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Comparative analysis of main clinical features in melanoma patients with and without sentinel lymph node biopsy

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ABSTRACT

Introduction. Sentinel lymph node biopsy is fundamental in the treatment and prognosis of cutaneous malignant melanoma. This study aims to identify differences in baseline clinical characteristics and survival of patients with melanoma with and without a sentinel lymph node biopsy (SLNB) performed.

Material and methods. In 2018, a retrospective study of 151 patients with malignant melanoma (MM) was conducted. The patients were hospitalized at the Second Clinic of University Hospital — Pleven, from 2012 to 2017. The patients were divided into two groups: Group A included 58 (38.4%) patients with SLNB performed; Group B included 93 (61.6%) patients who did not undergo SLNB. A double-detection method was used while performing SLNB.

Results. The incidence of achromatic malignant melanoma is significantly higher in patients without SLNB (12 or 12.9%) than in patients with SLNB (2 or 3.4%) — $\chi^2 = 3.796$, $df = 1$, $p = 0.051$. Of all 151 patients in the study, 46 died, representing 30.5% of patients with melanoma. The mortality rate was higher in the patients without SLNB (32.3% vs. 27.6% in Group A). However, the differences in the two groups are not statistically significant.

Conclusions. Patients with achromatic melanoma have significantly fewer sentinel lymph node (SLN) biopsies performed because of a late diagnosis. Most of our patients are diagnosed at a later stage when lymphatic metastases are already present, which leads to a significant increase in lymph node dissections performed. There is no significant difference in mortality and survival in the SLNB and non-SLNB groups.

Key words: Sentinel lymph node biopsy, Malignant melanoma of skin, Melanoma

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Introduction

The term *melanoma* was first employed by René Laennec, who, in his manuscript in 1812, describes a case of disseminated disease [1]. Cutaneous malignant melanoma develops after the malignant transformation

of its pigment-forming melanocytes [2]. Australia and New Zealand are world leaders in terms of morbidity and mortality rates of 54/100,000 and 5.6/100,000, respectively, for 2015 [3]. In Bulgaria, the morbidity rate for the same year is 6.5/100,000, and the mortality rate is 2.1/100,000. The main risk factors for its development

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are exposure to ultraviolet radiation [4], skin phototype [5], the presence of pigmented nevi [6], severe sunburn [7], and geographical location [8].

A sentinel lymph node biopsy is fundamental in the treatment and prognosis of cutaneous malignant melanoma. The sentinel lymph node is defined as the first stop for metastases accumulation from a malignant tumor process. Depending on the detection method used, the first sentinel lymph node detected is described as a *hot* node (radiocolloid labeled) or blue stained (Patent Blue V marked) [9]. Its histological examination provides an accurate prognosis of the involvement of other nodes in the lymphatic chain. During an SLN biopsy, the sentinel lymph node(s) is surgically removed. Patients with a sentinel lymph node histologically positive for metastases undergo compulsory complete lymph node dissection of the entire basin.

A sentinel lymph node biopsy in the management of cutaneous malignant melanoma was first performed by Donald Morthon and team in 1992 in order to avoid the frequent postoperative complications occurring with the previously used elective lymph node dissection [10, 11].

This study aims to identify differences in baseline clinical characteristics and survival rates of two groups of patients with cutaneous malignant melanoma — with and without a sentinel lymph node biopsy (SLNB) performed.

Material and methods

In 2018, a retrospective study of 151 patients with malignant melanoma (MM) was conducted. The patients were hospitalized at the Second Clinic of University Hospital — Pleven, from 2012 to 2017. Patients with a diagnosis other than MM were excluded from the study.

The patients were divided into two groups: Group A included 58 (38.4%) patients with SLNB performed; Group B included 93 (61.6%) patients who did not undergo SLNB (Tab. 1). A double-detection method was used while performing SLNB with the application of Technetium Tc-99m Sulfur Colloid radiopharmaceutical and Patent Blue V staining dye.

The documentary method is used to extract primary sociological information. Data are collected on: age, sex, Breslow thickness, the level of tumor invasion (Clark level), a histologic variant, the lymph node dissection performed, the stage of disease [pathoanatomical tumor staging system (pTNM) classification], and survival (expressed in months).

The statistical software used for data processing is SPSS v.24.0. Descriptive statistics were applied. Pearson's chi-squared test (χ^2) was used to identify differences in the groups, and Spearman's Rank cor-

relation coefficient was used to measure correlation dependencies. Results at a p-value significance level (p) less than or equal to 0.05 were considered statistically significant. Survival estimates for both groups of patients with MM were computed by log rank test and Kaplan-Meier survival curve.

Results

Demographic characteristics

Table 1 shows the distribution of patients in the two groups — total, by age, and sex.

The mean age of patients with MM is 65.0 years, with the youngest aged 17 and the oldest 91. The median age in Group B was 67.0 years and was higher than in Group A — 63.5 years.

The distribution of patients by sex indicates 78 (51.7%) males (44.8% in Group A, and 55.9% in Group B, respectively).

Clinical characteristics

Histological variant of the tumor

The incidence of achromatic malignant melanoma (Fig. 1) is significantly higher in the patients without SLNB (12 or 12.9%) than in patients with SLNB (2 or 3.4%) — $\chi^2 = 3.796$, $df = 1$, $p = 0.051$. There is a weak correlation ($r = 0.159$, $p = 0.050$, $N = 151$).

Melanoma thickness (Breslow classification)

The mean melanoma thickness was 2.50 mm (Mdn, 0–11 Min, Max) in the patients in Group B, and was higher than in the patients in Group A (1.8 Mdn, 1–5 Min, Max).

Using Breslow classification, we report that the proportion of patients with melanoma thickness greater than 4.1 mm in Group B (32.2%) was approx. three times higher compared to Group A (13.8%). Differences are significant ($\chi^2 = 29.563$, $df = 5$, $p = 0.001$). For the rest of the cases, there was a higher proportion of patients with MM and performed SLNB, with tumor invasion in the range of 0.76 — 1.0 mm, 1.1 — 2.0 mm, and 2.1 — 4.0 mm (Tab. 2). There was no correlation between the two variables ($p = 0.547$).

Performed lymph node dissection

Lymph node dissection was performed in 48 (31.8%) patients with MM, respectively in 18 (31.0%) patients in Group A and 30 (32.3%) patients in Group B (Tab. 2). The causes for lymph node dissection were different in the two comparative groups. The cause in non-SLNB patients was the discovery of a clinically positive lymph node, whereas, in SLNB patients, the cause was a posi-

Table 1. Distribution of patients with malignant melanoma according to sentinel lymph node biopsy performance — total, by sex and age (Valid N, %)

Variable	Group A Number (%)	Group B Number (%)	Total Number (%)
Gender			
Male	26 (44.8%)	52 (55.9%)	78 (51.7%)
Female	32 (55.2%)	41 (44.1%)	73 (48.3%)
Total	58 (100.0%)	93 (100.0%)	151 (100.0%)
Age			
Mean age (Mdn, Min–Max)	63.5 (17–81)	67.0 (32–91)	65.0 (17–91)
Total	58 (38.4%)	93 (61.6%)	151 (100.0%)

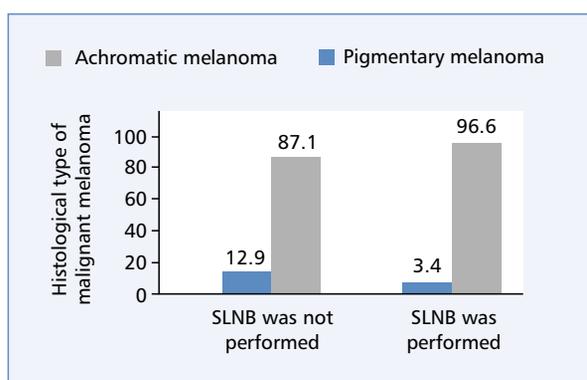


Figure 1. Distribution of patients with malignant melanoma according to the performance of sentinel lymph node biopsy (SLNB) and histologic variant of tumor (%)

tive sentinel lymph node identified by histological analysis. There were no statistically significant differences between the groups studied.

Tumor staging (pTNM classification system)

The pTNM classification in our study shows the latest data from the National Cancer Registry of Bulgaria for 2018. We found that every fourth patient with MM was in stage IV, respectively 20.7% of Group A and 28.0% of Group B (Tab. 2). Significantly higher was the proportion of Group-B patients classified in stage 0 (8.6% vs. 1.7% in Group A) and stage IA (18.1% vs. 6.9% in Group A). With disease progression (stage IB–IIC), the proportion of patients with SLNB increases ($\chi^2 = 27.287$, $df = 7$, $p = 0.001$). There is no correlation between the studied variables ($p = 0.567$).

Table 2. Distribution of the patients in Group A and Group B by Breslow`s thickness of malignant melanoma (MM), pathologoanatomical tumor staging system classification and lymph node dissection (Number, %)

Variable	Group A Number (%)	Group B Number (%)	Total Number (%)
Breslow`s thickness of MM			
<i>In situ</i>	0 (0.0%)	10 (10.8%)	10 (6.6%)
Thickness less than 0.75 cm	4 (6.9%)	15 (16.1%)	19 (12.6%)
Thickness 0.76–1.0 cm	5 (8.6%)	5 (5.4%)	10 (6.6%)
Thickness 1.1–2.0 cm	29 (39.7%)	9 (9.7%)	32 (21.2%)
Thickness 2.1–4.0 cm	18 (31.0%)	24 (25.8%)	42 (27.8%)
Thickness greater than 4.0 cm	8 (13.8%)	30 (32.2%)	38 (35.2%)
Total	58 (100.0%)	93 (100.0%)	151 (100.0%)
pTNM Classification			
Stage 0	1 (1.7%)	8 (8.6%)	9 (6.0%)
Stage IA	4 (6.9%)	17 (18.1%)	21 (13.9%)
Stage IB	17 (29.3%)	9 (9.7%)	26 (17.2%)
Stage IIA	8 (13.8%)	5 (5.4%)	13 (8.6%)
Stage IIB	7 (12.1%)	6 (6.5%)	13 (8.6%)
Stage IIC	9 (15.3%)	10 (10.8%)	19 (12.6%)
Stage III	0 (0.0%)	12 (12.9%)	12 (7.9%)
Stage IV	12 (20.7%)	26 (28.0%)	38 (25.2%)
Total	58 (100.0%)	93 (100.0%)	151 (100.0%)
Lymph node dissection			
Yes, done	18 (31.0%)	30 (32.3%)	48 (31.8%)
No, not done	40 (69.0%)	63 (67.7%)	103 (68.2%)
Total	58 (100.0%)	93 (100.0%)	151 (100.0%)
Total	58 (38.4%)	93 (61.6%)	151 (100.0%)

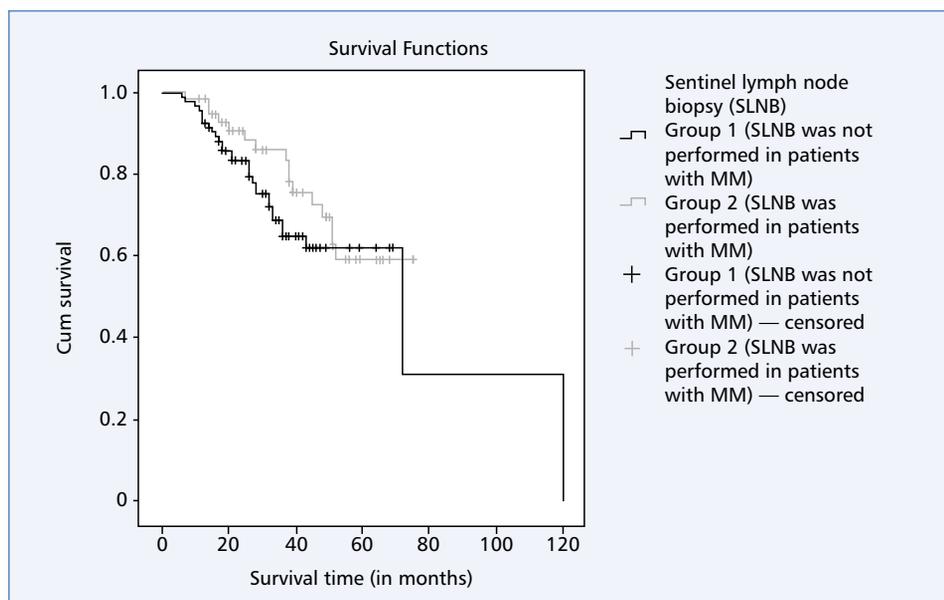


Figure 2. Kaplan-Meier Survival Curve for Patients with malignant melanoma (MM) in Group A and Group B; SLNB — sentinel lymph node biopsy

Mortality and survival

Of all 151 patients in the study, 46 died, representing 30.5 per 100 patients with malignant melanoma. The mortality rate was higher in the patients without SLNB (32.3% vs. 27.6% in Group A). However, the differences in the two groups are not statistically significant ($p = 0.544$).

Median survival (expressed in months) in patients with malignant melanoma (MM) is 72 months, $SE = 20.704$ at $S(t) = 0.5$. The median survival (\bar{x}) in patients with MM and SLNB performed is 59.1 months ($SE = 3.2$, $CI = 52.7-65.4$) and is lower than in patients with the same diagnosis but without SLNB ($\bar{x} = 68.8$ months, $SE = 11.5$ months, $CI = 46.2-91.5$). However, the log rank test does not confirm these differences to be significant (log rank = 1.372, $df = 1$, $p = 0.241$).

The likelihood of a patient with MM without SLNB to survive 7 months is 97.8%, and in patients with melanoma and performed SLNB – 98.3%. The 14-month probability was 91.2% for Group B and 94.7% for Group A. The survival curve for the patients in Group B has a steep downward trend which shows a worse prognosis in the first months after diagnosis compared to Group A (Fig. 2).

Discussion

For a sentinel lymph node biopsy to be performed, the sentinel node must be stained with a lymphotropic agent, which makes it easier to detect. It is a molecule weighing more than 5000 D, which is injected intrader-

mally and reaches predilectionally the lymphatic system. Patent blue V and radioactive Technetium ^{99}Tc Sulfur Colloid are used as tracers [12, 13].

The main advantages of sentinel lymph node biopsy in cutaneous malignant melanoma, according to the most recent trials (MSLT 1 and 2) are:

- the result is a powerful prognostic factor;
- complete lymph node dissection after detection of the positive sentinel lymph node in some patients with thin malignant melanomas, all medium-thick malignant melanomas, and thick malignant melanomas, improves their survival in good health;
- complete lymph node dissection after detection of the positive sentinel lymph node in some patients with thin malignant melanomas, and in all medium-thick malignant melanomas, improves their survival in good health and overall survival;
- the result is the basis for the implementation of effective postoperative therapy;
- it is a very sparing operative procedure [14, 15].

There is a direct correlation between the thickness of cutaneous malignant melanoma and the percentage of sentinel lymph nodes affected by the metastatic process, which is shown in Table 3.

A comprehensive analysis of data regarding patients' distribution by sex shows a slight prevalence of males 78 (51.7%). The differences are minimal and nonsignificant, however, still presenting a higher risk of developing malignant melanoma in men. This trend is reflected in other similar, large-scale surveys conducted in Australia and New Zealand [16, 17].

Table 3. Percentage of positive sentinel lymph node biopsies by thickness of malignant melanoma

Breslow Thickness (mm)	Positive sentinel lymph nodes
≤ 1	≤ 5%
1–4	15–20%
> 4	> 40%

The sex distribution of our patients in the two groups shows the prevalence of women in the SLN biopsy group — 32 (55.2%), whereas men were predominant in the non-SLN group — 52 (55.9%). The results of a multicenter study with 612 patients by Gershenwald et al. [18] contradict ours and demonstrate a predominance of men (57.5%) in the SLN biopsy group. The data are not straightforward, and the differences are not significant. This suggests that no significant causal link can be drawn.

The median age of 65.0 years in our patients with cutaneous malignant melanoma is higher than that reported by Ali et al. [19] — 57.0 years, in a worldwide study of the epidemiology of malignant melanoma. The majority of our patients were older, which should not reassure us because our youngest patient was only 17 years old. This is a particular concern meaning that the disease is affecting much younger people.

The differences between the median age of our patients in the two study groups are not significant, which correlates with the results of a multicenter study by Gutzmer et al. [20] involving 673 patients.

Achromatic skin melanoma is defined as a malignant lesion, lacking the pigment melanin or where said pigment is present in only a minimal amount. The significantly higher percentage of patients with achromatic melanoma was in the non-SLN biopsy group (12.9% to 3.4%) because this histologic variant of cutaneous melanoma is diagnosed at a later clinical stage because of its atypical clinical manifestation, which in most cases does not allow for an SLN biopsy [21].

We can report a lower mean Breslow tumor thickness of 1.8 mm (Mdn, 1–5 Min, Max) in the SLN biopsy group, compared to an average thickness of 2.5 mm (Mdn, 0–11 Min, Max) in the group without SLN biopsy. Additionally, we observed a significantly lower percentage of patients with a melanoma thickness greater than 4.1 mm — 13.2% in the same group, compared to 32.2% for the other one. This indicates that we have met precisely one of the main indications for performing SLNB, namely, for the Breslow thickness of malignant melanoma to be between 0.75 and 4.1 mm [22–25].

Statistical data analysis of the performed lymph node dissection in the two groups shows that their frequency was very close and was getting on for 31–32%. This is 10% higher than 20.8% reported by Morton et al. [26]

in the results of the largest MSLT I study to date and indicates that the majority of our patients were in an advanced stage of the disease when melanomas had already spread to lymphatic metastases. This is a very negative trend shown in our study, in all likelihood related to the late diagnosis of the disease.

Comparing our data on the MM stage for the SLNB group to those in the non-SLNB group, we observed that the percentage of patients in the first two and the last two stages of the disease was significantly higher in the non-SLNB group. This shows once again that we have strictly adhered to the rule that SLN biopsy is not recommended for patients with tumor thickness < 0.75 mm and stage 0 and IA, respectively, as the risk of lymphatic metastases, is below 5%. The same refers to the cases with tumor thickness > 4.1 mm because the risk of lymphatic metastases is greater than 40% and the benefit of SLN biopsy is unclear [22–25].

Statistical analysis of mortality in the groups with and without SLN biopsy shows slightly lower rates for the first one (27.6% to 32.3%); the differences are not significant. We did not find any significant differences between survival rates in the two groups. This matches the conclusion of Sladen et al., made upon summarizing data from the largest MSLT I study so far, that there is no significant difference in survival and mortality of patients from the two groups [27].

Conclusions

Patients with achromatic melanoma have significantly fewer SLN biopsies performed because of a late diagnosis. Most of our patients were diagnosed at a later stage when lymphatic metastases are already present, which led to a significant increase in the number of lymph node dissections performed. There is no significant difference in mortality and survival in the SLNB and non-SLNB groups.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

Conceptualization — S.S.
Methodology — S.S. and A.K.

Software — A.Y., M.V., and Y.S.
 Validation — S.S., A.Y., and A.K.
 Formal Analysis — S.S., M.V., and Y.S.
 Investigation — S.S. and A.K.
 Resources — S.S. and A.Y.
 Data Curation - S.S., M.V., and Y.S.
 Writing — Original Draft Preparation - S.S.
 Writing — Review & Editing - S.S., A.K., and A.Y.
 Visualization — S.S., M.V., and Y.S.
 Supervision — S.S. and Y.S.
 Project Administration — S.S.

Compliance with ethics requirements

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from the patient included in the study

The study was approved by the Ethics Committee of the Medical University of Pleven, Bulgaria through document number 454-КЕНИД / 21.06.2017.

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