Indonesian Journal of Electrical Engineering and Computer Science
Vol. 34, No. 1, April 2024, pp. 245~253
ISSN: 2502-4752, DOI: 10.11591/ijeecs.v34.i1.pp245-253

Available medical imaging modalities for melanoma screening

Hamza Abu Owida[1], Muhammad Saleh Al-Ayyad[1], Jamal Al-Nabulsi[1], Nidal Turab[2]
[1]Department of Medical Engineering, Faculty of Engineering, Al-Ahliyya Amman University, Amman, Jordan
[2]Department of Networks and Cyber Security, Faculty of Information Technology, Al-Ahliyya Amman University, Amman, Jordan

Article Info

Article history:

Received Nov 26, 2023
Revised Jan 1, 2024
Accepted Jan 3, 2024

Keywords:

Dermatofluoroscopy
Dermoscopy
Melanoma screening
Optical coherence tomography
Two-photon microscopy

ABSTRACT

The prevalence of melanoma of the skin has seen a significant rise in recent decades, constituting approximately one-third of all diagnosed cancer cases. Melanoma, the most fatal variant among cutaneous malignancies, exhibits a 4% probability of occurrence over an individual's lifetime. The increasing incidence and mortality rates of skin cancer impose a substantial burden on healthcare resources and the economy. In recent years, several optical modalities, including dermoscopy, reflectance confocal microscopy (RCM), optical coherence tomography, multiphoton excited fluorescence imaging, and dermatofluorescence, have been extensively studied and utilized to improve the non-invasive diagnosis of skin cancer. This review article provides an analysis of the approach employed in the recently developed optical non-invasive diagnostic technologies. It explores the clinical uses of these techniques, while also examining their respective advantages and disadvantages. Furthermore, the paper explores the possibility for additional advancements in these technologies in the future.

Corresponding Author:

Nidal Turab
Department of Networks and Cyber Security, Faculty of Information Technology
Al-Ahliyya Amman University
Amman, Jordan
Email: n.turab@ammanu.edu.jo

1. INTRODUCTION

The incidence of melanoma has seen a notable rise in recent decades, constituting approximately one-third of all diagnosed cancer cases [1]. According to research, individuals have a 4% probability of developing melanoma, which is recognized as the most lethal type of skin cancer due to its high tendency for metastasis and invasion [2]. The increasing incidence and fatality rates of cutaneous malignancies impose a substantial burden on healthcare infrastructure and the national economy. Nonetheless, timely identification and intervention significantly enhance the chances of survival among individuals afflicted with skin cancer. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the predominant forms of non-melanoma skin cancer, with BCC being the most prevalent and SCC being the second most frequently encountered subtype within this group. Cancers of this particular nature commonly present themselves on the facial region, ears, neck, and arms as a result of prolonged sun exposure, although they have the potential to arise in any location on the human body. While the metastasis of BCCs is infrequent, it is possible for them to disseminate to distant sites in the body if they are not promptly addressed, owing to their indolent growth kinetics. SCCs have a higher level of aggressiveness compared to other forms of skin cancer, since they possess the ability to infiltrate deeper layers of the skin and spread to distant sites within the body [3]-[6].

Histopathologic assessment through visual examination remains a primary diagnostic method in current medical practice, despite its limitations in accurately identifying lesions, leading to the exclusion of a significant number of patients. The diagnosis relies on the utilization of the "ABCDE rule," a framework that

outlines the symptoms commonly associated with prevalent types of melanoma. The asymmetry, border irregularity, hue, diameter, and development of a lesion are commonly described using the letters A, B, C, D, and E, respectively [7]. Histological examination, being the widely accepted and reliable method, requires the surgical removal of the tumor (biopsy). This contributes to the significant direct expenses incurred in the treatment of skin cancer [8]. Proficient surgeons are necessary to provide anaesthesia, perform the incision, and supervise the entirety of the surgical procedure. Subsequently, the provided specimen is subjected to microscopic analysis by a proficient histology specialist, who will proceed to process it and ascertain the underlying pathology. In addition to its high cost, the diagnostic process can be time-consuming, often spanning a period of up to three weeks from the initial removal of a lesion to the attainment of a conclusive diagnosis. This extended duration might be attributed to the participation of multiple experienced physicians in the evaluation process [9].

Despite histopathology being widely regarded as the definitive method for identifying skin cancer, individuals frequently decline to undergo this process due to its intrusive characteristics. Hence, enhancing diagnostic precision and minimizing the incidence of unnecessary biopsie holds significant clinical significance. Advancements in technology are continuously being made to facilitate the exploration of a more objective and visually non-intrusive method of diagnosis. Significant progress has been achieved in this particular domain [10]. This study intends to conduct a thorough evaluation of various medical imaging modalities for melanoma screening. This assessment encompasses a comprehensive analysis of the benefits and drawbacks associated with these technologies, their practical implementation in clinical settings, and their potential for future advancements.

2. TWO-PHOTON MICROSCOPY

Two-photon microscopy has the capability to investigate the skin to a depth of 200 m, providing sub-cellular resolution. The technique commonly involves the utilization of femtosecond laser pulses to stimulate the simultaneous excitation of two or more low-energy photons inside the near-infrared (NIR) region. Non-linear optical phenomena, such as multi-photon excited fluorescence (MPEF) and second harmonic generation (SHG), form the fundamental principles underlying these processes. MPEF signals have the capability to detect endogenous fluorophores, such as nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FAD). The assessment of the extracellular matrix's state can be inferred by analyzing the SHG that arises when incident light interacts with non-centrosymmetric entities, such as collagen fibers. Multiphoton imaging has the capability to uncover the functional and structural characteristics of an unstained lesion [11]. The analysis of both the intensity and duration of fluorescence can yield valuable insights and facilitate the acquisition of knowledge. Hence, it is possible to employ fluorescence lifetime imaging microscopy (FLIM) and multiphoton imaging interchangeably. The altered FLIM signals observed in malignant lesions [12] have the potential to be valuable for early detection. These changes can be attributed to various factors, including tissue vascularization, cell proliferation, and specific metabolic demand pathways. Multiphoton imaging offers several advantages compared to typical linear optical techniques: nonlinear signals have a strong reliance on the availability of a substantial number of photons, rendering their behavior highly contingent on spatial factors. This implies that optical sectioning can be achieved without the need for a confocal pinhole. An increase in wavelength results in a corresponding increase in the depth of penetration. Seidenari *et al.* [12] conducted a study on ex vivo samples to assess the performance of the combination of multi-photon tomography (MPT) and FLIM. The diagnostic sensitivity and specificity for melanoma were both 100%. In order to obtain high-quality evidence, it is important to first carry out extensive clinical studies. The examination has the potential to provide insights into the microenvironment of the lesion and the activity of the fluorophore. Figure 1 demonstrates the utilization of two-photon microscopy for the purpose of detecting melanoma skin cancer.

Distinct morphological differences were observed when comparing the fluorescence characteristics of melanoma and nevi. Six of the most diagnostic symptoms of melanoma are ascending melanocytes, a notable intercellular distance, architectural disorder, indistinct keratinocyte cell borders, cell pleomorphism, and the presence of dendritic cells [13]. The initial MPT system for human skin, known as DermaInspect® (JenLab, Jena, Germany) [12]. This technology possesses the capability to rapidly acquire in vivo signals from MPT and FLIM. A clinical examination conducted by Dimitrow *et al.* [13] assessed the performance of DermaInspect. The study reported sensitivity values ranging from 71% to 95% and specificity values ranging from 69% to 97%.

In addition to its numerous advantages, multiphoton imaging does possess certain significant drawbacks. The utilization of stronger lasers and longer detection times is necessary in multiphoton imaging due to the inherent limitations of weak signals. The high-resolution image has readily discernible motion artifacts. The effectiveness of this product is limited due to its elevated cost. Currently, researchers are

investigating the utilization of MPT and Optical coherence tomography (OCT) in order to overcome these aforementioned constraints [14]. The OCT is utilized as an initial evaluation method at the tissue level, whereas MPT provides additional insights at the subcellular level when used in conjunction. A growing body of research suggests that the combination of specific methods is effective in the identification of scars, nevi, and BCC.

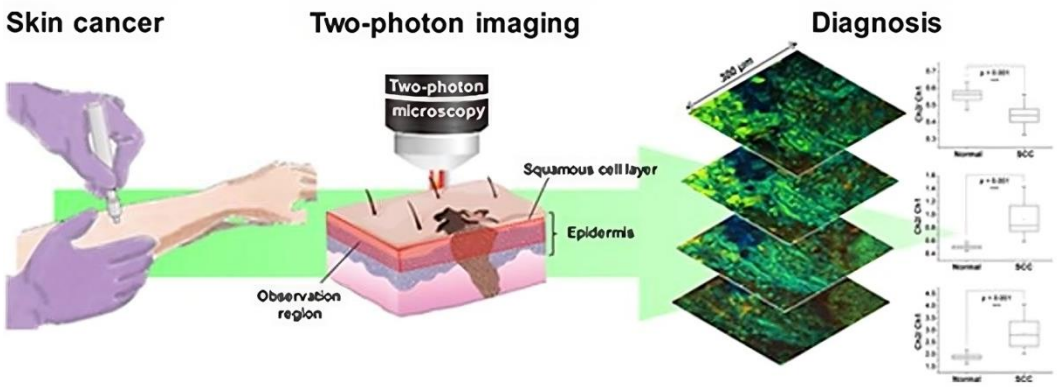

Figure 1. The application of two-photon microscopy in melanoma skin cancer detection

3. REFLECTANCE CONFOCAL MICROSCOPY

Reflectance confocal microscopy (RCM) enables the real-time examination of a lesion with cellular accuracy. RCM offers a lateral resolution ranging from 0.2 to 1.0 m and a vertical resolution of 1 to 3 m. This technique allows for imaging at a depth approximately similar to the upper papillary dermis, reaching depths of 200 m. The operational mechanism of the technology involves the utilization of a pinhole and a filter to inhibit reflection originating from the out-of-focus region, while selectively stimulating a particular spot by the emission of NIR light. By capturing a sequence of images at incremental depths that run parallel to the surface of the skin, this technique offers a comprehensive three-dimensional perspective of the lesion [15]. Through the comparison of reflection indices of different skin components, the RCM images have the potential to provide a substantial amount of information regarding the structure of the skin. Nuclei and collagen exhibit darker appearances due to their relatively low reflection indices [16], in contrast to melanin and keratin which possess higher indices. The findings obtained using RCM demonstrate a strong correlation with the results obtained from conventional histology [17].

The RCM is a valuable tool in the diagnostic process of melanoma due to the elevated reflection indices associated with melanin. Additionally, there are several discernible markers that differentiate melanoma from nevi [18]. Various scoring systems and algorithms have been devised throughout the years in order to establish a standardized approach to the diagnosis of melanoma [19]–[21]. Two widely utilized systems include the scoring system developed by Pellacani *et al.* [19] and the two-stage process proposed by Segura *et al*. [20]. The majority of cutaneous melanocytic neoplasms can be diagnosed with the help of these entities. However, it should be noted that they are currently not considered suitable for the treatment of melanoma in situ (MIS), which refers to melanomas that are confined to the epidermis. Bosari *et al.* [21] have developed an additional two-step scoring approach to address this gap. The utilization of grading systems can facilitate the integration of RCM in the diagnosis of melanocytic lesions, proving especially beneficial for practitioners who lack extensive knowledge in this field.

The VivaScope® 1500, manufactured by Caliber Imaging and Diagnostics, Inc. in New York, USA, is widely used in the field. It is equipped with a dermoscope and features wide-probe RCM functionality [42]. The device has the capability to capture photographs at a resolution of 0.5×0.5 mm. These individual images can subsequently be merged to provide a composite image of 8 mm by 8 mm.

Nevertheless, due to the necessity of adhering to the skin for proper functionality, the device has challenges in accurately recognizing surfaces that are microscopic or curved. Additionally, the detection process is susceptible to being influenced by the condition of the skin [22]. Fortunately, there exists a plethora of adaptations of medical equipment that have been specifically designed for utilization across a diverse range of medical environments. One example of the application of handheld equipment, such as the VivaScope® 3000 [22], is the detection of small and curved surfaces, such as the face.

The utilization of RCM as a supplementary diagnostic technique can be advantageous in cases where lesions exhibit clinical and dermoscopic ambiguity, as it aids in the avoidance of unnecessary biopsies. The reported research demonstrates that even with minimal melanin content, RCM pictures include sufficient

information to identify featureless subtypes of malignant melanoma, including atypical histological melanoma (AHM) and lentigo maligna/melanoma (LM/MM) [19]. The authors, Borsari *et al.* [23], provided more clarification on the indications for RCM. They specifically identified head-and-neck lesions, regressing lesions, and chronically sun-damaged skin as suitable areas for RCM examination. In addition to the identification of melanoma, the utilization of RCM can serve as a means to evaluate the likelihood of recurrence, monitor the efficacy of non-invasive skin treatments, and ensure the establishment of clear surgical margins [24]-[26].

RCM potentially possesses multiple clinical applications, rendering it a feasible adjunctive instrument. The high-resolution data provided by this technology is similar in quality to that obtained by histopathological analysis. Consequently, it has the potential to enhance the detection capabilities of dermoscopy and the accuracy of diagnostic procedures. Despite the longstanding presence and widespread recognition of RCM, its regular utilization among dermatologists is limited to a small proportion [27]. This restricted adoption may be attributed to certain technological limitations. The utility of this technique is limited for lesions that are widespread or deeply implanted due to its limited depth of penetration and narrow detection field. Furthermore, the presence of a substantial amount of reflective elements, such as ulceration, hyperkeratosis, or the application of supplementary therapies like sunscreen, significantly diminishes image resolution and detection depth in the superficial layer. Accurate interpretation of RCM images necessitates a substantial amount of clinical expertise and experience. In order for the utilization of RCM to become prevalent in clinical environments, particularly within primary care, there is a requirement for advancements in instruments that are portable, lightweight, and provide a high degree of accuracy.

Currently, scholars are actively exploring novel pathways for advancement. The development of computer-assisted automated diagnosis of RCM, similar to dermoscopy, is now underway and demonstrates considerable potential [28]-[30]. These types of computational models have the potential to develop quantitative tools in the future that can be used to guide the uniform transcription of acquired images and to provide platforms for training and education. Furthermore, potential progress could be achieved through the utilization of fluorescent confocal microscopy (FCM). The utilization of confocal microscopy in conjunction with fluorescent substances has been employed as a means to enhance the contrast of skin [24], [31]. Currently, FCM is predominantly employed for the examination of ex-vivo materials to evaluate surgical margins during intraoperative procedures. However, it is important to note that the utilization of FCM is still in the experimental phase. Scholars are currently investigating the possibility of further utilization of melanoma [32].

4. DERMATOFLUOROSCOPY

The unique characteristic of melanoma is attributed to the presence of melanin. Regrettably, the weak signal of this particular fluorophore can be easily disturbed by the presence of other fluorophores, hence rendering it almost imperceptible when used with typical one-photon- stimulated fluorescence techniques [33]. Furthermore, it should be noted that the melanin spectrum lacks distinct peaks that can be utilized for analytical purposes [34]. The utilization of a laser that emits nanosecond-pulsed pulses, in contrast to a laser that emits femtosecond-pulsed pulses, has facilitated the creation of an innovative method of stimulation involving sequential two-photon absorption. This phenomenon enables the targeted stimulation of melanin, resulting in a fluorescence spectrum primarily characterized by melanin emission. The technique was given the name "dermatofluoroscopy" to denote its specific methodology. The fluorescence observed in melanoma exhibits a distinct red shift in the fluorescence peak [35], [36]. This shift is attributed to changes in the ratio of pheomelanin to eumelanin, as compared to the fluorescence spectra of melanin in normal skin and melanocytic nevi.

Magnosco DermaFC®, a product developed by Magnosco GmbH located in Berlin, Germany, enables the in vivo diagnosis of pigmented skin lesions (PSLs). The gadget emits pulses that have the ability to penetrate the skin to a depth of 500 micrometers. These pulses have a wavelength of 810 nanometers and can illuminate an area with a diameter of 50 micrometers. The scanning head of the device has the capability to measure individual spots within an area measuring up to 20 by 20 mm. It is able to collect a sequence of melanin fluorescence spectra, which provide information on the degree of malignancy. Once all of these spectra have been organized and analyzed using an integrated, unbiased, and automated data processing system, a numerical value is generated to aid in differentiating melanomas from other PSLs [37]. In a study conducted across many centers, a total of 476 probable sleep disorders were identified using a predefined threshold score of 30 [37]. The sensitivity of the test was found to be 89.1%, indicating its ability to accurately detect true positive cases, while the specificity was determined to be 44.8%, reflecting its capacity to correctly identify true negative cases. According to a study conducted by researchers [38], the utilization of computer-assisted algorithms has been found to enhance the precision of dermatofluoroscopy examinations by around 0.917 and 0.83%, respectively. When compared to alternative non-invasive procedures, dermatofluoroscopy exhibits a higher degree of objectivity and specificity due to its independence from the individual characteristics of the

patient. While dermatofluoroscopy presents numerous advantages, it is not without significant limitations. Melanocytic lesions that exhibit light coloration or demonstrate quick regression are considered unsuitable candidates for the proposed treatment. Furthermore, it is deficient in its capacity to disclose information pertaining to the thickness of the lesion. As a result, it is subject to significant limitations.

5. OPTICAL COHERENCE TOMOGRAPHY

The OCT employs an interferometric imaging methodology to generate three-dimensional pictures. The examination of the structure and modifications of lesions in the skin is conducted throughthe utilization of an infrared broadband light source. The beam of light is divided into two different paths, namely the sample arm and the reference arm, through the utilization of an interferometer. To facilitate the recombination of the sample signal and the reference signal, the sample arm is oriented towards the specific location of interest within the lesion and subsequently undergoes reflection. In order for interference to occur, it is necessary that the pathlengths of both beams fall within the coherence length of light [39].

The OCT technique is employed to evaluate the interference signal, enabling the real-time collection of cross-sectional images with a resolution of 315 m and a depth of 1.52 mm [39]. The OCT demonstrates superior performance relative to alternative techniques due to its ability to effectively penetrate the deep borders of a lesion and concurrently present horizontal pictures through the fusion of many cross-sectional images. Consequently, since its original inception in 1995, OCT has witnessed a continuous growth in its utilization within the field of dermatology.

While traditional OCT has demonstrated potential in identifying non-melanoma skin cancers [40], it is generally acknowledged that its resolution is rather low and its image quality is poor, rendering it inappropriate for diagnosing melanoma. Consequently, researchers have developed more sophisticated OCT technologies, including high-definition OCT (HD-OCT) and dynamic OCT (D-OCT), in order to overcome these limitations. Although the investigation of PSLs is still in its early stages, they exhibit potential as a method for differentiating PSLs and offering other functionalities. Figure 2 illustrates the fundamental idea underlying optical coherence tomography.

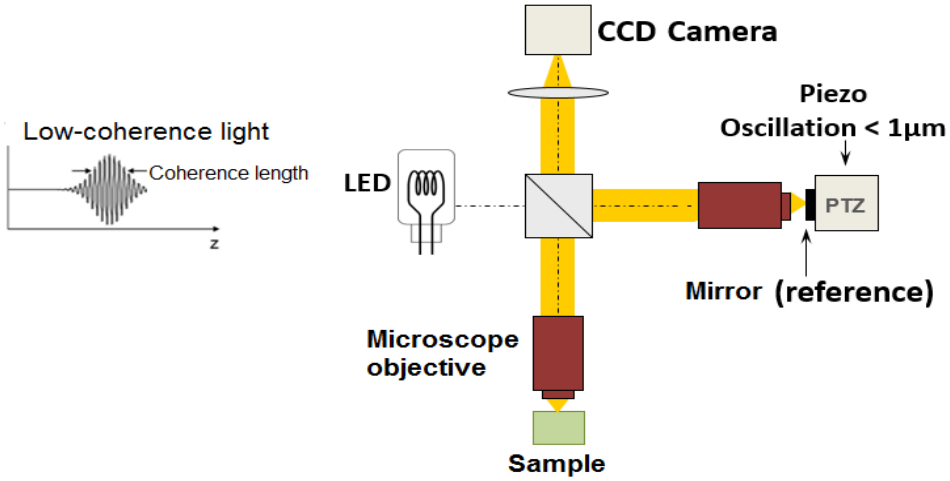

Figure 2. The main principle of optical coherence tomography

HD-OCT devices, such as Skintell® (manufactured by Agfa Healthcare, Mortsel, Belgium) [41], have the capability to capture images with a cellular resolution of 3 µm. However, this enhanced resolution is accompanied by certain limitations, including a reduced penetration depth of 750 m and a smaller scan area of 1.5 mm^2, which may not be optimal for certain applications. There is substantial evidence demonstrating a significant correlation between HD-OCT features and findings from RCM or histological examinations. The chaotic appearance of melanomas can be attributed to the invasion of atypical melanocytes, which distinguishes them from benign nevi [42]. HD-OCT has a broader detection field and enhanced penetration depth in comparison to RCM, hence enabling the acquisition of more comprehensive and intricate data compared to conventional OCT techniques. Several research studies have indicated that the specificity of high-definition specific OCT is notably high, with a value of 92.4%. However, its sensitivity is comparatively moderate, measuring at 74.1%. The elevated rate of false negatives in thin melanomas and the elevated rate of

false positives in dysplastic nevi [43] may be attributed to the reliance of HD-OCT diagnosis primarily on the assessment of tumor thickness and the delineation of lesion borders. In order to enhance accuracy, researchers are currently exploring a more comprehensive examination of optical characteristics, in addition to relying exclusively on morphological analysis [44].

D-OCT refers to a functional OCT technique known as speckle-variance OCT (SVOCT), which enables the non-invasive visualization of microvasculature in the skin. The utilization of OCT scans, which are conducted at rapid intervals and subjected to real-time analysis, is a fundamental aspect of technological advancements. The diagnostic efficacy of D-OCT can be augmented by obtaining a deeper understanding of the vascular system associated with dermatological conditions, since even slight alterations in data caused by blood flow can reveal their existence [45]. Discrete, regularly spaced dots can be observed on D-OCT in pigmented nevi, indicating the presence of vascularity. Nevertheless, in the context of melanoma, it is commonly observed that these vessels exhibit a more compact and disordered arrangement, characterized by irregular cylindrical forms when viewed in the vertical plane [46]. Recent research has demonstrated that Doppler optical coherence tomography (D-OCT) has the potential to contribute to the prognostication of patients with melanoma. Research has demonstrated a strong association between microvascularization and the Breslow index. There is a correlation between a higher score and a vascularization pattern that exhibits less regularity on D-OCT [47]. At present, the utilization of D-OCT can be carried out employing a 6 mm×6 mm visual field with the implementation of the Vivosight® device developed by Michelson Diagnostics, based in Kent, United Kingdom. The device possesses an axial resolution of 7.5 m and a lateral resolution of 5 m, enabling it to effectively visualize the extracellular matrix and microcirculation [48].

Nevertheless, the limited resolution of OCT and the optical properties of melanin have hindered its practicality for the diagnosis of melanoma. D-OCT and H-DOCT are developing technologies that hold promise in enhancing diagnostic precision through the integration of supplementary data with OCT. Nevertheless, it should be noted that the aforementioned methods are still in the early stages of development, and additional study is required to validate their efficacy in the diagnosis of melanoma. The evident usefulness of the aforementioned subject highlights a distinct requirement for further enhancements. Consequently, the creation of corresponding software for automated identification and classification is equally justified.

6. DERMOSCOPY

Dermoscopy has the longest history among non-invasive imaging procedures. The name "Dermoscopy" was coined in the 1950s to designate a novel technique for evaluating PSLs. The technology facilitates the integration of clinical and histopathologic assessments [49] through the capture of horizontal pictures of subsurface structures at magnifications ranging from 10 to 20 times across different strata. Consequently, it is presently regarded as a principal diagnostic approach. Digital dermoscopy was developed in order to address the increasing demand for storage and retrieval of picture data. The development of these developments has led to the creation of novel forms of image analysis software, that serve to facilitate the understanding of those images. Dermoscopy has the ability to enhance the significance of patient evaluation and diagnosis through the utilization of computer aids or even in the absence of human interaction [49], [50].

The initial observation of its therapeutic application occurred in 1987, subsequently leading to its widespread adoption as the prevailing choice. Although the medical community widely accepts and recognizes its dependability, the accuracy of its diagnosis still depends on the expertise of experienced experts rather than that of medical students [51]. In contemporary times, a multitude of significant breakthroughs and methodologies have been devised to enhance the efficiency of diagnosis. These include the Inclusion criteria of dermoscopy [52], the Menzies approach [53], and the 7-point assessment [54]. These enhancements have been widely utilized following their official support at the consensus net meeting on dermoscopy (CNMD) in 2001 [55], [56].

7. CONCLUSION

The investigation of optical properties in tissue can provide valuable insights into the interior architecture, biological components, and metabolic changes that are not readily observable without the use of specialized techniques. These advancements have the potential to decrease the occurrence of unnecessary surgical removals and provide reliable long-term monitoring for patients at high risk. Another possible application that has the ability to significantly improve the prognosis of patients with melanoma is non-invasive preoperative assessment. Dermoscopy and RCM are two prominent tools that have been widely utilized in diverse therapeutic situations worldwide. Both multiphoton imaging and step-wise two-photon fluorescence techniques already have commercially available solutions. However, more advancements are required in both domains in order to facilitate their wider use in primary care and specialty care settings. Despite the availability

of two promising derivative techniques, the OCT still offers significant potential for further advancement. Optical techniques have demonstrated considerable potential in the diagnosis of melanoma; nonetheless, further advancements and investigations are still required. There is a need for enhancements in several aspects of diagnostic precision, detection speed, mobility, and cost-effectiveness of devices. In the foreseeable future, there is a possibility of the emergence of more sophisticated technologies that could enhance the process of gathering data in a more efficient manner. In the future, the feasibility of remote diagnostics may be enhanced by the utilization of portable technologies and methodologies that are centered on cell-phone platforms. Furthermore, dermatologists may not derive significant assistance in the preliminary assessment of lesions prior to referral due to the growing adoption of computer-aided diagnosis and artificial intelligence-driven technologies. These advanced tools enable the evaluation of optical data and facilitate automatic and unbiased diagnosis.

ACKNOWLEDGEMENTS

This work was supported and sponsored by Al-Ahliyya Amman University. The authors would like to express gratitude for their financial support.

REFERENCES

[1] E. G. Dobre *et al.*, "Skin cancer pathobiology at a glance: a focus on imaging techniques and their potential for improved diagnosis and surveillance in clinical cohorts," *International Journal of Molecular Sciences*, vol. 24, no. 2, p. 1079, Jan. 2023, doi: 10.3390/ijms24021079.

[2] H. Bhatt, V. Shah, K. Shah, R. Shah, and M. Shah, "State-of-the-art machine learning techniques for melanoma skin cancer detection and classification: a comprehensive review," *Intelligent Medicine*, vol. 3, no. 3, pp. 180–190, 2023, doi: 10.1016/j.imed.2022.08.004.

[3] A. Gamal, M. Elshaer, M. Alabdely, A. Kadry, T. S. McCormick, and M. Ghannoum, "The Mycobiome: cancer pathogenesis, diagnosis, and therapy," *Cancers*, vol. 14, no. 12, p. 2875, 2022.

[4] S. Haggenmüller *et al.*, "Skin cancer classification via convolutional neural networks: systematic review of studies involving human experts," *European Journal of Cancer*, vol. 156, pp. 202–216, 2021, doi: 10.1016/j.ejca.2021.06.049.

[5] Y. R. Woo, S. H. Cho, J. D. Lee, and H. S. Kim, "The human microbiota and skin cancer," *International Journal of Molecular Sciences*, vol. 23, no. 3, 2022, doi: 10.3390/ijms23031813.

[6] H. Abu Owida, "Biomimetic nanoscale materials for skin cancer therapy and detection," *Journal of Skin Cancer*, vol. 2022, 2022, doi: 10.1155/2022/2961996.

[7] A. G. Goodson and D. Grossman, "Strategies for early melanoma detection: approaches to the patient with nevi," *Journal of the American Academy of Dermatology*, vol. 60, no. 5, pp. 719–735, 2009, doi: 10.1016/j.jaad.2008.10.065.

[8] F. Comito, R. Pagani, G. Grilli, F. Sperandi, A. Ardizzoni, and B. Melotti, "Emerging novel therapeutic approaches for treatment of advanced cutaneous melanoma," *Cancers*, vol. 14, no. 2, 2022, doi: 10.3390/cancers14020271.

[9] M. H. Trager, L. J. Geskin, F. H. Samie, and L. Liu, "Biomarkers in melanoma and non-melanoma skin cancer prevention and risk stratification," *Experimental Dermatology*, vol. 31, no. 1, pp. 4–12, 2022, doi: 10.1111/exd.14114.

[10] Y. S. Pathania, Z. Apalla, G. Salerni, A. Patil, S. Grabbe, and M. Goldust, "Non-invasive diagnostic techniques in pigmentary skin disorders and skin cancer," *Journal of Cosmetic Dermatology*, vol. 21, no. 2, pp. 444–450, 2022, doi: 10.1111/jocd.14547.

[11] G. Thomas, J. Van Voskuilen, H. C. Gerritsen, and H. J. C. M. Sterenborg, "Advances and challenges in label-free nonlinear optical imaging using two-photon excitation fluorescence and second harmonic generation for cancer research," *Journal of Photochemistry and Photobiology B: Biology*, vol. 141, pp. 128–138, 2014, doi: 10.1016/j.jphotobiol.2014.08.025.

[12] S. Seidenari *et al.*, "Multiphoton laser microscopy and fluorescence lifetime imaging for the evaluation of the skin," *Dermatology Research and Practice*, vol. 2012, 2012, doi: 10.1155/2012/810749.

[13] D. E. *et al.*, "Sensitivity and specificity of multiphoton laser tomography for in vivo and ex vivo diagnosis of malignant melanoma," *Journal of Investigative Dermatology*, 2009.

[14] K. König *et al.*, "Clinical optical coherence tomography combined with multiphoton tomography of patients with skin diseases," *Journal of Biophotonics*, vol. 2, no. 6–7, pp. 389–397, 2009, doi: 10.1002/jbio.200910013.

[15] A. Nwaneshiudu, C. Kuschal, F. H. Sakamoto, R. Rox Anderson, K. Schwarzenberger, and R. C. Young, "Introduction to confocal microscopy," *Journal of Investigative Dermatology*, vol. 132, no. 12, pp. 1–5, 2012, doi: 10.1038/jid.2012.429.

[16] P. Calzavara-Pinton, C. Longo, M. Venturini, R. Sala, and G. Pellacani, "Reflectance confocal microscopy for in vivo skin imaging," *Photochemistry and Photobiology*, vol. 84, no. 6, pp. 1421–1430, 2008, doi: 10.1111/j.1751-1097.2008.00443.x.

[17] G. Pellacani *et al.*, "In vivo confocal microscopic and histopathologic correlations of dermoscopic features in 202 melanocytic lesions," *Archives of Dermatology*, vol. 144, no. 12, pp. 1597–1608, 2008, doi: 10.1001/archderm.144.12.1597.

[18] A. Gerger *et al.*, "Diagnostic applicability of in vivo confocal laser scanning microscopy in melanocytic skin tumors," *Journal of Investigative Dermatology*, vol. 124, no. 3, pp. 493–498, 2005, doi: 10.1111/j.0022-202X.2004.23569.x.

[19] G. Pellacani, P. Guitera, C. Longo, M. Avramidis, S. Seidenari, and S. Menzies, "The impact of in vivo reflectance confocal microscopy for the diagnostic accuracy of melanoma and equivocal melanocytic lesions," *Journal of Investigative Dermatology*, vol. 127, no. 12, pp. 2759–2765, 2007, doi: 10.1038/sj.jid.5700993.

[20] S. Segura, S. Puig, C. Carrera, J. Palou, and J. Malvehy, "Development of a two-step method for the diagnosis of melanoma by reflectance confocal microscopy," *Journal of the American Academy of Dermatology*, vol. 61, no. 2, pp. 216–229, 2009, doi: 10.1016/j.jaad.2009.02.014.

[21] S. Borsari *et al.*, "In vivo dermoscopic and confocal microscopy multistep algorithm to detect in situ melanomas," *British Journal of Dermatology*, vol. 179, no. 1, pp. 163–172, 2018, doi: 10.1111/bjd.16364.

[22] S. K. T. Que, J. M. Grant-Kels, H. S. Rabinovitz, M. Oliviero, and A. Scope, "Application of handheld confocal microscopy for skin cancer diagnosis," *Dermatologic Clinics*, vol. 34, no. 4, pp. 469–475, 2016, doi: 10.1016/j.det.2016.05.009.

[23] S. Borsari *et al.*, "Clinical indications for use of reflectance confocal microscopy for skin cancer diagnosis," *JAMA Dermatology*, vol. 152, no. 10, pp. 1093–1098, 2016, doi: 10.1001/jamadermatol.2016.1188.

[24] C. Longo *et al*., "In vivo and ex vivo confocal microscopy for dermatologic and mohs surgeons," *Dermatologic Clinics*, vol. 34, no. 4, pp. 497–504, 2016, doi: 10.1016/j.det.2016.05.012.
[25] C. S. J. Chen, M. Elias, K. Busam, M. Rajadhyaksha, and A. A. Marghoob, "Multimodal in vivo optical imaging, including confocal microscopy, facilitates presurgical margin mapping for clinically complex lentigo maligna melanoma," *British Journal of Dermatology*, vol. 153, no. 5, pp. 1031–1036, 2005, doi: 10.1111/j.1365-2133.2005.06831.x.
[26] P. Guitera *et al*., "Surveillance for treatment failure of lentigo maligna with dermoscopy and in vivo confocal microscopy: new descriptors," *British Journal of Dermatology*, vol. 170, no. 6, pp. 1305–1312, 2014, doi: 10.1111/bjd.12839.
[27] E. Moscarella, M. Agozzino, C. Longo, G. Pellacani, and G. Argenziano, "A survey on the use of reflectance confocal microscopy among dermatologists in Italy," *Journal of the American Academy of Dermatology*, vol. 83, no. 5, pp. 1465–1466, 2020, doi: 10.1016/j.jaad.2020.03.018.
[28] S. Koller *et al.*, "In vivo reflectance confocal microscopy: Automated diagnostic image analysis of melanocytic skin tumours," *Journal of the European Academy of Dermatology and Venereology*, vol. 25, no. 5, pp. 554–558, 2011, doi: 10.1111/j.1468-3083.2010.03834.x.
[29] M. Wodzinski, A. Skalski, A. Witkowski, G. Pellacani, and J. Ludzik, "Convolutional neural network approach to classify skin lesions using reflectance confocal microscopy," *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS*, pp. 4754–4757, 2019, doi: 10.1109/EMBC.2019.8856731.
[30] D. S. Gareau, R. J. Hennessey, E. Wan, G. Pellacani, and S. L. Jacques, "Automated detection of malignant features in confocal microscopy on superficial spreading melanoma versus nevi," *Journal of Biomedical Optics*, vol. 15, no. 06, p. 1, 2010, doi: 10.1117/1.3524301.
[31] A. Bennàssar, A. Vilata, S. Puig, and J. Malvehy, "Ex vivo fluorescence confocal microscopy for fast evaluation of tumour margins during Mohs surgery," *British Journal of Dermatology*, vol. 170, no. 2, pp. 360–365, 2014, doi: 10.1111/bjd.12671.
[32] D. Hartmann *et al.*, "Immunofluorescence and confocal microscopy for ex-vivo diagnosis of melanocytic and non-melanocytic skin tumors: A pilot study," *Journal of Biophotonics*, vol. 11, no. 3, 2018, doi: 10.1002/jbio.201700211.
[33] H. Zeng, C. MacAulay, B. Palcic, and D. I. McLean, "Spectroscopic and microscopic characteristics of human skin autofluorescence emission," *Photochemistry and Photobiology*, vol. 61, no. 6, pp. 639–645, 1995, doi: 10.1111/j.1751-1097.1995.tb09881.x.
[34] S. Kalia, J. Zhao, H. Zeng, D. McLean, N. Kollias, and H. Lui, "Melanin quantification by in vitro and in vivo analysis of near-infrared fluorescence," *Pigment Cell and Melanoma Research*, vol. 31, no. 1, pp. 31–38, 2018, doi: 10.1111/pcmr.12624.
[35] R. Eichhorn *et al.*, "Early diagnosis of melanotic melanoma based on laser-induced melanin fluorescence.," *Journal of biomedical optics*, vol. 14, no. 3, p. 34033, 2009.
[36] D. Leupold *et al.*, "The stepwise two-photon excited melanin fluorescence is a unique diagnostic tool for the detection of malignant transformation in melanocytes," *Pigment Cell and Melanoma Research*, vol. 24, no. 3, pp. 438–445, 2011, doi: 10.1111/j.1755-148X.2011.00853.x.
[37] A. Forschner *et al.*, "Diagnostic accuracy of dermatofluoroscopy in cutaneous melanoma detection: results of a prospective multicentre clinical study in 476 pigmented lesions," *British Journal of Dermatology*, vol. 179, no. 2, pp. 478–485, 2018, doi: 10.1111/bjd.16565.
[38] Ł. Szyc, U. Hillen, C. Scharlach, F. Kauer, and C. Garbe, "Diagnostic performance of a support vector machine for dermatofluoroscopic melanoma recognition: The results of the retrospective clinical study on 214 pigmented skin lesions," *Diagnostics*, vol. 9, no. 3, 2019, doi: 10.3390/diagnostics9030103.
[39] M. Schwartz, A. Levine, and O. Markowitz, "Optical coherence tomography in dermatology," *Cutis*, vol. 100, no. 3, pp. 163–166, 2017, doi: 10.3109/9781420003307-38.
[40] J. Dinnes *et al.*, "Reflectance confocal microscopy for diagnosing keratinocyte skin cancers in adults," *Cochrane Database of Systematic Reviews*, vol. 2018, no. 12, 2018, doi: 10.1002/14651858.CD013191.
[41] M. A. L. M. Boone, S. Norrenberg, G. B. E. Jemec, and V. Del Marmol, "High-definition optical coherence tomography imaging of melanocytic lesions: A pilot study," *Archives of Dermatological Research*, vol. 306, no. 1, pp. 11–26, 2014, doi: 10.1007/s00403-013-1387-9.
[42] T. Gambichler *et al.*, "High-definition optical coherence tomography of melanocytic skin lesions," *Journal of Biophotonics*, vol. 8, no. 8, pp. 681–686, 2015, doi: 10.1002/jbio.201400085.
[43] T. Gambichler *et al*., "A multicentre pilot study investigating high-definition optical coherence tomography in the differentiation of cutaneous melanoma and melanocytic naevi," *Journal of the European Academy of Dermatology and Venereology*, vol. 29, no. 3, pp. 537–541, 2015, doi: 10.1111/jdv.12621.
[44] M. A. L. M. Boone *et al*., "In vivo assessment of optical properties of melanocytic skin lesions and differentiation of melanoma from non-malignant lesions by high-definition optical coherence tomography," *Archives of Dermatological Research*, vol. 308, no. 1, pp. 7–20, 2016, doi: 10.1007/s00403-015-1608-5.
[45] A. Mariampillai *et al.*, "Speckle variance detection of microvasculature using swept-source optical coherence tomography," *Optics Letters*, vol. 33, no. 13, p. 1530, 2008, doi: 10.1364/ol.33.001530.
[46] M. Ulrich *et al*., "Dynamic optical coherence tomography in dermatology," *Dermatology*, vol. 232, no. 3, pp. 298–311, 2016, doi: 10.1159/000444706.
[47] N. De Carvalho *et al.*, "The vascular morphology of melanoma is related to breslow index: an in vivo study with dynamic optical coherence tomography," *Experimental Dermatology*, vol. 27, no. 11, pp. 1280–1286, 2018, [Online]. Available: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L624273762%0Ahttp://dx.doi.org/10.1111/exd.13783.
[48] S. Schuh *et al.*, "Imaging blood vessel morphology in skin: dynamic optical coherence tomography as a novel potential diagnostic tool in dermatology," *Dermatology and Therapy*, vol. 7, no. 2, pp. 187–202, 2017, doi: 10.1007/s13555-017-0175-4.
[49] H. P. Soyer, R. O. Kenet, L. Cerroni, I. H. Wolf, and H. Kerl, "Clinicopathologic correlation of pigmented skin lesions using enhanced digital epiluminescence microscopy," *Melanoma Research*, vol. 7, no. Supplement 1, p. S34, 1997, doi: 10.1097/00008390-199706001-00118.
[50] H. D. Heibel, L. Hooey, and C. J. Cockerell, "A review of noninvasive techniques for skin cancer detection in dermatology," *American Journal of Clinical Dermatology*, vol. 21, no. 4, pp. 513–524, 2020, doi: 10.1007/s40257-020-00517-z.
[51] H. Pehamberger, M. Binder, A. Steiner, and K. Wolff, "In vivo epiluminescence microscopy: improvement of early diagnosis of melanoma.," *Journal of Investigative Dermatology*, vol. 100, no. 3, pp. 356S-362S, 1993, doi: 10.1111/1523-1747.ep12470285.
[52] W. Stolz, "The ABCD rule of dermatoscopy: high negative predictive value for the recognition of malignant melanomas," *Journal of the European Academy of Dermatology and Venereology*, vol. 5, no. 1, p. S59, 1995, doi: 10.1016/0926-9959(95)95977-9.
[53] S. W. Menzies, "Frequency and morphologic characteristics of invasive melanomas lacking specific surface microscopic features," *Archives of Dermatology*, vol. 132, no. 10, p. 1178, 1996, doi: 10.1001/archderm.1996.03890340038007.

[54] G. Argenziano, G. Fabbrocini, P. Carli, V. De Giorgi, E. Sammarco, and M. Delfino, "Epiluminescence microscopy for the diagnosis of doubtful melanocytic skin lesions," *Archives of Dermatology*, vol. 134, no. 12, 1998, doi: 10.1001/archderm.134.12.1563.
[55] G. Argenziano *et al.*, "Dermoscopy of pigmented skin lesions: results of a consensus meeting via the internet," *Journal of the American Academy of Dermatology*, vol. 48, no. 5, pp. 679–693, 2003, doi: 10.1067/mjd.2003.281.
[56] H. Kittler, H. Pehamberger, K. Wolff, and M. Binder, "Diagnostic accuracy of dermoscopy," *Lancet Oncology*, vol. 3, no. 3, pp. 159–165, 2002, doi: 10.1016/S1470-2045(02)00679-4.

BIOGRAPHIES OF AUTHORS

Hamza Abu Owida Ph.D. in Biomedical Engineering, Assistant Professor at the Medical Engineering Department, Al-Ahliyya Amman University, Jordan. Research interests focused on biomedical sensors, nanotechnology, and tissue engineering. He can be contacted at email: h.abuowida@ammanu.edu.jo.

Muhammad Saleh Al-Ayyad Ph.D. in Electrical Engineering, Biomedical Instrumentation, Associate Professor at the Medical Engineering Department, Al-Ahliyya Amman University, Jordan. His research interests are big home healthcare settings, medical rehabilitation instrumentation, biomedical measurements. He can be contacted at email: mayyad@ammanu.edu.jo.

Jamal Al-Nabulsi Ph.D. in Biomedical Engineering, Professor at the Medical Engineering Department, Al-Ahliyya Amman University, Jordan. His research interests are biomedical sensors, digital signal processing, and image processing. He can be contacted at email: j.nabulsi@amm.edu.jo.

Nidal Turab Ph.D. in computer science Professor at the Networks and Cyber Security Department, Al-Ahliyya Amman University, Jordan. His research interests include WLAN security, computer networks security and cloud computing security, eLearning, and internet of things (IoT). He can be contacted at email: n.turab@ammanu.edu.jo.