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REVIEW ARTICLE

A Review of Noninvasive Techniques for Skin Cancer Detection in Dermatology

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Abstract

As a result of increasing melanoma incidence and challenges with clinical and histopathologic evaluation of pigmented lesions, noninvasive techniques to assist in the assessment of skin lesions are highly sought after. This review discusses the methods, benefits, and limitations of adhesive patch biopsy, electrical impedance spectroscopy (EIS), multispectral imaging, high-frequency ultrasonography (HFUS), optical coherence tomography (OCT), and reflectance confocal microscopy (RCM) in the detection of skin cancer. Adhesive patch biopsy provides improved sensitivity and specificity for the detection of melanoma without a trade-off of higher sensitivity for lower specificity seen in other diagnostic tools to aid in skin cancer detection, including EIS and multispectral imaging. EIS and multispectral imaging provide objective information based on computer-assisted diagnosis to assist in the decision to biopsy and/or excise an atypical melanocytic lesion. HFUS may be useful for the determination of skin tumor depth and identification of surgical borders, although further studies are necessary to determine its accuracy in the detection of skin cancer. OCT and RCM provide enhanced resolution of skin tissue and have been applied for improved accuracy in skin cancer diagnosis, as well as monitoring the response of nonsurgical treatments of skin cancers and the determination of tumor margins and recurrences. These novel approaches to skin cancer assessment offer opportunities to dermatologists, but are dependent on the individual dermatologist's comfort, knowledge, and desire to invest in training and implementation of noninvasive techniques. These noninvasive modalities may have a role in the complementary assessment of skin cancers, although histopathologic diagnosis remains the gold standard for the evaluation of skin cancer.

1 Introduction

The incidence of melanoma is increasing in fair-skinned White populations at a faster rate than any other major cancer, although melanoma-related mortality remains stable and is increasing in certain patient populations [1]. Because thin melanomas have an excellent prognosis, tools that accurately facilitate in the early detection of melanoma are desirable for good treatment outcomes and patient survival [1–3]. However, concern missing early cases of skin cancer must be balanced against increased cost and patient anxiety associated with unnecessary referral and excision of benign lesions [4].

Clinical and histopathologic evaluation of pigmented lesions remains challenging, even for experienced dermatologists [5]. Accuracy of visual clinical examination with the unaided eye for cutaneous melanoma is approximately 60%, which can improve with the use of dermoscopy [3, 6].

The gold standard and established standard of care for the diagnosis of atypical pigmented lesions remains histopathologic evaluation of skin biopsy specimens through pattern recognition and immunohistochemistry, although it is associated with considerable interrater variability and relies on two-dimensional analysis at a single point in time [1, 2, 5]. Studies have shown a biopsy ratio of 8 for experienced dermoscopy users, to >30 for other health care professionals of benign lesions for the histopathologic diagnosis of one melanoma [1, 2, 5]. Currently, confirming the diagnosis of cutaneous melanoma requires histopathologic examination

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Key Points

The gold standard for the diagnosis of atypical pigmented lesions remains histopathologic evaluation of skin biopsy specimens, although the diagnosis of these lesions clinically and histologically can be challenging.

Noninvasive techniques, including adhesive patch biopsy, electrical impedance spectroscopy, multispectral imaging, high-frequency ultrasonography, optical coherence tomography, and reflectance confocal microscopy, may play a role in the detection and diagnosis of skin cancer.

The value of these instruments will depend on the user's knowledge and confidence in their use.

of a skin biopsy specimen, and patients with increased melanoma risk often undergo several biopsy procedures, associated with significant morbidity and cost [7]. Additionally, some lesions that may represent early melanoma clinically may not meet full diagnostic criteria for melanoma histologically [1]. Traditional histopathologic techniques may be insufficient in the reliable identification of malignant melanoma in biopsies of suspicious pigmented lesions, and ambiguous diagnoses of pigmented lesions are challenging for both patients and physicians when making treatment decisions [8].

Nonmelanoma skin cancer (NMSC) is the most common type of cancer in the Western world, commonly affecting older adults and increasing in the younger population [9, 10]. The majority of NMSCs consist of basal cell carcinomas (BCCs), which are frequently located on the head and neck [11]. To improve cosmetic outcomes, noninvasive treatment options have been used in an effort to limit invasive procedures and scarring [12]. Thus, noninvasive techniques to diagnose and monitor NMSC have become appealing.

Adjunctive diagnostic methods to support clinical decision making that are objective, reliable, accurate, noninvasive, and easy to use have been sought [5, 8]. Recently, several diagnostic methods have been developed to assist with the diagnosis of skin cancer beyond clinical inspection [13]. These include dermoscopy, total body photography, adhesive patch biopsy, electrical impedance spectroscopy (EIS), multispectral imaging, ultrasonography, optical coherence tomography (OCT), reflectance confocal microscopy (RCM), photoacoustic imaging, Raman spectroscopy, other radiological methods such as computed tomography (CT) and magnetic resonance imaging (MRI), and many others. Dermoscopy is a widely available, fast, and inexpensive method that allows for enhanced visualization of cutaneous neoplasms. Molecular analysis studies are appealing because they can differentiate pigmented skin lesions and can predict the behavior of melanocytic neoplasms, although many rely on tissue obtained via skin biopsy [5]. This review includes a discussion of the use of adhesive patch biopsy, EIS, multispectral imaging, high-frequency ultrasonography (HFUS), OCT, and RCM for the detection of skin cancer (Table 1).

2 Discussion

2.1 Adhesive Patch Biopsy

Adhesive patch biopsy, or tape stripping mRNA, consists of acquiring samples of RNA from the stratum corneum for epidermal genetic information retrieval via DNA microarray analysis and polymerase chain reactions [14, 15]. Although nuclei are absent in the stratum corneum, it is hypothesized that melanocytes disperse mRNA to this cell layer through the same mechanism as pigment migration [16]. Wachsman et al. [16] also proposed the potential activation of keratinocytes by malignant melanocytic cells to produce melanocytic mRNAs. Tape stripping has demonstrated the most clinical utility in melanoma diagnosis, with 100% sensitivity and 88% specificity in the detection of melanoma and melanocytic lesions in a 17-gene classification system developed by Wachsman et al. [16].

Gerami et al. [5] demonstrated similar accuracy in differentiating melanoma from nonmelanoma samples with a 2-gene subset of the original 17-gene classifier. They demonstrated a sensitivity of 91% and specificity of 69% for the distinction of melanoma from nonmelanoma pigmented lesions in a validation set. This method tested for Long Intergenic Non-Protein Coding RNA 518 (*LINC00518*) and preferentially expressed antigen in melanoma (*PRAME*). The gene expression signatures of *PRAME* and *LINC00518* are present in more than 90% of melanomas and can distinguish primary melanoma from nonmelanoma skin lesions with a negative predictive value > 99% [2, 5]. Benefits of the simplified 2-gene pigmented lesion assay (PLA) include decreased cost and turnaround time without a need for complex computer algorithmic data interpretation [5]. When integrated into clinical decision making, the 2-gene PLA significantly improved biopsy specificity and slightly improved biopsy sensitivity from 95.0 to 98.6% [2]. Identification of PRAME expression also provides prognostic information, as it has been identified as an important biomarker for metastatic risk in class 1 uveal melanoma, and is currently being explored as a potential therapeutic target [17]. Cockerell et al. [8] found that melanoma gene expression signature affects the treatment of melanocytic lesions and may improve patient outcomes through the provision of more definitive diagnoses by dermatopathologists and optimized treatment plans by dermatologists.

Table 1 Summary of benefits and limitations of noninvasive techniques used in dermatology

Noninvasive technique	Benefits	Limitations
Adhesive patch biopsy [1, 2, 5, 8, 16–18]	High sensitivity without trade-off for lower specificity With application, leads to a decrease in the number of biopsies, but an increase in the number of early melanomas detected Provides diagnostic information and allows for optimized treatment plans based on genetic profile Allows for observation of lesions without biopsy for patients who have poor wound healing, receive anticoagulation therapy, have a propensity to develop hypertrophic scars, and who have lesions in cosmetically sensitive areas	Difficult to use on mucous membranes, palms, or soles Cannot be used on bleeding or ulcerated lesions Repeated sampling may be required when insufficient mRNA is collected Some melanoma subtypes do not have expression of the genes included in the assay
Electrical impedance spectroscopy [2, 3, 5, 20–24]	High sensitivity Provides information to assist in decision for biopsy/excision Can detect both melanoma and NMSC Useful for monitoring melanocytic lesions over time and for the detection of early melanoma	Low specificity Not intended to confirm diagnosis of melanoma May not reduce the number of unnecessary biopsies A high proportion of seborrheic keratoses give false-positive readings Cannot accurately assess lesions with ulceration, inflammation, and scar tissue Limited efficacy on palms, soles, hairy scalp, and curved surfaces
Multispectral imaging [2, 7, 27, 32–34, 36, 37]	High sensitivity Fully automatic device No requirement for specific training and expertise Prebiopsy tool that aids in decision to biopsy a lesion to rule out melanoma Useful for primary care providers in the selection of melanocytic lesions for referral	Low specificity Does not decrease number of biopsies performed Operator-dependent Limited by constraints inherent to the device (malfunctioning of the machine) May not accurately assess NMSCs
High-frequency ultrasonography [43–53]	High sensitivity, with average specificity In vivo assessment of skin Serves as a complementary approach to assess tumor depth to assist with surgical planning and making therapeutic decisions	Operator-dependent Does not have histologic resolution Difficult to assess lesions on the plantar area and skin with extensive photoaging Difficult to accurately measure very thin and thick melanomas Tumor depth overestimation may occur with inflammatory infiltrates and dermal nevus tissue below the melanoma Tumor depth underestimation may occur when pressure is placed on vascularized tumors
Optical coherence tomography [9–11, 55–57, 59–61, 63, 64, 68, 69]	High sensitivity and specificity Can decrease biopsy rate Can 'rule in' lesions for surgery and refine surgical excision borders Improve earlier detection of skin cancer Can be used for monitoring the effectiveness of noninvasive treatments for skin cancer High resolution imaging of the skin, greater than HFUS Can image greater depth than RCM	Does not reach histological resolution Lower resolution than RCM Cannot produce quality images of lesions with crust or hyperkeratosis Misdiagnosis of amelanotic melanoma for BCC has occurred Greater diagnostic accuracy in experienced compared with inexperienced users
Reflectance confocal microscopy [59, 70, 72–75, 77–80]	High sensitivity and specificity Provides high-resolution imaging, close to histologic resolution Can decrease the number of unnecessary biopsies Can be used to improve accuracy in the detection of tumor margins and the recurrences of skin cancers Can be used to monitor the effectiveness of nonsurgical treatments Can differentiate benign and malignant skin lesions through recognition of specific confocal features Can accurately diagnose amelanotic melanomas	Limited depth of visualization Requires expensive equipment Involves extensive training in its use Is a time-intensive procedure False-negative readings may occur when diagnostic features are below the papillary dermis Lesions that are densely pigmented and with hyperkeratosis or ulceration are difficult to assess False-positive readings may occur with inflamed lesions and nevi with a high degree of dysplasia

BCC basal cell carcinoma, *HFUS* high-frequency ultrasonography, *NMSC* nonmelanoma skin cancer, *RCM* reflectance confocal microscopy

Lesions considered to be falsely identified as melanoma via mRNA analysis may represent early detection of genomic alterations that may precede the morphological changes of melanoma [2, 16]. The 2-gene PLA offers a unique approach to lesion analysis by relying on biologic information of gene expression profiles rather than visual information to detect early melanomas [2]. Ferris et al. [2] found that including PLA data in the clinical biopsy decision-making process of pigmented lesions led to a decrease in the total number of biopsies, but an increase in the number of early melanomas biopsied and detected. Differentiation of solar lentigo, lentigo maligna, and lentigo maligna melanoma via histology can be a diagnostic challenge, and tape stripping may be a useful adjunct in differentiating these entities [16].

Adhesive patch biopsy may allow for clinical observation of lesions without invasive biopsy and for a reduction in unnecessary biopsy procedures, which may benefit patients with poor wound healing, who receive anticoagulation therapy, who have a propensity to develop hypertrophic scars, and who have lesions in cosmetically sensitive areas [1, 5]. Additionally, this procedure allows for simultaneous evaluation of several pigmented lesions at one point in time without discomfort or the wound care required with skin biopsies, which may be useful for the evaluation of patients with dysplastic nevus syndrome [1]. This method has a cost comparable to histopathology, may improve patient outcomes, and reduce health care costs [2, 5].

Hornberger and Rigel [18] found a decrease in biopsy ratio from 12.5 with visual inspection to 2.4 when applying PLA to analysis, as well as the number needed to excise decreasing from 2.85 with visual inspection to 1.37 with PLA application. There were also lower costs for initial biopsy, excisions, surveillance of patients, and management of melanoma, as well as improvement in the patient experience with PLA use.

A limitation of adhesive patch biopsy is that it may not be used for evaluation of lesions on mucous membranes, palms, soles, or nails [2, 5]. It should not be used on lesions that are bleeding or ulcerated [2]. Additionally, repeated sampling may be required when insufficient mRNA is collected [1]. Although there is a high frequency of PRAME expression in primary cutaneous melanoma, there is variance of expression depending on the melanoma subtype [17]. Lezcano et al. [17] found PRAME expression to be present in only 35% of desmoplastic melanomas, although it was high (approximately 90%) for conventional melanomas.

PLAs may have more broad clinical application. For example, a more complex 23-gene assay has been used to provide additional information in excised specimens with histopathologic uncertainty [5]. Additionally, PRAME immunohistochemical analysis may be used for margin assessment in PRAME-positive melanomas and as an ancillary diagnostic tool in suspected melanomas [17].

2.2 Electrical Impedance Spectroscopy

The EIS device Nevisense (SciBase AB, Stockholm, Sweden) was designed as an adjunct diagnostic tool for melanoma detection for lesions with one or more historical or clinical features of melanoma [3]. However, the Nevisense system is not intended for confirmation of a clinical diagnosis of melanoma, but, instead, for the provision of additional clinical information when making a decision for excision [3].

EIS involves measurement of an evoked current by a voltage source through a skin lesion and conversion of the measured amplitude of the current gathered by the electrode into a digital signal for further analysis [15]. It computes a positive or negative outcome, along with a score that increases with lesion severity [3]. Information is obtained regarding conductivity of biological tissues, which is related to water content, including both free water in the extracellular fluid and water bound to proteins [15]. Electrical properties of human tissues are thought to be due to histological features, which change when cells undergo malignant transformation and are detected by EIS [19, 20]. Therefore, EIS is useful for monitoring lesions over time and for the detection of early melanoma in patients with multiple dysplastic nevi [21].

Nevisense accurately detects both NMSC and melanoma [3]. Most noninvasive techniques are limited to accurate detection of melanoma, and the broad scope of Nevisense to detect NMSC is a unique feature of the instrument [3]. Malvehy et al. [3] found the EIS-based Nevisense system to have a sensitivity of 96.6% and specificity of 34.4% in the detection of melanoma in a cohort of mostly in situ and early invasive melanoma in a multicenter, prospective, and blinded clinical study. In this study, the sensitivity of Nevisense increased with Breslow thickness, and there was an observed 100% sensitivity in the detection of NMSC [3].

However, Har-Shai et al. [22] reported electrical bioimpedance measured with a different instrument (TS2000M; TransScan Medical Ltd, Migdal Ha'Emek, Israel) as more sensitive in the detection of thin and in situ melanomas of smaller size (sensitivity of 100%) than thicker melanomas (sensitivity of 81%). Physicians diagnosed only 67% of the small and thin melanomas as malignant [22]. The overall sensitivity was 91% and specificity was 64% for the detection of melanoma on the extremities and trunk. The sensitivity for the detection of BCCs and squamous cell carcinomas (SCCs) was 71%.

In a pilot study, 12 melanoma lesions out of 178 benign and malignant skin lesions were detected by EIS with an overall sensitivity of 92% and 67% specificity, compared with physicians' diagnosis of melanoma with 75% sensitivity and 87% specificity [23]. Melanoma in situ was detected by EIS with a sensitivity of 88%, and more invasive melanomas were detected with a sensitivity of 100% [23]. In

this study, four of five BCCs were identified by EIS with a specificity of 67% [23].

A limitation of this method is the trade-off of a higher sensitivity (to minimize the risk of missing melanomas) for a lower specificity (linked to a higher rate of unnecessary invasive biopsies), also seen in several other diagnostic tools and dermatologists' clinical evaluation [2, 5, 24]. However, Svoboda et al. [20] found that inclusion of the EIS score in clinical decision making, compared with morphologic assessment alone, led to an increase in the mean sensitivity and specificity for ruling out melanoma. Sensitivity increased from 80.7 to 95.2% ($p < 0.001$) and specificity increased from 50.4 to 58.6% ($p < 0.001$). Although the total number of biopsies did not change considerably with the use of EIS results in the decision-making process, diagnostic accuracy improved, as there was an increase in biopsies of melanomas and a reduction in biopsies of benign lesions [20]. Therefore, EIS may enhance the decision-making process to biopsy a lesion when integrated with morphologic assessment [25].

False-negative readings occur in small lesions with minimal dermoscopic features and low cellularity, and may occur when the measurement procedure is not followed completely and with incomplete measurements of lesions [3]. EIS is limited by classifying a high proportion of seborrheic keratoses as falsely positive [3, 5]. However, in a study conducted by Glickman et al. [23], EIS demonstrated a specificity of 77% for 13 seborrheic keratoses. The authors suggested that EIS may assist physicians with classification of lentigo, seborrheic keratoses, and melanoma in situ [23]. EIS has not reliably differentiated between nodular and superficial BCC [19]. Bioimpedance does not seem to have the capability to accurately assess cutaneous photodamage [26].

Skin lesions with associated skin surface changes of ulceration, inflammation, and scar tissue are not accurately assessed by EIS [21]. Additionally, specific anatomic areas are not suited well for measurement by EIS, including palms, soles, hairy scalp, curved surfaces, and soft cutaneous regions, such as the abdomen [21]. The head and neck region has a difference in conductivity than the rest of the body, and this may affect the detection of melanoma by EIS, which may require different algorithms and/or thresholds for accurate assessment by EIS [22].

2.3 Multispectral Imaging

MelaFind (STRATA Skin Sciences; MELA Sciences Inc., Irvington, NY, USA) is a noninvasive and fully automatic multispectral imaging device and was approved by the US FDA for early detection of melanoma [2, 27]. MelaFind consists of a handheld scanner that obtains 10 digital multispectral images from visible to near-infrared wavelengths (430–950 nm) that penetrate to approximately 2.5 mm beneath the skin surface [27–29]. Lesions are identified by differences in the reflectance of light from the surrounding skin, then images are analyzed for the presence and distribution of specific dermoscopic features. Subsequently, MelaFind uses automatic image analyzers based on linear classifiers and statistical pattern recognition to determine the morphologic disorganization of the lesion [27, 30]. This imaging device functions as a prebiopsy tool to aid in the decision to biopsy a lesion to rule out melanoma by providing a lesion score and binary output based on the score relative to a set threshold value [7, 27]. Positive indicates the lesion should be considered for biopsy to rule out melanoma, and negative indicates the lesion should be considered for evaluation at a later time [27].

MelaFind has a sensitivity of 98.3%, but a low specificity of 9.9% [2, 27]. It has been criticized for its low specificity in melanoma detection and high rate of biopsy recommendation [7]. The low specificity of this device does not significantly decrease the number of biopsies performed with the current standard of care [2]. In a large multicenter, prospective study performed by Monheit et al. [27] to assess the performance of MelaFind in the evaluation of pigmented lesions, its biopsy ratio was 10.8:1 for melanoma and 7.6:1 for melanomas and borderline lesions [27].

However, MelaFind may improve biopsy decision making by dermatologists when used as a clinical adjunctive tool because, when integrated with clinical history and clinical and dermoscopic images by dermatologists, the reduced specificity may be acceptable with increased sensitivity to identify an increasing number of early melanomas [29, 30]. In this context, multispectral imaging may be helpful as a screening tool in patients with multiple dysplastic nevi [21].

However, Cukras [31] noted that MelaFind recommended biopsy in 44 of 47 lesions in the study conducted by Wells et al. [24], and, of the 3 nonbiopsy lesions, 1 was a melanoma. Cukras suggested that these data do not support MelaFind as a sensitive tool to guide dermatologists.

MelaFind is limited by operator dependence and constraints inherent to the device itself, such as malfunctioning of the machine, failure of automatic segmentation, and failure to produce a result if the image fails automatic quality control algorithms [27]. Due to MelaFind's assessment of overall structural disorganization rather than cellular atypia, this device may not accurately assess NMSCs [7]. It may require additional cost to a dermatologist's practice, with minimal impact [31].

Spectrophotometric intracutaneous analysis (SIA) is another noninvasive multispectral imaging device for assessment of pigmented lesions to identify melanoma [32]. It was developed to overcome the limitations of dermoscopy, including the high subjectivity and extensive training and experience required for diagnostic accuracy [32]. The SIAscope (Astron Clinica, Cambridge, UK) is a handheld device that probes the skin with wavelengths of light from

400 to 1000 nm (visible and infrared light) on 1.2–2.4 cm^2 areas of skin [32, 33]. It formulates SIAgraphs of the skin that are eight narrowband, spectrally filtered images, which are calibrated and subsequently used as inputs into a series of algorithms that rapidly analyze the composition, concentration, quantity, distribution, and position of chromophores (including eumelanin, hemoglobin, and collagen) within the papillary dermis and the relative position of melanin to the dermoepidermal junction to detect microscopic architecture [32, 33]. The proprietary algorithm (Astron Clinica) calculates a total score from a combination of features consistent with melanoma found on SIAscope to give a binary output of 'strong risk of melanoma' or 'low risk of melanoma' [34]. However, findings may not directly correlate with histology, specifically dermal melanin, blood displacement, and collagen holes [35]. New versions can extract information from dermoscopic images [7].

Moncrieff et al. [32] found a sensitivity of 82.7% and specificity of 80.1% in the diagnosis of melanoma in the evaluation of 348 pigmented lesions that had a lesion diameter ≥ 6 mm, dermal melanin, and erythematous blush from blood displacement on SIAscopy. Detection of dermal melanin alone by SIAscopy increased sensitivity of 94.4–96.2% at the expense of lower specificity of 56.8–64% for melanoma detection [7, 32, 33].

Glud et al. [34] found that when SIAscopy was compared with dermoscopy in the evaluation of pigmented lesions, it had a higher sensitivity (100% vs. 92%) but lower specificity (59% vs. 81%). They concluded that the lower specificity of SIAscopy did not support its use for routine screening of melanocytic lesions and suggested dermoscopy remain the preferred noninvasive diagnostic tool for assessment and diagnosis of pigmented lesions [34]. Similarly, Haniffa et al. [36] concluded from a prospective study in the clinical assessment of 881 pigmented lesions that there was no evidence for the use of SIAscopy for dermatologists to identify melanoma from benign pigmented lesions because the sensitivity and specificity for melanoma diagnosis before and after SIAscopy were 94% and 91% versus 87% and 91%, respectively. However, these findings demonstrate the potential value of the use of SIAscopy by general practitioners because it performed similarly to a dermatologist with 3 years of experience in dermoscopy when compared with histological diagnosis of pigmented lesions [37].

Because SIAscopy does not require specific training and expertise, it may be helpful for nondermatologists in the selection of pigmented lesions for referral, and it is designed for this purpose [7, 36]. It is simple to learn, reliable, and has reproducible findings [32].

SIAscopy may be limited in its application to primary care settings due to false-positive readings of seborrheic keratoses and hemangiomas [7, 33, 36, 38]. However, MoleMate is a new scoring algorithm designed for use by primary care providers and has additional features to correctly distinguish seborrheic keratoses and hemangiomas from melanoma. The MoleMate training program has led to improvement in performance by general practitioners [39, 40].

Older versions of the SIAscope may not be superior to dermoscopy, but newer versions of the SIAscope provide high-resolution images of dermoscopy and SIAscopy, allowing for simultaneous assessment of both methods and a valuable teaching resource [7, 37]. SIAscopy uses combinations of features to assess for the likelihood of melanoma and may require additional evaluation through pattern analysis of pigmented lesions by clinical and dermoscopic assessment to reduce the false-positive rate [32]. Melanomas missed by the SIAscope have included melanoma in situ and superficial spreading malignant melanoma with a Breslow thickness ranging from 0 to 1.2 mm [33, 36].

2.4 High-Frequency Ultrasonography

The value of ultrasonography as an imaging modality in dermatology was recognized around 1979, although ultrasonography has been applied as an imaging tool in general medicine since 1950 [41, 42]. The recent introduction of HFUS provided enhanced resolution and visualization of superficial structures. This has led to increasing interest and successful application of ultrasound in dermatology, including evaluation of benign and malignant tumors, inflammatory skin diseases, and cosmetic dermatology [43].

Ultrasonography is an imaging modality that relies on sound waves released from a transducer to identify structures and to accentuate structural heterogeneity [42]. Sound waves pass through structures with differences in density, causing a change in velocity that may result in refraction, reflection, scatter, or varying degrees of absorption of sound energy by the structures [42]. HFUS devices (20–100 MHz) are optimal for evaluation of the skin and surrounding structures, as higher frequencies allow for increased spatial resolution at the expense of diminished depth of penetration.

Benign tumors tend to have the presence of more internal echoes than invasive melanoma, which is usually characterized by a homogenous, well-defined structure with reduced echogenicity, likely as a result of decreased collagen bundles in melanoma [4, 42]. BCCs appear hypoechoic and are characterized by heterogeneous echostructures, frequently with irregular margins [44].

HFUS provides an 'in vivo' assessment of the skin, with quantitative parameters, detailed imaging of the skin structures up to 15 mm depth (with a 20 MHz transducer), and may be utilized as a complementary, noninvasive method to accurately and reliably identify tumor depth for the determination of tumor prognosis, therapeutic decisions, and surgical planning [43–53]. HFUS also demonstrates the potential to differentiate between melanoma, benign nevi,

and seborrheic keratoses, along with the monitoring of inflammatory conditions and photodamage [42, 54]. Limitations for measuring melanoma thickness by HFUS include very thin melanomas, very thick melanomas (exceeding the measurable depth of ultrasonography), lesions in the plantar area, skin with extensive photoaging, and overestimation of melanoma depth by the presence of inflammatory infiltrates and dermal nevus tissue below the melanoma [49, 52].

Dinnes et al. [4] evaluated six studies that met the authors' inclusion criteria for a comprehensive review of the diagnostic accuracy of HFUS in the evaluation of melanoma, cutaneous SCC, and BCC compared with a reference standard or clinical follow-up. The authors reported that previous studies should be considered as preliminary evaluations for the value of HFUS in accurately diagnosing skin cancer in adults, as insufficient data are currently available to determine how HFUS may be used in practice for the diagnosis of melanoma or BCC. No previous studies were identified that evaluated the use of HFUS for the diagnosis of cutaneous SCC in the comprehensive review conducted by Dinnes et al. [4].

The sensitivities for the identification of melanoma by qualitative HFUS features were at least 83% [47] and ranged to 100% [45]. Bessoud et al. [45] reported a sensitivity of 100% and specificity of 32% for the distinction of melanoma from nonmelanoma lesions, although the sensitivity of melanoma may have been overestimated, as 16 lesions that were not visualized by ultrasonography were excluded in the statistical analysis.

HFUS cannot identify cell types (compared with the gold standard of histology) and does not currently have the resolution for conclusive diagnosis as a sole imaging method for the characterization and diagnosis of skin cancer [43]. There are limits to the sound energy that may be applied to the skin for optimized imaging resolution without causing skin damage, and the required frequency of 40–60 MHz to obtain imaging resolution that corresponds to light microscopy is considered possible in *ex vivo* specimens [42].

Meyer et al. [50] compared the assessment of lesion thickness by OCT and HFUS with histopathology of 138 equivocal melanocytic lesions in a single-center prospective study and found that the interrater reproducibility ($G = 0.97$) and repeatability ($G = 0.99$) of HFUS were excellent. The agreement between HFUS and histopathological measurements demonstrated an intraclass correlation coefficient (ICC) of 0.807, with a confidence interval (CI) of 0.703–0.877 [50]. There was an increase in difference in the assessment of tumor depth between HFUS and histopathological examination as tumor thickness increased [50]. The authors concluded that HFUS is a reliable method with excellent intra- and interreproducibility for the measurement of melanoma depth *in vivo*. As a result, the noninvasive nature of the instrument may allow for single-step surgical excision of melanomas, with an appropriate margin and a reduction in re-excision rates [50].

Crisan et al. [43] compared the ultrasonographic depth index (measured with HFUS) with the histological depth index of 46 subjects with diagnoses of BCC (18 subjects), superficial spreading melanoma (SSM; 8 subjects), and nodular melanoma (NM; 20 subjects) in a prospective, controlled study. They found a correlation of 98.4% between the ultrasonographic and histological index for BCC and NM, and a correlation of 99.4% for subjects with SSM. They concluded that ultrasonographic depth index was comparable with histological depth index, with a very high sensitivity of 98–99%. However, HFUS provided slightly lower values for tumor depth than histology for BCC and NM and provided a higher value for SSM for tumor depth than histology [43]. Lower values of tumor depth for BCC by ultrasonography compared with histology have been reported previously, but without statistically significant differences [51]. The overestimation of tumor depth by ultrasonography for SSM may have been a result of identification of inflammatory infiltrates associated with the tumor or cutaneous appendages that may be hypertrophied [43].

Ultrasonography is operator-dependent. For example, BCCs and NMs may have been underestimated in the study of Crisan et al. [43] as a result of the presence of vascularization in the tumors and pressure applied by the transducer on the compliant vasculature of the tumors. The histological tissue depth and in vivo assessment of depth by ultrasonography may not precisely match as the histological tissue goes through processing. Crisan et al. [43] have proposed the development of a correlation coefficient to link the histological and ultrasonographic depths. Additionally, overestimation of tumor depth may occur as a result of difficulty with differentiating hypoechoic areas, which may resemble the melanoma itself, surrounding inflammatory infiltrate around the tumor, and extension of the tumor into the subcutaneous tissue [15].

2.5 Optical Coherence Tomography

OCT (VivoSight; Michelson Diagnostics, Kent, UK) offers high-resolution imaging of the skin (lateral resolution: 7.5 μm; vertical resolution: 10 μm), close to histological resolution, with a depth of 2 mm [55, 56]. OCT is routinely used in ophthalmology for imaging of the retina and cornea, and its use has been expanded in other specialties, including dermatology [9, 55, 57]. The technology of OCT is based on interferometry, and the backscatter and reflection of infrared light when directed toward the skin are measured to provide an image [56, 58]. Similar to ultrasonography, OCT produces cross-sectional representation of tissue in real time, although OCT has higher resolution than ultrasonography because OCT uses optics instead of acoustics [57]. However,

standard OCT does not have resolution to distinguish cellular details [55].

Several studies regarding OCT use in the diagnosis and management of BCC have been completed. In a multicenter, prospective, observational study of clinically challenging lesions, Markowitz et al. [11] found that OCT significantly improved ($p < 0.01$) the sensitivity and specificity for detection of BCC compared with clinical and dermoscopic evaluations. The sensitivity of OCT in this study was 92.9% and specificity was 80%, compared with the lower sensitivities of clinical (62.9%) and dermoscopic (78.6%) examinations and specificities of clinical (48.9%) and dermoscopic (55.6%) examinations. Diagnostic accuracy and diagnostic certainty by clinicians also improved with OCT use. The authors reported that the biopsy rate could be decreased by 36% by the use of OCT as a diagnostic aid.

Ulrich et al. [59] similarly reported a significant improvement in specificity with OCT use of lesions clinically difficult and suspicious for BCC compared with clinical and dermoscopic examinations, with reported specificity of 75.3% ($p < 0.001$) with the OCT application. The sensitivity for detection of BCC improved with OCT use (95.7%, from 90% by clinical examination), although this did not reach statistical significance. In another study, Olsen et al. [9] reported that skilled OCT users diagnosed BCC with a sensitivity of 86–95% and a specificity of 81–98%. Experienced OCT observers had a higher diagnostic accuracy compared with inexperienced observers.

OCT could be used in conjunction with clinical examination and dermoscopy to 'rule-in' lesions suspicious for BCC to be sent for immediate surgery [11, 59]. In addition, OCT has demonstrated the potential to refine clinically estimated excision borders in Mohs micrographic surgery (MMS), to reduce the final size of the Mohs defect, and to reduce the number of stages in MMS without diminishing the security of tumor-free borders [57, 60, 61]. The patient experience may also be enhanced, as patients may receive diagnosis and treatment of BCCs on the same day without the need for biopsy.

OCT also offers other benefits in the clinical setting, including earlier detection of BCC and improved clinical and cosmetic outcomes, as well as reduced morbidity [11]. One study [12] found that adjunct use of OCT with clinical and dermoscopic examination increased the detection rate of BCC recurrence. OCT is a valuable resource for treatment monitoring for patients with NMSCs undergoing photodynamic therapy [10, 56]. OCT may also be helpful for the management of patients with several suspicious skin lesions and field cancerization to evaluate skin lesions without requiring multiple biopsies [59]. A high correlation for tumor depth of BCCs estimated by OCT and measured by histopathologic examination has been reported [62]. The differentiation of BCCs from BCC imitators and subtypes of BCCs are possible with newer advances of OCT (high-definition OCT [HD-OCT] and multi-beam Swept Source – OCT [MSS-OCT]) [63, 64]. High correlation of key diagnostic features of BCCs with histopathologic findings has been reported with MSS-OCT [64]. Boone et al. [65] developed a diagnostic algorithm for the discrimination of SCC from actinic keratosis and normal skin based on a training set with HD-OCT.

The enhanced resolution of HD-OCT allows for visualization of structural and cellular details of melanocytic lesions [66]. Boone et al. [66] found, in a retrospective pilot study, a higher accuracy for melanoma diagnosis with in vivo HD-OCT analysis of optical properties than analysis of in vivo HD-OCT morphology alone. Gambichler et al. [67] reported a sensitivity of 74.1% and specificity of 92.4% of HD-OCT for melanoma diagnosis.

Overdiagnosis of NMSCs may occur with OCT use when OCT images are taken of healthy skin that is near NMSC lesions [9]. Because some OCT features of BCC are nonspecific and overlap with amelanotic melanoma, misdiagnosis of amelanotic melanoma, by clinical, dermoscopic, and OCT examinations as BCC has been reported [68, 69]. OCT cannot produce quality images of lesions with extensive ulcerative crust or hyperkeratosis and difficult-to-access areas [64, 65]. Additionally, artifacts in the imaging process may lead to poor imaging quality [58, 64].

A limitation of HD-OCT for visualization of melanocytic lesions is that the performance is dependent on tumor thickness [67]. High false-negative rates for very thin melanomas and high false-positive rates for dysplastic nevi have been reported [67].

2.6 Reflectance Confocal Microscopy

RCM offers high-resolution imaging, close to histologic resolution, but limited visualization of depth corresponding to the papillary dermis (200–300 μm) [70]. A low power laser beam with infrared wavelength of 830 nm illuminates a focal area of skin [70]. A computer software produces a two-dimensional, gray-scale image of the area after light is filtered through a small pinhole and imaged on the detector [70]. The RCM images are taken parallel to the skin at various depths and have correlation with histopathologic features [70, 71].

RCM can differentiate benign and malignant skin lesions through recognition of specific confocal features of different skin lesions, including differentiation of BCC subtypes and lentigo maligna from lentigo simplex [59, 70, 72]. Benign nevi that are atypical or equivocal on dermoscopic examination can often be differentiated from melanoma by RCM [73]. RCM can also accurately characterize dermoscopic feature-poor lesions, including amelanotic melanoma [73]. The overall sensitivity of RCM for melanoma detection

is 91–100%, and the specificity is 68–98% [74]. For BCC detection, the overall sensitivity is 85–97%, and the specificity ranges from 89% to 99% [74]. Borsari et al. [75] reported a sensitivity of 95.3% and specificity of 83.5% for RCM in the evaluation of 1279 equivocal skin tumors. The number needed to excise to rule out melanoma was 2.4.

RCM can improve diagnostic accuracy and reduce the number of unnecessary biopsies, leading to a reduction in costs and improved cosmetic outcomes [70, 74, 76]. It can be used to improve accuracy in the detection of tumor margins and recurrences of skin cancers, provide guidance for the selection of biopsy site when the procedure is necessary, follow melanocytic nevi over time, and to monitor the effectiveness of and response to nonsurgical treatments of skin cancers [74, 77–79].

RCM requires expensive equipment and involves extensive training in its use and is a time-intensive procedure, requiring 7–10 min for image processing [74, 79, 80]. There are few trained physicians who can read RCM images [70, 74]. Therefore, the benefits of improved diagnostic accuracy with the additional time required for RCM implementation in the workflow must be balanced [74].

Another limitation of RCM is the restricted depth of penetration, and potential for false-negative diagnoses when diagnostic features are below the papillary dermis, which may occur in pure NMs [73]. False-negative readings by RCM may occur in melanomas with minimal architectural disarray [73]. RCM of lesions that are densely pigmented and associated with hyperkeratosis or ulceration is difficult [73]. Spitz tumors are difficult to differentiate from melanoma via RCM imaging, and the detection of early invasion of SCC is challenging [73, 81]. False-positive cases of melanoma by RCM may occur with inflamed lesions and nevi with a high degree of dysplasia [73].

A handheld RCM has a small probe that is helpful for the diagnosis of skin lesions on curved and narrow surfaces, including the face, eyes, and mucosa, which are often inaccessible by conventional RCM [78]. It is also faster and easier to use than conventional RCM [78].

3 Conclusions

Novel, innovative approaches in skin cancer diagnosis offer great opportunity for dermatologists, but the usefulness of these instruments will depend on dermatologists' knowledge and confidence in the instruments [15]. Dermoscopy is fast, easy to use, widely available, and improves the diagnostic accuracy of cutaneous neoplasms [82]. However, dermoscopy requires training, and the diagnostic accuracy of dermoscopy is dependent on experience [6]. Dermoscopy improves the diagnostic sensitivity of melanoma, but only for experienced examiners [6]. For experienced dermatologists using dermoscopy, the sensitivity was 89.7%, and specificity was 92.0% for melanoma [53]. New advances in dermoscopy have included machine learning and automated diagnosis without the requirement for human expertise [82].

Sequential digital dermoscopy imaging (SDDI) has been used to monitor atypical or changing melanocytic lesions over time to detect melanoma in lesions that do not have classic dermoscopic features of melanoma [83]. The reported specificity for the diagnosis of melanoma with short-term SDDI is 84%, and the sensitivity is 93% for in situ melanomas and 96% for invasive melanomas [84]. SDDI may limit unnecessary excisions, while allowing for early melanoma detection, but relies on patients to appropriately attend follow-up visits and for longer follow-up periods for the detection of lentigo maligna melanoma [84, 85].

The noninvasive techniques discussed in this paper may complement clinical and dermoscopic examination to improve diagnostic accuracy and overcome their limitations. The integration of noninvasive techniques may also be beneficial. For example, the integration of OCT and RCM into a combined system may provide comprehensive three-dimensional, real-time imaging to enhance skin cancer diagnosis [62]. Sahu et al. [62] found in a pilot study that when OCT and RCM were combined into a single probe, the imaging techniques complemented each other for BCC diagnosis. RCM demonstrates an improvement in the number of lesions needed to excise to rule out melanoma, to approximately 2.1–2.4 [73, 75].

Limitations of EIS and multispectral imaging are high sensitivity at the expense of low specificity for melanoma detection. Low specificity of these diagnostic aids does not resolve the issue of potentially unnecessary skin biopsy procedures, but when combined with dermoscopy and clinical examination may improve diagnostic accuracy [5, 20, 85]. EIS used in conjunction with SDDI demonstrated a decreased need for SDDI [86]. Adhesive patch biopsy with PLA has the benefit of improved sensitivity and specificity, without a trade-off of higher sensitivity for lower specificity seen in many other diagnostic tools to guide dermatologists in decisions to biopsy pigmented lesions [2].

Prospective evaluation of HFUS is necessary to determine its accuracy in the diagnosis of skin cancers in clinical practice, along with visual assessment and other imaging modalities (for example, dermoscopy), with a representative and clearly defined population [4]. However, currently available data may be useful to assist with determination of diagnostic characteristics and interpretation of melanoma and BCC with HFUS [4].

Although new screening tools may increase detection of skin cancers at an early and curable stage, without efforts for population-based screening in the US, a large proportion of the population will continue to experience high morbidity and mortality rates associated with melanoma

and NMSCs. A public health experiment in the German state of Schleswig-Holstein demonstrated the importance of melanoma screening by a significant decrease of 40% in melanoma mortality when a population-based melanoma screening was implemented [87]. However, the melanoma mortality in the rest of Germany and Denmark changed minimally during the same period [87]. Many public health initiatives have been implemented in the US, including educating and increasing patients' awareness of the appearance of suspicious skin lesions and the risks associated with skin cancer, as well as mass skin cancer screening programs [13].

Because melanoma screening is associated with low costs and morbidity and the potential for a strong trend in decreased mortality, it is important to consider where attention and funding are directed in the US [87]. It is clear that funding should be focused on efforts to develop an effective population-based screening in the US and a national plan to reduce melanoma mortality [87]. Other considerations should include if, and by whom, new noninvasive devices should be used as an aid to visual examination [87]. Currently, clinical examination and histopathological diagnosis remain the gold standard for the evaluation of skin cancer.

Compliance with Ethical Standards

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