Differentiation of Different Nonmelanoma Skin Cancer Types Using OCT

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Keywords
Actinic keratosis · Basal cell carcinoma · Basalioma · Superficial basal cell carcinoma · Morbus Bowen · Squamous cell carcinoma · Optical coherence tomography

Abstract

Background: Early detection of various types of nonmelanoma skin cancer has been a challenge in dermatology. Noninvasive examination procedures such as optical coherence tomography (OCT) play an increasingly important role, besides the established gold standard of histological tissue sample analysis. OCT is a noninvasive, cross-sectional, real-time technique that allows conclusions to be drawn with regard to the presence of pathologies. Objective: The objective of this study was to investigate whether it is possible to distinguish between different types of nonmelanoma skin cancer using OCT or not. Methods: A study population of a total of 25 cases, comprising 5 cases, each, of 5 tumor entities (i.e., basal cell carcinoma, superficial basal cell carcinoma, actinic keratosis, squamous cell carcinoma, and Bowen disease) was examined. Relevant lesions were scanned both centrally and peripherally in the multislice mode. All OCT images were blinded, randomized, analyzed, and evaluated by 2 clinicians experienced in OCT. Results: This study demonstrated that it is possible to determine correlations between various types of tumors and recurring tumor characteristics. Conclusion: This study showed that it is possible to distinguish between the different nonmelanoma skin cancers by using OCT, but further prospective studies have to be conducted to validate the sensitivity and specificity of the criteria.

Introduction

A rapid increase in nonmelanoma skin cancer (NMSC) types has been observed in recent decades, especially affecting individuals in the age group 60 years and over. Moreover, studies have shown that this trend is more common in men than in women. Time-consuming and cost-intensive sampling and histopathological processing and dyeing of the samples is the gold standard in diagnosis of the various NMSC types to date. However, recently, noninvasive optical diagnostic methods have increasingly gained importance and show an increasing potential to complement the hitherto prevailing gold standard. For instance, procedures such as dermatoscopy, high-frequency ultrasound examination, and confocal microsco-
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Moreover, application OCT was first practically described by Huang et al. in 1991. Since then, it has undergone a continuous process of improvement and advancement along with an extended field of application.

Thus, OCT has become a firmly established examination tool in the special fields of dermatology and ophthalmology [6–8], and it has generally been tested and used in all medical fields. For instance, OCT is already used in gastroenterology to detect malignant lesions in the gastrointestinal tract as well as possible responses to the resulting cancer therapy [9–11]. Moreover, application possibilities of OCT regarding breast cancer have been investigated in gynecology [12, 13]. The application of OCT in the field of neurology is also highly interesting. In neurology, OCT can be used to observe the effects of intracranial hypertension and allows detection of the activity of demyelinating diseases even before neurological symptoms become apparent [14, 15].

Dermatology is another special field where OCT and its application have been under investigation for a long time. OCT itself and the requirements of OCT have continuously changed from the first examinations of human skin in 1997 to studies dealing with more complex topics such as the applicability of OCT in wound healing or the definition of surgical resection limits [4, 16, 17]. However, the greatest and most sophisticated challenge is to investigate the applicability of OCT in NMSC diagnosis. Several studies have already been dedicated to the topic of creating standard detection criteria for the different NMSC types [2, 18–23]. Such standard criteria have successfully been defined for actinic keratosis (AK) as well as basal cell carcinoma (BCC), but they have turned out to be rather difficult to determine for the other tumor entities. In this study, we aimed to show correlations between detection criteria and the different NMSC types by means of OCT.

Materials and Methods

Participants

A total of 35 patients (16 males and 19 females) with a large variety of nonmelanoma tumor entities and lesions were examined using OCT in the period between June 2012 and February 2013, and the results of those examinations were acquired for our study. All of the participants were informed in detail about their inclusion into this study and the general conditions of this study prior to the examination and gave their written consent. This study was approved by the ethics committee of the Charité – Universitätsmedizin Berlin (EA1/061/09). All scientific research and examinations were performed in compliance with the principles of the Declaration of Helsinki. At the time of the measurements, all participating patients had already been scheduled for verification by biopsy or surgical excision of their lesion. All examinations, measurements, and histopathological evaluations were performed at the Department of Dermatology, Venerology and Allergology of the Charité – Universitätsmedizin Berlin.

After the initial evaluation of the histopathological results and quality assessment of the OCT-specific images, the patient population of this study was reduced by 10 cases because images did not fulfill the quality criteria or histological results of the sample biopsies did not correspond to the tumor entities included in this study. Hence, 25 patients (15 males and 10 females) with a mean age of 69 years (range 32–88) were finally included and evaluated in this study. All examined lesions of the participants in this study were scanned both centrally and peripherally in the OCT multislice mode. Unaffected skin on the contralateral side was also scanned for reference.

OCT Device

OCT is a noninvasive, cross-sectional, real-time technique based on Michelson interferometry that is used to examine all kinds of benign and malignant skin diseases [18]. The lateral optical resolution is approximately 7.5 µm and the axial resolution is approximately <10 µm. The scan covers an area of 6 × 6 mm² at a maximum depth of 2 mm. Moreover, the examiner can choose between various acquisition modes such as, for example, the free run mode and the multislice mode. In the free run mode, the scan is only performed along the x axis, thus allowing free movability of the scan head. This is of special advantage if several regions are searched for potential lesions. By contrast, in the multislice mode, an entire series of images is acquired. Each area covered with this mode measures 6 × 6 mm² and represents 1 image. The individual images are scanned at increments of 0.1 mm along the y axis [4]. This mode is primarily selected to visualize the transition between tumor-free skin and tumor. All examinations were performed with the OCT scanner type Vivosight of Michelson Diagnostics (Kent, UK). All measurements regarding the various tumor entities were exclusively performed in the multislice mode.

Imaging Procedure

The actual examination was performed by means of a multibeam OCT scanner after the participants had given their written informed consent. The affected skin regions were not specifically prepared for the measurements. Very hairy areas (e.g., the back part of the head, the arms, and the abdomen) were shaved to prevent potential interference and achieve an undisturbed deep penetration. The patients were asked to lie down flat on their back on the examination table throughout the procedure. The examination was performed using standard OCT settings. Thus, a high quality of measurements was achieved and a high reproducibility was ensured. Each patient underwent 3 measurements in the multislice mode, each consisting of a series of 60 consecutive individual frames. The first measurement was always performed peripherally at the transition from unaffected skin towards the lesion. Then, the center of the lesion was scanned to cover the different characteristics within the lesion. Finally, a ref-

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ference scan of healthy skin on the contralateral side of the body was performed. This reference scan allowed differentiation between the characteristics of healthy and tumorous skin because healthy skin is exposed to all kinds of noxae over the years such as light and chemical substances as well as plain skin aging and, therefore, may also show pathologies. After the examination, all of the participants received their specific, previously planned therapy.

Statistics
Microsoft Office Excel 2007 was used to compile the data for the statistical analysis. The statistical data analysis was performed by means of SPSS 22 (SPSS Inc., Chicago, IL, USA). The normality of the age-specific distribution of the patient population was verified and confirmed beforehand with the Kolmogorov-Smirnov test. The actual statistical analysis of the 5 individual tumor criteria in relation to the 5 relevant tumor entities was performed by means of the $\chi^2$ test. The absolute presence of various criteria in the individual tumor entities was determined based on purely descriptive analysis. After the statistical analysis, all results with a positive or negative Pearson $\phi$ coefficient and a $p$ value $<0.05$ were rated as significant. Moreover, trends were determined within the range $0.005 < p \leq 0.1$.

Development of Detection Criteria
In view of the fact that the incidence of NMSC types has continuously increased in the past decades, several studies have already been performed to investigate the applicability of OCT and early detection of these diseases by means of OCT and create standard detection criteria [1, 2, 18–22, 24, 25]. In the so-called "Berlin Score," for instance, the focus was primarily placed on recurring OCT characteristics of BCC and their subtypes to investigate a possible correlation and its practical application to, and usefulness in, clinical routine [18]. In this study, similar characteristics were used as in previous studies [18] with regard to 5 different tumor entities, i.e., BCC, sBCC, AK, Bowen disease, and squamous cell carcinoma (SCC), to investigate any existing correlations. All characteristics were established based on clinical OCT experience and in close cooperation with dermatologists, students, and histopathologists. Other criteria such as parakeratosis, acanthosis, and occurrence of hyporeflective nests were analyzed besides the criteria established in the Berlin Score (e.g., noncompressible dark borders, ovoid structures, and hyporeflective nests) [18]. Similar to the Berlin Score all subtypes of BCC were included (e.g., nodular, micronodular, cystic BCC, etc.). A total of 25 cases corresponding to 5 cases

Fig. 1. Patient with medically normal skin. Different sections display the layers of normal skin (i.e., 1.1, epidermis; 1.2, dermis; and 1.3, subcutis). The arrows indicate hair follicles.

Fig. 2. Patient with histologically verified squamous cell carcinoma and well-defined continuous parakeratosis. The arrows indicate thickened/infiltrated skin layers.
per tumor entity were blinded, randomized, and passed on to a
team of 2 analysts experienced in OCT (a dermatologist and a hu-
man medicine student) for evaluation. A purely descriptive analy-
sis dealt only with the presence or absence of predefined criteria,
where the score 0 was assigned to absence and 1 to presence. After
the evaluation was completed, all OCT images were assigned to the
relevant patient data and histologies (Fig. 1–8; Table 1).

Results

The results were evaluated based on a population of
25 patients (15 males and 10 females). The ensuing Kol-
mogorov-Smirnov test showed normality of the age-spe-
cific distribution. The mean patient age was 69 years. The
Χ² test performed in relation to the gender-specific occur-
rence of tumor characteristics in the individual entities
did not reveal any significant difference between the sexes.
The followings results were obtained for the individual
characteristics in relation to the different tumor entities.

The occurrence of the specific characteristic paraker-
atinosis was negatively associated with the tumor entity BCC
(ϕ = –0.579, p = 0.004).

BCC was also negatively associated with the character-
istic generalized acanthosis (ϕ = –0.750, p < 0.001).

The results obtained for focal acanthosis with the tu-
mor entity sBCC were different; a significantly positive
association was found (ϕ = 0.500, p = 0.012).

The characteristic multifocal acanthosis showed a sig-
nificantly positive correlation with SCC (ϕ = 0.408, p = 0.041) and Bowen disease (ϕ = 0.408, p = 0.041). By con-
trast, a negative significance was found regarding BCC
(ϕ = –0.612, p = 0.002) and sBCC (ϕ = –0.408, p = 0.04).

Trends related to the characteristics were also shown
with the Χ² test. For instance, a negative trend was found

Fig. 3. Patient with histologically verified Bowen disease and a thickened spinous layer (marked by the arrows).

Fig. 4. Patient with histologically verified basal cell carcinoma and visible ovoid structures (+) and hyporeflective
nests (Δ).
Fig. 5. Another patient with histologically verified basal cell carcinoma and a noncompressible dark border beneath the tumor (indicated by the arrows).

Fig. 6. Patient with histologically verified squamous cell carcinoma and distinct hyperreflective nests (indicated by the arrows).

Fig. 7. Patient with histological verified superficial basal cell carcinoma. The arrows indicate tumor starting from the epidermis with minor hyperkeratosis.
for the criterion hyporeflective nests in relation to the tumor entities Bowen disease ($\phi = -0.343, p = 0.086$) and AK ($\phi = -0.343, p = 0.086$). By contrast, the presence of ovoid, hyporeflective nests was significantly positively correlated with the tumor entity BCC ($\phi = 0.729, p < 0.001$) and showed negative trends regarding the other 3 tumor entities, i.e., SCC ($\phi = -0.375, p = 0.061$), Bowen disease ($\phi = -0.375, p = 0.061$), and AK ($\phi = 0.375, p = 0.061$; Table 2).

The criterion hyperreflective nests showed a significantly positive association with SCC ($\phi = 0.590, p = 0.003$). Noncompressible dark border, the last recurring criterion analyzed, was significantly positively correlated with sBCC ($\phi = 0.458, p = 0.022$) and BCC ($\phi = 0.667, p = 0.001$) and showed negative trends regarding the other 3 tumor entities, i.e., SCC ($\phi = -0.375, p = 0.061$), Bowen disease ($\phi = -0.375, p = 0.061$), and AK ($\phi = 0.375, p = 0.061$; Table 2).

**Discussion**

OCT allows unambiguous differentiation between benign and malignant skin lesions already at an early stage. However, distinguishing between individual tumor enti-
ties is still problematic [18, 24, 26, 27]. In this purely descriptive study, it was shown that almost all tumor entities have recurring characteristics that might allow differentiation by means of OCT in the future. Correlation and discrimination of the individual tumor entities based on signal intensity and layer thickness as described in former studies were not included in this study [28].

The so-called trends are also a factor that should not be neglected. They might play a significant role in larger study populations with greater numbers of cases and also possibly contribute to improved differentiation between the individual types of tumors.

However, there are also disadvantages with regard to OCT and its evaluability in this study. For instance, the applicability of OCT is limited to body regions where an adequate contact area between the scan unit and the skin surface is ensured. This makes OCT more difficult to use on acra or bony structures of the body. Moreover, the examiner’s experience in handling OCT and his/her analytical skills influence the achieved image quality and the results of the evaluation of the obtained image material and present a source of error that should not be underestimated. It is mandatory in the evaluation of OCT images to include healthy skin of the contralateral side for reference because even healthy skin is exposed to natural aging, noxae, and the sun, thus causing pathologies and leading to misinterpretation.

Time-consuming and cost-intensive sampling, histopathological processing, and evaluation of the samples is still the gold standard for the early detection of the various NMSC types to date. To date, it is not yet possible to use OCT as the only tool in early detection of NMSC types because of technical limitations. However, like other non-invasive real-time techniques, OCT promises the possibility of a fast, easy, cost-effective, and painless means to replace the existing standard in the future. This assumption is especially encouraged by the latest developments such as HD-OCT (high-definition OCT) and SV-OCT (speckle-variance OCT) as well as D-OCT (dynamical OCT) [29–34]. D-OCT, a naval angiographic variant of OCT, for example, may aid in distinguishing between the different tumor entities because of its particular vascular morphology. This was already demonstrated using the example of AK, Bowen disease, and SCC [34]. In the context of further studies, the already established differentiation criteria could be complemented.

### Acknowledgement

The authors would like to thank all of the participants of this work, especially Michelson Diagnostics, for driving the results of this work with their assistance and critical comments. The authors would specifically like to thank Dr. Roland Sauer who always helped with words and deeds.

### Statement of Ethics

The study was approved by the Ethic Commission of the Charité-Universitätsmedizin Berlin (EA1/061/09). All patients provided written informed consent. The study was conducted according to the guidelines of Good Clinical Practice.

### Disclosure Statement

The authors have no conflict of interests to declare.

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Table 2. Overview of the significant results of the criteria with reference to the different tumor entities

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<th>Parakeratosis</th>
<th>Acanthosis multifocal</th>
<th>Acanthosis focal</th>
<th>Hyporeflective nests</th>
<th>Hyperreflective nests</th>
<th>Noncompressible dark border</th>
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AK, actinic keratosis; BCC, basal cell carcinoma; sBCC, superficial basal cell carcinoma; SCC, squamous cell carcinoma; +, positive significance; –, negative significance; (–), negative trend; (+), positive trend.
References