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Seminars in Cutaneous Medicine and Surgery

Optical Coherence Tomography for Imaging of Skin and Skin Diseases

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Optical coherence tomography (OCT) is an emerging imaging technology based on light reflection. It provides real-time images with up to 2-mm penetration into the skin and a resolution of approximately 10 μm. It is routinely used in ophthalmology. The normal skin and its appendages have been studied, as have many diseases. The method can provide accurate measures of epidermal and nail changes in normal tissue. Skin cancer and other tumors, as well as inflammatory diseases, have been studied and good agreement found between OCT images and histopathological architecture. OCT also allows noninvasive monitoring of morphologic changes in skin diseases and may have a particular role in the monitoring of medical treatment of nonmelanoma skin cancer. The technology is however still evolving and continued technological development will necessitate an ongoing evaluation of its diagnostic accuracy. Several technical solutions are being pursued to further improve the quality of the images and the data provided, and OCT is being integrated in multimodal imaging devices that would potentially be able to provide a quantum leap to the imaging of skin in vivo.

Semin Cutan Med Surg 28:196-202 © 2009 Elsevier Inc. All rights reserved.

Although skin is easily examined by visual inspection, the diagnostic accuracy of neither clinical nor histologic diagnosis is 100%,[1] and continuous efforts should be made to improve diagnostic accuracy and ease. Ideally, a diagnostic tool should provide a high sensitivity and specificity, be easy to use, and allow noninvasive monitoring of the disease process to allow not only follow-up but longitudinal studies of, for example, noninvasive therapies as well.

The obviously easy access to skin, the established hegemony of morphology, and the abundance of tissue has meant that the challenge of various new imaging techniques in dermatology has been feeble. Dermoscopy is the only technique that has managed a breakthrough.[2] High-frequency ultrasound (HFUS) is slowly establishing its role but is rarely used in routine work.[2] The main problem of ultrasound has been the limited resolution of the images. Optical coherence tomography (OCT) provides higher resolution but lower penetration than HFUS.[3]

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OCT Principle

OCT is a noninvasive optical imaging technique that has developed rapidly since the first realization in 1991.[3] It is often characterized as the optical analogue to ultrasound using light instead of sound to probe a biological sample and map the variation of reflected light as a function of depth. It can provide real-time imaging with a resolution typically better than 10-20 μm, but imaging with a depth resolution of 1 μm or less has been demonstrated.[4,5] The penetration depth is highly tissue-dependent and is typically limited to a few millimeters. The combination of high-resolution and relatively high-imaging depth places OCT in the imaging-gap between ultrasound and confocal microscopy. A recent thorough review of OCT technology, including frequency-domain OCT, and applications of OCT can be found in the *Handbook of Non-invasive Methods and the Skin*.[6]

The principle of OCT is shown in Figure 1. A Michelson interferometer (Fig. 1A) can be used to measure the ability of light to interfere with itself [ie, the ability to amplify or blur itself ("constructive" and "destructive" interference, respectively)]. Light is split into 2 paths using a beamsplitter (half-transparent mirror). The light directed against the mirrors are reflected, recombined at the beamsplitter, and detected. Interference between the 2 reflections is possible only when the pathlengths of the 2 arms are matched within the so-called

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doi:10.1016/j.sder.2009.07.002

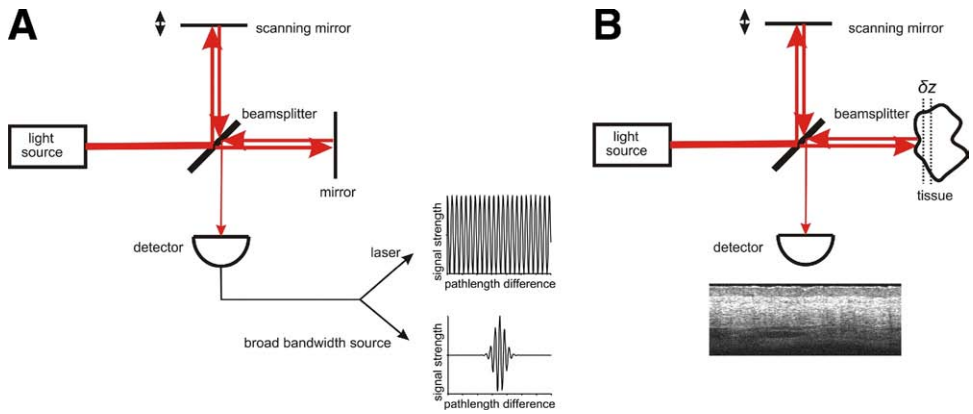

Figure 1 (A) A Michelson interferometer. (B) A Michelson interferometer with the fixed mirror replaced by a sample. An OCT image (B-scan) of the sample is shown below the detector.

coherence length of the light source. The coherence length is determined by the spectral width of the light—a broad optical spectrum corresponds to a short coherence length, and a narrow optical spectrum corresponds to a long coherence length. When using a light source with a large coherence length, interference arises for even very large differences in pathlength. When using a source with small coherence length, interference only arises when the 2 pathlengths are matched within the coherence length of the light, which may be micrometer size. It is exactly this effect that is used in OCT for distinguishing signals from different depths of the sample. The axial resolution is set by the coherence length, with a small coherence length corresponding to high axial resolution.

If one of the mirrors in the Michelson interferometer is replaced by a biological sample as shown in Figure 1B, every position of the scanning mirror corresponds to the collected signal from a thin slice in the sample. In other words, it becomes possible to determine from where the reflection originates. The thickness δz of the slice that contributes to the signal (Fig. 1B) is equal to the depth resolution of the system and inversely proportional to the bandwidth of the light source. The mechanism for selecting signal from a specific depth is also referred to as coherence gating. By moving the scanning mirror, the coherence gate successively selects an interference signal from different depths. In this way, a depth scan recording can be obtained, also referred to as an A-scan. The depth scanning range is limited by the mirror displacement. Transverse resolution is determined by the spot size, which is given by the focusing optics.

Two-dimensional data are obtained by moving the beam across the sample and acquiring data (B-scan). By translating the beam in 2 directions over a surface area, 3-dimensional data can be acquired. The time it takes to acquire a B-scan image is set by the time it takes to acquire an A-scan. A B-scan consisting of n A-scans is acquired in the time $n*t$, where t denotes the time needed to acquire an A-scan. Acquiring 2- and 3-dimensional data are in general possible in real-time. The interference signal is amplified, filtered to improve the signal-to-noise ratio, and then digitized and transferred to a computer. From the digital signal, the reflection strength is extracted and mapped, using either a gray scale or color palette, thereby generating an OCT image.[7]

Normal Skin

The skin is not an ideal optical medium. It is an optically complex, variable, and multilayered optical structure that poses many problems to imaging. OCT can reliably identify epidermis, and the dermo-epidermal junction (DEJ).[8-10] It is also able to identify the normal regional differences.[9] In general, structures that are anatomically well defined also produce well-defined OCT images, for example, the nail,[11] although epidermis and upper dermis are usually also well presented. Figure 2 provided a 3-dimensional OCT image of the normal skin, cuticle, and nail. In contrast, hair follicles and sebaceous glands tend to reduce the quality of the OCT images at the current level of resolution. Despite these reservations, quantitative effects of age, gender, skin type, and anatomic site on the epidermal thickness have been described using OCT.[8]

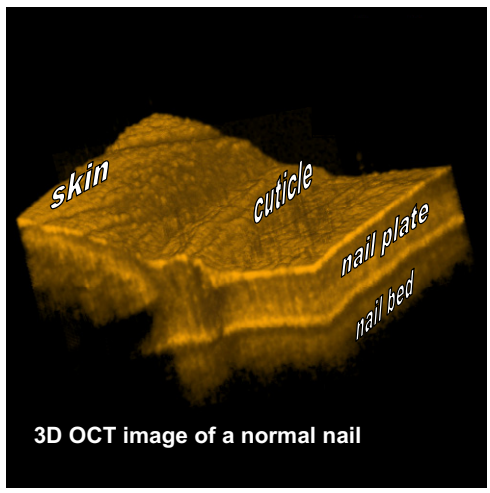

Figure 2 A 3-dimensional OCT image of a normal nail. The nail plate and the cuticle are easily identified and also the layered structure of the nail and the ridged contour of the skin are recognized.

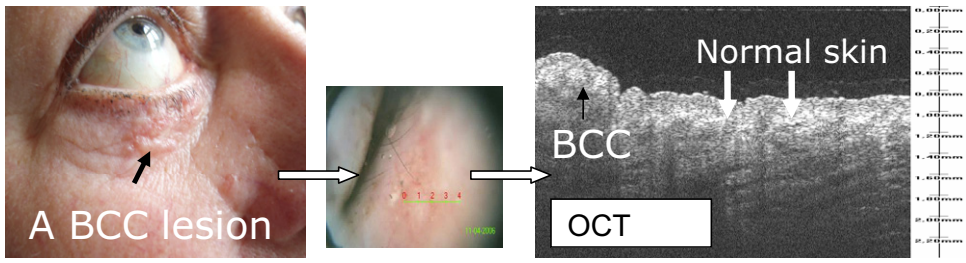

Figure 3 An example of a nodular BCC lesion that was easily delineated laterally with OCT is shown. The black arrow points at the lesion in the clinical photo and at the same lesion in the OCT image. In between, the image from the OCT probe is seen with a green line indicating where the OCT scan was performed. White arrows indicate the adjacent normal skin in the OCT image.

Nonmelanoma Skin Cancer

Nonmelanoma skin cancer (NMSC) has been a natural focus for applied OCT research. It is the most prevalent cancer in the Western world[12] and represents a significant burden of disease not only on the individual patients but on society as well.[13] OCT has been widely investigated in NMSC.[14-27] The studies have mainly focused on actinic keratosis (AK), basal cell carcinoma (BCC), and cutaneous malignant melanoma (MM), while squamous cell carcinoma (SCC) has predominantly been examined on oral mucosal surfaces.[28] The changes described in SCC appear similar to those seen in BCC.

The studies indicate that the characteristic layering of normal skin[8,9] found in OCT is lost both in NMSC[16,20,22,23,24,26,29] and in MM[30] lesions. However, loss of normal OCT architecture may also be seen in various benign lesions and additional OCT characteristics of malignant lesions have therefore been suggested[23,30]: focal changes of thickening of epidermis in AK lesions;[16,31] dark rounded areas, sometimes surrounded by a white structure in BCC lesions. An OCT image of a BCC lesion is demonstrated in Figure 3.

The diagnostic accuracy has been assessed.[16,31-33] In differentiating normal skin from lesions, a sensitivity of 79%-94% and specificity of 85%-96% was found for OCT. Discrimination of AK from BCC was not possible.[33] Other studies suggested a good match between OCT images and histopathology in BCC lesions,[20] although BCC subtypes could not be identified in OCT images.[19] For the diagnosis of AK the sensitivity ranged from 73% to 100% and the specificity from 65% to 70%.[16,31] A pilot study found a sensitivity of 62% and specificity of 91% when differentiating psoriasis from skin lymphoma.[32]

OCT provides high accuracy in distinguishing lesions from normal skin, which is of obvious importance in identifying tumor borders, although tumor thickness may be more difficult to measure accurately in thick tumors that stretch beyond the penetration of the OCT signal.[34] OCT however remains more precise and less biased than HFUS thickness measurement of thin lesions.[29] Thin tumors are of particular interest to noninvasive imaging as they are already amenable to treatment with noninvasive treatments, such as photodynamic therapy.[35]

Technical development of OCT, such as polarization-sensitive OCT (PS-OCT) or speckle-reduced OCT, may increase the diagnostic accuracy.[25,33,36] A speckle-reduced OCT image is shown in Figure 4. Finally the introduction of image analysis, machine learning algorithms, or neural networks may provide a more precise classification of AK and BCC lesions than relying on the human eye alone.[37]

Hemangiomas

Medically significant hemangiomas usually involve larger volume tumors and deep penetration of tissues. For these reasons, HFUS or magnetic resonance imaging is generally preferred. Just as HFUS,[38] OCT provides reliable images of superficial hemangiomas, which appear as oval to round sig-

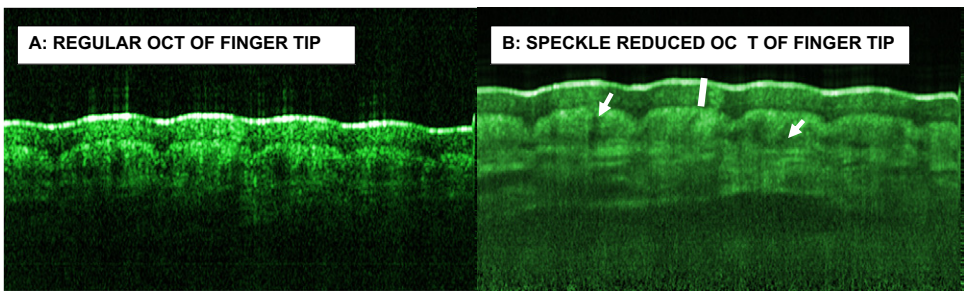

Figure 4 The OCT images display how the skin morphology is better visualized in the speckle reduced image. (A) OCT image from the palmar skin at the fingertip. (B) Speckle reduced OCT image obtained by combining 8 individual scans to suppress speckle noise. The stratum corneum is marked by a white bar, and the wavy DEJ is marked with white arrows. The DEJ is much more well defined in B.

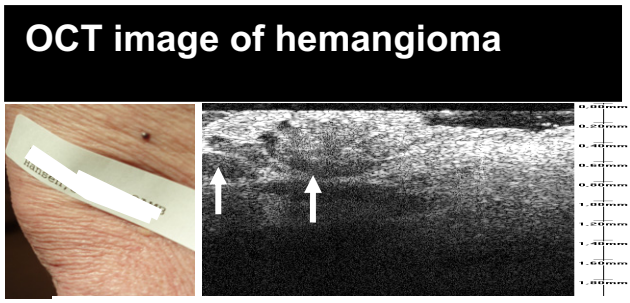

Figure 5 Clinical photo demonstrating a dark bluish nodule over the knee joined by the OCT image of the same lesion that was identified as a small hemangioma on histology. Note the cavernous nature of the dark vessels illustrated by OCT. Vessels indicated by white arrows.

nal-poor areas delineated by a surrounding signal-rich stroma. An OCT image of a small hemangioma is illustrated in Figure 5. Although HFUS has evolved to allow the imaging of small tumors in the MM range,[39] OCT may still have some applicability in the study of specific hemangioma therapies as it allows for higher resolution imaging.[40]

Melanomas

Melanomas are pigmented tumors which make imaging techniques based on the penetration of light more difficult. In contrast, the use of light reflected by the pigment (ie, dermoscopy) is well established and described.[41-44] In OCT images, the presence of large vertical, icicle-shaped structures has been associated with MM.[30] In distinguishing MM from benign nevi, a general architectural disarray and unclear DEJ have been suggested as important OCT features in MM; sensitivity and specificity studies have, however, not been performed. The full potential of OCT in MM diagnosis therefore remains to be described.

Infestations

Similar to tumors, infestations provide a well-defined, clinical focal point for imaging studies. In cutaneous larva migrans, clear images were obtained of the larva tunnel, which appeared as a well-defined oval round area with a surrounding increased signal.[15,45] The larva itself was not identified, but all 3 patients were treated with cryotherapy before the study and may therefore not have been present or have optical properties similar to that of the surrounding skin. Scabies mites have been identified in OCT.[46]

Tattoos

In tattoos, exogenous pigment is deposited in the skin and can be visualized. In OCT images, tattoo pigment appears as dark, homogeneous vertical columns and structures in the papillary dermis.[47] Depth and lateral distribution were described and may provide in vivo information about the effects of therapy as well as the wandering of tattoo pigment in the body.

Psoriasis and Dermatitis

OCT has been used to provide information about the thickness of the epidermis and the signal attenuation coefficient in the upper dermis (thought to correspond to edema) in irritant dermatitis and psoriasis. Thickening of the epidermis was measured and could be monitored. The signal attenuation coefficient (light scattering) in the upper dermis was lower than in healthy skin, suggesting that edema provided improved optical conditions for imaging of collagen fibers.[48] OCT of acute dermatitis induced by patch tests showed increased skin folds, thickened and/or disrupted entrance signals, and a significant increase in epidermal thickness; considerable reduction of dermal reflectivity was found. Clearly demarcated signal-free cavities within the epidermis were correlated strongly with clinical patch test grading, suggesting imaging of intraepidermal vesicles.[49]

Bullous Skin Diseases

Bullous diseases form an important group of skin diseases, where immediate diagnosis would be of great benefit. A pilot study suggests that OCT imaging appears able to distinguish intraepidermal and subepidermal bullae.[50] In Figure 6, 3 bullous pemphigoid lesions and a burn blister are illustrated in OCT images.

Burns

Both chronic and acute burns caused by ultraviolet (UV) radiation are thought to strongly influence normal morphology and skin cancer risk. A study evaluated the OCT skin morphology caused by UVB and UVA1 radiation. OCT measurements and skin biopsies revealed increased epidermal thickness on UVB exposed skin sites, and slightly increased epidermal thickening in UVA1 exposed sites.[51,52] Thermal burn depth and evolution are of particular interest and OCT may also provide important information in this area.[53,54] In burns, both intraepidermal and subepidermal bullae are identified,[55,56] which is also seen in Figure 6. In addition, qualitative changes in skin collagen have been described using OCT.[54,57-59]

Other Skin Diseases

Comparatively, few inflammatory skin diseases have been studied using OCT. A patchy reduction of reflectivity has been observed in the upper dermis in systemic lupus erythematosus[60] and a case of porokeratosis has also been described.[61] Obviously, the other diseases not studied are those with clear histologic features seen in low-power magnification in histology, for example, *Pityriasis rubra pilaris*.

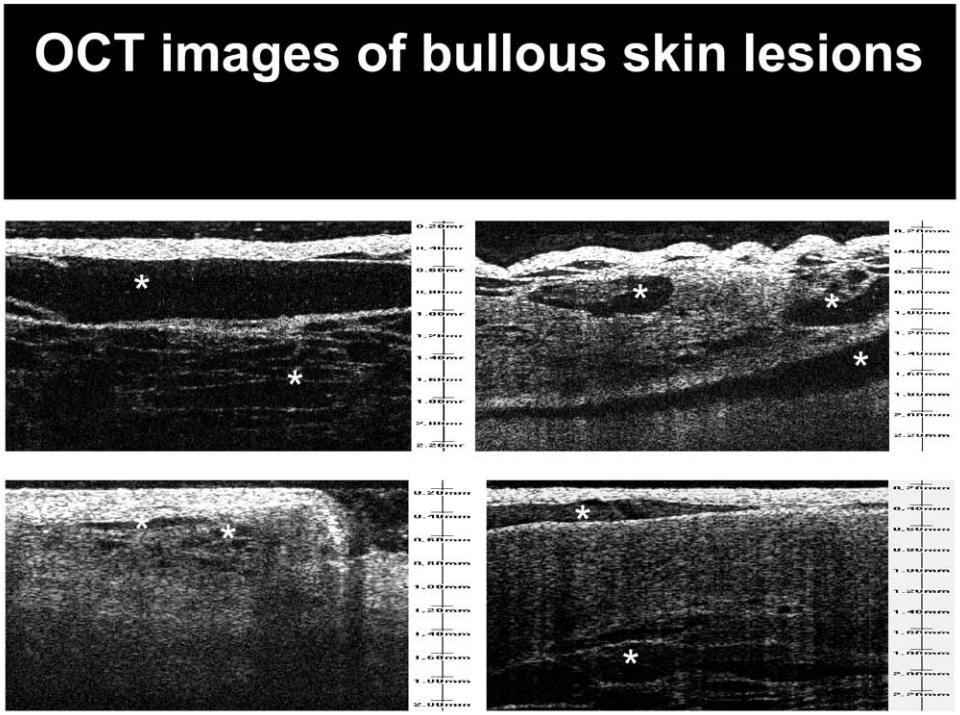

Figure 6 Characteristic OCT images of various blisters (blisters are marked by an asterisk). In the lower right corner a burn lesion is shown; the other OCT images are from patients with bullous pemphigoid. For corresponding histopathology, please refer to the article by Mogensen M, Morsy HA, Nurnberg BM, et al: Optical coherence tomography imaging of bullous diseases. J Eur Acad Dermatol Venereol 22:1458-1464, 2008.

Therapy

The potency of topical glucocorticoid is graded, and one of the important factors is the atrophogenic potential of the substances. This has been studied in vivo using OCT.[62] This allowed the detection and monitoring of significant epidermal atrophy and its reversibility. The changes found correlated with the potency of the steroids, and OCT was found to be more sensitive than ultrasound.

Discussion

Skin imaging technologies are in a tough competitive environment. The ease and tradition for clinical inspection coupled with the relative ease of biopsies meant that the first step for any new imaging technique is very high. Nevertheless, there are at least 3 factors speaking in favor of the continued development of skin imaging techniques. First, the noninvasive diagnostic methods allow for monitoring of therapeutic progress of all skin diseases. This potentially enables the treatment to be modified according to the response at an earlier point optimizing treatment outcomes for patients. Noninvasive monitoring of disease processes also allows for longitudinal studies of disease evolution and possibly pathogenesis. Second, in NMSC many noninvasive therapies are being increasingly used, for example, photodynamic therapy or imiquimod. The advantages of a nonscarring nonsurgical technique are much reduced if the diagnosis depends on a biopsy that leaves a scar. Third, there are groups of patients, such as organ transplant recipients, where the number of suspicious lesions is so great that biopsies of each become impossible. OCT is an emerging technology in the diagnosis of skin disease. The methodology provides an advantageous combination of resolution and penetration depth, but specific studies of diagnostic sensitivity and specificity are mostly lacking. Because it is an emerging technology, such studies will need to be repeated many times as the technology matures to give a fair representation of its full potential. It is speculated that the continued technological development will propel the method to a greater level of routine.

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