

## Streszczenie w języku angielskim

### Background

The following PhD thesis is based upon four thematically linked full-text scientific articles on new treatment and diagnostic modalities of melanoma.

Melanoma (*melanoma malignum*) is a malignant neoplasm originating from neuroectodermal melanocytic cells. In recent years, there has been a steady, significant increase in the incidence of melanoma, both in Poland and in the world. The diagnosis of this neoplasm at an early, non-invasive stage with subsequent excision biopsy gives a good chance of therapeutic success. The presence of distant metastases is associated with poor prognosis. The 5-year survival rate in the group of patients with early-stage melanoma is 70-95%, with regional advancement 20-70%, and with generalization 5-10%. In patients with advanced stage of the disease, adjuvant therapy with molecularly targeted therapies or non-specific immunotherapy should be considered. The phenomenon of the escape of neoplastic cells from the supervision of the immune system is considered as an important factor of therapeutic failure in this group of patients. One of the proteins that may play a role in the regulation of metabolic processes in the neoplastic microenvironment is the transcription factor Yin Yang 1 (YY1). The processes in the melanoma microenvironment are not fully understood. Intensive research is being carried out to identify the factors involved in melanoma oncogenesis and drug resistance. Recent reports indicate a possible role of YY1 transcription factor in the pathogenesis and drug resistance of this tumour.

Dermoscopy is a non-invasive technique that allows to assess the skin *in vivo*, increasing the sensitivity of the skin evaluation by approximately 30%. Nevertheless, proper dermoscopic evaluation depends largely on the experience of the physician and is often a challenge for junior doctors. In the future, artificial intelligence algorithms may prove to be a helpful tool. Deep learning is a field of artificial intelligence based on artificial neural networks, the structure of which is based on the structure of the human brain. Neural network models gained more popularity thanks to their ability to correctly detect and classify objects in images. A type of deep artificial neural networks that can be applied in dermatology are convolutional neural networks.



## **Aims**

The aim of the first part of the work included in the doctoral dissertation was to analyse the current state of knowledge on new therapeutic options for advanced melanoma. In addition, the focus was on identifying the role that the transcription factor YY1 may play in melanoma oncogenesis and drug resistance. In the second part of the study, the effectiveness and quality of deep neural networks in the correct classification of skin lesions on dermatoscopic images was assessed and the best model of neural network for the detection of melanoma was identified. In the final part of the research, the effectiveness of the selected neural network model was compared with the effectiveness of a group of dermatologists in an online classification test of skin lesions in dermatoscopic images.

## **Material and methods**

The literature analysis was carried out by searching the PubMed and ClinicalTrials.gov databases to assess new therapeutic options for advanced melanoma. Articles were included for analysis if they concerned the following malignant melanoma treatments: oncolytic immunotherapy, selective inhibitors of indoleamine 2,3-dioxygenase, anti-PD-(L)1 (programmed death ligand 1), immune checkpoint protein LAG-3 (lymphocyte-activation gene 3) antibodies, selective histone deacetylase (HDAC) inhibitors, B7H3 inhibitors. Selected combinations of the above-mentioned therapies with other medications were also included. Reports were excluded if they contained a description of the current standard therapy of advanced melanoma, such as checkpoint inhibitors (anti-PD-1 and anti-CTLA4 antibodies) and targeted therapy with BRAF and MEK inhibitors.

Subsequently, the importance of the overexpression of the transcription factor YY1 in the neoplastic microenvironment and its potential impact on melanoma drug resistance was assessed. For this purpose, the PubMed database was searched. The analysis included articles on the regulation of various metabolic processes by the transcription factor YY1 and its participation in the process of autophagy and lysosomal biogenesis.

Next, in the first part of the research the following models of convolutional neural networks were used: ResNet-101, ResNeXt-101, SE-ResNet-101, SE-ResNeXt-101. Moreover, we have evaluated the effect of the combination of all above mentioned models of convolutional neural networks (as a stacked ensemble) in the quality of predictions. In the research, we used a total of 10015 dermatoscopic images which were assigned to one of the 7



classess: melanoma - 1113, melanocytic nevus - 6705, basal cell carcinoma - 514, actinic keratosis/Bowen's disease - 327, benign keratosis - solar lentigo, seborrheic keratosis, lichen planus-like keratosis - 1099, dermatofibroma - 115, vascular lesion - angioma, angiokeratoma, pyogenic granuloma, microvenular hemangioma, angioma serpiginosum, port-wine stain, lymphangioma circumscriptum, targetoid hemosiderotic hemangioma, Kaposi's sarcoma, angiosarcoma - 142. Then, the dataset was divided into training (8123), validation (886), and test (1006) datasets. The best neural network model was selected, which was used in the second part of our study. From test dataset, we have randomly extracted 10% of images to create test set II in order to compare the best neural network model with 14 dermatologists, which were presented to them using an anonymous online test. The following metrics were used to evaluate their efficacy: precision, sensitivity, specificity and the F1 score calculated on the basis of the results from the test dataset. In order to verify whether the deep neural network has learned to recognize dermatoscopic images correctly, the *GradCAM* imaging method was used.

## Results

The conducted analysis of the literature showed that at the stage of clinical trials there are many new, promising therapeutic options dedicated to the group of patients with advanced melanoma. biogenesis, as well as numerous metabolic processes taking place in the neoplastic microenvironment. In the task of classifying melanoma on dermatoscopic images, the best results were achieved by the ResNeXt-101 model (precision - 77%, specificity - 97% respectively). The ensemble of convolutional neural networks achieved a better precision (80%) in the prediction of melanoma, while the sensitivity remained the same. The ResNeXt-101 model obtained a higher precision (86%) compared to the group of dermatologists in the classification of melanoma. However, the group of dermatologists showed better sensitivity in the detection of melanoma.

## Conclusions

The new therapeutic options, currently at the stage of clinical trials, dedicated to patients with advanced melanoma, may in the future constitute an alternative to the conventional treatment of advanced melanoma. The detailed understanding of the relationship of the transcription factor YY1 with the development of melanoma may contribute to a better understanding of its pathogenesis and the development of new, more effective therapeutic strategies. Convolutional neural network models achieve satisfactory results in the



classification of malignant melanoma on dermoscopic images, however, this method still requires improvement. The obtained result of higher sensitivity and, at the same time, lower precision in the detection of malignant melanoma in the group of dermatologists may be explained by the fact that physicians are more careful when excluding a malignant lesion. In order to increase the sensitivity of convolutional neural networks, it is necessary to extend the resources of the dermoscopic database. Including additional medical information about the image, such as, for example, gender, age, location of the lesion or history of disease, could further improve the classification of convolutional neural network models. Future research should focus on the still unresolved problem of how to explain the exact way in which convolutional neural networks make decisions.

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