Beyond the Surface: Biophotonics Technologies for Skin Disease Diagnosis and Monitoring

Renzhe Bi, Malini Olivo*, U. S Dinish*

A*STAR Skin Research Labs (A*SRL), Agency for Science, Technology and Research (A*STAR), 31 Biopolis Way, #07- 01, Nanos, Singapore 138669, Republic of Singapore

*: malini_olivo@asrl.a-star.edu.sg; dinish@asrl.a-star.edu.sg

Biophotonics technologies-Photoacoustic imaging, two photon microscopy, Raman spectroscopy, optical coherence tomography and diffuse reflectance spectroscopy and imaging provide noninvasive clinical skin diagnostics by providing structural, functional and biochemical information. This piece explores their clinical potential, highlighting key advancements and challenges to overcome to translate into a routine dermatological diagnostic tool.

Introduction

Accurate diagnosis of skin diseases including tumors, inflammatory dermatoses, and autoimmune conditions remains a major challenge in clinical dermatology. Current practice primarily relies on visual inspection, often supplemented by dermoscopy or invasive punch biopsies. Although dermoscopy enhances visualization of skin surface and supports lesion assessment, its diagnostic performance is operator-dependent and limited to two-dimensional morphological interpretation[1]. Biopsies, though considered the gold standard for definitive diagnosis, are inherently invasive, unsuitable for repeated operation, and constrained to small areas, limiting their utility for monitoring disease progression or treatment response [2].

To advance skin diagnostics, it is essential to move beyond conventional paradigms and focus on the most relevant physiological attributes. Clinically, multifaceted features are particularly critical, including structural and mechanical integrity, biochemical composition, and functional information. Together, these parameters provide a multidimensional perspective on disease root cause, progression, and therapeutic response. This Comment highlights the recent advances in biophotonics technologies encompassing both imaging and sensing modalities that enable close to real-time, in vivo interrogation. The integration of such tools into clinical practice promises to enhance diagnostic accuracy, reduce reliance on invasive biopsies, and support longitudinal monitoring, paving the way for more precise and personalized dermatological care.

Structural and mechanical integrity

A thorough evaluation of the skin's structural and mechanical integrity, microarchitectural changes, and tissue stiffness, is essential for diagnosing dermatological diseases. Subtle morphological changes can reveal early malignancy, while vascular remodeling and increased stiffness are characteristic of inflammatory conditions such as eczema and scleroderma. Several biophotonics imaging techniques were developed to examine the skin's structural and mechanical integrity.

Optical Coherence Tomography (OCT) is a non-invasive imaging modality that generates contrast based on mismatch of tissue refractive index, enabling micrometer-resolution, cross-sectional visualization of skin architecture. Advancements such as high-resolution line-field confocal OCT have enhanced its capability toward near-histological visualization, allowing detailed assessment of epidermal thickness, dermal-epidermal junctions, and adnexal structures. Ruini *et al*. demonstrated that high-definition OCT can correlate imaging features with histopathological findings in basal cell carcinoma [3]. Building upon this, Optical Coherence Elastography (OCE) extends functionality of OCT by quantifying tissue deformation in response to mechanical or optical excitation. It can assess skin features like stiffness and elasticity. Together, OCT and OCE provide complementary structural and mechanical insights, facilitating the diagnosis and monitoring of malignancy, fibrosis, and other dermal pathologies.

Photoacoustic imaging (PAI) is a hybrid imaging technique that generates contrast based on optical absorption of tissues. By delivering pulsed laser light into the skin, PAI induces ultrasonic waves through thermoelastic expansion, which are then detected by transducers to form 3D images of skin morphology, especially the epidermal layer, microvasculature and melanin distribution. A specialized form of PAI, Raster Scanning Optoacoustic Mesoscopy (RSOM), has shown promise in inflammatory dermatoses. For instance, RSOM reveals disrupted vascular networks and changes in epidermal thickness in psoriasis subjects correlating with disease severity, a feature not captured by standard optical imaging [4].

Two-Photon Microscopy (TPM) is a nonlinear imaging technique that utilizes near-infrared light to excite fluorophores through simultaneous absorption of two photons, allowing label-free, high-resolution imaging of skin at subcellular depth. TPM captures intrinsic signals such as autofluorescence and second harmonic generation (SHG), offering detailed 3D imaging of keratinocyte structure and collagen fiber organization. In clinical settings, TPM can accurately identify nonmelanoma skin cancers, including basal cell carcinoma and squamous cell carcinoma, by revealing characteristic histological features noninvasively. Balu *et al*. demonstrated the application of TPM as a novel diagnostic tool for skin cancers, providing high-resolution images that correlate well with

histopathological findings [5]. These biophotonics technologies constitute a powerful toolbox for assessing the structural and mechanical integrity of the skin.

Biochemical composition

The biochemical composition of the skin is a crucial diagnostic marker, often alters before visible structural changes happen. Non-invasive profiling of proteins, lipids, and metabolic cofactors can aid in early detection, disease classification, and treatment monitoring. Confocal Raman Spectroscopy (CRS) detects molecular vibrations via inelastic light scattering, enabling depth-resolved, label-free biochemical analysis of skin. It is valuable for distinguishing lesions based on their intrinsic biochemical signatures, independent of morphological information. CRS has been clinically validated in objective assessment of skin barrier integrity and severity stratification of eczema [6].

Beyond structural imaging, TPM can also provide complementary biochemical insights by capturing endogenous fluorescence like NADH and FAD, as well as collagen structure via second harmonic generation, without the need for contrast agents. It has been used to study the cellular metabolism and extracellular matrix remodelling, which are hallmarks of neoplastic and photoaging processes. As an example, a clinical study has shown the metabolic heterogeneity in diabetic wounds through non-invasive imaging of optical redox and other biochemical components using TPM [7].

Diffuse Reflectance Spectroscopy (DRS) captures broadband reflected light to quantify chromophores such as hemoglobin, lipid, water and melanin from skin layers. This modality enables rapid and non-invasive assessment of oxygenation, pigmentation, and hydration. These measurements are critical in inflammatory, vascular, and pigmentary diseases. Clinically, DRS has been demonstrated to objectively evaluate psoriasis severity in comparison against Psoriasis Area and Severity Index [8]. Detection of biochemical changes in the skin can be reliably achieved using the biophotonics technologies described above.

Functional information

Microvascular oxygenation provides functional information, which serves as a crucial physiological biomarker for the early disease diagnosis and for evaluating treatment efficacy. Functional imaging techniques such as PAI and hyperspectral imaging (HSI) provide non-invasive, label-free methods to quantify oxygen saturation (sO_2) at high spatial and temporal resolution. Tomographic PAI has demonstrated high utility in skin cancer diagnostics by providing 3D maps of oxygenated and deoxygenated hemoglobin, thus delineating tumor hypoxia, angiogenesis, and margins. PAI also provides mapping of tumor dimension of basal cell carcinoma using endogenous signal from oxy and deoxy haemoglobin along with Melanin in Asian skin [2]. This is quite significant in accurate surgical planning without compromising on cosmetic outcomes. Similarly, multispectral

RSOM, a high-resolution variant of PAI, has emerged as a promising tool in assessing inflammatory skin conditions such as psoriasis and eczema by providing information on sO_2, which vary as function of severity [9]. It also offers quantitative monitoring of the efficacy of treatment, which is not possible by any other existing methods.

Hyperspectral imaging (HSI) relies on the principle of capturing spatially resolved reflectance spectra across a wide range of wavelengths. By analysing the spectral signatures of oxy- and deoxy-hemoglobin, HSI has gained interest as a cost-effective, wide-field technique for functional skin imaging. Its ability to monitor changes in tissue oxygenation non-invasively and in real time has been explored for chronic wound assessment, burn severity classification, and melanoma detection [10]. By integrating with machine learning (ML) algorithms, HSI can enhance diagnostic accuracy and standardize decision-making, particularly in outpatient or point-of-care settings.

Conclusion

To translate biophotonics technologies into routine dermatological diagnostics, several challenges must be addressed. Imaging performance must be standardized across diverse skin tones, particularly for melanin-rich, where optical contrast varies. Integration of ML can enhance diagnostic accuracy and workflow efficiency, but requires large, diverse datasets and regulatory validation. Multimodal platforms that synergize structural, functional, and biochemical information offer clinical promise but demand miniaturization and ergonomic hand-held designs. Affordability and ease of use remain critical for widespread adoption, particularly in primary care and low-resource settings. Overcoming these hurdles will accelerate equitable, accessible skin diagnostics at the point of care.

References

1. H. Kittler, H. Pehamberger, K. Wolff, and M. Binder, "Diagnostic accuracy of dermoscopy," Lancet Oncol **3**(3), 159–165 (2002).

2. Xiuting Li, Valerie Xinhui Teo, Cheng Yi Kwa, Amalina Binte Ebrahim Attia, Renzhe Bi, Sai Yee Chuah, Melissa Wee Ping Tan, Hui Yi Chia, Sze Hon Chua, Joyce Xiong See Lee, Suzanne Wei Na Cheng, U. S Dinish, Steven Tien Guan Thng, Malini Olivo, A Proof-of-Concept Study for Precise Mapping of Pigmented Basal Cell Carcinoma in Asian Skin using Multispectral Optoacoustic Tomography Imaging with Level Set Segmentation, E. J. Nuclear Med and Mol Imaging, doi: 10.1007/s00259-025-07072-x (2025).

3. C. Ruini, S. Schuh, C. Gust, B. Kendziora, L. Frommherz, L. E. French, D. Hartmann, J. Welzel, and E. C. Sattler, "Line-field confocal optical coherence tomography for the in vivo real-time diagnosis of different stages of keratinocyte skin cancer: a preliminary study," Journal of the European Academy of Dermatology and Venereology **35**(12), 2388–2397 (2021).

4. J. Aguirre, M. Schwarz, N. Garzorz, M. Omar, A. Buehler, K. Eyerich, and V. Ntziachristos, "Precision assessment of label-free psoriasis biomarkers with ultra-broadband optoacoustic mesoscopy," Nat Biomed Eng **1**(5), 1–8 (2017).

5. M. Balu, C. B. Zachary, R. M. Harris, T. B. Krasieva, K. König, B. J. Tromberg, and K. M. Kelly, "In vivo multiphoton microscopy of basal cell carcinoma," JAMA Dermatol **151**(10), 1068–1074 (2015).

6. C. J. H. Ho, Y. W. Yew, U. S. Dinish, A. H. Y. Kuan, M. K. W. Wong, R. Bi, K. Dev, X. Li, G. Singh, M. Moothanchery, J. Perumal, S. T. G. Thng, and M. Olivo, "Handheld confocal Raman spectroscopy (CRS) for objective assessment of skin barrier function and stratification of severity in atopic dermatitis (AD) patients," J Dermatol Sci **98**(1), 20–25 (2020).

7. K. P. Quinn, E. C. Leal, A. Tellechea, A. Kafanas, M. E. Auster, A. Veves, and I. Georgakoudi, "Diabetic wounds exhibit distinct microstructural and metabolic heterogeneity through label-free multiphoton microscopy," Journal of Investigative Dermatology **136**(1), 342–344 (2016).

8. S.-Y. Tzeng, J.-Y. Guo, C.-C. Yang, C.-K. Hsu, H. J. Huang, S.-J. Chou, C.-H. Hwang, and S.-H. Tseng, "Portable handheld diffuse reflectance spectroscopy system for clinical evaluation of skin: a pilot study in psoriasis patients," Biomed Opt Express **7**(2), 616 (2016).

9. Xiuting Li, Mohesh Moothanchery, Cheng Yi Kwa, Wan Ling Tan, Yik Weng Yew, Steven Tien Guan Thng, U. S. Dinish, Amalina Binte Ebrahim Attia, Malini Olivo. "Multispectral raster-scanning optoacoustic mesoscopy differentiate lesional from non-lesional atopic dermatitis skin using structural and functional imaging markers. Photoacoustics,DOI: 10.1016/j.pacs.2022.100399. 28:100399, 2022

10. Lu, G., Fei, B. Medical hyperspectral imaging: a review. J. Biomed. Opt. **19**, 010901 (2014).

Acknowledgements

We acknowledge the support of all members of the Translational Biophotonics Laboratory (TBL) at A*STAR Skin Research Labs, A*STAR Singapore, and our clinical collaborators at the National Skin Centre, Singapore.

Competing interests statement

All the authors declare no competing interests.