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ORIGINAL ARTICLE

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Main risk factors for local recurrence in patients with cutaneous melanoma — single center study

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ABSTRACT

Introduction. True scar recurrence (persistent disease) that develops at the site of wide excision of primary cutaneous melanoma is defined as the presence of in situ and/or radial phase of growth of a melanoma that is within or near the surgical scar This study aims to present the main risk factors associated with the appearance of local recurrence in patients with melanoma of the skin, as well as the negative impact of local recurrence on overall survival.

Material and methods. We included 144 patients with skin melanoma in the study who were operated on at UMHAT "Dr. Georgi Stranski" Pleven, Bulgaria, during the period 2012–2017.

Results. Achromic skin melanoma was significantly (χ^2 = 15.668; df = 1; p = 0.001) more frequent in patients with locally recurrent melanoma. Metastatic melanoma was more common in patients with local recurrence (73% *vs.* 16.3%; χ^2 = 25.308; df = 1; p = 0.001). The overall median survival of all patients was 75.9 [95% confidence interval (CI) 69.7–82.0] months and it was lower [95% CI 52.8 (39.8–65.8) *vs.* 95% CI 77.7 (71.1–84.2)] in patients with local melanoma recurrence, although the differences were not significant (p = 0.076).

Conclusions. The achromic type and the greater thickness and depth of invasion of the primary skin melanoma are major risk factors for the development of local recurrence. The presence of local recurrence of the disease is associated with a high rate of distant metastases. The development of local recurrence in patients with cutaneous melanoma significantly worsens the overall survival of the disease.

Keywords: local recurrences, melanoma, achromic melanoma, pigment melanoma, reexcision, excision

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Introduction

True scar recurrence (persistent disease) that develops at the site of wide excision of primary cutaneous melanoma is defined as the presence of *in situ* and/or radial phase of growth of a melanoma that is within or near the surgical scar [1]. Its frequency varies from 1 to 9.41% and applies to all thicknesses of invasive melanoma of the skin when a wide excision within a radius of at least 1 cm from the previous biopsy scar is performed [2–5]. Local recurrence in skin melanoma must be distinguished from satellite and in-transit metastases. The satellite metastases are defined as skin and subcutaneous tissue lesions outside the scar from previous wide local excision of the primary tumour which extends up to 2 cm. The in-transit metastases in

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Table 1. Thickness of local melanoma recurrences according to Breslow's classification and resection borders

Thickness of local melanoma recurrence according to Breslow's classification [mm]	Surgical borders
In situ	0.5 cm
≤ 2	1.0 cm
> 2	2.0 cm

cutaneous melanoma are defined as skin and subcutaneous lesions located more than 2 cm from the re-excision scar of the primary tumour but within the regional lymphatic basin of the relevant anatomical area. The satellite and in-transit metastases in patients with melanoma are lymphatic metastases, not re-growth of melanoma cells at the primary area [6–10]. Clinically, local recurrences present as nodules with varying sizes and colours, ranging from pink for the achromic to black for the pigmented variant. The diagnosis is confirmed after a biopsy and histological examination. The treatment of these recurrences includes surgical re-excision in healthy tissue, and the depth is dependent on melanoma thickness (Tab. 1) [11, 12].

The volume of re-excision includes the scar from the previous excision, and the main goal is the achievement of clear skin margins [1, 11, 12]. In individual cases with absolute contraindications to surgical treatment at the site of local recurrence of melanoma (severe comorbidity), local definitive radiotherapy can be applied [11, 12]. After surgical treatment, these patients require targeted (dabrafenib-trametinib), systemic immune (nivolumab, pembrolizumab) or mixed therapy. Treatment options for unresectable cases include regional chemotherapy, intralesional thermo-ablation, local immunotherapy [11–14] and local T-Vec therapy [11, 12]. The presence of local recurrence in patients with skin melanoma significantly worsens the prognosis [15].

This article aims to present the main risk factors associated with the appearance of local recurrence in skin melanoma patients and the negative impact of local recurrence on overall survival.

Material and methods

This prospective study was approved by the Ethics Committee of Medical University — Pleven, Bulgaria. We included 144 patients with skin melanoma (SM) who were operated in the University Multiprofile Hospital for Active Treatment (UMHAT) "Dr Georgi Stranski" Pleven, Bulgaria from 2012 to 2017. All subjects involved in the study gave informed consent. The patients were treated comprehensively based on the same protocol depending on the stage of the disease and clinical guidelines. All patients in stages III and IV of cutaneous melanoma received targeted treatment and immunotherapy, in combination or separately. All patients included in the study were allocated to two groups according to the "presence" (Group 1) or "absence" (Group 2) of local recurrence of skin melanoma. Group 1 included patients with primary cutaneous melanoma who, after a physical exam and suspicious findings, had a biopsy and meticulous histopathological examination confirming the presence of melanoma cells within the scar from the previous wide excision of the primary tumour.

Data analysis was performed by SPSS v.25.0. Descriptive statistics was used for categorical (absolute and relative frequencies) and continuous (median, minimum, and maximum values of variables) variables. Pearson chi-square and Mann-Whitney tests were used to analyse group differences (significant differences if the p-value was less than or equal to 0.05). Risk factors of MM were classified as demographic (sex, age) and clinical (primary anatomic location of MM, histological variant, tumour thickness and depth, T, N and M categories of tumor–node–metastasis (TNM) classification, time from diagnosis to recurrence). The 8th TNM classification for staging melanoma, Clark level and Breslow's thickness were used [16].

Patients in both studied groups were followed until 2022. The Kaplan-Meier method [17] was used to evaluate median survival and computed from diagnosis of SM until death or the last date of follow-up.

Results

Demographic characteristics of skin melanoma patients

Of all 144 studied patients, local recurrence of SM was detected in 15 (10.4%). Most of them (60%) were females and were assigned to two age groups (61–70 years and 71–80 years). The median age of patients in Group 1 was 67 years *vs.* 65 years in Group 2 (Tab. 2).

Clinical characteristics of skin melanoma

We identified the prevalence of 7 different clinical risk factors (RFs) in patients in Groups 1 and 2. The median time from melanoma diagnosis to local recurrence was 12 months. Patients with and without local SM recurrence had a similar common sites of the primary tumour (back, lower leg, face).

There was a significant difference between the two groups (in favour of the first) regarding the percentage of cases with Breslow's tumour thickness greater

Table 2. Demographical and clinical characteristics of the patients in the studied groups

	Locally SM recurrence		p
	Group 1 (Yes)	**Group 2 (No)**	
Sex			
Males	6 (40.0)	66 (51.2)	
Females	9 (60.0)	63 (48.8)	
Total	**15 (100.0)**	**129 (100.0)**	**0.413**
Age			
Median	67.0 (32, 82)	65.0 (17, 91)	0.283[1]
≤ 40 yrs.	1 (6.7)	16 (12.4)	
41–50 yrs.	1 (6.7)	17 (13.2)	
51–60 yrs.	1 (6.7)	17 (13.2)	
61–70 yrs.	5 (33.3)	35 (27.1)	
71–80 yrs.	6 (39.9)	38 (29.4)	
≥ 80 yrs.	1 (6.7)	6 (4.7)	
Total	**15 (100.0)**	**129 (100.0)**	**0.392**
Site of primary melanoma			
Face	2 (13.1)	20 (15.4)	
Walked	0 (0.0)	4 (3.1)	
Abdomen	1 (6.7)	5 (3.9)	
Brachium	1 (6.7)	16 (12.4)	
Back	4 (26.7)	35 (27.1)	
Waist	1 (6.7)	2 (1.6)	
Lower leg	4 (26.7)	18 (14.0)	
Scalp	1 (6.7)	8 (6.2)	
Front chest	0 (0.0)	11 (8.5)	
Femur	1 (6.7)	5 (3.9)	
Forearm	0 (0.0)	5 (3.9)	
Total	**15 (100.0)**	**129 (100.0)**	**0.784**
Histological type of SM			
Pigmentary SM	10 (66.7)	123 (95.3)	
Achromic SM	5 (33.3)	6 (4.7)	
Total	**15 (100.0)**	**129 (100.0)**	**0.001**
Breslow's thickness			
Median	4.4 (0.9, 11.0)	2.4 (0.0, 26.0)	0.009[3]
In situ	0 (0.0)	8 (6.2)	
Invasion less than 0.75 mm	0 (0.0)	14 (10.9)	
Invasion 0.76 –1.0 mm	1 (6.7)	9 (7.0)	
Invasion 1.1–2.0 mm	2 (13.3)	29 (22.4)	
Invasion 2.1–4.0 mm	4 (26.7)	34 (26.4)	
Invasion greater than 4.1 mm	8 (53.3)	35 (27.1)	
Total	**15 (100.0)**	**129 (100.0)**	**0.290**
Tumour depth of invasion (Clark level)[2]			
Level 1	0 (0.0)	11 (8.5)	
Level 2	0 (0.0)	13 (10.1)	
Level 3	5 (33.3)	36 (27.9)	
Level 4	7 (46.7)	58 (45.0)	
Level 5	3 (20.0)	11 (8.5)	
Total	**15 (100.0)**	**129 (100.0)**	**0.313**

→

Table 2 cont. Demographical and clinical characteristics of the patients in the studied groups

	Locally SM recurrence		p
	Group 1 (Yes)	Group 2 (No)	
T category[4]			
T0	0 (0.0)	8 (6.2)	
T1a	1 (6.7)	17 (13.2)	
T1b	0 (0.0)	4 (3.1)	
T2a	1 (6.7)	27 (20.9)	
T2b	1 (6.7)	4 (3.1)	
T3a	3 (20.0)	14 (10.9)	
T3b	1 (6.7)	19 (14.7)	
T4a	3 (20.0)	10 (7.8)	
T4b	5 (33.3)	26 (20.1)	
Total	**15 (100.0)**	**129 (100.0)**	**0.373**
N category[5]			
N0	10 (66.7)	84 (65.1)	
N1	2 (13.3)	25 (19.4)	
N2	1 (6.7)	18 (14.0)	
N3	2 (13.3)	2 (1.6)	
Total	**15 (100.0)**	**129 (100.0)**	**0.057**
M category[6]			
M0	4 (26.7)	108 (83.7)	
M1	11 (73.3)	21 (16.3)	
Total	**15 (100.0)**	**129 (100.0)**	**0.001**

[1, 3]Mann-Whitney test was used; [2]Clark level of invasion — Level 1: MM cells are in the epidermis, Level 2: tumour invades into the papillary dermis, Level 3: MM cells are spread throughout the papillary dermis and touching on reticular dermis, Level 4: tumour invades the reticular dermis, Level 5: tumour invasion of subcutaneous tissue; [4]T category — T0: melanoma *in situ*, T1 (a: no ulceration, b: ulceration) ≤ 1.0 mm, T2: 1.1–2.0 mm, T3: 2.1–4.0 mm, T4: ≥ 4.1 mm; [5]N category — N0: 0 positive lymph nodes (LN+), N1: 1 LN+, N2: 2–3 LN+, N3: ≥ 4 LN+; [6]M category — M0: no evidence of distant metastasis, M1: distant metastasis; SM — skin melanoma

than 2.1 mm respectively category T3 + T4. In addition, the percentage of patients with local recurrence and Clark IV and V invasion was higher than in the group without invasion. Regarding the ratio of the N category in the two groups, we observed a greater percentage of patients with the N3 category in the group with local recurrence.

We found statistically significant differences regarding the prevalence of 3 RFs in the two compared groups (with and without local recurrence of skin melanoma) (Tab. 2):

1. Histological type of SM

Achromic SM was significantly ($\chi^2 = 15.668$; df = 1; p = 0.001) more often encountered in patients with locally recurrent melanoma.

2. Breslow's thickness

Median tumour thickness was significantly higher in Group 1 (4.4 *vs.* 2.2 mm; U = 569; p = 0.009). Cases of advanced-stage melanomas (invasion ≥ 2.1 mm) were more often in the same group.

3. M category

Metastatic melanoma was more often encountered in patients with local recurrence (73% *vs.* 16.3%; $\chi^2 = 25.308$, df = 1; p = 0.001). Eight patients (72.7%) of all 11 patients with local recurrence and distant metastases had metastases in the skin only, 1 patient (9.1%) had metastases in the muscles, 1 patient (9.1%) had metastases in the skin and brain, and 1 patient (9.1%) had metastases in the skin and lung.

Adjuvant treatment of skin melanoma patients

A total of 56.25% of the patients included in our study received adjuvant therapy, significantly ($\chi^2 = 3.838$; df = 1; p = 0.025) more patients in Group 1 (80.0%) compared to Group 2 (53.5%) (Tab. 3).

Survival

In total, 62.5% of patients were alive at the end of the study. Significantly more patients in Group 2 (65.1%) ($\chi^2 = 3.617$; df = 1; p = 0.050) were alive compared to Group 1 (40.0%). The ratio of deaths from SM was 2 times higher (60.0% *vs.* 34.9%) in the patients with local recurrence.

Table 4 and Figure 1 present the Kaplan-Meier estimates for local melanoma recurrence.

Table 3. Results of the adjuvant treatment analysis

	Locally SM recurrence		p
Adjuvant therapy	Group 1 (Yes)	Group 2 (No)	
Yes	12 (80.0)	69 (53.5)	
No	3 (20.0)	60 (46.5)	
Total	**15 (100.0)**	**129 (100.0)**	**0.025**

SM — skin melanoma

Table 4. Results of the survival analysis

	Locally SM recurrence		p
Vital status	**Group 1 (Yes)**	**Group 2 (No)**	
Alive	6 (40.0)	84 (65.1)	
Dead	9 (60.0)	45 (34.9)	
Total	**15 (100.0)**	**129 (100.0)**	**0.050**
Overall survival [months]	52.8	77.7	0.076

SM — skin melanoma

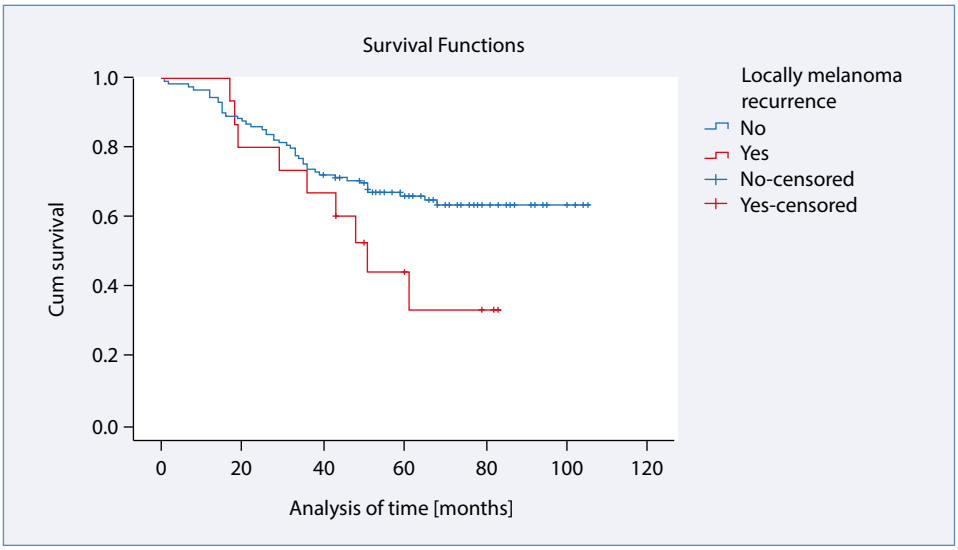

Figure 1. Kaplan-Meier survival estimates stratified by local melanoma recurrence

Overall median survival of all patients was 75.9 [95% confidence interval (CI) 69.7–82.0] months, and it was lower [95 CI 52.8 (39.8–65.8) *vs.* 95 CI 77.7 (71.1–84.2)] in patients with locally recurrent melanoma although the differences were not significant (p = 0.076) — Table 4.

The probability that the patients with local melanoma recurrence would survive 18 months was 86.7%, and it was lower compared with the patients without local melanoma recurrence (88.4%) — Figure 1.

Discussion

The incidence of skin melanoma is constantly increasing worldwide. This disease is the number one cause of death resulting from skin malignancies, followed by squamous cell carcinoma of the skin [18]. Adequate and timely complex treatment of the disease significantly enhances the prognosis. Surgical treatment is the main treatment. During its implementation, our team adhered to the last guidelines [1, 11, 19, 20].

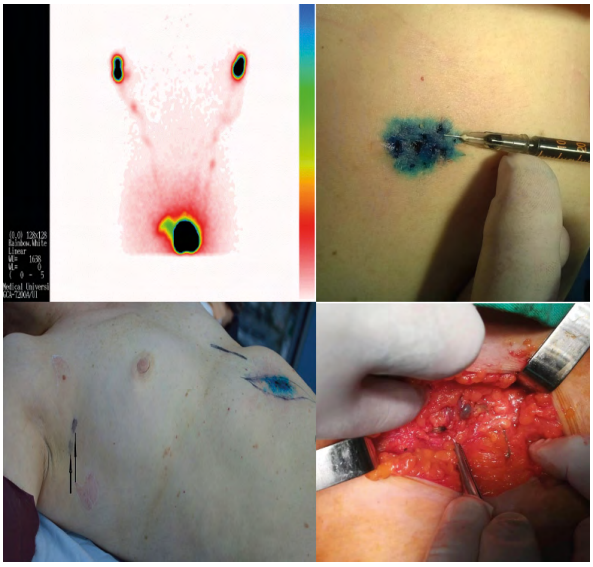

Figure 2. Points of sentinel lymph node biopsy

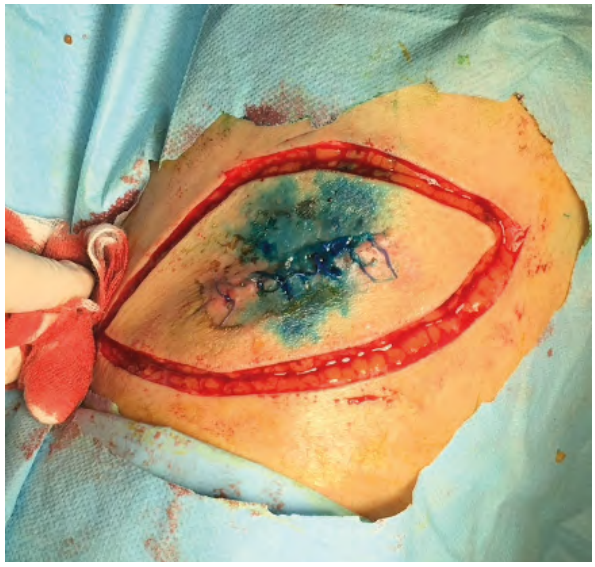

Figure 3. Wide local excision of the biopsy site of cutaneous melanoma

The macroscopic diagnosis of the tumour preceded its surgical treatment. It was performed by a dermatologist using a dermatoscope. He/she made the diagnosis based on the basic dermatoscopic criteria for detecting malignancy of pigmented skin lesions.

After the pre-operative diagnosis, we proceeded to an excisional (total) biopsy of the tumour with an apparently healthy skin border of 1–3 m from the edge of the lesion. With regards to depth, we reached the underlying fascia without interfering with it. We did not go further from the tumour in order not to affect the draining lymphatics of the area, which could lead to wrong determination of the sentinel lymph node in the subsequent sentinel lymph node biopsy (SLNB). After the histological verification of the tumour, including mandatory determination of its histological variant, presence of ulcerations, evaluation of mitotic activity, Breslow's thickness, and Clark level, we proceed to perform a sentinel biopsy of the regional lymph nodes using a previously made lymphoscintigraphic map.

Lymphatic mapping was performed by injecting a radiopharmaceutical (99Tc sulfocolloid) around the scar from the previous biopsy of the primary melanoma in the Department of Radiology with subsequent whole-body Gamma camera of the patient's lymphatic system. During the procedure, skin markers were placed corresponding to the location of sentinel lymph nodes within the lymph pool of the primary tumour. The patient was transported to the operating room, where we injected the dye Patent Blue V strictly intradermally in a dose of 1 ml in 10 places around the scar from the previous diagnostic biopsy, after executing and reporting a negative skin-allergy test.

We applied warm gauze to the injection site to stain faster the sentinel lymph node. After 15 minutes, we looked for the sentinel lymph node by skin incision in the area of the previously placed skin markers during the scintigraphy. The sentinel lymph node was identified as a blue-stained node that corresponded topographically to the lymphoscintigraphic map. We removed the relevant nodes by ligation of their efferent and afferent lymph nodes and sent them for histological examination. We performed meticulous haemostasis of the site and lavage with an antiseptic. Occasionally, before wound closure, we placed drainage. The procedure was completed with a sterile dressing at the site (Fig. 2).

We did not perform sentinel biopsy in low-risk tumours less than 0.75 mm thick (without ulceration and with a low mitotic index), in cases of clinically confirmed, puncture-biopsy positive regional lymph nodes, in patients with previous lymph node biopsy of the relevant region, or cases of extensive biopsy of the primary focus.

After SLNB, we performed a wide local excision around the biopsy scar of the primary melanoma. The volume of the excision correlated with the Breslow's thickness of the primary tumour. We did not exceed the limits of 2 cm in all directions relative to the biopsy cicatrix, always reaching the underlying fascia but leaving it intact (Fig. 3).

When larger skin defects were obtained, it was necessary to perform non-free skin grafts, and in the remaining cases, the wounds were closed using different types of stitches. In the subsequent histological examination of the specimen, there were single residual tumour cells inside only one of them, but the resection margins were

intact (clear resection lines). Dissection of the regional lymph nodes was executed in metastatic involvement established histologically after sentinel biopsy, cytologically by fine needle aspiration biopsy or after clinical and instrumental examination. Satellite and in transit skin metastases were removed, if possible, with a visible 2 cm healthy halo.

In the presence of local cutaneous recurrence of melanoma, the surgical strategy is similar to that of primary cutaneous melanoma. It begins with an excisional biopsy followed by pathologic verification. At the next stage, a sentinel biopsy of the regional lymph basin is performed in compliance with all the rules and re-excision of the biopsy site in a volume of up to 2 cm in all directions within healthy borders depending on melanoma thickness according to Breslow's classification. In addition to the surgical treatment, systemic adjuvant therapy is also applied in patients with local skin recurrence of melanoma in stages III and IV. In those with a *BRAF* mutation of melanoma, treatment includes targeted therapy (dabarafenib/trametinib) and immunotherapy (nivolumab or/and pembrolizumab), and in patients without *BRAF* mutations, it includes only immunotherapy (nivolumab or/and pembrolizumab).

Our result of 10.4% local recurrences of skin melanoma significantly exceeds the results of other studies (between 0.7% and 9.41%) [2–5, 21, 22]. This may be related to the late diagnosis in our patients. The median time for the appearance of local recurrence after the primary diagnosis and treatment of skin melanoma in our study was 12 months. That period is about 2 times longer than that reported by Woodford et al. [23] (6.2 months in a study on 711 patients from Australia) and is similar to that presented by Staker et al. [21] [13 months in a study of 1,203 US patients with cutaneous malignant melanoma conducted over 10 years (2006–2016)]. Compared to other similar studies [24–26], the percentage of local recurrences in our study was lower. Most of our patients in the group with local recurrence were women over 61 years of age. These results are fully consistent with those of Marcoval et al. [27] obtained in a study of 1,080 patients with primary, cutaneous melanoma in Spain. According to another study by Staker et al. [21] in a group with local recurrence of cutaneous malignant melanoma, men over this age predominated. In our study, we found that skin melanomas localised on the head, body, and lower limbs give the most frequent local recurrences. Our results fully match those of similar studies by Staker et al. [21] in the US and von Schuckmann et al. [28] conducted on 700 patients in Australia [28].

According to Balch et al. [29], local recurrence of skin melanoma is not caused by residual tumour cells at the site of the wide excision but by those detached from the primary tumour, circulating with the blood flow and later reaching the place of the scar [29]. Our patients with a histological type of achromic (amelanotic) melanoma were significantly more numerous in the group with local recurrence compared to the group with no recurrence ($\chi^2 = 15.668$; df = 1; p = 0.001). Macroscopically, achromic melanoma is a red or pink-pigmented skin lesion. Its histological subtypes are identical to the pigment type of skin melanoma and include the nodular, superficially spreading, lentigo maligna, and acral-lentiginous types. The main difference between pigmented and achromic melanoma is that the cells of the second one do not have, or have a minimal amount of, the pigment melanin. This difference is established by means of melanoma, which gives us reason to consider achromic skin melanoma as one of the main risk factors for the development of local recurrence due to its mitotic activity, excessive growth and dissemination by blood and lymph [30, 31]. Our opinion is confirmed by the results of a study conducted in the US by Hopkins et al. [32], including 359,927 patients with melanoma of the skin in the years 2004–2015 [32]. According to another result of our study, there was a significant difference between the Breslow tumour thickness in the groups "with" and "without" local recurrence in favour of the former (4.4 *vs.* 2.2 mm; U = 569; p = 0.009). In addition, 80% of the patients in Group 1 had Breslow thickness over 2.1 mm (T3 and T4), and only 53.5% in Group 2. The patients with Clark levels IV and V accounted for 66.7% of patients in group 1 and 53.5% in Group 2. These data, as well as the fact that thicker and deeper-penetrating melanomas are spreading more quickly and easily through the lymphatic and circulatory system, give us reason to believe that the thickness of the skin melanoma according to Breslow's classification and its depth according to Clark levels are the main risk factors for developing local recurrence. This thesis has been also confirmed by numerous studies and meta-analyses [5, 21–23, 33–35]. Our data on the N-category in the studied groups show a higher relative proportion of N3 in the group with local recurrence. This fact can be explained by the higher metastatic potential of achromic melanomas [30, 31] and those with greater thickness and depth of invasion [5, 33–35], whose share was significantly higher in the same group. Our results in the M category a significantly higher relative proportion of the patients with distant metastases in the group with local recurrence (73% *vs.* 16.3%; $\chi^2 = 25.308$; df = 1; p = 0.001). Despite adequate and complex treatment patients with local recurrence are more likely to develop distant metastases compared to those without recurrence. This fact can also be explained by the higher rate of patients with achromic [30, 31] thicker and deeper-penetrating skin melanoma in this group [5, 33–35].

Adjuvant treatment was significantly more common in our group of patients with local recurrence (Group 1) (80% *vs.* 53.5%; $\chi^2 = 3.838$; df =1; p = 0.025).

These data are completely in line with the results of similar international studies [21–23]. This result indicates the more aggressive nature of skin melanoma in cases with local recurrence.

Analysing our results, we found a significantly lower survivor rate in the group with local recurrence ($\chi^2 = 3.617$, df = 1; p = 0.050). Regarding overall and 18-month patient survival, we found that these were also lower in the group with local recurrence. Based on these results, we can conclude that the presence of local recurrence is a poor prognostic factor for survival of skin melanoma patients. Numerous similar studies around the world have the same conclusions [21–23, 36].

Conclusions

The achromic type and the greater thickness and depth of invasion of the primary skin melanoma are the major risk factors for the development of local recurrence. The presence of local recurrence of the disease is associated with a high rate of distant metastases. Adjuvant treatment is significantly more common in patients with local recurrence of cutaneous malignant melanoma. The development of local recurrence in patients with cutaneous melanoma significantly worsens their overall survival.

Article Information and Declarations

Data availability statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Medical University — Pleven, Bulgaria; protocol code 454-КЕНИД from 21.06.2017.

Author contributions

S.S.: conceptualization, methodology, software, validation, investigation, resources, data curation, writing — original draft preparation, writing (review and editing), visualization, supervision, project administration; A.Y.: conceptualization, validation, investigation, resources, writing (review and editing); V.N.: methodology, validation, investigation, resources, writing (review and editing), supervision; G.K.: software, validation, investigation, resources, writing (review and editing), supervision; J.S.: software, validation, formal analysis, resources, data curation, writing (original draft preparation, review and editing), visualization.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

None.

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