An Introduction to Reflectance Confocal Microscopy

With recent advancements, this technology is gaining more use in practice.

BY STEPHEN HAMMOND, MD, BABAR RAO, MD AND ANTHONY ROSSI, MD

The technology sector has made leaps and bounds over the past decades, and this has been mirrored, albeit in slower motion, by substantive changes in diagnostic medicine. Non-invasive tools aiding diagnosis have been the bedrock of modern medicine—from early stethoscopes to X-rays to a plethora of modern imaging devices now readily available.

In dermatology, the gold standard for diagnosis has been tissue sampling for microscopic examination. While this remains true, it is now possible to achieve microscopic examination without the prior necessity of obtaining tissue through biopsy with the careful application of laser reflective technology. This translates into a painless photographic experience for patients while still providing microscopic images for accurate diagnoses. Reflectance confocal microscopy (RCM) is the tool that achieves this goal.

The RCM device uses a diode laser as a source of monochromatic light. The light penetrates into the skin and illuminates a small point inside the tissue. The light is reflected through a small pinhole and then forms an image in the detector. The images can be collected as a mosaic (horizontal stitched images at the same depth), a stack (vertical images at different depths), and cubes (a combination of mosaic and stacks). The images can then be reviewed by the trained confocalist (a board-certified dermatologist or dermatopathologist) and a diagnostic opinion rendered in the form of a report.

This has the advantage of increased resolution over other non-invasive modalities, such as dermoscopy, with studies demonstrating higher sensitivity and specificity. And can diminish confounding sampling issues in histologic preparation where only a small portion of lesions are actually visualized microscopically.

Skin cancers are the most common malignancies in the US, with significant morbidity, and screening is a mainstay service of dermatology providers. Non-invasive microscopic imaging has the potential to transform the delivery of this service in positive ways for patients and providers alike. CPT codes are now available for reimbursement.

Below, three confocalists in different clinical settings describe how they integrate this new technology into their practices.

—Stephen Hammond, MD

Dermatopathology View

By Stephen Hammond, MD

During my dermatopathology fellowship at the Ackerman Academy in New York City, I had the opportunity to observe an earlier model of a confocal microscope, the Vivascope (Caliber ID), in operation.

I grasped and was excited by the implications of a tool that could non-invasively bridge the gap between dermoscopy and histopathology. The technology rapidly improved with an increase in resolution, accompanied by a decrease in capture time. The published literature on confocal microscopy also began to grow, and I could see a strong case for adoption in dermatology diagnostic practice. There were very few training opportunities in the US, so I attended several training courses in Europe, where confocal microscopy is widely used, to improve my knowl-
edge base and diagnostic acumen. And now, with the designation of CPT codes for re-imbursement and the growing support of the dermatology community, I have daily confocal cases that I diagnose and often correlate with my histopathologic findings.

**CURRENT USE**

I am not based in a dermatology office, so our model is smoothly adapted to allow for integration of RCM. The images are captured at a referring clinician’s office and uploaded to a HIPAA-compliant server. I’m alerted by email and text message any time an image is ready to view. I can then login remotely, review the images, come to a diagnosis, and generate a report. As soon as the report is signed, the referring clinician’s office is alerted that a report is ready to view. Based on the report, much like with a traditional pathology report, appropriate management is taken. Initially, our patient population were adult females and children; those we assumed would be most sensitive to pain or cosmetic considerations. But with increasing publicity, confocal microscopy has featured on multiple TV stations locally, the demographic is broadening. The disadvantage of this model is that bedside confocal diagnosis cannot be made and immediate action taken. The advantages include: no additional diagnostic microscopy training or liability for dermatologist, limited disruption to dermatologist schedule as images are typically captured by a trained medical assistant, and 12-24 hour turnaround time (no transport or processing needed).

**CHALLENGES**

I can roughly divide challenges into three parts:

**Technology Limitations.** Confocal microscopy is limited to the epidermis and very superficial papillary dermis, so it is not ideal for evaluating dermal based lesions, and I still recommend tissue biopsy of nodular lesions. Although this is a limitation, a majority of skin cancers originate in the epidermis or dermoeppidermal junction, so for most lesions, confocal microscopy remains a useful tool for accurate actionable diagnoses.

**Training Limitations.** There are still only a few confocal practitioners in the US, and a majority of us have trained independently and within Europe. This has the effect of limiting the availability of confocal experts geographically for consultation with dermatologists in the community. The “tele” capability of confocal microscopy with remote diagnosis mitigates this limitation, and with the formation of the American Confocal Group and other confocal interest groups, there are several CME accredited courses now available in the US for training new confocal users.
Reimbursement Limitations. With this relatively new technology and the new CPT codes for RCM, payor education is essential to ensure reimbursement. This limitation varies geographically with some providers achieving good reimbursement. There is a billing support unit associated with the confocal microscope supplier, and the national confocal user network is a valuable resource. I believe with the ever-expanding use of, and patient demand for confocal microscopy, reimbursement will become as established as other dermatology codes.

Clinical View

By Babar Rao, MD

Reflectance confocal microscopy (RCM) is a non-invasive, cutting edge diagnostic technique for cutaneous conditions that enables visualization of different skin layers without cutting.

Marvin Minsky first introduced RCM in 1957. It was not until 1995 that RCM gained popularity and was used in dermatology as a tool for clinical dermatology research and in Moh’s research at the Wellman Laboratories of Photomedicine at Massachusetts General Hospital in Boston. By the early 2000s, researchers from prestigious academic centers including Memorial Sloan-Kettering Cancer Center (New York, NY), Loma Linda University (Loma Linda, CA), the Sydney Melanoma Unit (Sydney, Australia), University of Modena and Reggio Emilia (Modena, Italy), the Charite (Berlin, Germany) and University of Graz (Graz, Austria) were using RCM routinely, both as a research tool and a clinical diagnostic imaging device.

The principle of RCM is based on focal point illumination, and the device uses a low power laser beam with a wavelength of 830nm. This light illuminates a small point inside the skin tissue and then this light is reflected back through a small pinhole and is imaged on the detector. With this input, a computer generates a two-dimensional gray scale image that corresponds to a transverse tissue section (i.e., parallel to the skin surface). The contrast visualized by RCM is determined by the differential reflectance capability of various skin structures. The end result is a high-resolution image of the epidermis and superficial dermis that is obtained non-invasively and in real time.

CURRENT USE AND ADVANTAGES IN PRACTICE

Biopsy is currently the gold standard for diagnosis of suspicious cutaneous lesions. However, biopsy can result in pain, scars, and in some cases infection, as well. After biopsy, tissue goes through multiple phases of processing, staining, and slide preparation. With this multiple, labor, time, and money consuming process, it takes a week to two weeks to get dermatopathology results. In most cases, the results are benign. All these steps could be avoided by using RCM in the first place in daily dermatology clinic.

In the last decade, RCM has not only been proven beneficial in differentiating between benign and malignant skin lesions but has recently proven effective in reporting prognosis of various inflammatory conditions. Current clinical application of RCM is to study and diagnose skin cancers, including melanoma, basal cell carcinoma, and squamous cell carcinoma. Benign conditions, such seborrheic keratosis; actinic keratosis, dermatofibroma, benign melanocytic nevi, and lentigo can be easily diagnosed with RCM.

More interestingly, RCM is now used to study various inflammatory conditions such as psoriasis, dermatitis, rosacea, and lichen planus. Parasites like Sarcoptes scabiei can be visualized in real time with RCM. I believe RCM has already had an impact on patient care and imagine that this impact will continue and expand in the future. In a recent multicenter study, it has been shown that RCM has an overall sensitivity of 98.2 percent and specificity of 99.8 percent.

I have been using RCM for more than 10 years in my daily dermatology clinic. Following are just few scenarios where RCM could be really helpful and practical alternative to conventional biopsies.

1. Diagnose a mole in a child
2. Lesions on aesthetically significant sites such as face
3. Patient with numerous atypical lesions who have had multiple biopsies with multiple scars and most of the lesions were either benign or mild atypia

These sensitive cases now have an alternative non-invasive diagnostic approach providing valuable information to guide management decisions.

Although other non-invasive technologies like a dermatoscope permit visualization of subsurface structures that are otherwise not visible to the naked eye, novel RCM technology allows clinicians to visualize the cellular details of the skin without surgical intervention.

CHALLENGES TO CLINICAL INTEGRATION

As RCM is an FDA-approved device and the procedure can be billed, RCM is rapidly gaining attention from not only dermatologists but also getting popular among patients. Currently the only challenge to clinical integration of RCM is learning how to read RCM images.

There are various ways available to learn RCM in a time-efficient manner. These include courses such as courses organized by NIDIskin.com by me, MSK RCM course
Future Developments for RCM

**COMBINATION TECHNOLOGY**
Combining confocal microscopy with other imaging tools that can image greater depths of the dermis, such as optical coherence tomography, will result in second generation non-invasive imaging techniques with even more versatility for diagnosing and staging skin cancers.

**COLOR CONTRAST TECHNOLOGY**
Superimposing color contrast on to confocal imaging, creating a digital image more akin to the traditional H&E sections, has the potential to increase diagnostic accuracy and flatten out the learning curve of training in confocal microscopy.

**ARTIFICIAL INTELLIGENCE**
After enough data (images with accurate histologically confirmed diagnoses) has been gathered, there is a definite space for collaboration of AI engineers and confocal experts to develop technologies that further engage physicians and patients in quick, accurate, and painless skin diagnosis.

Directed by MSK dermatology department, websites, online training modules, and RCM images Atlas. I believe that the utmost need of 21st century era to not only embrace this innovative technique, but also educate young dermatologists, including residents and fellows, and expand through RCM integration in daily clinic and research.

Research View

**By Anthony Rossi, MD**
I was the Mohs micrographic, laser, and cosmetic dermatology fellow at the Memorial Sloan Kettering (MSK) Cancer Center and Weill Cornell Medical College. While I was a fellow, I worked with Dr. Kishwer Nehal for Mohs surgery and Milind Rajadhyaksha PhD, who pioneered the clinical confocal microscope. I learned to obtain images and read them, and we furthered the use of in vivo margin mapping for melanoma of the head and neck. As full-time faculty at MSK, I utilize in vivo confocal microscopy on a daily basis for diagnosis, management, and follow-up of melanoma and keratinocyte carcinomas. I am also very fortunate to work alongside the team of engineers and computer scientists who are augmenting the hardware and software that allow faster mosaicking and video mosaicking. My current research includes mapping complex facial melanomas, utilizing the video mosaicking approach we pioneered at MSKCC.

I also perform confocal guided laser ablation for basal cell and squamous cell carcinoma, as well as utilizing RCM for monitoring responses to nonsurgical treatment approaches, such as imiquimod for melanoma in situ and photodynamic therapy for keratinocyte carcinomas.

The use of RCM in vivo has really augmented my non-surgical and surgical approach to cutaneous carcinomas. It has allowed non-invasive imaging over time to detect recurrences earlier. I am also currently working on utilizing the ex vivo vivascope diangose freshly excised tissue and biopsy samples.

The challenges to integration include the learning curve needed to acquire and interpret images. It is helpful to have a technician who is trained to acquire good reliable images, similar to how an ultrasound technician works.

**A FLUORESCENT FUTURE**
The future of confocal microscopy is fluorescent! The use of in vivo dyes to enhance contrast is an exciting new area of research focus. Additionally, digitally stained coloring of images to mimic H&E from histology is promising for confocal readers and enthusiasts. This may help with diagnosis and readability of images.

Stephen Hammond, MD is a triple board-certified physician in anatomic-, clinical-, and dermatopathology. He is the Medical Director and Section Head of Dermatopathology of a laboratory in South Carolina, a pioneer in the clinical integration of reflectance confocal microscopy, and a Founding and Board member of the American Confocal Group.

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