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REVIEW ARTICLE

Non-invasive diagnostic techniques in pigmentary skin disorders and skin cancer

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Abstract

Background: Diagnosis of pigmentary skin disorders, pre-cancerous and cancerous skin diseases is traditionally relied on visual assessment. The most widely applied invasive diagnostic technique is the skin biopsy. There have been significant technological advances in non-invasive diagnostic methods for skin disorders.

Objective: The objective of this article is to discuss different non-invasive diagnostic modalities, used in the diagnosis of pigmentary skin disorders and cutaneous cancers.

Methods: Comprehensive literature search was performed to screen articles related to non-invasive diagnostic techniques in pigmentary skin disorders and cutaneous cancers. Articles published in journals indexed in PubMed were searched along with those in Google Scholar. Clinical trials, review articles, case series, case reports and other relevant articles were considered for review. References of relevant articles were also considered for review.

Results: Dermoscopy and ultrasonography were the only non-invasive diagnostic and imaging techniques available to dermatologists for many years. The advent of computed tomography (CT) and magnetic resonance imaging (MRI) augmented the visualization of deeper structures. Confocal laser microscopy (CLM) and reflectance spectrophotometers have showed promising results in the non-invasive detection of pigmented lesions. Optical coherence tomography (OCT), electrical impedance spectroscopy (EIS), multispectral imaging, high frequency ultrasonography (HFUS) and adhesive patch biopsy aid in the accurate diagnosis of benign, as well as neoplastic skin diseases.

Conclusion: There have been significant advancements in non-invasive methods for diagnosis of dermatological diseases. These techniques can be repeatedly used in a comfort manner for the patient, and may offer an objective way to follow the course of a disease.

KEYWORDS
diagnosis, diagnostic techniques, pigmentary skin disorders, skin cancer

1 | INTRODUCTION

The dermatologist's eyes remain the ultimate assessment tool for most of the dermatological conditions; however, this subjective evaluation may be associated with significant inter-observer variations. In order to overcome this limitation, several additional tools and techniques have been developed and are regularly used by the clinicians. As an example, examination with ultraviolet light is considered a mainstay in the assessment of pigmentary skin lesions. Moreover, polarized light photography is useful in discerning dermal changes, especially vascularity. In the field of skin cancers, there is a constant need for tools that can improve early detection, optimizing in this way treatment outcome and patients' survival. Neoplastic skin lesions add significant financial and psychological burden on the patients and family. The clinicopathological evaluation of pigmentary skin lesions remains a challenging task. The diagnostic accuracy of clinical examination of cutaneous melanoma by the naked eye is about 60%, but it significantly improves with the use of dermoscopy.[1] In the scenario of atypical lesions, histopathological evaluation remains the gold standard of the diagnosis, although pigmentary skin diseases can be challenging also on the histological basis. Pigmentary skin diseases and cancerous conditions are difficult to "pick" early in their course and may require serial biopsies to establish the correct diagnosis. The biopsy of skin tissue for histopathological evaluation involves topical anesthesia and partial or complete excision that are both invasive and have been associated with pain, increased chances of infection and scar formation. Skin biopsies are also associated with significant morbidity and cost. In this context, non-invasive diagnostic techniques have become highly appealing.

The rising incidence rate of pigmentary lesions and skin tumors in the past two decades has prompted non-invasive diagnostic techniques to act as ancillary diagnostic tools. Dermoscopy and ultrasonography were the only non-invasive diagnostic and imaging techniques available to dermatologists for many years. The advent of computed tomography (CT) and magnetic resonance imaging (MRI) augmented the visualization of deeper structures, but these modalities are expensive and lack adequate resolution providing useful information in limited scenarios. The introduction of newer modern instruments, such as confocal laser microscopy (CLM) and reflectance spectrophotometers has showed promising results in the non-invasive detection of pigmented lesions. Techniques like optical coherence tomography (OCT), electrical impedance spectroscopy (EIS), multispectral imaging, high frequency ultrasonography (HFUS) and adhesive patch biopsy aid in the accurate diagnosis of benign, as well as neoplastic skin diseases.

In this review, non-invasive methods in pigmentary skin disorders and skin cancers are discussed.

2 | DERMOSCOPY

Dermoscopy, also known as epiluminescence microscopy is the most widely applied, non-invasive technique for evaluation of pigmentary, inflammatory, and neoplastic skin lesions. It is a handheld device having light emitting diodes as an internal source of light. It can be used in association with digital cameras and multiple computer softwares to enhance better analysis of the image and documentation. It provides additional information at a sub-macroscopic level that facilitates dermatologists to differentiate between two or more conditions that are difficult to distinguish by the naked eye clinical examination. The skin features observed in dermoscopy are usually defined in terms of overall pattern and special structures' shape, coloration and distribution.

The application of dermoscopy has been implied both in pigmented and non-pigmented skin lesions. The presence or absence of pigment network, globules, dots, streaks, homogeneity and pattern recognition help in diagnosing pigmentary lesions such as melanocytic lesions. The dermoscopic structures and patterns are described using standardized terminology to augment in differentiating between benign and malignant tumors, as well as to help in the diagnosis of non-tumoral skin conditions.

This in-vivo technique is particularly useful in the diagnosis of melanoma.[2] A meta-analysis has shown 49% improvement in the diagnostic accuracy for melanoma with dermoscopy than without its use. The results were statistically significant. The accuracy was significantly dependent on the experience of person.[1]

Sequential digital dermoscopy (SDD) of melanocytic lesions has been proposed as a strategy to recognize melanomas that may lack distinct dermoscopic features at baseline. It acquires and stores the sequential digital dermoscopic images for observation of minimal changes of a particular lesion over time.[3] This is truly advantageous since has proved to be efficient in detecting melanoma in early stages without increasing the number of unnecessary excisions. A met-analysis published in 2013 provided evidence that SSD allowed for the early detection of melanoma with a low rate of excisions; with this approach the proportion of in-situ melanoma and thin melanomas were higher than expected in general population.[4]

Overall, dermoscopy holds advantages in clinical practice due to its cost-effectiveness and the minimal time needed to perform it. It augments an improvement in diagnosis certainty as compared to the unaided clinical examination. On the contrary, potential disadvantages as compared to histology, include the low magnification of the underlying anatomic alterations and the restriction of view of the superficial skin layers exclusively.

3 | CONFOCAL LASER MICROSCOPY (CLM) OR REFLECTANCE CONFOCAL MICROSCOPY (RCM)

CLM has been routinely used in clinical practice since the 1990s. It is an office-based non-invasive procedure, which enables real time imaging of the epidermis and upper dermis at cellular level with high-resolution. The primary role of CLM has been in the diagnosis of pigmented lesions.

In the year 1995, Rajaadhayksha et al.[5] first developed a commercially available system based on laser diode (830 nm). It used a point

light source in a scanning mode, obtaining horizontal, tomographic images. With CLM the tissues are visualized depending on the different refractive indices of distinct cell structures and the tissue chromophores. Addition of exogenous fluorescent dyes allows the visualization of specific structures. CLM may have a better accuracy of detection of initial melanomas than dermoscopy. CLM has also shown to reduce the excision rate of benign versus malignant lesions.[6]

In a study of 117 melanocytic lesions, also including 27 malignant melanomas, CLM sensitivity ranged from 59% to 96% and specificity from 94% to 100%, as performed by five observers.[7] In another study of 125 melanocytic lesions, CLM had a higher sensitivity (97%) as compared to dermoscopy (89%), but almost equal specificities.[8] In another study, Borsari et al. recorded a CLM sensitivity of 95.3% and a specificity of 83.5%, in evaluation of 1278 equivocal skin tumors. CLM may enhance the diagnostic accuracy and decrease the number of unnecessary biopsies, leading to a decrease in expenses and a better cosmetic results.[9] The combination of dermoscopy, SDD, and confocal microscopy in equivocal lesions have shown to be useful reducing the number of excisions of benign lesions in atypical mole syndrome patients.[10] The disadvantage of CLM is that it requires an expensive equipment and a degree of expertise for its use. Another limitation of CLM is the restricted depth of penetration and increased chances of false negative diagnosis when pathology lies below the papillary dermis. Moreover, application of CLM is difficult in the presence of ulceration, hyperkeratosis, or dense pigmentation.[11]

4 | OPTIMAL COHERENCE TOMOGRAPHY (OCT)

Optical coherence tomography is a relatively newer technique as compared to CLM. It firstly established its use in ophthalmology and later in dermatology. It is primarily used in the diagnosis of basal cell carcinoma (BCC). OCT is an imaging technique with high-resolution, way close to histological resolution, with a depth of 2 mm.[12] It is based on interferometry, backscattering, and infrared light reflection that when directed toward skin, furnishes an image.[13]

In a study by Markowitz et al.,[14] it was shown that OCT significantly improved the sensitivity (92.9%) and specificity (80%) in the detection of BCC as compared to lower sensitivities and specificities by clinical (62.9%; 48.9%) and dermoscopic examination (78.6%; 55.6%).[14] OCT has demonstrated potential applicability in Mohs micrographic surgery for refining the clinically estimated excision margins and thereby in reducing the number of stages and final size of Mohs defect in the surgery.[15] The advantage of OCT is the enhanced experience of patient who may be managed for BCC on the same day without the need for biopsy. OCT offers improved clinical and cosmetic outcome, as well as reduced morbidity and mortality.[13] The disadvantage of OCT is the overdiagnosis of lesions as skin tumors especially non-melanoma skin cancers (NMSCs). OCT has reported both high false negative (thin melanomas) and positive (dysplastic nevi) rates.[16]

5 | ELECTRICAL IMPEDANCE SPECTROSCOPY (EIS)

EIS is not an imaging procedure but it generates a score, which indicates the heterogeneous degree of cellularity. Based on the impedance pattern obtained in the tumor, conclusions are formed regarding regular or irregular cell arrangements. EIS involves measurement of an evoked current through a skin lesion by a voltage source and conversion into current amplitude by electrodes for analysis.[17]

EIS is advantageous in detection of early melanoma in patients with multiple dysplastic nevi and monitoring of pigmentary lesions over a period of time.[18] EIS cannot differentiate other tumors like BCC and seborrheic keratosis, hence it is used for melanocytic lesions. The score yielded from EIS is useful in monitoring and checking of lesions culminating toward malignancy. Inflammation, ulceration and scar tissue limit the validity of this procedure. EIS may enhance the decision to biopsy a suspicious malignant lesion when integrated with the clinical morphologic assessment.[19]

Significant impedance difference between the skin lesions, such as pigmented cellular nevus, basal cell carcinoma and dysplastic nevus, and control skin has been recorded in a study.[20] A prospective study has reported 96.6% and 34.4% sensitivity and specificity of Nevisense, respectively, with positive and negative predictive values of 21.1% and 98.2%, respectively. The sensitivity for non-melanoma skin cancer was 100%.[21] According to the results of a retrospective study, addition of EIS to short-term sequential digital dermoscopic monitoring did not identify additional malignant lesions.[22]

6 | MULTISPECTRAL IMAGING

Similarly to dermoscopy, multispectral analysis involves illumination of the skin, but with different wavelengths of light. It may be used as a screening tool in multiple dysplastic nevi in order to detect any suspicious or atypical lesion. MelaFind is a non-invasive and fully automated multispectral imaging device, approved by the United States Food and Drug Administration for early detection of melanomas.[23]

Different groups of investigators have studied its potential in the diagnosis of pigmentary skin conditions and cutaneous melanoma.[24-26] An algorithm developed for the automatic segmentation of multispectral images of pigmented skin lesions was tested in a study involving 1700 patients (1856 pigmented lesions) and reached a 97.1% contour accuracy.[24]

In 2020, MacLellan et al conducted a prospective diagnostic accuracy study comparing non-invasive imaging techniques in 209 lesions; the authors reported a sensitivity of 82.5% and specificity of 52.4% with the use of MelaFind.[27]

7 | MULTIPHOTON LASER IMAGING

Multiphoton laser imaging is a non-invasive diagnostic technique, which uses the phenomenon of simultaneous absorption of two or more photons by a fluorophore and emission of one photon at a

shorter wavelength, with high energy to generate an image. The process uses high laser power or ultra-short pulses of high peak power to produce high photon flux densities.[28]

Multiphoton imaging is not often used in clinical routine, but has been applied in investigational study settings for skin tumors diagnosis (malignant melanoma, BCC, squamous cell carcinoma) and photoaging. The generation of high-resolution images is an additional advantage of this technique. Its main limitation is the narrow field of view and the relatively small penetration depth. Thus, viewing dermal tumors including their architecture and margins, is not feasible.[29] A study has evaluated and reported the potential of multiphoton imaging in melasma.[30]

Another study reported sensitivity and specificity values of multiphoton laser tomography up to 95% and 97%, respectively, in the diagnostic classification of melanoma.[31]

8 | ADHESIVE PATCH BIOPSY OR TAPE STRIPPING mRNA

It is a non-invasive diagnostic technique, which consists of obtaining samples of RNA, including epidermal genetic information from the stratum corneum and retrieved via polymerase chain reactions and DNA microarray analysis.[32] Tape stripping has demonstrated a specificity and sensitivity of 88% and 100%, correspondingly, for the diagnosis of melanoma and melanocytic lesions.[33] mRNA analysis of melanocytic lesions may present early genomic alterations preceding morphological changes of melanoma.[34] The main advantage of this non-invasive technique over invasive is that it may allow monitoring of lesions without invasive procedures like the biopsy, which may eventually benefit patients with poor wound healing, patients who are on anticoagulation therapy or have a tendency to develop hypertrophic scars and lesions involving cosmetically important sites.[35] This procedure permits simultaneous evaluation of multiple pigmented lesions like in patients with multiple dysplastic nevi at one point in time, without the discomfort and need of biopsy. However, the main limitation is that this technique is not suitable for lesions on palms, soles, mucous membranes and nails.[34] Furthermore, it may not be easy to use in ulcerated or bleeding lesions. In the end, additional repeated sampling may be required, if insufficient mRNA is collected.

According to a study, epidermal genetic information retrieval (EGIR) harvested specimens can be of use for the accurate diagnosis of melanoma by 17-gene genomic biomarker.[33] Non-invasive pigmented lesion assays can help to improve specificity of biopsy while maintaining or enhancing sensitivity.[34] The adhesive patch skin sampling can be used to collect skin samples, as well as RNA, DNA, and microbiome samples as an alternative to surgical biopsy.[36]

9 | HIGH FREQUENCY ULTRASONOGRAPHY (HFUS)

The introduction of high frequency ultrasonography has provided enhanced resolution for the visualization of superficial structures of skin. This has led to its successful application in dermatology including evaluation of neoplastic skin lesions and an area of increasing interest.[37]

HFUS device frequency varies between 20–100 MHz that is optimal for evaluation of skin and related structures. Benign tumors are more hyperechoic than invasive melanoma, which has reduced echogenicity due to decreased collagen bundles.[38] Basal cell carcinoma lesions appear hypoechoic and are characterized by heterogeneous echo structures with irregular margins.[39] The sensitivities for the identification of melanoma by qualitative HFUS features ranged from 83% to 100%.[40] In a study, 34 out of 54 nodular lesions were diagnosed as non-melanoma and in all (except of Spitz nevus) lesions, HFUS diagnosis was in agreement at least with dermoscopy, or/and histopathology images.[41]

In another study HFUS recognized 114 of the 130 pigmented skin lesions. Among the detected lesions, there was a 100% sensitivity and specificity for differentiation of melanoma/nevi from other lesions. Sensitivity and specificity for differentiating melanomas from non-melanoma lesions was 100% and 32%, respectively.[40] It can also be useful in differentiating morphea and lichen sclerosus lesions.[42]

The major disadvantage of HFUS is that it cannot identify the types of cells as compared to the invasive skin biopsy (histology). Furthermore, its resolution is not enough for characterization and establishment of diagnosis in skin cancers.[37]

Advantages and limitations of non-invasive diagnostic methods in pigmentary skin disorders and cutaneous cancer are summarized in Table 1.

10 | ROLE OF ARTIFICIAL INTELLIGENCE (AI) IN DIAGNOSIS OF PIGMENTARY SKIN DISORDERS AND SKIN CANCER

AI has significant potential in diagnosis of pigmentary skin disorders, classifying them into appropriate lesion and differentiating the lesions from one another. In a study, different AI techniques were studied for classification and differentiation of pigmentary lesions common nevi, dysplastic nevi, and melanoma. The results showed usefulness of machine-learning methods in this process with similar potential of logistic regression, artificial neural networks and support vector machines.[43]

In a recently published study, Yang and colleagues[44] reported slightly higher performance of the diagnostic model based on convolutional neural networks for benign, pigmented lesions as compared to skin specialist. Similarly, significant progress has been made in AI and its utility in diagnosis of skin cancers. Most of the models mainly use only patient images; other associated factors are often not taken into consideration. Although it has many advantages, there are several challenges associated with AI to become an accurate, sensitive and specific diagnostic method. Most of the studies with AI are performed in controlled set up. Hence, one of the major challenges is its testing in real-life settings.[45]

TABLE 1 Advantages and limitations of non-invasive diagnostic methods in pigmentary skin disorders and cutaneous cancer

Non-invasive diagnostic method	Advantages	Limitations
Dermoscopy	Useful in pigmented, as well as non-pigmented skin lesions Cost-effective Minimal time required for the procedure	Low magnification of underlying anatomic alterations Restriction of view of the superficial skin layers only
Confocal laser microscopy or reflectance confocal microscopy	Real time imaging of the epidermis and upper dermis at cellular level with high-resolution	Expensive equipment and a need of expertise Limited depth of penetration Difficultly in use in the presence of ulceration, hyperkeratosis, or dense pigmentation[11]
Optimal Coherence Tomography	Useful in the diagnosis of basal cell carcinoma	Chances of high false negative and positive rates[16]
Electrical impedance spectroscopy	Useful in diagnosis of early melanoma in patients with multiple dysplastic nevi and long-term monitoring of pigmentary lesions[18]	Cannot differentiate tumors like basal cell carcinoma and seborrheic keratosis
Multispectral imaging	Can be useful screening tool in multiple dysplastic nevi High contour accuracy in pigmented skin lesions[24]	Requires good spatial overlap of images Need of specialized image sensor based on the spectral channels
Multiphoton laser imaging	High sensitivity and specificity in diagnostic classification of melanoma[31] Generation of high-resolution images	Narrow field of view and the relatively small penetration depth makes visualization of architecture and margins of dermal tumors difficult[29]
Adhesive patch biopsy or Tape stripping mRNA	High sensitivity and specificity for diagnosis of melanoma and melanocytic lesions[33] Simultaneous evaluation of multiple pigmented lesions in a patient with multiple dysplastic nevi is possible[34] Ability to monitor lesions without invasive procedure[35]	Not suitable for skin lesions on areas like palms, soles, mucous membranes, and nails,[34] ulcerated or bleeding lesions
High frequency ultrasonography	Good resolution for the visualization of superficial skin structures	Inability to distinguish the types of cells as biopsy[37] No sufficient resolution for characterization and establishment of diagnosis in skin cancers[37]

11 | CONCLUSION

The introduction and advancement of non-invasive diagnostic techniques in dermatology has been evidenced in the past few years. Non-invasive techniques may supplement or replace invasive techniques, such as excision biopsy, for the diagnosis of pigmentary and neoplastic skin disorders. It may also be utilized to preoperatively assess the tumor margins and monitor treatment response. One of the advantages of non-invasive diagnostic techniques is that they can be repeatedly used in a comfort manner for the patient, and may offer an objective way to follow the course of a disease. Albeit, skin biopsy and histopathological examination, although painful, costly and time consuming, still remain the gold standard for lesions that are deep seated, ulcerated and hyperkeratotic. In the latter scenarios, there is still a role for non-invasive modalities, since they may augment in the establishment of the diagnosis.

CONFLICT OF INTEREST

No conflict of interest to declare.

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Yashdeep Singh Pathania: Writing and revising the manuscript. **Zoe Apalla:** Review and revising the manuscript. **Gabriel Salerni:** Review and revising the manuscript. **Anant Patil:** Review and revising the manuscript. **Stephan Grabbe:** Review and revising the manuscript. **Mohamad Goldust:** Conception, writing, review and revising the manuscript.

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.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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