Photoacoustic endoscopy and EUS: Shaking the future of multimodal endoscopy

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Malignant tumors in the digestive system are some of the leading reasons for mortality worldwide. Early-stage detection or in situ characterization of diseased tissues is crucial for treatment.[1] In the past years, the diagnosis of gastrointestinal tumors has mainly relied on computed tomography (CT), magnetic resonance imaging (MRI), endoscopy, EUS, and so on. CT and MRI show excellent penetration depth, with a relatively low spatial resolution. Endoscopy, which is essentially an optical imaging method, enables the provision of an outstanding spatial resolution as high as several microns but with penetration depth of less than 1 mm below the mucosa. Therefore, EUS is usually used instead of endoscopy to characterize lesions that are located deep in the mucosa. EUS, nevertheless, suffers from low image contrast since it detects the ultrasonic echo signals reflected by differently layered structures. These limitations pose a challenge in the identification and characterization of gastrointestinal tumors in their early stage.

Photoacoustic imaging (PAI) was developed in the 1990s and has been a promising alternative in improving the accuracy of tumor diagnosis. Photoacoustic signals are ultrasonic signals generated from photon absorption, followed by the thermal expansion of tissue; they are converted to the corresponding photoacoustic images through certain image reconstruction algorithms. For example, oxyhemoglobin and deoxyhemoglobin show difference under PAIs, so the total hemoglobin concentration can be calculated through the system. Taking advantage of deep imaging depth, high image contrast, and high spatial resolution, PAI is able to extract abundant structural and functional information regarding the tissue, including the microvascular network, lymphatics, and oxyhemoglobin saturation.[2,3] The successful combination of photoacoustic endoscopy (PAE) with EUS will greatly increase the sensitivity of endoscopy for the diagnosis of digestive system tumors. Tumor

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In addition, the differences in vascular patterns and thickness of tissues/organs, according to different acoustic impedance. However, it is not capable of observing cancer clearly because of its low contrast due to its mechanical properties. PAE/EUS will address the issues because of its high optical contrast and greater acoustic penetration depth. In addition to the ability to detect blood flow and lymphatic vessels, it also has an excellent ability to identify some targeted molecules that contribute to the early diagnosis of cancer.

Mechanical waves are produced when a substance is irradiated by light modulated by a periodic intensity, a phenomenon called the PAE. PAI is a technique that uses PAE, where a tissue could be irradiated with a pulsed laser, and the chromophores inside the tissue absorb the photon energy and the heat is generated, resulting in the expansion of the volume and induction of acoustic waves. These acoustic waves are recorded by a tiny transducer, amplified, and digitized to form an image through a reconstruction algorithm. There are many advantages of PAI. First, the principles of PAI confer a high optical resolution and depth of acoustic penetration. Second, PAI is safer than radiography or CT because it uses nonionizing radiation. It is also less time-consuming than MRI.

In 2012, Yang et al. developed PAE with a decrescent imaging probe. The PAE is able to provide circumferential sector scanning, which produces B-scan images. The researchers have imaged the gastrointestinal tract of rats ex vivo or in situ through PAE. However, the diameter of the probe was 3.8 mm, and the probe may not be compatible with the instrument channels of standard endoscopes, which are usually 2.8 mm or 3.7 mm in diameter. In 2012, Yang et al. introduced simultaneous PAE and ultrasonic dual-mode endoscope, which can provide information about blood vessels and adjacent lymphatic vessels. This technique did not provide a 360° field of vision and the probe diameter was large; therefore, it could not be used with EUS in clinical settings. Photoacoustic and EUS images of two complete rabbit esophagi were observed with the help of the said instrument. They observed the first photoacoustic images of the esophagus of a vertebrate organism, including a map of blood vessels surrounding the wall of the esophagus and extending into the adjacent mediastinal region. In addition, the anatomy of the esophagus was also better demonstrated, such as the esophageal mucosa, submucosa, and an esophageal branch of the thoracic aorta. In 2014, Yang et al. produced a flexible axle-based mechanical scanning PAE system, which can image the human gastrointestinal tract through the instrument channel of a clinical video endoscope. In 2018, Li et al. worked on a PAE/ultrasonic two-channel endoscope system and miniaturization of the system. The encapsulated imaging catheter provided a 360° field of vision. The catheter diameter was 2.5 mm and was comparable with the 2.8-mm instrument channel of conventional endoscopes; thus, it was considered to have the potential to be introduced in clinic practice. In addition,
researchers are trying to utilize new materials to make ultrasonic sensors for dual-mode photoacoustic/ultrasound (PA/US) systems. A small single-element 32-MHz lead magnesium niobate-lead titanate epoxy 1-3 composite-based ultrasonic transducer was produced by Li et al. Compared with traditional sensors, the new ultrasonic transducer had an enhanced bandwidth, and the signal-to-noise ratio of PA and US images of the colorectal wall in rats was improved in 2019.[20]

Although PAE was not introduced in clinical practice, it has great potential as a diagnostic and adjuvant therapy tool. Researchers are working on combining PAE with traditional endoscopic methods, such as EUS. However, the problem associated with this technique, specifically the use of a larger probe and operational difficulties, has not been completely resolved. In addition, suitable contrast agents are required. Furthermore, the animals that are currently used for testing experimental endoscopy are mostly small animals, and the results cannot be extended to humans; thus, clinical trials involving large animals are needed in the future. Currently, there are no relevant parameters and standards for the early diagnosis of cancer and inflammatory diseases using PAE. In the future, relevant modeling and indication confirmation are required. Finally, the existing modality that is combined with PAE is mainly circum-scan EUS; linear EUS as a mainstream tool for both diagnosis and treatment is less studied.[21] Linear EUS can scan organs near the digestive tract to determine appropriate locations for needle sampling or surgery. However, this technique has the inherent limitations of EUS. In the future, multimodal endoscopy of PAE and linear EUS is expected to be developed so that tissue conditions can be better observed through blood flow, oxyhemoglobin saturation, and lymphatic vessels. Tumor angiogenesis is an essential pathological feature of tumors as it delivers oxygen and nutrients to growing tumors.[8,3] The differences in vascular patterns and total hemoglobin concentrations may help differentiate between benign and malignant tumors. Therefore, under the guidance of PEA/EUS, puncture sampling can be performed more accurately. PEA/EUS may improve the success rate of EUS-guided fine needle aspiration.

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Conflicts of interest
Siyu Sun is a consultant of SonoScape Medical Corporation and also the Editor-in-Chief of the journal. The other authors have no conflicts of interests to declare.

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