Skin cancer detection using in vivo Raman spectroscopy

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A Raman spectroscopy-based clinical device rapidly detects and distinguishes melanomas from benign lesions.

Skin cancer is the most common cancer, with over 3.5 million cases diagnosed annually in the United States and incidence increasing at a staggering 3% per year. The American Cancer Society estimated that about 68,130 new melanomas—the most dangerous form of skin cancer—were diagnosed in 2010. Melanoma is lethal in 85% of cases after metastasis. However, when diagnosed early, the survival rate can be as high as 99%. Thus, sensitive screening and early detection are critical for improved patient prognosis. Identification of melanomas is generally performed by dermatologists and definitive evaluation of suspicious skin lesions requires surgical biopsy. Unfortunately, this results in scarring and is impractical for individuals with many lesions. Therefore, there is an unmet need for clinical approaches or devices capable of rapidly screening and distinguishing melanomas from benign lesions.

Optical techniques—such as visual inspection or dermascope use—are most suitable for clinical skin cancer detection. Recently, Raman spectroscopy was identified as an alternative clinical tool to improve diagnostic specificity (i.e., reducing false positives) because of its ability to detect molecular changes associated with tissue pathology. Importantly, it is simple to perform, can be fully automated, and yields results in seconds. Based on inelastic light scattering, Raman spectroscopy measures molecular vibrations and provides ‘fingerprint’ signatures for various biomolecules in tissues, such as proteins, lipids, and nucleic acids. Traditional, single-channel laboratory Fourier-transform (FT) Raman systems add many scans to obtain spectra with good signal to noise ratios. This can take up to 30 min and therefore has limited clinical utility. The first major advancement toward real-time in vivo Raman spectroscopy was reported almost two decades ago. The instrument was a dispersive spectrograph with a CCD, multi-channel near-infrared (NIR) detector. In contrast to FT-Raman systems, this instrument simultaneously detected photons of different wavelengths to obtain spectra from excised human aortic tissue with short, 5 min integration times. Since then, optimized dispersive-type Raman instruments based on fiber-optic light delivery and collection, compact diode lasers, and highly efficient spectrograph-detector combinations have been reported. These advances have lead to increased sensitivity and decreased in vivo measurement time of seconds and subseconds. Here, we provide an overview of our progress toward the clinical application of Raman spectroscopy for skin cancer detection.

In 2001, we constructed a clinical research prototype that was capable of obtaining Raman spectra from skin in vivo in less than 1 s (see Figure 1). Our instrument consisted of a stabilized diode laser (785 nm), transmissive imaging spectrograph, CCD detector (NIR-optimized and back-illuminated), and a
specially-designed Raman probe. (For rapid spectral acquisition, the spectrograph uses a volume phase technology holographic grating for high-throughput light dispersion to facilitate simultaneous whole spectrum detection by the CCD array detector.) We designed the probe to maximize the collection of Raman signals from the tissues while reducing interfering fluorescence and Raman signals from the fibers. Figure 2 shows the probe, which consists of illumination and Raman collection arms. To enhance signal detection, we packed as many fibers into the collection arm as permitted by the CCD height (6.9mm). The fiber bundle consisted of 58 fibers (each 100μm in diameter) arranged in a circle at the input end and a linear array at the output end, which is connected to the spectrograph. We arranged the fibers of the linear array along a parabolic curve to correct for spectrograph image aberration (see Figure 3). This also allowed hardware binning of the vertical spectral line on the CCD. Hardware binning is the capability of the CCD to accumulate electrons from different pixels in one vertical column (i.e., channel) that correspond to the same photon wavelength. We found this preserved spectral resolution and yielded a 16-fold improvement in the signal to noise ratio. Using our system, a spectrum can be acquired within 1s, a vast improvement compared to 20–90s acquisition time for other systems at the time.

More recently, we developed and tested an endoscopic Raman probe for real-time in vivo lung cancer detection. To achieve this, we miniaturized the probe to 1.8mm in diameter, which is small enough to pass through a bronchoscope instrument channel. We placed one excitation fiber in the center of the catheter with 27 collection fibers surrounding it. To obtain high quality measurements, we used first-order optical filtering at the distal tip of the catheter and second stage, and high-performance filtering immediately after the catheter emerges from the bronchoscope channel. Standard filters can be used in the second stage filtering, but we directly coated the first-stage filters onto the fiber end face. We collected enough signal to acquire Raman spectra within 2s.

To process raw spectral data—including Raman signals superimposed on strong fluorescence background signals—we developed a unique polynomial-fitting algorithm to remove background fluorescence. Our algorithm facilitated real-time data processing during in vivo Raman measurements. Our algorithm is freely available to academic users online.

Building on this progress, we analyzed data from 274 skin lesions including cancers (31 melanomas, 18 basal cell carcinomas, and 39 squamous cell carcinomas), precancerous lesions (20 actinic keratoses), and benign lesions (48 seborrheic keratoses and 118 various nevi). Rather than following specific molecules in skin and individual peaks of the Raman spectra, we analyzed changes in the overall spectral shape. Our results showed that,

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by using Raman spectroscopy, precancerous lesions and cancerous lesions can be differentiated from benign lesions with a sensitivity of 90% and specificity of 75%. Additionally, melanomas are differentiated from other pigmented lesions with nearly 100% sensitivity and 70% specificity. This is very encouraging for introducing Raman spectroscopy to clinical use. We have acquired in vivo Raman data from approximately 1000 skin lesions and are currently analyzing the data to develop an optimized algorithm for melanoma detection.

In summary, we have developed a sensitive, Raman instrument for rapid in vivo measurement. We are currently collaborating with Verisante Technology, Inc. to develop our Raman system into a more compact, robust, and cost-effective clinical device. We are also expanding the applications of our Raman technology beyond dermal and pulmonary tissues sites.

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References


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