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High-Definition Optical Coherence Tomography in the Diagnosis of Basal Cell Carcinoma Evaluated by an Experienced Versus Inexperienced Investigator

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Abstract

Background: Histopathology is the gold standard in the diagnosis of basal cell carcinoma (BCC) but biopsies are invasive and often not the preferred diagnostic method for patients. In this context, non-invasive diagnostic imaging tools such as high definition optical coherence tomography (HD-OCT) have shown promising results in diagnosing BCC in real time, atraumatically and repeatedly.

Objective: To evaluate the sensitivity and specificity of HD-OCT in the diagnosis of BCC by an experienced versus an inexperienced investigator and describe typical features in common differential diagnosis of BCC.

Patients and methods: Forty three patients with clinical suspicion for BCC were included. The HD-OCT images were evaluated in a blinded manner by an experienced and inexperienced investigator. The results were compared to the histopathological diagnosis.

Results: Histopathology revealed 22 BCC, 10 fibrous papules of the face, 5 actinic keratoses, 3 intradermal nevi, 2 squamous cell carcinomas and 1 sebaceous hyperplasia. The sensitivity and specificity in diagnosing BCCs correctly by HD-OCT in the experienced investigator was 86.4% and 90.5%, respectively. In the inexperienced investigator the sensitivity and the specificity was 77.3% and 81.0%, respectively. There was a good inter-observer agreement found between experienced and inexperienced investigators.

Conclusion: HD-OCT can be used as auxiliary diagnostic tool in the evaluation and treatment of BCC even by inexperienced investigators.

Keywords: Basal cell carcinoma; Optical coherence tomography; Diagnosis; Differential

Introduction

Basal cell carcinoma (BCC) is the most common skin cancer in the fair skinned population, with an increasing global incidence of 10% per year worldwide particularly in younger age groups [1-3]. Even though it rarely metastasizes, BCC causes significant morbidity due to local tissue invasion and destruction. It represents a significant economic burden and impacts severely on the quality of life as it occurs most frequently on the head and face (70%) [1,4]. Accordingly BCC become a growing public health problem [1,5]. The differentiation to benign facial lesions such as fibrous papules or sebaceous hyperplasia or other malignancies, which are also found frequently in the face, can be quite challenging. To date the gold standard for confirming the clinical and dermatoscopic diagnosis is the punch biopsy, but it is invasive and leads to scarring, which is specifically not preferable in the face. Furthermore it may be leading to false negative results in case of discontinuous growth caused of the lesion following previous treatment [6]. Since a dermatoscope usually magnifies only ten times, it may not be precise enough to distinctly define the diagnosis of BCC in some cases. Additional non-invasise diagnostic tools with a higher magnification may therefore be helpful to further secure the diagnosis before taking a biopsy.

Optical Coherence Tomography (OCT) is based on the interference of infrared radiation with living tissue and has been shown to be useful as in vivo diagnostic tool of skin lesions. It provides a real-time, cross sectional, vertical representation of living tissue [7-11]. Lately high definition OCT scanners have been developed, which offer major advantages compared to conventional OCT. The lateral and axial resolution of 3 µm exceeds the resolution of conventional OCT devices with a reported lateral resolution of 10-25 µm and an axial resolution of 5-10 µm [12,13]. It has already shown to be useful in recognizing BCC non-invasively and chacracteritic features of BCC have been described by us and others. The images are taken directly on the patient, in a traumatic and painless way. It is therefore a useful adjunctive tool for non-invasive diagnosis.

We assessed in this study, whether this diagnostic device should be reserved for the experienced dermatologist or may be useful for beginners as well. Here we show, that the method is easy to master since complete inexperienced dermatologist were able to gain valid results after a short training period.

Patients

Patients with a clinical suspicion of a BCC were included consecutively at the Department of Dermatology and Allergology, Ludwig-Maximilian University of Munich, Germany from December

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2011 to August 2012 after getting informed consent. Patients with ulcerous lesions were excluded. Forty three patients with 43 lesions including 25 (58%) males and 18 (42%) females were included; age 65.3 ± 13.0 (range 38-87) years.

Methods

The OCT images were taken using a commercially available full-field high definition HD-OCT system (Skintell®, AgfaHealthCare, Belgium), which has been described in detail before [12,13]. The HD-OCT system provides two real-time imaging modes, a cross-sectional (slice-) mode and a horizontal (en-face) imaging mode with a visual field of 1.5×1.8 mm. According to the manufacturer´s information the lateral and axial resolution is 3 µm and the penetration depth is about 570 µm. A minimum of two HD-OCT images were taken in a central position of the lesion. After the imaging a biopsy, excision or shave biopsy was performed for the histological diagnosis. The histopathological results were evaluated by an expert dermatopathologist and were regarded as gold standard.

The HD-OCT images were evaluated blinded to the investigators by an experienced (T.M.) and unexperienced investigator (G.L.), respectively. The latter investigator was a dermatologist who was unfamiliar with OCT technology and received a 30 minutes training of HD-OCT criteria in the diagnosis of BCC. The diagnostic results of the inexperienced dermatologist, the OCT expert and the histopathology were compared to each other. The HD-OCT diagnosis of BCC was defined using criteria described previously [12,13].

Statistical analysis

The histopathological results of the investigated lesions were regarded as gold standard. The sensitivity, the specificity, the positive predictive value, the negative predictive value, the correct rate and the Youden index of the two investigators were calculated respectively. Inter-rater agreement was calculated with kappa value which interpreted as $\kappa \leq 0.20$ was poor, $0.20<\kappa \leq 0.40$ was fair, $0.40<\kappa \leq 0.60$ was moderate, $0.60<\kappa \leq 0.80$ was good, $0.80<\kappa \leq 1.00$ was excellent.

Results

The histopathology results revealed 22 BCCs including 14 cicatricial BCCs, 4 superficial BCCs and 4 nodular BCCs, and 21 non-BCC lesions including 10 fibrous papules of the face, 5 actinic keratosis (AK), 3 intradermal nevi, 2 squamous cell carcinomas (SCCs) and 1 sebaceous hyperplasia.

The sensitivity of HD-OCT in the diagnosis of BCC by the experienced investigator was 86.4%, the specificity 90.5%. The technique showed a positive predictive value of 90.5% and a negative predictive value of 86.4%, the correct rate was 88.4% and the Youden index was 76.9% (Table 1).

The inexperienced investigator showed a sensitivity of 77.3%, a specificity of 81.0%, a positive predictive value of 81.0% and a negative predictive value of 77.3% in recognizing correctly a BCC. The correct rate was 79.1% and the Youden index was 58.3% (Table 2). Comparing the results of the experienced and inexperienced investigator in the diagnosis of BCC by HD-OCT the inter-observer agreement showed a Kappa value of 0.72. Regarding the non-BCC lesions one main BCC feature namely the dark peripheral rim surrounding the dark-grey tumor nodules could not be found in the investigated fibrous papules, AKs, nevi, SCCs and sebaceous hyperplasia (SH) (Figure 1) (Table 3). SH displayed with nodular features similar to BCC but with brighter granular structures consistent with the sebaceous gland globules (Figure 2). Fibrous papules of the face displayed with a broadening of the skin but without changes in structure in the slice mode, in the en-face mode just a higher frequence of close standing follicular openings could be detected not comparable with the BCC globules (Figure 3). The AKs and SCC displayed with typical features as described earlier [9]. Out of the 19/21 non-BCC lesions which were correctly identified by the experienced investigator by HD-OCT, 15/19 could be categorized correctly. Two SCC were diagnosed as non-BCC lesions but no further classification could be performed and 2 histologically

Experienced investigator	Histopathology Results		
	BCC	No BCC	Total
BCC	19	2	21
No BCC	3	19	22
Total	22	21	43

Table 1: Comparison between the results of the experienced investigator and the histopathology.

Inexperienced investigator	Histopathology Results		
	BCC	No BCC	Total
BCC	17	4	21
No BCC	5	17	22
Total	22	21	43

Table 2: Comparison of the results of the inexperienced investigator and the histopathology results.

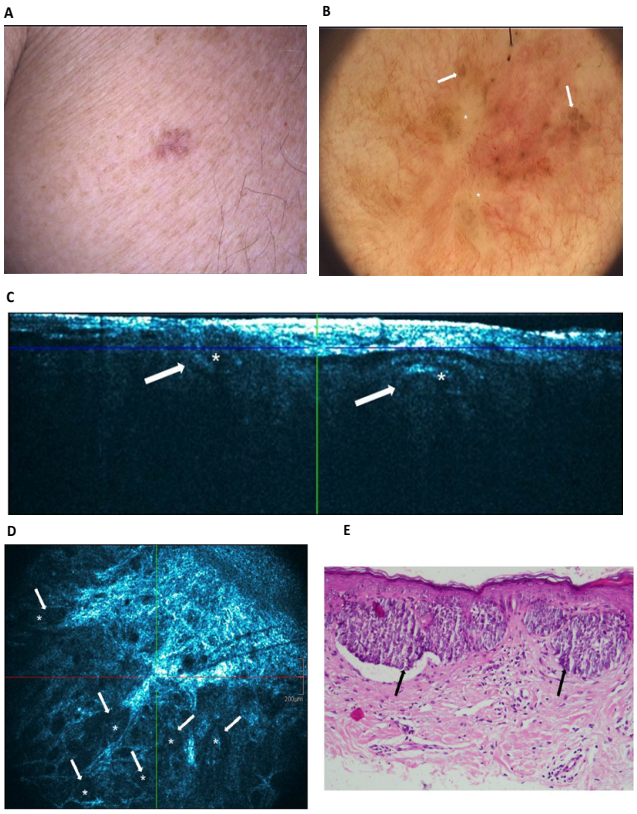

Figure 1: BCC on the chest (a) with whitish areas (asterisks), grey-brown ovoid structures (arrows) and teleangiectasia in dermatoscopy (b) and characteristic dark nodules (asterisks) with a darker rim (arrows) and surrounding bright peritumoralstroma in HD-OCT in the slice (c) and en-face mode (d) and the corresponding histopathology with basophilic BCC-nests showing palisading of the nuclei and clefting (arrows) (e, hematoxyline-eosin staining, x 20).

HD-OCT criteria	BCC	SCC	nevus	AK	Fibrous Papule	Sebacecous hyperplasia
Pleomorphism of the epidermis	(+)	+	-	+	-	-
Grey/dark lobular structure	+	-	(+)	-	-	+ (granular)
Peritumoural bright streaks	+	-	-	-	(+)	-
Dark peripheral rimming	+	-	-	-	-	-
Increased vasculature	+	+	-	+	-	(+)
Presence of elongated monomorphic basaloid nuclei	+	-	-	-	-	-
Destruction of layering	+	+	+	+	-	-

Table 3: HD-OCT criteria in BCC (n=22) and lesions of the differential diagnosis (n=10 fibrous papules, 5 AK, 3 nevi, 2 SCC, 1sebaceous hyperplasia).

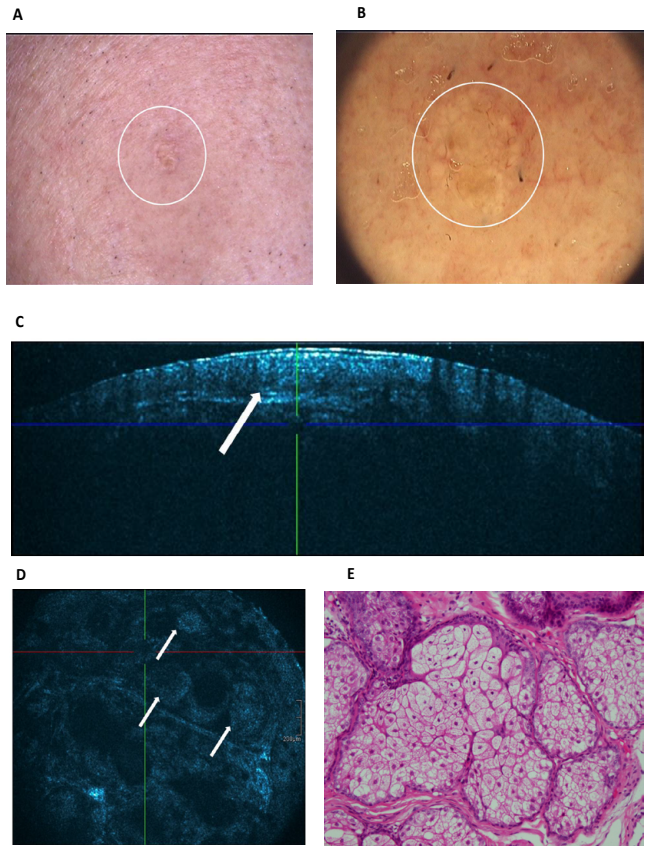

Figure 2: Sebaceous hyperplasia on the cheek (a, circle) with a circular white-yellow formation(circle) in dermatoscopy (b) and bright broadening of the epidermis(slice mode (c), arrows) and aggregated nodules with a tiny granular pattern in HD-OCT en-face mode (d, arrows) Histopathology presents foamy sebaceous glands (e, hematoxyline-eosin staining, x 40).

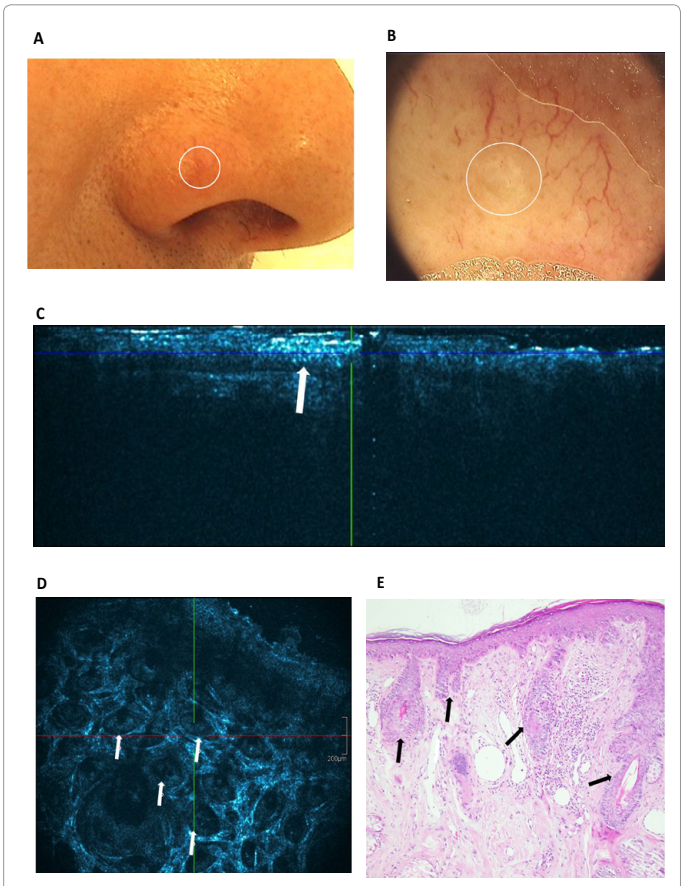

Figure 3: Fibrous papule of the face (a) with whitish nodule with follicular openingsindermatoscopy (b, circle) and broadening of the skin (arrow) in the HD-OCT slice mode (c) and cumulative follicular openings (arrows) in HD-OCT en-face mode (d), histopathologically follicles (arrows) and interstitiell fibrosis is present(e, hematoxyline-eosin staining, x 20).

dermal nevi were evaluated as fibrous papules via HD-OCT by the expert. The inexperienced investigator did only classify the lesions as BCC or non-BCC, a further classification was not performed here.

Discussion

Between the non-invasive imaging tools in dermatology the very established dermatoscopy represents a very high impact on the clinical diagnosis to differentiate benign from malignant skin lesions [14]. Nevertheless the positive predictive value differs among dermatologists between 68 to 89% probably depending on the level of experience [15-17]. Another very sensitive device in the diagnosis of BCC is the reflectance confocal microscopy [14] which demands also a certain grade of experience to reach a high level of accuracy.

Since BCC features in HD-OCT have been described already by different groups, we investigated whether it is possible after a straight forward 30 minute training of an inexperienced dermatologist to diagnose BCC. Using HD-OCT by an inexperienced investigator the positive predictive value recognizing correctly a BCC was 81.0% and the negative predictive value was 77.3%. The sensitivity of HD-OCT in the diagnosis of BCC by the experienced investigator was 86.4% the specificity 90.5% and the positive predictive value was 90.5%.

The accuracy of the clinical diagnostic is of upmost importance to ensure adequate treatment. Excision of skin lesions represent a significant cost to the health system, in the U.S. non melanoma skin cancer excision cost about 426$ million per year, therefore avoiding unnecessary operations are favourable for the patients and the health system [18]. Nevertheless patients given a benign diagnosis are unlikely to remove the lesion; therefore it is essential to be highly secure on the

diagnosis, since misdiagnosis may lead to treatment delay and poorer prognosis [1].

Since the inexperienced investigator received only half an hour of training, HD-OCT may be very helpful specifically for the inexperienced clinicians to correctly decide on BCC versus non-BCC lesions as the primary diagnosis also in adjunction to dermatoscopy. Additionally, we found as a characteristic feature for BCC in HD-OCT the dark peripheral rim surrounding the grey BCC nodules which was not present in the lesions of the differential diagnosis especially in fibrous papules and sebaceous hyperplasia. The experienced investigator was able to further differentiate non-BCC lesions and evaluated them correctly.

Recently, the differentiation of BCC subtypes using HD-OCT has been performed successfully, but this was no primary objective to our study and was not performed due to limited numbers of lesions [19,20].

HD-OCT may also be valuable in assessing treatment success either after non-surgical topical treatments such as PDT, fluouracile or imiquimod since it is often difficult to decide using the dermatoscope only whether the BCC is completely healed or rests of the former BCC are still existent.

Another aspect of which HD OCT may become specifically useful in future is to evaluate the treatment success of perorally administered hedgehog-inhibitors such as vismodegib. Vismodegib is currently approved for the treatment of adult patients with symptomatic metastatic BCC, or locally advanced BCC inappropriate for surgery or radiotherapy and it is currently tested for patients with multiple BCCs [21]. After this treatment with hedgehog inhibitors there are regularly remaining scars, which may resemble remnants of BCC. But since the residual areas are often too large or there are multiple lesions it is often not feasible to perform punch biopsies to confirm the diagnosis. In a pilot study we recently found non-invasive imaging techniques useful to monitor and evaluate treatment success of hedgehog inhibitors in BCC [22].

We assume the high-definition OCT may contribute as a useful diagnostic tool for primary skin lesion and to access treatment success for the experienced but also for the inexperienced clinicians.

Conflicts of Interest

T. Maier served as lecturer/consultant for AGFA Healthcare GmbH.

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