Acta Dermatovenerol Croat 2013;21(3):174-179 CLINICAL ARTICLE

The Patterns of Melanoma Presentation in Rijeka Region

Ira Pavlović-Ružić[1], Nives Jonjić[2], Gordana Zamolo[2], Marta Žuvić-Butorac[3], Miljenko Katunarić[2], Sanja Pečanić[2]

[1]Clinic for Radiotherapy and Oncology, [2]Department of Pathology, Rijeka University Hospital Center; [3]Faculty of Engineering, University of Rijeka, Rijeka, Croatia

Corresponding author:
Ira Pavlović-Ružić, MD, MSc
Clinic for Radiotherapy and Oncology
Rijeka University Hospital Center
Krešimirova 42
HR-51000 Rijeka
Croatia
Ira.pavlovic-ruzic@ri.t-com.hr

Received: June 4, 2012
Accepted: December 14, 2012.

SUMMARY There is a global rising incidence of melanoma. For different reasons, the patterns of the incidence, appearance, gender, anatomical distribution and outcome vary among different geographic areas. Screening programs have led to better early detection of melanoma in Australia and some world areas. National Cancer Registry and practice data show the incidence in Croatia to be constantly rising. Despite public education programs about early detection, at clinical departments there are still many new advanced stage melanoma patients. We analyzed data on 157 patients treated and followed up for 10 years for T1b-T4aN0 skin melanoma. There was a difference in anatomical distribution of melanoma lesions in correlation with patient age (ANOVA test, F=3.51, p=0.009). A higher prevalence of shoulder melanoma was found in young people and of head/neck melanoma in the elderly (post-hoc Sheffe test, p=0.038). T4 lesions were more commonly found in men and T1 mainly in women (Pearson χ^2-test, χ^2=12.08, p=0.016). There was no difference in Clark level, but a significantly higher Breslow stage was found in men (t=-2.52, p=0.013). Men were much more prone to have head and neck, body and shoulder melanoma, whereas women had more melanoma on their legs and arms. Clark and Breslow levels were strongly correlated in leg melanoma; head localization showed no correlation at all. In conclusion, more attention should be devoted to improve the results in melanoma detection in men, especially considering the prevalence of body (back) and head/neck localizations, sometimes not readily accessible for visual detection. The pattern of distribution also pointed to the need for more attention to pay to shoulder melanoma in younger people.

KEY WORDS: cutaneous melanoma, incidence, gender difference, localization

INTRODUCTION

The rising incidence of malignant melanoma in recent years and still many unknown facts in the etiology, epidemiology, treatment and prognosis have opened many questions (1,2). Despite intensive experimental and clinical studies, the outcome is still poor (3). Five year survival as related to therapy is still not satisfying; from 62% for Clark III and 37% for Clark V patients in 1976 it has not improved significantly to the present (3,4).

The patterns of melanoma incidence, appearance, gender and body anatomical distribution and outcome vary among different geographic areas (5-

Acta Dermatovenerol Croat
2013;21(3):174-179

7). There are several large studies on the Australian, Scandinavian or US population melanoma incidence and prevalence. Generally, it is considered that northern Europe and Australia have a higher melanoma incidence (8,9). Therefore, more extensive prevention and epidemiological studies have been conducted in these areas (9). Public health projects in order to alert people of the risk and need of early nevi screening are known, especially in Australia. According to recent publications, it has helped lower the incidence of newly detected high stage melanoma. Australia is known as having most patients in T1a stage, a level that directly influences and guarantees better outcome and survival rate of melanoma patients (8,10). Studies done in the Mediterranean area are more rare, the pattern of disease is less known, and general population behavior concerning prevention and early detection and removal has not been analyzed either. In everyday clinical practice and according to data from the Croatia National Cancer Registry (10-12), the melanoma incidence in Croatia is constantly rising from 9.3 *per* 100,000 inhabitants in 2003 to 11.2 *per* 100,000 in 2007 (13-15). There are several public education programs about early cancer and skin melanoma detection, but as to clinical observation, we still see many advanced stage melanoma cases at first presentation for medical treatment. Therefore, there was an urgent need to evaluate the factors contributing to better understanding the basic clinical presentation of melanoma in our region.

PATIENTS AND METHODS

In a complex follow up patient registry and study, we evaluated data on 157 skin melanoma patients treated at Rijeka University Hospital Center in Rijeka, Croatia during the 1988-1998 period. All patients were diagnosed with localized melanoma, which was radically excised and histologically confirmed (data from Department of Pathology, School of Medicine, University of Rijeka). According to TNM classification, patients were classified as T1b to T4a, with no extent to lymph nodes (N0) or distant metastasis (M0), as stated by physical examination and diagnostic evaluation. The extent of invasion was Clark II/III to Clark V (Clark I level patients were excluded from the study) and thickness according to Breslow was >0.75.

Clinical data included age at diagnosis, gender, living place (urban or rural, data not shown), date of surgical treatment, primary tumor localization, extent of disease, and treatment applied. Patients were regularly controlled by oncologists and/or dermatologists and followed for the next 10 years (until 2009) at regular intervals.

Histopathologic evaluation consisted of the type of melanoma (nodular or superficial), growth phase (radial or vertical), Clark and Breslow level, pT stage, presence of ulceration, border and normal tissue, lymphocytic invasion, and regression.

We present the part of data from the study, which were separately analyzed for tendencies of melanoma onset and distribution in the population of this region of Croatia. Our aim was to evaluate the results and see if there are patterns of melanoma behavior in the population that could be of general public importance and used in the prevention and early detection programs in our region.

All procedures were done and data collected with approval from the Hospital and University Ethics Board and according to WHO recommendations and revised Helsinki declaration respecting privacy and identity protection of each patient and his/her human rights, and according to good clinical practice policy.

Statistical tests used for each part are given in parentheses together with the result. The software used was Statistica ver. 10.0. (StatSoft Inc.).

RESULTS

In the group of 157 patients, 86 (55%) were female and 71 (45%) male. The mean age at diagnosis confirmation (date of surgical removal and histologic confirmation) was 52±15 years (age is a normally distributed variable (Kolmogorov-Smirnov test, p>0.20), and it is expressed as mean and standard deviation. The median is also correlating to the mean (age median = 52 years, q25-q75 = 41-65 years).

The age of patients was well balanced between genders, i.e. there was no statistically significant difference in the age to gender balance (52±16 years for women *vs.* 52±15 years for men, Student's t-test t=-0.092, p=0.927). According to anatomical localization of primary melanoma, patients were divided into five groups: arm, leg, head and neck, shoulder and trunk (body) localization.

There was a significant difference in patient age in correlation with anatomical localization of primary melanoma (ANOVA test, F=3.51, p=0.009) (Fig. 1). Separate analysis showed that patients with melanoma of the head and neck region were statistically significantly older than patients with shoulder melanoma (post-hoc Sheffe test, p=0.038). Patients with melanoma located on the shoulder were youngest, mean age 38 years, as compared to other groups with mean age 50.

Acta Dermatovenerol Croat
2013;21(3):174-179

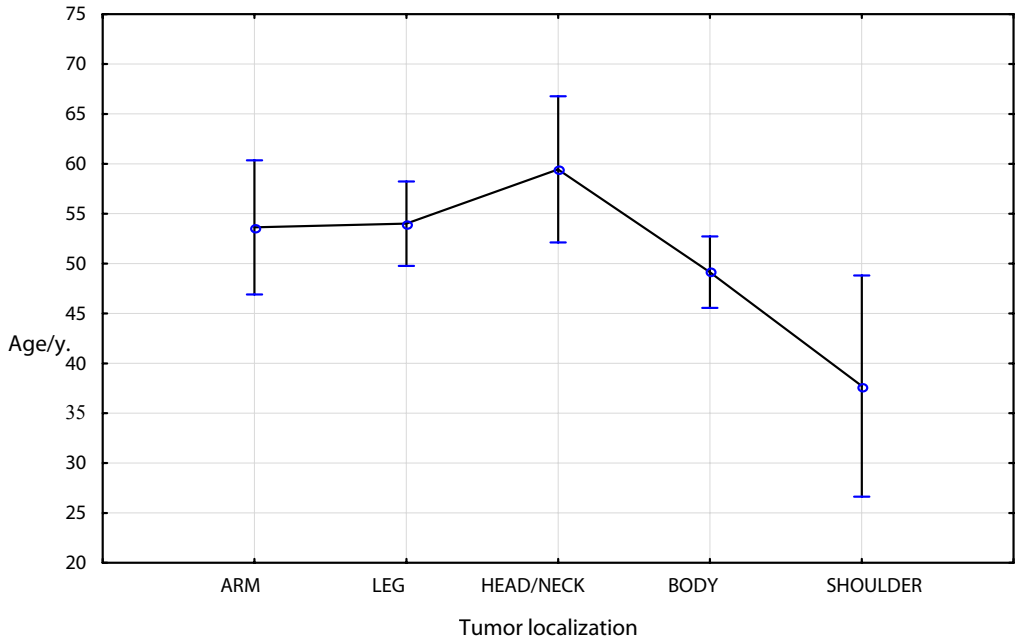

Figure 1. Patient age in different body localizations of melanoma; mean values are presented with 95% interval of confidence.

There was a difference in the distribution of melanoma according to gender and tumor anatomical localization (Pearson χ^2-test, χ^2=12.08, p=0.016) (Fig. 2). Leg localization of melanoma showed highest proportion in female, who had the lowest incidence of shoulder and body melanoma.

Correlation analysis was employed to evaluate the Clark level and Breslow depth correlation. There was a good and statistically significant correlation (correlation factor r=0.32, p<0.001) (Fig. 3).

Correlation analysis between Clark and Breslow values in different tumor localizations is shown in Table 1. The results showed a significantly highest correlation of Clark and Breslow in melanoma located in the leg area. There was practically no correlation in the head and neck region. If melanoma was found on the body, the correlation was weak and its statistical significance was due to the greatest number of correlations analyzed.

The values of Clark and Breslow classification in correlation with patient gender and age and tumor anatomical localization are shown in Table 2. The level of invasion by Clark did not differ between genders (Mann-Whitney U test, U=2791, z=-0.539, p=0.590), but the value of Breslow was significantly higher in men (t-test, t=-2-52, p=0.013).

Table 1. Values of the factor of correlation between Clark and Breslow stage and its statistical significance in different anatomical localizations of primary melanoma

Localization of melanoma	n	(Clark-Breslow correlation)	p
Arm	19	0.34	0.164
Leg	48	0.55	<0.001
Head/neck	16	0.06	0.833
Body	67	0.27	0.027
Shoulder	7	0.67	0.999

Acta Dermatovenerol Croat
2013;21(3):174-179

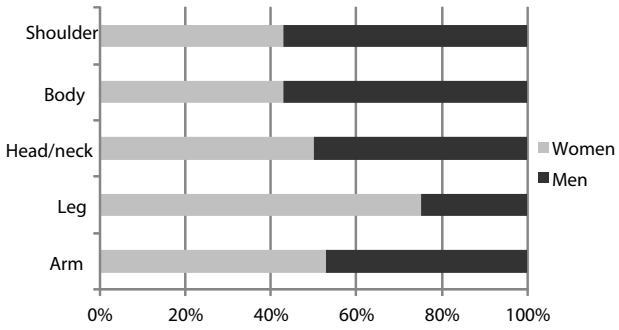

Figure 2. Gender distribution of melanoma incidence in different anatomical parts of the body.

There were no statistically significant differences in Clark values in tumors of different body regions (Kruskal-Wallis test, H=4.66, p=0.24); the same held true for Breslow values (ANOVA, F=0.545, p=0.703).

We evaluated the correlation of Clark and Breslow levels (values) with patient age. There was neither correlation of age with Clark value (Spearman correlation factor r=0.11, p=0.104) nor with Breslow (Pearson factor of correlation r=0-01, p=0.879) values.

TNM classification was correlated with age and gender, as shown in Figure 4 .Gender distribution was significantly deviated as compared to the expected values (Pearson χ^2-test, χ^2=8.12, p=0.043).

We also analyzed TNM distribution at different anatomical sites, but no statistically significant differences were found compared to the expected distribution (Pearson χ^2-test, χ^2=15.86, p=0.197). Moreover, there was no difference in age distribution of patients in correlation to TNM classification (ANOVA; F=0.324, p=0.808).

DISCUSSION

Approximately 350,000-450,000 inhabitants of Croatia lived in the region in study years and were referred to our oncology center if needed. In this study, we analyzed data on 157 patients with localized skin melanoma at first medical examination, that presented during a period of 10 years, yielding a mean yearly incidence of 3.48 to 4.48 new localized invasive melanoma patients *per* 100,000 inhabitants.

Our study indicated different patterns of tumor presentation in two genders. Even more, it alerts on a higher stage and grade of melanoma in men. According to our study, tumors of a lower grade are more often found in women. Of the total number of patients, the prevalence of T1 tumors in women was 61% (men 39%), whilst the prevalence of T4 tumors in men was 74% (women 36%). The same results were obtained by comparing Breslow level as another indicator of the potential tumor aggressiveness (16-18): the mean value for men was higher than for melanoma found in women, with statistical significance of p=0.013. It might indicate that men in this region are more prone to neglect or not notice the tumor in its early stage. It can also be the result of different anatomical distribution of melanoma in men and women (7), where most of melanoma in women are located in the leg area, which is easily accessible for inspection. The results on our patients are consistent with the findings

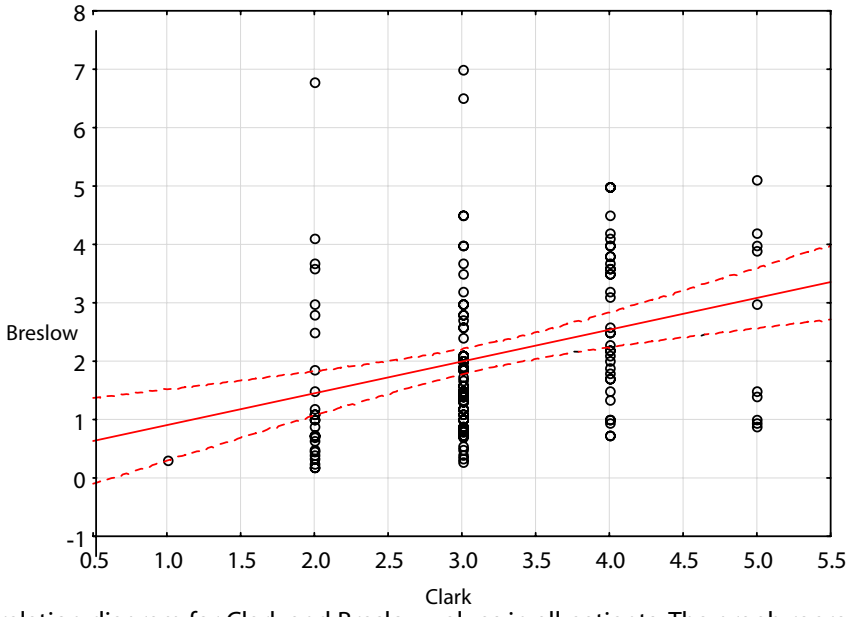

Figure 3. Correlation diagram for Clark and Breslow values in all patients. The graph represents regression line with 95% interval of confidence.

Acta Dermatovenerol Croat
2013;21(3):174-179

Table 2. Values of Clark and Breslow classification in correlation with patient gender and age and tumor anatomical localization

		Clark		Breslow	
		Median	q25-q75	Mean	SD
Total		3	3-4	2.01	1.41
Gender	Women	3	3-4	1.84	1.21
	Men	3	3-4	2.40	1.58
Localization	Arm	3	3-4	1.79	1.16
	Leg	3	3-4	2.04	1.21
	Head/neck	3	2-4	1.88	1.69
	Body	3	3-4	2.25	1.55
	Shoulder	3	2-3	2.29	1.35

reported by other authors (2,7,19,20). Men, on the contrary, have more melanomas in the body and shoulder area, which are, especially if on the back, maybe not accessible to early visual detection by the host.

The differences in Clark and Breslow relations in various anatomical localizations are also interesting. The lack of correlation in the head and neck area is probably mainly due to the very thin skin and subcutaneous layers in the head area, especially forehead, zygomatic or hair area. Therefore, depth expressed in millimeters maybe is not an appropriate risk and prognostic factor for melanoma in this localization (17). As these localizations are mainly very well and abundantly vascularized, probably the extent of blood vessels (i.e. vascularization) or the presence of angiogenic factors could be considered as a more appropriate risk factor.

There is also a different pattern of melanoma localization connected to age at onset. Mainly, shoulder localization has often been detected in young people, whereas head skin melanoma is found in older patients (18). This may be connected to the customs in this mainly coastal region; in children and young adults, head is usually protected (wearing hat is usual) from direct sun exposure (7). At the same time, shoulders are exposed to sun and often to sunburn, mostly in very young children and young people. Knowing the etiologic influence of sunburn in childhood to later development of melanoma, a shift to younger age could offer an explanation for shoulder localization (7,9,21,22). Time interval for developing head melanoma was probably shifted to elderly years. There is a well proven fact of a higher incidence of other skin cancers in the head and scalp area in elderly men in coastal region, connected to their profession and habits (22-24).

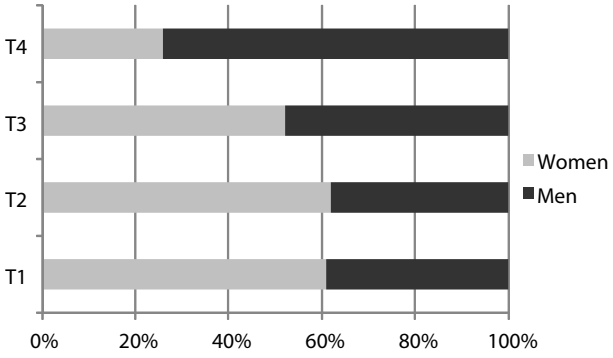

Figure 4. Gender distribution in different TNM stages of melanoma.

Detection of melanoma, especially in its initial stage is of great importance. The recent introduction of Melanoma Day in Croatia with organized dermatoscopic screening of pigmented lesions and prompt recommendation for removal of suspected ones (25) has improved the rate of early stage melanoma detection.

CONCLUSION

According to data from our patient pool, men in this region presented with a higher stage of cutaneous melanoma, with a more unfavorable presentation and body localization for early visual self-detection, which potentially leads to a worse course of disease and prognosis. Therefore, we recommend that more care be directed to male population in the general public melanoma alert and early detection activities. Programs for public education should also be in a way remodeled to attract men and stimulate their skin self-assessment. This could improve their chances for cure and better survival.

Acta Dermatovenerol Croat
2013;21(3):174-179

References

1. MacKie RM, Hauschild A, Eggermont AM. Epidemiology of invasive cutaneous melanoma. Ann Oncol 2009;20(Suppl 6):vi 1-7.
2. Melanoma Center. Melanoma Basic Melanoma Statistics. 2010; www.melanomacenter.org.
3. 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.
4. DeVita VT, Fisher RI. Natural history of malignant melanoma as related to therapy. Cancer Treat Rep 1976;60:153-62.
5. Aase A, Bentham G. Gender, geography and socio-economic status in the diffusion of malignant melanoma risk. Soc Sci Med 1996;42:1621-37.
6. Cancer Epidemiology in Older Adolescents & Young Adults. SEER AYA Monograph 2007:53-57.
7. Šitum M. Malignant tumours of skin and soft tissue. Medicus 2001;10:237-45.
8. Czarnecki D, Meehan J. Is the incidence of malignant melanoma decreasing in young Australians? J Am Acad Dermatol 2000;42:672-4.
9. Hemminki K, Li X. Level of education and the risk of cancer in Sweden. Cancer Epidemiol Biomarkers Prev 2003;12:796-802.
10. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P, *et al.* Meta-analysis of risk factors for cutaneous melanoma: II Sun exposure. Eur J Cancer 2005;41:45-60.
11. Croatian Institute for public Health. Cancer registry. Incidencija raka u Hrvatskoj 2007. Bilten 32.
12. Croatian Institute of Public Health. Cancer registry. Incidencija raka u Hrvatskoj 2006. Bilten 31.
13. Croatian Institute of Public Health. Cancer registry. Incidencija raka u Hrvatskoj 2003. Bilten 28.
14. Pašić A, Strnad M, Lipozenčić J. Epidemiology and etiology of melanoma. In: Lipozenčić J, Pašić A, editors. Dermatološka onkologija. Zagreb: Medicinska naklada, 2009:87-102.
15. Gruber F, Zamolo G, Jonjić N, Pavlović-Ružić I, Brajac I. Tumour thickness in cutaneous melanoma in the Croatian region of Rijeka (1988-1997). 3rd International Conference The Adjuvant Therapy of Malignant Melanoma Abstract Booklet, London, UK, 1999;25:P-2.
16. Morton DL, Davtyan DG, Wanek LA, Foshag LJ, Cochran AJ. Multivariate analysis of the relationship between survival and the microstage of primary melanoma by Clark level and Breslow thickness. Cancer 1993;71:3737-43.
17. Marghoob AA, Koenig K, Bittencourt FV, Kopf AW, Bart RS. Breslow thickness and Clark level in melanoma: support for including level in pathology reports and in American Joint Committee on Cancer Staging. Cancer 2000;88:589-95.
18. Büttner P, Garbe C, Bertz J, Burg G, d'Hoedt B, Drepper H, *et al.* Primary cutaneous melanoma: optimized cutoff points of tumor thickness and importance of Clark's level for prognostic classification. Cancer 1995;75:2499-506.
19. Joosse A, Collette S, Suciu S, Nijsten T, Lejeune F, Kleeberg UR, *et al.* Superior outcome of women with stage I/II cutaneous melanoma: pooled analysis of four European Organisation for Research and Treatment of Cancer phase III trials. J Clin Oncol doi: 10.1200/JCO.2011.38.0584.
20. Sondak VK, Swetter SM, Berwicj MA. Gender disparities in patients with melanoma: breaking the glass ceiling. Journal of Clinical Oncology, Vol 30, 2012:http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2011.41.3849
21. Šitum M, Buljan M, Ožanić Bulić S, Šimić D. The mechanisms of UV radiation in the development of malignant melanoma. Coll Antropol 2007;31(Suppl 1):13-6.
22. World Health Organization. Solar ultraviolet radiation: global burden of disease from solar ultraviolet radiation. Environmental Burden of Disease Series, No. 13, 2006.
23. Gruber F, Peharda V, Kaštelan M, Brajac I. Occupational skin diseases caused by UV radiation. Acta Dermatovenerol Croat 2007;15:191-8.
24. Buljan M, Šitum M, Bolanča Ž, Vurnek Živković M, Lugović Mihić L. Multiple primary melanoma. Coll Antropol 2010;34(Suppl 2):131-4.
25. Lipozenčić J, Marinović-Kulišić S, Pašić A. Prevention and risk factors in melanoma development. In: Lipozenčić J, Pašić A, editors. Dermatološka onkologija. Zagreb: Medicinska naklada, 2009:87-102.