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Clinicopathologic characteristics of cutaneous melanoma – a single-center retrospective study

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SUMMARY

Introduction/Objective Epidemiology of melanoma including the number of new cases and mortality have been established in most developed countries, but data on pathohistological features are mostly missing. The objective of the study was to investigate epidemiological, clinical, and pathohistological features of melanoma patients and compare the results with trends in other countries.

Methods Our sample comprised patients surgically treated for skin melanoma at the Hospital for Burns, Plastic and Reconstructive Surgery during the 2015–2017 period. Pathohistological, clinical, and demographic features of melanoma were studied.

Results The retrospective study comprised 201 patients (109 men and 92 women) aged 25–87 years. Melanoma was more common in men than in women (54.2% *vs*. 45.8%). Melanoma in male population most commonly presented on the trunk, while in females presentation on the trunk and lower extremities was almost equal. Superficial spreading melanoma was the most common type of melanoma (68.7%), without correlation to the sex. No correlation was observed in relation to the stage of the disease and the patient's sex ($p = 0.294$). A statistical difference was observed in relation to the type of melanoma and the Breslow classification ($p < 0.001$). Breslow's thickness correlated with neither age nor sex. In relation to tumor invasiveness, 12.4% of the lesions were classified as *in situ* lesions, while 87.6% of the lesions were invasive. The majority of patients were identified as stage pT1a.

Conclusion This study can help to identify patients at high risk for melanoma and contribute to optimize screening efforts in a defined target population.

Keywords: melanoma; Breslow; Serbian population; melanoma pathology; melanoma epidemiology

INTRODUCTION

Melanoma still represents a major diagnostic and therapeutic problem, with its rapid incidence rise worldwide [1]. The incidence of melanoma has been rising continuously over the last 50 years [2], with an approximate 3% annual rate according to age–period–cohort studies published so far [3]. The incidence and mortality rates vary by the regions, depending on the primary and secondary prevention strategies, early detection, and access to the latest treatment protocols [3].

Melanoma is among less commonly diagnosed skin tumors on the annual level (1–5%). According to the latest available data, 324,635 new cases were recorded in 2020, accounting for 1.7% of all newly diagnosed carcinoma on the global level, and with 57,043 related deaths its share in global carcinoma mortality is 0.6% [3]. In spite of development of new protocols and modalities for treatment and diagnostics, melanoma is still associated with the highest mortality rate of all skin tumors [1, 4]. In 2020, the age-standardized (for the world population) rate (ASR-W) was 3.4/100,000 on the global level, 18.9/100,000 in the Western Europe, and 35.8/100,000 in Australia and New Zealand as countries with the highest number of newly diagnosed cases [2]. In the same year, the standardized mortality rates were 0.56, 1.5, and 2.7/100,000, respectively [2]. It is more common in the 50+ years age population, with 59 years as the median age at diagnosis, but it is not uncommon among younger population either, particularly among women. Overall, melanoma is more common in men, but before the age of 50 it is more common in women [1]. It usually appears on the trunk, followed by the head and neck, lower and upper extremities, and finally the acral parts (hand, foot). Sex distribution shows that it is common on the trunk in men and on the lower extremities in women. In the USA, according to the SEER database, that keeps track of the five-year survival rates in patients diagnosed between 2011 and 2017, while reviewing cases of localized disease, the survival rate reaches 99.4%. In case of spreading to the lymph nodes, the percentage of the five-year survival is 68%, while in cases of distant metastases, the survival rate is only 29.8% [5]. In the light of the factual survival statistics, it is quite clear that early diagnosis of skin melanoma and easy access to clinical and dermoscopic examinations are very important factors in subsequent treatment. According to the National Cancer Registry of the Republic of Serbia, melanoma was the 12th most common

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malignant tumor in 2018, and 18th according to the number of fatal outcomes [6]. In 2018, the Dr. Milan Jovanović Batut Public Health Institute reported 709 new cases of melanoma, and 269 fatal outcomes. The ASR incidence was 10.6/100,000 in men and 8.6/100,000 in women [6], while the ASR mortality was 4.9/100,000 in men and 2.9/100,000 in women. The objective of the study was to investigate epidemiological, clinical and pathohistological features of melanoma patients and compare the results with trends in other countries.

METHODS

A retrospective study was conducted, with the data obtained from the medical records. Patients surgically treated for skin melanoma at the Hospital for Burns, Plastic and Reconstructive Surgery of the University Medical Center of Serbia (UKCS) in the period 2015–2017 were reviewed. The study was approved by the UKCS Ethics Committee (No: 602/1 Date: 30.12.2021).

The study comprised 201 patients (109 men and 92 women). The patients were divided into four age groups: < 40 years, 41–60 years, 61–80 years, and > 80 years. Tumor localization was divided into four regions: (a) head and neck, (b) trunk, (c) upper extremities, (d) lower extremities, (e) acral. The primary melanoma stage was determined according to the 2017 American Joint Committee on Cancer (AJCC) pT classification. Initially, narrow margin excisional biopsy with 1–3 mm margins was performed. The biopsy was interpreted by a pathologist experienced in melanocytic neoplasms. All patients had a confirmed diagnosis of cutaneous melanoma by histopathology, with all reported elements – histologic subtype: nodular melanoma (NM), superficial melanoma (SM), lentigo maligna (LM), acral, and others (desmoplastic and amelanotic); Breslow thickness (< 1 mm, 1.01–2 mm, 2.01–4 mm, > 4 mm), dermal mitotic rate per mm^2; present or absent ulceration and microsatellites, as well as the pT stage of the disease.

The study investigated clinical and histopathological features of melanoma and compared them between the sexes. The incidence of melanoma subtypes by the localization on the body was also investigated. Tumor thickness determined by Breslow classification was examined against patient age, melanoma subtype, stage of the disease, number of mitoses, presence of ulcerations and microsatellites.

Statistical analysis

The statistical software package SPSS for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA) was used. Parametric and nonparametric features were analyzed by using the χ^2 test, the Mann–Whitney test, the Kruskal–Wallis tests. Afterwards, the Kolmogorov–Smirnov normality test and Spearman's rank correlation coefficient were used.

P-values < 0.05 were considered statistically significant.

Ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the UKCS ethics committee (No.: 602/1 Date: 30.12.2021).

RESULTS

We evaluated a total of 201 tumor samples that were identified histologically as melanoma. All specimens were obtained from complete tumor excisions/excisional biopsy, which is the recommended excision technique if melanoma is suspected clinically.

Out of 201 confirmed melanoma samples, 25 were classified as *in situ* lesions (12.4%), defined by tumor growth confined to the epidermis with an intact basement membrane. The remaining 176 samples (87.6%) were identified as invasive melanoma. *In situ* tumors were almost equally common in both sexes. We assessed differences in the samples by sex (Table 1). The mean age of the patients was 61.47 ± 13.9 years and statistically significantly lower in women (63.39 ± 12.62 *vs.* 59.20 ± 15.03 [p = 0.036]). The majority of patients were in the 61–80 years old group. Patients under 40 years of age were more commonly women (6.4% of men, 15.2% of women), while men predominated among the elderly patients (7.3% of men and 4.3% of women).

Breslow's thickness did not differ between the sexes (p = 0.241) (Figures 1 and 2). The majority of patients (54.7%) had thin melanomas, less than 1-mm-thick tumors (49.6% of men and 60.9% of women). The incidence of 1.01–2 mm and 2.01–4-mm-thick tumors was almost identical in both groups (13.4% and 13.9%, respectively), with 1.01–2-mm-thick tumors slightly more common in men than in women. Breslow thickness above 4 mm was noted in 27 patients (17.9%), most of whom (59.3%) were 60–80 years of age, and slightly more frequent among male population. The patient age did not significantly correlate with tumor depth. On the other hand, a statistically significant difference was observed in relation to the type of melanoma and the Breslow classification (p < 0.001). SSM, LMM, and acral subtypes were mostly thin melanomas (79.1%, 17.3%, and 1.8%, respectively). In contrast, NM accounted for the majority of tumors thicker than 3 mm. Thin melanomas (< 1 mm) were almost equally distributed in the location of thorax and upper extremities, while thick melanomas (> 1 mm) were more frequent in the head and neck region and in the lower extremities (Figure 3).

No major differences between the sexes were detected in the histologic subtype. The most common subtype in both groups was SM, accounting for 68.7% of all tumors, followed by the nodular subtype. Melanoma localization by tumor type is shown in Table 2. The superficial type of melanoma was most often localized on the trunk (45.7%).

Table 1. Comparison of melanoma characteristics according to sex

Variable	Men n (%)	Women n (%)	Total n (%)	p
Age (years)				
≤ 40	7 (6.4)	14 (15.2)	21 (10.4)	0.123
41–60	27 (24.8)	27 (29.3)	54 (26.9)	
61–80	67 (61.5)	47 (51.1)	114 (56.7)	
> 80	8 (7.3)	4 (4.3)	12 (6)	
Total	109 (100)	92 (100)	201 (100)	
Melanoma localization				
Upper extremities	19 (17.4)	15 (16.3)	34 (16.9)	0.001
Head and neck	22 (20.2)	11 (12)	33 (16.4)	
Trunk	50 (45.9)	32 (34.8)	82 (40.8)	
Lower extremities	10 (9.2)	27 (29.3)	37 (18.4)	
Acral	8 (7.3)	7 (7.6)	15 (7.5)	
Total	109 (100)	92 (100)	201 (100)	
Histological type				
Superficial	70 (64.2)	68 (73.9)	138 (68.7)	0.232
Nodular	16 (14.7)	15 (16.3)	31 (15.4)	
Lentigo melanoma	15 (13.8)	6 (6.5)	21 (10.4)	
Acral	2 (1.8)	0 (0)	2 (1)	
Other	6 (5.5)	3 (3.3)	9 (4.5)	
Total	109 (100)	92 (100)	201 (100)	
Breslow thickness				
≤ 1	54 (49.6)	56 (60.9)	110 (54.7)	0.241
1.01–2	19 (17.4)	8 (8.7)	27 (13.4)	
2.01–4	16 (14.7)	12 (13)	28 (13.9)	
> 4	20 (18.3)	16 (17.4)	36 (17.9)	
Total	109 (100)	92 (100)	201 (100)	
pT stage				
Tis	12 (11)	13 (14.1)	25 (12.3)	0.370
T1a	32 (29.4)	35 (38.1)	67 (33.3)	
T1b	11 (10)	8 (8.7)	19 (9.4)	
T2a	14 (12.8)	4 (4.3)	18 (9)	
T2b	4 (3.7)	4 (4.3)	8 (4)	
T3a	8 (7.3)	8 (8.7)	16 (8)	
T3b	9 (8.3)	5 (5.5)	14 (7)	
T4a	10 (9.2)	8 (8.7)	18 (9)	
T4b	9 (8.3)	7 (7.6)	16 (8)	
Total	109 (100)	92 (100)	201 (100)	
Mitosis	55 (50.9)	40 (43.5)	95 (47.5)	0.293
Ulcerations	25 (22.9)	20 (21.7)	45 (22.4)	0.893
Microsatellites	7 (6.4)	1 (1.1)	8 (4)	0.073
Elevated S protein	17 (15.6)	14 (15.2)	31 (15.4)	0.941
Elevated LDH	42 (38.5)	36 (39.1)	78 (38.8)	0.931

LDH – lactate dehydrogenase

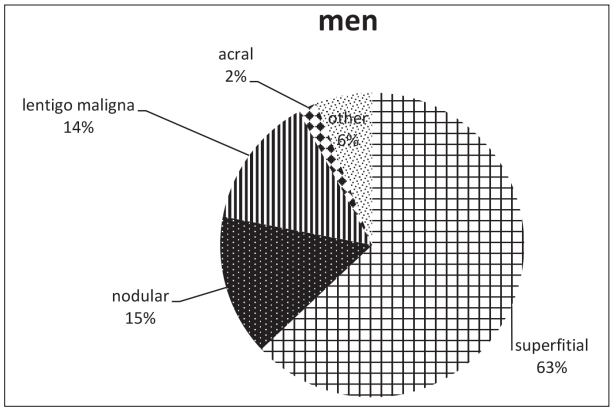


Figure 1. Distribution of melanoma subtype in male population

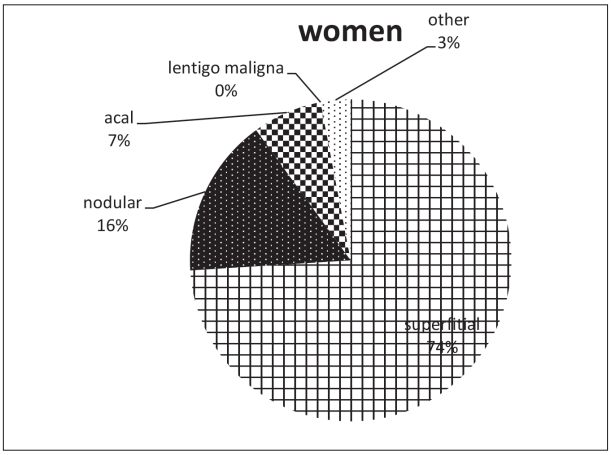


Figure 2. Distribution of melanoma subtype in female population

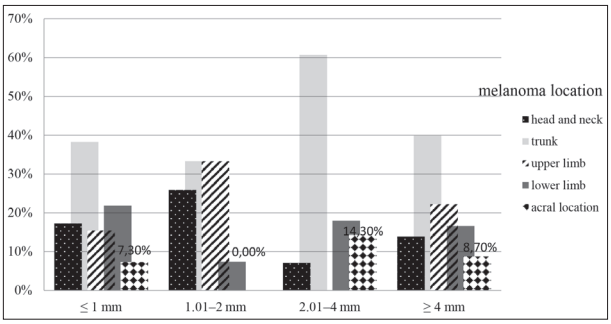


Figure 3. Distribution of melanoma thickness according to localization

Table 2. Comparison of melanoma location according to tumor type

Melanoma localization		Melanoma type					Total
		Superficial	Nodular	Lentigo melanoma	Acral	Other	
Upper extremities	n	25	7	3	0	0	35
	%	18.1%	22.6%	14.3%	0%	0%	17.4%
Head and neck	n	20	4	13	0	3	40
	%	14.5%	12.9%	61.9%	0%	33.3%	19.9%
Trunk	n	63	11	4	0	3	81
	%	45.7%	35.5%	19%	0%	33.3%	40.3%
Lower extremities	n	30	9	1	2	3	45
	%	21.7%	29%	4.8%	100%	33.3%	22.4%
Total	n	138	31	21	2	9	201
	%	100%	100%	100%	100%	100%	100%

The nodular type of tumor was also most commonly localized on the trunk (35.5% of cases). On the other hand, the most common type of tumor localized on the head and neck was lentigo melanoma, registered in 13 out of 21 patients (61.9%). The acral type of melanoma was registered only in two patients and it was localized on the lower extremities in both cases. Considering age distribution and melanoma subtype, superficial spreading, nodular and lentigo maligna were the most common subtypes of melanoma among the population 61–80 years of age (Figure 4). Also, in all locations of the body, melanoma was most frequently found in the age group above 61 years of age (Figure 5).

The study showed statistically significant difference in melanoma location between the sexes (p = 0.001).

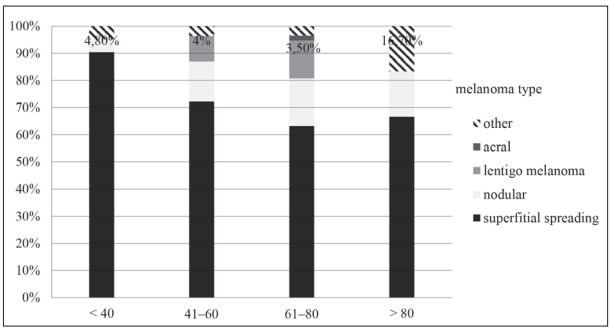


Figure 4. Distribution of type of melanoma according to age

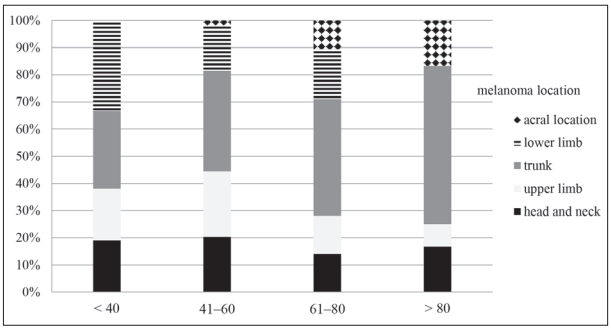


Figure 5. Distribution of melanoma location according to age

Melanoma was most often localized on the trunk 45.9%, followed by the head and neck 24.8% in male population, while in women, the incidence of melanoma was almost identical on the trunk and lower extremities (33.7% and 34.8%, respectively). No statistically significant difference was noted in the pT stage of the disease between the sexes (p = 0.370). Ulcerations were present in 22.4% of primary tumors. Mitoses and ulcerations were almost evenly distributed between the sexes with no significant difference (p = 0.293 and p = 0.893). Microsatellites were more often present in men than in women (p = 0.073), while distant metastases were registered in 2.5% of the patients, with no difference in frequency between the men and the women in our group of patients.

Table 3. Patient characteristics by the Breslow classification

Variable	Breslow				Total n (%)	p
	≤ 1 mm n (%)	1.01–2 mm n (%)	2.01–4 mm n (%)	> 4 mm n (%)		
Age (years)						
< 40	16 (14.5)	2 (7.4)	1 (3.6)	2 (5.6)	21 (10.4)	0.233
41–60	29 (26.4)	7 (25.9)	7 (25)	11 (30.6)	54 (26.9)	
61–80	58 (52.7)	16 (59.3)	20 (71.4)	20 (55.6)	114 (56.7)	
> 80	7 (6.4)	2 (7.4)	0 (0)	3 (8.3)	12 (6.30)	
Total	110 (100)	27 (100)	28 (100)	36 (100)	201 (100)	
Sex						
Men	54 (49.1)	19 (70.4)	16 (57.1)	20 (55.6)	109 (54.2)	0.241
Women	56 (50.9)	8 (29.6)	12 (42.9)	16 (44.4)	92 (45.8)	
Total	110 (100)	27 (100)	28 (100)	36 (100)	201 (100)	
Melanoma type						
Superficial	87 (79.1)	25 (92.6)	13 (36.1)	13 (36.1)	138 (68.7)	< 0.001
Nodular	0 (0)	2 (7.4)	8 (28.6)	21 (58.3)	31 (15.4)	
Lentigo melanoma	19 (17.3)	0 (0)	2 (7.1)	0 (0)	21 (10.4)	
Acral	2 (1.8)	0 (0)	0 (0)	0 (0)	2 (1)	
Other	2 (1.8)	0 (0)	5 (17.9)	2 (5.6)	9 (4.5)	
Total	110 (100)	27 (100)	28 (100)	36 (100)	201 (100)	
Mitosis	16 (14.5)	21 (17.7)	25 (89.3)	33 (94.3)	95 (47.5)	< 0.001
Ulcerations	3 (2.7)	8 (29.6)	13 (46.4)	21 (58.3)	45 (22.4)	< 0.001
Microsatellites	0 (0)	1 (3.7)	2 (7.1)	5 (13.9)	8 (4)	< 0.001

DISCUSSION

General epidemiological features of melanoma relating to the number of newly diagnosed cases and related mortality are mainly well established in many developed countries, but we miss the data on the histopathological features of melanoma [7]. The National Cancer Registry in Serbia keeps only the data on newly diagnosed cases and the number of related deaths, while important prognostic data, such as tumor thickness according to Breslow and the presence of ulcerations, are missing [6].

The results of our study have shown that most patients were over 60 years of age at the time of diagnosis establishing. Men were affected more frequently than women, but women were affected at an earlier age. In the age group under 40 years the number of women was twice the number of men. These results are in line with the latest published sex-specific trends published for populations all over Europe and USA indicating higher incidence among younger women, while men are affected mostly in their middle age [7–11]. These results coincide with the results published in the National Cancer Registry in the Republic of Serbia. This can be explained by different habits of sexes: men are less inclined to self-examine or present for an examination with a specialist. This probably contributes to detection of melanoma later and in more advanced stages [12, 13].

Localization of melanoma on the trunk may also be related to the later detection. The truncal melanomas, more common in men, are less visible and thus detected later. Melanomas in women are detected earlier so that they are thinner according to Breslow classification [14]. Men and women also differ in skin anatomy and physiology. The skin of men is thicker and richer in collagen and elastic fibers. It has less subcutaneous fat and different hair distribution, which responds differently to UV-induced skin trauma and is considered more photosensitive than the skin of women [15, 16]. The results of our study show greater prevalence of stage III I IV melanoma in men, which is in line with a study published by Behbahani et al. [14], suggesting the survival advantage of women, since simple surgical excision is the sufficient treatment method for thin melanoma. Analysis of the results of previous studies relating to anatomic localization and sex has shown that melanoma in men is most commonly localized on the trunk, while in women it usually affects the lower extremities [17].

However, recent studies show that this difference is fading out [18]. Our results also corroborate the trend showing that melanoma most commonly appears on the trunk (45.9%), and head and neck (24.8%) in men, while in women the incidence of melanoma on the trunk and lower extremities was almost identical (33.7% *vs*. 34.8%).

Our results show no statistical difference in the incidence of different types of melanomas between men and women. SM was the most common type of melanoma (68.7%), followed by NM (15.4%), LM (10.4%), and AM (1%), coinciding with the results published for the US and EU [19]. Comparisons of anatomic localizations of UV-exposed regions, as expected, showed LM presence most commonly on the head and neck regions (61.9%), while AM was present on the lower extremities only [9].

The most important prognostic factor was tumor thickness by Breslow, while penetration depth by Clark is still registered in HP reports although AJCC classification does not require it [20]. Most of our patients had melanoma less than 1 mm thick according to Breslow, while other groups were represented equally. Our study did not show statistically significant correlation of age and tumor thickness or sex and tumor thickness either.

The presence of ulcerations, mitotic activity and micro satellites is increased and is very much correlated with tumor thickness, as expected [20]. Numerous studies have shown that ulcerations, as a bad prognostic sign, are more common in men [18]. Our study, however, failed to identify any difference in the incidence of ulceration between the sexes.

CONCLUSION

Further investigations in the field of demographic and clinicopathological characteristics of melanoma are necessary to improve melanoma prevention, diagnosis, and treatment. Professional examination and self-examination should consider all parts of the body, including hidden localizations and particular attention should be paid in the population beyond 60 years. Understanding melanoma behavior and clearly identifying groups at risk in both sexes would allow us to create national programs of prevention and early detection of melanoma that could lead to better overall survival.

Conflict of interest: None declared.

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Клиничкопатолошке карактеристике кожног меланома – ретроспективна студија појединачног центра

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САЖЕТАК

Увод/Циљ Опште епидемиолошке карактеристике меланома, број новооболелих и морталитет, углавном су познате у већини развијених земаља, али оно што недостаје јесу подаци о хистопатолошким карактеристикама меланома. Циљ овог истраживања је било испитивање епидемиолошких, клиничких и патохистолошких карактеристика болесника и упоређивање резултата са трендовима у другим земљама.

Методе Наш узорак су чинили болесници оперисани због меланома коже на Клиници за опекотине, пластичну и реконструктивну хирургију у периоду од 2015. до 2017. године. Испитиване су хистопатолошке, клиничке и демографске карактеристике меланома.

Резултати Ова ретроспективна студија је обухватила 201 болесника (109 мушкараца и 92 жене), старости од 25 до 87 година. Мушкарци су оболевали чешће у односу на жене (54,2% према 45,8%). Меланом се код мушкараца најчешће јавља на трупу, док је код жена инциденца меланома на трупу и доњим екстремитетима идентична. Најчешћи тип био је меланом површног ширења (68,7%), без статистички значајне разлике међу половима. Није уочена корелација у односу на стадијум болести и пол болесника ($p = 0,294$). Статистички значајна разлика је уочена при поређењу дебљине меланома према класификацији по Бреслоу и типа меланома ($p < 0,001$). Није уочена разлика у дебљини меланома по Бреслоу међу половима и према старости болесника. Према инвазивности, 12,4% лезија су класификоване као *in situ* лезије, а 87,6% као инвазивне. Већина болесника је идентификована као стадијум *pT1a*.

Закључак Ова студија може олакшати идентификацију болесника са високим ризиком оболевања од кожног меланома и допринети оптимизацији скрининга у дефинисаној циљној популацији.

Кључне речи: меланом; Бреслоу (*Breslow*); популација Србије; патологија меланома; епидемиологија меланома