

RESEARCH ARTICLE

Physiopathological mechanisms and morphological parameters involved in the progression of cutaneous melanoma

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Abstract

Objective: To analyze the associations between clinical and histopathological parameters in cutaneous melanoma from a single-center perspective.

Methods: We conducted a retrospective analytical study including melanoma cases diagnosed in the Pathology Department of the Clinical County Hospital Mureș, Romania, over two years. The cohort included both primary tumors and metastases.

Results: The study included 49 cases (30 primary tumors and 19 metastases). Primary melanoma was more frequent in men (mean age 65.2 years), predominantly located on the trunk. Nodular melanoma was the most common subtype (24 cases) and was associated with higher Clark levels ($p = 0.0015$), increased Breslow thickness ($p = 0.007$), and ulceration (18 cases, $p = 0.025$), without a significant association with metastasis. Ulceration was associated with increased Breslow thickness ($p = 0.018$) and older patient age ($p = 0.002$). Ki-67 and mitotic rate were significantly associated with Breslow thickness, Clark level, and ulceration ($p < 0.05$). Metastases were more frequent in women (mean age 66 years), mainly involving inguinal and axillary lymph nodes. A significant association was observed between primary tumor location and lymph node metastasis distribution ($p = 0.034$).

Conclusions: Melanoma progression is associated with morphological parameters reflecting tumor biology and invasion. Routine histopathological markers, including Breslow thickness, ulceration, mitotic rate, and Ki-67, remain essential for prognostic assessment and risk stratification.

Keywords: melanoma, proliferative markers, Breslow thickness, metastases.

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Introduction

Melanoma is an aggressive cutaneous cancer and presents with fast growth and rapid dissemination. The tumor is often associated with long UV exposure. Although it has a lower incidence compared to other skin cancers, melanoma is responsible for the majority of deaths within this group [1,2].

The definitive diagnosis is based on the histopathological examination, supported by clinical findings and, in some cases, immunohistochemical investigations [3,4].

Molecular alterations contribute to the pathogenesis of melanoma and differ due to the etiological background. Sun-related lesions often present with BRAF and NRAS mutations. Routine prognosis in daily practice continues to rely on histopathological examination [5,6].

Biopsy examination remains an essential tool for diagnosis and staging. Standard parameters include the following: Breslow thickness, Clark level, ulceration, inflammatory infiltrate, mitotic rate, lymphatic and vascular invasion, and vertical growth pattern. These are important

to view the mechanisms of invasion and progression. High Breslow thickness along with the mentioned features is associated with indicators of a rapid and aggressive tumor phenotype [1,3,7-12].

Melanoma presents multiple microscopic subtypes, some more aggressive than others. Biomarkers such as tumor mutational burden (TMB), tumor-infiltrating lymphocytes, and an IFN- γ gene signature are linked to a better response to immunotherapy. Therefore, melanoma prognosis is complicated and depends on histopathological, genetic, and immune factors. More recently, the use of molecular biomarkers allows better risk classification [9-11,13]. The sample requires careful examination, as any of these parameters can significantly influence the management trajectory. [12]. Our study objective is to highlight the association between routine histopathological markers and tumor progression mechanisms.

Methods

We retrospectively analyzed all diagnosed cases of cutaneous melanoma and its metastases diagnosed in the Pathology Department of the Clinical County Hospital Mureș, Târgu Mureș, Romania, over a two-year interval

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from January 2024 to December 2025. (study approved by Hospital's Ethics Committee number 14867/09.10.2025).

Among these, there were 30 primary tumors and 19 metastases. This study is based on histopathologically confirmed cases of cutaneous melanoma retrieved from the institutional database. It included primary cutaneous melanomas of all pathological stages (pT1a–pT4b), re-excision specimens following incomplete prior removal, local or distant recurrences, and melanoma metastases of cutaneous origin. We excluded cases if they corresponded to mucosal melanomas, melanoma in situ, melanocytic tumors of uncertain malignant potential, or non-melanocytic tumors.

For histological examination, we processed tissue samples according to the manufacturer's protocols, beginning with fixation in 10% neutral-buffered formalin, followed by paraffin embedding. The samples were stained with hematoxylin and eosin. For immunohistochemistry reactions, 4-µm sections were cut, and an automated immunostaining platform was used. All reagents and incubation steps followed the antibody manufacturers' recommendations. Signal detection was performed using the OmniMap 3,3'-diaminobenzidine system, and hematoxylin was used as the counterstain. Immunohistochemical markers are described in Table 1.

Descriptive statistics were used to summarize clinico-pathological data. Proportions are presented with 95% confidence intervals (CI), using the Wilson score method.

For the statistical analysis, we used GraphPad Prism version 9.0, with a criterion of a p-value threshold of 0.05 to determine statistical significance. We performed different tests depending on the data. We evaluated categorical associations using the chi-square test, where we separated the different variables into two main groups, based on the established oncological guides. For Breslow thickness a 2.0 mm threshold was set (<2.0 mm vs > 2.0 mm), Clark Level was split into low (I-II) and high (III-V) binary groups. For mitotic rate we used the standard <1.0 mm² vs >1.0 mm² classification and for the Ki-67 index, we set a 10% cutoff. The student's t-test was performed to compare numerical data between two independent groups, therefore data such as Breslow thickness and age were analyzed as continuous numerical variables. In smaller subgroups, Fisher's exact test was more relevant. Ultimately, for this test, we divided the locations of the primary tumor into four anatomical regions: trunk, lower limbs, upper limbs, and head/neck, while the lymph node metastases were categorized by their main drainage basins: axillary or inguinal.

Table I. – Immunohistochemical markers and clones used for the reactions

Marker	Clone	Manufacturer	Internal Control	External Control
S100	Polyclonal	VENTANA	Melanocytes, adipocytes, neural structures	Known positive melanoma tissue
SOX10	SP267	CELL MARQUE	Melanocytes, neural structures	Known positive melanoma tissue
Melan A (MART-1)	A103	VENTANA	Melanocytes	Known positive melanoma tissue
HMB45	Melanosome	VENTANA	Melanocytes	Known positive melanoma tissue
Ki-67	30-9	VENTANA	Basal layer of epidermis and adnexal structures	Known proliferative tissue.

Results

We identified 49 patients diagnosed with primary or metastatic melanoma, 30 with primary tumors, and 19 with metastatic tumors.

For the primary tumor group, patients had a mean age of 65.2 years. We identified 17 male and 13 female patients. The most common location of the tumor was the dorsal region (seven cases). The anatomical sites involved varied by gender. We found a predominance of trunk lesions in males (9 cases, 5 dorsal), while females presented tumors mostly on the lower limbs (6 cases) or the trunk (4 cases). From a histopathological perspective, most cases

were nodular melanoma (n=24), followed by superficial spreading melanoma (SSM) (n=4), acral melanoma, and desmoplastic melanoma (1 case of each).

Cytologically, the tumors were epithelioid (n=25), mixed (n=4), and spindle (n=1). The majority of patients were first diagnosed in the late stages (pT3 and pT4); 10 patients were in pT4b. Lymphatic and vascular invasion were present in seven cases. Satellites and microsattellites were found in six cases.

During follow-up, nine patients from the primary group of cutaneous melanomas presented metastases. (Table II)

For the group comprising metastatic tumors, the major-

Table II. – Characteristics of the Primary Tumor Group (n=30)

Parameter	Results
Mean Age	65.2 years
Gender	Predominantly Male
Most Frequent Location	Dorsal
Histological Subtype	Nodular (24 cases), Superficial spreading (4), Acral (1), Desmoplastic (1)
Cellular Subtype	Epithelioid, spindle cell, rhabdoid, and mixed
Staging	Predominantly pT4b
Ulceration	18 cases
Lymphovascular Invasion	7 cases
Growth Pattern	Mostly both vertical and radial
Follow-up Findings	Satellites (6 cases), Metastases (9 patients)

Table III. – Characteristics of the Metastatic Cases Group (n=19)

Parameter	Results
Mean Age	66 years
Gender	Predominantly Female
Main Metastatic Sites	Inguinal lymph nodes (10 cases), Axillary lymph nodes (7 cases)
Primary Tumor Locations	Calf, anterior thorax, dorsal region, heel, shoulder
Histological Subtype	All Nodular
Predominant Cellular Subtype	Epithelioid, followed by spindle cell and mixed
Involved Tissues	Lymph nodes (16), Intestine (2), Adipose tissue (1)
Clinical Phenomena	Necrosis (4 cases), Bleeding (2 cases)

Table IV. – 95% Confidence intervals

Subgroup	Count (n/N)	Percentage (%)	95% CI
Primary Tumors	30/49	61.2%	(47.2% – 73.6%)
Metastatic Tumors	19/49	38.8%	(26.4% – 52.8%)
Nodular Melanoma	24/30	80.0%	(62.7% – 90.5%)
Advanced Tumor(pT4b)	10/30	33.3%	(19.2% – 51.2%)
Lymphovascular invasion	7/30	23.3%	(11.8% – 40.9%)
Microsatellitosis	6/30	20.0%	(9.5% – 37.3%)
Lymph Node metastatic site	16/19	84.2%	(62.4% – 94.5%)

n=number of cases in the subgroup, N=total number of cases belonging to the main group: 49 for the whole cohort, 30 for the primary tumors, 19 for metastases.

ity of patients were female, with a mean age of 66 years. The tumor was identified mostly in the lymph nodes: inguinal (10 cases) and axillary (7 cases). The metastases presented as solid tumor proliferations composed of epithelioid cells (14 cases) and mixed-epithelioid and spindle cells (9 cases). Metastases were found in the following areas: lymph nodes (16 cases), the small intestine (2 cases), and adipose tissue (1 case).

The primary tumor remained unidentified in nearly half of the patients. Among cases with an identifiable primary lesion, the calf, anterior thorax, and dorsal region were the most frequently involved sites.

Phenomena such as bleeding were observed in two cases, whereas necrosis was observed in four cases. (Table III)

The clinicopathological characteristics and their corresponding confidence intervals are summarized in Table IV.

Analytic statistics revealed various correlations between the parameters targeted in our study. The chi-square test was used to identify associations between prognostic factors, histological parameters, and melanoma subtypes.

Nodular melanoma was associated with advanced Clark level ($p=0.0015$), Breslow thickness larger than 2 mm ($p=0.007$), and the presence of ulceration ($p=0.025$). We were unable to establish a direct link between the nodular type and metastases ($p=0.310$). (Figure 1)

We found a correlation between ulceration and the Breslow thickness ($p=0.018$): tumors deeper than 2 mm were associated more frequently with ulceration. For proliferation indexes, we compared the Ki-67 marker to the Breslow thickness ($p=0.011$), Clark level ($p=0.006$), ulceration ($p=0.041$), and mitotic rate ($p=0.015$) and, separately, the mitotic rate with the Breslow thickness ($p=0.016$), Clark

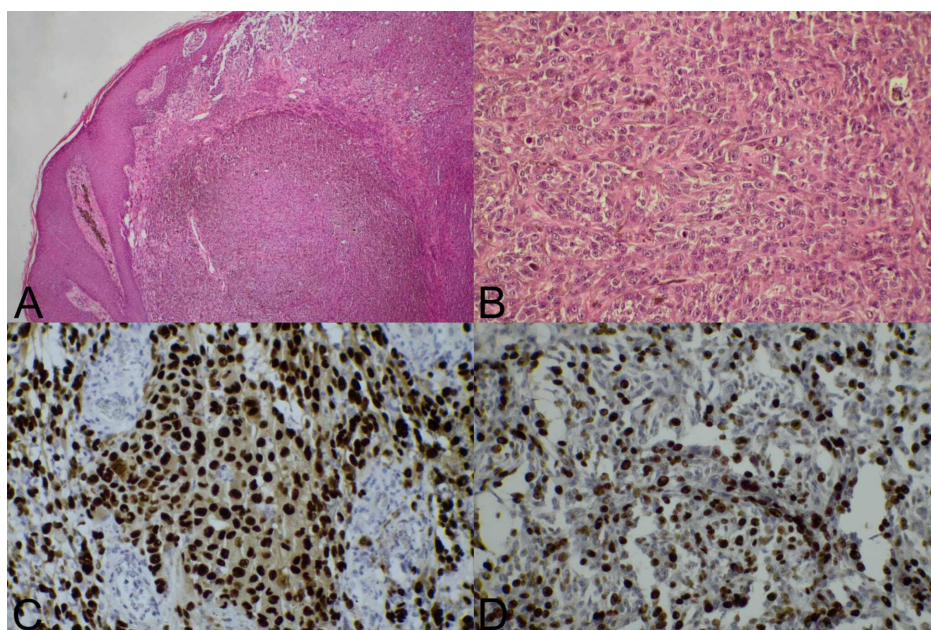


Fig. 1. Nodular melanoma. A. Tumor proliferation with solid architecture invades the dermis. Melanin pigment can be observed, HE, 5x objective. **B.** Cytological details are identified; the tumor cells present epithelioid shape, eosinophilic to pale cytoplasm, and enlarged, pleomorphic nuclei with prominent nucleoli, HE, 20x objective. **C.** Immunohistochemistry shows nuclear positivity for marker SOX10, 20x objective. **D.** Immunohistochemistry reaction with tumor proliferation index Ki-67 shows nuclear expression in tumor cells, 20x objective.

level ($p=0.009$), and ulceration ($p<0.001$). (Figure 2)

We performed the Student's t-test for numerical data. Median age was associated with ulceration ($p=0.002$); patients with ulcerated tumors were 12 years older than those without. In contrast, the presence of metastases did not show a significant age gap between patients ($p=0.353$). No association was observed between the patient's gender and age. A significant correlation was found between the Bres-

low thickness and ulceration ($p=0.001$); ulcerated tumors were usually three times thicker than non-ulcerated ones.

Fisher's exact test was used for categorical variables in small-sample subgroups. Microsatellitosis and ulceration were associated with metastases ($p=0.049$). A statistically significant association was also found between the primary tumor location and the anatomical distribution of regional lymph node metastases ($p=0.034$). (Figure 3)

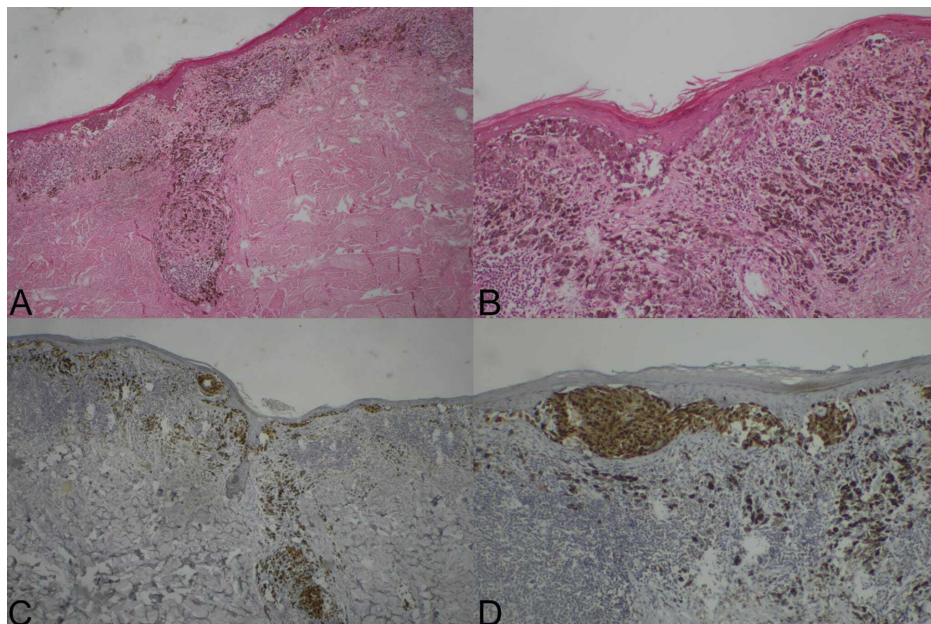


Fig. 2. Superficial spreading melanoma. A. Tumor proliferation with solid architecture in the papillary dermis, extending through the adnexal structures. Melanin pigment can be observed, HE, 5x objective. B. The tumor cells present an epithelioid shape, eosinophilic to pale cytoplasm, and enlarged nuclei. Melanophages and lymphocytes are also present, surrounding the tumor, HE, 20x objective. C. Immunohistochemistry shows nuclear positivity for marker SOX10, 5x objective. D. Immunohistochemistry reaction for S100 shows the distribution of the cells in the epidermal junction, 20x objective.

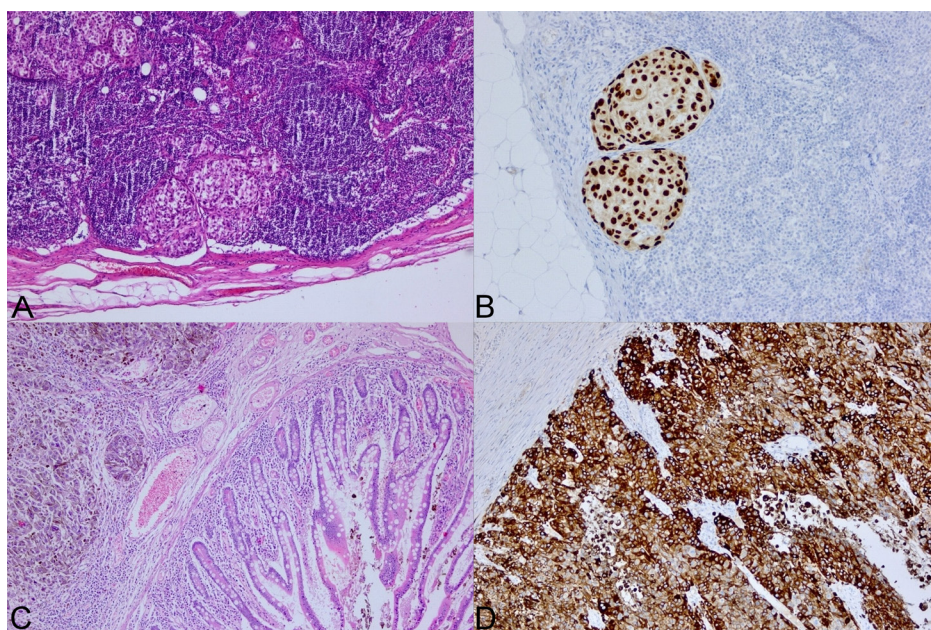


Fig. 3. . A,B. Lymph node metastasis. A Lymph node showing a solid tumor proliferation in the periphery, below the capsular level, HE, 5x objective. B. Immunohistochemistry reaction with marker SOX10 showing nuclear positivity in the tumor cells, 10x objective. C,D. Intestinal metastasis. C. The small intestine presents melanoma metastasis, invading the wall from the outer layers to the mucosa. The tumor is solid, composed of epithelioid cells with melanin pigment in the cytoplasm, HE, 5x objective. D. Immunohistochemistry reaction with cytoplasmic marker MelanA (MART-1) in the tumor cells, 10 objective.

The confirmation of melanocytic origin of the tumor was aided by the immunohistochemical profile of the tumor cells, which showed positivity for SOX10, S100, HNB45, and Melan A.

Discussion

Melanoma remains a significant issue worldwide. It is known that its incidence increases with age, as predisposing factors accumulate. Previous studies show that melanoma is usually diagnosed at a mean age of 60 years old [14-17]. Our study's demographic results show a mean age of approximately 65-66 years for both primary and metastatic tumors, aligning with worldwide data.

In general, older age is associated with a worse prognosis, high mortality, and a greater possibility to develop distance metastasis or recurrence. Still, some studies report that older patients have a lower chance of a positive sentinel node diagnosis [18]. In the present analysis, no significant age difference was observed between patients who developed metastases and those who did not. However, it is important to note that both sentinel lymph node spread and distant metastases were considered as one identity. In this case, the metastatic progression was independent of biological age.

In both males and females, the trunk was frequently affected. Male and female patients presented a difference in the location of the tumors. The dorsal region predominated in men, while women showed a predilection for the lower limb.

Recent data describe the SSM as the most common subtype, while nodular melanoma (NM) and other subtypes are seen less frequently. In our study, the nodular subtype characterized by vertical growth was predominant, likely due to a delay in clinical diagnosis. The switch from radial to vertical growth is linked to an increased metastatic potential. In many cases, both growth patterns can be identified, and vertical growth is seen only after the tumor has gained aggressive potential [19-21].

Despite the Breslow thickness being the most important known predictor of survival, tumor thickness should be viewed as a continuous variable rather than a fixed checkpoint. Our data suggests a significant correlation between the Breslow thickness and vertical growth, most of the cases being a T4b stage. Ulceration, increased mitotic count, invasion, and the presence of satellites were all associated with thickness and showed the biological behavior of the tumor [21,22]. The malignant cells' potency influences the transition from a localized lesion to a systemic disease. The lymphatic system is the main route by which melanomas spread. Following the blood flow, the most common sites are the lymph nodes closest to the primary lesion; in our study, the inguinal and axillary lymph nodes were the most frequently affected because of their proximity to the lower limbs and trunk lesions. Sentinel lymph node biopsy is always performed if Breslow >1 mm; the risk of regional metastases is significant in this case [20,21].

Most often, melanoma spreads to the skin, lungs, brain,

liver, and intestine. Intestinal metastases are very rare as a first sign of spread [23]. In our study, we encountered subcutaneous and intestinal metastases. Essentially, these serve as a clinical bridge, linking the biological aggressiveness of the primary tumor to the advanced stage.

The metastatic tumors in our study consistently displayed a solid histological architecture. Most cases showed epithelioid cytology, linking them to the primary tumor. Epithelioid cases are also associated with a poor outcome. Early diagnosis of NM is difficult because of its rapid, vertical growth. Data shows that NM grows vertically by about 0.49 mm per month, which is almost four times faster than Superficial Spreading Melanoma, which grows by about 0.12 mm per month. Beyond just growing faster, NM is also biologically more dangerous; even in the early stages, it has a worse survival rate than SSM, likely because NM tumors are linked to the upregulation of over 200 genes related to immunity [24,25].

Our analytical data confirmed the strong tie between the nodular histologic type and high aggressiveness, as it was correlated with important prognostic factors such as ulceration, vascular invasion, high mitotic rate, and depth. However, some studies show that the nodular subtype is an independent predictor of positive sentinel lymph nodes and is associated with a higher risk of recurrence. Compared with other melanoma variants, NM demonstrates a greater propensity for metastasis [26,27]. In the context of our study, although the NM was consistently thicker, the high risk of metastasis was not associated with histology alone.

According to the literature, Ki-67 is an essential tool for evaluating the way melanoma will progress. Studies show that high levels are directly linked to greater tumor thickness and a less favorable prognosis. [28]. Besides that, Ki-67 also provides useful information about the rate of cell multiplication. Therefore, when the mitotic rate is high, even in a thin melanoma, like the pT1 tumors (and more than 2 mitoses/mm²), a positive sentinel lymph node biopsy is probable. This suggests that the speed at which cells divide is sometimes more important than the actual thickness of the tumor when assessing the appropriate therapeutic decision [29,30]. Our study found that a higher Ki-67 was associated with tumors thicker than 2 mm, a Clark level of IV/V, an elevated mitotic rate, and the presence of ulceration.

The mitotic rate is an important parameter that can predict lymph node dissemination; when compared to ulcerated tumors, they almost always have a higher mitotic rate. Deep Clark levels and high Breslow thickness were also strongly tied to this parameter. [29]. This was also seen in our cohort.

Known data reinforces that microscopic satellitosis should be treated as an early form of regional metastasis. It is important to consider satellites as the starting point because metastases often originate from them, regardless of lesion thickness. Newer reports suggest that their ge-

netic material is different from that in the primary tumor, more prone to metastasize, with an important defect in the immune background, which stops them from apoptosis, because they lack protective cells like cytotoxic T lymphocytes. They activate pathways involved in vascular invasion and tissue remodeling which are connected with an increased aggressiveness compared to the main tumor body. Thus, the immune response is absent in these areas, facilitating the dispersion of malignant cells. The second indicator, ulceration with thickness as a parameter, was proportionately associated with the possibility of tumor relapse. [31,32]. We found that these indicators are associated with the metastatic progression of the tumor, being present in both cases of sentinel node involvement and the distant metastases we gathered information on.

There is a specific way for the spread from the primary location to the lymph node involvement, which we also observed in our results. The pathway is directed by the anatomical flow of blood, depending on the vascular network surrounding the primary lesion. For the limbs, we see a straight drainage to the inguinal or axillary lymph nodes; for the trunk, where tumor cells can advance through the multidirectional drainage to different nodal basins, it is hard to anticipate which direction it took [33,34].

Limitations: the size of our cohort (N=49) is important, as this implies certain limitations regarding the interpretation of our data. The small sample size determines a lower statistical power and an increased risk of Type I errors. Therefore, the associations identified in this study between various morphological parameters should be viewed as exploratory. To confirm these results, it is necessary to compare them with larger, multi-center studies to prove they are representative of a broader patient population.

Conclusion

Our study describes the prognostic factors in melanoma and creates a link between pathophysiological mechanisms of progression as reflected by histopathological features. The targeted parameters are part of the routine examination and are important in themselves but also depend on one another to reveal an accurate overall prognosis. In the era of advancing molecular and immunological methods, routine histopathological parameters remain central to clinical management and risk stratification in melanoma.

Authors' contributions

Conceptualization, A.C.T.; Methodology, A.C.T.; Resources, O.S.C.; Supervision, O.S.C.; Visualization, M.M.; Writing—original draft, M.M.; Writing—review & editing, M.M.

Conflict of interest

The authors declare no conflict of interest.

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