The Value of High-frequency 20 MHz Ultrasonography for Preoperative Measurement of Cutaneous Melanoma Thickness

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ABSTRACT High-frequency ultrasonography has become an important diagnostic tool in dermatovenerology. It is used for assessment of the cutaneous layers in diverse benign and malignant skin lesions and diseases. Herein we present the practical value of preoperative measurement of cutaneous melanoma thickness, the explanation of the possible reasons for different sonographic and histologic Breslow thickness, and the practical importance of high-frequency 20 MHz ultrasonography in preoperative measurements of cutaneous melanoma thickness. Fifty patients (31 women aged 41.6±15.4 years, 19 males aged 54.5±11.4 year (mean ± Standard Deviation) were examined in the Skin Cancer Clinic from January 2014 to December 2015. Suspected cutaneous melanomas were investigated with skin ultrasound Dermascan C (Cortex Technology, Denmark) before surgical removal. The Breslow thickness of cutaneous melanomas was analyzed by precise pathological examination after extirpation. Statistical analysis revealed a significant positive correlation between ultrasonographic melanoma thickness and Breslow thickness (r=0.92, $P<0.001$). The mean thickness of invasive tumors evaluated by high frequency ultrasonography was 6.77 % higher compared with the mean Breslow thickness. The high-frequency ultrasonography provides a sensitive, noninvasive and reproducible method of skin evaluation, which enables objective visualization *in vivo*, providing valuable information, especially about cutaneous melanoma. The results of our study indicate that high frequency ultrasonography may be a useful adjunctive tool in the evaluation of cutaneous melanoma in daily practice.

KEY WORDS: 20 MHz high-frequency ultrasound, cutaneous melanoma, Breslow thickness

INTRODUCTION

The skin is the largest organ of the body that can be evaluated by non-invasive procedures such as dermoscopy and confocal microscopy or by invasive procedures – biopsy and histology. Even though histology represents a "gold standard" for the diagnosis of skin disorders, researchers are always looking for new

non-invasive methods that can offer reliable markers (1,2). High-frequency ultrasonography has become an important diagnostic tool in dermatovenerology. The first dermatologic application of ultrasound was in 1979, when Alexander and Miller used ultrasound with a frequency of 15 MHz for the measurement of skin thickness by using an A-mode device (3). Since this time, high-frequency ultrasonography has been used for assessment of the cutaneous layers in diverse benign and malignant skin lesions and diseases because of its many advantages – it is a painless, low-risk, and non-invasive procedure that can be performed and repeated in time. Despite the fact that high-frequency ultrasonography was previously used in several studies for assessment of many skin diseases such as psoriasis, atopic dermatitis, morphea, and skin photoaging, its major importance is still in preoperative measurement of cutaneous melanoma thickness. The incidence of this malignant disease has been increasing. Fortunately, many melanomas are detected at an earlier stage, but deeply invasive lesions are still frequently seen later (4). It has a high mortality rate, and thus establishing a timely and correct diagnosis and treatment is very important (5,6). The diagnosis of melanocytic lesions is initially clinical, assisted by dermoscopy, and the surgical removal and histological examination are implemented in case of suspected malignancy (7). Moreover, the histological depth of the tumor – Breslow thickness – is the most important factor for prognosis and treatment approach (5,6). Breslow thickness, measured in millimeters, is the distance between the stratum granulosum of the epidermis and the deepest point of tumor penetration (8). According to the thickness of the primary tumor, decisions such as the size of excision or extirpation of sentinel lymph nodes are made (9). According to the NCCN Clinical Practice Guidelines in Oncology Version 1.2017, biopsy of sentinel lymph nodes is recommended for patients with Breslow thickness ≥1.0 mm, for melanomas 0.76 to 1.0 mm thick, and biopsy of the sentinel lymph node may be considered in the appropriate clinical context (10).

High-frequency ultrasonography was first applied for skin cancer diagnosis in the early 1990s in Germany (11). The probes with a 20 MHz frequency are conventionally used in preoperative assessment and postoperative follow-up of skin tumors, especially cutaneous melanoma (12). In general, in ultrasonographic image cutaneous melanoma appears as a hypoechogenic, homogenous focal lesion within the hyperechogenic dermis (Figures 1-3). In cases with ulcerations, the epidermis may be irregular or discontinuous, and increased echogenicity of the surrounding subcutaneous tissue may be present (13,14). Several studies have shown that high-frequency 20 MHz ultrasound allowed preoperative assessment of melanoma thickness that correlated well with histologic Breslow thickness (15-19). This is a very important factor in future therapeutic approach, correct identification of the surgical excision borders, and the approach to the sentinel lymph node (12,13).

The main aim of this study was to assess the practical value of preoperative sonographic cutaneous melanoma measurement.

PATIENTS AND METHODS

The study included 50 subjects, 31 women aged 41.6±15.4 (mean ± Standard Deviation) years and 19 men aged 54.5±11.4 years examined in the Skin Cancer Clinic of the University Hospital in Martin, Slovakia, from January 2014 to December 2015. All subjects had lesions with typical dermoscopic features of melanoma (blue-white veil, multiple brown dots, pseudopods, radial streaming, multiple colors especially red and blue, focal sharply cut-off border, irregular vascularity and network). The lesions with macroscopic ulceration and bleeding were not included in the study, and the melanomas located on the ears, face, limb extremities, and genital area were not evaluated due to the large size of the ultrasonographic probe. Before surgical removal, all suspected lesions were investigated with skin ultrasound. High resolution 20 MHz ultrasound imaging equipment

Table 1. Descriptive statistics

	n	AM	Median	SD	SEM	IQR
Breslow ≤1.0 mm	26	0.606	0.600	0.233	0.046	0.500-0.800
US ≤1.0 mm	26	0.835	0.700	0.308	0.060	0.600-0.900
Breslow 1.01-2.00 mm	17	1.506	1.600	0.301	0.073	1.200-1.800
US 1.01-2.00 mm	17	1.676	1.700	0.385	0.093	1.200-2.025
Breslow >2.0 mm	7	3.671	2.700	2.261	0.855	2.225-4.900
US >2.0 mm	7	3.343	2.900	2.078	0.786	1.775-4.450

US: Ultrasonographic thickness; n: Number of lesions; AM: Arithmetic mean; SD: Standard Deviation; SEM: Standard error of arithmetic mean; IQR: Interquartile range

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Table 2. Results taken from previously published studies correlating high-frequency ultrasonography with histologic measurements

STUDY	Frequency (Mhz)	Number of melanomas	r: correlation coefficient
Lassau *et.al.* 2006 (16)	20	111	>0.93
Bessoud *et al.* 2003 (15)	20	70	>0.96
Pellacani *et al.* 2003 (18)	20	88	0.89
Serrone *et al.* 2002 (19)	20	152	0.95
Machet *et al.* 2009 (17)	20	32	0.94
Present study 2016	20	50	0.92

(Dermascan C, Cortex Technology, Denmark) was used with an axial resolution of 50 µm, lateral resolution of 300 µm, and maximum measurable depth of 7.0 mm.

The thickness of malignant melanomas was measured on a vertical axis perpendicular to the surface, from the skin surface to the deepest point of the lesion using an electronic caliper (Figure 2). Since the tumor can show asymmetry in its shape, the measurement of thickness should be performed at the deepest point. The measurement of symmetric lesions was repeated 2 times from the deepest point by the same observer, and the greater depth was used for comparison with the depth measured on the histology slide (Breslow thickness). Postoperative Breslow thickness was analyzed by standard histological examination at the Institute of Pathologic Anatomy in University Hospital in Martin. The data were statistically analyzed using the program Systat version 12. The Wilcoxon test was used for comparison of the ultrasonographic and histologic Breslow thickness. Correlation analysis between the values of ultrasonographic and histologic Breslow thickness was performed using Spearman test. $P<0.05$ was considered significant. The data were expressed in form of tables and graphs.

RESULTS

The ultrasonographic and Breslow thickness of 50 malignant melanomas ranged from 0.4 to 5.3 mm (interquartile range (IQR) 0.7-0.9) and from 0.2 to 6.0 mm (IQR 0.6-1.8), respectively.

From 50 subjects in 26 cases, which represented 52 % of all patients, the Breslow thickness was ≤1.0 mm. From these 26 cases, ultrasonographic thickness was between 1.01-2.00 mm in 5 patients. In these patients, the extirpation of sentinel lymph nodes was indicated with negative results and the surgical margin of lesions was 1.0 cm. In all 5 cases, brisk lymphocytic infiltrate was found after histologic investigation. In 12 cases there was non-brisk lymphocytic infiltrate, and in 9 cases the lymphocytic infiltrate was absent. All 26 cases were superficial spreading cutaneous melanoma. Correlational analysis revealed a significant positive correlation between histology and ultrasonography thickness ≤1.0 mm (r=0.581, $P=0.002$).

Breslow thickness 1.01-2.0 mm was found in 17 cases, which represented 34% of all patients. Ultrasonographic thickness was 1.01-2.0 mm in all 17 cases. The extirpation of sentinel lymph nodes was indicated in these patients with negative results. The lymphocytic infiltrate was non-brisk in 11 cases and absent in 6 cases. Superficial spreading cutaneous melanomas were present in 14 cases, while the nodular type was found in 3 cases. Correlational analysis revealed a significant positive correlation between histology and ultrasonography thickness in the interval 1.01-2.00 mm (r=0.736, $P=0.0008$).

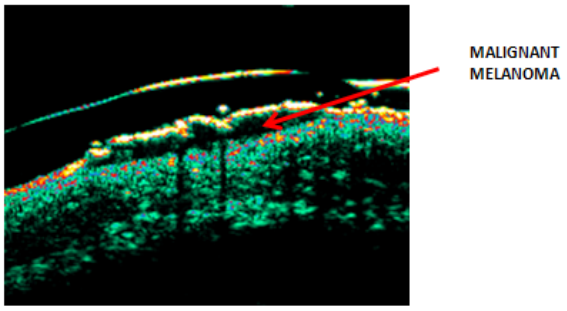

Figure 1. Superficial spreading melanoma (SSM) located on the back – Breslow thickness 0.6 mm, ultrasonographic thickness 0.7 mm.

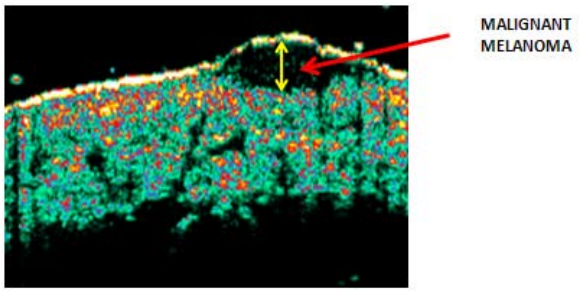

Figure 2. Superficial spreading melanoma (SSM) located on the back – Breslow thickness 2.0 mm, ultrasonographic thickness 1.3 mm.

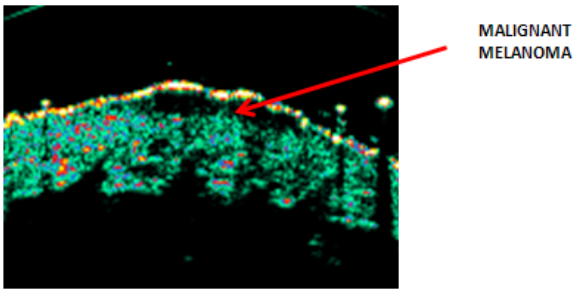

Figure 3. Superficial spreading melanoma (SSM) located on the arm – Breslow thickness 1.2 mm, ultrasonographic thickness 1.16 mm.

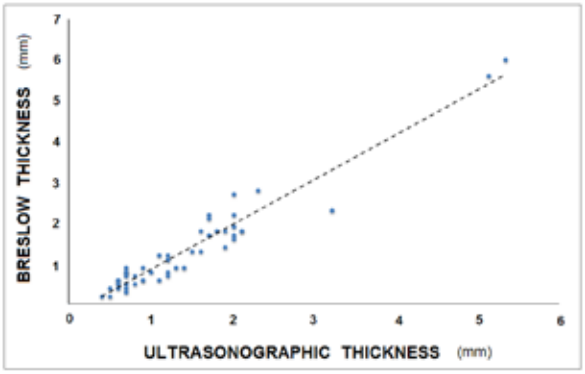

Figure 4. Linear relationship between ultrasonographic and histologic measurements.

Breslow thickness >2.0 mm was identified in 7 patients, 14 % of all cases. Ultrasonographic thickness in the interval 1.01-2.00 mm was measured in 2 cases, and 2 mm surgical margins were indicated as these were nodular types of cutaneous melanoma located on the back. The other 5 cases were superficial spreading cutaneous melanomas. In all 7 cases, the lymphocytic infiltrate was non-brisk. Statistical analysis revealed a significant positive correlation between histology and ultrasonography thickness in the interval 1.01-2.00 (r=0.857, *P*=0.01). Complete descriptive statistics are shown in Table 1.

The same values of histological and ultrasound thickness were identified in 7 out of 50 cases (14%) of malignant melanomas (Figure 4).

DISCUSSION

The main aim of this study was to assess the practical value of preoperative measurement of malignant melanoma thickness. We focused on the explanation of the possible reasons of different sonographic and histologic Breslow thickness and the practical importance of high-frequency 20 MHz ultrasonography in preoperative measurements of malignant melanoma thickness. Extirpation of the sentinel lymphatic node was indicated in patients with ultrasonographic thickness ≥1.0 mm and performed simultaneously with surgical removal of cutaneous melanoma in a single surgical procedure.

It has been suggested that the discrete overestimation of the ultrasonographic values could be due to the lymphocytic inflammatory infiltrate associated with the tumor. This infiltrate is also hypoechogenic, so one has to keep in mind that the inflammatory reaction cannot be distinguished by means of ultrasound. In our study, there was ultrasonographic overestimation in 5 cases; after histological investigation there was brisk lymphocytic infiltration in all cases. The cutaneous appendages may also appear as thin hypoechogenic structures (hypertrophied sebaceous glands, hair follicles) (7,20,21). Potentially explaining the difference between *in vivo* and *ex vivo* measurements is the natural shrinkage and dehydration of the skin occurring after excision, particularly evident for the dermis (22,23).

In contrast, histological thickness was greater than preoperative ultrasound thickness in 2 cases of cutaneous melanomas – nodular type – which were

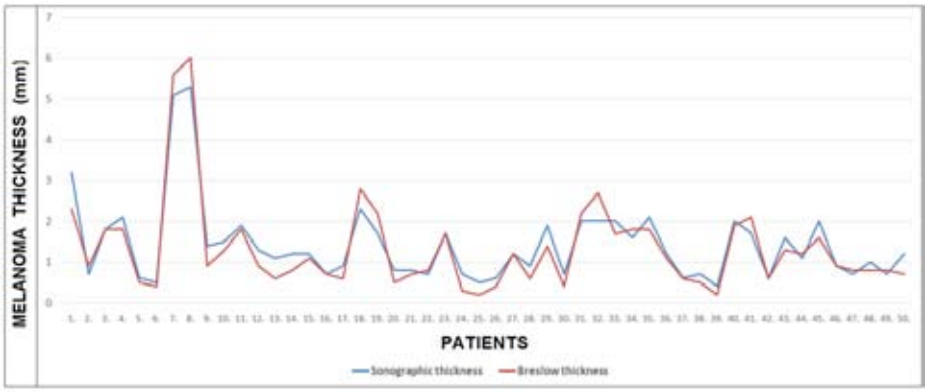

Figure 5. A comparison between preoperative ultrasonographic thickness of malignant melanoma and postoperative histological Breslow thickness in 50 patients.

located on the back and elevated up to 2.0 mm. This may be caused by the presence of microscopic exulcerations, regression, and dermal fibrosis. In addition, a slight underestimation of the ultrasonography values could be caused by compressing on the probe investigated elevated lesion, especially in cases of nodular type of cutaneous melanomas (23). Compressing should always be avoided in superficial tumors, because this may result in false thinning (17).

The same values of histological and ultrasound thickness were found in 7 cases (14%) of malignant melanomas. However, it has to be admitted that the differences between ultrasonographic and histological thickness was only a tenth of a millimeter (Figure 5).

The results of our study demonstrate the significant positive correlation between ultrasonography and histology investigation (r=0.92). These results corroborate our hypothesis that ultrasonography is a sufficient and sensitive method of detecting malignant melanomas. Other studies reported a very good correlation between the tumoral depth measured sonographically and histologically, with correlation coefficients that ranged from r=0.89 to r=0.96 (Table 2). Compared with these studies, our results indicate ultrasonography is a very important tool for future therapeutic approach, correct identification of the surgical excision borders, and the approach to the sentinel lymph-node.

CONCLUSION

High-frequency ultrasonography represents a sensitive, noninvasive, and reproducible method of skin evaluation providing information about various skin diseases, especially malignant melanoma, based on objective visualization *in vivo*. This imaging method is not intended to replace histology, but the anatomical information gained from ultrasonographic investigation can provide the missing link between clinical evaluation and appropriate treatment. Our results indicated that ultrasound examination may reduce the number of surgical procedures and favor the decision of a one-time surgical treatment (removal of primary tumor and sentinel lymph node biopsy).

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