# Advanced Imaging Techniques for the Pathologist

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**KEYWORDS**

• Advanced imaging • Digital pathology • Optical coherence tomography • OCT • Digital pathology • In vivo microscopy • Ex vivo microscopy

## ABSTRACT

Advanced imaging refers to direct microscopic imaging of tissue, without the need for traditional hematoxylin-eosin (H&E) microscopy, including microscope slides or whole-slide images. A detailed example is presented of optical coherence tomography (OCT), an imaging technique based on reflected light. Experience and example images are discussed in the larger context of the evolving relationship of surgical pathology to clinical patient care providers. Although these techniques are diagnostically promising, it is unlikely that they will directly supplant H&E histopathology. It is likely that OCT and related technologies will provide narrow, targeted diagnosis in a variety of in vivo (patient) and ex vivo (specimen) applications.

## OVERVIEW

This article discusses a group of novel imaging techniques that are exciting because they may disrupt traditional pathology diagnosis. Such technologies permit direct tissue imaging without delays for histology preparation or for slide scanning, which may mean that turnaround time for pathology diagnosis could radically diminish even if a pathologist is off-site. In vivo imaging is also a possibility, which might blur or diminish traditional boundaries between pathology and other medical specialties. Finally, this might represent a fabulous opportunity to fundamentally re-evaluate current surgical pathology practice, with more emphasis placed on creating clinically valuable tests versus traditional all-inclusive histopathology examination. There are unprecedented pressures related to simultaneously increasing clinical expectations and decreasing access to resources. It is the author's opinion that traditional pathology diagnosis may not continue to be feasible for all applications; bright-field microscopy may not be rapid enough or inexpensive enough despite its current status as gold standard for most histopathology diagnosis. Furthermore, nonpathology specialties are vigorously developing new clinical applications based on advanced imaging; if pathologists wish to be involved in such diagnostic efforts then proactive involvement is essential. Rather than present an exhaustive list of the various advanced imaging modalities,[1] an in-depth presentation of OCT is chosen. The aim is to present a pathologist-friendly introduction, so that interested pathologists will be better able to participate in these advanced imaging efforts.

## OPTICAL COHERENCE TOMOGRAPHY

OCT was originally developed more than 20 years ago and found its first application in ophthalmology,[2] with additional early work with blood vessel and gastrointestinal imaging.[3,4] There are many variants of OCT but it is generally understand that these mean differences in speed, resolution, tissue depth, and image orientation. Specifics are less important than understanding the general idea of what OCT is and how it could be used in a particular situation. Briefly, a specimen is illuminated and the reflected light is used to create a 2-D image or a stack of 2-D images that are virtual slices of the tissue (**Fig. 1**). An

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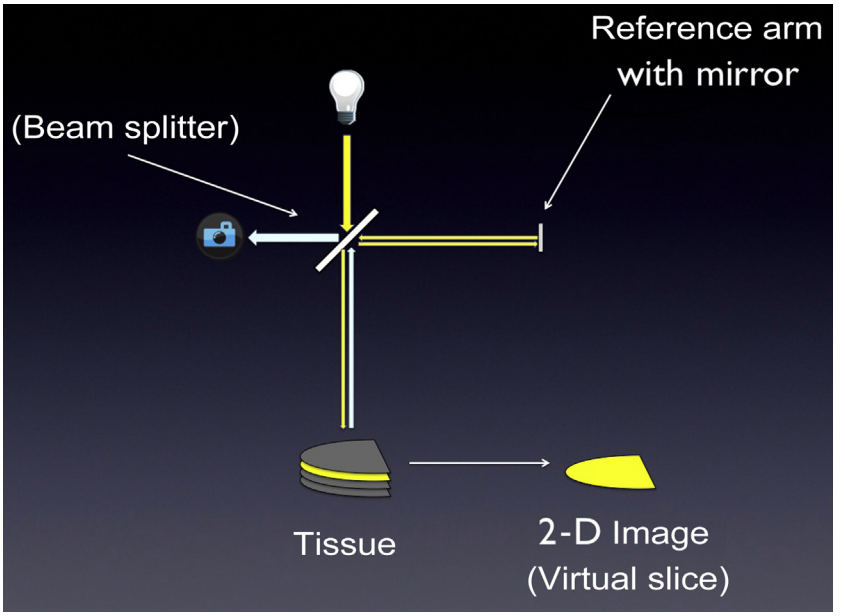


*Fig. 1.* OCT explained. Light is emitted from a source (*light bulb* and *yellow arrows*) and passes through a beam splitter. Some light travels along a reference arm and is reflected from a mirror back into the beam splitter (*more yellow arrows*). Some light travels into the tissue (*yellow arrow*), interacts with the tissue, and is then reflected back into the beam splitter (*white arrow*). Reflected light, both from reference arm and from tissue, combines in the beam splitter and undergoes interference. This interference pattern is imaged (*blue camera icon*) and is a 2-D image of the tissue due to the interaction of light with tissue. By varying the length of the reference arm, the imaged depth into the tissue can be varied. Depth is limited by the amount of reflected light; infrared light permits deeper imaging but offers less resolution than broad-spectrum visible light.

OCT image shows differences in reflectivity; nearly transparent tissues (eg, fat) reflect little light and are contrasted with other shinier tissues (**Fig. 2**). OCT can be simplistically explained by comparison with 3 other imaging techniques that may be more familiar: ultrasound, phase-contrast microscopy, and CT. The ultrasound similarity is easily understood, and that is reflection;

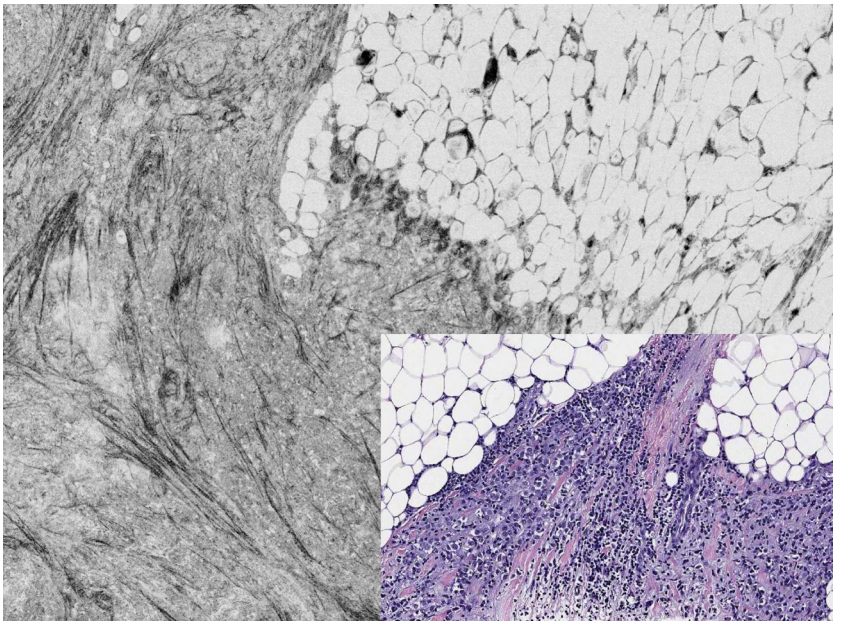

*Fig. 2.* Example OCT image (invasive lobular carcinoma of breast). The larger image is an OCT image of invasive lobular breast carcinoma with infiltration into fat. Fat is perhaps the most easily identified tissue due to the difference in reflectivity between cell membranes and cytoplasm of individual fat cells. The sharpness of the cell membranes visually conveys the high resolution of the image (approximately 1 μm per pixel in the original image). The inset H&E photomicrograph is derived from a WSI of the same tissue (approximately 0.5 μm per pixel, ×20 objective magnification). In the OCT image, individual tumor cell nuclei are visible as white spots in the gray background.