

**POSSIBILITIES OF APPLICATION OF MODERN INSTRUMENTAL AND DIGITAL METHODS FOR EARLY DIAGNOSIS OF PATIENTS WITH MELANOCYTIC NEOPLASMS**Polatova D. Sh.<sup>\*1,2a</sup>, Tagaev J. A.<sup>2b</sup>, Ibragimova D. A.<sup>2c</sup>, Khamidullaeva O. O.<sup>2d</sup> and Savkin A. V.<sup>2e</sup><sup>1</sup>Center for Pediatric Hematology, Oncology and Clinical Immunology.<sup>2</sup>Tashkent State Dental Institute.

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**ABSTRACT**

**The purpose of the research** – to evaluate the role and possibilities of using modern methods of digital photodermatoscopy and morphological immunohistochemical analysis using an automated program based on artificial intelligence in the early stages among patients with melanocytic neoplasms. **Materials and Methods.** A randomized controlled clinical trial conducted based on the consultative and diagnostic department of RSNPMCOR, Tashkent, Republic of Uzbekistan, from September 2021 to January 2023. Among the participants who completed the clinical study, there were 89 patients with melanocytic neoplasms. Group I consisted of 44 patients, among whom were 24 (54.5%) men and 20 (45.6%) women, who underwent a primary appointment in the field of oncodermatology with a standard pool of diagnostic measures, which include an appointment with an oncologist with visual examination of the type "ABCDE" and the possibility of using dermatoscopy if necessary (at the discretion of the specialist); The II group of patients consisted of 45 patients, among which there were 25 (55.5%) men and 20 (44.5%) women, who underwent visual assessment according to the "ABCDE" type, while dermatoscopy performed in all patients of group II, using automated system "ATVM master" of the FotoFinder® company (Columbia, USA). When conducting a biopsy for the purpose of morphological examination and determination of the type of melanoma and differentiation of neoplasms, for participant's in-group I, a standard morphological analysis used using microscopy; for group II, immunohistochemical analysis used with FISH staining and an automated analytical system Visiopharm® (Hoersholm, Denmark) based artificial intelligence algorithm. **Results.** Taking into account the conducted clinical study among patients with melanocytic neoplasms, 42.7% of patients with a confirmed diagnosis of melanoma were identified. Among the morphological forms of melanoma, superficial spreading melanoma was identified - 24 (66.7%) patients, nodular form - 6 (16.6%), lentigo melanoma - 3 (8.3%), acral melanoma - 3 (8.3%) of the patient. **Conclusions.** Because of the clinical study, it was possible to identify the effectiveness of the use of modern methods for diagnosing melanoma among patients with MN. The use of an improved diagnostic model among both dermatologists and oncologists will potentially allow synchronizing the process of multidisciplinary work of specialists in relation to the diagnosis and treatment of melanoma.

**KEYWORDS:** Differential diagnosis of melanoma; melanocytic neoplasms; digital photodermatoscopy; immunohistochemistry.

**INTRODUCTION**

In recent years, cases of skin melanoma have increased significantly in the Republic of Uzbekistan. Thus, according to epidemiological data for 2021, more than 1 thousand newly diagnosed cases of malignant skin tumors, including melanoma, were recorded.<sup>[1]</sup> The increase in the number of detected melanomas among patients with melanocytic neoplasms (MN) around the world has inevitably led to an analysis of existing methods for screening skin neoplasms at early stages.<sup>[2]</sup> Despite the significant development of the technical component in the diagnosis of MN, specialists often use standard routine methods.<sup>[3]</sup> These include visual

examination followed by surgical excision of the formation and histological evaluation, which is a standard procedure for diagnosing melanoma.<sup>[4]</sup> As a rule, when visually assessing, the "ABCDE Rule" is used - the standard by which MNs are assessed. However, this diagnostic format is relatively subjective and the success of the measures largely depends on the experience of the specialist.<sup>[5]</sup> In this regard, when using standard methods for diagnosing MN, about 30.0% of malignant neoplasms remain unverified. In particular, early-stage melanomas are more likely to go undetected due to the fact that the tumors are typically quite small and lack other visually distinctive characteristics.<sup>[6]</sup>

These observations directly prove the need to reorganize the format of early differential diagnosis in the structures of dermatovenereology and oncology departments that encounter patients suffering from MN and at risk of developing melanoma.

**The purpose of the study** was to evaluate the current situation and awareness of specialists in the field of screening and early differential diagnosis of melanoma among patients with melanocytic neoplasms within the framework of a one-stage parallel study.

## MATERIALS AND METHODS

A randomized controlled clinical trial was conducted on the basis of the advisory clinic of the Russian Scientific and Practical Medical Center, Tashkent, Republic of Uzbekistan, from September 2021 to January 2023. The study was completed by 89 (100%) patients with MN, among whom there were 49 (45.1%) men and 40 (44.9%) women, aged from 21 to 90 years, the average age of patients in the study was  $45.6 \pm 8.3$  years. Patients were randomly assigned to groups using a third party and a random numerical assignment program running on the Windows 10® operating system. Thus, two groups of patients were formed depending on the program for early differential diagnosis of melanoma among patients with MN: Group I consisted of 44 patients, among whom there were 24 (54.5%) men and 20 (45.6%) women, who underwent option of an initial appointment in the profile of oncodermatology with a standard pool of diagnostic measures, which include – an appointment with an oncologist with a visual examination of the “ABCDE” type and the possibility of using dermatoscopy if necessary (at the discretion of the specialist); Group II patients consisted of 45 patients, among whom there were 25 (55.5%) men and 20 (44.5%) women, who underwent a visual assessment according to the “ABCDE” type, while dermatoscopy was performed in all patients of group II, using automated system “ATVM master” from FotoFinder® (Columbia, USA). When performing a biopsy for the purpose of morphological examination and determining the type of melanoma and differentiation of the neoplasm, standard morphological analysis using microscopy was used for participants in group I; for group II, immunohistochemical analysis was used with FISH staining and the Visiopharm® automated analytical system (Hoersholm, Denmark) based on the work artificial intelligence algorithm.

Methodology of statistical analysis Statistical processing of the obtained data was carried out using the Excel 2000 and STATISTICA-13 packages.

## RESULTS

When assessing the obtained clinical data among 89 (100%) patients with MN who underwent a comprehensive diagnostic pool of measures, the following results were obtained when analyzing the localization of MN relative to its location on the body: among men, in most cases, MN was localized on the

anterior part of the body in 11 (22, 4%) cases; among women, in most cases, MN was localized in the upper extremities - 11 (27.5%) cases. Among all patients, MN was localized on the anterior surface of the torso in 21 (23.6%) cases, upper extremities – 21 (23.6%), posterior part of the torso – 19 (21.3%), lower extremities – 7 (7, 9%), head area – 7 (7.9%), neck area – 6 (6.7%). For characteristic signs of risk of malignancy of MN among patients participating in the study, cases of more than one episode of severe sunburn in the anamnesis were identified in 16 (40.0%) women and 30 (61.2%) men, in the vast majority of cases, patients in the study 37 (41.6%) women and 47 (52.8) men had black-brown hair color, 2 (2.2%) women and 1 (1.2%) men had light hair color, red hair color noted in 1 (1.2%) woman and 1 (1.2%) man. Based on the presence of nevi with a diameter of more than 5.0 mm, among patients with MN there were 22 (24.7%) women and 27 (30.3%) men with 3 or more nevi with a diameter of more than 5.0 mm. Also, among the patients in most cases – 86 (96.6%), there was no information about genetic predisposition. The presence of freckles was noted among 6 (6.7%) patients. Group I - 45 (100%) patients who underwent a standard procedure: an appointment with an oncologist with a visual examination according to the “ABCDE” type and the possibility of using dermatoscopy; 12 (26.6%) patients with a visual clinical picture of MN were identified - ABC, 11 (24.4%) - ACD, 11 (24.4%) - ADB and 11 (24.4%) - ABCDE. What did not differ significantly from group II - 44 (100%) patients who underwent a visual assessment according to the ABCDE type, while dermatoscopy was performed in all patients using the automated ATVM master system from FotoFinder®, where the visual clinical indicator of MN was 11 (25.0%) patients – ABC, 11 (25.0%) – ACD, 11 (25.0%) – ABD and 11 (25.0%) – ABCDE, ( $p=0.998$ ). Of the 89 patients with MN, histological studies were performed in 67 (75.3%), 22 (100%) patients with the clinical parameter “ABCDE”, 21 (95.5%) patients with “ABD”, 18 (81.8 %) – “ACD” and 6 (26.1%) patients with the “ABC” criterion ( $p < 0.001$ ). It is worth noting that among 28 (63.6%) patients from group II who underwent a biopsy based on the results of dermatoscopy using the automated “ATVM master” system, 21 (47.7%) showed a clinical picture of MN malignancy. In contrast to group I of patients, where the biopsy was performed both according to the results of dermatoscopy and the results of a visual examination. Among 39 (86.6%) patients who underwent a biopsy, the diagnosis of melanoma was detected in only 17 (37.7%) study participants ( $p < 0.001$ ).

Thus, among patients in group I of 17 (44.7%), the classic version of histological analysis was performed. In group II, 21 (55.3%) IHC were performed using the automated Visiopharm® program. IHC included the study of such biomarkers of lymphovascular invasion as MART1/Ki67, p16, PRAME, BRAF V600E, as well as the protein structures of PD-L1, TERT and PTEN (Fig. 1 – 2).

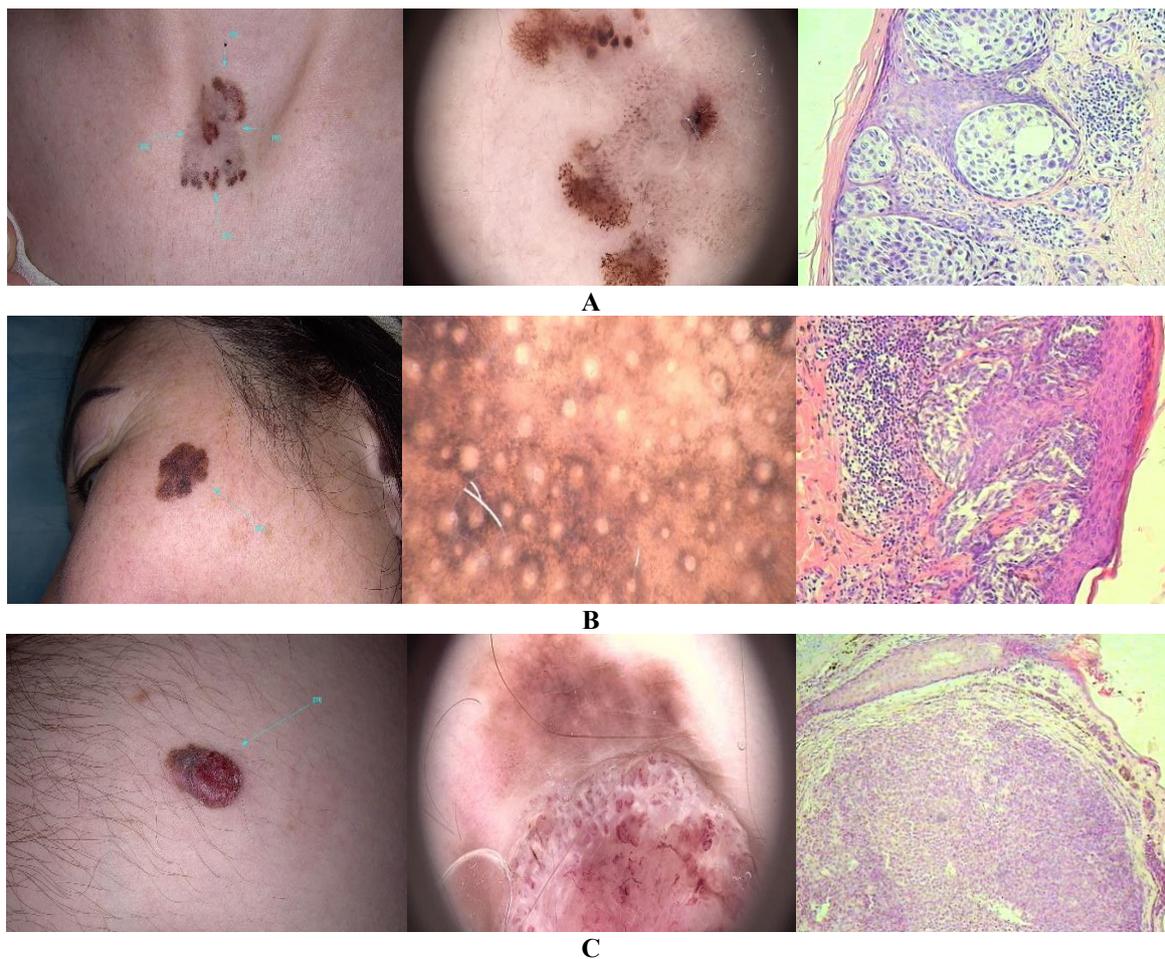


Figure 1: (A) standard microscopy with methylene blue staining with optical magnification x100: the picture on the preparations is more consistent with the superficial spreading form of melanoma; (B) standard microscopy with methylene blue staining with optical magnification x100: the picture on the preparations is more consistent with lentigo melanoma; (C) standard microscopy with methylene blue staining with optical magnification x40: the picture on the specimen is more consistent with nodular (nodular) melanoma.

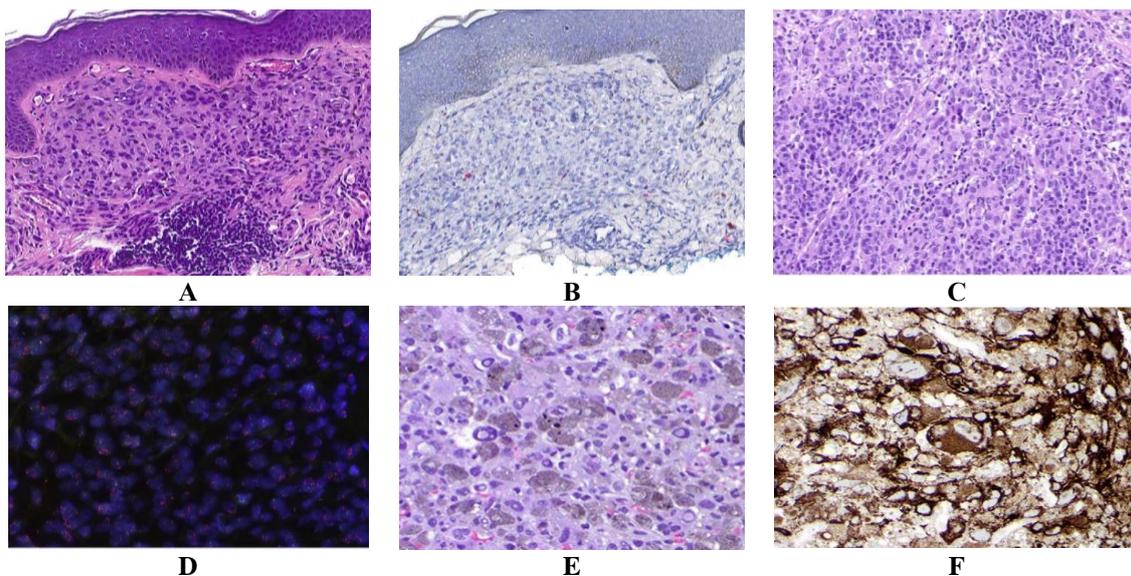


Figure 2 - (A) IHC analysis with hematoxylin-eosin staining with optical magnification x100. In the study preparation, pronounced melanocytic proliferation was observed, involving the dermis in the process; (B) a high proportion of loss of expression of the p16 biomarker was revealed under the condition of scattered distribution of melanocytes, coloring according to the type of image hybridization, x100: superficial spreading form of

melanoma; (C) IHC analysis with hematoxylin-eosin staining at  $\times 100$  optical magnification. The study specimen exhibited atypical lymphocytic proliferation affecting the dermis. The analysis revealed a high number of biomarkers MART-1 and Ki67: lentigo melanoma; (D) a high level of TERT amplification was detected, green fluorescence in situ hybridization staining,  $\times 200$ : lentigo melanoma; (E) IHC analysis with hematoxylin-eosin staining at  $\times 200$  optical magnification. The analysis revealed melanocytic mutations with heterogeneous expression, as well as the absence of signs of tumor gene expression: nodular melanoma; (F) a high level of biomarkers BRAF V600E and less than 10% – PTEN was detected, red chromogen staining for fluorescent in situ hybridization,  $\times 200$ : nodular melanoma.

As demonstrated by the results of morphological analysis, the most common clinical form of melanoma associated with malignancy of MN was superficial spreading melanoma (SPM), diagnosed in 24 people

(66.7%), the nodular form (UM) was established in 6 patients (16.6 %), lentigo melanoma (LM) – in 3 (8.3%), acral melanoma (AM) – in 3 (8.3%) patients (Table 1)

**Table 1: Analysis of The Prevalence of The Malignant Form of Melanocytic Formation Among Study Participants.**

Indicator	Category	Clinical form of melanoma (%)				p
		PRM	UM	LM	AM	
Patient group	I group	11 (42,3)	3 (50,0)	1 (33,3)	2 (66,7)	0,503
	II group	15 (57,7)	3 (50,0)	2 (66,7)	1 (33,3)	

\* – differences in indicators are statistically significant ( $p < 0.05$ ), method used: Pearson Xi-square

For a more detailed descriptive description of the diagnosis of melanoma identified through histological examination, the classification of melanoma according to

the TNM criterion, Breslow and Clark, ( $p = 0.434$ ), was used (Table 2)

**Table 2: Analysis of The "Patient Group" Indicator Depending on The Classification of Melanoma According To The Tnm, Breslow, Clark Criteria.**

Indicator	Category	Melanoma criteria (%)					p
		IA	IB	IIA	IIB	III	
Patient group	I group	4 (66,7)	5 (41,7)	6 (54,5)	2 (28,6)	-	0,434
	II group	2 (33,3)	7 (58,3)	5 (45,5)	5 (71,4)	2 (100,0)	

\* – differences in indicators are statistically significant ( $p < 0.05$ ), method used: Pearson Xi-square

## CONCLUSION

Taking into account the data obtained, when conducting a comprehensive differential diagnosis among patients with melanocytic neoplasms, 42.7% of study participants were identified with melanoma against the background of MN. Certainly an improved program for the early differential diagnosis of melanoma using digital

photodermatoscopy and IHC using the automated Visiopharm® system. However, to assess the effectiveness of the improved diagnostic model, an analysis was carried out of the time period from the moment of the initial consultation with the oncologist until the patient's immediate transition to adjuvant postoperative therapy (Table 3)

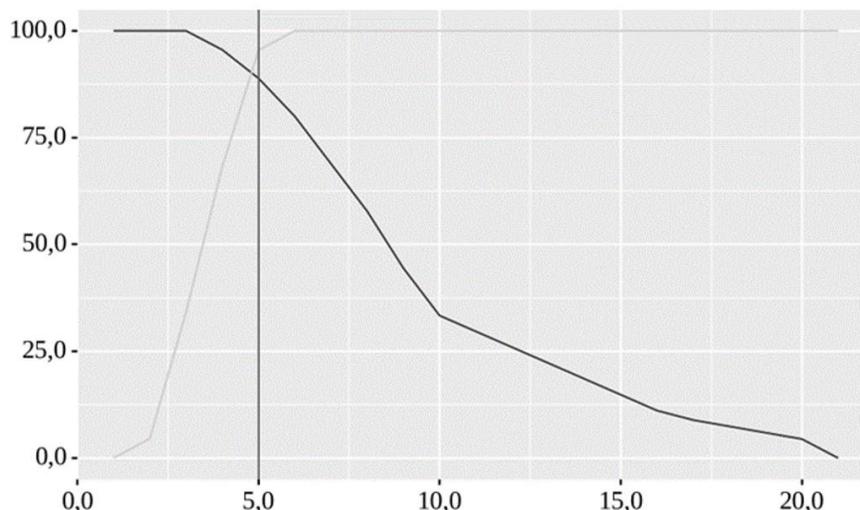
**Table 3: Analysis of The Time Period From The Moment of Initial Treatment of A Patient With Mn To The Appointment of Treatment.**

Indicator	Category	Time to therapy (weeks)			p
		Mi	Q <sub>1</sub> – Q <sub>3</sub>	n	
Patient group	I group	5	3 – 8	17	< 0,001*
	II group	3	2 – 4	21	

\* – differences in indicators are statistically significant ( $p < 0.05$ ), method used: Mann-Whitney U test

A comparative analysis of the sensitivity and specificity of the model for early differential diagnosis of patients at risk of MN malignancy revealed significant differences between the groups of patients ( $p < 0.05$ ). Thus, the threshold value of the time period from the moment of initial treatment of a patient with MN to the appointment of treatment in the case of detection of melanoma for group I was 5.0 weeks. For group II of patients who underwent complete photodermatoscopy using the automated ATVM master system and morphological

studies using IHC, as well as the automated Visiopharm® program, lower values of the time period from the moment of initial treatment to the prescription of a course of antitumor therapy were predicted. Sensitivity and specificity of the model were 95.5% and 88.9%, respectively (Fig. 3).



Vertical line numbers: percent (%); Horizontal line numbers: time until therapy is prescribed (weeks); Dark line: Specificity; Light line: Sensitivity

**Figure 3: Analysis of the sensitivity and specificity of the model for early diagnosis of melanoma among patients with mn: the area under the roc curve was  $0.964 \pm 0.020$  with 95%ci: 0.924 – 1.000. The resulting model was statistically significant ( $p < 0.001$ )**

## CONCLUSIONS

As a result of the clinical study, it was possible to identify the effectiveness of using modern methods for diagnosing melanoma among patients with MN. The use of an improved diagnostic model among both dermatologists and oncologists has the potential to synchronize the multidisciplinary work of specialists regarding the diagnosis and treatment of melanoma. As practice shows, the lack of use of dermatoscopy as such, or the use of classical dermatoscopy, often leads to a certain proportion of missed forms of melanoma against the background of MN. The use of modern automated photodermatoscopy in combination with IHC based on the work of artificial intelligence has a high auxiliary potential for clinicians. The combination of visual methods for diagnosing melanoma among people with MN and digital photodermatoscopy allows us to most accurately give a preliminary conclusion and conduct an adequate histopathological assessment.

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