Specialty Area: Cross Cutting and Emerging Technologies Course
Speaker Name: Arthur F. Gmitro (gmitro@radiology.arizona.edu)
Highlights

- Provide overview of latest developments in optical imaging for disease diagnosis.
- Describe advantages and limitations of optical imaging compared to MRI.
- Identify how MRI and optical imaging can complement one another.

Title: Optical Imaging

Target Audience: Clinicians and basic scientists working to improve diagnostic accuracy and assessment of therapeutic response.

Outcome/Objectives: Attendees will learn about recent advances in optical imaging and spectroscopy methods for disease diagnosis, gain an understanding of the advantages and disadvantages of optical vs. MR imaging, and see how these two imaging modalities might complement one another in clinical care and basic science research.

Purpose: Improving the diagnosis and therapy of disease requires knowledge of the capabilities and fundamental limitations of available approaches and technologies. Optical imaging for disease diagnosis and therapy monitoring is advancing rapidly as a technology with capabilities and limitations that differ from those of MRI. This presentation will describe advanced methods in endoscopic imaging, optical biopsy, and diffuse optical tomography, as well as provide an assessment of what these imaging methods can and cannot achieve in key medical applications.

Methods: Endoscopes for imaging inside the human body have existed for nearly two hundred years. Modern instruments allow direct optical imaging of tissue surfaces (colon, esophagus, stomach, bladder, bronchi, cervix, uterus, fallopian tubes) accessible through natural orifices, or tissues (abdominal and pelvic organs, joint spaces) accessible through a small incision. The major uses of endoscopes are for direct visualization of abnormalities (diagnosis), guidance to a site of pathology for tissue extraction (biopsy), and for assistance in carrying out surgical procedures (therapy). Some endoscopic instruments, especially smaller diameter ones, utilize relay optics or fiber optic imaging bundles to relay an image to an external viewport or imaging detector. Others incorporate the image detector in the distal end of the endoscopic instrument itself. Illumination of the image field is necessary and accomplished typically with bright light sources coupled into fiber optic light guides. Many endoscopes have additional ports that allow specialized instruments to extract tissue biopsy samples. Use of dyes (chromoendoscopy) alters tissue contrast and can improve detection of pathology. Magnifying endoscopy produces images with higher magnification for more detailed evaluation of tissue structure. A relatively new technology, called capsule endoscopy[1], has the illumination source, imaging system, detector, and wireless signal transmission all encapsulated in a structure the size of pill that can be swallowed enabling imaging of the entire gastrointestinal tract including the small bowel.

A new class of endoscopic imaging techniques, broadly referred to as optical biopsy[2], seeks to replace the need for extracting tissue in order to make the diagnosis in situ. The advantages are real-time diagnosis and the potential to image more sites, partially mitigating the sampling error common in conventional biopsy. To image a thick three-dimensional biological tissue microscopically at the cellular level some form of “optical sectioning” is necessary. This can be accomplished by confocal microscopy, which is a type of scanning microscopy where a point (or line) of illumination is imaged into the tissue and the scattered or fluorescence light generated from the sample is imaged onto a confocal pinhole (or slit) aperture to reject light that is coming from out of focus planes in the sample. A 2D or 3D image is built up by scanning the illumination profile through the sample. A number of approaches have been taken to implement

confocal microscopy in an endoscopic instrument[3-7]. Research and commercial confocal microendoscopes have been developed for a variety of clinical applications including imaging of colon, esophagus, cervix, and the surface of internal organs, such as the ovary during a laparoscopic procedure. Variants of the confocal approach include techniques that exploit non-linear optical interactions of light with tissue, such as two-photon fluorescence, three-photon fluorescence, and second harmonic generation. The advantage of these non-linear techniques is that the interaction that creates the emission of light occurs only at very high power density and is therefore localized to a small focal volume inside the 3D tissue. To achieve sufficient intensity high power pulsed laser sources are required. As is the case with confocal imaging, the focal point must be scanned through the object to build up a 2D or 3D image, but in the case of these nonlinear effects, no confocal aperture is required because the light is only generated at the focal point of the illumination.

Optical coherence tomography (OCT) is another type of optical imaging technique. Originally developed as a high-resolution method for imaging the structures of the eye, it too has been developed for endoscopic applications[8-10]. OCT is an interferometric technique that records the interference of light reflected (or backscattered) from tissue with light reflected from a reference arm of the interferometer. Two distinct classes of OCT systems exist, which are known as time-domain OCT and frequency-domain OCT. In time-domain OCT a broad-band low temporal coherence light source, such as a superluminescent diode, is used. Because of the low coherence, interference only occurs when the path lengths of the sample arm and reference arm of the interferometer are closely matched (within microns of each other). By scanning the reference arm path length, the location of signal (interference) sensitivity can be scanned through the depth of the sample. One can collect an optical “A-scan” of the sample in this way, which is akin to an ultrasound “A-scan” except that in ultrasound the location of sensitivity is determined by the round trip propagation time of the ultrasound pulse rather than location of interference path length matching. In frequency-domain OCT, an interferometer is still employed, but in this case the reference arm path length is held stationary. In detection either the interfering light from a broad-band source is spectrally dispersed onto a 1D detector array, or a source whose emission wavelength can be swept across the spectral bandwidth is employed and the signal is read out by a point detector as a function of time. In either case, a Fourier transform of the detected 1D signal yields a 1D A-scan through the tissue. To build up a 2D cross-sectional image in any of the OCT techniques, the location where the light enters the tissue must be spatially scanned, which can be done mechanically (moving the probe) or optically (deflecting the beam).

Optical biopsy techniques are generally high-resolution imaging methods, but are limited by light scattering in how deep they can image below the tissue surface. Somewhat deeper imaging can be achieved using near infrared light, where scattering is less, but optical biopsy is generally limited to depths of a few hundred microns to a millimeter or two depending on the technique employed. Light will penetrate much deeper into tissue, but it is highly scattered and difficult to directly image deep-lying structures. Diffuse optical tomography is a technique that attempts to image the distribution of optical absorption and/or scattering in larger tissue structures, such as breast or brain[11]. If light is launched into tissue at a specific location, the spatial distribution of light coming out at another location is described by the radiative transport equation. The spatial distribution of absorption, scattering, and index of refraction must be known in order to solve this forward problem. If the distribution of light coming out of the tissue is measured at a number of locations, in principle the spatial distribution of absorption and/or scattering coefficients can be solved as an inverse problem. Input of light at multiple locations is required as the problem is highly ill-posed. Nevertheless, this approach has gained traction with a number of variations that include use of multiple wavelengths of illumination and alternative temporal behaviors for the illumination (CW, pulsed, modulation at specific temporal frequencies).

Like MR spectroscopy, optical spectroscopy can also be implemented as a localized measurement or in a spatially resolved manner. Absorption spectra, fluorescence spectra, and Raman spectra can all provide molecularly specific information about the biology of the tissue under study. As in optical imaging, probe-based instruments can make such measurements at locations throughout the human body.

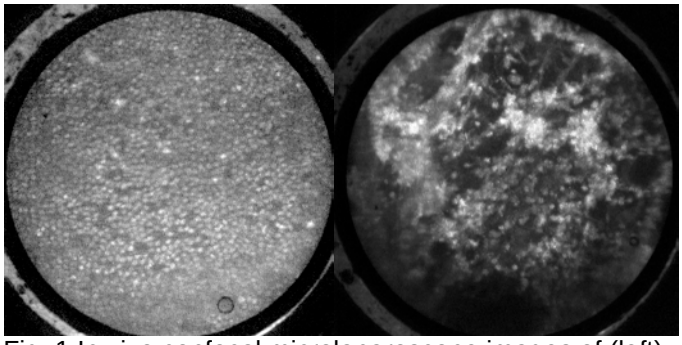

Fig. 1 In vivo confocal microlaparoscope images of (left) human normal ovary, and (right) human ovarian cancer.

Results: Figure 1 shows example images of the surface of the ovary obtained in vivo with a fluorescence confocal microlaparoscope[12]. The tissue was stained with acridine orange, which is an intravital nuclear stain. The regular pattern of cells in the epithelial surface layer of a normal ovary is clearly observed. The heterogeneous distribution and size of cells and cell nuclei in high-grade serous carcinoma of the ovary are also easily identified. These images are single frames from a real time sequence of images recorded at 30 frames/sec. The in-plane spatial resolution in these images is approximately 3 μm and the optical section thickness (axial resolution) using this slit-scan confocal microlaparoscope is approximately 25 μm. The circular field of view in these images is 480 μm. Images of equal or even higher spatial resolution over equal or larger fields have been obtained with commercial systems, albeit with lower temporal resolution due to the use of a point scanning confocal system configuration. In all confocal microendoscope systems, imaging depth is limited to 100-200 μm in most tissues. Two-photon fluorescence microendoscopy has also being developed for optical biopsy[13].

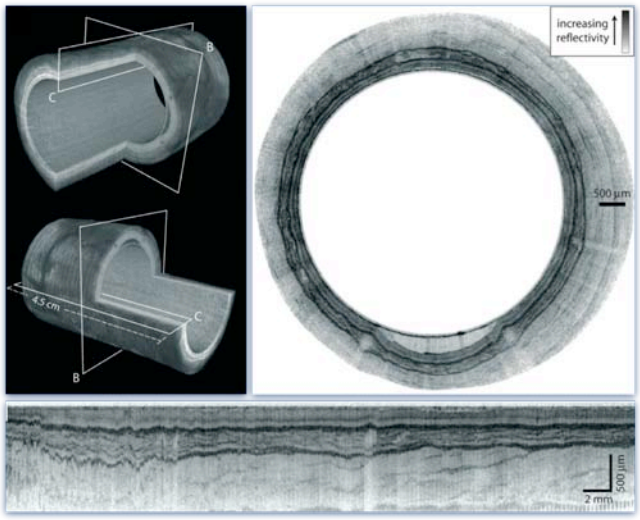

Fig. 2. OCT image of swine esophagus. Cross sections thru the 3D data set are shown to the upper right and

Figure 2 shows an in vivo OCT image of swine esophagus (courtesy of Dr. Gary Tearney, MGH Wellman Center). This 3D image was obtained by a rotary device, which changes the angle of tissue illumination/backscatter collection, and mechanical translation back along the length of the tubular esophagus structure[14]. A balloon in the catheter is inflated to provide a cylindrical geometry in which the tissue surface is located at an equal distance from the catheter center. No optical reflection occurs from the balloon in the center. High optical reflection is shown as darker image values. Cross sections perpendicular and parallel to the cylindrical esophagus are shown. Fine detail of the layers of the esophagus can be appreciated in these images. The lateral resolution of this OCT instrument is approximately 34 μm and the axial (depth) resolution is approximately 10 μm. Imaging to depths greater than 1 mm is achievable because of the reduced tissue scattering in the infrared wavelength used and the high dynamic range of the interferometric detection technique employed in OCT.

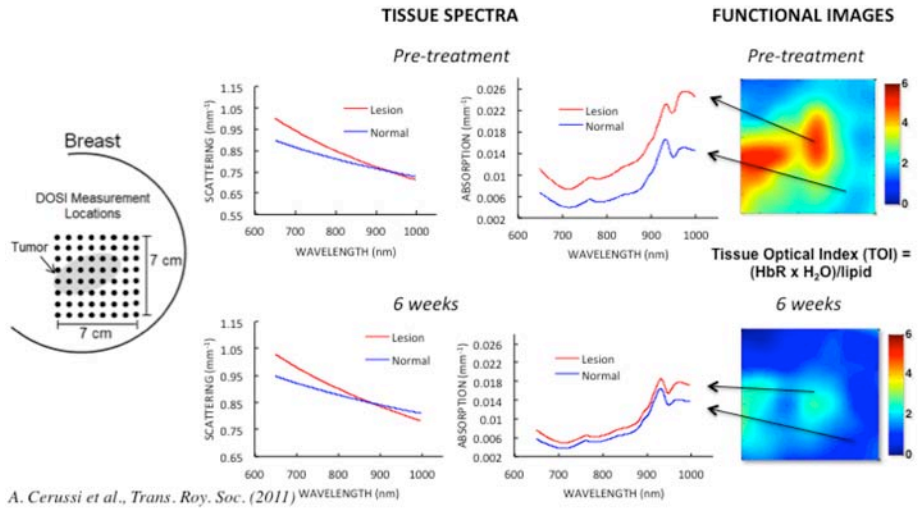

Fig. 3. DOSI results showing functional response to neoadjuvant chemotherapy of breast cancer.

Figure 3 shows results of Diffuse Optical Spectroscopic Imaging (DOSI) of breast cancer patient (courtesy of Dr. Bruce Tromberg, UC Irvine Beckman Laser Institute)[15]. The instrumentation consists of a fiber-optic probe that launches either CW or temporally modulated laser light into tissue and records the return optical signal at a grid of spatial locations across the tissue. Absorption and scattering coefficients can be measured as a function of wavelength and these data used to estimate hemoglobin concentrations and water and lipid content in the tissue. A measure called the tissue optical index (TOI), which is the ratio of oxy- to deoxy-hemoglobin times the water/lipid ratio is shown in the images. The tumor has a high TOI relative to normal breast tissue. The spatial resolution of this technique is on the order of 0.5-1.0 cm. Dr. Tromberg's group has shown that this technique can be used to identify tumors as well as serve as an imaging biomarker of chemotherapeutic response.

Discussion: Optical imaging has distinct advantages and disadvantages as an imaging modality compared to MRI. As shown, some forms of optical imaging can achieve very high spatial resolution (on the order of microns) and allow cellular-level or microstructural-level evaluation of tissues that are unattainable with MRI. With appropriate optical contrast agents, molecular imaging is possible with the potential for sub-cellular localization at picomolar or lower agent concentrations. Although MRI molecular imaging methods continue to progress, they are still far from competitive compared to optical and nuclear techniques in this arena. Optical imaging systems can also be small, lightweight, mobile, and relatively inexpensive compared to MRI. The major limitation of high-resolution optical imaging is depth sensitivity. To some extent this can be overcome with optical imaging devices delivered to dense deep-lying structures through a biopsy needle, but this requires some form of image guidance (US, CT, fluoro, MRI) to get the optical probe to the proper location. While this may be a useful approach in some circumstances, it is an invasive procedure. Imaging deeper into tissue using diffuse optical tomography is another approach, but this is achieved with a significant sacrifice in spatial resolution. Nevertheless, in some applications the functional or metabolic information provided with lower spatial resolution methods, such as diffuse optical tomography or nuclear imaging, may be effective for diagnosis and/or therapy monitoring. MRI capabilities are also rapidly advancing and becoming increasingly more powerful in this arena of functional imaging.

One important viewpoint is to consider where optical and MRI techniques can be combined and/or are complementary to one another rather than competitive. As mentioned, MRI guidance of high-resolution optical imaging procedures is one such area. Another is in

technique validation, where one modality can serve as a gold standard (or method of comparison) for the other modality. Dynamic contrast enhancement (DCE) measurement of vascular permeability is one example. Direct visualization of tumor vasculature down to the capillary level can be achieved with optical imaging in animal window-chamber models. MRI can be done in the same window-chamber models if they are constructed using MRI compatible materials. Injection of a dual-labeled MRI and optical contrast agent into the vessels can be followed dynamically with either modality or done simultaneously using a system capable of dual-modality imaging. Many other types of comparison or technique validation that exploit the strengths of each modality are certainly possible.

Conclusion: Both optical imaging and MRI modalities are advancing rapidly in terms of technology, instrumentation, methods, and clinical applications. Having an appreciation for both in terms of fundamental capabilities and limitations is useful for researchers seeking to expand the reach and impact of either modality. Although competition is healthy, collaboration and cooperation between imaging scientists and clinicians seeking to solve clinical and basic science problems is the best approach to real progress.

References:

1. Ell C, et.al., “The first prospective controlled trial comparing wireless capsule endoscopy with push endoscopy in chronic gastrointestinal bleeding”, Endoscopy **34**(9) 685-689 (2002).
2. Wang TD, et.al., “Optical biopsy: A new frontier in endoscopic detection and diagnosis”, Clin Gastroenterol Hepatol, **2**(9) 744-753 (2004).
3. Gmitro AF, Aziz, D., "Confocal Microscopy Through a Fiber-Optic Imaging Bundle," Opt Lett **18** 565-567 (1993).
4. Dickensheets DL, et.al. “A micromachined scanning confocal optical microscope”, Opt Lett, **21** 764-766 (1996).
5. Sabharwal YS, et.al., “Slit-scanning confocal microendoscope for high resolution in vivo imaging”, Applied Optics, **38**(34) 7133-7144 (1999).
6. Kiesslich R, et.al., “Confocal laser endoscopy for diagnosing intraepithelial neoplasias and colorectal cancer in vivo”, Gastroenterology, **127**(3) 706-713 (2004).
7. Wang TD, et.al., “Confocal fluorescence microscope with dual axis architecture and biaxial postobjective scanning”, Opt Lett, **28** 1915-1917 (2004).
8. Tearney GJ, et.al., “In vivo endoscopic optical biopsy with optical coherence tomography”, Science, **276** 2037-2039 (1997).
9. Kobayashi K, et.al., “ High resolution cross-sectional imaging of the gastrointestinal tract using optical coherence tomography, preliminary results”, Gastrointest Endosc **47** 515-523 (1998).
10. Li XD, et.al., “Optical coherence tomography: advanced technology for the endoscopic imaging of Barrett’s esophagus”, Endoscopy **32**(12) 921-930 (2000).
11. Boas DA, et.al., “Imaging the body with diffuse optical tomography.” IEEE Signal Processing Magazine, Nov. 57-75 (2001).
12. Tanbakuchi AA, et.al., “In vivo imaging of ovarian tissue using a novel confocal microlaparoscpe”, Am J. Obstet Gynecol, **202**(1) 90.e1-9 (2010).
13. Konig K, et.al., “Clinical two-photon microendoscopy” Microscopy Research And Techniques **70** 398-402 (2007).
14. Vakoc VJ, et.al., “Comprehensive esophageal microscopy by using optical frequency-domain imaging (with video)” Gastrointest Endosc, **65**(6) 898-905 (2007).
15. Cerussi A, et.al., “Diffuse optical spectroscopic imaging correlates with final pathological response in breast cancer neoadjuvant chemotherapy”, Philos Trans A Math Phys Eng Sci **369**(1955) 4512-4530 (2011).