https://doi.org/10.17116/engklinderma201817292-97

Diagnosis of melanoma using optical coherence tomography

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Diagnosing of melanoma is based on conventional excisional biopsy. Suspected melanoma necessitates the radical removal of the whole element in order to avoid early metastases, which seems to be unjustified to a patient in the case of ultimate diagnosis of a benign process. Apprehension for the consequences of "undue" biopsy forces doctors to postpone its implementation, which leads to late diagnosis and increased mortality. Optical coherence tomography (OCT) can be used as an alternative to biopsy.

Objective — the objective of the study was to explore the use of OCT and polarization-sensitive OCT modification (PS OCT) for the *in vivo* diagnosis and differential diagnosis of melanoma.

Material and methods. The study included 24 patients with melanoma. We carried out the clinical, dermatoscopic, OCT, and PS OCT studies (a total of 1580 images were analyzed) followed by surgical excision of tumors, histological examination of post-operative material, and histo-tomographic comparison. Diagnostic accuracy, sensitivity, and specificity of the method was assessed using a "blind" melanoma and melanocytic nevi image recognition test.

Results. It was found that OCT and PS OCT images of melanoma are characterized by specific features, which enable the diagnosis and differential diagnosis of melanoma from melanocytic nevus at the pre-histologic stage to develop adequate tactics, as evidenced by high indices of sensitivity (84.2—94.5%), specificity (84.7—93.9%), and diagnostic accuracy (87.8—88.3%) of the method.

Keywords: melanoma, dermoscopy, OCT and PS OCT.

Late diagnosis associated with the development of invasive forms and diagnostic errors leading to inappropriate intervention are the main reasons for high mortality rates in patients with melanoma.

For many years, the diagnosis of melanoma was based on clinical methods, which enabled suspecting melanoma followed by validation or rejection of this diagnosis using conventional excisional biopsy, which is the "gold standard" for the diagnosis of melanoma [1, 2].

At the same time, it is well known that the injury associated with biopsy harvesting is one of the main causes of early metastasis of the tumor. The need for histological examination for suspected melanoma necessitates radical removal of the whole suspicious element with an overlap, which seems to be totally unjustified to a patient in the case of the ultimate diagnosis of a nevus or other benign process.

Apprehension for the consequences of "undue" biopsy forces doctors to postpone its implementation. Melanoma is very often suspected in dermatological practice in connection with a clinical similarity of melanoma to melanocytic nevus and other pigmented tumors and high probability of melanocytic nevi transformation to melanoma, reaching 20% [3, 4].

Thus, the need for histological examination occurs much more often than it is carried out, which causes numerous diagnostic errors and determines the search for non-invasive instrumented methods that can be an alternative to conventional excisional biopsy and allow for *in vivo* diagnosis and differential diagnosis of melanoma and clinically similar skin tumors.

Optical coherence tomography (OCT) is one of these method [5]. The possibility of using OCT for the diagnosis of melanoma has been insufficiently explored. Previously published OCT images of melanoma, as well as images of other epithelial malignant tumors, are characterized by the absence of normal structure characteristic of OCT images of the normal skin, but in contrast to other tumors, they lack another typical differential-diagnostic feature, characteristic of the images of malignant epithelial tumors, namely amplified signal intensity in the tumor area, which hindered further research towards the possibility of using OCT for *in vivo* diagnosis of melanoma [6—15].

It is believed that informativity of OCT may be improved using the polarization-sensitive modification of OCT (PS OCT), which enables evaluating changes in the probe light polarization due to the influence of the medium under study, and thus differentiating tissue structures that are poorly visualized or not visualized on conventional OCT images [16]. PS OCT has not been previously used to obtain images of melanoma.

This study was aimed at investigating the possibility of using OCT and PS OCT for *in vivo* diagnosis and differential diagnosis of melanoma.

Material and methods

We used the computerized optical coherent visualizing topographer VOK (registration certificate No FS 022a2005/2035-05 dated August 5, 2005 manufactured by the Institute of Applied Physics of the Russian Acad-

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emy of Sciences, Nizhniy Novgorod, RNNBO 04683326) for non-invasive study of the internal structure of the human superficial tissue. The instrument has the following characteristics: wavelength of the probing radiation — 920 nm, source power at the detector output — 1.5 mW, power at the object — 0.75 mW (below the ANSI-standard for a safe light exposure), longitudinal resolution — 20 μm, transverse resolution — 25 μm, scanning depth — 1.5 mm, transverse scan range — 1.8 mm, scanning rate — 7—150 Hz, the time to obtain a 2D image of 200x200 dots — 1.5—2 seconds. OCT images can be obtained in the direct and orthogonal polarization [17].

A total of 24 patients with melanoma were examined.

All patients provided a written voluntary consent to participate in the study in accordance with the World Medical Association's Declaration of Helsinki. The research was approved by the Ethical Committee of the Nizhniy Novgorod State Medical Academy of the Russian Ministry of Health (Protocol No 8 dated 02.18.2013).

The examination included:

- clinical examination using ABCD clinical test system;

- dermatoscopic study of the neoplasm using a Heine Delta 20 Dermatoscope (Heine Optotechnik, Germany), Canon D1000 digital camera (Canon Inc., Japan) to obtain digital dermatoscopy images with 10x zoom, Hein Delta 20/Canon photo adapter (Hein Optotechnik, Germany), diagnostic algorithms of model analysis (pattern analysis), and ABCD algorithm to analyze the results;

- OCT study of neoplasms (along two perpendicular axes, sequentially moving the probe so that overlapping the previous position of the probe by 1/3, starting from clinically healthy skin and the boundary of the element; in the case of non-uniform pigmentation, along additional axes to obtain 2—4 continuous OCT images of the vertical section of the whole neoplasm to a depth of 1.5 mm in the direct and orthogonal polarization) and the equivalent portion of healthy skin on the opposite side to compare the images;

- surgical removal of malignancies at the Nizhniy Novgorod Regional Clinical Oncology Center;

- histological examination of postoperative samples using conventional H & E stain; sections were prepared along the OCT scanning axis between two tattooing labels at the visual and optical margin of the neoplasm; transmitted light microscope Eclips (Nikon, Germany), Pentium IV IBM computer, DS digital video camera, DS-U1 control unit (Nikon Germany), and FST-2U software were used for the study of the samples; special protocol was developed to describe the preparations;

- histo-tomographic comparison using digital images with 100-fold magnification, corresponding to the OCT image scale.

Medium viscosity ultrasonic diagnostic paste was used as the immersion medium for dermatoscopy and OCT studies.

The software developed in the Biophotonics laboratory of the Institute of Applied Physics of the Russian Academy of Science, Nizhny Novgorod, was used to process OCT images (recording, saving, and semi-automated processing). OCT images were assessed using the following concepts: structural properties of the image, contrast of image layers, signal strength within the layer, layer height, uniformity of the layer height, layer uniformity, layer boundary, the depth of the desired signal.

"Blind" detection test was used to determine diagnostic accuracy, sensitivity, and specificity. It consisted of 30 tests, including OCT images in direct and orthogonal polarization: 11 images of melanoma and 19 images of melanocytic nevi (marginal, intradermal, mixed, dysplastic). Ten dermatologists who were not familiar with the OCT participated in the test. The problem was reduces to determining whether OCT image belongs to melanoma or melanocytic nevus based on formulated differential diagnostic OCT features.

Test results were determined based on the ratio of responses: true positives (TP), true negatives (TN), false positives (FP), false negatives (FN), and were calculated according to the formula:

TP/TP+FN (sensitivity);

TN/TN+FP (specificity);

TN+TP/TP+TN+FP+FN (diagnostic accuracy).

Results

We analyzed 1580 OCT images obtained in the study of 24 melanomas in the direct and orthogonal polarization.

Superficial melanoma occurred in 19 cases, lentigo melanoma — in 2 cases, acral lentiginous melanoma — in 2 cases, nodular melanoma – in 1 case.

De novo melanoma developed in 9 (45%) cases and resulted from malignant transformation of a nevus in 11 (55%) cases. The time from the onset of a nevus until transformation into melanoma ranged 3 to 15 years.

In 16 (67%) out of 24 cases, melanoma was suspected based on clinical data, which was the reason for histological examination.

It should be noted that clinical signs of melanoma were detected during examination of 3 more melanocytic neoplasms, where the diagnosis was rejected after removal within safe limits followed by histological examination.

In 18 cases of histologically confirmed tumors, there were dermatoscopic signs of melanoma, including an asymmetric arrangement of atypical dermatoscopic structures, such as pigmented network, dots, globules, peripheral pseudopodia and radiation, white-and-blue veil, large areas of structureless areas, and polymorphous vessels.

Dermatoscopic features characteristic of melanoma were found during examination of 17 more pigmented tumors with no OCT-signs of melanoma. Detected dermatoscopic signs occasioned removal of the whole pigment

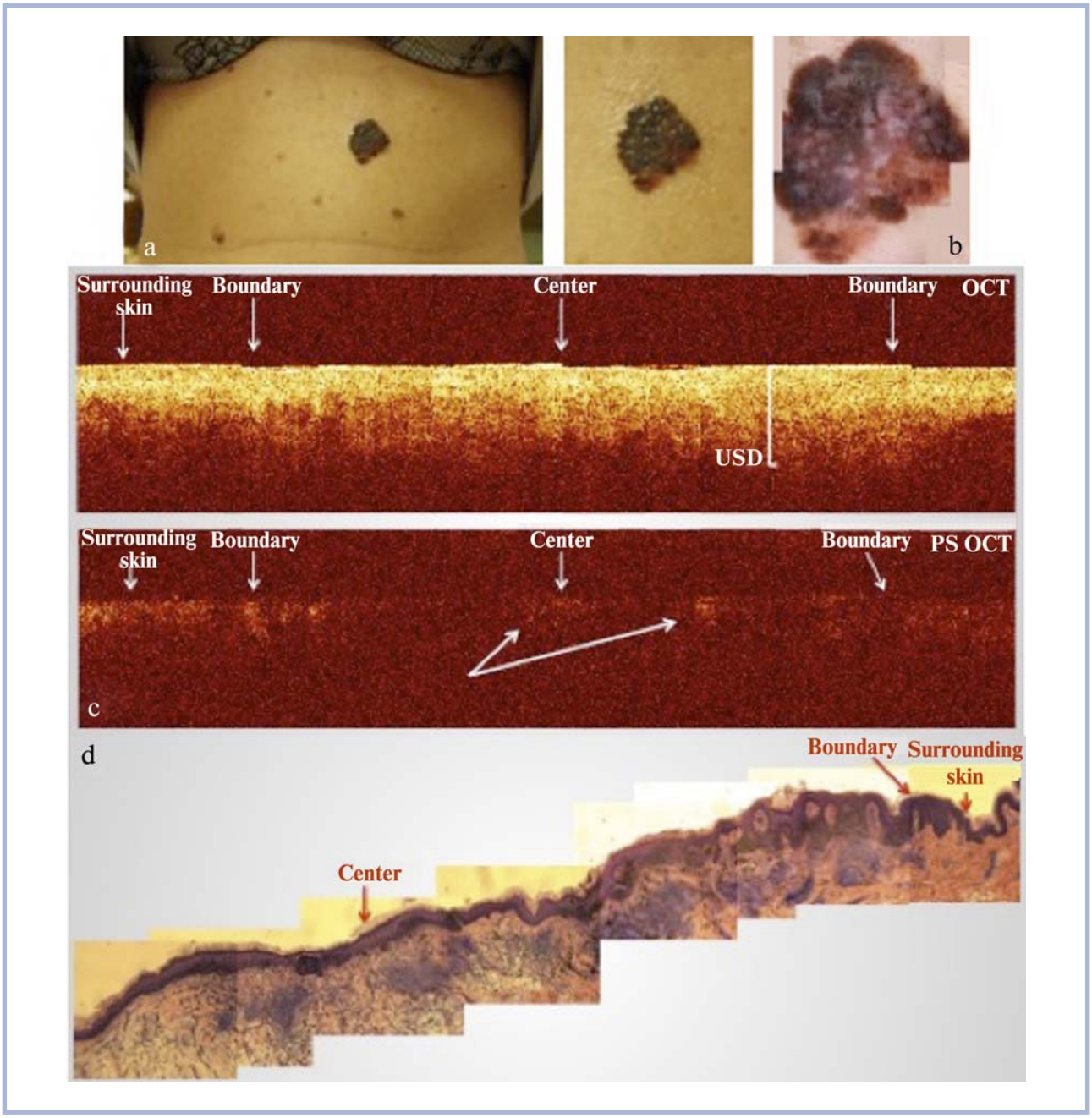

Fig. 1. **The images of Clark's invasive growth level I melanoma: clinical (a), dermatoscopic (b), tomographic (c), and histological (d).**

neoplasm within the safe limits with a wide overlap followed by histological study, which resulted in rejection of the diagnosis of melanoma (melanocytic nevus was diagnosed in 7 cases, basal cell carcinoma — in 3 cases, squamous cell carcinoma — in 2 cases, dermatofibroma — in 1 case, hemangioma — in 1 case, seborrheic keratosis — in 3 cases).

In 2 (8%) cases, the results of OCT examination showing signs of nevus-to-melanoma transformation were the only reason for suspected melanoma and removal of the neoplasm.

In 4 (16.5%) cases, melanoma was diagnosed based only on morphological signs when examining postoperative material after removal of the suspected nevus.

It was found that the characteristics of the OCT image of melanoma are determined by Clark's invasive growth level.

Fundamental differences between OCT signs of Clark's invasive growth level I melanoma (Fig. 1) and OCT images of melanocytic nevi, including dysplastic ones, observed on 95% of the images were as follows: non-uniform height and increased signal within the 2nd

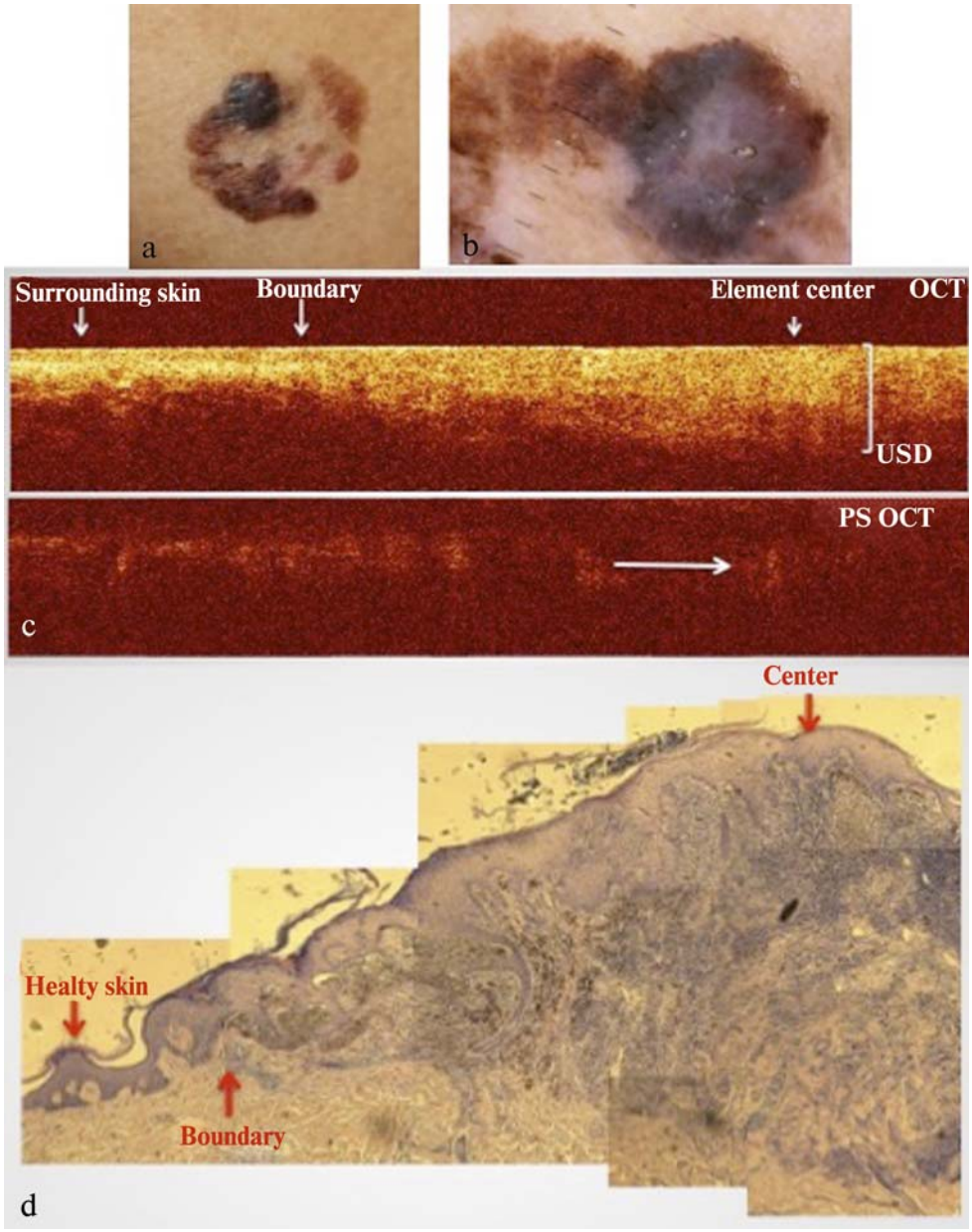

Fig. 2. **The images of Clark's invasive growth level II, III, IV melanoma: clinical (a), dermatoscopic (b), tomographic (c), and histological (d).**

layer; non-uniform increase in height and non-uniform significant attenuation of signal intensity within the 3rd layer; increase in signal height and intensity within the 4th layer; increase in the total height of 2nd—4th layers without their differentiated visualization within the tumor; increase in the depth of the desired signal. In the orthogonal polarization, OCT images of Clark's invasive growth level I melanoma were characterized by the lack of visualization of the 3rd layer with preserved individual fragments in the peripheral part of the tumor, which was a fundamental difference from OCT images of dysplastic nevus, while their OCT images were similar in direct polarization.

The characteristic OCT signs of Clark's invasive growth level II, III, IV melanoma (Fig. 2) found in 97% of images were as follows: increase in signal intensity within the 2nd layer; attenuation of signal intensity within the 3rd—5th layers; disappearance of contrast between the layers up to the absence of visualization of the boundaries and differentiated visualization of image layers; increase in useful signal depth with a maximum in the central portion of the neoplasm. Sharp attenuation of signal inten-

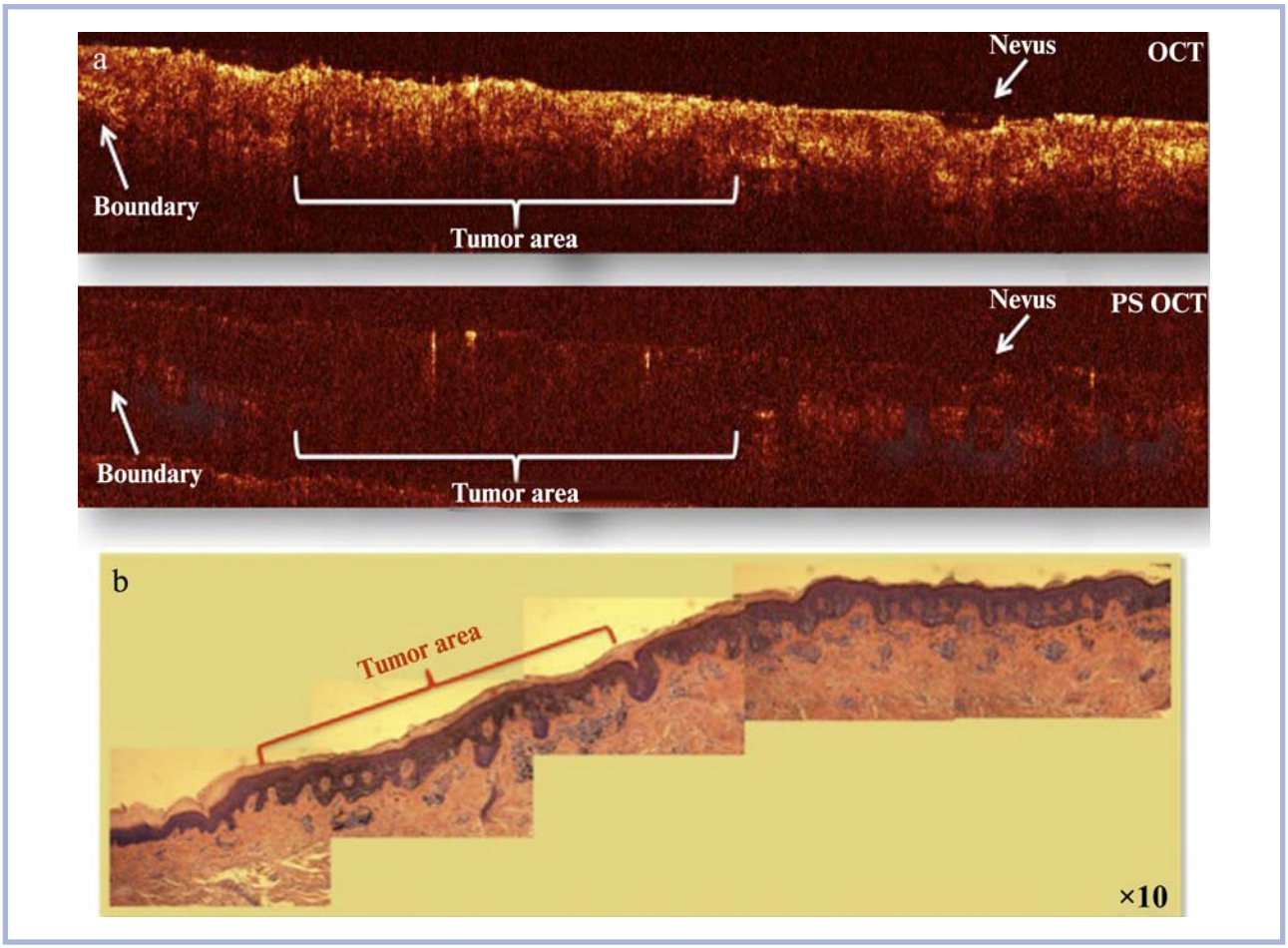

Fig. 3. **The images of the site of nevus to melanoma transformation: tomographic (a) and histological (b).**

sity within the 3rd layer up to complete absence of its visualization was the main feature of the OCT image of the Clark's invasive growth level II, III, IV melanoma in the orthogonal polarization.

The results of the studies indicate the existence of fundamental differences between OCT images of Clark's invasive growth level II, III, IV melanoma and OCT images of nevi, namely the absence of visualization of the layers even in the orthogonal polarization, whereas layered structure of OCT images in the orthogonal polarization is preserved in the case of dysplastic nevus.

Significant attenuation of signal intensity in the tumor area along with increased depth of the desired signal was a common feature of OCT images of any stage of melanoma, which was especially pronounced in the case of Clark's invasive growth levels II, III, IV.

Specified OCT signs of melanoma were also detected in OCT images of nevi at the sites of initial transformation to melanoma (Fig. 3).

Research results have shown that OCT cannot be used to determine the lower margin of the tumor in the case of invasive growth stages II, III, IV.

The possibility of using OCT for *in vivo* differential diagnosis of melanoma and melanocytic nevus, including dysplastic ones, based on the specified characteristics at the pre-histological stage in order to select an adequate strategy was confirmed by high levels of sensitivity (84.2—94.5%), specificity (84.7—93.9%), and diagnostic accuracy (87.8—88.3%) obtained during the "blind" test for detection of OCT images of melanocytic nevi and melanoma.

Conclusions

Characteristic features of OCT images of melanoma are determined by Clark's invasive growth stage and characterized by specific features: stage I —non-uniform increase in signal height and attenuation of signal intensity within the 3rd layer on OCT images obtained in direct polarization and lack of visualization of the 3rd layer with preserved individual fragments in the peripheral part of the tumor on OCT images in the orthogonal polarization; the absence of visualization of the layered structure of OCT images obtained both in direct and orthogonal

polarization in the case of stages II, III, and IV; increased depth of the desired signal in the tumor area along with decreased intensity in direct polarization is a common feature for all melanomas, which is a fundamental difference between OCT images of melanoma and melanocytic nevi.

OCT can be used for differential diagnosis of melanoma and melanocytic nevus, including dysplastic one, at the pre-histological stage to select an adequate strategy.

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