

Basal cell carcinoma invasion depth determined with 30 and 75 MHz high-frequency ultrasound and histopathology – a comparative study

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Abstract

Aim: To compare the depth spread of basal cell carcinoma (BCC) measured by histological examination and high-frequency ultrasound (HFUS) imaging with 30-MHz and 75-MHz probes. **Materials and methods:** HFUS skin imaging was used to examine 27 BCCs. A specialized high-resolution digital ultrasound imaging system DUB (TPM GmbH, Germany) with 75-MHz and 30-MHz probes was used. After HFUS scanning, the BCCs biopsy samples were collected by punch biopsy or surgical excision for the morphological examination. Based on the histomorphology results obtained, the tumors were divided into thin (≤ 1 mm invasion depth) and thick (> 1 mm invasion depth). Each BCC spread depth was measured during the HFUS examination with 75-MHz and 30-MHz ultrasound probes and morphological examination. **Results:** Thin BCCs average invasion depth measured histologically was 0.494 ± 0.212 mm. Its average depth obtained with HFU examination with 75-MHz and 30-MHz probes was 0.591 ± 0.265 and 0.734 ± 0.123 mm, respectively. High, statistically significant correlation between the histological and 75 MHz HFU measurements was obtained ($r=0.870$). The correlation was weak ($r=0.290$) when using a 30 MHz transducer. The average thick BCC invasion depth values obtained with the histological examination and 30 MHz HFUS scanning was 1.845 ± 0.718 mm and 1.995 ± 0.699 mm, respectively. High, statistically significant ($r=0.951$) correlation between the thick BCC spread depth measured with 30 MHz transducer and histomorphological examination was obtained. **Conclusions:** In cases of BCCs with thickness of ≤ 1 mm, there was a high correlation ($r=0.870$) of the tumor spread depth between micromorphological measurements and the results obtained using a 75 MHz transducer and in cases of BCCs with thickness of > 1 mm, a very high correlation ($r=0.951$) of the tumor spread depth was observed between histomorphometry and 30 MHz transducer measurements.

Keywords: basal cell carcinoma (BCC); high-frequency ultrasound skin imaging; micromorphological measurement

Introduction

Basal cell carcinoma (BCC) is the most common malignant skin tumor among the white-skinned population.

According to the various data throughout the world, over the past few decades the incidence of BCC has increased by 20–80% [1]. This was related to prolonged exposure to UV radiation (especially spectrum B), adverse environmental conditions, chemical carcinogens and ionizing radiation [2-4]. A particular role is assigned to hereditary and immune disorders [5].

The BCC treatment methods should ensure the complete elimination of tumor cells and the most acceptable cosmetic result [6]. Surgical excision is the “gold standard” of BCC therapy and the method of choice in the case of a tumor which is at high recurrence risk [7,8]. Accord-

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ing to the 7th edition of the American Joint Committee on Cancer (AJCC), one of the factors determining the affiliation of BCC to this group is thickness >2 mm [9]. In the case of superficial neoplasms with the low recurrence risk and located in open body areas, this treatment method may be impractical or cosmetically significant [8]. In such cases, non-surgical methods are used, such as cryodestruction, photodynamic therapy (PDT) and imiquimod [10-12]. Thus, PDT was an effective and reliable method of the BCC treatment for tumors with invasion depth ≤ 2 mm. Only 5.5% of tumors with ≤ 0.7 mm thickness recurred [13]. The imiquimod BCC treatment effectiveness approached 100% for tumors with a depth of ≤ 0.4 mm. In the case of neoplasm thickness of >0.4 mm, the efficiency did not exceed 42% [14].

Histological examination is the main diagnostic method of BCC. However, the non-invasive technologies are becoming more common [15]. One of them is high-frequency ultrasound scanning (HFUS). The main task of HFUS in BCC diagnosis is to examine the tumor structure and size, measure the depth of spread and the location relative to the surrounding tissues [16-18]. These data are especially crucial for BCCs localizing in areas of high recurrence risk [19-21]. The HFUS importance in the subsequent planning of both surgical and non-invasive BCC treatment methods was emphasized [22-24]. The ultrasound transducers with a frequency of 20–100 MHz are most commonly used for these purposes [25,26]. High-resolution 20 MHz and higher ultrasound transducers have been reported to determine the boundaries and depth of BCC invasion [20,27]. However, Jambusaria-Pahalajani et al reported low sensitivity (32%) and insignificant predictive value (47%) of HFUS (20-50 MHz) in BCC diagnosis [23]. Medium-frequency ultrasound transducers (10-14 MHz) were useful in assessing the BCC invasive potential regardless of the spread depth (≤ 1 mm and >1 mm) [28,29].

Considering the contradictions in the literature data, it seems appropriate to study the diagnostic value of HFUS with the different frequencies in order to determine the BCC invasion depth. In this regard, the aim of this study was a comparative measurement of the BCC spread depth using the histological examination and HFUS with 30 MHz and 75 MHz ultrasound transducers.

Materials and methods

Nineteen patients with BCC admitted to the dermatovenereology and dermatooncology department of the Moscow Regional Research Clinical Institute between April 2017 and April 2018 were enrolled in this prospective study. The inclusion criteria were: age over 18

years, clinical diagnosis of previously untreated primary BCC localized on any part of the body, except the upper eyelids, ears, nose and scalp, up to 1 cm in diameter for nodular BCCs. Patients with ulcerous BCC, nodular BCC with a diameter more than 1 cm, BCCs located on the upper eyelid, ears, nose, scalp and those which HFUS was difficult to be realized were excluded. The HFUS examination informative value was low in the hairy part of the scalp due to the large number of hair follicles impeding visualization of the tumor. Inflammatory infiltrate at ulcerated BCCs makes difficult posterior tumor border identification.

We enrolled 9 women and 10 men, aged from 48 to 82 years (average 65.3 ± 7.5 years). The number of BCCs per patient varied from 1 to 6. The local research Ethics Committee approved the study. All patients were informed of the study protocol and the requirements for the study participation, and signed an informed consent prior to the study. Clinical BCC diagnosis was confirmed by cytology.

Totally, 27 pathological areas were examined with HFUS, using the specialized high-resolution digital ultrasound system DUB SkinScanner (tpm GmbH, Germany) fitted with 75 and 30 MHz probes with resolution of 21 and 48 μ , and the scan depth of 4 to 8 mm, respectively. Each BCC was scanned alternately by both ultrasound transducers. The tumor spread depth was measured. After the ultrasound examination, biopsy material was taken from BCC by means of punch biopsy or surgical excision for morphological examination. Paraffin sections of the biopsy material were stained with hematoxylin and eosin. The BCC spread depth was measured using a specialized program AxioVision Rev 4.8. According to the micromorphological examination, the tumors were divided into 2 groups: thin with invasion depth of ≤ 1 mm (13 cases) and thick with invasion depth of >1 mm (14 cases) (fig 1).

Thin BCC during the 75 MHz and 30 MHz ultrasound scanning was noted in the form of echonegative

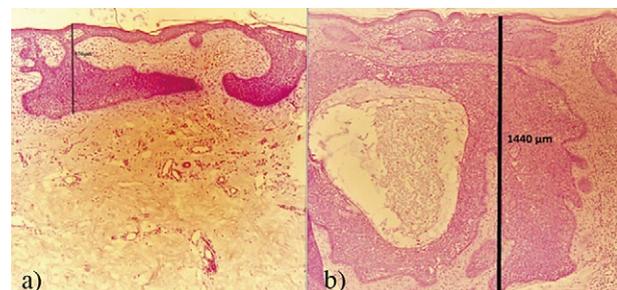


Fig 1. Basal cell carcinoma (BCC) histopathology: a) thin BCC. H&E stain, $\times 50$ original magnification; b) thick BCC. H&E stain, $\times 50$ original magnification.

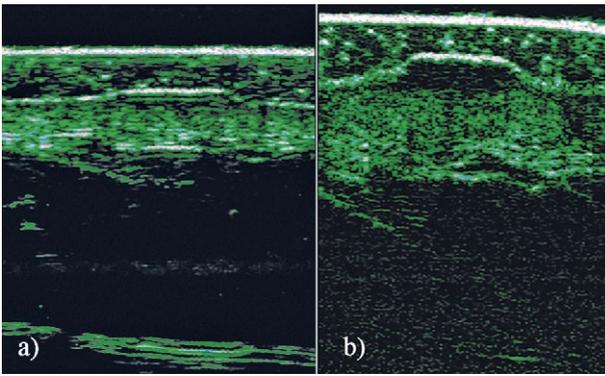


Fig 2. Thin basal cell carcinoma (BCC), high-frequency ultrasound examination using a) 75-MHz transducer and b) 30-MHz transducer.

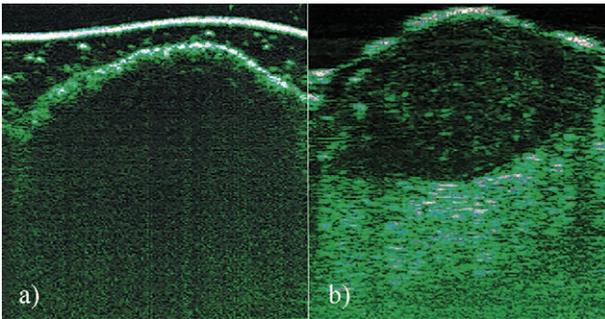


Fig 3. Thick basal cell carcinoma (BCC), high-frequency ultrasound examination using a) 75-MHz transducer and b) 30-MHz transducer.

zones located directly below the epidermis, most often of elongated shape with clear lateral contours. Echonegative zones had a clear lower boundary during 75 MHz HFUS examination, while during 30 MHz scanning, the lower boundary was not clearly visualized in many cases) (fig 2). Thick BCC at 30 MHz scans mainly was hypoechonegative with round or oval shape, rising above the unchanged skin surface and having the diffusely hypoechonegative structure with clear lateral and lower boundaries. In rare cases, the thick BCCs were visualized as the echonegative zones with irregular waveform shape and unclear boundaries infiltrating the dermis. In many cases at 75 MHz HFUS scans the lateral and lower boundaries of the thick BCCs were not identified and, as a result, it was not possible to determine the tumor spread depth (fig 3).

For the quantitative indicators computing the software developed by tpm GmbH (Germany) and ANTA-Med (Russia) was used. The structures identified by HFUS scanning and micromorphological study were measured in millimetres. HFUS examination and punch-biopsy were performed by a dermatologist with 8 years of experience in the HFUS technique and with 10 years

of experience in the punch-biopsy technique. Excisional biopsy was performed by a plastic surgeon with 12 years of surgical experience.

Statistical analysis

Data obtained were analyzed using parametric statistics techniques. The mean value and standard deviation in the compared groups were calculated. The Student's t-test was used to determine the statistical significance of differences in mean values. Statistical significance was set at a p level of less than 0.05. The Pearson's correlation coefficient was used to compute the correlation between the quantitative indicators of the tumor spread depth during the ultrasound scanning and the morphological examination, as well as its statistical significance. The strength of correlation was estimated using the Chaddock's scale (weak – less than 0.3; moderate – 0.3 to 0.5; noticeable – 0.5 to 0.7; high – 0.7 to 0.9). Study results statistical processing was carried out with the licensed software package Statistica 7.

Results

During 75 MHz HFUS, the slight increase in the average depth of the thin BCC was observed compared with the histomorphological examination, but the differences were not statistically significant ($p=0.78$). A correlation-regression analysis revealed a high statistically significant correlation ($r=0.870$) between the thin BCCs spread depth measured by 75 MHz HFUS and histometry (fig 4). The statistically insignificant ($p=0.339$) predominance of the thin BCCs average depth was observed at the comparison between the 30 MHz HFUS and morphological examination results. A weak ($r=0.290$), statistically insignificant correlation between the thin BCCs spread depth was observed between 30 MHz HFUS and micromorphometry values (Table I, fig 5).

The thick BCC measurements result at 30 MHz HFUS and histomorphometry almost coincided. The minimal predominance of the thick BCCs average depth during at 30 MHz HFUS was insignificant ($p=0.882$). Correlation-regression analysis revealed a direct, very high ($r=0.951$), statistically significant correlation between the thick BCCs spread depth measured by histomorphometry and 30 MHz HFUS (fig 6).

Discussion

A comparative study of the BCC spread depth measured with 30 MHz and 75 MHz HFUS and histomorphometry allowed us to evaluate the effectiveness of HFUS examination in determining the thin and thick BCCs invasion depth. It has been previously reported that the

Table I. Thin (≤ 1 mm) and thick (> 1 mm) basal cell carcinoma spread depth obtained by high-frequency ultrasound and histological examinations.

BCC type	N	Histometric thickness (mm)	HFUS thickness (mm)	p value	r	
Thin (≤ 1 mm)	11	0.494 \pm 0.212	75 MHz	0.591 \pm 0.265	0.78	0.870
			30 MHz	0.734 \pm 0.123	0.339	0.290
Thick (> 1 mm)	16	1.845 \pm 0.718	75 MHz	-	-	-
			30 MHz	1.995 \pm 0.699	0.882	0.951

The results are expressed as mean \pm standard deviation. BCC, basal cell carcinoma; N – number; HFUS, high-frequency ultrasound.

BCC average depth was similar during the morphological examination and the 20 MHz ultrasound scanning, the correlation being strong ($r=0.59$) [30] but also, low efficiency of 20 MHz ultrasound transducer for depth measuring of the tumors with a thickness of < 1 mm [31]. The concordance was observed for both superficial surface and nodular BCCs [20]. In our study, a high, statistically significant correlation between histological and 75 MHz HFUS data for thin BCC spread depth was observed ($r=0.870$). The correlation between thin BCCs thicknesses values obtained with micromorphometry and the 30 MHz HFUS was weak ($r=0.290$) but we found a very high ($r=0.951$), statistically significant correlation between the thick BCC spread depth assessed by histology and 30 MHz HFUS. In many cases it was difficult to visualize the thick BCC boundaries with the 75 MHz HFUS.

Kučinskiene et al, using 14-MHz ultrasound transducer, noted significant correlation between ultrasonographic and histological data during measuring the depth of invasion of thick (> 1 mm) skin tumors compared with thin tumors (≤ 1 mm) ($r=0.694$ and $r=0.336$, respectively) [28]. Contrary results were obtained by Ballester-Sánchez et al using 18-MHz ultrasound transducer [32]. The invasion depth of superficial BCC during histological examination in most cases (8/10) coincided with the same value during ultrasound scanning but no significant match was found with the nodular BCC [32]. Performing the BCC biopsy before ultrasound scanning could be the explanation of these discordances. Biopsy could lead to the removal of the deepest part of the tumor, while a scar or inflammation after the biopsy could lead to distortion of the ultrasonographic image.

Our study had some limits. The tumors with a diameter of more than 10 mm were excluded because of the probes maximal scan width 12.8 mm. In addition, HFU skin imaging has limitations in scanning depth 8 mm at 30 MHz, and 4 mm at 75 MHz. Also, we did not evaluate the intra- and interobserver agreement for HFUS examination. In **conclusion**, in BCC with a thickness of ≤ 1 mm, a high correlation of tumor spread depth measured by the histomorphological examination and

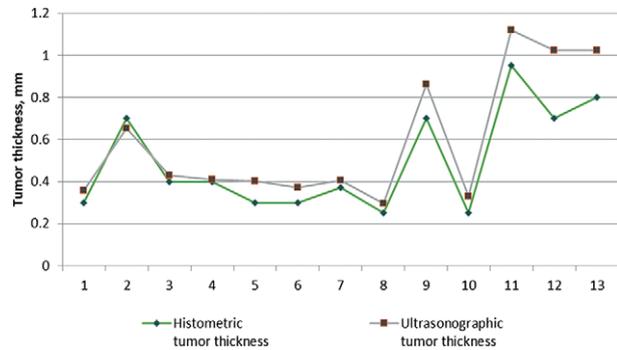


Fig 4. Thin basal cell carcinoma thickness measured with 75-MHz HFU versus histological measurements

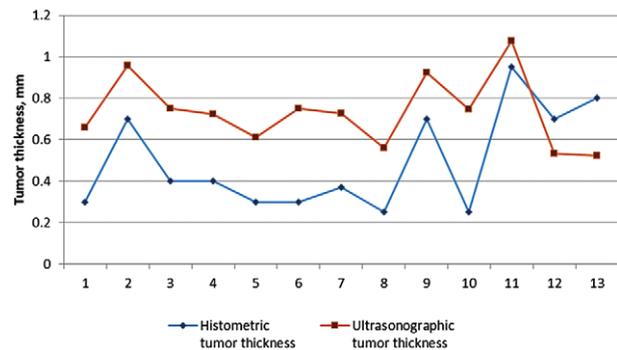


Fig 5. Thin basal cell carcinoma thickness measured with 30-MHz HFU versus histological measurements

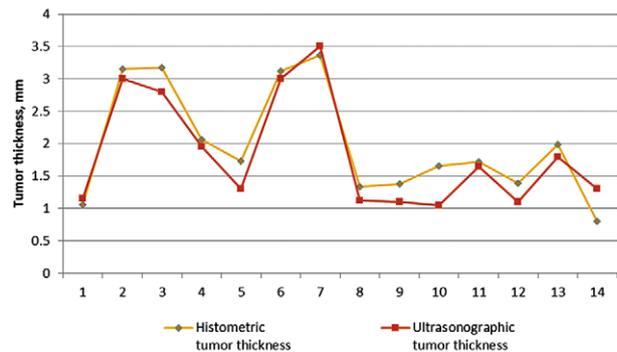


Fig 6. Thick basal cell carcinoma thickness measured with 30-MHz HFU versus histological measurements

75 MHz HFUS was observed, but for 30 MHz HFUS the correlation was weak. In BCC with a thickness of >1 mm, a very high correlation of the tumor spread depth at histomorphological, and 30 MHz HFU examinations were observed but were difficult to visualize the lower and lateral tumor margins with the 75 MHz HFUS.

Conflict of interest: none

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