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Diagnostic and Prognostic Value of Immunohistochemical Markers HMB-45, Melan-A/MART-1, and S100 in Different Histological Subtypes of Melanoma

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ABSTRACT

BACKGROUND: Melanoma is a malignant neoplasm that arises from melanocytes, which are melanin-producing cells primarily found in the skin. Although rare, melanoma is highly aggressive. In 2023, 13,270 cases of skin melanoma were identified in Russia. The primary risk factor is excessive exposure to ultraviolet radiation. Immunohistochemical studies using markers such as HMB-45 (Human Melanoma Black-45), Melan-A/MART-1 (Melanoma Antigen Recognized by T Cells 1), and S100 are crucial for diagnosing skin melanoma, improving the accuracy of tumor detection, and optimizing treatment.

AIM: This study aimed to assess the prognostic significance of melanocytic markers HMB-45, Melan-A/MART-1, and S100 in skin melanoma, taking into account tumor histological subtypes and stages according to the pTNM classification.

METHODS: Skin melanoma samples from patients (n = 117) were assessed using immunohistochemistry with antibodies to HMB-45, Melan-A/MART-1, and S100. The results were interpreted based on the histological subtype of the tumor and the Breslow thickness, which was used to determine the disease stage.

RESULTS: The count of atypical melanoma cells, considering the histological subtype of the tumor, showed that the S100 marker had the highest sensitivity (91.2%) compared to Melan-A/MART-1 and HMB-45, especially in desmoplastic melanoma. Moreover, S100 and Melan-A/MART-1 demonstrated stable staining regardless of the degree of invasion, whereas the number of HMB-45-positive atypical melanocytes increased as the tumor progressed according to the pTNM classification.

CONCLUSION: Immunohistochemical analysis of various histological subtypes of skin melanoma revealed stable expression of S100, Melan-A/MART-1, and HMB-45 proteins in superficial spreading and nodular tumors. In desmoplastic melanoma, the expression of Melan-A/MART-1 and HMB-45 was absent, whereas S100 expression remained. The proportion of S100- and Melan-A/MART-1-positive atypical cells was independent of the degree of tumor invasion (according to pTNM stages). The percentage of HMB-45-positive atypical melanocytes increased proportionally with the thickness of invasion, supporting its prognostic significance.

Keywords: skin melanoma; immunohistochemistry; S100; Melan-A/MART-1; HMB-45; Breslow thickness.

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Диагностическая и прогностическая ценность иммуногистохимических маркеров HMB-45, Melan-A/MART-1 и S100 при различных гистологических подтипах меланомы

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АННОТАЦИЯ

Обоснование. Меланома — злокачественное новообразование, развивающееся из меланоцитов — клеток, синтезирующих меланин и локализующихся преимущественно в коже. Несмотря на редкость, меланома обладает высокой агрессивностью. В 2023 году в России выявлено 13 270 случаев меланомы кожи. Основным фактором риска является избыточное воздействие ультрафиолетового излучения. Иммуногистохимические исследования с использованием маркеров HMB-45 (Human Melanoma Black-45), Melan-A/MART-1 (Melanoma Antigen Recognized by T cells 1) и S100 играют ключевую роль в диагностике меланомы кожи и позволяют повысить точность выявления опухоли и оптимизировать лечение.

Цель — оценить прогностическую значимость меланоцитарных маркеров HMB-45, Melan-A/MART-1 и S100 при меланоме кожи с учётом гистологических подтипов опухоли и стадий согласно классификации pTNM.

Методы. Образцы меланомы кожи пациентов (n=117) исследовали иммуногистохимическим методом с использованием антител к HMB-45, Melan-A/MART-1 и S100. При интерпретации результатов учитывали гистологический подтип опухоли и толщину инвазии по Breslow, на основании которой определяли стадию заболевания.

Результаты. Подсчёт атипичных клеток меланомы с учётом её гистологического подтипа показал наибольшую чувствительность маркера S100 (91,2%) по сравнению с Melan-A/MART-1 и HMB-45, особенно при десмопластическом типе опухоли. Кроме того, маркеры S100 и Melan-A/MART-1 демонстрируют стабильное окрашивание независимо от степени инвазии, в то время как количество HMB-45-позитивных атипичных меланоцитов увеличивается по мере прогрессирования опухоли в соответствии с классификацией по системе pTNM (Tumor, Node, Metastasis).

Заключение. При иммуногистохимическом исследовании различных гистологических подтипов меланомы кожи обнаружена стабильная экспрессия белков S100, Melan-A/MART-1 и HMB-45 в поверхностно-распространяющейся и узловой формах опухоли. При десмопластическом подтипе меланомы кожи экспрессия Melan-A/MART-1 и HMB-45 отсутствует, тогда как экспрессия S100 сохраняется. Доля S100- и Melan-A/MART-1-позитивных атипичных клеток не зависит от степени инвазии опухоли (в соответствии со стадиями pTNM). В то же время, процент HMB-45-позитивных атипичных меланоцитов пропорционально увеличивается с ростом толщины инвазии, что не исключает его прогностическую значимость.

Ключевые слова: меланома кожи; иммуногистохимия; S100; Melan-A/MART-1; HMB-45; толщина инвазии по Breslow.

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免疫组化标记物HMB-45、Melan-A/MART-1和S100在不同类型黑色素瘤组织学亚型中的诊断和预后价值

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摘要

论证。黑色素瘤是一种恶性肿瘤，源自黑色素细胞——这些细胞主要位于皮肤中，负责合成黑色素。尽管这种病相对罕见，但其侵袭性很强。在2023年，俄罗斯确诊皮肤黑色素瘤病例为13,270例。过度的紫外线辐射是主要的风险因素。使用HMB-45（Human Melanoma Black-45）、Melan-A/MART-1（Melanoma Antigen Recognized by T cells 1）和S100等免疫组化研究方法在黑色素瘤的诊断中起着关键作用，能提高肿瘤的检测准确性并优化治疗方案。

目的。评估皮肤黑色素瘤在不同组织学亚型和pTNM分期下，HMB-45、Melan-A/MART-1和S100黑色素细胞标记物的预后价值。

方法。对皮肤黑色素瘤样本（n=117）进行免疫组化分析，使用了针对HMB-45、Melan-A/MART-1和S100的抗体。结果的解释基于肿瘤的组织学亚型和Breslow浸润厚度，并依据此确定了疾病的分期。

结果。通过对不同组织学亚型黑色素瘤中不典型细胞的计数，发现S100标记物的灵敏度最高（91.2%），尤其是在类纤维化型肿瘤中，较Melan-A/MART-1和HMB-45更为敏感。与此同时，S100和Melan-A/MART-1标记物无论在浸润程度上如何，都会保持稳定的染色，而HMB-45阳性不典型黑色素细胞的数量随着肿瘤进展和pTNM（Tumor, Node, Metastasis）分期的增加而增加。

结论。在免疫组化研究中，不同组织学亚型的皮肤黑色素瘤表现出S100、Melan-A/MART-1和HMB-45的稳定表达，特别是在表浅扩展型和结节型肿瘤中。对于纤维化型皮肤黑色素瘤，Melan-A/MART-1和HMB-45的表达缺失，而S100表达保持不变。S100和Melan-A/MART-1阳性不典型细胞的比例不受肿瘤浸润程度的影响（依据pTNM分期）。然而，HMB-45阳性不典型黑色素细胞的百分比随着浸润厚度的增加而增加，因此它具有较强的预后意义。

关键词：皮肤黑色素瘤；免疫组化；S100；Melan-A/MART-1；HMB-45；Breslow浸润厚度。

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BACKGROUND

Melanoma is a cancer that develops from melanocytes—neural crest–derived cells primarily localized in the skin, as well as in the uveal tract, retina, and other tissues [1, 2]. Although relatively rare, melanoma is characterized by high aggressiveness. In 2023, 13,270 cases of cutaneous melanoma were registered in Russia, accounting for approximately 2% of all newly diagnosed malignant neoplasms (674,587 cases) [3]. Melanoma has a multifactorial etiology that includes genetic and racial factors. The most significant risk factor for most melanocytic tumors is excessive exposure to ultraviolet (UV) radiation, which increases disease risk by approximately 1.7 times, particularly in individuals with fair skin. In people of African descent, cutaneous melanoma is much less common due to high melanin production, except in nonpigmented areas (such as nail beds, palms, soles, and mucous membranes). The carcinogenic trigger is the formation of free radicals within melanocytes, leading to pyrimidine base dimerization in DNA; the resulting mutations underlie cellular atypia. In individuals with reduced endonuclease activity, such as those with xeroderma pigmentosum, the risk of malignant skin tumors, including melanoma, is significantly increased [4].

According to the 5th edition of the World Health Organization Classification of Skin Tumors (2022), melanocytic neoplasms are divided into nine groups, each comprising several histological subtypes [5]. For instance, the group "Melanocytic tumors of the skin with intermittent sun exposure" includes simple lentigo, dysplastic nevus, superficial spreading melanoma, and other subtypes. Melanoma of lentigo maligna type and desmoplastic melanoma are classified under "Melanocytic tumors of the skin with chronic sun exposure." Nodular melanoma belongs to the group "Nodular, naevoid, and metastatic melanomas" [6]. Immunohistochemistry is one of the key diagnostic tools for melanomas of various localizations, since histologically, melanoma can mimic both benign melanocytic lesions and other types of neoplasms. This morphological similarity complicates histopathological verification and necessitates the use of specific immunohistochemical markers, such as HMB-45 (Human Melanoma Black-45), Melan-A/MART-1 (Melanoma Antigen Recognized by T cells 1), and S100.

The S100 protein is characterized by high sensitivity, making it an effective marker for identifying melanocytic cells. However, its specificity is limited, as S100 is also expressed in other neoplastic cells, which may result in false-positive findings.

Beyond their diagnostic utility, HMB-45, Melan-A/MART-1, and S100 proteins may possess prognostic potential, particularly when analyzed in relation to histological subtype and Breslow thickness. Overall, immunohistochemical diagnostics based on the combined use of multiple markers is an indispensable tool in modern pathology and oncology, especially in personalized medicine [7].

The work aimed to assess the prognostic significance of melanocytic markers HMB-45, Melan-A/MART-1, and S100 in skin melanoma, taking into account tumor histological subtypes and stages according to the pTNM classification.

METHODS

The study sample included patients diagnosed with skin melanoma (n = 117) who underwent treatment at the A.F. Tsyb Medical Radiological Research Center, a branch of the National Medical Research Center of Radiology, Ministry of Health of the Russian Federation, in the outpatient department with a day hospital and the Research Group. Melanomas were classified according to the pTNM system (Tumor, Node, Metastasis; 8th edition, 2017) based on Breslow invasion thickness and histological subtype following the WHO Classification of Skin Tumors (2022) [5, 8].

Histological examination was performed using light microscopy. Skin melanoma samples were fixed in formalin, embedded in paraffin, and sectioned at 2–3 μm thickness. Immunohistochemical staining was carried out in automated mode using a Roche Ventana BenchMark Ultra immunostainer (Roche Diagnostics, Switzerland) with primary antibodies to HMB-45, Melan-A/MART-1, and S100 (Ventana Medical Systems, USA; see Table 1), including both internal and external reaction controls.

Immunopositive cells were counted in 10 high-power fields with ×400 magnification.

Study Design

A retrospective, selective, controlled, non-randomized study was conducted.

Table 1. Antibodies used in the study

Antibody	Clone and catalog No.	Specificity and characteristics
S100	clone 4C4.9 (760-2523)	Cytoplasmic marker; normally expressed in cells derived from the neural crest (Schwann cells, melanocytes, and others)
Melan-A/MART-1	clone A103 (790-2990)	Cytoplasmic marker; normally expressed in melanocytes
HMB-45	clone HMB45 (790-4366)	Cytoplasmic marker; normally expressed in immature and activated melanocytes

Eligibility Criteria

Inclusion criteria: morphologically confirmed skin melanoma, patient age ⩾18 years, and ECOG performance status of 0–2 (Eastern Cooperative Oncology Group Performance Status).

Exclusion criteria: prior anticancer therapy, presence of distant metastases or disease recurrence, multiple primary malignancies (synchronous or metachronous), as well as infectious or autoimmune diseases.

Morphological analysis was performed at the Research and Educational Center for Innovative Technologies of Immunophenotyping, Digital Spatial Profiling, and Ultrastructural Analysis (Molecular Morphology) of the Peoples' Friendship University of Russia.

Study Duration

The study was conducted over a six-month period during 2023–2024.

Intervention

All patients underwent surgical treatment, which included wide local excision of the tumor with resection margin control followed by morphological examination.

Main Study Outcome

Assessment of the prognostic significance of melanocytic markers across various histological subtypes and pTNM stages of cutaneous melanoma.

Group Analysis

The study included 117 patients with a primary diagnosis of skin melanoma, comprising 67 women and 50 men. The mean age was 64.2 ± 6.8 years.

Outcomes Registration

An electronic database was created in Microsoft Excel, incorporating the results of histological, immunohistochemical, and molecular analyses of skin melanoma samples.

Statistical Analysis

Statistical analysis was performed using StatTech v.4.5.0 (StatTech LLC, Russia). The values of quantitative parameters (number of immunopositive cells) were assessed for normality of distribution using the Shapiro–Wilk and Kolmogorov–Smirnov tests. Both tests were applied to improve the reliability of the normality assessment: the Shapiro–Wilk test is more accurate for small samples ($n < 50$), whereas the Kolmogorov–Smirnov test is more suitable for larger datasets and enables comparison with a reference distribution. The combined use of these tests minimized the risk of misclassification of distribution type, which is critical for selecting appropriate statistical procedures.

Categorical data were described using absolute values and percentages. Quantitative data were presented as minimum and maximum values. Comparison of percentage ratios in multi-field contingency tables was performed using the Pearson chi-square test. For comparison of three or more groups based on quantitative parameters, the Fisher's F-test was used when data were normally distributed; otherwise, the Kruskal–Wallis test was applied. Differences were considered significant at $p < 0.05$.

RESULTS

Study Object

The study object comprised skin melanoma samples obtained from previously untreated patients ($n = 117$). The distribution of patients according to histological subtypes and Breslow invasion thickness is presented in Tables 2 and 3.

Primary Results

In all patients ($n = 117$), morphological features of cutaneous melanoma were identified: nests of polymorphic atypical cells of oval, polygonal, and spindle shape with poorly developed eosinophilic cytoplasm; in some cells, brown pigment granules were present; the nuclei were hyperchromatic (see Fig. 1).

In the immunohistochemical analysis for S100, HMB-45, and Melan-A/MART-1 markers, the highest sensitivity was observed for S100 and HMB-45 in superficial spreading and nodular melanomas (see Fig. 2). In these subtypes, the proportion of positively stained cells ranged from 76.2% (HMB-45 in superficial spreading melanoma) to 89.9% (S100

Table 2. Distribution of patients with skin melanoma by Breslow thickness and pathomorphological stages (pT) according to the Pathological Tumor-Node-Metastasis (pTNM) classification

Breslow invasion thickness	pT stage	Number of patients
<0.8–1.0 mm	pT1a	23 (19.7%)
	pT1b	8 (6.8%)
>1.0–2.0 mm	pT2a	20 (17.1%)
	pT2b	7 (5.9%)
>2.0–4.0 mm	pT3a	18 (15.4%)
	pT3b	11 (9.4%)
>4.0 mm	pT4a	17 (14.5%)
	pT4b	13 (11.1%)

Table 3. Distribution of patients with skin melanoma by histological subtypes

Histological subtype	International designation, ICD-O code	Number of patients
Superficial spreading melanoma	Superficial spreading melanoma, 8743/3	58 (49.6%)
Nodular melanoma	Nodular melanoma, 8721/3	48 (41.0%)
Desmoplastic melanoma	Desmoplastic melanoma, 8745/3	11 (9.4%)

Note: ICD-O, International Classification of Diseases for Oncology.

in nodular melanoma) (see Table 4). Among the studied markers, HMB-45 showed the lowest sensitivity, whereas S100 demonstrated the highest. In desmoplastic melanoma, the proportion of atypical cells positive for HMB-45 and Melan-A/MART-1 was markedly reduced (1.6% and 3.8%, respectively), whereas the IHC reaction with S100 antibodies retained high sensitivity (up to 91.2%) (see Fig. 3).

Thus, among all the evaluated markers, S100 exhibited the greatest sensitivity, regardless of the histological subtype, underscoring its potential as one of the key diagnostic markers for skin melanoma.

When analyzing samples according to the pTNM classification, S100 and Melan-A/MART-1 demonstrated consistent immunostaining irrespective of the degree of invasion, with 89.8%–90.1% and 75.3%–85.3% of atypical cells staining positive, respectively. These data confirm the high diagnostic value of these markers and their potential utility for early skin melanoma detection. The proportion of HMB-45–positive cells ranged between 41.9% and 86.2%, showing a direct correlation with tumor vertical growth, that is, invasion thickness. In this regard, HMB-45 may have limited application in the diagnosis of early-stage skin melanoma, when the neoplasm thickness remains minimal; however, this does not preclude its prognostic significance.

Based on the obtained results, the combined use of S100, Melan-A/MART-1, and HMB-45 markers in histopathological practice appears justified. This approach can substantially improve prognostic accuracy and contribute to the personalization of treatment for patients with skin melanoma.

DISCUSSION

Summary of Primary Results

The immunohistochemical characteristics of skin melanoma were identified, showing dependence on both the histological subtype and Breslow invasion thickness. All three markers (S100, Melan-A/MART-1, and HMB-45) demonstrated high sensitivity to atypical cells, except in the desmoplastic subtype, where Melan-A/MART-1 and HMB-45 showed low reactivity, whereas S100 maintained high sensitivity. The proportions of S100- and Melan-A/MART-1–positive atypical cells remained stable regardless of invasion thickness, whereas HMB-45 expression increased with greater invasion depth, which may indicate its additional prognostic value.

Discussion of Primary Results

This study evaluated the sensitivity of the S100, HMB-45, and Melan-A/MART-1 markers across different histological subtypes of skin melanoma, as well as their dependence on Breslow tumor thickness. It was established that the S100 marker demonstrates higher sensitivity compared to the other selected markers, particularly in cases of desmoplastic melanoma, which is consistent with the published data [9]. The expression pattern of markers in desmoplastic melanoma is determined by the presence of numerous mutations characteristic of this histological subtype. Against the background of histological and genetic loss of melanocytic differentiation, specific markers such as HMB-45 and Melan-A/MART-1 are lost [9, 10]. At the

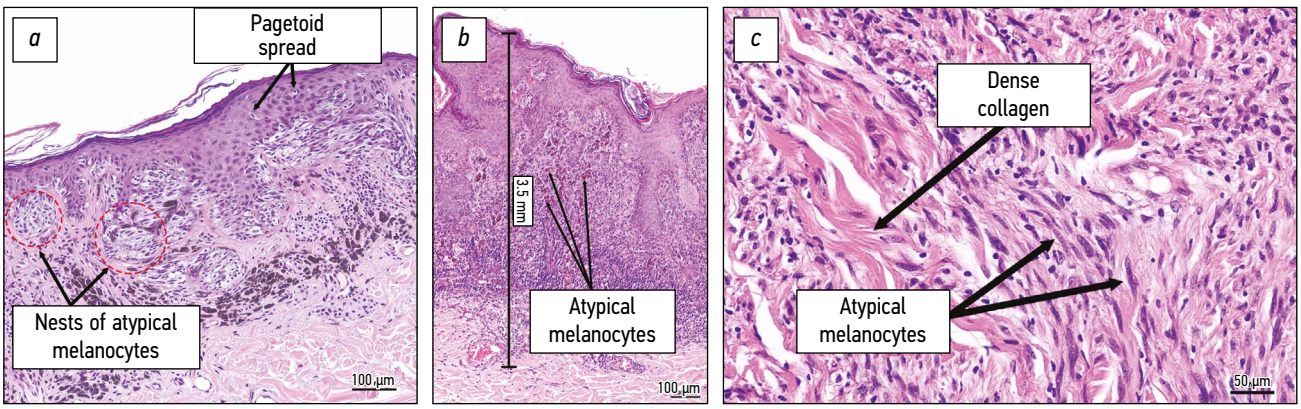

Fig. 1. Histological subtypes of skin melanoma: *a*, superficial spreading melanoma (8743/3), Breslow thickness 0.7 mm (pT1a); *b*, nodular melanoma (8721/3), Breslow thickness 3.5 mm (pT3a); *c*, desmoplastic melanoma (8745/3), Breslow thickness 4.2 mm (pT4a). Hematoxylin and eosin staining; magnification: *a*, *b*, ×200; *c*, ×400.

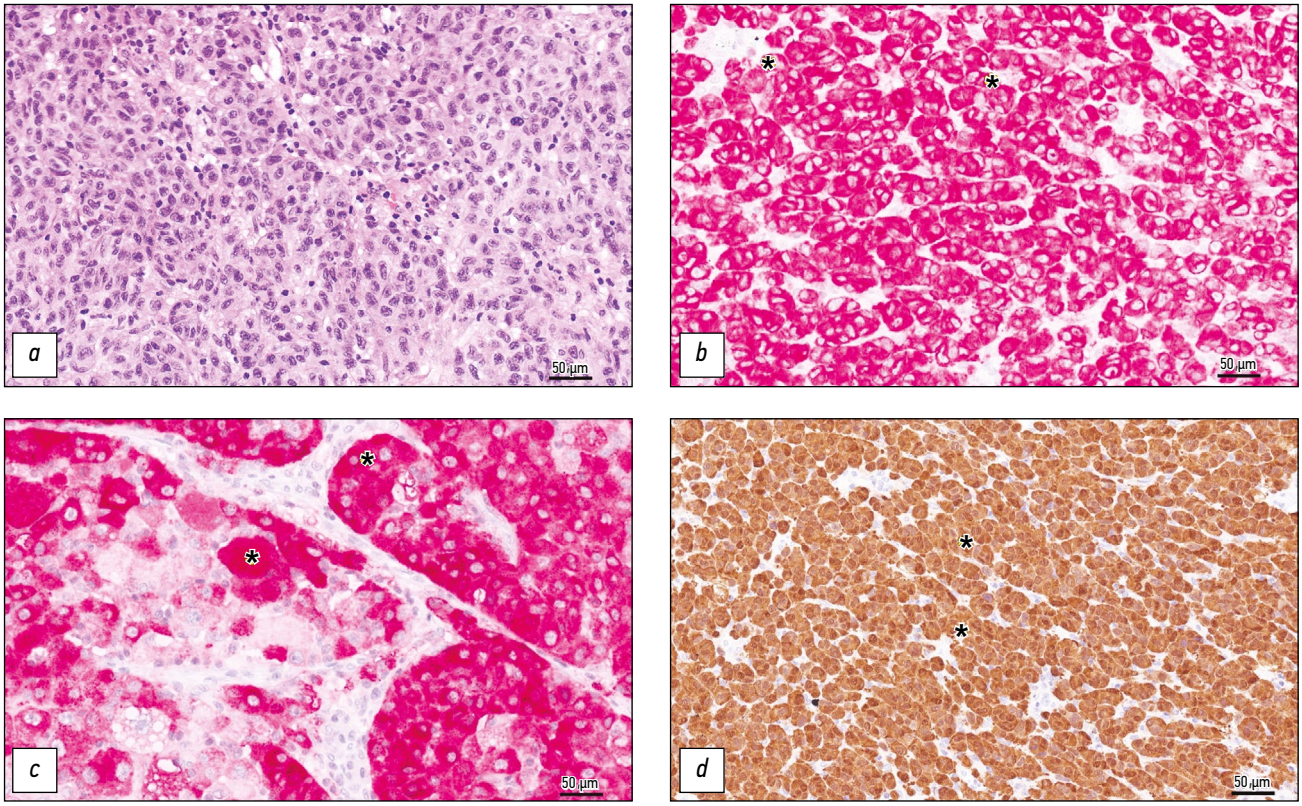

Fig. 2. Nodular melanoma of the skin (8721/3), Breslow thickness 4.2 mm (pT4a): *a*, hematoxylin and eosin staining; *b*, staining using antibodies to Melan-A/MART-1, granular cytoplasmic expression approximately 95%; *c*, staining using antibodies to HMB-45, cytoplasmic expression approximately 75%; d, staining using antibodies to S100, cytoplasmic expression approximately 95%. * indicates the expression of the studied markers in atypical cells; magnification ×400.

same time, the interaction of S100 with the receptor for advanced glycation end-products (RAGE) activates the MAPK/ERK (mitogen-activated protein kinase/extracellular signal-regulated kinase) signaling pathway, promoting atypical cell proliferation and migration. This mechanism plays a key role in the carcinogenesis of various melanoma subtypes, which is supported by the preservation of the S100 immunohistochemical pattern even in the desmoplastic subtype. Thus, despite the loss of other melanocytic markers, S100 remains one of the important prognostic factors for this melanoma subtype [11, 12].

In the immunohistochemical analysis of cutaneous melanoma, the S100 and Melan-A/MART-1 markers demonstrated stable sensitivity regardless of Breslow invasion thickness, indicating their high diagnostic significance at all stages of the disease. These findings are consistent with reports from other authors [13, 14]. The greatest variability was observed for the HMB-45 marker, which is characterized by low expression at early stages followed by a progressive increase proportional to tumor thickness (from 41.9% to 86.2%). This pattern suggests its potential prognostic value and warrants further investigation.

Table 4. Percentage of immunopositive atypical cells depending on the histological subtype of skin melanoma and Breslow thickness

Melanoma	Immunohistochemical marker		
	S100	HMB-45	Melan-A/MART-1
Histological subtype			
Superficial spreading	88.6%	76.2%	84.6%
Nodular	89.9%	84.1%	87.1%
Desmoplastic	91.2%	1.6%	3.8%
Breslow thickness			
<0.8–1.0 mm	89.8%	41.9%	75.3%
>1.0–2.0 mm	90.1%	68.7%	78.2%
>2.0–4.0 mm	89.8%	80.8%	81.6%
>4.0 mm	89.9%	86.2%	83.3%

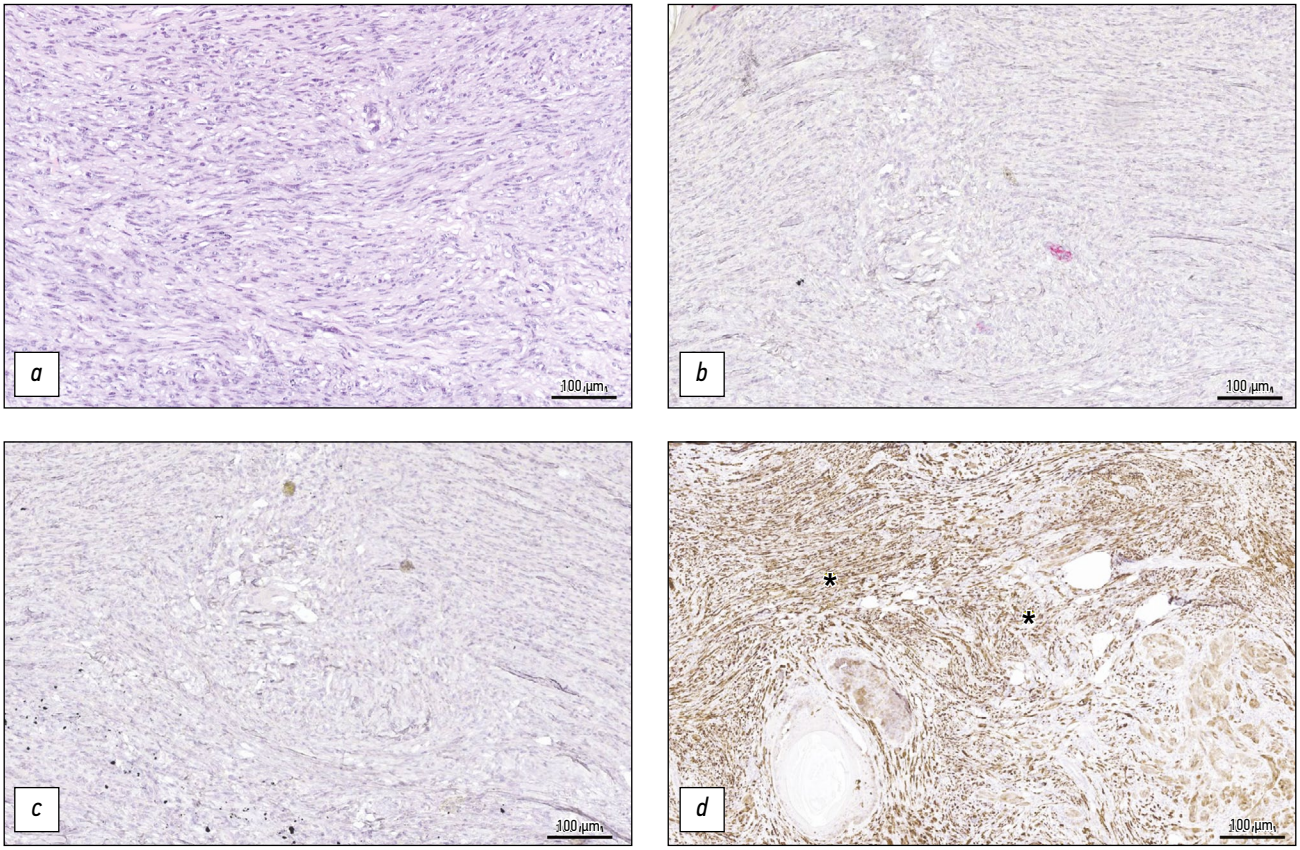

Fig. 3. Desmoplastic melanoma of the skin (8745/3), Breslow thickness 4.4 mm (pT4a): *a*, hematoxylin and eosin staining; *b*, staining using antibodies to Melan-A/MART-1, granular cytoplasmic expression in 3% of cells; *c*, staining using antibodies to HMB-45, no cytoplasmic expression; *d*, staining using antibodies to S100, cytoplasmic expression approximately 85%. * indicates the expression of the studied markers in atypical cells; magnification ×200.

Study Limitations

One of the main limitations of this study is the relatively small sample size. The prognostic significance of HMB-45 identified in our work requires further validation using additional methods, including immunophenotypic profiling, multiplex immunohistochemistry, and molecular genetic analysis.

CONCLUSION

Immunohistochemical analysis of various histological subtypes of skin melanoma demonstrated stable expression of S100, Melan-A/MART-1, and HMB-45 in superficial spreading and nodular melanomas. However, in the desmoplastic subtype, Melan-A/MART-1 and HMB-45 expression was lost, whereas S100 expression was preserved.

The proportions of S100- and Melan-A/MART-1–positive atypical cells did not depend on the degree of tumor invasion. At the same time, the percentage of HMB-45–positive atypical melanocytes increased proportionally with invasion thickness, indicating its potential prognostic significance.

ADDITIONAL INFORMATION

Author contributions: K.A. Silakov: formal analysis, investigation, writing—original draft; E.Yu. Demenkova: writing—review & editing; V.I. Shchekin: formal analysis; G.A. Demyashkin: conceptualization, resources, writing—review & editing; M.A. Bobrov: formal analysis, visualization, writing—review & editing. All the authors approved the version of the manuscript to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. К.А. Силаков — анализ данных, написание черновика рукописи, проведение гистологического и иммуногистохимического исследования; Е.Ю. Деменкова — пересмотр и редактирование рукописи; В.И. Щекин — анализ данных; Г.А. Демяшкин — определение концепции, обеспечение исследования, пересмотр и редактирование рукописи; М.А. Бобров — анализ данных, визуализация, пересмотр и редактирование рукописи. Все авторы одобрили рукопись (версию для публикации), а также согласились нести ответственность за все аспекты настоящей работы, гарантируя надлежащее рассмотрение и решение вопросов, связанных с точностью и добросовестностью любой её части.

Этическая экспертиза. Все участники исследования добровольно подписали форму информированного согласия, утверждённую этическим комитетом в составе протокола исследования. Проведение исследования одобрено Локальным этическим комитетом Медицинского радиологического научного центра им. А.Ф. Цыба — филиал ФГБУ «НМИЦ радиологии», протокол № 841а от 15 ноября 2023 г.

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Раскрытие интересов. Авторы заявляют об отсутствии отношений, деятельности и интересов за последние три года, связанных с третьими лицами (коммерческими и некоммерческими организациями), интересы которых могут быть затронуты содержанием статьи.

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Рассмотрение и рецензирование. Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали два внешних рецензента, член редакционной коллегии и научный редактор издания..

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