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REVIEW

Functional imaging and endoscopy

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Abstract

The emergence of endoscopy for the diagnosis of gastrointestinal diseases and the treatment of gastrointestinal diseases has brought great changes. The mere observation of anatomy with the imaging mode using modern endoscopy has played a significant role in this regard. However, increasing numbers of endoscopies have exposed additional deficiencies and defects such as anatomically similar diseases. Endoscopy can be used to examine lesions that are difficult to identify and diagnose. Early disease detection requires that substantive changes in biological function should be observed, but in the absence of marked morphological changes, endoscopic detection and diagnosis are difficult. Disease detection requires not only anatomic but also functional imaging to achieve a comprehensive interpretation and understanding. Therefore, we must ask if endoscopic examination can be integrated with both anatomic imaging and functional imaging. In recent years, as molecular biology and medical imaging technology have further developed, more functional imaging methods have emerged. This paper is a review of the literature related to endoscopic optical imaging methods in the hopes of initiating integration of functional imaging and anatomical imaging to yield a new and more effective type of endoscopy.

Key words: Endoscopy; Functional imaging; Multi-modal imaging; Optical coherence tomography; Fluorescence molecular imaging; Photoacoustic tomography; Cerenkov luminescence tomography

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INTRODUCTION

Traditional endoscopic imaging of anatomical lesions has mainly been used for disease diagnosis. This imaging modality for diagnosing gastrointestinal diseases has been very successful, but the use of only anatomic imaging as an endoscopic imaging modality has exposed a number of shortcomings. Many diseases show not only anatomical abnormalities, but also dysfunction, which can be difficult to diagnose based solely on anatomical observations and differential diagnosis. Thus, it seems important to combine endoscopy with anatomical and functional imaging. In recent years, as molecular biology and medical imaging have rapidly developed, more functional imaging methods have emerged and may be the future of endoscopy. This paper will focus on the latest imaging methods, especially those closely related to endoscopic methods for optical imaging. We hope a combination of functional imaging and anatomical imaging will be developed for endoscopy.

OPTICAL COHERENCE TOMOGRAPHY

In 1990, the Austrian scientist Fercher first reported the

use of low-time coherent optical interferometric techniques (low time_coherence interferometry) to observe the topology of the human retina[1]. The following year, Huang *et al*[1] at the Massachusetts Institute of Technology used optical coherence tomography (OCT) technology to image microstructure of the coronary artery. OCT technology has since developed rapidly[2,3]. OCT technology as a low-coherence interferometer has been used together with confocal scanning microscopy and heterodyne detection techniques to non-invasively obtain internal information on living structures and physiological functions. The imaging depth is in the millimeter range, and the spatial resolution is in the micrometer range. Thus, OCT technology has quickly become a focus in biomedical imaging research. It is now considered a promising, non-destructive, high-resolution, real-time imaging technique and is the next most promising technique for optical imaging[4,5].

OCT technology provides micrometer-scale images of opaque or translucent tissue superficial cross-sectional imaging. OCT imaging and ultrasound imaging are similar, except that OCT uses near-infrared light instead of ultrasound, and is aptly called "light ultrasound imaging"[2]. OCT is generally composed of five parameters: the light source, beam splitter, reference mirror, detector and image sample. First, given the low temporal coherence light source, exposure to the beam splitter causes part of the sample to be exposed to light through the spectroscope. Another portion of light is reflected to the reference beam splitter mirror and generates a Doppler shift effect. Then, the beam from the reference mirror and different depths of the sample are reflected back together and are received by the detector. When the optical path between the two beams is less than the low-coherent light coherence length of time, it will produce more obvious interference, which is called the "coherence gate". With the use of coherent gate technology, OCT can differentiate sample depths due to separation of the reflected light to reveal structural information and thus the direction of imaging[6].

Currently, OCT technology has developed into a new, cutting-edge diagnostic technique and plays an important role in examing the eye, heart, gastrointestinal tract and skin and in diagnosing cancer and other diseases. In 2005, Evans *et al*[7] described technical monitoring and diagnosis using OCT to examine Barrett' s esophagus and reported that this technology can be used to view a certain depth of the digestive tract with cross-sectional imaging and can reliably identify high-level changes and intestinal tumors of Barrett's esophagus. In 2010, Woitkowski[8] reported basic and applied research reports describing high-speed OCT imaging. OCT technology has the potential to distinguish between metabolism and function to achieve functional imaging[9-13]. In the same year, Fercher[4] pub-lished reports showing that endoscopic OCT technology can not overcome the traditional shortcomings of the depth of imaging. However it is very good for examining the mucosa, lamina propria, mucosal primary and submucosa and can accurately assess the esophagus, stomach, duodenum, pancreas and bile duct, and diagnose colorectal and other diseases, especially atypical hyperplasia, intestinal metaplasia, Barrett's esophagus and pancreatic duct diseases. In 2011, Srinivasan *et al*[14] reported the use of OCT technology to examine cerebral blood flow and removed the quantitative determination of hydrogen ions. This study showed the huge potential of using cerebral vascular imaging to examine physiological functions, thus confirming OCT technology as a non-invasive method for quantitative determination of cerebral blood flow and metabolism.

Currently, OCT technology is carried out first for digestive diseases and reports of functional imaging studies are increasing. Given the non-invasive, high resolution, multi-level, real-time imaging and functional imaging features, as well as many other advantages, OCT technology will likely play an increasingly important role in the diagnosis of gastrointestinal diseases

FLUORESCENCE MOLECULAR IMAGING

Fluorescence molecular imaging (FMI) is an important branch of optical molecular imaging. FMI is non-invasive, uses non-ionizing radiation, has high resolution and sensitivity, is quick, easy and inexpensive, has relatively high access, and has many other advantages, which have developed rapidly in recent years[15]. The 2008 Nobel Prize in Chemistry was awarded for discovering uses for green fluorescent protein, which is widely used in the scientific community. Green fluorescent protein is a molecular probe in FMI technology, and the clinical application of imaging methods has great potential in the field of optical imaging.

Molecules in different states and at different energy levels absorb photons of different wavelengths. Molecular absorption of light involves upward transitions from ground state molecules to the excited state, called the excitation light. When molecules are excited, they transition from the excited state to the ground state and emit light. When a molecule absorbs a photon of energy and transitions from one electronic state to another low-energy electronic state, the luminescence is called fluorescence[15]. In short, the production of fluorescent molecular probes involves the process of absorbing fluorescent energy to the excited state after the transition, which occurs after a short stay and returns to the ground state emitting fluorescence[16]. According to different fluorescent substances, FMI can be divided into two broad categories: direct fluorescence imaging and indirect fluorescence imaging. In the direct fluorescence imaging mode, a fluorescent substance is injected. Exogenous dyes or fluorescent probes then target specific molecules. For example, such probes are currently used for fluorescence imaging of human breast tissue. In the indirect fluorescence imaging mode, the fluorescent material is fluorescent protein. In this imaging mode,

no fluorescent substances are injected to find the target. Due to the need for genetic modification for indirect fluorescence imaging, this technology can not be applied to the human body. Currently, FMI technology can be divided into a two-dimensional technique and three-dimensional space-oriented fluorescence molecular tomography (FMT) technology[13-18]. Charge-coupled device (CCD) cameras are used in the two-dimensional FMI system by directly inducing the tissue imaging surface to fluoresce. The fluorescent image is added to the white image, which shows the general distribution of fluorescence in the body. However, because of high scattering in biological tissue, fluorescence images obtained this way do not accurately reflect the organization or spatial distribution of fluorescent material. Furthermore, FMI is difficult to use for quantitative analysis, and therefore, its application in some studies is limited. Three-dimensional FMT utilizes optical imaging to analyze absorption and scattering in the sample and the receiving surface of the light intensity. Mathematical methods are used to reconstruct the distribution in body tissue and the concentration of fluorescent material. Thus, three-dimensional FMT provides relatively accurate quantitative analysis.

In 2007, Montet[19] used FMT in experimental animals to examine tumor blood vessels and thus demonstrated the success of functional imaging. In the same year, Corlu *et al*[20] reported the use of FMT technology in human breast cancer and showed clear imaging. Using indocyanine green (ICG) as a fluorescent dye and magnetic resonance imaging, diffuse optical tomography images were compared showing the accuracy of FMT imaging, the optical FMT image and the high contrast ratio of diffuse optical tomography[20]. In 2008, Willmann[21] and others used FMI imaging technology in the field of drug discovery. Currently, reports of the use of FMI technology for human body imaging are few, partly because only ICG is approved for use in humans and because fluorescence spreads a short distance, limiting its application in the human body. AS FMI technology continues to improve, its application will be further expanded.

PHOTOACOUSTIC TOMOGRAPHY

As early as 1880, workers at Bell Labs discovered the photoacoustic phenomenon. Over the last century, combinations of the photoacoustic effect, modern laser technology and weak signal monitoring technology have developed rapidly. In the 1970s, the photoacoustic effect was used to develop photoacoustic spectroscopy. In the 1980s, photoacoustic imaging of biological tissues was introduced. Currently, photoacoustic tomography (PAT) technology represents a new generation of biomedical imaging technology. Combined with the optical advantages of imaging and ultrasound imaging, PAT can provide high resolution and high contrast imaging and can provide structural and functional imaging of biological tissues to study tissue morphology, physiological characteristics, pathological characteristics and metabolic functions[22-24].

Beam irradiation occurs with a varying absorber that cause thermal expansion of ultrasound, a phenomenon known as the photoacoustic effect, which is the "light" produced by the ultrasonic acoustic signal[25]. PAT imaging involves a beam of pulsed light that shines on a sample. Multiple ultrasonic detectors detect the light emitted by the acoustic signal, and then mathematical methods are used to reconstruct the photoacoustic signals to produce a three-dimensional image. An advantage of traditional optical imaging is that the image is better. However, a significant limitation involves the depth and spatial resolution. Thus, the light diffusion caused by the strong high spatial resolution is accompanied by a sharp drop in the imaging depth, and vice versa. Ultrasound imaging increases the depth of tissue that can be examined and has the advantages of larger, higher spatial resolution, but has the disadvantage of an image with poor contrast between the different types of tissues. PAT is a hybrid type of imaging technology, which combines optical imaging and ultrasound imaging with the advantages of both, utilizing the absorption properties of biological tissues to obtain an image with higher image contrast and higher resolution[26].

For early diagnosis of disease, PAT light absorption for tissue imaging, and the optical absorption properties to examine biological tissues, tissue function and pathological features of a structure are closely related to differences in the parameters of optical imaging. In recent years, research on the application of PAT imaging has increased. Oraevsky *et al*[27] used PAT technology to examine hamster buccal squamous cell carcinoma at different stages of capsule imaging, using a wavelength of 532 nm and 12 ns of YAG (Yttrium aluminum garnet) pulsed laser excitation to clearly show photoacoustic images of pre-cancerous tissue. Wang *et al*[28] used three-dimensional PAT to show clear images of rat brain structures such as blood vessels, cerebellum and hippocampal processes. Further photoacoustic images of optical information reflected in the quantitative analysis and calibration were obtained with a photoacoustic signal corresponding to physiological parameters to achieve functional imaging of the rat brain. Esenaliev *et al*[29] performed a photoacoustic imaging study of brain structure and blood vessel dynamics in the brain by monitoring dynamic changes in cerebral blood oxygenation. Ku *et al*[30] used PAT to image blood vessels, to more clearly distinguish the location of a tumor. Several groups took advantage of the nature of differences in absorption and PAT to image tumor tissue and surrounding normal tissue for early diagnosis of breast cancer, showing that this technology can be combined with traditional techniques such as X-radiography and breast ultrasound imaging to produce high contrast, high resolution, non-ionizing images[31-33]. Li *et al*[34] reported a molecular probe that was used as a PAT contrast agent, to show that the absorption spectra of hemoglobin are different in specific molecules in biological tissue. After calibra-

tion, an imaging experiment with multi-wavelength PAT and mathematical modeling of the contribution of the molecular probe to the optical image was used to subtract the background to achieve specific photoacoustic imaging.

Currently, despite high-resolution three-dimensional optical imaging modes, including confocal microscopy and two-photon microscopy, OCT has become fundamentally embedded in bio-medical research. However, these imaging methods cannot image deeper tissues. Photoacoustic imaging in the same signal mode, combined with a powerful optical joint ultrasound contrast and resolution, results in exceeding previous depth limits, resulting in deep tissue high-resolution optical images. At the same time, use of this technology can provide functional imaging, including analysis of oxygen use, blood flow, tumor blood vessels, and many other functions. In the future, photoacoustic imaging is expected to become the mainstream optical imaging mode and should result in development of this technology for endoscopic examination[35].

CERENKOV LUMINESCENCE TOMOGRAPHY

Cerenkov luminescence Tomography (CLT) technology has progressed from the emergence of modern physics and detectors resulting in technological progress. In 1901, Kelvin proposed that the speed of particle radiation may exceed the speed of light[36]. In 1933, Soviet scientist Vavilov Cerenkov used photometric technology in guided research and accidentally discovered faint blue fluorescence[37]. In 1934, Cerenkov and colleagues confirmed that this faint blue Cerenkov radiation was fluorescence and was a new physical phenomenon. A charged particle moves in medium faster than the speed of light and emits electromagnetic radiation, known as Cerenkov radiation. In 1958 Cerenkov, Frank and Tamm won the Nobel Prize in Physics for this discovery. Since then, research involving Cerenkov radiation has been widely performed.

CLT technology is based on the principles of Cerenkov radiation physics. Small amounts of high-speed charged particles are emitted following in vivo injection of radioactive molecular probes. The use of low-light imaging devices in the body provides non-invasive detection of fluorescent molecular probes due to the release of Cerenkov signals. These signals are detected with a computer, which is used for data processing to produce Cerenkov luminescence imaging (CLI). Recently, in vivo molecular imaging probes and systems technology have been developed for CLT. ^{18}F-FDG is a molecular probe in nuclear medicine and has played an increasingly important role in the development of low-light CCD imaging in both basic and clinical research.

In 2009, Cho *et al*[38] used the blue spectrum, its highly sensitive quantum effects and a dominant photomultiplier tube to detect a microchip with weak ^{18}F-FDG-induced fluorescence. Robertson *et al*[39] used a highly sensitive CCD and semiconductor cooling to detect in vivo-induced weak fluorescence in animals. Spinelli *et al*[40] used a multi-spectrum fluorescent light source in the body to successfully obtain the deep information. The essence of these experiments is the Cerenkov effect. CLT technologies employ commonly available optical detectors to observe the release of high-speed charged particles with the high sensitivity of radionuclide isotope imaging. These probes that are used in such studies in molecular nuclear medicine and functional imaging are new tools. In 2010, at the Sloan--Kettering Cancer Center in the United States Ruggiero *et al*[41] suggested that neither the CLI value nor positron emission is adopted to achieve gamma-ray radionuclide imaging, which can be achieved with radioactive tracers. CLI optical imaging technology is a potential new imaging mode because it can be used for quantitative assessment of exposure. In 2011, Boschi *et al*[42] used Cerenkov radiation in small animals in vivo to measure ^{18}F-FDG uptake in tumors. This experiment showed the feasibility of using a traditional optical imaging device to study the metabolism of tumor tissue in vivo and that ^{18}F-FDG PET and conventional optical imaging could be used as a dual-mode device.

Although CLT technology is still in the exploratory stage and has not been used for functional imaging in humans, functional imaging experiments in animals have shown excellent potential. In the future, the use of CLT technology combined with traditional endoscopic techniques for functional imaging may be meaningful.

ANALYSIS AND PERSPECTIVES

Endoscopy was invented 100 years ago, and has gone from hard to soft endoscopy, from endoscopy to the electronic endoscope, from ordinary white light endoscopy to new types of endoscopy, such as magnifying endoscopy, FICE endoscopy, NBI endoscopy, i-scan endoscopy, fluorescence endoscopy, confocal endoscopy, *etc*. and today's doctors are almost overwhelmed by the different types of endoscope. However, looking at the history of endoscopy over the last hundred years highlights both changing and unchanging eternal themes. One change is that high magnification endoscopy is gradually moving towards the micro-microscopic world, and endoscopy continues to develop with the unchanging goal of observing anatomic morphology. Diagnosis of gastrointestinal disease has greatly improved with endoscopy over the past 45 years. During this time, we have discovered approximately 200 types of gastrointestinal diseases. Abandoning endoscopy will be almost impossible. Therefore, the past 45 years have been a brilliant era in endoscopy[43].

However, endoscopic diagnosis at this stage is also facing many challenges including the following: (1) early diagnosis of digestive tract cancer, because endoscopic intervention has not significantly increased; (2) the deep

mucosa and submucosa and lesions of the mucous membrane are difficult to imaging and assess; (3) microvascular imaging of the mucosa and submucosa is difficult to assess; and (4) anatomic lesions with similar endoscopic images are difficult to distinguish, etc. For these problems, the existing endoscopic imaging of morphology as the only mode has deficiencies and shortcomings. Using only gastrointestinal endoscopy for early cancer diagnosis, for example, may require introduction of new endoscopic techniques. Many experts have attempted to develop advanced endoscopic procedures to find cancer earlier despite the economic concerns and the fact that awareness of the public concerning their health has significantly improved. Today, more and more people undergo endoscopy, even though all the external conditions are favorable for developing endoscopic techniques for early diagnosis of cancer. The rate of early diagnosis of gastric cancer in China still hovers around 10%. Little has changed over the last 10 years, even with a focus on early endoscopic diagnosis of carcinoma in the top domestic endoscopy center. Similar results are seen in most of the rest of the world. Indeed, early diagnosis of cancer is a very complex issue, and in addition to endoscopy, there are many other factors. However, other factors aside, what role does endoscopy play in the early diagnosis of digestive tract cancer? Can endoscopic morphology be used solely to identify early cancer? In addition to anatomical observation, can functional endoscopic imaging also be used? Although endoscopic diagnosis of only early cancer has been discussed, other diseases, including Crohn's disease, intestinal tuberculosis, and other gastrointestinal diseases, can be diagnosed relying on existing morphology-based imaging. Endoscopic identification and diagnosis will be very difficult and challenging. Changes to the existing single anatomic endoscopic imaging modality are necessary and may include the integration of a functional imaging mode. The new Multimode endoscopy with functional imaging and anatomical imaging integration may be an effective way to solve these problems. These changes will allow earlier examination of morphological changes. In addition, functional imaging of the organism, metabolism, blood flow, and many other biological parameters offer a more comprehensive interpretation of lesions. Combined with anatomical imaging, functional imaging may permit a view of shape and function of living tissue. Changing the present single form of endoscopic morphology to include functional imaging will be a revolutionary change in modern endoscopy.

Currently, multi-modal fusion of modern medical imaging technology has become a major technology trend[44]. Positron Emission Computed Tomography (PET-CT) is an example of this idea. Recently, multimodal integration of new imaging technologies has emerged, such as development of Optical PET (O-PET) detectors at the University of California, Los Angeles by Prout *et al*[45]. O-PET can detect spontaneous and gamma-ray fluorescence signals, enabling optical signals and the integration of PET imaging. Undoubtedly, future research and development of endoscopic techniques provides a new way of thinking. A critical moment for the future of endoscopy has occurred. Should anatomical imaging continue or should it conform to multimodal fusion imaging trends with the integration of a bolder change? Careful consideration is required. In our opinion, the future should involve functional imaging, anatomical imaging, two-dimensional imaging, and three-dimensional imaging combined with a variety of newly integrated imaging and endoscopic technologies.

CONCLUSION

The basic anatomical observation available with existing endoscopy is a brilliant achievement, but it has also exposed many shortcomings. Development of more powerful endoscopic techniques in the future is an important issue. New optical imaging technology may soon be available for us to learn from. The future involves actively developing a set of functional imaging and anatomical imaging techniques which result in a multi-modal fusion of endoscopic techniques.

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