Morphology of basal cell carcinoma in high definition optical coherence tomography: en-face and slice imaging mode, and comparison with histology

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Abstract

Background Optical coherence tomography (OCT) allows real-time, in vivo examination of basal cell carcinoma (BCC). A new high definition OCT with high lateral and axial resolution in a horizontal (en-face) and vertical (slice) imaging mode offers additional information in the diagnosis of BCC and may potentially replace invasive diagnostic biopsies.

Objectives To define the characteristic morphologic features of BCC by using high definition optical coherence tomography (HD-OCT) compared to conventional histology.

Methods A total of 22 BCCs were examined preoperatively by HD-OCT in the en-face and slice imaging mode and characteristic features were evaluated in comparison to the histopathological findings.

Results The following features were found in the en-face mode of HD-OCT: lobulated nodules (20/22), peripheral rimming (17/22), epidermal disarray (21/22), dilated vessels (11/22) and variably refractile stroma (19/22). In the slice imaging mode the following characteristics were found: grey/dark oval structures (18/22), peripheral rimming (13/22), destruction of layering (22/22), dilated vessels (7/22) and peritumoural bright stroma (11/22). In the en-face mode the lobulated structure of the BCC was more distinct than in the slice mode compared to histology.

Conclusion HD-OCT with a horizontal and vertical imaging mode offers additional information in the diagnosis of BCC compared to conventional OCT imaging and enhances the feasibility of non-invasive diagnostics of BCC.

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Conflict of interests

The authors declare that they have no conflicts of interest.

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non-invasive in vivo diagnostics of skin and has proved to be a valuable tool in the diagnosis of skin tumours such as BCC.9–11 Although RCM has a higher resolution than OCT, the main advantage of OCT is the fast and easy examination procedure which is feasible in daily practice. Additionally, OCT has a higher penetration depth of about 2 mm compared to RCM with a penetration depth of approximately 250 μm. The conventional OCT imaging is characterized by vertical (slice) images of the investigated tissue. With this technique BCCs present as more or less defined grey or dark ovoid structures.5,12,13 Recently, a new high definition (HD-) OCT device has been developed, which in addition to the vertical OCT imaging mode offers a real-time, horizontal, so-called en-face imaging mode, which allows the immediate visualization of OCT pictures with high resolution in both dimensions.

The purpose of this study was to characterize OCT features in the en-face imaging mode in addition to the conventional vertical imaging mode in the preoperative in vivo diagnostics of BCC and to compare it with the histopathological analysis of the tumours.

Subjects and methods

Participants

We investigated 22 skin tumours clinically suspicious of BCC which were seen at the Department of Dermatology, Ludwig-Maximilian University of Munich between September and December 2011. From all patients written informed consent was obtained. The study population consisted of 14 male patients with one or more tumours and an age range of 51–82 years (Table 1). After obtaining OCT images of the tumours, surgical excision was performed followed by histopathological examination. The study had been approved by the local ethics committee and followed the principles expressed in the declaration of Helsinki.

High definition optical coherence tomography (HD-OCT)

OCT was performed using a commercially available full field high definition (HD-) OCT system (Skintell®, AgfaHealthCare, Belgium). It is based on the principle of a ‘time domain’ OCT system including dynamic focus tracking. A halogen lamp with a Gaussian filter and an ultra-high bandwidth centred at 1300 nm (infrared light) serves as the light source and results in a high depth resolution and no lateral cross talk (speckling). In the Skintell® system an ultra high speed infrared camera instead of a point detector is used which allows a high scanning speed especially in the 3D mode. According to the producer’s instruction, Skintell® allows a resolution of 3 μm in all three dimensions (Table 2). The penetration depth in skin is about 750 μm.

The HD-OCT uses dynamic focus tracking (Fig. 1), which is a synchronized motion of the imaging lens system and the reference optical system. This guarantees that the position of the coherence gate and the position of the focal plane are at the same depth location thus a sharp image is generated at all depths. Skintell® can work in two different modes (Fig. 2): real time b-scan and en-face and additionally allows fast capture of a 3D tomogram. The OCT probe is applied directly onto the skin with an optical gel (SkinTell® optical gel, AgfaHealthCare) as coupling medium. The field of view in the en-face mode is 1.8 × 1.5 mm.

The clinically suspicious lesions were systematically evaluated by HD-OCT in the slice and en-face mode and images were recorded. The lesions were examined by an experienced investigator (TM) prior to excision and characteristic features were documented.

Histological evaluation

All 14 patients underwent a total excision or shave excision of the suspicious lesions and tissue sections were prepared as usual for conventional histology. As a result of the large diameter of the HD-OCT probe, there was no specific identification mark within the lesion possible. The probe was placed whenever possible in the centre of the lesion to allow a rough co-localization with the histological section. The histological evaluation was performed by a board-certified dermatopathologist (MBF).

Results

High definition optical coherence tomography (HD-OCT)

The evaluation of the documented images of the lesions revealed certain features which presented repeatedly in the examined tumours (see Figs 3–5). In the classical vertical OCT imaging mode the tumour nodules presented as grey/dark ovoid structures with a darker surrounding rim. With this technique BCCs present as more or less defined grey or dark ovoid structures.5,12,13 Recently, a new high definition (HD-) OCT device has been developed, which in addition to the vertical OCT imaging mode offers a real-time, horizontal, so-called en-face imaging mode, which allows the immediate visualization of OCT pictures with high resolution in both dimensions.

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Results

High definition optical coherence tomography (HD-OCT)

The evaluation of the documented images of the lesions revealed certain features which presented repeatedly in the examined tumours (see Figs 3–5). In the classical vertical OCT imaging mode the tumour nodules presented as grey/dark ovoid areas and the typical layering of the epidermis and dermis was disarranged as it has been described elsewhere.13 In the HD-OCT images we noted a dark rim surrounding frequently the grey tumour nodules which we called ‘peripheral rimming’ and which has not been described explicitly in the literature of conventional OCT before. This feature was found not only in the slice mode, but also in the en-face mode. In the en-face mode of HD-OCT the basaloid tumour nodules presented as lobulated round to oval grey/dark structures with a darker surrounding rim.

In addition, we looked for dilated vessels presenting as dark round to oval structures corresponding to the clinically and by dermoscopy commonly visible telangiectasia and arborizing vessels in BCC.

Another feature were peritumoural bright streaks interpreted as stroma, which has been described in previous studies of conventional OCT.13 In the en-face mode of HD-OCT architectural disarray of the epidermis, which could not be observed in the vertical mode, as well as a variably refractile stroma could be detected and was defined as the destruction of the regular honeycomb pattern as described in RCM analysis of normal stratum spinosum.14 The honeycomb pattern is formed by the polygonal keratinocytes of the stratum spinosum with a dark central area corresponding to the nucleus surrounded by a rim of bright cytoplasm.

Taken together, the following characteristics of BCC in the classical vertical (slice) mode of HD-OCT were defined: grey/dark
There were no significant differences between the various BCC subtypes concerning the investigated features, but tumour nodules were more pronounced in the nodular BCCs than in the infiltrative BCCs.

When comparing both modes with each other, the typical nests of basaloïd tumour cells were more distinct and easier to detect in the en-face than in the slice mode. The structure of the typical tumour nests with aggregated lobules and buds separated by bright streaks and bundles consistent with peritumoural stroma as displayed by histopathology could be visualized more clearly in the en-face mode of HD-OCT.

**Table 1** Clinical and histopathological characteristics of the 22 basal cell carcinomas

| Tumour | Age (years)/sex | Site       | Histopathological type | Palisading | Clefting | Basaloïd cells | Peritumoural stroma reaction |
|--------|-----------------|------------|------------------------|------------|----------|----------------|-----------------------------|
| 1      | 73/m            | Chest      | Nodular BCC            | –          | +        | +              | +                           |
| 2      | 73/m            | Back       | Superficial BCC        | +          | +        | +              | +                           |
| 3      | 73/m            | Nose       | Nodular BCC            | +          | +        | +              | +                           |
| 4      | 51/m            | Chest      | Nodular BCC            | +          | +        | +              | +                           |
| 5      | 71/m            | Back       | Pigmented BCC          | +          | +        | +              | +                           |
| 6      | 77/m            | Chest      | Nodular BCC            | +          | +        | +              | +                           |
| 7      | 77/m            | Back       | Superficial BCC        | +          | +        | +              | +                           |
| 8      | 81/m            | Nose       | Nodular BCC            | +          | +        | +              | +                           |
| 9      | 67/m            | Back       | Superficial BCC        | +          | +        | +              | +                           |
| 10     | 69/m            | Nose       | Infiltrative BCC       | +          | +        | +              | +                           |
| 11     | 57/m            | Occipital  | Nodular BCC            | +          | +        | +              | +                           |
| 12     | 57/m            | Front      | Infiltrative BCC       | –          | –        | +              | +                           |
| 13     | 57/m            | Parietal   | Infiltrative BCC       | –          | –        | +              | +                           |
| 14     | 82/m            | Chin       | Nodular BCC            | +          | +        | +              | +                           |
| 15     | 76/m            | Cheek      | Nodular BCC            | +          | +        | +              | +                           |
| 16     | 70/m            | Neck       | Nodular BCC            | +          | +        | +              | +                           |
| 17     | 79/m            | Shoulder   | Superficial BCC        | +          | +        | +              | +                           |
| 18     | 82/m            | Lower arm  | Adenoid BCC            | +          | –        | +              | +                           |
| 19     | 82/m            | Upper arm  | Nodular BCC            | +          | +        | +              | +                           |
| 20     | 82/m            | Upper arm  | Superficial BCC        | +          | +        | +              | +                           |
| 21     | 70/m            | Forehead right | Infiltrative BCC | –          | –        | +              | +                           |
| 22     | 70/m            | Forehead left | Nodular BCC        | +          | +        | +              | +                           |

BCC, basal cell carcinomas.

**Table 2** Technical data on HD-OCT

**HD-OCT**

| Parameter               | Value             |
|-------------------------|-------------------|
| Light source            | Halogen lamp with Gaussian filter |
| Wavelength              | 1300 nm           |
| Lateral resolution      | 3 µm              |
| Axial resolution        | 3 µm              |
| Penetration depth       | 750 µm            |
| Field of view           | 1.8 × 1.5 mm      |

HD-OCT, high definition optical coherence tomography.

Ovoid structures, destruction of layering, dilated vessels, peritumoural bright streaks and peripheral rimming.

For the new en-face (horizontal) imaging mode of HD-OCT, the following criteria were defined: lobulated nodules, peripheral rimming, dilated vessels, epidermal disarray and variably refractile stroma.

In the slice imaging mode the described characteristics were found in the following frequencies (Table 3): grey/dark oval structures (18/22), peripheral rimming (13/22), destruction of layering (22/22), dilated vessels (7/22) and peritumoural bright stroma (11/22). In the en-face mode of HD-OCT the frequencies of the newly described criteria were as follows (Table 4): lobulated nodules (20/22), peripheral rimming (17/22), epidermal disarray (21/22), dilated vessels (11/22) and variably refractile stroma (19/22).

Histology

The histopathological evaluation of the tumours (Table 1) revealed 11 nodular, 5 superficial, 4 infiltrative, 1 pigmented and 1 adenoid BCC. The nodular types of BCC showed the typical tumour cell aggregates of atypical basaloïd cells organized in nodules or lobules. The peripheral palisading which is caused by the polarization of elongated nuclei along the same axis around the tumour could be detected histologically in 18 of 22 BCCs (Figs 3–5), while it was absent in three infiltrative BCCs and one nodular BCC.

In 18 of 22 BCCs 'clefting' around the tumour was observed. Basaloïd cell formations were present in all of the 22 BCCs in the histopathological evaluation. Inflammatory peritumoural stroma reaction was seen in all of the examined tumours histologically.
In comparison with the findings of HD-OCT the feature of peritumoural bright stroma could be detected in only 9 of 22 tumours in the slice mode, while variably refractile stroma in the en-face imaging mode was found in 18 of 22 BCCs although peritumoural stroma reaction was histologically present in all tumours.

Regarding the HD-OCT feature of peripheral rimming, there was no apparent correlation with the histological criteria of ‘palisading’ or ‘clefting’.

**Discussion**

BCC is a common non-melanoma skin cancer and has been investigated by OCT in the past. In this study a new HD-OCT device was used to define and evaluate previously described and new characteristic morphological features of BCCs in comparison with the histopathological findings as the gold standard.

HD-OCT offers two major advantages compared to conventional OCT. The axial and lateral 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 depending on the system. The possibility of the horizontal en-face imaging mode of HD-OCT in addition to the vertical slice mode permits the visualization of further skin structures and architectural changes, such as the typical basaloid tumour formation of lobules and buds separated by bright streaks and bundles consistent with peritumoural stroma as well as cellular changes of the epidermis with destruction of the regular honeycomb pattern.

In previous studies using different conventional OCT devices BCC was characterized by dark (grey to black), rounded or ovoid areas sometimes lined with a bright border representing the peritumoural stroma. In addition, destruction of the typical layering of the skin was reported. However, the sensitivity of recognizing BCC vs. actinic keratosis with this technique was low with 46% in an observer-blinded study by Mogensen et al. They found that the diagnosis of BCC and actinic keratosis by OCT was
less reliable than by clinical examination, even though the pathological lesions could be distinguished from healthy skin by OCT. It was concluded by various studies that conventional OCT was a useful tool for the delineation of tumour borders as well as tumour thickness. Gambichler et al. described the capability of OCT to visualize altered skin architecture of BCC and the correlation with histopathological findings by waterproof marking of the region of interest prior to OCT and excision. This was achieved by a camera integrated in the sensor head of the OCT scanner in this setting. In contrast to conventional OCT, the technique of RCM was shown to be highly accurate in the diagnostics of BCC. In a multicentre, investigator-blinded study, Nori et al. found a sensitivity of 100% for the diagnosis of BCC if two or more of the described typical BCC criteria were present. In addition, they could show that there was no major variability of the results when comparing different study centres and different BCC subtypes.

The new HD-OCT used in this study combines features of conventional OCT with features of RCM, i.e. the delineation and thickness of tumours in the slice mode and the visualization of specific structures such as tumour buds, lobules and disarrangement of epidermal architecture in the en-face mode and it enables a fast, real-time, in vivo visualization of the skin in the vertical and horizontal dimension. There is one current study on periocular BCC, in which en-face OCT was used for ex vivo examination of

**Figure 4** (a) BCC no. 5 (pigmented BCC) presents with subepidermal dark/grey nodules (asterisk), peritumoural white stroma (arrow) and subtle peritumoural dark rims (arrowhead). (b) In the en-face mode at the subepidermal layer small dark nodules (asterisk) surrounded by dark rings (arrowhead) are depicted due to the pigmentation of this BCC. (c) Histology reveals the typical basophilic tumour nodules with characteristic palisading. (d) The tumour presents clinically as bluish nodules which show the typical leaf-like structure in dermoscopy (e).

**Figure 5** (a) In the HD-OCT image in the slice mode BCC no. 3 (nodular BCC) is characterized by grey nodules (asterisk), peritumoural white stroma (arrow) and subtle peritumoural dark rims (arrowhead). (b) The en-face mode at the dermopeidermal layer reveals dark/grey nodules (asterisk) with surrounding dark rims (arrowhead); epidermal disarray and high refractile peritumoural stroma (arrows) are depicted. (c) Histology reveals typical tumour nodules with infiltration of the epidermis in consistency with the HD-OCT and characteristic palisading and clefting peritumourally. (d) The tumour presents clinically as translucent centrally ulcerated nodule with telangiectasia as shown by dermoscopy (e).
formalin-fixed tissue. Comparable to our findings the en-face imaging mode depicted the lobular architecture of the dark tumour nodules which were separated clearly from the surrounding tissue by highly reflective structures.18

The two major findings of this study were: The typical tumour formations of BCC, i.e. dark/grey lobules within the epidermis and dermis could be detected faster and in more detail in the en-face mode than in the slice mode. These typical lobulated structures were found in 91% (20/22) of the analyzed BCCs in the en-face mode. In the slice mode the structures were not displayed in their lobulated form but as dark/grey round to oval structures in 81% (18/22). The only two BCCs without these features in HD-OCT were of a superficial and an infiltrative subtype. However, in two other infiltrative BCCs of our series these typical nodules could be observed in the en-face mode of HD-OCT.

Secondly, we found a characteristic structure which we called ‘rimming’. It was defined as a dark rim surrounding the tumour nodules and separating them from the brighter peritumoural band corresponding to the stroma adjacent to the tumour. This feature was present in 77% (17/22) of the examined BCCs in the en-face mode and in 64% (14/22) in the slice mode. The absence of rimming in five of the examined tumours could not be correlated with a specific tumour subtype and was not exactly connected with the finding of ‘palisading’ or ‘clefting’ of tumour cells as commonly described in histology. Interestingly, a similar finding was described by Olmedo et al. who found in the periphery of BCC a surrounding darker border, which was again encircled by brighter structures corresponding to fibrous stroma.19

The histological correlate of rimming is not yet clear. It does not seem to be identical to the artificial clefting, which occurs after histological tissue preparation and should not be present in vivo. Nevertheless, clefting has been reported in in vivo RCM imaging of BCC.20 The peritumoural collagen presented as bright fibers around the tumour area in OCT. Possibly, the dark rim is composed of peritumoural mucin as it has been proposed in studies using RCM.20 However, peritumoural mucin is often very subtle in histology and it cannot be explained why it should be so prominent using HD-OCT imaging. In addition, it could be discussed that the dark rim surrounding the tumour nodules might present peritumoural edema which is only visible in vivo and therefore has no histological correlate. Another possibility is the typical palisading of BCC cells which occurs in consequence of the orientation of the elongated nuclei along the same axis around the tumour. Generally, basal cells appear as bright structures at the basal layer due to their melanin content, but the nuclei are dark in OCT. It is questionable if the accumulation of the elongated nuclei around the tumour is sufficient to generate a visible dark rim around the tumour nodules. However, comparing the en-face HD-OCT

| Patients | Grey/dark oval structures | Peripheral rimming | Destruction of layering | Dilated vessels | Peritumoural white stroma |
|----------|--------------------------|--------------------|------------------------|----------------|--------------------------|
| 1        | +                        | +                  | +                      | –              | +                        |
| 2        | –                        | +                  | +                      | –              | –                        |
| 3        | +                        | +                  | +                      | +              | +                        |
| 4        | +                        | +                  | +                      | –              | +                        |
| 5        | +                        | –                  | +                      | –              | –                        |
| 6        | +                        | –                  | +                      | –              | –                        |
| 7        | +                        | –                  | +                      | –              | –                        |
| 8        | –                        | –                  | +                      | –              | –                        |
| 9        | –                        | –                  | –                      | –              | –                        |
| 10       | +                        | –                  | +                      | –              | +                        |
| 11       | +                        | +                  | +                      | –              | –                        |
| 12       | +                        | –                  | +                      | –              | –                        |
| 13       | +                        | –                  | +                      | –              | –                        |
| 14       | –                        | –                  | +                      | –              | –                        |
| 15       | +                        | +                  | +                      | –              | –                        |
| 16       | +                        | +                  | +                      | +              | –                        |
| 17       | +                        | –                  | +                      | –              | –                        |
| 18       | +                        | –                  | +                      | –              | –                        |
| 19       | +                        | +                  | +                      | –              | +                        |
| 20       | +                        | +                  | +                      | –              | –                        |
| 21       | +                        | –                  | +                      | –              | +                        |
| 22       | +                        | +                  | +                      | –              | +                        |

BCC, basal cell carcinomas; HD-OCT, high definition optical coherence tomography; OCT, optical coherence tomography.
images with the corresponding histology an intriguing correlation of the dark peritumoural nuclei and the dark rim can be observed. In any case, we found that rimming could be consistently detected around the tumour structures in the en-face mode of HD-OCT and thus seems to be a valuable feature for the in vivo diagnosis of BCC.

Epidermal disarray in the en-face mode and destruction of layering of the epidermis and dermis in the slice mode could be identified commonly in BCC, but were not regarded as highly specific characteristics because they have also been described in actinic keratosis and in benign tumours such as seborrhoeic keratosis or nevi, too. Another common feature of BCC is the presence of dilated vessels, which were not as commonly found as expected in our investigations but with a higher detection rate in the en-face mode (50%) compared to the slice mode (32%). This is in consistence with the limited findings of dilated vessels in BCC by RCM analysis.

HD-OCT has the potential to build a bridge between RCM and conventional OCT. Like the classical OCT it is superior to HFUS with respect to the resolution. It is coming close to the resolution of RCM with the possibility of depicting special histological features of BCC like tumour formation in lobules and possibly peritumoural mucin. On the other hand, the higher resolution results in a reduced penetration depth making HD-OCT not the medium of choice for the measurement of tumour thickness in thicker tumours similar to the limits described for RCM. Here, conventional OCT with a reported penetration depth of nearly 1–2 mm seems to be superior. One disadvantage of the HD-OCT device used in this study is the lack of a localization tracking within the lesion as it is currently possible in RCM.

As shown in this study, HD-OCT is suitable for the confirmation of the clinical diagnosis of BCC and may facilitate the delineation of tumour borders before surgical excision. Future studies are needed to confirm these findings and to further validate this new technique.

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