Arch Dermatol Res (2013) 305:305–313
DOI 10.1007/s00403-013-1321-1

ORIGINAL PAPER

Ultrasonographic staging of cutaneous malignant tumors: an ultrasonographic depth index

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Received: 16 November 2012 / Revised: 22 January 2013 / Accepted: 25 January 2013 / Published online: 12 February 2013

Abstract The objective of this paper is to assess the role of conventional and high-frequency ultrasound in the evaluation of the depth of cutaneous skin cancer. The study was performed on 46 subjects, divided into 3 categories, according to their skin pathology [basal cell carcinoma (BCC), 18 subjects; superficial spreading melanoma (SSM), 8 subjects; nodular melanoma (NM), 20 subjects]. Conventional and high-frequency ultrasonographic measurements were performed in order to assess the thickness of the tumors and the vascularization degree. We compared the mean values of the tumoral thickness obtained by using ultrasound (ultrasonographic depth index) with the histological depth index, obtained after performing histological sections stained with hematoxylin–eosin, and specific monoclonal antibodies in case of pigmented tumors. We established a correlation index between the histological and ultrasonographic values of the tumoral thickness. We found a strong correlation between the ultrasonographic index (measured by high-frequency sonography) and the histological index for nodular BCC (correlation of 98.4 %), NM subjects (correlation of 98.4 %), and SSM subjects (correlation of 99.4 %). An increase of the blood supply was noticed in nodular lesions only. Ultrasonography allows a very accurate assessment of skin cancer. The ultrasonographic depth index can be considered an objective, non-invasive marker for cutaneous tumors, comparable to the histological one, with a very good sensitivity (98–99 %).

Keywords Ultrasound · Skin cancer · Breslow index

Introduction

The skin is a complex organ that represents a continuous challenge for research. Being the only organ completely displayed at the body surface, it represents a "window" for internal medicine, allowing at the same time non-invasive investigations and diagnosis procedures. Nowadays, we witness an increased incidence of skin cancer (epitheliomas and melanomas) due to an increased life expectancy, climatic changes, and overexposure to ultraviolet rays [20, 22].

The integumentary system can be evaluated by non-invasive (visual methods such as dermoscopy and imagistic methods such as sonography) or invasive procedures (biopsy and histology). Even though histology still represents the *"gold standard"* for the diagnosis of tumoral skin pathology, researchers are permanently looking for new non-invasive methods of assessment that can offer reliable markers to the histological ones. Ultrasound can be successfully applied as a non-invasive technique for the study of the cutaneous structure and associated pathology [2, 4, 11].

This study was financed by grants SERENO no.2624/2008 to MC and of the University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania, no. 22714/2011 to DC.

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Ultrasound imaging started to be applied in the dermatological field about three decades ago, in addition to the basic diagnosis procedures, having as main purpose the assessment of skin thickness [2, 7]. Ever since, the introduction of transducers using higher frequencies, made ultrasounds of even greater interest to dermatologists, due to reduced wavelengths, allowing enhanced assessment of superficial structures with improved resolution [15, 26]. Thus, more applications of ultrasounds in clinical dermatology are now available, and are successfully applied as non-invasive techniques for the accurate study of the skin, evaluation of benign and malignant tumors, inflammatory diseases as well as in the field of cosmetic dermatology [2, 4, 11, 19].

In principle, the ultrasound spatial resolution increases with frequency while the depth of penetration decreases. The standard 7.5–15 MHz sonographic equipments can be used for the assessment of the skin and more profound structures (around 7–10 cm), but do not precisely differentiate dermis from epidermis. Intermediate range (15–20 MHz) probes have improved this aspect; however, high-frequency ultrasound devices (20–100 MHz) are best suited for high-resolution and superficial measurements [10, 14]. High-frequency ultrasound allows an "in vivo assessment" of the integument and adjacent structures (hair follicles, sebaceous glands), several studies showing important similarities between sonograms and histological sections [17, 19].

The extensive use of high-frequency ultrasound is justified by its ability to illustrate in great detail the cutaneous components up to 15 mm depth (if 20 MHz transducers are used), to assess the lateral and axial extension of the tumoral pathologies, inflammatory, and degenerative lesions [19].

Unfortunately, high-frequency devices are not available in many clinics; therefore, most of the studies in literature used 10–14 MHz devices for the tumoral thickness assessment. Thus, the aim of this study is to elaborate on the reliability of ultrasound reading (conventional and high-frequency ultrasound −20 MHz) applied to skin and to provide a translational ultrasonographic depth scale for the non-invasive evaluation of tumors' thickness.

Materials and methods

We performed a prospective, controlled study during 2009–2012 at the Dermatology Department of the University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania. The study included 46 subjects, 26 females aged 42.3 ± 21.3 and 20 males aged 51.5 ± 12.4 diagnosed with basal cell carcinoma (BCC, 18 subjects), superficial spreading melanoma (SSM, 8 subjects), and nodular melanoma (NM, 20 subjects). The study followed in sequence three research directions: clinical, imagistic, and histological.

The clinical study included the initial grouping of subjects according to the cutaneous tumoral type, as well as the acquisition of clinical photographs (Sony Cyber-Shot DSC-HX9 V, Tokyo, Japan) and dermoscopy images (Heine Delta 20 Dermatoscop, Heine, Herrsching, Germany) of the tumoral lesions.

All patients displayed primary tumors, located at facial level, trunk or limbs, without clinically evident ulcerations, allowing the application of the transducer.

The imagistic study involved two methods: conventional ultrasound (Logiq 7–14 MHz, General Electric, Munich, Germany) used in B mode for the assessment of cutaneous tumors, their dimensions and degree of vascularization using Color-Doppler sonography, and high-frequency ultrasound (Dermascan −20 MHz, Cortex Technology, Hadsund, Denmark) for the more precise imagistic in vivo assessment of the cutaneous structure and evaluation of tumor thickness. The system's features were: 0.06 mm axial resolution, 0.3 mm lateral resolution, depth of field 23 mm, and focus position 13 mm.

The conventional ultrasound focused on the region of interest to identify the lesion shape, echogenicity, and vascular supply. However, this approach did not produce consistent readings of the depth extent of lesions in all cases. The transducers were placed perpendicularly above the lesion after previous application of ultrasonographic gel and the ensuing sonograms were further assessed by evaluating the parameters of interest.

The ultrasound index was measured (in millimeters) only on the 20 MHz sonograms (Dermascan), by using the Dermavision software, in A mode, from the hyperechoic entrance line to the deepest part of the lesion. For a given patient, the depth of the lesion was evaluated on each section taken. Then the highest of all values was retained for further analysis.

The histological study was performed on excised lesions that were removed with a 2–4 mm safety border. Common stain with hematoxylin–eosin was used for certainty diagnosis of the tumoral type and assessment of tumoral thickness. Specific stains for malignant melanoma using monoclonal antibodies (Melan A) for the identification of melanocytes that may be hidden by the peritumoral inflammatory infiltrate ("*shoulder phenomenon*") were used [1]. We measured the histological index for all lesions (in millimeters), from the granular layer of the epidermis to the deepest part of the tumor [30], using an ocular micrometer placed on the microscope (Olympus CX41, Olympus, Hamburg, Germany). Histology confirmed the clinical diagnostic in all cases and no adjustments were required to the study groups.

The subjects were all informed of the nature of the study and provided informed consent before the enrollment. The study was approved by the Ethical Committee of the University of Medicine and Pharmacy "Iuliu Hatieganu," Cluj-Napoca, Romania.

Data analysis

One of the important aspects of this paper relied on establishing correlations between the histological index and the ultrasonographic depth index (the depth of the tumor measured by high-frequency ultrasound from the hyperechoic entrance line to the deepest part of the tumor). In order to achieve this purpose, the individual values measured with both methods were plotted one against the other. Then a best fit (linear or Lorentz, according to the lowest Chi-square value) was calculated (Igor software, Wavemetrics, OR, USA), together with the correlation factor and the parameters of the fitting equation ($y = ax + b$ or $y = y_0 + c/((x - x_0)^2 + d)$, respectively). In the linear fit, the factor a (slope) provides the sensitivity of the correlation (higher values reflect better sensitivity), while b (ordinate value at $x = 0$) represents the offset from an ideal translation. The correlation factor designates the likeness of the experimental data to a linear distribution. Its values might be situated between 0 (no correlation) and 100 % (perfect linear relationship). Once the experimental linear relationship between histological and ultrasonographic index established, the same linear function was used to translate the clinical limits of various tumor stages from histology to ultrasound.

Results

Nodular BCCs (Fig. 1), located at facial level, were identified in 18 patients. From a clinical point of view, dome-shaped

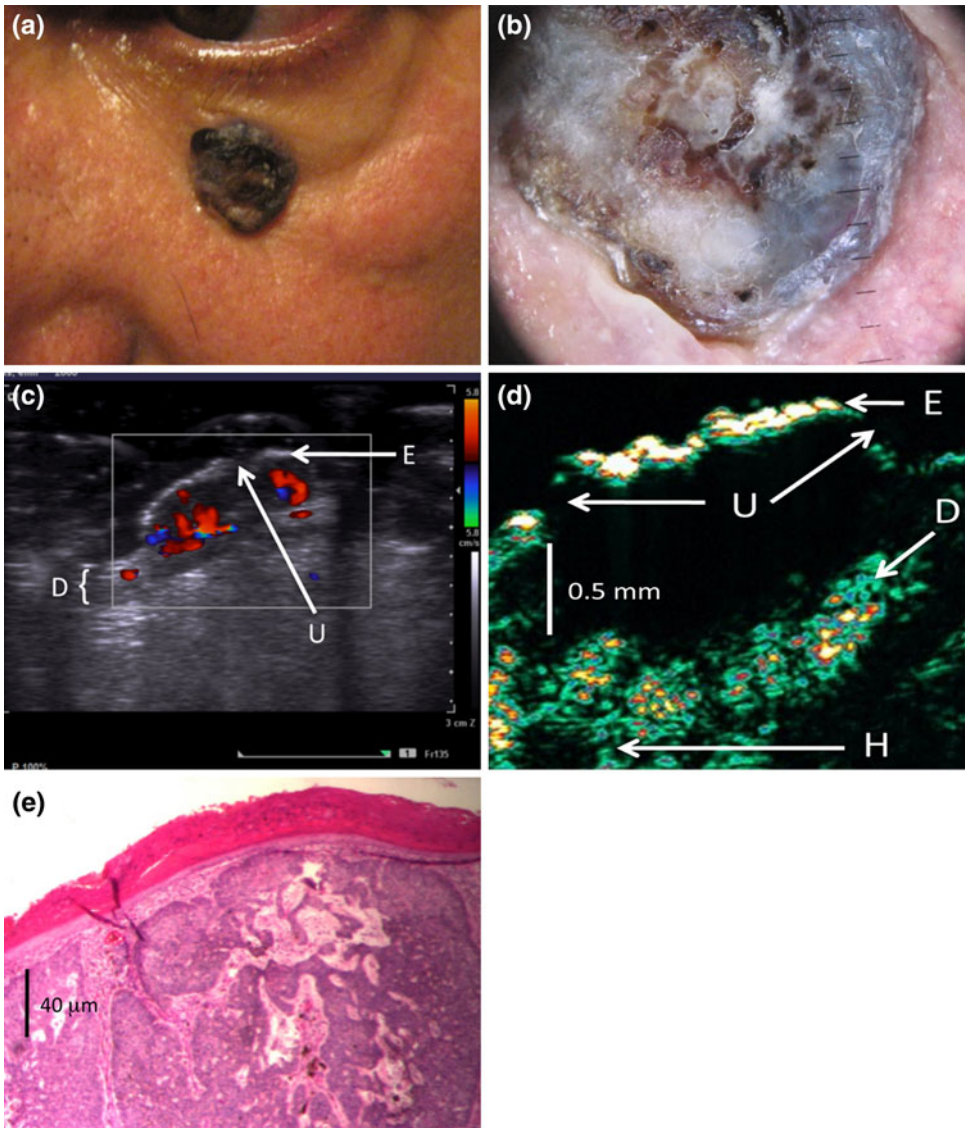

Fig. 1 Basal cell carcinoma (BCC): **a** Clinical aspect: basal cell carcinoma, with elevated, pearly white, translucent border; **b** Dermoscopy: large gray-blue ovoid nests and gray-blue globules. The distance between two consecutive markers is 1 mm. **c** Conventional ultrasound (color Doppler): hypoechoic structure in the dermis (*D*) with a depth of 3 mm; the lesion has heterogeneous echoic patterns and irregular borders; a small superficial ulceration (*U*) of the epidermis (*E*) is shown; color Doppler sonography shows increased blood flow of the same lesion; **d** High frequency 20 MHz ultrasound (gain 20): hypoechoic tumor, with an irregular border, infiltrating the superficial and mid dermis (*D*); two small, superficial ulcerations are shown at the epidermis (*E*) level; *H* indicates the hypodermis. **e** Histology (H&E): nests of typical basal cells and inflammatory cells located in the dermis

papules with prominent telangiectatic vessels, or flat papules, partial pigmented or colored skin, were identified in all patients. Dermoscopy revealed arborizing "*tree-like*" telangiectasia, the lack of pigment network as well as specks of brown and grey pigment. Conventional ultrasound revealed hypoechoic, highly vascularized structures, located at dermal level. High-frequency ultrasound of the lesions, after removal of the superficial scales (keratin deposits) allowed the identification of the tumoral depth. The mean depth of the tumors was 1.27 ± 0.6 mm (mean $\pm$ SD). Histology (routine hematoxylin–eosin stain) revealed highly vascularized tumors consisting of clusters of malignant cells infiltrating the dermis, surrounded by inflammatory cells. Clusters of pigment were visible as brown dots. The mean depth of the tumors, as measured in histology, was 1.43 ± 0.7 mm.

Superficial spreading melanoma (Fig. 2) was identified in eight subjects, being localized at troncular level in men and on the lower limbs in women. Clinically, the lesions appeared as bizarre-shaped structures, having irregular asymmetric borders, irregular pigmentation, and white areas indicating regression. Three of the lesions measuring more than 2 cm in diameter displayed small nodules on the surface. Dermoscopy revealed irregular combinations of many colors and white areas. Conventional ultrasound showed hypoechoic, very thin structures at cutaneous level with a depth of 0.75–1.34 mm, and color Doppler

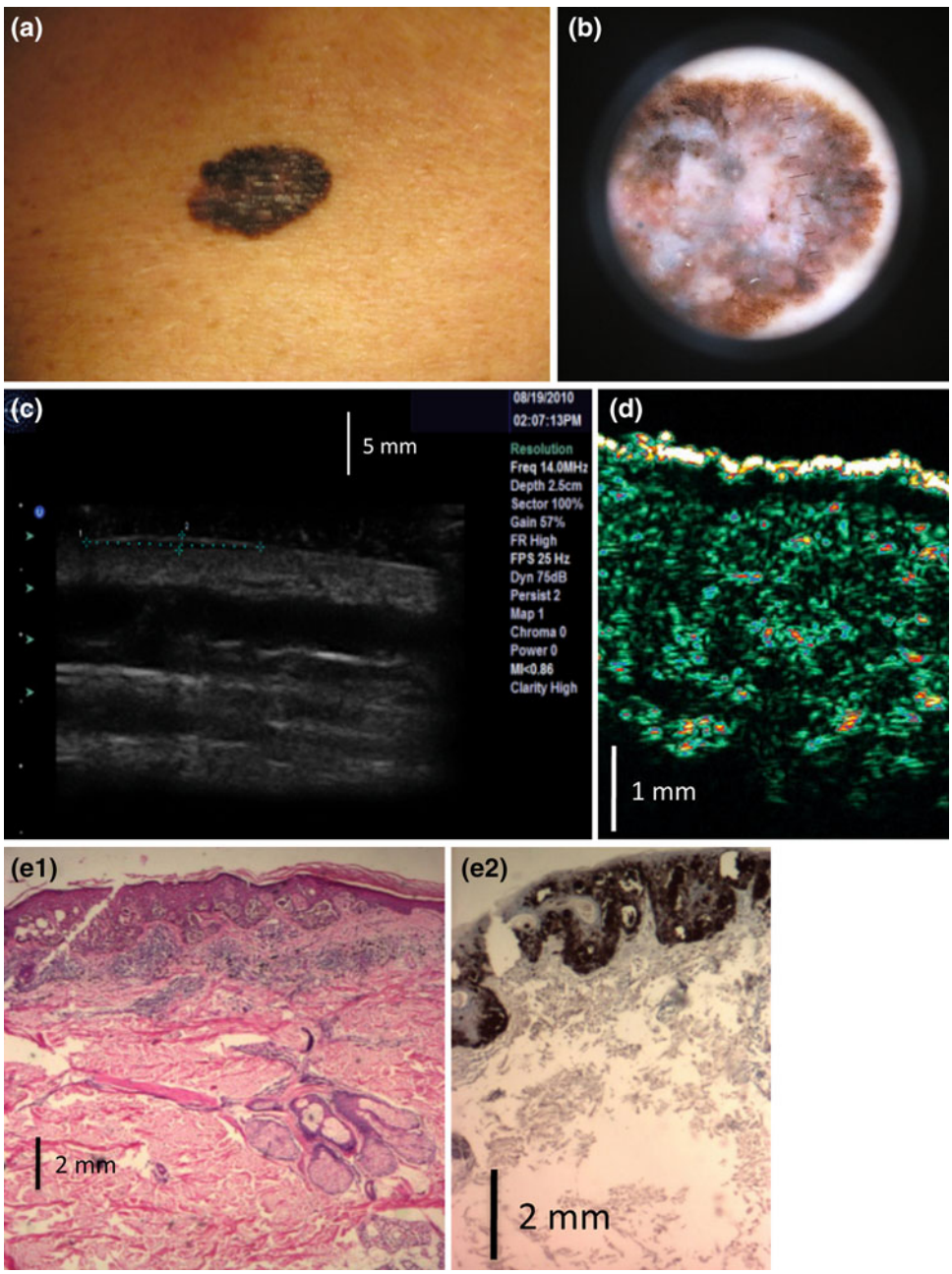

Fig. 2 Superficial spreading melanoma: **a** Clinical aspect: small lesion with irregular borders, irregular pigmentation and a small white area indicating a typical regression. **b** Dermoscopy: irregular pigmentation, irregular dots and globules. The distance between two consecutive markers is 1 mm. **c** Conventional ultrasound: hypoechogenic structures at cutaneous level, with a penetration index of 1.22 mm. **d** High frequency ultrasound (gain 20) displaying a hypoechoic tumor. **e1** Histology (H&E stain): intraepidermal spread of large cells in the horizontal growth phase associated with atypical cells located in the papillary dermis, accompanied by an intense lymphocytic response, marker of the vertical growth phase. **e2** Immunohistochemical staining: (MELAN A) reveals melanocytic atypia in the epidermis and dermis, including the cells hidden by the inflammatory infiltrate

investigation revealed no vascular signal (not shown). High-frequency ultrasound revealed thin ovoid, hypoechoic structures located just beneath the hyperechoic entrance line level in the very superficial dermis (papillary dermis). The depth of the tumor was measured from the entrance hyperechoic line to the deepest part of the hypoechoic image. The mean value of sonographic depth was 0.92 ± 0.24 mm. Histology confirmed the diagnosis in all cases, displaying atypical melanocytes singly or in nest throughout the acanthotic epidermis. The intraepidermal spread of atypical melanocytes confirmed the horizontal growth phase in five cases. In three lesions, clusters of tumoral melanocytes in the papillary dermis associated with intense lymphocytic response confirmed the initiation of vertical growth. The Breslow index had a mean value of 0.7 ± 0.22 mm. Immunohistochemical staining with MELAN A confirmed the presence of tumoral cells, even though the cells were masked by the presence of the inflammatory infiltrate. The depth of the tumor included the deeper tumoral cells identified between the lymphocytes. Small areas of fibrosis were identified as corresponding to the regression area.

Nodular melanomas (Fig. 3) were found in 20 subjects. Clinically, the lesions resembled dark brown or black dome-shaped, or polypoid nodules. Dermoscopy allowed the identification of characteristic features of which the most frequent were blue-grey veils, atypical pigment networks, and irregular pigmentation. Conventional ultrasound revealed solid, hypoechoic tumors, highly vascularized, containing multiple arterial vessels, and vascular pedicles. High-frequency ultrasound identified hypoechoic structures in the upper and lower dermis, with a mean depth of 1.72 ± 0.57 mm. Five subjects displayed in transit metastasis, with a mean depth up to 1.06 mm, and two subjects presented regional metastasis. Histology confirmed the diagnosis of nodular malignant melanoma in all subjects. The Breslow index was <1 mm in two subjects, between 1 and 2 mm in seven subjects, between 2 and 4 mm in three subjects. The histological mean depth was 1.91 ± 0.7 mm.

The analysis and comparison of the ultrasonographic index and histological depth index for the three different types of lesions, showed correlations that are displayed in Table 1 and Fig. 4.

As a result of the high correlation (>98 %) and slope values (>0.85) for the three types of tumors, we propose to translate the histological depth index into an ultrasonographic index by using the respective fitting functions previously obtained (Fig. 5). We left out, however, the translation for the case of SSM considering that the lower number of cases in our study calls for prudence.

We therefore identified, for BCC, the following four ultrasonographic stages corresponding to the histological index: stage I: <0.91 mm, stage II: 0.91–1.76 mm, stage III: 1.76–3.46 mm, stage IV: >3.46 mm. In case of NMs, the following four stages corresponding to the histological index were found: stage I: <0.8 mm, stage II: 0.8–1.88 mm, stage III: 1.88–3 mm, stage IV: >3 mm.

Discussion

Cutaneous skin cancer represents a major concern for clinicians nowadays due to its significant incidence increase [25, 27] and to its potential lethal outcome. According to the literature BCC is the most common skin cancer representing 75–90 % of all cutaneous cancers. The primary tumor is characterized by a slow growing, but with occasional destructive extension into the underlying tissues. Identification of tumor borders is an important factor for the appropriate therapy in order to maintain the functional and aesthetic aspect and to avoid local recurrences.

Malignant melanoma is the least frequent type of primary skin cancer, but it has a high mortality rate. The standard treatment for melanoma is surgery. The histological depth of the tumor or Breslow index is the most important factor for prognosis and treatment approach. There is thus an ongoing concern for the preoperatory assessment of the tumoral depth.

The ultrasonographic assessment represents a new method for the non-invasive evaluation in dermatology. Although the first studies in this field date back 30 years, the technological improvements that made this method applicable in dermatology, only appeared recently [3, 18].

Histology represents nowadays the gold standard for the diagnosis of cutaneous tumoral pathology. The immunohistochemical staining for certain antigenic markers of melanocytes used in this study (P100, MBH45, Melan A) was useful for identifying the full extension of tumoral cells of a primary tumor [9]. This might have contributed to the excellent correlation coefficient obtained (see below). High-frequency ultrasonography has not reached so far the required resolution for conclusive diagnosis, especially because cellular identification remains elusive. Nevertheless, high-frequency ultrasound can be successfully implemented as a complementary, non-invasive method that can identify several parameters (e.g., depth extension of a tumor) with histological precision, contributing to the tumoral prognosis, and therapeutic approach [17, 31].

Some studies report a very good correlation between the tumoral depth, measured sonographically and histologically, which represents a very important aspect for the future therapeutical approach, correct identification of the surgical excision borders and the approach of the sentinel lymph-node [8].

High-frequency ultrasound revealed in our study slightly lower values than those of histology for BCC and NM,

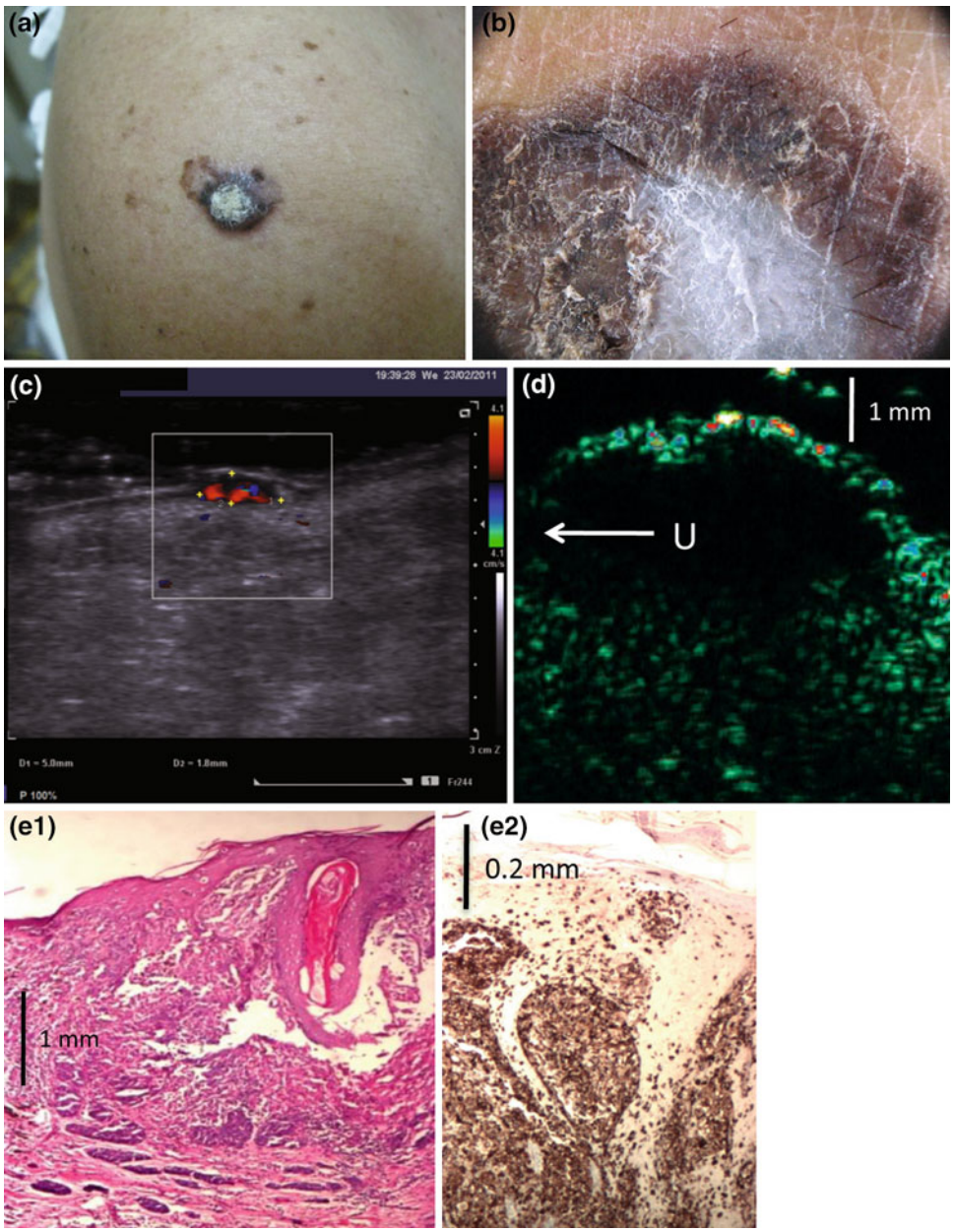

Fig. 3 Nodular melanoma: **a** Clinical aspect:intense dark nodule with small cutaneous metastases around. **b** Dermoscopy: black structure displaying black dots of different sizes and a characteristic white-blue veil. The distance between two consecutive markers is 1 mm. **c** Conventional ultrasound: hypoechoic structure located at skin level, involving epidermis and dermis, measuring 1.8 mm in depth; Echo-Doppler shows the presence of blood vessels. **d** High frequency ultrasound: hypoechoic structure with homogenous attenuation; a small superficial ulceration (*U*) is identified. **e1** Histology (H&E): a solid tumor consisting of clusters of clear, polymorphous cells with a prominent host response that invades the dermis. **e2** Immunohistochemical staining: (MELAN-A) reveals all tumoral cells hidden by the inflammatory infiltrate

Table 1 Correlation coefficient of the ultrasonographic index and histological index

	BBC	SSM	NM
N	18	8	20
Correlation coefficient (%)	98.4	99.4	98.4
Ch-square	0.2	0.005	0.29
Slope factor	0.85	1.07	0.93*
Equation	UIF = HIS × 0.85 + 0.06	UIF = HIS × 1.07 + 0.16	UIF = 3.8 – 16/ (HIS – 0.0005)^2 + 4.3

Note that the retained fit for the NM was a Lorentz function

* The slope factor for the NM is given from a linear fit, which was however less performing than the Lorentz fit. *N* represents the number of cases

increased values for SSM, and strong correlations between histological and ultrasonographical values (>98 %), in agreement with the literature. Bobadilla et al. [5], using conventional ultrasonography, also report lower sonographic values compared to histology in case of BCC (25 subjects), stating that ultrasound plays an important role in

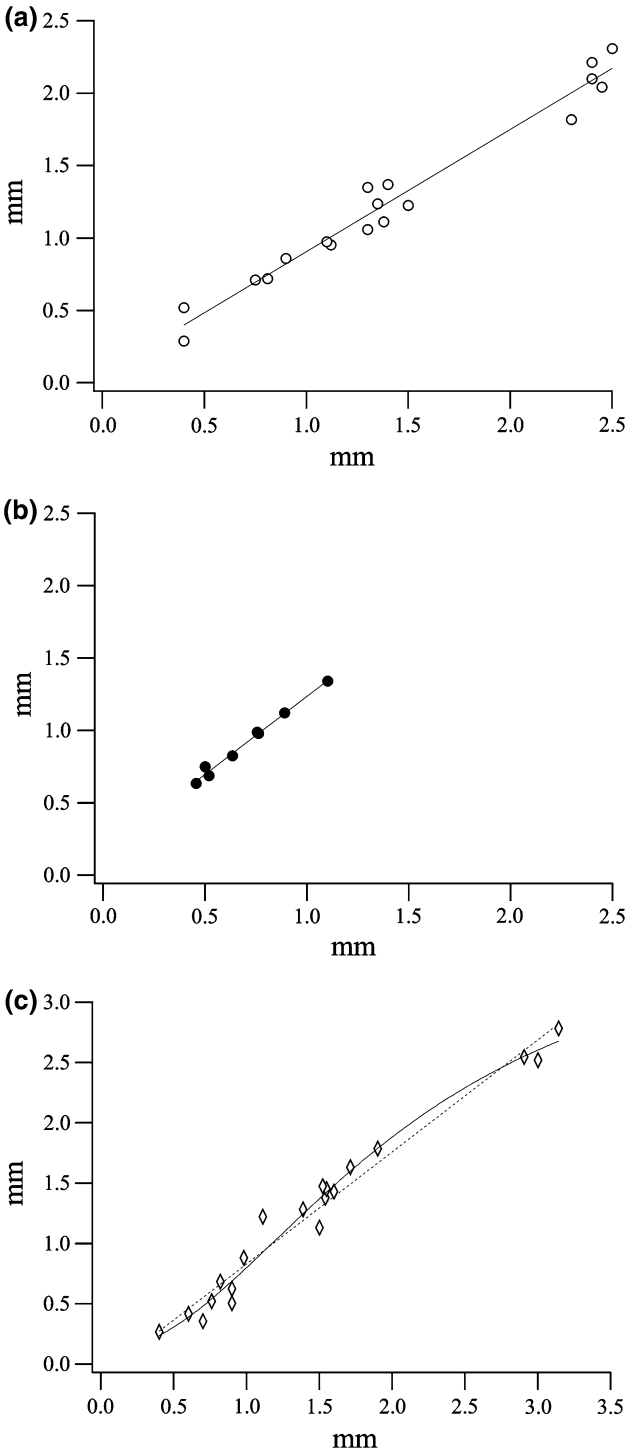

Fig. 4 Correlation between ultrasonographic depth and histological depth. Ultrasonographic values are on the ordinates (in mm) while histological readings are on the abscissae (in mm). The three panels represent results for basal cell carcinoma (BCC; **a**), superficial spreading melanoma (SSM; **b**) and nodular melanoma (NM; **c**). Lines represent best fits of the data: linear fit for BCC and SSM, and Lorentz fit for NM. For the latter the linear fit is displayed as a *dotted line*

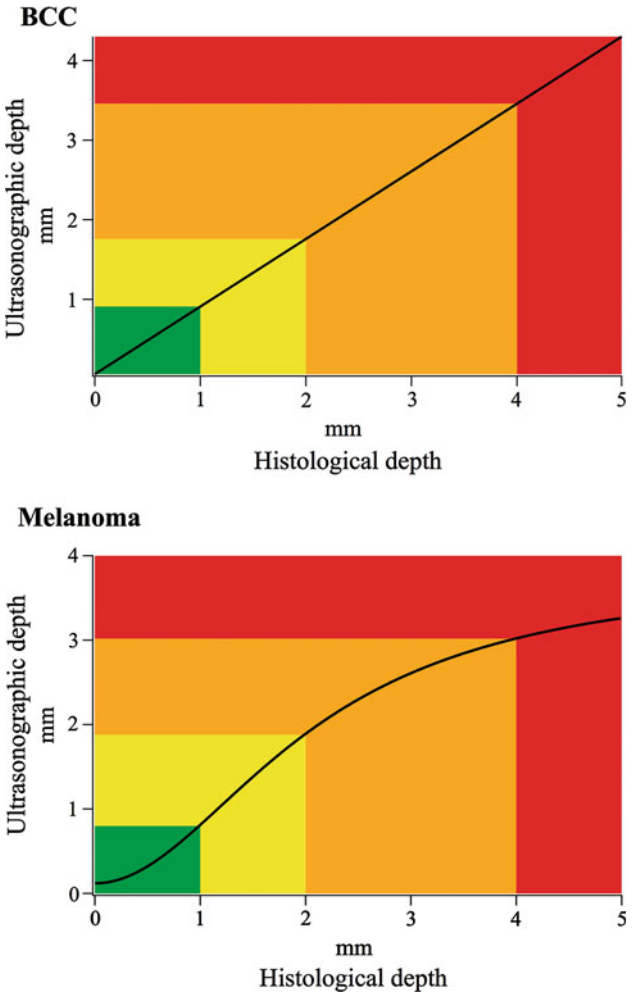

Fig. 5 The tumoral depth scale translation from histological (*abscissa*) to ultrasonographic (*ordinate*) measurements. Color codes, according to melanoma TNM classification [6] reflect clinical prognosis: stage IV (*red*), stage III (*orange*), stage II (*yellow*), and stage I (*green*)

the establishment of surgical borders since the correlation index between histology and ultrasonography was very strong. The authors also mention the possibility of an early non-invasive identification of subclinical satellite lesions, similar to our cases of NM. Another study performed on 56 subjects with BCC also reports lower ultrasonographic values compared to histology, but with a moderate correlation index and not statistically significant differences [23]. Literature also mentions a clear limit of the high-frequency ultrasound for the identification of small infiltrative tumoral areas at the dermal level [16].

The few SSM cases of our study showed robust results, but we believe one needs larger populations for definite conclusions. Unlike nodular tumors, histology displayed lower values than sonography, but the correlation coeffi-

cient was excellent (99.4 %). It has been proposed that the discrete overestimation of the ultrasonographic values could be due either to the inflammatory infiltrate associated to the tumor, or to the cutaneous appendages that may appear as thin hypoechogenic structures (hypertrophied sebaceous glands, hair follicles) [5, 24].

Our data on NM show a peculiar transformation rule based on the best fit that proved to be a Lorentz function. The consequence of this finding is that the transformation function from histological to ultrasound index is not linear. The skewness implies that our ultrasonographic reading was less sensitive for stages III and IV, probably due to uncontrolled variables (such as a possible minute increased pressure on the transducer applied in the presence of larger tumors). Since they were systematical, this aspect might be pertinent to other investigators. The translation curve provides excellent reliability during the initial phases of tumoral growth. A similar study performed by Pellacani et al. [24] on 88 cases of malignant melanoma, also shows a good correlation coefficient of 89 %, although lower than ours, between the mean sonographic depth (1.26 mm) and mean histological depth of the tumors (1.14 mm). Nevertheless, in 21 cases (out of the 88), ultrasonography underestimated the histological index, as was also the case in our present study.

In the current clinical practice, due to the absence of a precise knowledge of the tumoral depth, tumors are removed with what is considered a safe margin. If this was overestimated, the patient might bear unnecessary marks. In the contrary, an underestimation will be signaled only after the histological examination of the excised tissue and will thus necessitate a second surgery. This is why the availability of an accurate sonographic depth index will prompt for a safe, but conservative removal of the tumor, and possibly of the sentinel lymph node, within only one procedure.

Our study confirms the importance and potential of high-frequency ultrasound in the prognosis and screening of cutaneous tumors, revealing a very good corresponding coefficient between the histological (inclusion of the tumoral cell clusters hidden by the inflammatory infiltrate) and ultrasonographic depth index. Moreover, one cannot expect a precise match between histological readings and ultrasonographic depth indexes since the former are performed on ex vivo, dehydrated tissue, while the latter stem from real time examinations, which, due to resolution limitations, also cannot discern cellular types. This implies that histological values generally underestimate the real in situ size. On the other hand, the ultrasonographic evaluation may produce overestimated or underestimated values with respect to the histological index. This issue has no clarification in the literature. In our study BCCs and NMs were underestimated, while SSMs were overestimated by sonography. This incongruity might be related to the presence of vascularization within the former types of tumors rendering them more compliant to the pressure exerted by the transducer. The really important issue here is whether one can establish an excellent correlation coefficient between the histological and ultrasonographic readings, regardless whether the latter underestimate or overestimate the real depth extension of the tumors.

Moreover, we provide in this study a methodology to link the traditional Breslow index to the ultrasonographic readings not only for melanoma but also for BCC (Fig. 5). This may have far reaching consequences in predicting the aggressiveness, degree of malignancy of the tumor, as well as the prognosis and therapeutic approach. The ultrasonographic evaluation includes, in addition to the tumoral depth, the pattern of vascularization and the presence of ulcerations, which cannot be identified at the de visu evaluation. However, for this aspect conventional echography combined with Doppler was helpful only in BCCs and NMs, and proved its limits for small blood vessels such as those of SSMs. Further development of high-frequency echographs coupled with Doppler systems might provide a solution to the analysis of both vascularization and structure of superficial tumors.

In this case, ultrasonography may become a non-invasive virtual biopsy, thus eliminating the risk of dissemination. Moreover it provides an ultrasound staging that, if completed with other investigations (lymphatic nodes, distant metastasis), would become similar to the TNM classification with the possibility to be extended to other forms of cutaneous cancers. However, we anticipate that histological examination will remain, post-operation, a necessary procedure because it brings a myriad of other information concerning the nature of the tumor, thus establishing the prognostic. Alternatively, a more recent technique, optical coherence tomography also provides in vivo imaging that allows non-invasive, high-resolution assessment, and visualization of microstructures up to 1.6 mm depth [12, 13, 21, 28, 29].

On the downside, the limits of the method consist in the fact that it is operator-sensitive. Errors (positive or negative) may result if the pressure applied to the transducer is not correct. The method is also unable to detect the lesions situated only at epidermal level (in situ cancer).

Conclusion

Ultrasonography is a reliable tool for the assessment of the cutaneous tumors. It offers critical information, such as tumor depth, that cannot be assessed clinically. The sonographic index may become a marker with a strong histological correspondent, highly reliable for the prognosis and therapeutical approach in cutaneous cancers.

Acknowledgments The authors gratefully acknowledge Cortex Technologies, Denmark, for allowing the use of the 20 MHz high-frequency DERMASCAN device during this study. This study was financed by grants SERENO no.2624/2008 to MC and of the University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania, no. 22714/2011 to DC.

Conflict of interest None.

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