Noninvasive Diagnostic Tools for Skin Cancer

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This session reviewed existing noninvasive technologies in dermatology, including imaging and nonimaging tools. The speakers presented data on these technologies and discussed their clinical applicability, as well as new technology concepts from preclinical research.

MORE EVIDENCE NEEDED ON QUALITY AND CONSISTENCY OF NONINVASIVE DIAGNOSTIC TOOLS

The diagnosis of melanoma by simple visual examination using the ABCD method is incorrect in almost 1 of every 3 invasive melanoma diagnoses. A number of new techniques have improved the noninvasive diagnosis of slow-growing superficial spreading melanoma. Early diagnosis of fast-growing nodular melanoma may not be possible (or practical), however, using these costly diagnostic technologies. Josep Malvehy, MD, Hospital Clinic of Barcelona, Barcelona, Spain, reviewed the utility of available noninvasive methods for early melanoma diagnosis.

Qualitative imaging methods for melanoma diagnosis include dermoscopy, total body photography, multiphoton tomography, reflectance confocal microscopy (RCM), and optical coherence tomography (OCT). Quantitative methods using automated analysis include multispectral imaging, electrical impedance spectroscopy, and Raman spectroscopy. The features and key study results of the first 3 qualitative methods and the first 3 quantitative methods are shown in Table 1. RCM and OCT were discussed in the subsequent presentations.

A study of a new noninvasive adhesive patch test for evaluation of pigmented lesions using a 2-gene (CMIP and LINC00518) signature assay for differentiating melanomas from pigmented lesions reported a sensitivity of 97.6% and specificity of 72.7% [Gerami P et al. *J Am Acad Dermatol.* 2014]. Limitations of this study included the loss of cases due to messenger RNA insufficiency, inclusion of limited melanoma subtypes, and a minimum lesion diameter of 4 mm.

Prof Malvehy concluded that new technologies for noninvasive detection of skin cancer will be developed and others will disappear. The optimal method for diagnosis depends on the physician, patient population, technical issues, and stage of development. Important questions remain about the clinical benefit, cost, and evidence for quality and consistency of noninvasive tools for diagnosing skin cancer.

NEAR HISTOLOGIC RESOLUTION OF MELANOMA WITH RCM

Giovanni Pellacani, MD, University of Modena, Modena, Italy, spoke about in vivo imaging of the skin with RCM in clinical practice and research. RCM provides lateral resolution of 0.5 to 1 µm and axial resolution of 3 to 4 µm. The technique is noninvasive and painless, and it takes 7 minutes to acquire an image, providing an optical biopsy with cellular resolution. The confocal technology produces a composite grayscale image that is formed by consecutive confocal frames and mounted together to form a horizontal section of an area up to 8 × 8 mm to a maximum depth of 300 µm.

Melanoma is diagnosed on an RCM image by looking for the same features observed on histopathology, including large round pagetoid cells and nonhomogeneous junctional nests of atypical cells. Nevi, on the other hand, are characterized by a ringed, meshwork, or clod pattern without the large atypical cells seen in melanoma.

Guitera and colleagues [*J Invest Dermatol.* 2009] demonstrated superior specificity with RCM (68%; 95% CI, 61.1% to 74.3%) vs dermoscopy (32%; 95% CI, 25.9% to 38.7%) and similar sensitivity with RCM (91%; 95% CI, 84.6% to 95.5%) and dermoscopy (88%; 95% CI, 80.7% to 92.6%) in the secondary evaluation of melanocytic lesions (Figure 1).

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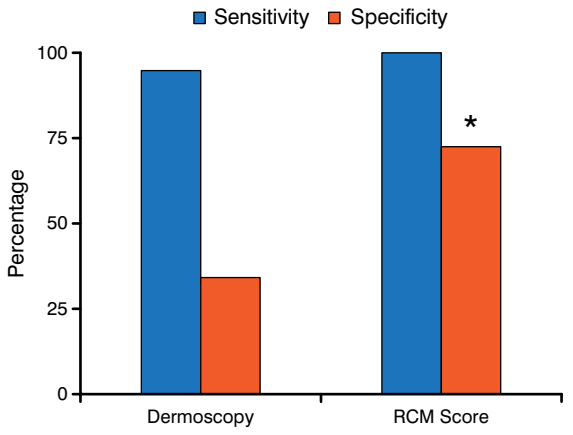
Table 1. Noninvasive Qualitative and Quantitative Methods for Melanoma Diagnosis

Diagnostic Method	Features and Studies
	Qualitative Imaging
Dermoscopy	Used for differential diagnosis of pigmented lesions; 89% sensitivity, 79% specificity [Garbe C et al. *Eur J Cancer.* 2012] Helps diagnose early melanoma; use constrained by lack of training [Terushkin V et al. *J Am Acad Dermatol.* 2010] Improves PCP accuracy in triaging lesions [Argenziano A et al. *J Clin Oncol.* 2006]
Total body photography	Comprehensive body imaging (85% coverage) High-resolution color imaging in 10 min Detects new lesions and changes in moles; leads to fewer biopsies [Terushkin V et al. *J Am Acad Dermatol.* 2010] More established in the United States
Multiphoton tomography	Simultaneous excitation of endogenous fluorophores by ≥2 photons of low near-infrared energy [Kaatz M, König K. *Hautarzt*. 2010] Sensitive and specific for differentiating between melanocytic nevi and nonmelanocytic lesions [Arginelli F et al. *Skin Res Technol*. 2013]
	Quantitative Analysis
Multispectral imaging	Noninvasive, fully automatic, computer-vision diagnostic system Aid to detection of early melanoma Acquires digital multispectral images of pigmented lesions Image analysis and statistical pattern recognition help identify lesions to consider for biopsy 98.4% sensitivity and 10.5% specificity for melanoma [Monheit G et al. *Arch Dermatol*. 2011] Greater sensitivity (96.9% vs 69.5%; $P < .00001$) and lower specificity (9.2% vs 55.9%; $P < .00001$) for biopsy decisions than dermatologists alone [Hauschild A et al. *J Dtsch Dermatol Ges.* 2014]
Electrical impedance spectroscopy	Measure of overall resistance within tissue at alternating currents of various frequencies Harmless alternating electrical current applied to skin, and response measured On-screen results within seconds In a multicenter study of 2416 lesions, electrical impedance spectroscopy had 96.6% sensitivity and 34.4% specificity for melanoma, 21.1% PPV and 98.2% NPV, and 100% sensitivity for nonmelanoma skin cancer [Malvehy J et al. *Br J Dermatol.* 2014]
Raman spectroscopy	Photon-induced vibration profiles specific to molecules in tissue used for skin tumor diagnosis [Gniadecka M et al. *J Invest Dermatol.* 2004] Study of benign and malignant skin lesions [Lui H et al. *Cancer Res.* 2012] For sensitivities between 95% and 99%, specificities were 15% to 54% Melanoma vs pigmented lesions: AUC of the ROC, 0.829 ± 0.0929 ($P < .0001$)

AUC, area under the curve; NPV, negative predictive value; PCP, primary care physician; PPV, positive predictive value; ROC, receiver operating characteristic.

Figure 1. Sensitivity and Specificity of Reflectance Ccnfocal Microscopy vs Dermoscopy in Secondary Evaluation of Melanocytic Lesions



RCM, reflectance confocal microscopy.
*$P < .001$.
Data source: Guitera P et al. *J Invest Dermatol.* 2009.
Reproduced with permission from G Pellacani, MD.

An analysis of 710 consecutive clinically equivocal lesions found that RCM had 87.6% sensitivity and 70.8% specificity for melanoma [Guitera P et al. *J Invest Dermatol.* 2012].

A 10-year study of the accuracy of melanoma detection found that the number needed to excise a melanoma was 8.7 in specialized centers and 29.4 in nonspecialized centers [Argenziano G et al. *J Am Acad Dermatol.* 2011]. Pellacani and colleagues [*Br J Dermatol.* 2014] recently reported that the number needed to excise a melanoma with RCM examination at a melanoma clinic was 6.8.

A study correlating melanoma biomarker levels with RCM found that melanomas with higher Bak serum levels had more junctional activity on RCM, whereas those with weak Bak expression had sparse dermal nests on RCM [Longo C et al. *Exp Dermatol.* 2011]. Another study reported that distinct melanoma subtypes were identified by RCM analysis of cell morphology [Pellacani G et al. *Exp Dermatol.* 2014]. Furthermore, melanoma risk identification and early diagnosis were improved with

Table 2. Studies of OCT for Diagnosis of Nonmelanoma Skin Cancer

Study	Results
BCC tumor thickness measurement [Olmedo JM et al. *Dermatol Surg.* 2007]	Excellent correlation of tumor thickness measurements with OCT compared with histology up to 1 mm
Nonmelanoma margin assessment [Alawi SA et al. *Exp Dermatol.* 2013]	OCT-defined lateral margins correctly indicated complete removal of the tumor in 84% of cases
Subclinical residual lesions after photodynamic therapy for nonmelanoma skin cancer [Themstrup L et al. *Photodiagnosis Photodyn Ther.* 2014]	OCT identified 29% more recurrences than clinical examination alone
Noninvasive monitoring of BCC after treatment with HHI [Maier T et al. *J Am Acad Dermatol.* 2014]	HHI-induced regression of BCC was visualized in the skin with OCT

BCC, basal cell cancer; HHI, hedgehog inhibitor; OCT, optical coherence tomography.

both RCM and dermoscopy when combined with genetic studies [Bassoli S et al. *Exp Dermatol.* 2013].

RCM analyzes skin lesions in vivo with similar resolution as observed with histology. According to Prof Pellacani, in vivo morphology may represent the missing link to bridge clinical and laboratory research.

OCT IMPROVES DIAGNOSTIC ACCURACY AND SPECIFICITY IN NONMELANOMA SKIN CANCER

Martina Ulrich, MD, Collegium Medicum Berlin, Berlin, Germany, discussed the use of OCT for diagnosing nonmelanoma skin cancer. OCT provides up to 60 images per scan of vertical and horizontal skin sections with a resolution of 7.5 µm up to 2 mm deep. High-resolution OCT combines horizontal and vertical imaging and has a 1.6 × 1.8 mm imaging field, 3 µm resolution, and 570 µm penetration. Multibeam OCT also combines horizontal and vertical imaging, and it has a 6 × 6 mm imaging field, 7.5 µm resolution, and 1 to 2 mm penetration.

OCT is used for differentiating nonmelanoma skin cancers from benign lesions, defining tumor thickness, and assessing tumor margins. A study of basal cell carcinoma diagnosis with OCT vs clinical evaluation and dermoscopy in 235 lesions demonstrated a diagnostic accuracy of 65.8% for histology, 76.2% for dermoscopy, and 87.4% for OCT. The positive predictive value and negative predictive value were greatest with OCT.

In the same study, OCT significantly improved specificity vs clinical and vs dermoscopy ($P < .0001$ for both) but not sensitivity vs clinical evaluation ($P = .099$) and dermoscopy ($P = .121$). Table 2 shows the results of additional studies of OCT for the diagnosis and evaluation of nonmelanoma skin cancers.

OCT is applicable for the primary diagnosis of nonmelanoma skin cancer. It may prove to be a useful tool for determining vertical tumor thickness. OCT also allows monitoring of lesions throughout time, and improves the diagnostic accuracy when evaluating pink patches. OCT increases diagnostic specificity in equivocal lesions compared with dermoscopy and clinical examination.