Beyond images: Emerging role of Raman spectroscopy-based artificial intelligence in diagnosis of gastric neoplasia

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Abstract

White-light endoscopy with tissue biopsy is the gold standard interface for diagnosing gastric neoplastic lesions. However, misdiagnosis of lesions is a challenge because of operator variability and learning curve issues. These issues have not been resolved despite the introduction of advanced imaging technologies, including narrow band imaging, and confocal laser endomicroscopy. To ensure consistently high diagnostic accuracy among endoscopists, artificial intelligence (AI) has recently been introduced to assist endoscopists in the diagnosis of gastric neoplasia. Current endoscopic AI systems for endoscopic diagnosis are mostly based upon interpretation of endoscopic images. In real-life application, the image-based AI system remains reliant upon skilful operators who will need to capture sufficiently good quality images for the AI system to analyze. Such an ideal situation may not always be possible in routine practice. In contrast, non-image-based AI is less constraint by these requirements. Our group has recently developed an endoscopic Raman fibre-optic probe that can be delivered into the gastrointestinal tract via the working channel of any endoscopy for Raman measurements. We have also successfully incorporated the endoscopic Raman spectroscopic system with an AI system. Proof of effectiveness has been demonstrated in *in vivo* studies using the Raman endoscopic system in close to 1,000 patients. The system was able to classify normal gastric tissue, gastric intestinal metaplasia, gastric dysplasia and gastric cancer, with diagnostic accuracy of >85%. Because of the excellent correlation between Raman spectra and histopathology, the Raman-AI system can provide optical diagnosis, thus allowing the endoscopists to make clinical decisions on the spot. Furthermore, by allowing non-expert endoscopists to make real-time decisions as well as expert endoscopists, the system will enable consistency of care.

Keywords: Raman spectroscopy; artificial intelligence; gastric cancer; diagnosis

In the diagnosis of gastric cancer and its related pre-cancerous lesions, three key components will need to be considered: the lesion itself, the interface (i.e., diagnostic modality), and the operator. By definition, the lesion is the "variable" that needs to be "solved" by diagnosis. Thus, to diagnose the "variable" with high certainty, one needs to ensure the interface and operator are as standardized as possible. The currently recommended gold standard diagnostic modality of gastric neoplasm is white light endoscopy (WLE), which has drawbacks including its dependency on the endoscopist's visualization and cognitive skills. Misdiagnosis/underdiagnosis of gastric lesions remains a challenge in inexperienced hands. In fact, up to 14% of gastric cancer could be missed during routine endoscopy (1). As endoscopic diagnosis is problematic, tissue biopsy for histopathologic examination is often done to confirm the presence of a lesion that is suspected during endoscopy. Pathologic diagnosis is not ideal as it is not real-time. As a result, multiple and random biopsy sampling is typically done during endoscopy to minimize sampling

errors, adding significantly to the procedural time and cost. If the endoscopic diagnosis of early gastric cancer is challenging, the endoscopic diagnosis of gastric intestinal metaplastic (GIM) lesions is even more challenging because subtle morphological changes in GIM may not be readily apparent under conventional WLE. In particular, focal GIM lesions tend to be missed during investigation even among experts (2).

To address the unmet needs of real-time diagnosis by endoscopy, emerging and novel advanced imaging technologies, including narrow band imaging (NBI), and confocal laser endomicroscopy (CLE), have been introduced. These technologies were meant to fulfill the strategies as recommended by The Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) initiative courtesy of the American Society for Gastrointestinal Endoscopy, namely 1) Diagnose & Leave: this will obviate or limit the need for unnecessary biopsies, and save time and cost; 2) Diagnose & Target: this will facilitate targeted biopsies for histopathological examination, and improve diagnostic yield; 3) Diagnose & Resect: this will allow therapy at the time of diagnosis; and finally 4) Diagnose & Mark: this will enable the endoscopist to do precise resection, thus ensuring R0 resection. To achieve the optical "diagnose and leave" strategy, the PIVI recommended the imaging technology to have negative predictive values of at least 90% (3).

However, while these technologies can achieve excellent diagnostic performance in expert hands, their diagnostic accuracies are far from satisfactory when used by the less trained endoscopists. Furthermore, CLE requires a long and extensive learning curve in interpreting the images with sufficient accuracy. A previous study from Department of Medicine, National University of Singapore showed significant difference in accuracy between experienced and inexperienced operators in term of image interpretation (4).

To overcome interobserver variability and learning curve issues, artificial intelligence (AI) has recently been "trained" to assist endoscopists in the diagnosis of gastric neoplasia. Current endoscopic AI systems for the diagnosis of gastric cancer are mostly based upon interpretation of endoscopic images. For instance, using >10,000 high quality still images from >2,000 gastric cancers, Hirasawa *et al.* developed an AI system that was able to optically detect and diagnose gastric cancer with a sensitivity of 92% (5). Using a dataset of close to 500 magnifying endoscopy with NBI images of non-cancerous lesions and >1,000 images of early gastric cancer, Li *et al.* showed their AI model was more

sensitive (91%) than the diagnoses made by experts (6).

Despite these impressive results, the image-based AI system has certain limitations. To achieve reliable results, the image-based system requires a large amount of well annotated, and high-quality datasets for training and validation. In real-life application, the image-based AI system is also dependent upon skilful and trained operators who will need to capture sufficiently good quality images for the AI system to optimally compute. Such an ideal situation sometimes requires prolonged examination, which may not always be possible in routine non-ideal clinical practice. Thus, interface and interoperate variability issues may continue to limit the full potential of the image-based AI.

In contrast, non-image-based AI, which is less constraint by these requirements, has recently been proposed as a possible alternative to image-based AI. The non-endoscopic image-based AI system is designed and trained on data that do not require endoscopic or histologic images. These data can include clinical data, biomarkers, and spectra. While spectra are not as commonly used in clinical medicine as other data form, they have been applied to test the purity of drugs. The potential of using spectra is beginning to be recognized in many fields of medicine. Mass spectrometry is one such platform. Raman spectroscopy is another.

The Raman spectroscopy is a technique that applies a laser beam to agitate tissue molecules, causing transient polarization changes in protein, DNA, and lipid content of the tissue cells, thus inducing inelastic scattering of the incident photons. The scattering, which corresponds to the Raman vibrational modes of the molecules in question, can be captured as changes in the Raman spectral pattern. The latter biomolecular information, which is essentially a molecular "fingerprint", can be correlated with the tissue pathology. Neoplastic tissues have different molecular "fingerprints" from healthy tissues. Thus, by analyzing the Raman spectral pattern, one will be able to differentiate healthy tissues from cancerous, and precancerous tissues (7).

Our group has recently developed an endoscopic Raman fibre-optic probe that can be delivered into the upper and lower gastrointestinal tract via the working channel of any commercially available endoscopy for *in vivo* Raman measurements. We have also successfully incorporated the endoscopic Raman spectroscopic system with an AI analytic system. Thus, once the probe arrives at the site of interest during endoscopy, it is capable of both delivering a laser

beam and capturing the molecular "fingerprint" of any tissue it encounters (7). This information can be analyzed by AI in real-time, and a diagnosis displayed in less than a second. The Raman spectroscopy has several advantages over the traditional advanced imaging technologies. Firstly, unlike CLE, it does not require contrast agent for spectral acquisition. Secondly, it does not rely upon morphological information for annotation, training, and validation of the AI system. Thirdly, it does not also require morphological information for the computer-assisted AI system to analyze during the procedure. Lastly, as the Raman probe interrogates the tissue of interest by point contact, it allows precise targeting, i.e., optical biopsy. Because of those unique advantages, the Raman-AI system can provide real-time and operator-independent diagnosis of gastric tissues during endoscopic examination.

Proof of effectiveness has been demonstrated in *in vivo* studies using the Raman endoscopic system in close to 1,000 patients. The system was able to classify normal gastric tissues, gastric intestinal metaplasia, gastric dysplasia, and gastric cancer, with diagnostic accuracy of >85% (8-11). Studies are now ongoing to demonstrate the ability of the Raman-AI system to efficiently guide operators in performing gastric mapping for GIM, targeted biopsies of dysplasia, and in determining the margin of early gastric cancer during endoscopic resection. By allowing endoscopists to make clinical decisions on the spot, whether to "diagnose & discard", "diagnose and target", "diagnose & resect", "diagnose & mark", or "resect & discard", this system will help them to potentially save time and cost, and minimize complications by obviating unnecessary biopsy, and limiting resection margin. At the same time, by allowing non-expert endoscopists to do the same real-time decision making as expert endoscopists, this will potentially enable consistency of care at scale and improve clinical practice — the ultimate goal of translational research.

In conclusion, advanced endoscopic platforms such as NBI and CLE all suffer from the shortcoming of operator variability, which may not always be apparent because most publications come from expert centers. A real-time and objective diagnostic tool is much needed to overcome this shortcoming. AI will likely improve the ability of generalists to do more accurate optical diagnosis, potentially closing the gap between non-experts and experts. Most of the currently available endoscopic AI systems are based on image analysis. While image-based AI is able to overcome inter-operator variability, there is

requirement for large amount of high-quality images to support its optimal application. Non-image-based AI platforms such as Raman spectroscopy, which does not require morphologic data and image quality, appear to be a promising alternative in achieving the PIVI's vision.

Acknowledgements

Footnote

Conflicts of Interest: The author is the co-founder of Endofotonics Pte Ltd.

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