

Depth determination of skin cancers treated with superficial brachytherapy: ultrasound vs. histopathology

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Abstract

Purpose: The purpose of this study is to compare high frequency ultrasonography (HFUS) and histopathologic assessment done by punch biopsy in order to determine depth of basal cell carcinoma (BCC), in both superficial and nodular BCCs prior to brachytherapy treatment.

Material and methods: This study includes 20 patients with 10 superficial and 10 nodular BCCs. First, punch biopsy was done to confirm the diagnosis and to measure tumour depth (Breslow rate). Subsequently, HFUS was done to measure tumour depth to search for correlation of these two techniques.

Results: Neither clear tendency nor significance of the punch biopsy vs. HFUS depth determination is observed. Depth value differences with both modalities resulted patient dependent and then consequence of its uncertainty. Conceptually, HFUS should determine the macroscopic lesion (gross tumour volume - GTV), while punch biopsy is able to detect the microscopic extension (clinical target volume - CTV). Uncertainties of HFUS are difficult to address, while punch biopsy is done just on a small lesion section, not necessarily the deepest one.

Conclusions: According to the results, HFUS is less accurate at very shallow depths. Nodular cases present higher depth determination differences than superficial ones. In our clinical practice, we decided to prescribe at 3 mm depth when HFUS measurements give depth lesion values smaller than this value.

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Key words: basal cell carcinoma, electronic brachytherapy, punch biopsy, skin brachytherapy, skin cancer, ultrasound.

Purpose

Basal cell carcinoma (BCC) is a common skin cancer arising from the basal layer of the epidermis and its appendages. It is particularly common in Caucasian people, increases with age and is basically related to exposure to ultraviolet radiation [1]. The incidence of BCC is increasing worldwide [1]. It is a malignant locally invasive epidermal tumour with a good prognosis due to a slow growth-rate and low metastatic potential. Local invasion and tissue destruction, however, cause patient morbidity.

There are several clinical and histopathologic types of BCC. The most common types are nodular and superficial BCC, which occur for the most part on the face [1]. Less frequent types include micronodular, morpheaform, and basoesquamous cell carcinomas. The diagnosis of BCC is

made clinically, aided by dermoscopy. A skin biopsy is usually also performed to provide histological confirmation. Once the diagnosis is established, appropriate treatment offers a high probability of cure. The patient does, however, have an increased risk of additional skin malignancies. The choice of appropriate therapy is dependent upon the characteristics of the lesion and patient-specific factors. Treatment modalities include electrodesiccation and curettage, cryotherapy, surgical excision including Mohs surgery, topical 5-fluouracil or imiquimod, photodynamic therapy, and radiotherapy [2-5].

Determining tumour extension, and defining accurate lateral and deep safety margins are very important aspects in the treatment approach for BCC. It is not possible to determine lesion depth based on clinical observations alone, because there might be an overestimation of the extension,

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which may lead to unnecessary tissue excision or radiation. This in turn could then result in aesthetic problems for the patient [6]. In addition, the rate of incomplete excision of BCCs has been reported to be 5-25% [7-14]. Although surgery is the first-line treatment for nonmelanoma skin cancers, radiotherapy can be indicated in selected cases. When radiotherapy is the treatment of choice, brachytherapy (BT) may be a good option for shallow, widespread lesions, or lesions on anatomic sites (e.g., hand, full scalp) that lie immediately above structures, which are vulnerable to irradiation [15]. High-dose-rate (HDR) BT approaches offer significant advantages in this setting due to adaptability, patient protection, and variable dose fractionation schedules, and achieve excellent cure rates and cosmetic results [16]. Several innovative applicators have been introduced to the BT community, and the use of skin BT has significantly increased over the years. The Valencia applicator [17-20] (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden) is a new superficial device that improves the dose distribution compared with that of the Leipzig applicator [21-24] (Elekta, Stockholm, Sweden and Varian Medical Systems, Palo Alto, CA, USA). Recently, electronic brachytherapy using specific applicators has also become available, as Xofig [15,25] (Xofig Inc., San Jose, CA, USA) and Esteya [26] (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden).

Brachytherapy provides minimal dose delivery to surrounding healthy tissue, thus enabling good functional and cosmetic results. Brachytherapy appears to be most effective for small, primary, and/or superficial squamous cell carcinomas and basal cell carcinomas, where it is associated with excellent cosmetic results. The primary benefit of BT compared to external beam radiation therapy is the ability of BT to deliver radiation to the target tissue, with less injury to surrounding normal-appearing skin.

Lateral and deep tumour delimitations are the main challenges when treating basal cell carcinomas with BT. Lateral delimitation may be aided by dermoscopy [27], and deep demarcation can be estimated by biopsy and/or imaging techniques. In superficial BT, the dose is prescribed to the deepest point of the target, which results in a higher dose between the source and this prescription point [20,28]. A punch biopsy provides confirmation of the tumour's histopathology as well as determining its depth. However, it is an invasive technique, which only measures the depth in a portion of the tumour which cannot be representative. Ultrasonography, on the other hand, is a non-invasive, painless, non-ionizing, low risk, and non-expensive method, which is of academic interest in diagnosing BCC [29]. In normal skin, the dermis is markedly echogenic and sharply demarcated from hypoechoic subcutaneous fat [30]. Basal cell carcinomas will appear more hypoechoic than adjacent, normal dermis due to a medium change. The use of high frequency ultrasonography (HFUS) between 10 MHz and 50 MHz has made it possible to visualize deep layers of skin, and to define very small hypo-echoic masses. Using the refraction of ultrasonography waves at the interface between the perilesional hyper-echoic area and the hypo-echoic area of the tumour itself, it is possible to precisely define the lesion [31].

High frequency ultrasonography has been shown to be potentially quite useful in BCC for both tumour measurement (for planning surgical resection) [32] and as a diagnostic technique [33, 34]. Most of the published research in this field deals with the study of tumour size, delineation of surgical margins, and comparison of ultrasound findings with histologic results obtained following subsequent excisional biopsy of the lesion [35-39]. Concordance rates between HFUS findings and histology results for tumour size are between 73-98% [34]. Published rates of tumour-free margins assessed by HFUS are as high as 95% [40], but this has never been studied prior to radiotherapy treatment.

The purpose of this study is to compare both HFUS and punch biopsy methods in determining the depth of basal cell carcinomas prior to brachytherapy. We also present the strategy adopted at our department as a result of this present study.

Material and methods

Patients

This study included 10 men and 10 women, all of them Caucasian, with 10 superficial and 10 nodular BCCs. All tumours were primary, maximum 20 mm in diameter and were located in a regular or flat area that was not adjacent to or over a burn, scar or inflammatory process. Only clinically apparent nodular and superficial BCCs were included in this study. Exclusion criteria included other BCC varieties, recurrent BCCs, and BCCs that were in locations difficult to image or treat with isotope or electronic brachytherapy applicators. All lesions were studied by histopathology and HFUS to determine tumour depth (Breslow thickness) prior to BT treatment. The mean time between the two techniques was 53 days (range 30-92 days). In the first instance, a punch biopsy was taken. This technique allowed us to confirm the diagnosis of BCC and to measure the microscopic depth of the tumour that represents the clinical target volume (CTV) depth. Subsequently, HFUS imaging was done to measure the macroscopic depth of the tumour, which represents the gross tumour volume (GTV) depth. In every case, HFUS was done at least one month after the biopsy in order to avoid peritumoral inflammation due to the biopsy scar.

To investigate whether HFUS is sufficient to determine a correct prescription depth dose, the correlation between both techniques was studied. This study was conducted under Helsinki II ethical principles after approval by the Medical Ethics Committee at our hospital.

Punch biopsy technique. Histopathology

A 3 mm diameter punch biopsy, including the whole dermis, was performed in all lesions. The deepest site estimated clinically was the site chosen for the biopsy; this is the usual method practised by dermatologists. The more nodular part usually corresponds to the deepest part of the tumour. An intralesional injection of mepivacaine was administered prior to the biopsy and a silk suture was used to close the wound. Histopathologic

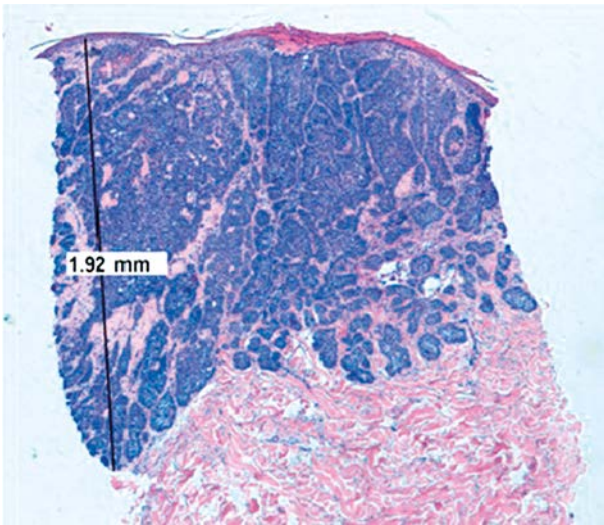


Fig. 1. Example of depth histopathologic assessment (Breslow rate) using a Leica DMD108 digital microimaging network



Fig. 2. Illustration of the probe plus gel pad use during the acquisition

assessment of depth was done with the Leica DMD108 digital microimaging network (Leica Microsystems SLU, Barcelona, Spain). Tumour thickness was measured from the granular layer to the deepest portion of the tumour, as shown in Figure 1.

High frequency ultrasound imaging

After the biopsy, a radiologist who was an expert in skin lesions, estimated the depth of the lesions. All BCCs were scanned *in vivo* using a high resolution B-scan with an 18 MHz hand-held transducer (Siemens Acuson S2000, Munich, Germany). A 2 cm × 9 cm gel pad (Aquaflex, Pallejà, Barcelona, Spain) was applied over the skin to enhance the air-skin interface (Fig. 2). High frequencies have better resolution, but lower frequencies are often used in hospital, and it has been reported in the literature that there is a good correlation between ultrasonic and histologic measurements (with complete lesion excision), even with probes emitting frequencies of 15 MHz or lower [34]. In each lesion, the depth (from the epidermal surface to the deepest hypo-echoic point of the tumour) was measured. Because the epidermis thickness is approximately 0.1 mm, when HFUS did not show any value, 0.1 mm was assigned. Examples are given in Figure 3 for both superficial and nodular lesions.

Results

The clinical and histological characteristics of the lesions of the 20 patients studied are presented in Table 1. There were 10 men and 10 women, with 10 superficial and 10 nodular BCCs. The mean age of the patients was 67 years (range 51-89 years). Fifteen lesions were located on the face and 5 on the trunk. Resulting lesion depths with HFUS and Breslow are presented in Figure 4 for both superficial and nodular lesions, respectively. In the superficial lesions, the Breslow rate was similar or higher than HFUS in most cases (8/10). In the nodular lesions, however, there was no clear trend. The largest difference between the two techniques was 2.7 mm.

Statistical analyses were performed calculating covariance and correlation matrices for the HFUS and Breslow depths. A value of $p = 0.05007 > 0.05$ was found. So, although it could be considered that some correlation exists for the scatter plot in Figure 4, it does not show any clear dependence between both variables. We also found no correlation when the different types of BCC were analysed separately.

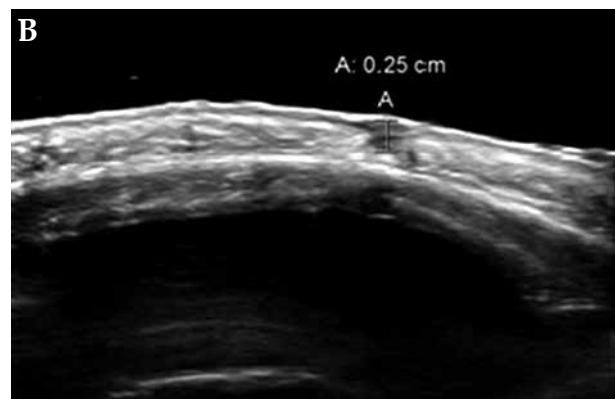


Fig. 3. High frequency ultrasonography examples of depth measurement. A) Superficial basal cell carcinoma. B) Nodular basal cell carcinoma

Table 1. Clinical and histological characteristics

Tumour	Sex	Age (years)	Histological subtype	Location	HFUS (mm)	Breslow (mm)
1	Male	65	Superficial	Preauricular	0.1	1.0
2	Female	75	Nodular	Retroauricular	1.5	1.1
3	Male	89	Nodular	Forehead	1.3	1.4
4	Male	88	Nodular	Preauricular	0.1	2.8
5	Male	63	Superficial	Trunk	0.1	0.5
6	Female	51	Nodular	Glabellar	2.7	2.3
7	Male	70	Nodular	Cheek	3.7	2.6
8	Female	80	Nodular	Nose	1.3	1.8
9	Male	70	Superficial	Trunk	0.1	0.3
10	Female	59	Superficial	Trunk	0.1	0.3
11	Male	56	Superficial	Trunk	0.1	0.3
12	Male	67	Superficial	Cheek	0.1	0.8
13	Female	57	Nodular	Forehead	2.0	3.1
14	Male	67	Nodular	Forehead	1.6	1.4
15	Female	56	Nodular	Forehead	1.6	3.2
16	Female	66	Superficial	Trunk	0.1	1.9
17	Female	57	Superficial	Cheek	0.1	0.5
18	Male	84	Nodular	Forehead	1.3	1.2
19	Female	73	Superficial	Forehead	1.1	1.3
20	Female	81	Superficial	Forehead	1.3	0.8

HFUS – high frequency ultrasonography

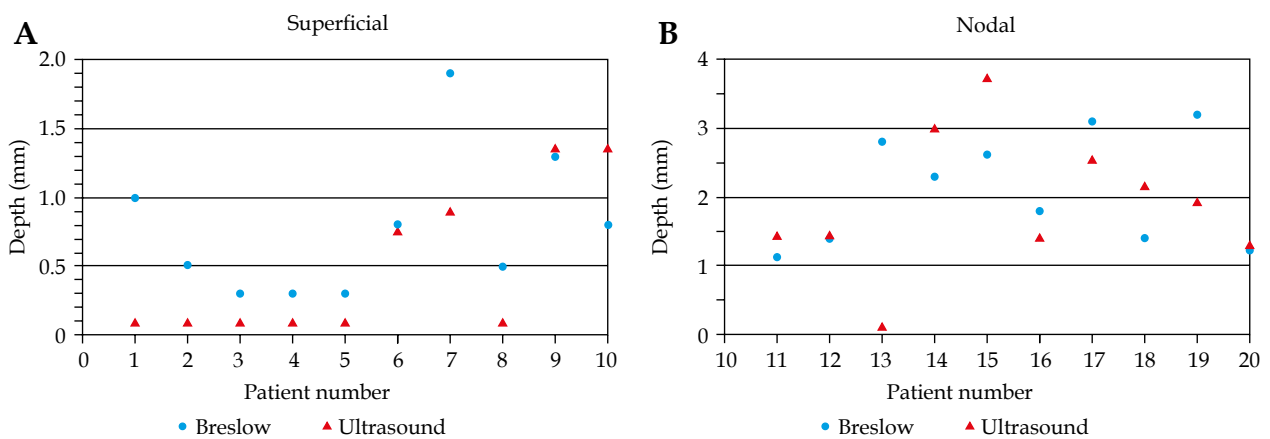


Fig. 4. A) Histopathology (Breslow rate) vs. high frequency ultrasonography (HFUS) depth determination for the 10 patients evaluated with superficial basal cell carcinoma (BCC). B) The same but with nodular BCC

Discussion

Conceptually, HFUS should determine the GTV while histopathology is able to detect the CTV. Uncertainty of HFUS depth measurements are difficult to address. Histopathologic measurements are done just on a small lesion section, which is not necessarily the deepest one. There

are some limitations in the use of HFUS in BCC. The large ultrasound probe makes access difficult in certain tumour locations, although brachytherapy is also not typically used in these locations anyway. Assessment with HFUS can also be difficult in the vicinity of scars. Small tumour aggregates are not detected by HFUS and it is also not possible to differentiate between the tumour and adjacent in-

flammation. Furthermore, HFUS is an operator-dependent technique. On the other hand, HFUS has an important advantage over punch-biopsy as it allows a three-dimensional analysis of the tumour, whereas clinical measurements only permit a two-dimensional view [40].

In this study, all US acquisitions were done by the same radiologist. In order to explore the intraobserver variability, the images were reviewed by the radiologist 3 times with a sufficient time interval in between. The resulting differences were negligible. According to the results, HFUS was less accurate at very shallow depths. The nodular cases presented with larger depth differences than the superficial ones. In most cases of superficial BCCs, the HFUS depth measurement was lower than the histopathologic one, which was in contrast to the nodular cases. Neither clear tendency nor significance was observed from this depth comparison after applying standard statistical tests to search for depth measurement correlations between the two techniques.

Limitations in our study

We used an 18 MHz ultrasound probe. High frequencies have better resolution, but lower frequencies are usually used in hospital. It has been reported in the literature that there is a good correlations between ultrasonic and histologic measurements, even with probes emitting frequencies of 15 MHz or lower [34]. In our study, punch biopsy was done prior to HFUS to confirm the diagnosis before measuring the tumour depth. This can lead to two problems: the biopsy could potentially remove the deepest part of the tumour, and both the scar and the inflammation after biopsy could distort/change the echographic image. Trying to avoid the latter problem, ultrasound was performed at least one month after the biopsy. There were a limited number of patients (20) included in this study. However, the number is sufficient to demonstrate that there is no clear correlation between these two methods.

Conclusions

High frequency ultrasonography vs. histopathologic depth determination have been compared for 10 superficial and 10 nodular basal cell carcinomas. Neither a clear trend nor a significant difference in histopathology compared to HFUS depth determination was observed. As a result of: 1) the comparison results of the present study, 2) the depth dose gradient, 3) the maximum skin dose using radionuclide applicators or electronic BT, and 4) the cosmesis experienced in clinical practice, we have decided in our protocol to prescribe to 3 mm depth when HFUS measurements give lesion depths smaller than this threshold depth.

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Disclosure

Authors report no conflict of interest.

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