Confocal Scanning Laser Reflectance Microscopy

Why Bother?

Technology is a gift of God. After the gift of life it is perhaps the greatest of God’s gifts. It is the mother of civilizations, of arts, and of sciences.1 Freeman Dyson, physicist (1923–)

THE ABILITY TO NONINVASIVELY VISUALIZE THE body’s organs in vivo at the macroscopic and microscopic levels has been a goal of clinicians and researchers alike for more than a century. In recent decades, enormous strides have been made in macroscopic and functional imaging with the development and refinement of computed tomography, magnetic resonance imaging, and positron emission tomography technologies, just to name a few. The impetus to continuously improve existing technologies and to invent new imaging modalities lies in the potential of these technologies to empower physicians to detect subclinical life-threatening disease and to less invasively diagnose clinically evident disease. Today, we take for granted the availability of sophisticated imaging modalities such as computed tomography and magnetic resonance imaging. However, it must be remembered that these advances in imaging technology were initially met with significant resistance and skepticism. The resistance to technological innovations in medicine stems partly from the recognition of the increased costs associated with their development and implementation. Nonetheless, expensive technologies are readily incorporated into our health care delivery system if they are perceived to improve quality of care. The skepticism associated with the adoption of new technologies stems partly from the innate resistance of clinicians to change. This was true for ultrasonography, computed tomography, magnetic resonance imaging, and dermoscopy, among others; however, the passage of time has proved that many of these imaging technologies did indeed revolutionize the way medicine is practiced, and each new advance continues to improve our ability to noninvasively examine patients. These advances ultimately increase our ability to identify patients who may benefit from invasive procedures while reducing the number of patients subjected to unnecessary procedures and therapies. Furthermore, each advance heralds new ideas and innovative research that may open up the possibility of assisting clinicians in differentiating benign nevi from melanomas. Their study builds on a growing body of literature that supports the ability of CSLM to noninvasively visualize cellular detail, approaching that of histology in the superficial component of some melanocytic lesions.3-15 The logical next question is: why is this important?

In this month’s issue of the ARCHIVES, Pellacani et al8 describe the in vivo cellular architecture of dermoscopic pigment network in nevi and melanomas. The authors meticulously analyzed the cellular morphologic characteristics and architecture of nevi and melanomas and have correlated the confocal findings with dermoscopic and histologic findings. They have shown that the cellular detail seen with confocal microscopy approaches histologic detail (“quasi-histology”), and this may open up the possibility of assisting clinicians in differentiating benign nevi from melanomas. Their study builds on a growing body of literature that supports the ability of CSLM to noninvasively visualize cellular detail, approaching that of histology in the superficial component of some melanocytic lesions.3-15 The logical next question is: why is this important?

Given the rising incidence of melanoma and the consequences of failing to diagnose melanoma in its earliest stages, even small advances in diagnostic accuracy can

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translate into significant clinical gains. In its current iteration CSLM is too expensive and laborious to be considered a screening tool, even if it were determined to have good sensitivity for diagnosing early melanoma. However, with minor modification this technology may become practical for assessing selected pigmented lesions of concern on the basis of clinical examination and/or dermoscopic findings. If CSLM improves our ability to differentiate between benign nevi and melanomas, it could lead to an improvement of the malignant-benign ratio for biopsy results. Dermatologists who evaluate skin lesions with nothing more than perhaps a magnifying lens have a ratio of approximately 1 malignant specimen for every 12 to 18 benign lesions undergoing biopsy.16 Dermatologists who use dermoscopy may improve that ratio to 1 in 4 to 5.18 However, the improved malignant-benign ratio comes at a cost of missing some melanomas, most of which are diagnosed on short-term follow-up as a result of detectable changes.17 Confocal microscopy may significantly improve the diagnostic accuracy currently achieved with dermoscopy, thus avoiding many unnecessary biopsies while maintaining excellent sensitivity for melanoma. Although a skin biopsy is an “easy” procedure for the dermatologist, the associated morbidity and scarring, especially on the face, is not trivial from the patient’s perspective. Finally, the cost savings of fewer unnecessary biopsies and the decrease in associated morbidity will partially offset the cost of these new imaging technologies.

Large suspicious cutaneous lesions that are not amenable to excisional biopsies present the challenge of sampling error when partial biopsies are performed. Because confocal microscopy scans the skin in the horizontal plane, it allows for the ability to scan the entire area of the lesion in question. Focal areas that show cellular or architectural atypia can thus be slated for directed biopsies. As an example, this technology may prove useful for correctly diagnosing some lentigo maligna melanomas (LMMs) that possess skip areas and foci of invasion.11 Somach et al18 showed that clinicians are unable to predict the most diagnostically significant area to biopsy in LMM lesions. It is intuitively obvious that the ability to noninvasively determine the most diagnostically and prognostically significant area within the LMM lesion will help streamline the management of this malignancy. An example of the use of confocal microscopy is the patient with a large LMM on her cheek who is contemplating off-label treatment of her LMM with topical imiquimod (Figure). Given this scenario, the confocal microscope can be used during her follow-up to determine whether the atypical/malignant LMM cells have resolved (“virtual biopsies”) at the end of imiquimod therapy. Although sampling errors most commonly occur in large, complex pigmented lesions, they also occur in melanomas arising in precursor nevi. Most biopsy specimens undergo limited sectioning before the histologic evaluation. Even when step sectioned, less than 1% of the entire lesion is actually evaluated histologically, which permits small foci of melanoma to go undetected. Confocal microscopy, which images lesions en face in the horizontal plane, can be used to scan the entire profile of the lesion. This procedure can be done at the patient’s bedside, in which case foci of concern can be marked with ink or a suture to direct pathological sectioning. The confocal examination could also be performed on the ex vivo specimen in the pathology laboratory before fixation and sectioning.

Another potential clinical use for CSLM is presurgical and intraoperative margin detection for skin cancer surgery. Amelanotic melanomas and melanomas with ill-defined borders, especially those occurring on the face, present a significant clinical challenge.13 Most of these cases are currently managed by serial excisions with permanent sections. Once the excision margins are deemed clear, the patient is scheduled for delayed closure. In such complex cases, which often take many days to complete, confocal microscopy may assist by noninvasively delineating the border between normal skin and melanoma. Once this confocally determined border has been identified, the surgeon can plan for the excision and repair of the melanoma as a one-step procedure. However, there are some melanomas in which it is difficult to determine the border of the malignancy even when using fixed-tissue histology. It is unlikely that any in vivo imaging technique will outperform ex vivo histologic evaluation. The potential of CSLM as an aid to presurgical and intraoperative margin detection for skin cancer is even greater for nonmelanoma skin cancer.19-21 The confocal microscope may one day be used by dermatologic surgeons in the presurgical mapping of lateral tumor margins prior to full-thickness excisions. Confocal scanning laser reflectance microscopy can also potentially be used for intraoperative assessment of the base of the resection for persistence of tumor cells during Mohs surgery.22,23 Furthermore, the confocal microscope may someday also lead to simplification of the processing and assessment of excised tissue specimens during Mohs surgery.24,25 An inverted confocal microscope is currently available that is intended for use in surgical pathology for examination of unprepared, unstained tissue specimens without freezing, staining, sectioning, or fixing the specimen.1 The excised fresh Mohs tissue layer can be placed on the confocal microscope stage without the need for tissue processing and then be evaluated by the surgeon at the patient’s bedside to determine whether the layer is free of or positive for tumor cells. If proved reliable, this technology could dramatically shorten what are often extended procedures.

In addition to its potential as an aid in the detection, diagnosis, and surgical management of skin cancer, CSLM may play a role in clinical assessment for persistence and recurrence of tumors.26 After cutaneous malignancies have been excised, it is recommended that the scars be followed for the detection of local recurrence. However, there are some malignancies, such as amelanotic LMM, in which the detection of recurrence can be challenging. This is another scenario in which confocal microscopy can assist in the follow-up of these patients by allowing for the periodic and noninvasive scanning of the skin surrounding the excision scars for the detection of recurrence. Finally, another area in which confocal microscopy can be of benefit is the evaluation of persistence or recurrence of malignant lesions undergoing topical therapy. With the introduction of topical agents such as imiquimod,
many cutaneous malignancies may be treated topically without posttreatment biopsy to confirm cancer clearance. However, it is not uncommon for physicians to misinterpret post–topical therapy–induced erythema as evidence of cancer persistence. The confocal microscope potentially allows for the ability to perform virtual biopsies to diagnose the existence of cancer and to confirm whether the cancer has been successfully “cured” on completion of topical therapy.27,28

In summary, the future of technology like confocal microscopy looks bright. However, much work is needed before the application of these technologies in routine clinical practice. The work presented by Pellacani et al8 represents a significant contribution to the body of research necessary for the evaluation and implementation of CSLM in clinical practice. The confocal instrument used by Pellacani et al8 was a first-generation machine. Such first-generation confocal microscopes are rather time-consuming to use and, because of their bulky configuration, cannot be conveniently placed on certain anatomical areas such as the ear, the medial canthus, or intertriginous areas. However, as with other imaging technologies, one can anticipate that future-generation instruments will be more robust, delivering more consistent images of better resolution in increasingly compact and cost-effective packages. Advances in noninvasive quasi-histologic skin imaging will not, however, be limited to improvements in point-scanning reflectance confocal microscopy. Recent advances in the development of line-scanning reflectance confocal microscopy, fluorescence confocal microscopy, multispectral confocal microscopy, and broad-wavelength optical coherence tomography all hold promise for improved noninvasive quasi-histologic imaging of the skin.29,30 It is quite conceivable that some of these imaging devices will ultimately move the art of histologic diagnosis closer to the bedside.

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REFERENCES


