Use of noninvasive imaging in the management of skin cancer

Roberta Giuffrida[a], *Claudio Conforti*[b], *Nicola Di Meo*[b], *Teresa Deinlein*[c], *Stefania Guida*[d], *and Iris Zalaudek*[b]

Purpose of review
To evaluate noninvasive imaging techniques in the management of skin cancers.

Recent findings
In the last decades, a wide range of noninvasive imaging methods has been developed in the field of dermatooncology with the aim to detect and assess the several structural and molecular changes that characterize skin cancer development and progression.

Summary
In this review, we discuss the current and emerging applications of noninvasive imaging approaches in skin cancer management, such as digital photography, dermoscopy, ultrasound sonography, reflectance confocal microscopy, optical coherence tomography, electrical impedance techniques, Raman spectroscopy, multispectral imaging, fluorescence imaging, and multispectral optoacustic tomography.

Keywords
dermoscopy, keratinocyte carcinomas, melanoma, noninvasive skin imaging, skin cancer

INTRODUCTION

The use of imaging techniques has revolutionized the way in which the physicians take care of the patients. In the last decades, a wide variety of noninvasive imaging methods has been involved in diagnosis and monitoring of treatment response for many dermatologic diseases. Among them, total body photography and dermoscopy improved the ability of clinicians to detect, diagnose, and manage skin conditions beyond unaided visual inspection [1▪▪], becoming the most used techniques for detecting and monitoring atypical skin lesions and for the early detection of melanoma and nonmelanoma skin cancer.

The present paper reviews the literature on the currently available cutaneous imaging devices and emergent technologies in the field of noninvasive management of skin cancer.

DIGITAL PHOTOGRAPHY

Dermatology is a very visually based specialty, which can be aided by clinical imaging, useful for documentation of lesions, follow-up, and response to treatment. Total body photography (TBP), also known as 'whole body photography' or 'total body mapping', is a type of digital photography that has become an essential tool for the early detection and monitoring of skin cancers [2]. Indeed, it allows acquiring and recording patients' entire skin surface at a static time, with standardized images. Newer commercial systems, through a camera mounted in standard position, allow taking pictures with similar positioning and lighting [3]. In classical TBP, a photographer (physician, nurse or professional photographer) takes a series of 24 (range 4–50) segmental baseline photos of the patients in various positions with a handheld camera. Photos may be stored electronically and used for side-by-side comparisons at follow-up, or may be analyzed by software make computer-assisted diagnoses of skin cancer [4].

[a]Department of Clinical and Experimental Medicine, Dermatology, University of Messina, Messina, [b]Dermatology Clinic, Maggiore Hospital, University of Trieste, Trieste, Italy, [c]Department of Dermatology and Venereology, Medical University of Graz, Austria and [d]Dermatology Unit, Department of Surgical, Medical, Dental and Morphological Sciences with Interest in Transplant, Oncological and Regenerative Medicine, University of Modena and Reggio Emilia, Modena, Italy

Correspondence to Roberta Giuffrida, MD, Department of Clinical and Experimental Medicine, Dermatology, University of Messina, Italy, via Consolare Valeria n1, 98125 Messina, Italy. Tel: +39 090 2212891; fax: +39 0902927691; e-mail: roberta_giuffrida@hotmail.it

KEY POINTS

- Skin cancer is one of the most common types of cancer worldwide.
- A wide variety of noninvasive imaging methods has been involved in diagnosis of skin cancers.
- Total-body photography and sequential digital dermoscopy assist in early melanoma detection in high-risk individuals.
- Noninvasive imaging techniques have become indispensable not only for diagnosis but also for adequate management of patients.

Especially in high-risk patients with numerous melanocytic lesions, this monitoring approach allows to detect new developing lesions or grossly change in size, shape, or color of individual lesions, that then could be recommended for surgical biopsy. Moreover, several digital photo cameras can capture clinical and dermoscopic images in tandem, allowing recording and reassessing them over the time.

Most of current commercially available TBP systems make 2-dimensional (2D) photography and the manipulation of a 3D surface, such as the human skin, into a 2D image could be a limitation of the technique. Recently, 3D imaging devices have been developed and promise to be more accurate and time-saving than 2D-based systems, increasing patient's comprehension of the images [5].

Finally, digital photography in dermatology forms the basis of *Teledermatology*, a tool that involves the use of telecommunications to send or forward digital images linked with medical information to a dermatologist for remote evaluation [5,6]. This approach, although is less accurate than in-person physical exam, improved access of care to underserved patients, making diagnosis and screening of skin cancer possible in places where it would not be otherwise. Its use was enhanced by the increasing diffusion of smartphones, which allows for easier transmission of patient information between providers [5,6].

DERMOSCOPY

In the 1990s, dermoscopy (also known as 'dermatoscopy' or 'epiluminescence microscopy') [7▪] was added as a noninvasive tool to the physical examination, and further improved the diagnostic accuracy of clinicians, particularly for which concerns to diagnose skin cancers, showing a sensitivity and specificity in the detection of melanoma significantly higher than the naked-eye examination (Fig. 1) [1▪▪,8,9]. It is a fast, inexpensive, and essentially free of complications technique, allowing a rapid and magnified (10×) in-vivo observation of the skin surface, with the visualization of morphologic structures in the epidermis and papillary dermis, correlated with specific histopathologic features [10]. Videodermatoscopy is performed with a video camera fitted to a headpiece equipped with optic fibers and lenses, providing higher magnification (10× to 1000×) and allowing visualization of the image on the computer screen and video recording.

Sequential digital dermatoscopic imaging (SDDI) is a monitoring approach that records and assesses successive dermoscopic images of melanocytic and

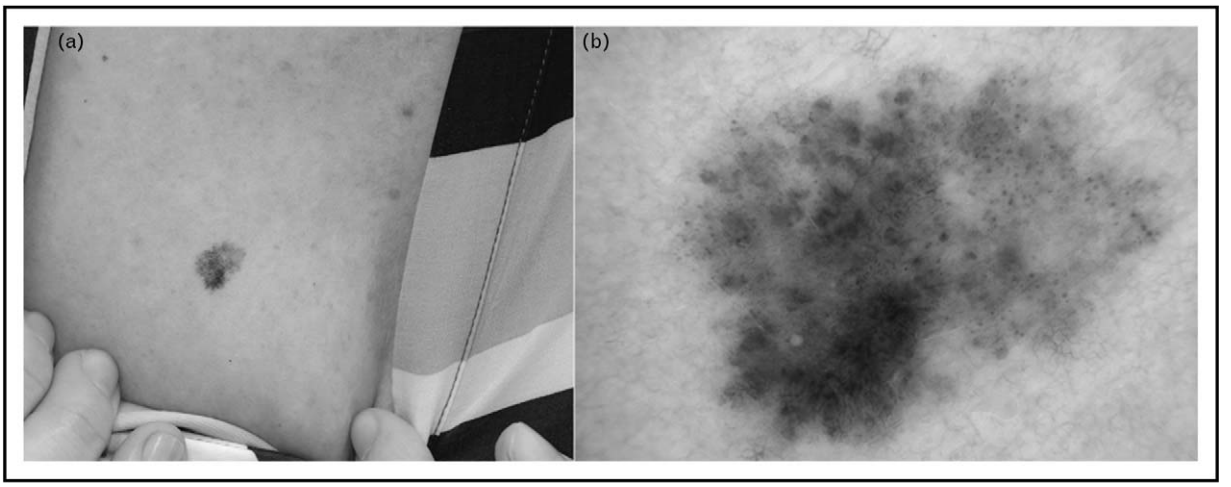

FIGURE 1. Clinical (a) and dermoscopic (b) picture of a lentigo maligna on the right chest detected by digital dermoscopy. Clinically, an irregularly demarcated lesion of about 1 cm in diameter, with different shades of brown, is observable. In dermoscopy, multiple brownish dots of different size, spread over the entire lesion, and an irregular reticular network on a light-brown to dark-brown background are visible.

nonmelanocytic lesions, separated by an interval of time, in order to detect any suspicious change [11]. It is mainly used to increase specificity, leading to a more precise selection of lesions requiring excision and avoiding unnecessary biopsies of biologically benign lesions [12,13].

A large meta-analysis found that, by using SDDI, 54.6% of melanomas can be excised *in situ* [14,15].

In addition, for differentiating benign pigmented lesions from melanoma and detecting early-stage melanoma, dermoscopy is an effective tool for the diagnosis of keratinocyte skin cancers (basal cell carcinoma, actinic keratosis, Bowen's disease and invasive squamous cell carcinoma) [16,17], and for their preoperative evaluation or assessment of response to topical treatment and long-term follow-up [18,19].

To date, several dermoscopic structures and diagnostic algorithms have been described, to help the clinician to determine the melanocytic or nonmelanocytic and benign or malignant nature of a lesion and to choose management and treatment options for specific types of skin cancers (Fig. 2) [9,20▪].

The importance of the combined use of TBP and dermoscopy for melanoma detection has been well described in literature [21]. Argenziano *et al.* reported that melanoma may grow slowly and thus changes can only be seen after long-term follow-up [22]. From this perspective, a monitoring approach consisting of the combination of TBD and dermoscopy results more accurate than the two strategies separately, allowing to detect melanomas in early stages with a low rate of excisions [23].

The use of dermoscopy is increasing in popularity among dermatologists and nondermatologists; however, it should be remembered that, to be effective, this technique requires proper training and expertise [24].

REFLECTANCE CONFOCAL MICROSCOPY

The first use of reflectance confocal microscopy (RCM) in dermatology dates back to 1990 [25]. It is an innovative noninvasive imaging tool that enables real-time in-vivo or ex-vivo characterization of skin lesions at cellular level resolution (0.5–1 μm) and provides serial horizontal images of the different layers of the skin (from the epidermis to the papillary dermis) up to a thickness of 200–300 μm [26].

RCM has been widely used for the diagnosis and therapeutic monitoring of skin cancers [27,28].

The light source is a low-power near-infrared (830 nm wavelength) laser, emitting light from a diode at a power up to 35 mW, which penetrates the skin in a nondestructive way and is reflected from subcellular structures at a desired focal point [29]. A small pinhole permits to collect only the light reflected from the focal plane, rejecting that coming back from out-of-focus planes (confocal principle) [30▪].

RCM uses the different refraction indexes of tissues and cell structures, providing the source of contrast (bright white for refractive structures, dark for nonrefractive ones) and generating a black and white image [29]. Highly refractive skin components are melanin (refractive index = 1.72), contained in

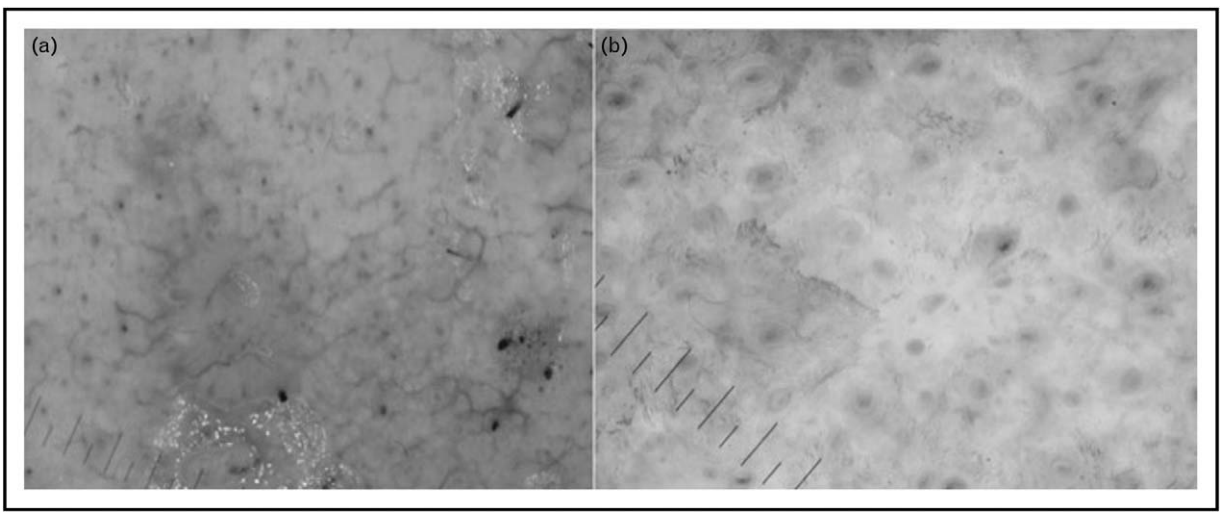

FIGURE 2. (a) Dermoscopic image of a basal cell carcinoma (BCC) on the right cheek in a patient with multiple BCCs in the context of a Gorlin-Goltz syndrome. After therapy with imiquimod cream over a period of 6 weeks, no features of a basal cell carcinoma are evident dermoscopically (b). Of note, the lack of tumor-specific criteria in dermoscopy is equivalent to healing of the tumor histologically.

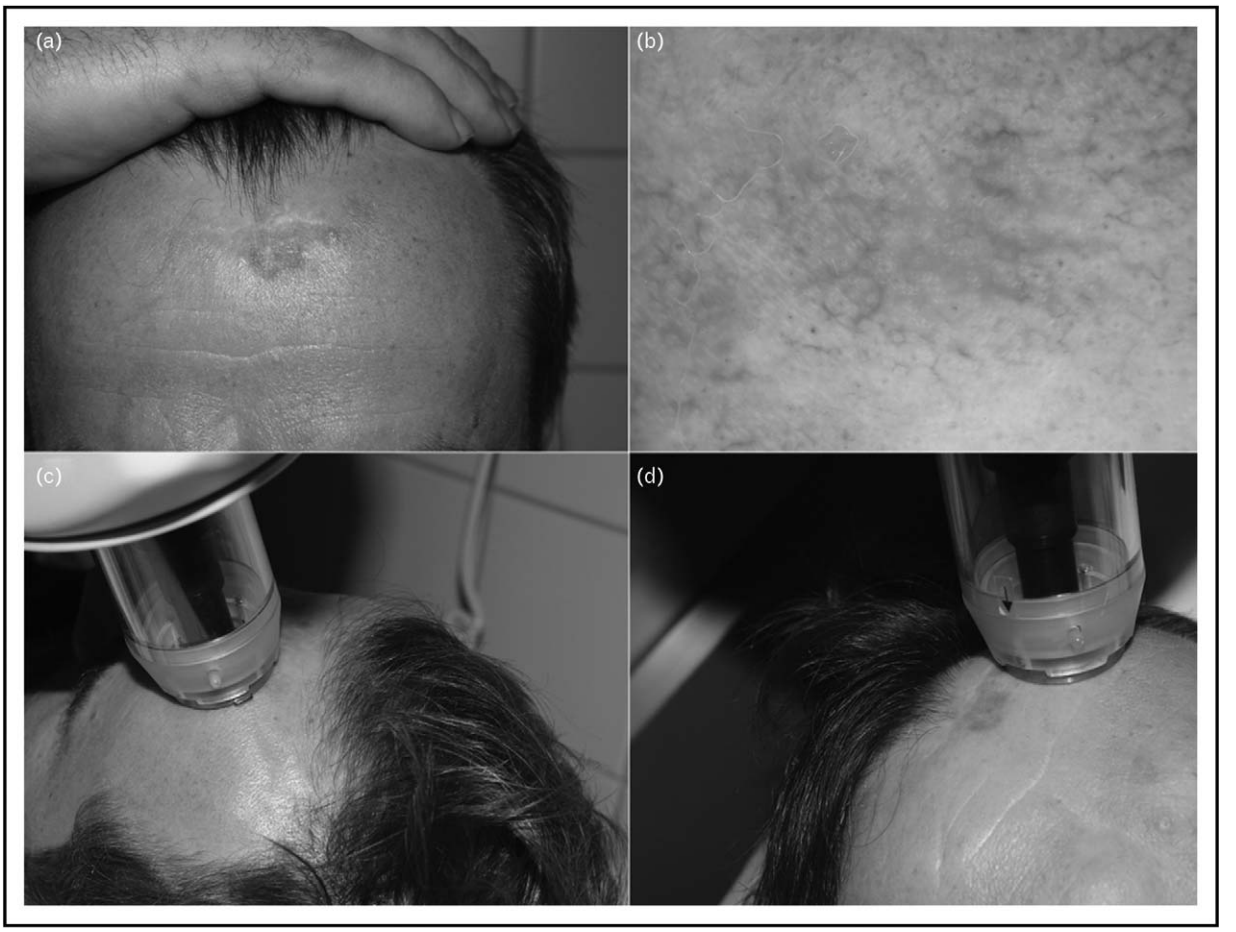

FIGURE 3. Brownish, well demarcated lesion on the forehead of a 32-year-old male patient. Dermoscopically, the lesion exhibits multiple white lines around the hair follicles on a brown-yellowish background (a, b). In uncertain cases, especially if the lesions are located on the face, reflectance confocal microscopy (RCM) is additionally performed (c, d). However, punch biopsy of the lesion was performed and histology revealed a granuloma faciale.

melanosomes, melanocytes, melanophages and pigmented keratinocytes, and keratin (refractive index = 1.51) [31▪]. Fluorescence confocal microscopy is based on the same optical principles of RCM, but uses an exogenous fluorescent dye to produce highly specific contrast.

RCM has been used in several skin conditions; however, its main application remains the diagnosis of suspect lesions presenting with equivocal clinical and/or dermoscopic features and requiring a biopsy, especially when located on cosmetically sensitive areas (i.e., pigmented macules of the face) or large enough to require assistance in targeting the area for incisional biopsy (Fig. 3) [25,32]

Imaging of normal skin surface with RCM shows uniformly bright and regular keratinocytes in the spinous-granular layer of the epidermis with a 'honeycomb' appearance, where the bright lines correlate to cytoplasm of keratinocytes and their intercellular connections and the dark holes correlate to the nuclei that are regular in size and shape. Below the dermo-epidermal junction, basal keratinocytes appear as bright rings surrounding dark dermal papillae, termed 'edged papillae' [33].

With regard to in-situ and invasive squamous cell carcinoma (SCC), Nguyen *et al.* recently performed a systematic review on the role of RCM in the diagnosis of actinic keratosis, actinic cheilitis, erythroplasia of Queyrat, Bowen's disease, keratoacanthoma, and invasive SCC reporting an overall value of sensitivity and specificity of 79–100% and 78–100%, respectively [34,35▪▪].

The most known RCM features of SCC are the presence of an atypical honeycomb or a disarranged pattern of the stratum granulosum and spinosum, with pleomorfism of keratinocytes and round blood vessels traversing through the dermal papilla [25,34]. However, to date, RCM does not allow differentiating actinic keratosis, Bowen's disease, keratoacanthoma, and invasive SCC with high specificity.

Conversely, RCM features of basal cell carcinoma (BCC) are well established and characterized

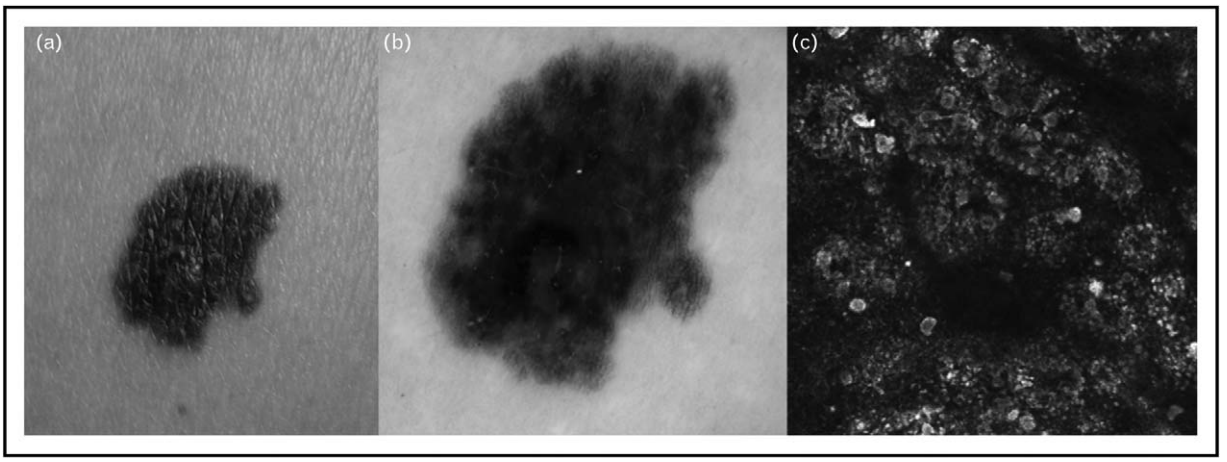

FIGURE 4. (a) Clinical picture of a dark brown to black irregular shaped lesion of the back of a 50-year-old female patient which proved to be melanoma (Breslow 0.5). (b) Dermoscopy showing an atypical pigment network with blotches and blue-white veil. (c) Reflectance confocal microscopy revealing roundish pagetoid cells at epidermal level.

by large and basaloid tumor islands, sharply separated from the dermis by dark cleft-like space. A recent systematic review and meta-analysis showed a 92% sensitivity and 93% specificity for RCM diagnosis of BCCs [36].

For which concerns melanocytic lesions, two different algorithms with similar sensitivity and specificity have been developed for the differentiation of melanoma from nevi [37] (Fig. 4).

Finally, RCM proved useful for therapeutic management of skin cancers, being able to assist in delineating surgical borders of the tumor in the preoperative phase [31▪].

As for dermoscopy, also in the case of RCM an extensive training to acquire and interpret images is needed. Practical limitations of the method include its cost and time required for assessment of large or multiple lesions.

HIGH-FREQUENCY ULTRASONOGRAPHY

Ultrasonography is a fast, noninvasive diagnostic tool widely used in medicine. Recently, several studies described that high-frequency ultrasound (HFUS) could be applied to initial differential skin cancer diagnosis, measurement of tumor depth, preoperative mapping of skin neoplasm margins, loco-regional staging, detection of tumor recurrence, and efficacy of treatments [3].

Compared to conventional ultrasound, HFSU has higher resolution that is directly proportional to depth of penetration and inversely proportional to frequency. In the field of dermatology, the most common used frequencies are between 20 and 50 MHz [38].

Ultrasound imaging is based on the principle of wave reflection off of interfaces with different acoustic impedances (resistance to the passage of ultrasound waves). To generate an image, it is necessary that a transducer probe (containing piezoelectric crystals), applied on the skin, generates sound waves and receives echoes (back waves) that are converted in electrical signals, processed and displayed to form an image [38]. The attached color Doppler function enables the visualization of vascular morphology and blood flow in real time [3].

All skin neoplasms appear as hypoechoic areas in ultrasound images. SCC mainly differs from BCCs because of more prominent vascularity. Melanoma, instead, appears as a homogeneous hypoechoic area, oval or spindle-shaped, with a prominent vascular pattern and dermal invasion [3].

Some authors reported that HFUS does not improve the accuracy of traditional clinical and dermoscopic diagnosis of skin cancers, limiting its role to the evaluation of size and depth of tumors [38,39].

OPTICAL COHERENCE TOMOGRAPHY

Optical coherence tomography (OCT) is a noninvasive, near-infrared imaging technique, first developed in the field of ophthalmology and introduced in dermatology about 20 years ago. It operates analogously to ultrasound, and allows creating real-time 2D and 3D images of the tissue [29]. Compared with RCM, conventional OCT enables to assess skin structures at a depth of approximately 0.5–1,5 mm, with optical resolution of 3–15 μm (structural resolution) [40]. In the last years, studies have explored the role of OCT in diagnosis of skin cancers [41]. Basal cell carcinoma is the skin neoplasm most investigated with OCT, and is characterized by a signal-poor, well circumscribed tumor nodules surrounded by dark

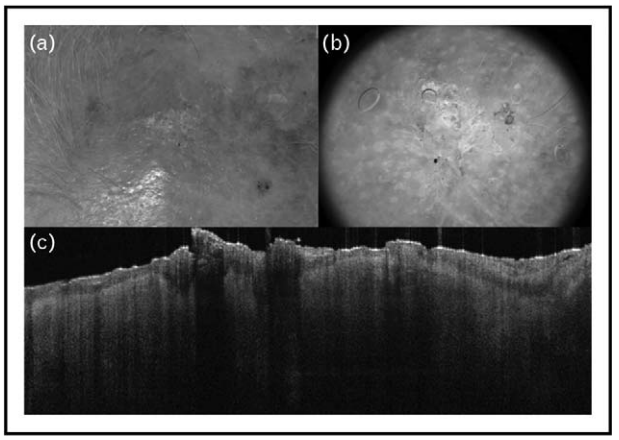

FIGURE 5. (a) Clinical picture of a slightly raised hyperkeratotic lesion of the scalp of a 96-year-old male patient histopathologically revealing an invasive well differentiated squamous cell carcinoma. (b) Dermoscopic picture showing a predominant central keratin mass. (c) Optical coherence tomography showing bright surface, focal hyperkeratosis, acanthosis, and interruption of the dermo-epidermal junction.

rims (corresponding to basaloid islands in histology) [42]. Dilated branching vessels become visible by using dynamic OCT, which allows to study superficial blood vessels via rapid and repetitive scanning of the same site [33].

In melanoma, OCT shows evident architecture disarray and an indistinct dermo-epidermal border. Rete ridges are not finger-shaped and elongated as in benign nevi, but broadened. Dermal invasion is defined by the loss of visualization of dermis and the presence of large vertically arranged icicle-shaped structures [42].

OCT has also been assessed for in-situ and invasive SCC. Actinic keratoses present a thickened epidermis, frequently with a multilayered stratum corneum. Invasive squamous cell carcinoma also shows alteration in the dermo-epidermal junction [43]. (Fig. 5)

OCT is frequently used in combination with other noninvasive techniques (dermoscopy, RCM, multiphoton tomography). It is expensive and needs specialized training for image interpretation.

ELECTRICAL IMPEDANCE SPECTROSCOPY AND TOMOGRAPHY

Electrical impedance spectroscopy (EIS) was developed as a well tolerated and noninvasive diagnostic method for melanoma detection, considering that malignant transformation of the cells alters their innate electrical impedance (resistance to an injected electrical stimulus) [44,45].

EIS is performed using a handheld probe containing a disposable electrode that applies an electrical current to the skin, receiving back the resulting current from the tissue. Two measurements are performed, one on lesional skin and one on unaffected neighboring area (intraindividual reference measurement), resulting in a score between 0 and 10. Lesions with a score of less than 4 are considered benign, whereas lesions with a score of 4 or more are identified as malignant. The ability to differentiate benign from malignant lesions on the basis of innate electrical impedance has been investigated in a large multicenter study, showing high sensitivity (96.6%) but low specificity (34.4%) for melanoma diagnosis [46].

The new generation of EIS devices integrates dermoscopy images into the patient chart with the EIS score [47]. This painless and rapid procedure is not meant to distinguish between different skin cancers, but to help physicians differentiate between benign and malignant lesions (melanocytic and nonmelanocytic). In this respect, its use may also be extended to the assessment of epithelial neoplasms. Electrical impedance tomography (EIT) has been studied with the intent to overcome the limitations of EIS lesions (measurements on strongly vascularized body parts or small lesions). It is used for imaging the differences in impedance of a body region by using low-frequency electrical current. Hartinger *et al.*[48] elaborated a hybrid technique allows imaging skin lesions by using an electrode matrix combined with 3D image reconstruction algorithms. However, future studies are required to investigate the use of this methods in skin cancer management.

RAMAN SPECTROSCOPY

Raman spectroscopy is an optical technique that studies the inelastic monochromatic light scattering in a substance where the incident light transfers energy to molecular vibrations. Raman spectroscopy of the skin, performed by applying on the cutaneous surface a handheld probe that emits a 758-nm laser, causes inelastic optical scattering that is plotted on a spectrum to obtain a molecular fingerprint of the tissue [49]. Based on such spectral information, analyzed by an internal algorithm of the device, a skin lesion can be defined as benign or malignant. Raman spectroscopy has a 95–99% sensitivity and a 15–54% specificity in discriminating between benign and malignant (melanoma and nonmelanoma skin cancer – NMSC) skin lesions [50].

OTHER EMERGING METHODS AND FUTURE DIRECTIONS

Multispectral imaging is a noninvasive technique in which light of multiple wavelengths penetrates the

skin to different depths, taking sequences of images that are then analyzed by a computer algorithm for color, border, orientation, and pattern. Studies reported a high sensitivity but a low specificity for melanoma detection [38].

Fluorescence imaging methods utilize the fluorescent properties of endogenous and exogenous molecules (fluorophores) to create images, and have been used in detecting skin cancers, characteristically more fluorescent than normal tissue [3].

Multispectral optoacustic tomography (MSOT) is a high-resolution noninvasive imaging technique based on the photoacoustic effect. It has been studied in patients with NMSC for presurgical mapping [29,44].

Further novel noninvasive tools, combination imaging technologies and machine-learning algorithms are currently under investigation and aim to improve the management of patients with melanoma and NMSC.

CONCLUSION

The advent and advancement of technology has offered considerable benefits to medical clinical practice. This is dramatically true for imaging in dermatology, used to transfer patient's information, document skin conditions, differentiate benign and malignant lesions, assess response to treatment and perform follow-up. In the field of skin cancers, noninvasive imaging techniques have become indispensable not only for diagnosis but also for adequate management of patients.

Acknowledgements

We thank Prof. Giovanni Pellacani and Dr Silvana Ciardo for kindly providing Figs. 4 and 5.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Conforti C, Giuffrida R, Vezzoni R, *et al.* Dermoscopy and the experienced ■■ clinicians. Int J Dermatol 2019. [Epub ahead of print]

This review summarizes the history of dermoscopy since its inception, addressing the practical implications and limitations of the method.

2. Psaty EL, Halpern AC. Current and emerging technologies in melanoma diagnosis: the state of the art. Clin Dermatol 2009; 27:35–45.
3. Schneider SL, Kohli I, Hamzavi IH, *et al.* Emerging imaging technologies in dermatology. Part I: Basic principles. J Am Acad Dermatol 2019; 80:1114–1120.
4. Dengel LT, Petroni GR, Judge J, *et al.* Total body photography for skin cancer screening. Int J Dermatol 2015; 54:1250–1254.
5. Tensen E, van der Heijden JP, Jaspers MW, Witkamp L. Two decades of teledermatology: current status and integration in national healthcare systems. Curr Dermatol Rep 2016; 5:96–104.
6. Walocko FM, Tejasvi T. Teledermatology applications in skin cancer diagnosis. Dermatol Clin 2017; 35:559–563.
7. Conforti C, Giuffrida R, Retrosi C, *et al.* Two controversies confronting ■ dermoscopy or dermatoscopy: nomenclature and results. Clin Dermatol 2019. [Epub ahead of print]

Nomenclature is one of the most important aspects in dermatoscopic description although in the past it has been difficult to reach a consensus for the name of this technique.

8. Vestergaard ME, Macaskill P, Holt PE, Menzies SW. Dermoscopy compared with naked eye examination for the diagnosis of primary melanoma: a meta-analysis of studies performed in a clinical setting. Br J Dermatol 2008; 159:669–676.
9. Resende FS, Conforti C, Giuffrida R, *et al.* Raised vulvar lesions: be aware! Dermatol Pract Concept 2018; 8:158–161.
10. Micali G, Lacarrubba F, Massimino D, Schwartz RA. Dermatoscopy: alternative uses in daily clinical practice. J Am Acad Dermatol 2011; 64:1135–1146.
11. Kittler H, Guitera P, Riedl E, *et al.* Identification of clinically featureless incipient melanoma using sequential dermoscopy imaging. Arch Dermatol 2006; 142:1113–1119.
12. Tschandl P. Sequential digital dermatoscopic imaging of patients with multiple atypical nevi. Dermatol Pract Concept 2018; 8:231–237.
13. Wu X, Marchetti MA, Marghoob AA. Dermoscopy: not just for dermatologists. Melanoma Manag 2015; 2:63–73.
14. Salerni G, Terán T, Puig S, *et al.* Meta-analysis of digital dermoscopy follow-up of melanocytic skin lesions: a study on behalf of the International Dermoscopy Society. J Eur Acad Dermatol Venereol 2013; 27:805–814.
15. Dinnes J, Deeks JJ, Chuchu N, *et al.* Dermoscopy, with and without visual inspection, for diagnosing melanoma in adults. Cochrane Database Syst Rev 2018; 12:CD011902.
16. Giuffrida R, Conforti C, Resende FSS, *et al.* Clinical and dermoscopic features of genital pigmented Bowen disease. Clin Exp Dermatol 2018; 43:813–816.
17. Fargnoli MC, Kostaki D, Piccioni A, *et al.* Dermoscopy in the diagnosis and management of nonmelanoma skin cancers. Eur J Dermatol 2012; 22:456–463.
18. Hamilko de Barros M, Conforti C, Giuffrida R, *et al.* Clinical usefulness of dermoscopy in the management of lentigo malignant melanoma treated with topical imiquimod: a case report. Dermatol Ther 2019; 32:e13048.
19. Giuffrida R, Borgia F, Cannavò SP. Two cases of erosive pustular dermatosis of the scalp occurring after topical 3.75% imiquimod for actinic keratoses. Dermatol Ther 2019; 32:e12770.
20. Seabra Resende FS, Conforti C, Giuffrida R, *et al.* Balloon cell primary nodular ■ melanoma: dermoscopy evidence. Dermatol Pract Concept 2019; 9:155–156.

In literature few reports of balloon nodular melanoma are reported. In this manuscript authors provide four specific clues to correctly diagnose this rare tumor.

21. Drugge ED, Volpicelli ER, Sarac RM, *et al.* Micromelanomas identified with time-lapse total body photography and dermoscopy. J Am Acad Dermatol 2018; 78:182–183.
22. Argenziano G, Kittler H, Ferrara G, *et al.* Slow-growing melanoma: a dermoscopy follow-up study. Br J Dermatol 2010; 162:267–273.
23. Salerni G, Carrera C, Lovatto L, *et al.* Benefits of total body photography and digital dermatoscopy ('two-step method of digital follow-up') in the early diagnosis of melanoma in patients at high risk for melanoma. J Am Acad Dermatol 2012; 67:e17–e27.
24. Pagnanelli G, Soyer HP, Argenziano G, *et al.* Diagnosis of pigmented skin lesions by dermoscopy: web-based training improves diagnostic performance of nonexperts. Br J Dermatol 2003; 148:698–702.
25. Ahlgrimm-Siess V, Laimer M, Rabinovitz HS, *et al.* Confocal microscopy in skin cancer. Curr Dermatol Rep 2018; 7:105–118.
26. Guida S, Longo C, Casari A, *et al.* Update on the use of confocal microscopy in melanoma and nonmelanoma skin cancer. G Ital Dermatol Venereol 2015; 150:547–563.
27. Farnetani F, Scope A, Coco V, *et al.* Paradigmatic cases of pigmented lesions: how to not miss melanoma. J Dermatol 2016; 43:1433–1437.
28. Guida S, Pellacani G, Cesinaro AM, *et al.* Spitz naevi and melanomas with similar dermoscopic patterns: can confocal microscopy differentiate? Br J Dermatol 2016; 174:610–616.
29. Hibler BP, Qi Q, Rossi AM. Current state of imaging in dermatology. Semin Cutan Med Surg 2016; 35:2–8.
30. Schneider SL, Kohli I, Hamzavi IH, *et al.* Emerging imaging technologies in ■ dermatology. Part II: Applications and limitations. J Am Acad Dermatol 2019; 80:1121–1131.

Among different types of technologies available, this paper describes the applications and limitations of each technique.

31. Farnetani F, Manfredini M, Chester J, *et al.* Reflectance confocal microscopy ■ in the diagnosis of pigmented macules of the face: differential diagnosis and margin definition. Photochem Photobiol Sci 2019; 18:963–969.
The role of noninvasive diagnosis currently can be used for the definition tumor's margins. In this paper authors described how to correctly detect the presence of tumor in the surrounding skin of the clinical visible area.
32. Moscarella E, Rabinovitz H, Zalaudek I, *et al.* Dermoscopy and reflectance confocal microscopy of pigmented actinic keratoses: a morphological study. J Eur Acad Dermatol Venereol 2015; 29:307–314.
33. Dorrell DN, Strowd LC. Skin cancer detection technology. Dermatol Clin 2019; 37:527–536.
34. Nguyen KP, Peppelman M, Hoogedoorn L, *et al.* The current role of in vivo reflectance confocal microscopy within the continuum of actinic keratosis and squamous cell carcinoma: a systematic review. Eur J Dermatol 2016; 26:549–565.
35. Conforti C, Paolini F, Venuti A, *et al.* The detection rate of human papilloma- ■■ virus in well differentiated squamous cell carcinoma and keratoacanthoma: is there new evidence for a viral pathogenesis of keratoacanthoma? Br J Dermatol 2019; 181:1345–1346.
This paper suggests a change in the nomenclature of skin tumors and lead to a better understanding of pathogenetic mechanisms of nonmelanoma skin cancer.
36. Lupu M, Popa IM, Voiculescu VM, *et al.* A systematic review and meta-analysis of the accuracy of in vivo reflectance confocal microscopy for the diagnosis of primary basal cell carcinoma. J Clin Med 2019; 8:pii: E1462.
37. Segura S, Puig S, Carrera C, *et al.* Development of a two-step method for the diagnosis of melanoma by reflectance confocal microscopy. J Am Acad Dermatol 2009; 61:216–229.
38. Wortsman X, Wortsman J. Clinical usefulness of variable-frequency ultrasound in localized lesions of the skin. J Am Acad Dermatol 2010; 62:247–256.
39. Maj M, Warszawik-Hendzel O, Szymanska E, *et al.* High frequency ultrasonography: a complementary diagnostic method in evaluation of primary cutaneous melanoma. G Ital Dermatol Venereol 2015; 150:595–601.
40. Bakos RM, Blumetti TP, Roldán-Marín R, Salerni G. Noninvasive imaging tools in the diagnosis and treatment of skin cancers. Am J Clin Dermatol 2018; 19(Suppl 1):3–14.
41. Reggiani C, Manfredini M, Mandel VD, *et al.* Update on noninvasive imaging techniques in early diagnosis of nonmelanoma skin cancer. G Ital Dermatol Venereol 2015; 150:393–405.
42. Wang J, Xu Y, Boppart SA. Review of optical coherence tomography in oncology. J Biomed Opt 2017; 22:1–23.
43. Welzel J, Schuh S. Noninvasive diagnosis in dermatology. J Dtsch Dermatol Ges 2017; 15:999–1016.
44. Fink C, Haenssle HA. Noninvasive tools for the diagnosis of cutaneous melanoma. Skin Res Technol 2017; 23:261–271.
45. Mohr P, Birgersson U, Berking C, *et al.* Electrical impedance spectroscopy as a potential adjunct diagnostic tool for cutaneous melanoma. Skin Res Technol 2013; 19:75–83.
46. Malvehy J, Hauschild A, Curiel-Lewandrowski C, *et al.* Clinical performance of the Nevisense system in cutaneous melanoma detection: an international, multicentre, prospective and blinded clinical trial on efficacy and safety. Br J Dermatol 2014; 171:1099–1107.
47. Braun RP, Mangana J, Goldinger S, *et al.* Electrical impedance spectroscopy in skin cancer diagnosis. Dermatol Clin 2017; 35:489–493.
48. Hartinger AE, Guardo R, Kokta V, Gagnon H. A 3-D hybrid finite element model to characterize the electrical behavior of cutaneous tissues. IEEE Trans Biomed Eng 2010; 57:780–789.
49. Zhao J, Zeng H, Kalia S, Lui H. Using Raman spectroscopy to detect and diagnose skin cancer in vivo. Dermatol Clin 2017; 35:495–504.
50. Lui H, Zhao J, McLean D, Zeng H. Real-time Raman spectroscopy for in vivo skin cancer diagnosis. Cancer Res 2012; 72:2491–2500.