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High-frequency ultrasound: an essential non-invasive tool for the pre-therapeutic assessment of basal cell carcinoma

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Abstract

Aim: While histology remains the "gold standard" for cutaneous tumoral pathology, high-frequency ultrasound (HFUS) was shown to play a significant role in the non-invasive, pre-therapeutic assessment of skin tumors. The aim of our study was to determine whether there is a significant correlation between the ultrasound (US) and histological measurements of basal cell carcinoma (BCC) tumor depth. *Materials and Methods*: The present study retrospectively analyzed clinical, dermoscopy, HFUS and histological examinations of 90 patients (52 men and 38 women) with histologically confirmed BCC, with focus on tumor depth index (DI). *Results*: On clinical examination, 54 lesions were nodular (32 presented ulcerations) and 36 superficial lesions. Dermoscopy showed suggestive signs of BCC, most frequently "in focus" arborising superficial vessels (n=81), blue-grey ovoid nests (n=48) and specks of brown pigment (n=7). HFUS revealed well-defined (n=88) or poorly defined (n=2) hypoechoic, vascularized lesions, with inhomogeneous structure (n=90) and characteristic hyperechoic dots (n=36). A strong correlation (Pearson's r=0.92) between the HFUS (mean measured US depth = 1.33 mm) and histological (mean measured histological depth = 1.47 mm) DI of the investigated skin lesions was found, although significant differences (p<0.001 – t-test for paired samples) between the two measurements were observed. *Conclusions*: HFUS provides reliable information about BCC depth of invasion that cannot be otherwise obtained prior to surgery. In this manner, it completes the preclinical evaluation and can have an impact on the choice of the optimal therapeutic method.

Keywords: ultrasound, basal cell carcinoma, histology, morphology.

Introduction

Of all skin malignancies, basal cell carcinoma (BCC) has the highest incidence rate worldwide. These tumors are considered semi-malignant tumors, with predilection for the head and neck region, and, while they used to be known as tumors of the elderly, nowadays an increasing incidence in younger subjects is found [1–5]. Chronic ultraviolet-rays exposure is the most important factor involved in the development of BCCs [2, 6] and for this reason these tumors are being commonly seen in sun-exposed areas [1, 7]. Other well-known risk factors for BCC development are fair skin, exposure to radiation or chemical substances (*e.g.*, arsenic), immunosuppressant and genetic factors (*e.g.*, Gorlin–Goltz syndrome) [3, 8, 9].

Current guidelines for cutaneous skin malignancies consider the histological analysis as the "gold standard" for diagnosis [1, 2, 10]; however, high-frequency ultrasound (HFUS) was also shown to play a significant role in the non-invasive assessment of cutaneous tumoral pathology prior to treatment [11–13]. While it does not replace the histological diagnosis, it does provide real-time complementary data regarding tumor morphology and vascularization, which adds additional value to the clinical diagnosis and may orient the therapeutical approach.

HFUS is used in dermatology as an important tool for the preoperative assessment of cutaneous lesions as well as for oncological follow-up and identification of recurrences [4, 14, 15]. Regarding BCCs, gray scale HFUS provides significant data regarding lesion morphology, contour, structure, relationship to adjacent structures such as bone, cartilage, or muscle, as well as information regarding dimension, lateral and depth extension, one of the most important measurements being the tumor depth index (DI) [4, 16–19]. Color flow map and pulse mode on Doppler examination provide important data related to the tumor blood supply, more precisely branching of vessels, blood flow model, blood velocity, number of vascular pedicles, etc. [4, 16, 20]. Furthermore, qualitative, and semi-quantitative elastography measurements can assess the stiffness of the lesions; a common malignancy trade seen in cutaneous tumoral pathology is the increased rigidity of the lesions when compared to the surrounding non-tumoral tissue [21–23].

Although BCCs rarely metastasize (0.0028–0.55%) [24–26], they show a locally destructive pattern, hence recent Guidelines recommend dividing BCCs into low and high-risk groups [12, 22] or "easy-to-treat" and "difficult-to-treat" groups [1], orienting treatment options. Therapeutic

options vary from surgical excision to photodynamic therapy, topical treatment, electro-dissection, cryotherapy, laser ablation, radiotherapy, or combined therapies [1, 27–30]. It is however mandatory to keep in mind that the histological assessment of the tumor and surgical margins is not possible when using treatment options that destroy the tissue.

The importance of tumor depth measurement lies in patient's management, in particular in the choice of treatment. Nonsurgical therapy may be considered in low-risk BCCs. For example, tumors with depth <2 mm can be treated using photodynamic therapy instead of surgical excision, thus having a better aesthetical outcome and minimal loss of healthy tissue [31]. Regarding the HFUS measurement, various authors used different probe frequencies. HFUS implies the use of high-frequency probes up to 100 MHz [31, 32]. Frequencies greater than 15 MHz enabled the differentiation of skin layers [33–35]. Frequency of 20 MHz to 25 MHz visualize the epidermis and dermis, thus having the highest resolution for observing surface structures (such as superficial tumors), while frequencies between 50 MHz and 100 MHz are limited to the epidermis, because of their reduced penetration [33, 36, 37]. In terms of probe choice for tumor thickness measurement, researchers proposed different frequencies. Using a compact linear 15–7 MHz probe, Bobadilla *et al.* obtained a good correlation [intraclass correlation coefficient (ICC) 0.9] between ultrasound (US) and histological depth measurements of BCC [38]. When Khlebnikova *et al.* compared a 30 MHz probe to a 75 MHz probe, they found that the 75 MHz probe had a greater correlation between sonographic and histological depth measurements (r=0.870) than the 30 MHz probe (r=0.290) when measuring BCC with thickness smaller than 1 mm and had a better correlation with the 30 MHz probe while measuring tumors greater that 1 mm (r=0.951) [16]. Even medium frequency probes can be used in tumor depth measurements. Researchers such as Kučinskienė *et al.* and Kaikaris *et al.* used a 14 MHz probe for thickness measurements and obtained better results in measurement of thicker lesions (>2 mm in the Kaikaris *et al.* study and >1 mm in Kučinskienė *et al.* study) when compared to thinner ones [32, 39]. As a response to the discrepancies in literature, we propose an evaluation on the usefulness of an 18 MHz probe.

Aim

The aim of this study was to compare US examination of BCC to histopathology, focusing on the measurement of tumor DI, to determine whether US measurement is similar to the histological one.

Materials and Methods

The present study is analytical, retrospective, observational and longitudinal. Data was collected after receiving approval from the research Ethics Committee of the Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania (No. 564/03.12.2019). All patients participating in the study have given their written informed consent.

The dataset consists of 90 consecutive cases diagnosed with BCC in the Department of Pathology, Emergency County Hospital, Cluj-Napoca, between January 2016 and December 2018, that had HFUS prior to surgery. Cases with US suspected BCC that were not histologically confirmed were excluded from the study. Cases with histologically confirmed BCC but without US examination prior to surgery were also excluded from the present study.

Multimodal HFUS (gray scale, fine flow color Doppler and strain elastography) was performed using a high-resolution lineal electronic probe at the frequency of 18 MHz probe (HI-Vision Noblus US system, Hitachi, L64 probe). All HFUS examinations were performed by the same physician with eight years' experience in skin US.

Gray scale examination was performed using the superficial preset which enables the visualization of superficial structures (scanning mode: HdTHI-R – high definition). The tumor depth measurements were performed in longitudinal and transverse sections, starting from the granular layer (just beneath the hyperechoic band of the *stratum cornosum*) to the deepest border. An increased amount of gel was used for optimal acoustic coupling. The highest of all values of tumor depth measurements was retained. Fine flow color Doppler (L64 probe) was used to qualitatively assess tumor vascularization. For strain elastography, a layer of about 5 mm of gel was used on the lesion and a light pressure. The algorithm automatically eliminates the frames with artifacts and makes possible an accurate interpretation on tissue hardness of a lesion, in the case of images obtained in stable compression. The system assists the operator by providing a real-time indicator of the compression. The elastographic image uses the following colormap: blue for hard tissue and red for soft tissue. Malignant tissues were considered to have increased rigidity (hard tissue – blue) when compared to the surrounding dermis or hypodermis (elastic, soft tissue – green, red) according to the already published data [4]. Following US examination, all patients underwent surgical excision with adequate safety margins in local anesthesia.

A pathologist, using routine Hematoxylin–Eosin (HE) staining, analyzed the pathological specimens. Histological data, such as DI (Breslow), level of anatomical invasion (Clark), surgical margins status, tumor stage and tumor type were collected. The DI was measured from the granular layer of the epidermis to the deepest part of the tumor. The presence of microcalcifications, clusters of apoptotic bodies and keratin globules were also assessed. Slides were examined using Leica DM1000 optical microscopes and measurements and pictures were obtained using Leica ICC50 camera and Leica LAS EZ software. The pathologist was blinded to the US report.

Statistical analysis

The statistical analysis regarding the correlation between the US and the histological DI was conducted using Pearson's correlation coefficient. A paired Student's t-test has also been used, to verify whether the values of the ultrasonographic DI and those of the histological DI differ significantly. Analyses have been performed using Microsoft Excel. The level of statistical significance has been chosen at α=0.05.

Results

The 90 BCC cases included consisted of 52 men and 38 women with mean age of 68±10.45 years. Clinical examination showed 54 exophytic, nodular lesions (32 with ulcerations and crusts) and 36 superficial, plane lesions. Seven of the nodular lesions presented superficial pigment, which made the differential diagnosis with melanoma challenging.

Dermoscopy showcased "in focus" arborising superficial vessels in 81 of the examined lesions, blue-grey ovoid nests in 48 of the examined lesions and specks of brown and pigment in seven lesions.

Multimodal HFUS evaluation of the lesions revealed various aspects regarding morphology, vascularization, and rigidity. Most lesions (*n*=54) involved the epidermis, superficial or deep dermis, some of them (*n*=2) imprinting the hypodermis. Grey scale examination of tumor morphology shows hypoechoic, inhomogeneous structure (*n*=90), with well (*n*=88) or poorly defined margins (*n*=2).

Nineteen lesions displayed hypoechoic/anechoic areas corresponding histologically to nodulocystic or adenoid variants of nodular BCC (Table 1). Other lesions (*n*=4) presented hyperechoic structures (keratinization areas) corresponding histologically to nodular BCC keratotic variant (Table 1). The BCCs with hyperechoic US spots (*n*=36) had a histological correspondent in microcalcifications (*n*=30), clusters of apoptotic bodies (*n*=2) or keratin globules (*n*=4) (Figure 1), seen with routine HE staining. The histological examination of the lesions revealed the following subtypes: superficial (*n*=24), nodular (*n*=57, of which 11 nodulocystic variant, eight adenoid variant and four keratotic variant), pigmented (*n*=7) and infiltrating (*n*=2) (Table 1).

Table 1 – ***Comparison between HFUS and histological examinations depending on histological subtype***

BCC histological subtype	*n*	HFUS hyperechoic spots			Average DI [mm]		SD	
		Histology			*HFUS*	*Histology*	*HFUS*	*Histology*
		MC	*K*	*AB*				
Nodular	34	22			1.529	1.648	0.485	0.469
Nodulocystic	11	5		1	1.787	2.027	0.588	0.69
Adenoid	8	2		1	1.452	1.62	0.471	0.401
Keratotic	4		4		1.81	2.053	0.652	0.826
Superficial	24				0.621	0.632	0.246	0.248
Pigmented	7	1			1.157	1.586	0.481	0.489
Infiltrating	2				3.102	3.286	0.45	0.203

AB: Clusters of apoptotic bodies; BCC: Basal cell carcinoma; DI: Depth index; HFUS: High-frequency ultrasound; K: Keratin globules; MC: Microcalcifications; *n*: No. of cases; SD: Standard deviation.

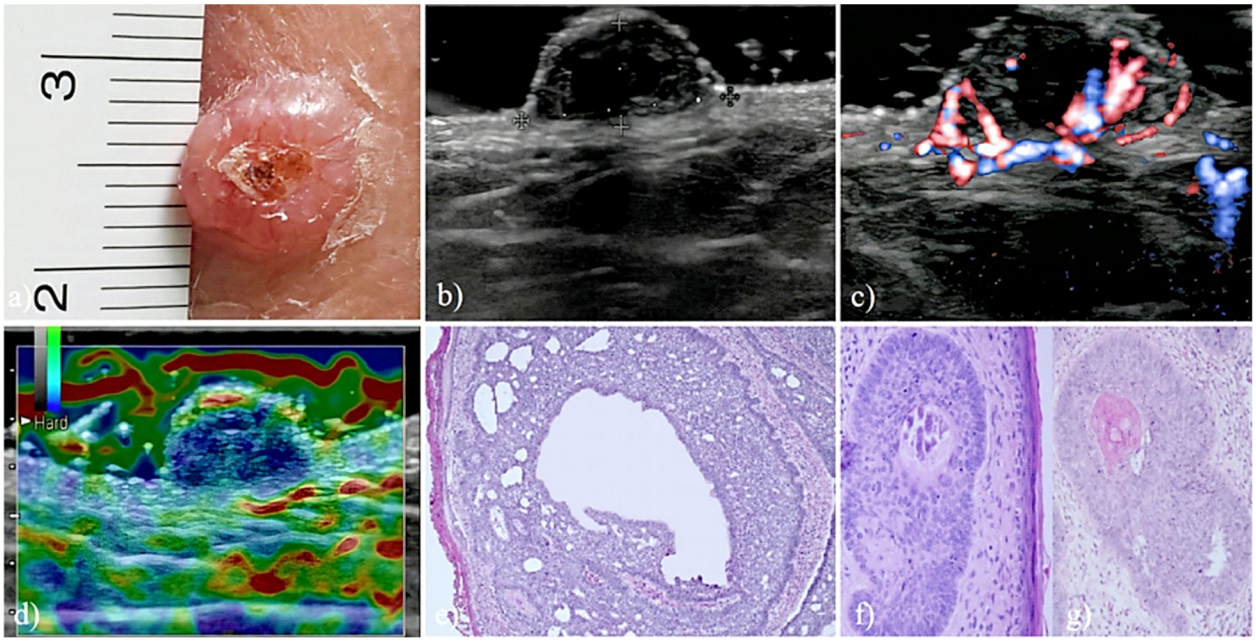

Figure 1 – ***(a) BCC: clinical aspect showing a nodular, exophytic tumor with central ulceration and hemorrhagic crusts located at facial level; (b) Gray scale US: well-defined, exophytic, oval-shaped lesion located in the dermis; notice the hypoechoic inhomogeneous structure, corresponding to the histological nodular BCC type with cystic differentiation (central hypoechoic space) and characteristic hyperechoic spots; the DI was 5.5 mm; (c) Color Doppler US: increased blood flow within the lesion, displaying an arborizing pattern and two vascular pedicles; (d) Strain elastography: increased rigidity of the lesion, suggesting malignant lesion; (e) Histology: macro- and micronodular infiltrate of basaloid cells with palisade arrangement and fibrous stroma containing inflammatory cells; the DI (Breslow) was 5.4 mm; the tumor was a nodular-type BCC (nodulocystic variant); (f and g) Histology of different cases with microcalcifications corresponding to the US-identified hyperechoic spots within the tumor (f) and keratin formation (g). HE staining: (e) ×100; (f and g) ×400. BCC: Basal cell carcinoma; DI: Depth index; HE: Hematoxylin–Eosin; US: Ultrasound.***

Color Doppler showed an increased blood supply, at the bottom of the lesions, with two (n=74) or three (n=16) vascular pedicles. Qualitative elastography revealed increased rigidity in all tumoral lesions (blue) when compared to the surrounding tissue (red, green) represented by dermis or hypodermis by using the color scale from real-time tissue elastography mode (Figure 1). We interpreted increased rigidity (blue) compared to surrounding tissue (dermis, hypodermis – red and green) as an argument of malignancy [4].

Although significant differences (p<0.001 – t-test for paired samples) were found between tumor thickness measured by HFUS (mean measured ultrasonographic depth = 1.33 mm) and by histology (mean measured DI = 1.47 mm) (Figure 2), a strong correlation was found (Pearson's r=0.92) between ultrasonographic measurements and histological findings quantified by the DI (Figure 3).

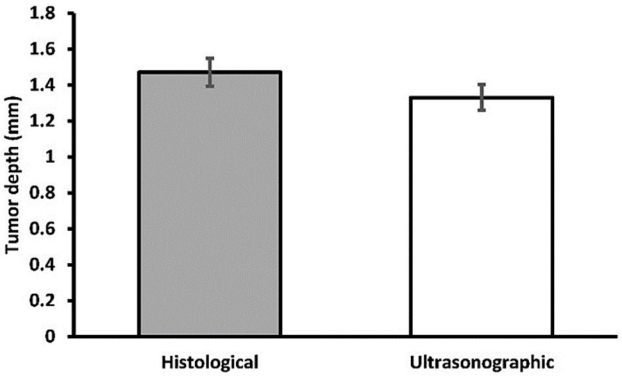

Figure 2 – ***Tumor depth measurement Quality Bar Graphic.***

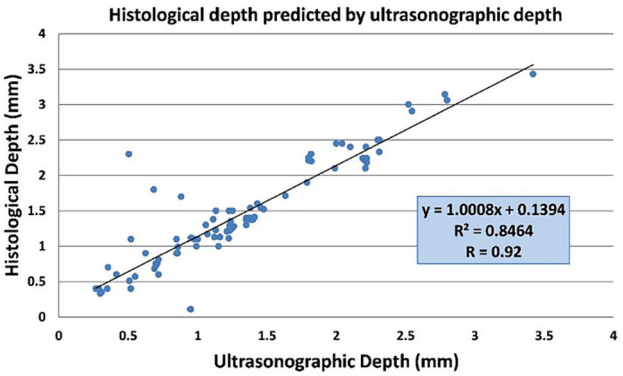

Figure 3 – ***Correlation between the ultrasonographic and histological tumor thickness index.***

Discussions

Cutaneous neoplasms represent a major challenge for dermatologist. US is an important non-invasive imaging technique that completes and improves the diagnostic accuracy in dermatological tumoral lesions such as BCC, by providing detailed information about tumor vascularization, elasticity and morphology that can be suggestive for certain histological subtypes. Although ultrasonography is being used in the dermatological filed for years, the use of high-frequency probes (15–75 MHz) has considerably improved the correlation between US and histology.

The image accuracy depends on the probe frequency and on the operator skills. Regarding the probe frequency various authors using different frequencies (14 MHz to 75 MHz) reported a good correlation between sonographic and histological measurements of skin tumors (tumor thickness, depth of invasion). Khlebnikova *et al.* obtained a higher correlation between the sonographic and histological depth measurements of BCC thinner than 1 mm when using a 75 MHz probe (r=0.870) when compared to the 30 MHz probe (r=0.290), and a better correlation for the 30 MHz (r=0.951) probe on thicker tumors (>1 mm) [16]. Using a 14 MHz transducer, Kučinskienė *et al.* reports a better correlation between the histological and sonographic DI for thicker lesions in comparison with thinner ones (<1 mm) [32]. Ballester-Sánchez *et al.* used an 18 MHz transducer and describes more accurate HFUS measurements in shallow depth (p=0.05007 >0.05) [40]. In our study, we evaluated 90 cases of BCCs using an 18 MHz transducer and we showed the presence of a strong correlation between the ultrasonographic and histological tumor depth measurements (Pearson's r=0.92). Therefore, it is noticeable that results can vary depending on the transducer used for the examination of the lesions. Although the higher the frequency, the better the sonographic accuracy, literature data [11, 32, 40] and our data suggests that accurate measurements of cutaneous tumors can be obtained while using probes with frequencies higher or equal to 14 MHz.

Small differences in reported data of various authors can also be explained by operator skills [41–43], certain artefacts (inflammatory infiltrate, solar elastosis, sebaceous gland hyperplasia), as well as anatomical particularities [4]. In our study, the good correlation coefficient (Pearson's r=0.92) can be explained by the fact that all patients were evaluated by the same experienced sonographer using an appropriate amount of gel.

In the most recent *World Health Organization* (WHO) Classification of skin tumors, size and invasiveness plays an important role in determining tumor stage and grading, thus making this index crucial in the management of BCCs [44]. In this context, the practical benefit of having an accurate sonographic DI, can guide and optimize the choice of treatment in an individualized manner, to reduce recurrence rates. Furthermore, in selected cases of BCCs, having a DI ≤2 mm, the therapeutic approach can also be limited to photodynamic therapy for instance, sparing an invasive surgical procedure [28, 45–47].

Wortsman *et al.* showed that hyperechoic spots are a common sonographic finding in BCCs and are likely pathognomonic for this skin neoplasm [48]. Those findings were also described by other authors [49, 50] and are consistent with our results where we observed hyperechoic spots in all the examined lesions, which were histologically confirmed as calcifications, keratinization, or clusters of apoptotic bodies.

Because of its high accuracy, HFUS can non-invasively identify important histological parameters prior to therapy, thus contributing to identifying the optimal choice of therapy for our patients. Although histology brings detailed information about any tumors' vascularization and stroma, especially using special staining and immunohistochemistry [51, 52], HFUS can offer clinicians pre-treatment real-

time information regarding vascularization and stiffness degree of the tumoral pathology, by doppler US and elastography [4, 53], in this manner being a real biomicroscope with histological precision. As a result of our findings along with recent literature data [4, 18, 32, 53], we strongly recommend the implementation of sonography as an important diagnostic and follow-up tool for dermatologists.

Study limitations

One of the limitations of our study was constituted by the small number of patients who fitted the inclusion criteria, a reason for this might be the fact that in our hospital there are few dermatologists with experience in HFUS, therefore not all clinically suspected tumors undergo HFUS examination. Another limitation was the fact that the ultrasonographic and the histological assessments are operator-dependent, which can lead to minor measurement errors. The fact that not all BCC subtypes were present in our study represents another limitation. Of all 10 histological subtypes of BCC, only four were encountered in our study. Also, our study only assesses the measurement of tumor depth and does not appraise or statistically analyses the US prediction of BCC histological subtype. Our study did not appraise the reproducibility of these assessments to see interobserver variability.

Conclusions

Our study shows a strong correlation between HFUS and histological measurements of BCC thickness in our cases, therefore clinicians may use HFUS as a non-invasive, pre-therapeutic investigation tool of these skin tumors to establish the best therapeutic choice for their patients (surgery *vs.* local therapies) and achieve the best oncological and aesthetic outcome, sparing patients from unnecessary invasive procedures.

Conflict of interests

The authors declare that they have no conflict of interests.

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