lek. Agnieszka Kardynał

NIEINWAZYJNE METODY OBRAZOWANIA W ROZPOZNAWANIU WCZESNEGO CZERNIAKA SKÓRY

Rozprawa na stopień naukowy doktora nauk medycznych w zakresie medycyny

Promotor: prof. dr hab. n. med. Małgorzata Olszewska

Katedra i Klinika Dermatologiczna Warszawskiego Uniwersytetu Medycznego

Obrona rozprawy doktorskiej przed Radą I Wydziału Lekarskiego Warszawskiego Uniwersytetu Medycznego

Warszawa 2019

NON-INVASIVE IMAGING METHODS IN THE DIAGNOSIS OF EARLY SKIN MELANOMA

Skin melanoma is a malignant tumor developing from melanocytes. It can develop *"de novo"* (50-80% of cases) or may be derived from melanocytic nevi. The incidence of melanoma in the last 30 years has increased about three times. Genetic and environmental factors take part in its development. Literature data indicate that the risk factors for melanoma include: phototypes I and II, intense UV radiation exposure, numerous sunburns, high number of pigmented nevi, positive family history or an individual history of melanoma. However, there are no data on factors that could determine the late diagnosis of melanoma.

The histopathological examination is the gold standard in the diagnosis of skin melanoma. However, non-invasive diagnostic methods in dermatology, such as videodermoscopy and reflectance confocal microscopy has been developed in recent years. They help in the detection melanomas with different local advancement.

The aim of the study was to determine the possibility of using non-invasive skin imaging methods for the diagnosis of early stage melanoma, including in particular: determining the possibility of differentiating with the use of videodermoscopy melanoma at early local stage (thin, $\leq$ 1mm in Breslow thickness) and locally more advanced melanoma (thick, > 1 mm on the Breslow scale) and differentiating early melanomas from melanocytic nevi. The aim of the study was also to determine by using reflectance confocal microscopy method the possibility of differentiation early stage melanomas from more advanced melanomas and early stage melanomas from melanocytic nevi. Additionally, the aim of the study was to determine endogenous and exogenous factors that can have influence on the thickness of local melanoma at the moment of diagnosis.

The study included 347 patients (192 women and 155 men) with histopathologically confirmed skin melanoma. The age of the patients ranged from 18 to 90 years. The average age was 53.3 years. The analysis of risk factors based on a detailed, standardized medical history and physical examination was performed in 264 patients (151 women and 113 men).

260 patients with melanoma (148 women and 112 men) underwent detailed laboratory tests. The videodermoscopic examination of melanomas was performed in 121 patients (in 65 women and 56 men). The examination of melanomas by reflectance confocal microscopy was carried out in 47 patients (23 women and 24 men). The control group consisted of 265 healthy people (162 women and 103 men) aged 19-85, matched to the study group in terms of sex and age. Videodermoscopy examination was performed at 20-fold and 70-fold magnification of the FotoFinder Dermoscope II device (FotoFinder Systems, Germany). Reflectance confocal microscopy examination was performed using the Vivascope 1500 microscope (Lucid, Inc.NY, Rochester, USA). Data for statistical analysis consisted of nominal, ordinal and interval variables. The results of the study were presented as mean values, standard deviation (SD) and median, in the case of results not meeting the criterion of normal distribution. The normality of the Breslow distribution was checked by the Lillefors test and the Shapiro-Wilk test. In further statistical analyzes, non-parametric tests were used: U Mann-Whitney test to compare two groups and Kruskal-Wallis K-W test to compare three or more groups. The student's t-test was used to assess statistical significance that met the assumptions of the normality of distribution. All hypotheses were tested at the significance level of 0.05.

Statistical analysis of parameters assessed by videodermoscopy showed that diagnostic features for melanomas with a thickness of ≤1mm on Breslow scale compared to melanomas >1 mm of thickness were: the presence of a light brown colour (91.5% compared to 71.8%, $p<0.001$), the presence of an atypical pigmented network (82.9% compared to 66.7% for melanomas >1 mm on Breslow scale, $p<0.05$). Atypical pigmented globules or dots appeared in 36.6% thin melanomas as compared to 17.9% of melanomas >1 mm thickness in Breslow scale ($p<0.05$), streaks in 46.3% of melanomas ≤1 mm in Breslow scale compared to the incidence of 12.8% in melanomas >1 mm ($p<0.01$). The occurrence of an irregular edge was found in 61% of melanomas ≤1mm in Breslow scale and in 35.9% of melanomas >1 mm ($p<0.01$). Statistical analysis of parameters assessed by videodermoscopy showed that diagnostic features for melanomas >1 mm in Breslow scale compared to melanomas ≤1 mm were: the presence of red colour (56.4% and 31.7% respectively, $p<0.01$), the presence of atypical blood vessels (43.6% and 20.7%, $p < 0.05$) and pink areas (43.6%

and 17%, p <0.01). Asymmetric distribution of dermoscopic structures and the presence of regression were found statistically more frequent in thin melanomas compared to nevi ($p<0.05$ and $p<0.001$, respectively). Black colour, white colour and blue-white veil phenomenon were not found in any of the examined nevi (the difference compared to melanomas was statistically significant at $p<0.001$, $p<0.001$ and $p<0.001$). Statistical analysis of parameters assessed by reflectance confocal microscopy showed that statistically signifficant feature for melanomas ≤ 1 mm of thickness was the presence of edged papillae (17.9%). This feature was absent in all cases of melanomas >1 mm of thickness ($p<0.05$). Statistical analysis of parameters assessed by reflectance confocal microscopy showed that diagnostics features for melanoma >1 mm in Breslow scale were: non-edged papillae (frequency of 100% compared to 78.6% for melanomas ≤ 1 mm thickness, $p<0.05$), the presence of round cells in the epidermis (94.7% melanomas >1 mm and 60.7% melanomas <1 mm in Breslow scale, $p<0.01$) and the occurrence of numerous atypical cells in the epidermis (73.7% of melanomas with a thickness >1 mm and 57.1% melanomas with a thickness of ≤ 1 mm, $p<0.01$). In the pigmented nevi, compared to the melanomas with a thickness ≤ 1 mm on Breslow scale, statistically significantly more frequently occurred the honeycomb pattern ($p<0.001$), edged papillae ($p<0,001$) and regular melanocytic nests ($p<0,001$). Statistical analysis of endogenous and exogenous factors showed that the average thickness of melanoma was statistically significantly lower in women than in men (1.56 mm, SD 2.86 and 1.87 mm, SD 2.44, $p<0.05$, respectively). In patients with less than 50 melanocytic nevi, the mean melanoma thickness was 2.5 mm (SD 3.08) compared to 1.79 mm in patients with the number of nevi ≥ 50 (SD 2.92, $p<0.05$). The highest average melanoma thickness concerned the skin of the upper limbs (2.71 mm), the lowest – the head and neck location (0.46 mm). The average thickness of melanoma localized on trunk was 2.23 mm and on the skin of the lower limbs was 1.51 mm. The average thickness of melanoma in patients who were sunscreen users was 1.65 mm and was statistically significantly lower compared to the average thickness of melanoma in patients who have never used sunscreens (3.2 mm, $p<0.001$). The average thickness of melanoma was statistically significantly lower and was 1.81 mm in patients who have stayed ≤ 4 hours/day outdoor for at least 5 years in comparison to the mean melanoma thickness in patients who

have spent >4 hours daily outside (3.13 mm, $p<0.05$). The average thickness of melanoma in patients who had performed at least one dermoscopic examination in the period preceding the diagnosis of melanoma was 1.72 mm and was lower than the average thickness of melanoma in patients who have never had any dermoscopy screening before the diagnosis of melanoma (2.46 mm, $p<0.05$). In the issue of smoking cigarettes it was found that the average thickness of melanoma was the highest in patients who were cigarette smokers more than 10 pack years of smoking.

The conclusions stated that the videodermocopy method allows differentiation of thin melanomas (≤1mm on Breslow scale) and locally more advanced melanomas (>1mm on Breslow scale). Videodermoscopic features of thin melanomas were: atypical network, atypical dots or globules, atypical streaks and irregular border of the lesion. The presence of red colour, pinky-red areas and atypical blood vessels within the lesion were the features of thick melanomas. The feature of early melanomas (≤1mm of thickness in Breslow scale) in reflectance confocal microscopy examination was the presence of edged papillae. The features of melanomas in more advanced local stages (with a thickness >1mm in Breslow scale) in reflectance confocal microscopy examination were: numerous atypical melanocytes in the epidermis, round cells in the epidermis and non-edged papillae. The factors associated with a higher stage of local melanoma advancement at the moment of diagnosis were: male gender, the number of melanocytic nevi <50, localization of melanoma on the upper limbs or trunk, spending more than 4 hours a day for at least 5 years outdoor, lack of use sunscreens, no having any prophylactic dermoscopic examination in the period preciding the diagnosis of melanoma and smoking cigarettes longer than 10 pack years of smoking.

A. Mendyka
21.03.2019

Prof. dr hab. n. med.
Małgorzata Olszewska
specjalista dermatolog - wenerolog