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REVIEW ARTICLE

New diagnostic and imaging technologies in dermatology

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Abstract

Introduction: Diagnosis of dermatological disorders is primarily based on clinical examination in combination with histopathology. However, clinical findings alone may not be sufficient for accurate diagnosis and cutaneous biopsies are being associated with morbidity.

Objective: The objective of this article is to review the newer technologies along with their applications, limitation and future prospectus.

Methodology: Comprehensive literature search was performed using electronic online databases "PubMed" and "Google Scholar". Articles published in English language were considered for the review.

Results: In order to improve and/or widen the armamentarium in dermatologic disease diagnosis and therapy, newer emerging technologies are being made available which aid in diagnosis and management. New emerging technologies include confocal microscopy, digital photographic imaging, optical coherence tomography, high frequency ultrasonography, and artificial intelligence. There have been advancements in the dermoscopes.

Conclusion: Significant progress is seen in the diagnostic methods and imaging technologies in dermatology, each having its advantages and limitations. Artificial intelligence/machine-based learning software may have a great scope to influence the dermatological practice.

KEYWORDS
dermatology, diagnosis, technology

1 | INTRODUCTION

There has been significant progress in all branches of medical sciences including dermatology with advent of newer technologies. Newer trends in the field of dermatology have revolutionized clinical approach to patient concerns. There has been a significant advancement in the ancillary imaging technologies aiding in clinical diagnosis and effective management.[1] The objective of this review is to discuss clinical applications, advantage, and limitation of these advances. Comprehensive literature search was performed using electronic online databases "PubMed" and "Google Scholar." Articles published in English language were considered for the review.

[Correction added on October 24, 2021 after first online publication: The lead author's first name was inadvertently misspelled and has been corrected]

2 | MACHINE LEARNING

Machine-based learning, a type of artificial intelligence, is an important advancement in medical research that is being integrated into many emerging imaging modalities. A computer learns using the wide range of image database of known diagnosis via variation of image pixels. This pixel variation is extrapolated by computer to diagnose unknown digital images. Computer algorithm can make clinical diagnosis with higher accuracy, at times even more accurate than the dermatologists. However, this is possible with the use of large image database.[2] The algorithm can use clinical photographs, dermoscopic and histopathological images to come to an appropriate diagnosis.[3] In a study, Esteva, et al reporting their observations of classification of skin cancer using deep convoluted neural network (CNN). In this study, they trained a dataset of 129 450 clinical images and tested it versus dermatologists' diagnosis on biopsy-proven clinical images. They showed that performance of CNN is similar to experts involved in the study.[3]

3 | DIGITAL PHOTOGRAPHIC IMAGING

With advent of new generation digital cameras, dermatologists are capable to monitor therapeutic responses both quantitatively and qualitatively.[4] Reflectance and black scatter are the main concepts of imaging discussions where reflectance allows visualization of the skin surface features and back-scattered light aids in identification of subsurface structures. Polarized light, when oriented parallel, visualizes skin texture and scales and when oriented orthogonally, enhance vascularity and pigmentation,[5,6] hence helps in differentiating different types of rosacea and in monitoring vitiligo or chronic wounds. Total body digital photography (TBDP) quickly images the entire skin. The entire skin surface can be imaged, which can be useful in monitoring patients with different melanocytic lesions and also in detecting any variations and improving biopsy efficacy.[7,8] 3-dimensional (3-D) TBDP captures 360 degrees, head-to-toe images effectively. The image reconstructs the patients accurately with life like quality.[9,10] This advancement is used in smartphone, which utilizes software to perform self-skin examination and identify any evolving lesion.[11,12] In a randomized controlled trial, Marek, et al studied the use of smartphone application for skin self-examination in patients new to total body photography. In this trial, patients were randomized into two cohorts. In the "usual care" cohorts, patients only had printed photographs and CD of photographs (n=35) whereas in the intervention cohort patients had the digital photographs in their smartphones in addition to prints and the CD (n = 36). Satisfaction increased significantly in the cohort with electronical devices in comparison with the cohort with standard of care. This may result in better compliance to skin self-examination by the patients.[11] Digital photography is also used in nevi mapping and monitoring and early detection of melanoma. It cannot be standardized with respect to positioning and lighting. 3-D photography poses difficulties in capturing and interpreting hair, hence decreased accuracy for scalp and facial dermatoses.[13] A possible limiting factor may be the increased expenses that are associated with new technology.[14] With increasing incidence of skin cancers, longitudinal nevi monitoring with TBDP will hopefully be covered under medical insurance. Accessibility for self-skin examination on smartphones, helping in monitoring lesions at home.[15]

4 | DERMOSCOPY

Dermoscopy, also known as epiluminescence microscope, considered as a dermatologist stethoscope has offered an effective diagnostic tool not only to differentiate melanoma from other melanocytic lesions but also to aid in the clinical diagnoses in inflammatory dermatoses.[16] The basic principle is illumination and transillumination of a lesion, which aids in better visualization of subtle surface and subsurface structures. The newest generation dermoscopes include in-built crossed polarizers, which aid to filter out the peripheral scattered light, reduces glare and helps in visualization of substratal structure in the absence of linkage fluid.[17] The new generation of dermoscopes also possess in-built photography with software to capture and store and analyze the image. Advanced devices have whole body mapping systems that help in detailed analyses and follow-up. Through interaction with smartphones, the storage and documentation of those images is becoming more convenient and handy.[18] Though clinicopathological correlation remains the mainstay of diagnosis, dermoscopy often helps in clinical differentials as it identifies distinct pattern. It is used to differentiate melanocytic nevi and melanomas, hence can avoid the need of biopsies especially in the head and neck and mucosal areas, where biopsies can lead to some degree of morbidity.[19,20] A study involving three centers in Europe evaluated usefulness of digital dermoscopy in 1308 patients in routine practice. A total of 3544 pigmented lesions were considered for evaluation in this study of which 466 were excised surgically and subjected to histological examination. A total of 52 melanomas were identified by this method. In the centers involved, sensitivity and specificity of digital dermoscopy were 90%–95% and 79.6%–93.3%, respectively.[20] It can also be used to evaluate various disorders of hair, nail, pigmentation, disorders of appendages, inflammatory dermatoses like psoriasis, lichen planus, collagen vascular disorders and also for evaluation of therapeutic procedures. The advances have led to shift from clinicopathological correlation (CPC) to clinic-dermoscopic pathological correlation (CDPC).[21] Beyond diagnosis, it is used in disease activity evaluation, early evaluation of pre- and post-treatment, ex-vivo dermoscopy improve histopathological correlation,[22] better patient-physician communication, use of dermoscopy in esthetic dermatology and dermatosurgery—for assessing outcome of laser hair reduction, outcomes of hair transplantation and also for early diagnosis of post-transplant complications like folliculitis.[23] Though it has high sensitivity, specificity may be low in contrast to melanoma diagnosis even when performed by experts.[24] It does not completely rule out

the need for biopsy and is difficult to perform in certain areas like the mucosa. It also needs adequate training.[25]

Tele-dermoscopy[26] refers to transferring digitalized dermoscopic images for diagnosis, treatment, education, and follow-up. Its advantages included reduced unnecessary referrals, wait time, and cost of skin care. Mobile dermoscope uses a smartphone to deliver the same type of service. This not only helps in improving reliability of telediagnosis but also helps in better delivery of skin care services especially in regions with limited access to advanced health care.

5 | CONFOCAL MICROSCOPY

It provides cellular resolution of skin and cutaneous structures. It has 830 nm laser, and images are created by utilizing intrinsic differences between refractive indices of cellular structures like melanin, collagen, and keratin. A pin-hole only permits the reflected light to be collected by the detector, hence provides high-resolution images. The obtained images are horizontal and parallel to skin surface in contrast to perpendicular images viewed on histopathology. They are of two types—reflectance (RCM) and fluorescence (FCM). RCM highlights the refractive index differences to provide contrast and is mainly used to identify benign and malignant lesions in vivo. FCM involves use of exogenous contrast to enhance refractility and provide contrast and is used ex-vivo.[27,28] It improves the diagnosis of basal cell carcinoma, squamous cell carcinoma, and malignant melanoma.

However, it needs extensive training. In addition to depth, even anatomic contour also impede image generation. It is expensive and time consuming.[29]

Advancement in RCM is being made to improve the range of motion of microscope head, reduce motion artifact and also to increase the speed.

6 | OPTICAL COHERENCE TOMOGRAPHY

It utilizes back-scattered light to generate images. optical coherence tomography (OCT) is gaining recognition and is increasingly being applied in dermatological research.[14] A key dermatological parameter that can be inferred from an OCT image is epidermal thickness, which can be an indicator of skin disease. Second important parameter is optical resolution, which presents a lower limit on the spatial details of skin structures.[30] OCT is performed in real time with ability to rapid image capture (<1 min). Here, echo time delay and intensity of back-scattered light from the tissue microstructures are measured. OCT is based on more than 100 years principle of Michelson interferometry.[31] Since light travels very fast, time delay between reflected echoes need to be measured by correlation/ interferometry technique where back-scattered light from a source is compared with a known reference. In OCT, near-infrared (NIR) and infrared (IR) are applied to skin. The incident beam is scanned transversely while the back-scattered beam is analyzed at various positions resulting in a gray-scale image.[13] Longer wavelength enables better visualization of deeper structures while shorter wavelength provides better resolution. These devices enable visualization of stratum corneum, epidermis, upper dermis, appendages, and blood vessels. OCT cannot visualize individual cells and thus has lesser resolution than histology. It is used to visualize melanomas and non-melanoma skin cancers (NMSC), for tumor diagnosis and delineation. OCT can also monitor progression of inflammatory, infectious, blistering dermatoses and also wound healing and photoaging.[32]

Its limitation is that it cannot visualize individual cells, hence limits its diagnostic capabilities. The devices are expensive and needs advanced training.[28] In future, it may be with multiphoton tomography for better visualization of cellular structures.

7 | HIGH-FREQUENCY ULTRASOUND

It is a quick, readily available non-invasive technique for diagnosis, surgery planning and lesion monitoring.[33] Ultrasound imaging uses high-frequency sound waves that cannot be heard by human ear. The principle is creation of image using ultrasound waves of interface with various acoustic impedance. Color Doppler with high-frequency ultrasound enables visualization of blood flow. High-frequency ultrasound provides images of superficial cutaneous structures. In ultrasound, the frequency is inversely proportional to the depth of penetration and directly proportion to image resolution.[34] HFUS has lower resolution than OCT but has higher scan depth.

It determines the skin thickness and measures the depth of tumor, tumor recurrence, and efficacy of therapeutic interventions. Most important application is in diagnosis and identification of skin cancer margins, to rule out infiltrative lesions and to delineate tumor margins. It is most useful in detecting depth >/<1 mm and in determining satellite, in-transit/ nodal metastases.

Because of its low resolution, it has limited use in diagnosis. It lacks functional contrast; image acquisition and the quality of images obtained are operator based and need advanced training. It is mainly used in delineating tumor margins and monitoring therapeutic response.

8 | MULTISPECTRAL OPTOACOUSTIC TOMOGRAPHY

It is an under-investigation technique in dermatology. The principle of image generation is based on identification of exogenous chromophores like nanoparticle fluorescent dyes/ endogenous chromophores like hemoglobin and melanin. On application of pulsed infrared light (680–980 nm) to the skin, there is thermo-elastic expansion and ultrasound wave are created. It is still being optimized and not readily available. It can be used in vivo, in real-time and can image depths up to 1cm as well as 3D images.[35] It aids in presurgical mapping,[35] in classification of psoriasis plaque severity,[36] and as a non-invasive method of sentinel lymph-node biopsy for malignant melanoma.[37]

9 | FLUORESCENCE IMAGING

Fluorescence imaging (FI) creates images using fluorescent properties of endogenous/ exogenous fluorophores, which absorb energy from ultraviolet/ visible light radiation.[38] Multiphoton microscopy involves use of near-infrared laser. This is a technique which uses fluorescence released after excitation from absorbing 2 photons simultaneously with low energy and longer wavelength. It helps in observation of vital phenomena in cells and in vivo at molecular level. It is able to identify dermal collagen. It has been used in skin cancer, aging, and inflammatory dermatoses.

FI occurs through two main modalities—autofluorescence and quenched activity-based imaging. The former is used to identify NMSC, as they have more tryptophan residues resulting in enhanced fluorescence, enabling the physician to make the diagnosis. The latter helps to differentiate NMSC from normal benign tissue, thus accurately helps determine margins during Mohs microscopic surgery. It requires longer incubation time.

10 | MULTISPECTRAL AND HYPERSPECTRAL IMAGING

Multi- and hyperspectral skin imaging is a promising technique for those clinical applications where the local distribution of oxygen in tissue is of major importance. The technology offers the opportunity of extracting spatial-spectral information from a tissue image. The method acquires a set of images in multiple adjacent narrow spectral bands. That allows to reconstruct the reflectance spectrum for every pixel of the image. The evaluation of a broad spectrum instead of a few spectral channels provides additional information and improves the accuracy of parameter determination. Wavelengths >650 nm offer to evaluate sO_2 of deeper vascular layers of skin, whereas spectra between 500 nm and 600 nm reflect sO_2 of the upper capillary vascular layer.[39,40]

A combined approach with multispectral and hyperspectral cameras has been used by Zimmermann et al. to evaluated chronic leg ulcers. The authors demonstrated a highly variable tissue oxygenation within the ulcers and the surrounding skin.[41] An objective evaluation of therapeutic approaches is possible by such a technique.

11 | MULTIPHOTON TOMOGRAPHY

Multiphoton tomography using femtosecond lasers has been primarily developed for microscopy of (human) tissue allowing high-resolution and 3-D microscopy,[42] but the non-invasive technology has also been used to investigate human skin in vivo from early on. The non-linear induced autofluorescence originates mainly from naturally endogenous fluorophores/protein structures like NAD(P)H, flavins, keratin, collagen, elastin, porphyrins, and melanin. Second harmonic generation was observed in the stratum corneum and in the dermis.[43] The next generation introduced a two-beam multiphoton tomograph for clinical coherent anti-Stokes Raman spectroscopy (CARS). The methods were used successfully to characterized diseased skin in atopic dermatitis and pemphigus vulgaris.[44] Further possible applications in dermatology include measurement of the intradermal water content, to assess intracutaneous distribution of topically applied lipid-rich products, and evaluate the stratum corneum barrier function.[45,46]

12 | SPECTROSCOPY

Fluorescence spectroscopy is useful to measure fluoresce of skin.[38] In remittance spectroscopy, light reflected from the skin is registered and can be of use to determine microcirculation and assessment of erythema or pigmentation. It can also be of use in clinical pharmacology and toxicology evaluation.[47] Rocha and colleagues showed usefulness of electrical impedance spectroscopy in suspicious melanocytic lesions undergoing regular short-term sequential digital dermoscopy imaging.[48] In another an in vivo clinical evaluation, use of Raman spectroscopy with fiber-coupled probe was evaluated in 104 patients scheduled for excision of suspected malignant melanoma, basal cell carcinoma, and squamous cell carcinoma. In this study, non-melanoma skin cancers were differentiated from normal skin. Accuracy for basal cell carcinoma and squamous cell carcinoma was 73% and 85%, respectively. Differentiation of malignant melanoma and pigmented nevi provided 91% balanced accuracy.[49] Standardization of evaluation with spectroscopy is important to avoid biased results.[47]

13 | ARTIFICIAL INTELLIGENCE

It is a branch of computer science that deals with simulation of intelligent human behavior in computers.[50,51] Dermatology has taken a leading position in artificial intelligence implementation due to its large clinical, dermoscopic, and histopathological image database. Machine learning is a subset of artificial intelligence, where the computer learns by creating various algorithms to solve problems and an output is generated. It can be supervised, semisupervised, or unsupervised. AI is currently used extensively in distinguishing benign versus malignant lesions, for example, to differentiate benign nevi from malignant melanoma. It is also used to predict the complexity of malignant melanoma and assist in histopathological diagnosis of malignancy.

It can also be used in ulcer assessment in diabetic or decubitus ulcer. AI applications are capable of measuring wound boundaries and also help in identifying the type of tissue involved. In inflammatory dermatoses like psoriasis, it helps in clinical assessments and in designing customized treatment protocol and predicting outcome. In atopic dermatitis, artificial neural network is used in distinguishing atopic skin from unaffected skin using information from the image database.[52] AI can improve diagnostic accuracy of onychomycosis. It also has application in dermatopathology and teledermatology.

Teledermatology is one of the fastest growing field especially in areas with limited access to a skin specialist/ advanced health care. AI are integrated into smartphone applications to image the lesions, analyze and generate referrals if required. Smartphone applications

are also available for diagnosis of melanoma risk assessment. Sensitivity and specificity range from 7%–73% and 37%–94%, respectively.[53] With the help of wide image database and AI algorithm, the dermoscope can support/ aid dermatologists in training and also in identification of dermoscopic patterns which in turn enables in better clinical diagnosis.

Currently, its use is limited, because of its availability mainly in developed countries. It needs large image databases. It also lacks standardization. Technical variation in image acquisition and quality issues can affect the final interpretation. Patient acceptance needs to be considered, as a holistic approach cannot be replaced by AI. Ethical issues also need to be addressed. AI warrants a multidisciplinary approach.

14 | CONCLUSION

With newer technological advancement, new devices, imaging technologies, and therapeutic modalities will be more readily available. In future, dermatological practice may be greatly influenced by artificial intelligence/ machine-based learning software. Newer technologies have potential in augmenting clinical acumen, minimizing invasive procedures, differentiating benign/ malignant lesions, and monitoring the treatment outcome. With time, these advances may become a routine part of our diagnostic and imaging armamentarium.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Shishiria R Jartarkar involved in writing and revising the manuscript. Anant Patil, Uwe Wollina, Michael H. Gold, Henner Stege, and Stephan Grabbe involved in review and revising the manuscript. Mohamad Goldust involved in conception, writing, review and revising the manuscript.

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DISCLAIMER

"We confirm that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met and that each author believes that the manuscript represents honest work."

ETHICAL APPROVAL

This review article required no ethical approval.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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