin melanomas with less than 1 mitosis/mm^2 was 95%, but it fell to 88% if at least 1 mitosis/mm^2 was present (7).

In the seventh edition of the AJCC melanoma staging system, the primary tumor's mitotic rate is a required element (8).

Clark level of invasion

In 1967 Wallace H. Clark Jr. characterized melanomas into five histopathological levels of invasion. This was the first widely accepted method of microstaging for melanoma (21). In level I lesions, melanoma cells are restricted to the epidermis, constituting an in situ melanoma. Level II invasion is characterized by the extension of melanoma cells from the epidermis into the papillary dermis, but the papillary dermis is not filled with tumor cells or expanded. A true tumor with a vertical growth-phase nodule is categorized as a level III invasion, in which tumor cells fill and expand the papillary dermis. The infiltration of reticular dermis collagen fibers by melanoma cells constitutes a level IV invasion. Level V invasion is categorized by infiltration of melanoma cells from the reticular dermis into the subcutaneous fat. When considered as a single variable, level of invasion is strongly associated with melanoma outcome. Patients with level II melanoma had 98.8% 5-year survival, which dropped to 92.5% in patients with level III melanoma, 76.7% in patients with level IV melanoma, and 75% in patients with level V melanoma (12). For a subgroup of patients with thin melanomas, level of invasion predicted survival better than tumor ulceration, while the opposite was true for melanomas thicker than 1.0 mm (6). In the 2002 AJCC classification, level of invasion was included for thin melanomas only. In the currently valid 2010 AJCC classification, the Clark level of invasion is no longer suggested as a staging criterion. When mitotic rate is taken into consideration, Clark level of invasion is no longer an independent prognostic factor (6, 7). However, if there are no data about the mitotic rate or the mitotic rate cannot be accurately assessed in the subgroup of thin melanomas, level of invasion can still provide additional prognostic information (7).

Anatomic location

The location of a melanoma is an independent predictor of melanoma patient outcomes (6, 7, 20). Melanomas on the trunk, head, and neck have a worse prognosis than tumors located on the extremities. Tumors in the first group are designated as axial melanomas and they more frequently spread to distant locations compared to tumors located on the extremities. On the other hand, melanomas on the extremities metastasize locally more frequently than axial melanomas, giving rise to satellite or in-transit metastasis (22). Therefore, primary tumor sites that are prognostically unfavorable have been classified as BANS regions, which include the back, upper arm, neck, and scalp, or TANS regions, which include the trunk, upper arm, neck, and scalp (23, 24). The different clinical course of melanomas at different anatomical

locations could be explained by the differences in the lymphatic drainage from these locations. The longer length of the lymph vessels on the extremities and the greater number of lymph nodes on the way to the venous angle and blood circulation could be important factors for the better prognosis of melanomas located on the extremities (22).

Age

Numerous studies have showed worse survival in older melanoma patients. An important high-risk group consists especially of patients older than 60. Despite the fact that older patients more often have thicker and ulcerated melanomas that are prognostically unfavorable, the age of the patient at the time of establishing the diagnosis has proved to be an independent prognostic factor predicting the outcome (6, 7, 25, 26). In an analysis of 17,600 patients, a consistent decline in melanoma patient survival rates with advancing age was recorded (6). Perhaps with advancing age the progressive decline in immune function (immunosenescence) is a factor. The organism's reduced ability to fight against malignant cells can lead to more cancer morbidity and mortality. Moreover, advanced age may represent a risk factor for melanoma undertreatment. The present understanding of the influence of aging on immunity to malignancy is still limited (27, 28).

Sex

Sex is an important factor predicting outcome in melanoma patients. There are significant differences between men and women regarding the incidence of melanoma, primary tumor characteristics, and survival (26, 29, 30). Sex patterns in incidence differ from continent to continent. In the United States and Australia, men have a higher incidence of melanoma, whereas women have higher incidence rates in Europe. Despite the differences in incidence patterns around the world, the survival of women with melanoma is consistently better compared to men. (1, 6, 26, 29–33). Women as a group more often have prognostically favorable primary melanomas, namely thinner and nonulcerated tumors located on the extremities, and are younger at the first presentation of disease compared to men (26, 29, 30). However, these differences in the primary melanoma features do not fully explain the sex differences in survival. Several studies using multivariate analyses determined that sex is an independent predictor of survival (6, 7, 15). In a study analyzing 7,338 patients with primary cutaneous melanoma from southern Germany, men had lower 10-year melanoma-specific survival compared with women, at 83.9% and 89.5%, respectively. Sex was an independent predictor of survival in multivariate analysis after the adjustment for other factors: Breslow tumor thickness, presence of ulceration, Clark invasion level, melanoma location, histopathological type of melanoma, age of the patient at the time of diagnosis, and decade of diagnosis. Interestingly, the female advantage in survival disappeared after age 60 (15). Conflicting results were reported by studies that stratified sex survival differences across age categories. Some reported superior survival for women in all age categories (34, 35), whereas other reported loss of survival advantage in older women (26, 36–39). For the time being, the molecular mechanisms of melanoma survival differences between the sexes remain undiscovered. Hormonal factors, sex differences in immunity, or sex differences in oxidative stress could be of relevance (27, 34, 38, 40–42).

Conclusion

Three histopathological characteristics of melanoma are the basis for the currently valid AJCC staging of the primary melanoma without evidence of metastasis at the time of diagnosis (stage I and II melanoma): Breslow tumor thickness, presence or absence of ulceration, and mitotic rate. Other independent predictors of primary melanoma survival that are not included in the AJCC system include the age and sex of the patient and the primary tumor's anatomic location. These factors, combined with the histopathological features of melanoma, could predict an individual patient's prognosis more precisely than the AJCC staging system currently in use. With increasing knowledge, our understanding of melanoma stage-specific prognostic features will further improve. Still unknown factors will probably refine the prognoses for individual patients.

References

1. Mackie RM, Hauschild A, Eggermont AM. Epidemiology of invasive cutaneous melanoma. Ann Oncol. 2009;20 Suppl 6:vi 1-7.
2. Elwood JM, Gallagher RP. Body site distribution of cutaneous malignant melanoma in relationship to patterns of sun exposure. Int J Cancer. 1998;78:276-80.
3. Thirlwell C, Nathan P. Melanoma-part 2: management. BMJ. 2008;337:1345-8.
4. Balch CM, Murad TM, Soong SJ, Ingalls AL, Halpern NB, Maddox WA. A multifactorial analysis of melanoma: prognostic histopathological features comparing Clark's and Breslow's staging methods. Ann Surg. 1978;188:732-42.
5. Garbe C, Hauschild A, Volkenandt M, Schadendorf D, Stolz W, Reinhold U, et al. Evidence and interdisciplinary consense [sic]-based German guidelines: diagnosis and surveillance of melanoma. Melanoma Res. 2007;17:393-9.
6. 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.
7. 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;27:6199-206.
8. Balch CM, Gershenwald JE, Soong SJ, et al. Melanoma of the skin. In: Edge SE, Byrd DR, Carducci MA, et al., editors. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2009. p. 325-44.
9. Gershenwald JE, Soong SJ, Balch CM. 2010 TNM staging system for cutaneous melanoma . . . and beyond. Ann Surg Oncol. 2010;17:1475-7.
10. Soong SJ, Ding S, Coit D, Balch CM, Gershenwald JE, Thompson JF, et al. Predicting survival outcome of localized melanoma: an electronic prediction tool based on the AJCC Melanoma Database. Ann Surg Oncol. 2010;17:2006-14.
11. Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. Ann Surg. 1970;172:902-8.
12. Barnhill RL, Fine JA, Roush GC, Berwick M. Predicting five-year outcome for patients with cutaneous melanoma in a population-based study. Cancer. 1996; 78:427-32.
13. Balch CM, Buzaid AC, Atkins MB, Cascinelli N, Coit DG, Fleming ID, et al. A new American Joint Committee on Cancer staging system for cutaneous melanoma. Cancer. 2000;88:1484-91.
14. Balch CM, Soong SJ, Murad TM, Ingalls AL, Maddox WA. A multifactorial analysis of melanoma. II. Prognostic factors in patients with stage I (localized) melanoma. Surgery. 1979;86:343-51.
15. Mervic L, Leiter U, Meier F, Eigentler T, Forschner A, Metzler G, et al. Sex differences in survival of cutaneous melanoma are age dependent: an analysis of 7338 patients. Melanoma Res. 2011;21:244-52.
16. Spatz A, Cook MG, Elder DE, Piepkorn M, Ruiter DJ, Barnhill RL. Interobserver reproducibility of ulceration assessment in primary cutaneous melanomas. Eur J Cancer. 2003;39:1861-5.
17. Elder DE, Gimotty PA, Guerry D. Cutaneous melanoma: estimating survival and recurrence risk based on histopathologic features. Dermatol Ther. 2005;18:369-85.
18. Scolyer RA, Shaw HM, Thompson JF, Li LX, Colman MH, Lo SK, et al. Interobserver reproducibility of histopathologic prognostic variables in primary cutaneous melanomas. Am J Surg Pathol. 2003;27:1571-6.
19. Clark WH, Jr., Elder DE, Guerry D, Braitman LE, Trock BJ, Schultz D, et al. Model predicting survival in stage I melanoma based on tumor progression. J Natl Cancer Inst. 1989;81:1893-904.

20. Thompson JF, Soong SJ, Balch CM, Gershenwald JE, Ding S, Coit DG, et al. Prognostic significance of mitotic rate in localized primary cutaneous melanoma: an analysis of patients in the multi-institutional American Joint Committee on Cancer melanoma staging database. J Clin Oncol. 2011;29:2199-205.
21. Clark WH Jr. A classification of malignant melanoma in man correlated with histogenesis and biologic behavior. In: Montagna W, Hu F, editors. Advances in the biology of the skin. Vol. 8, The pigmentary system. New York: Pergamon Press; 1967. p. 621-47.
22. Leiter U, Meier F, Schittek B, Garbe C. The natural course of cutaneous melanoma. J Surg Oncol. 2004;86:172-8.
23. Bernengo MG, Reali UM, Doveil GC, Cappello N, Lisa F, Moretti S. BANS: a discussion of the problem. Melanoma Res. 1992;2:157-62.
24. Garbe C, Buttner P, Bertz J, Burg G, d'Hoedt B, Drepper H, et al. Primary cutaneous melanoma. Prognostic classification of anatomic location. Cancer. 1995; 75:2492-8.
25. Chao C, Martin RC, 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.
26. 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.
27. Malaguarnera L, Ferlito L, Di Mauro S, Imbesi RM, Scalia G, Malaguarnera M. Immunosenescence and cancer: a review. Arch Gerontol Geriatr. 2001;32:77-93.
28. Nomellini V, Gomez CR, Kovacs EJ. Aging and impairment of innate immunity. Contrib Microbiol. 2008;15:188-205.
29. Kolmel KF, Kulle B, Lippold A, Seebacher C. Survival probabilities and hazard functions of malignant melanoma in Germany 1972-1996, an analysis of 10433 patients. Evolution of gender differences and malignancy. Eur J Cancer. 2002;38:1388-94.
30. Scoggins CR, Ross MI, Reintgen DS, Noyes RD, Goydos JS, Beitsch PD, et al. Gender-related differences in outcome for melanoma patients. Ann Surg. 2006; 243:693-8.
31. Aase A, Bentham G. Gender, geography and socio-economic status in the diffusion of malignant melanoma risk. Soc Sci Med. 1996;42:1621-37.
32. Lasithiotakis KG, Leiter U, Eigentler T, Breuninger H, Metzler G, Meier F, et al. Improvement of overall survival of patients with cutaneous melanoma in Germany, 1976-2001: which factors contributed? Cancer. 2007;109:1174-82.
33. Quatresooz P, Uhoda I, Fumal I, Pierard-Franchimont C, Pierard GE. Revisiting the gender-linked melanoma burden. Dermatology. 2004;209:197-201.
34. de Vries E, Nijsten TE, 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.
35. Micheli A, Ciampichini R, Oberaigner W, Ciccolallo L, de Vries E, Izarzugaza I, et al. The advantage of women in cancer survival: an analysis of EUROCARE-4 data. Eur J Cancer. 2009;45:1017-27.
36. Cocconi G, Bella M, Calabresi F, Tonato M, Canaletti R, Boni C, et al. Treatment of metastatic malignant melanoma with dacarbazine plus tamoxifen. N Engl J Med. 1992;327:516-23.
37 Karjalainen S, Hakulinen T. Survival and prognostic factors of patients with skin melanoma. A regression-model analysis based on nationwide cancer registry data. Cancer. 1988;62:2274-80.
38. Kemeny MM, Busch E, Stewart AK, Menck HR. Superior survival of young women with malignant melanoma. Am J Surg. 1998;175:437-44.
39. Shaw HM, McGovern VJ, Milton GW, Farago GA, McCarthy WH. Malignant melanoma: influence of site of lesion and age of patient in the female superiority in survival. Cancer. 1980;46:2731-5.
40. Joosse A, de Vries E, van Eijck CH, Eggermont AM, Nijsten T, Coebergh JW. Reactive oxygen species and melanoma: an explanation for gender differences in survival? Pigment Cell Melanoma Res. 2010;23:352-64.
41. Miller JG, Mac NS. Gender and cutaneous melanoma. Br J Dermatol. 1997; 136: 657-65.
42. Richardson B, Price A, Wagner M, Williams V, Lorigan P, Browne S, et al. Investigation of female survival benefit in metastatic melanoma. Br J Cancer. 1999; 80: 2025-33.