Applications and future directions for optical coherence tomography in dermatology*

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Summary

Optical coherence tomography (OCT) is a noninvasive optical imaging method that can generate high-resolution en face and cross-sectional images of the skin in vivo to a maximum depth of 2 mm. While OCT holds considerable potential for noninvasive diagnosis and disease monitoring, it is poorly understood by many dermatologists. Here we aim to equip the practising dermatologist with an understanding of the principles of skin OCT and the potential clinical indications.

We begin with an introduction to the technology and discuss the different modalities of OCT including angiographic (dynamic) OCT, which can image cutaneous blood vessels at high resolution. Next we review clinical applications. OCT has been most extensively investigated in the diagnosis of keratinocyte carcinomas, particularly basal cell carcinoma. To date, OCT has not proven sufficiently accurate for the robust diagnosis of malignant melanoma; however, the evaluation of abnormal vasculature with angiographic OCT is an area of active investigation. OCT, and in particular angiographic OCT, also shows promise in monitoring the response to therapy of inflammatory dermatoses, such as psoriasis and connective tissue disease. We additionally discuss a potential role for artificial intelligence in improving the accuracy of interpretation of OCT imaging data.

Optical coherence tomography (OCT) is a noninvasive optical imaging method that can generate high-resolution en face and cross-sectional images of the skin and cutaneous vasculature in vivo to a maximum depth of 2 mm (Figure 1A, D). While OCT holds considerable promise for noninvasive diagnosis and disease monitoring, it is poorly understood by many dermatologists. Here, our goal is to equip the practising dermatologist with an understanding of the principles of skin OCT and the potential clinical indications.

As skin is an accessible organ, noninvasive diagnosis has long been a goal of dermatologists. For centuries, visual inspection was the main guide to diagnosis, and more recently dermoscopy has assumed a prominent role. In recent decades, a number of additional approaches have emerged permitting noninvasive evaluation of the skin. These can broadly be divided into point probe devices and those that generate images. Apart from high-frequency ultrasound, most imaging techniques have been optically based. These include OCT,1 reflectance confocal microscopy (RCM),2 hyperspectral imaging,3 optoacoustic imaging,4 coherent anti-Stokes Raman scattering imaging,5 terahertz imaging6 and multiphoton microscopy imaging.7 The most pervasive imaging technologies currently used in clinical practice are RCM and OCT.

The ideal noninvasive imaging device would have unlimited imaging depth and subcellular resolution equivalent to histological images. However, current techniques must balance between depth and resolution (Table 1). For example, high-frequency ultrasound (HFUS) has the greatest imaging depth but the lowest image resolution of the modalities currently applied to skin imaging. Similarly, RCM can achieve ‘cellular resolution’, but the depth of imaging is restricted to the epidermis and superficial (papillary) dermis.8 Although a number of OCT variants exist, they lie between HFUS and RCM. The unique advantage of OCT is that it is noncontact. It achieves high axial resolutions of 3–15 μm with penetration depth of 0.4–2 mm,9 which renders it useful for defining structural boundaries but not at a cellular resolution.

Mechanism and nomenclature

The contrast from OCT imaging arises from the direct reflection (backscatter) of light as it passes through structures with
different optical densities. The depths of these boundaries cannot be measured by recording the time taken between the emitted light and reflected light, as is the case with sound in ultrasound, because the speed of light is too fast to be measured directly in this way. Instead the depth can be measured indirectly using a technique called interferometry. This measures the depth according to the amount of disruption to the coherence of the laser light beam as it passes through a sample and is compared with a reference light beam. The reference beam and the beam directed into the sample are split from the original laser beam so initially have the same coherence. After passing through the sample, the beams are recombined. If the distances travelled by the light in the reference beam and reflected sample beam are identical, constructive interference occurs and the signal increases. This allows the depth of the signal (the interface between two structures with different optical densities) to be measured as long as it is within the distance that the light beam itself remains coherent (termed coherence length) (Figure 1B, C).

The terminology used to describe OCT technology can be confusing. OCT imaging can be realized by three main techniques: physically changing the length of the reference arm (time-domain OCT), measuring the interference in the spectrum of light (spectral-domain OCT) or using the interference from a laser source that is varying or ‘sweeping’ over a wide frequency band (swept-source or optical frequency-domain OCT). The latter two techniques measure changes across multiple wavelengths, requiring Fourier transformation for analysis. They are therefore also classified as Fourier-domain OCT. 9 HD-OCT, or high-definition OCT, was originally a manufacturer-defined term for a device (SKINTELL®) that had a greater horizontal and axial resolution than standard OCT. It was a variant of Fourier-domain OCT and used ‘full-field’ illumination to acquire a whole en face image at once. This technique was termed full-field optical coherence microscopy, but that particular device is no longer available. 10 Speckle variance OCT and angiographic OCT (also known as dynamic OCT) use the principle of speckle variance to detect blood flow by measuring small variations in the signal intensity between two consecutive images taken in rapid succession. 11–14

Angiographic OCT can achieve high-resolution two-dimensional and three-dimensional images of combined vascular structures within the skin structural organization (Figure 2). Polarization-sensitive OCT measures the state of polarity of the backscattered light from the sample, which can be used to assess changes in cutaneous collagen, as it is highly polarizing. The main attraction of OCT compared with its current clinical competitor, RCM, is its significantly increased depth of imaging (up to 2 mm vs. < 0.2 mm). This permits imaging to the level of the reticular dermis and generates horizontally oriented images (called B scans) that are similar to the standard histological orientation of tissue on slides. Unfortunately this increased depth of imaging is at the expense of reduced image resolution.

Line-field confocal OCT (LC-OCT) is a new technique that has been developed to address this. It is most similar to time-domain OCT but acquires a whole B scan image at once instead of generating a B scan by combining many recordings from single points. This allows imaging at greater resolution than other OCT techniques, enabling some cytological evaluation, but with lower depth, positioning it between RCM and speckle variance OCT. The most noticeable difference compared with other OCT techniques is that the skin must remain in contact with the probe for LC-OCT to function. 10,15–17

Table 1 Features of different optical imaging methods for in vivo skin imaging

| Method                        | Penetration depth (mm) | Lateral resolution (μm) | Axial resolution (μm) | FOV (mm) | Advantages                                      | Disadvantages                                      |
|-------------------------------|------------------------|-------------------------|-----------------------|----------|------------------------------------------------|-----------------------------------------------------|
| RCM (VivaScope 1500)          | 0.2                    | < 1.25                  | < 5.0                 | 0.5 × 0.5 | Cellular resolution                            | Limited penetration depth (up to papillary dermis layer) |
| Multiphoton microscopy (MPTFlex) | 0.2                | < 0.5                   | < 2.0                 | 0.35 × 0.35 | Excellent cellular resolution and contrast       | Narrow FOV and limited penetration depth (to top of papillary dermis layer) |
| HFUS (20–100 MHz)             | 0.35–15               | 33–250                  | 17–80                 | 8.0–12   | Deep penetration depth and good FOV            | Unsatisfactory cellular resolution                   |
| LC-OCT (Damae Medical)        | 0.5                    | 1.3                     | 1.1                   | 1.2 × 1.2 | Excellent spatial resolution for OCT            | Limited penetration depth for OCT                    |
| FF-OCM (SkinTell)             | 1.0                    | 3.0                     | 3.0                   | 1.8 × 1.5 | Good resolution for OCT                        | Long acquisition time                                |
| FD-OCT (VivoSight)            | 1.0                    | < 7.5                   | < 5.0                 | 6.0 × 6.0 | Good penetration depth to dermis, good imaging speed, excellent FOV | Not cellular resolution                             |

FD-OCT, frequency-domain optical coherence tomography; FF-OCM, full-field optical coherence microscopy; FOV, field of view; HFUS, high-frequency ultrasound; LC-OCT, line-field confocal optical coherence tomography; RCM, reflectance confocal microscopy.
The first application of OCT tissue imaging was in ophthalmology\textsuperscript{18–20} and it is now an established method for imaging of the retina and anterior segment.\textsuperscript{21} Other applications have included the imaging of coronary arteries during percutaneous intervention procedures,\textsuperscript{22} renal imaging\textsuperscript{23} and endoscopic imaging of the gastrointestinal tract.\textsuperscript{24}

The development of optical coherence tomography in dermatology

Dermatology would appear to be an ideal application for OCT imaging as the skin surface is readily accessible and much of skin pathology occurs within the surface of the skin. Initial attempts to develop skin OCT were frustrated by the higher refractive index of skin in comparison with the eye.\textsuperscript{1} This was resolved by a shift from the visible-light wavelengths employed for ophthalmic OCT to infrared wavelengths, which are less attenuated by skin, and all commercially available systems now use the 1300-nm wavelength.\textsuperscript{9}

Optical coherence tomography in normal skin

Earlier studies investigated the correlation of OCT findings with histopathological appearances.\textsuperscript{25–28} Angiographic OCT studies of normal skin have revealed characteristic differences in the

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**Figure 1** Optical coherence tomography (OCT): illustrations, principle and OCT images from different skin anatomical areas. (A) Illustration of an optical coherence tomography device (a), scanning a healthy donor’s skin (b) using a probe detector (c). (B) OCT imaging systems operate according to the physical principle of low-coherence interferometry in two dimensions (a). Interferometry refers to the process of projecting coherent light waves onto the tissue specimen and measuring the delay ($\tau$) and the intensity $|I(\tau)|$ of its echo (b). (C) An analogy can be made to the complex patterns of constructive and destructive interference that are observed in waves of water. Two waves are said to be coherent when the phase of the wave is synchronous. (D) Two-dimensional OCT images representing skin structure of different skin anatomical areas: abdomen (a), back (b), forearm (c), palm (d), lip (e), nose (f), ear (g) and forehead (h) from a 37-year-old healthy donor. Scale bar = 500 $\mu$m.
structure of the vasculature according to body site. This reflects both differences in the thickness of the epidermis and intrinsic differences in the morphology of blood vessels at different anatomical sites.14,29 Polarization-sensitive OCT detects layered, well-organized collagen in normal skin and disordered organization of collagen fibres in the dermis, which can result from pathology such as burns30 and basal cell cancer.31,32

Optical coherence tomography in the diagnosis of keratinocyte carcinomas

OCT is an attractive imaging modality for the diagnosis of keratinocyte carcinoma (nonmelanoma skin cancer), offering the potential for noninvasive detection of early disease. OCT has been most extensively studied for the diagnosis of basal cell carcinoma (BCC) – the most common form of malignancy in humans. In a study of 142 OCT images presented in the absence of additional clinical information the diagnostic accuracy for dermatologists experienced with OCT imaging was a sensitivity of 86–95% and a specificity of 81–98%.33 When used in combination with clinical evaluation for the evaluation of nonpigmented lesions suspicious for BCC, the addition of OCT did not significantly improve sensitivity, but specificity increased significantly from 29% by clinical assessment to 54% using dermoscopy and to 75% with the addition of OCT.34

Scoring systems have been developed to aid the diagnosis of BCC.35,36 For example, the Berlin score evaluates the presence of features including a dark border beneath the tumour, hyporeflective nests, ovoid structures and disruption of the dermoepidermal junction.36 A systematic review, published in the British Journal of Dermatology, included 901 cases of BCC in 31 studies from 2003 to 2015.37 The overall sensitivity and specificity for BCC diagnosis by OCT were 89-3% and 60-3%, respectively, with Fourier-domain OCT exhibiting the best accuracy: 93-7% sensitivity and 61-4% specificity.

A few studies have evaluated the role of angiographic OCT in the diagnosis of BCC. Characteristic features of angiographic OCT imaging include elongated perpendicular vessels in cross-section and dilated vessels.38,39 There is preliminary evidence that vascular morphology may correlate with the subtype of BCC.40 A potential application of OCT is in defining tumour margins for BCC preoperatively. This can reduce the number of stages
required for staged tumour excision. OCT may also have a role in monitoring for recurrence following treatment of BCC with topical therapies, photodynamic therapy and laser, all of which are associated with substantially higher recurrence rates than surgical excision. OCT has also been used to evaluate the response of BCCs to systemic hedgehog inhibitors.

Cutaneous squamous cell carcinoma (SCC) is another common form of keratinocyte carcinoma that, unlike BCC, has the potential to metastasize. Early recognition and treatment are paramount in reducing this risk. OCT has been assessed for its use in diagnosing SCC and in distinguishing preinvasive disease – actinic keratosis (AK) and Bowen disease – from invasive SCC. Morphological features that distinguish SCC from preinvasive disease include thickened or disorganized upper epidermis, disruption of the normal skin layers and abnormalities of the dermoepidermal junction.

Diagnostic algorithms have been proposed to distinguish healthy skin and AK from SCC by OCT. The sensitivity and specificity for experienced operators were 93.8% and 98.9%, respectively, for SCC diagnosis and 81.6% and 92.6% for AK diagnosis. However, it is noted that hyperkeratotic AKs, which are thought more likely to progress to SCC, were excluded from the study and therefore this high level of accuracy may not translate to lesions typically encountered in the clinic.

Angiographic OCT has also been evaluated in the differentiation of AK, Bowen disease and invasive SCC. A blinded, randomized analysis of 162 angiographic OCT images identified characteristic features from each subtype. Another study of 52 lesions (including AK, BCC and SCC) supported the hypothesis that these exhibit distinct features of angiographic OCT.

**Optical coherence tomography imaging of melanoma**

Malignant melanoma is the most serious form of skin cancer with the highest risk of metastasis, and its incidence is increasing dramatically. The risk of metastasis is minimized by early detection and removal. However, the diagnostic accuracy of visual inspection and dermoscopy is limited and a majority of pigmented lesions removed are found to be histologically benign. In view of this there is considerable need for the development of noninvasive imaging methodologies for the detection of melanoma. Early studies of OCT in diagnosis of pigmented lesions evaluated the correlation between the appearance of OCT and histological features. Evaluation of pigmented lesions is challenging with OCT as the technology does not have the capability to achieve cellular resolution and melanin pigment is opaque to light.

Diagnostic features of melanoma in comparison with benign naevi on OCT images include epidermal psoriasiform hyperplasia, melanocytic nests and vertical icicle-shaped structures. However, evaluation of OCT in a diagnostic setting has found that the levels of sensitivity and specificity are not presently sufficient for accurate diagnosis. For example, in a blinded study of 93 melanocytic lesions the sensitivity of OCT was 74.1% and the specificity was 92.4%. In addition to diagnosis, OCT may come to play a role in the preoperative risk stratification of patients, and OCT findings have been shown to correlate with tumour thickness.

In comparison with conventional OCT, angiographic OCT shows potential in the diagnosis of melanoma. Angiographic OCT is able to detect lesion progression via early alteration in vessel morphology from dysplastic naevus to melanoma. Those vascular changes were confirmed by angiographic OCT in a retrospective analysis of 127 histologically verified melanomas. At 150 μm (the most superficial depth), the authors identified early changes such as serpiginous and branching vessels with bulges in melanomas thicker than 2 mm. Those features were also observed at 300 μm. The role of angiographic OCT in diagnosis and staging of melanoma is likely to prove a fertile area for investigation.

**Optical coherence tomography imaging in inflammatory dermatoses**

OCT holds considerable promise for the diagnosis and monitoring of inflammatory skin diseases as these are frequently associated with abnormalities of the cutaneous vasculature, and pathology is typically localized to the upper region of the skin. An early study of OCT in inflammatory dermatology evaluated OCT imaging in contact dermatitis and psoriasis. OCT of psoriasis reveals characteristic features, including hyperkeratosis, acanthosis and dilated capillary loops. Angiographic OCT imaging of psoriasis reveals ‘spikes’, which correspond to dilated capillary loops located in the papillary dermis. Angiographic OCT has also been used to evaluate abnormalities of the vasculature in nail psoriasis. Angiographic OCT in particular has the potential for monitoring of treatment efficacy and disease activity. For example, OCT has been used to monitor the response of patients with severe eczema to dupilumab and (in a single case report) the response of patients with psoriasis to secukinumab.

Other inflammatory dermatoses investigated with angiographic OCT include acne, rosacea (where the superficial blood vessels are dilated), dermatomyositis and scleroderma (in which the dermis exhibits increased density with loss of cutaneous appendages). Angiographic OCT has also been used to evaluate scalp seborrhoeic dermatitis, psoriasis and contact dermatitis, and in an effort to differentiate irritant and allergic contact dermatitis.

**Other applications of optical coherence tomography imaging in dermatology**

OCT has additionally been evaluated for a variety of other dermatological indications. In general, while several of these areas show promise, studies are at a relatively early stage and lack detailed quantification of sensitivity and specificity.

OCT studies of skin ageing and photodamage have identified surface irregularity and thickening of the stratum corneum. Another area of investigation is scars, which
can have significant functional, cosmetic and psychological consequences. Existing scoring systems for the quantification of scarring have a large subjective component, making it challenging to evaluate robustly the efficacy of novel therapeutic modalities. In view of this, there have been efforts to develop OCT-based metrics in scar assessment, for example by measuring the depth and vascularity.

OCT has been evaluated for the diagnosis of Malassezia folliculitis. OCT revealed characteristic morphological features of Malassezia pustules; however, Malassezia fungal bodies were not discernible by OCT. OCT can also be used to visualize the nail plate, nailbed and nail matrix and has been employed for the diagnosis of onychomycosis.

OCT and angiographic OCT can also provide objective metrics for the assessment of chronic wounds including burns, and ulcers resulting from the genetic condition epidermolysis bullosa, where there is a particular concern of SCC formation. Here, OCT has been shown to aid in wound assessment and in reducing requirements for skin biopsy. For bullous dermatoses, such as bullous pemphigoid and pemphigus, OCT associated with RCM can aid with diagnosis and the identification of appropriate biopsy sites. A case report also described the capacity of OCT imaging to reveal in vivo and real-time bullae in mucous membrane pemphigoid.

Discussion

OCT is an in vivo imaging modality within dermatology. It fills a gap between the cellular resolution achievable by RCM and the lower resolution of ultrasound. The technology is of interest to dermatologists as it offers the potential for rapid, noninvasive diagnosis for skin cancer and disease monitoring in inflammatory dermatoses.

To date, OCT has been most extensively investigated for the diagnosis of keratinocyte carcinomas, particularly BCC. A large number of studies have been performed, with considerable variability in reported values for sensitivity and specificity. A systematic review published in the British Journal of Dermatology found considerable variability between studies. The explanations for this degree of variation are likely multifactorial, including differences in technology and the specifics of study design; however, it is likely that operator experience and skill play key roles. With regard to the latter, it will be of great interest to explore a potential role for artificial intelligence approaches in automating and improving the accuracy of the diagnosis of BCC. Deep-learning algorithms have been applied to OCT in ophthalmology. In dermatology, a study used nonparametric machine learning algorithms for skin cancer classification and machine learning has also been used to analyse polarization-sensitive OCT data.

As for any new technology, it is important to explore health economic considerations. OCT machines are currently expensive and require a skilled clinician for interpretation of imaging data. The amortized cost of the machine in combination with the time taken for the clinician to perform scans will have to be weighed against cost savings resulting from a reduction in the need for biopsies and reduced patient visits. The time taken to train a clinician in the use of an OCT machine with a high degree of accuracy will also need to be incorporated in this calculation.

While OCT does not achieve accuracy of diagnosis comparable with that of conventional histopathology, an advantage is the possibility of rapid noninvasive diagnosis, reducing the requirements for skin biopsy and reducing patient anxiety waiting for results. This is potentially of great value as many healthcare systems have an intense resource pressure on the provision of skin cancer services. There is also the possibility that OCT could serve as an adjunct to teledermatology in primary care settings including general practice. Another clinical scenario where OCT may be of value is in screening patients at very high risk of skin cancer – due to either extensive ultraviolet exposure, immunosuppression or genetic conditions such as epidermolysis bullosa or xeroderma pigmentosum, where it is impractical to biopsy all indeterminate lesions. The noninvasive nature of OCT additionally facilitates serial imaging for the assessment of disease activity. This is desirable in monitoring the response to systemic therapy of inflammatory dermatoses such as psoriasis, and connective tissue diseases such as scleroderma. It can also potentially be of value in other conditions, including scarring alopecia.

While OCT has demonstrated accuracy in the diagnosis of keratinocyte carcinomas and has received Food and Drug Administration approval, it has not achieved the same degree of clinical maturity – namely documented impact on routine patient outcomes – as visual inspection or dermoscopy. If it is to bridge this gap, rather than remaining a niche diagnostic tool employed predominantly in specialist centres, there will need to be more widespread adoption in combination with larger and more robust multicentre studies of diagnostic accuracy. This will likely require a decrease in the cost of the equipment, which is currently too expensive for most departments, in combination with a reduction in the degree of training required to achieve accurate diagnosis, which might be achieved through the assistance of artificial intelligence.

In summary, OCT is a promising technology for the noninvasive imaging of skin, while the technology and potential indications continue to evolve. It shows particular promise in the early diagnosis of keratinocyte carcinomas and for disease monitoring in inflammatory dermatoses.

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