



## Successful ex-vivo probe-based confocal laser endomicroscopy of a superficial nonampullary duodenal epithelial tumor with dripping of food additives: a case of tubular adenocarcinoma

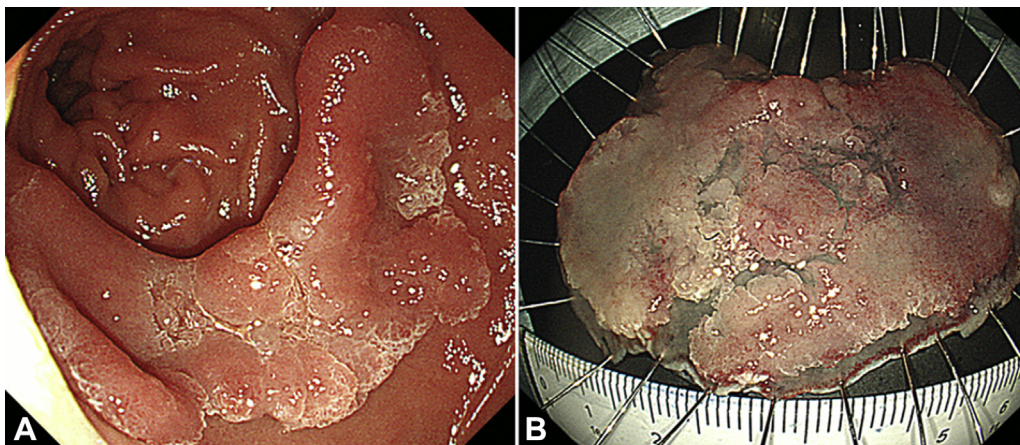
Tomoaki Tashima, MD,<sup>1</sup> Kouichi Nonaka, MD, PhD,<sup>1</sup> Shomei Ryozaawa, MD, PhD,<sup>1</sup> Yuki Tanisaka, MD, PhD,<sup>1</sup> Takashi Fujino, MD, PhD<sup>2</sup>

Endoscopic qualitative diagnosis of a superficial nonampullary duodenal epithelial tumor (SNADET) is difficult. The accuracy of biopsy sampling for SNADET also is not perfect.<sup>1</sup> At present, endoscopic diagnosis of SNADETs is still controversial, and early establishment of standards for endoscopic diagnosis is awaited. Meanwhile, probe-based confocal laser endomicroscopy (pCLE) is an innovative endoscopic technique that enables “optical biopsy” by enabling real-time imaging of biotissue by the intravenous injection of a fluorescent dye.<sup>2</sup>

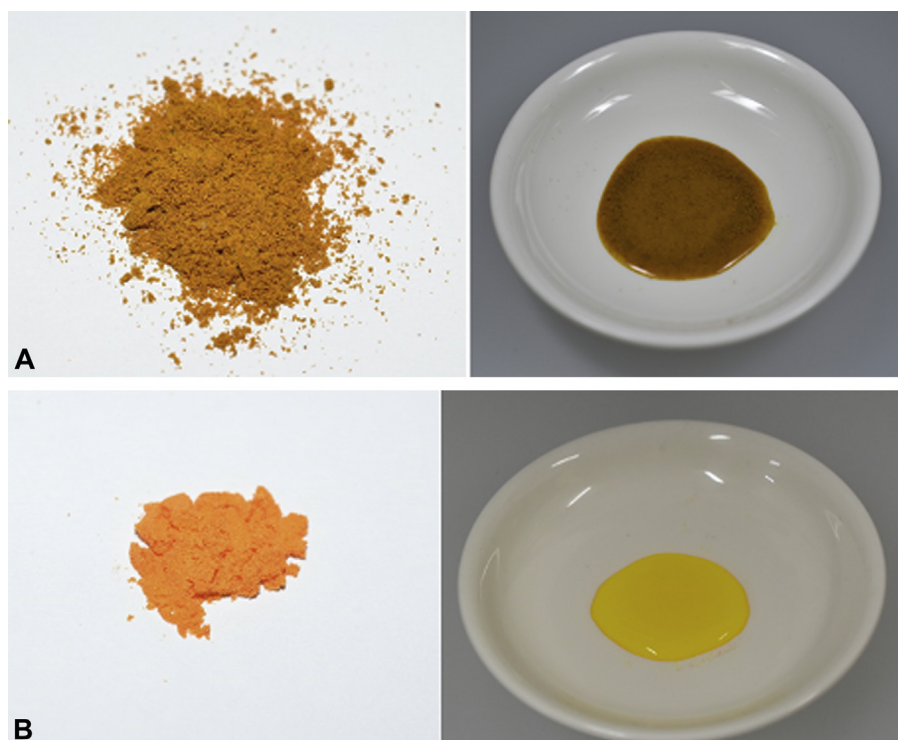
Fluorescein, a fluorescent dye with established safety,<sup>3</sup> is used worldwide not only in the ophthalmologic field but also for confocal endoscopy. However, its use is limited in Japan because it has not been approved for application in the endoscopy field. Nonaka et al<sup>4</sup> previously demonstrated that the fluorescein dripping method could produce pCLE images of a quality equivalent to those obtained by ordinary fluorescein intravenous injection; they reported the safety of this method while proposing a new classification for the diagnosis of SNADETs with pCLE.<sup>2</sup> For more widespread use of pCLE, the development of a fluorescent dye that is safer and more convenient to use than fluorescein is awaited.

We hypothesized that edible fluorescent dyes that are widely used as food additives would allow safer and more convenient pCLE. Thus, we examined whether pCLE can be performed with curcumin<sup>5</sup> and tartrazine,<sup>6</sup> which are edible fluorescent dyes with excitation wavelengths nearly identical to the laser wavelength of the confocal endoscope (488 nm), with the use of a resected specimen of the duodenum. Curcumin is a yellow polyphenol compound contained in turmeric, a plant related to ginger. A representative food that contains turmeric is curry. Curcumin is the compound that gives turmeric its yellow color. The other dye, tartrazine, is a synthetic lemon-yellow dye primarily used as a food coloring. It is a colorant commonly used in diverse products including cosmetics, clothing, and foods such as jelly and syrup. This study was approved by the institutional review board of Saitama Medical University International Medical Center.

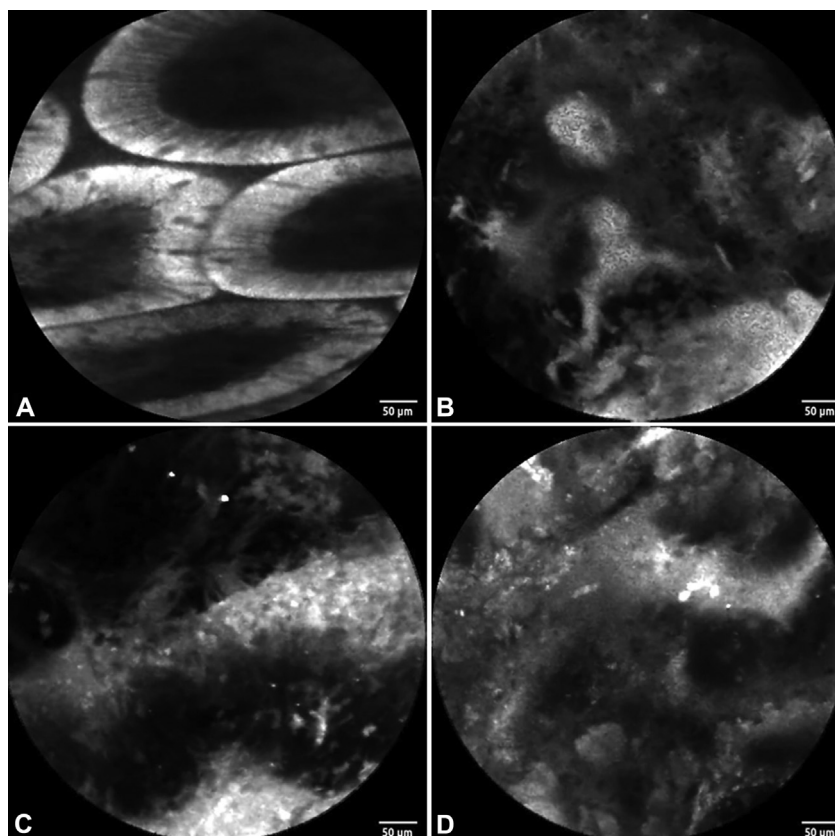
A 65-year-old woman was found, by endoscopy, to have a flat elevated tumor approximately 55 mm in diameter in the second part of the duodenum. The preoperative histologic diagnosis by biopsy sampling was high-grade intraepithelial neoplasia. Endoscopic submucosal dissection (ESD) was performed for the lesion (Fig. 1). After ESD,



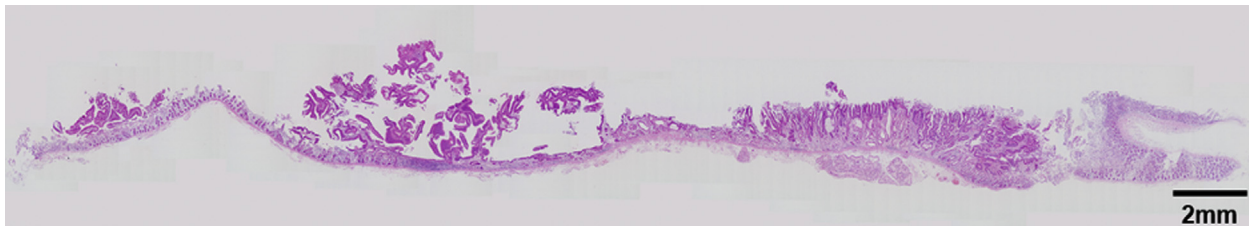
**Figure 1.** **A**, Endoscopic view showing a 55-mm flat-elevated tumor in the second part of the duodenum. **B**, Duodenal specimen after endoscopic submucosal dissection.



**Figure 2.** Edible fluorescent dyes. **A**, Curcumin powder and solution. **B**, Tartrazine powder and solution.



**Figure 3.** Probe-based confocal laser endomicroscopic (pCLE) images of the resected specimen after dripping of each fluorescent dye. **A**, Nontumor site after fluorescein dripping. **B**, Tumor site after fluorescein dripping. **C**, Tumor site after curcumin dripping. **D**, Tumor site after tartrazine dripping.



**Figure 4.** Histopathologic examination of resected specimen with a loupe, revealing the lesion to be noninvasive adenocarcinoma (H&E, orig. mag.  $\times 1$ ).

fluorescein was dripped onto nontumor and tumor sites of the specimen outside of the patient's body.

At other tumor sites, a 29% curcumin solution prepared by dissolving 1.0 g of curcumin (Orihiro Plantdew Corporation, Gumma, Japan) in 2.5 mL saline solution or a 1.1% tartrazine solution prepared by dissolving 0.03 g of tartrazine (Kyoritsu-foods Corporation, Tokyo, Japan) in 2.5 mL saline solution (Fig. 2) was dripped in such a way that these solutions were not mixed. Five minutes later, the sites were observed with pCLE (GastroFlex UHD, Cellvizio; Mauna Kea Technologies, Paris, France). At the nontumor site, a villiform architecture with uniformly bright, tall columnar epithelium and dark goblet cells was observed. All fluorescent dyes dripped at the tumor sites revealed irregular architecture, which was likely glandular architecture suggesting cancer (Fig. 3; Video 1, available online at [www.VideoGIE.org](http://www.VideoGIE.org)). The pCLE findings were confirmed by histopathologic examination, which revealed the lesion to be noninvasive carcinoma (Fig. 4).

Our results suggest that pCLE can be performed by dripping a food additive such as curcumin or tartrazine on the tissue. This technique may lead to simple and safe pCLE by avoiding intravenous injection and the dripping of fluorescein onto the mucosal surface.

## DISCLOSURE

*All authors disclosed no financial relationships relevant to this publication.*

*Abbreviations: ESD, endoscopic submucosal dissection; pCLE, probe-based confocal laser endomicroscopy; SNADET, superficial nonampullary duodenal epithelial tumor.*

## REFERENCES

1. Kinoshita S, Nishizawa T, Ochiai Y, et al. Accuracy of biopsy for the pre-operative diagnosis of superficial nonampullary duodenal adenocarcinoma. *Gastrointest Endosc* 2017;86:329-32.
2. Nonaka K, Ohata K, Ichihara S, et al. Development of a new classification for in vivo diagnosis of duodenal epithelial tumors with confocal laser endomicroscopy: a pilot study. *Dig Endosc* 2016;28:186-93.
3. Wallace MB, Meining A, Canto MI, et al. The safety of intravenous fluorescein for confocal laser endomicroscopy in the gastrointestinal tract. *Aliment Pharmacol Ther* 2010;31:548-52.
4. Nonaka K, Ohata K, Nakai Y. Probe-based confocal laser endomicroscopy of the duodenal mucosa with fluorescein dispersion. *Dig Endosc* 2014;26:604.
5. Lohan SB, Saeidpour S, Solik A, et al. Investigation of the cutaneous penetration behavior of dexamethasone loaded to nano-sized lipid particles by EPR spectroscopy, and confocal Raman and laser scanning microscopy. *Eur J Pharm Biopharm* 2017;116:102-10.
6. Uhlemann U, Strelau KK, Weber K, et al. Raman spectroscopic determination of norbixin and tartrazine in sugar. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 2012;29:1244-55.

Department of Gastroenterology (1), Department of Pathology (2), Saitama Medical University International Medical Center, Saitama, Japan.

Copyright © 2018 American Society for Gastrointestinal Endoscopy. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.vgie.2018.10.014>