





## REVIEW PAPER

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# New fluorescent imaging technics in gastrology

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## ABSTRACT

**Introduction.** There is a need to develop a new imaging technique in medicine. Gastroenterology is the branch of medicine focused on the digestive system and its disorders therefore for this branch is needed to detect all problems affecting the gastrointestinal tract.

**Aim.** The aim of this article is to complete discuss the possibility of the new fluorescent imaging technics in gastrology to use innovative screening to identify individuals at an early stage.

**Material and methods.** We discuss here imaging techniques such as include x-rays, computed tomography, scans, and magnetic resonance imaging in gastrology. Spectroscopy is the study of the formation and interpretation of spectra resulting from the interaction of all types of radiation on matter understood as a community of atoms and molecules. Various spectroscopic techniques are obtained by combining different types of radiation with different ways of its interaction with the test sample. They provide the opportunity to obtain detailed information about the tested substance – from its atomic composition, through its chemical structure, to its surface structure.

**Analysis of the literatue.** The tissue fluorescence spectrum can be obtained by: (1) autofluorescence, or natural or primary fluorescence, i.e. by direct irradiation of the tissue with laser radiation (laser-induced fluorescence – LIF) and (2) photodynamic diagnosis (PDD), where spectrum analysis is preceded by systemic or local administration of the photosensitizer.

**Conclusion.** The use of fluorescence imaging in colon cancer patient has potential to improve quality of treatment and diagnosis.

**Keywords.** diagnostics, fluorescent imaging, gastrology

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## Introduction

It is estimated that, in Europe in 2020, colorectal cancer accounted for 12.7% of all new cancer diagnoses and 12.4% of all deaths due to cancer. That made it the second most frequently occurring cancer (after breast cancer) and the second cause of cancer death (after lung cancer).<sup>1</sup> Screening, used to identify individuals at an early stage, has improved outcome therefore, is increasingly used treatment of minimally invasive surgery, where preoperative endoscopic marking is necessary.<sup>2</sup> Most colorectal cancer develop from colorectal adenomas, and colonoscopy is regarded as the gold standard method for both detection and resection of such lesions.<sup>3</sup> Tumours in colonoscopy are described in relation to major anatomic landmarks such as the ileocecal valve, hepatic or splenic flexure, but these make anatomical measurements challenging and inaccurate. If the surgeon anticipates intraoperative localization may be difficult, lesions other than rectal or cecal ones should probably be marked by preoperative tattooing.<sup>4</sup> In the context of laparoscopic colorectal resection, preoperative endoscopic tattooing is a safe and reliable method of tumor localization in most cases. Localizing colon and proximal rectal lesions with tattoos may be preferable to other localization techniques including intraoperative endoscopy.<sup>5</sup>

## Aim

We investigated the feasibility of a fluorescence imaging technique using light-emitting diode (LED)-activated indocyanine green (ICG) fluorescence in gastroenterology.

## Material and methods

According to the recommendations, gastrointestinal diseases, neoplasms and neuroendocrine tumours have been investigated in data base such as PubMed, Science Direct and Medline. This paper cover only newest technological solution for fluorescent imaging.

## Analysis of the literature

As early as 1958, Sauntry and Knudtson first introduced the idea of tattooing a colonic polyp using methylene blue.<sup>6</sup> But in 1975, when Ponsky and King suggested that endoscopic tattooing could be useful for intraoperative localisation of colonic lesions, that the technique became more widely used.<sup>7</sup> From initial studies, it was demonstrated that India ink is the most effective agent based on permanence and limited biologic reaction the tattoo dye.<sup>8,9</sup>

Since the colonoscopist cannot reliably predict which portion of the bowel wall will be best visualized at the time of laparotomy, Hyman and Wayne have proposed the use of a “four quadrant” circumferential tattooing in the colon, which is now used.<sup>10</sup> Fu et al. introduced conventional technique, where saline were injected

into the submucosal layer and next the syringe of saline was replaced by another syringe containing India ink and injected, next India ink syringe was replaced by the first syringe of saline and added saline to push out India Ink.<sup>11</sup> Unfortunately, this dye produces a permanent and easily visible staining, complications such as abscess formation, focal peritonitis, inflammatory tumours, idiopathic inflammatory bowel disease. Current practices are variable and are operator-dependent. There are no evidence-based guidelines to aid endoscopists in clinical practice. Despite the National Bowel Cancer Screening Programme guidelines, a significant proportion of colorectal lesions are still not tattooed during their first endoscopy or they are tattooed in wrong place.<sup>12</sup> Researchers are looking for new ways of tattooing. An alternative to tattooing is the endoscopic placement of endoclips adjacent to the lesion, which can then be localized using intraoperative fluoroscopy or used preoperative endoscopic tattooing using indocyanine green (ICG), an exogenous fluorophore visible in real time using near-infrared (NIR) cameras.

Indocyanine green is an amphiphilic, tricarbo-cyanine iodide dye that is reconstituted in aqueous solution of pH 6.5 for intravenous injection in patients. Indocyanine green fluorescence has high contrast and sensitivity because the near-infrared light used to measure fluorescence makes tissues appear more translucent, probing several millimetres into the tissue, than at other wavelengths. The molecule is generally excited between 750 and 800 nm, and fluorescence is viewed around the maximum peak of 832 nm.<sup>13</sup> Ushimaru et al retrospectively analysed preoperative and perioperative data from consecutive gastric cancer patients undergoing elective laparoscopic distal gastrectomy and concluded ICG fluorescence imaging are feasible and safe and could potentially serve as a tumour marker to determine the surgical resection line.<sup>14</sup> For example Tanaka et al was injected Indocyanine green into the submucosa layer of the stomach approximately 1 cm away from the tumour edge by using an endoscopic puncture needle 1 or 3 days before surgery and next used laparoscopic system for ICG detection. The imaging was generated by a high-end full high-definition camera system connected to a laparoscope with a 30° field of direction and a powerful xenon light source and then detecting indocyanine green identified the tumour location.<sup>15</sup> Nagata et al injected India ink near the lesion and then ICG was injected on the other side of the lesion. During subsequent laparoscopic colorectal resection, the colon and rectum were first observed with white light. Then, ICG was activated with a near-infrared LED at 760nm as the light source with a laparoscopic imaging system [16]. Ozawa et al made local injection of 0.5-mL 0.25% ICG solution in the submucosal layer around the tumour in the large intestine concomitantly with normal India ink injec-

tion (0.2 mL). Identification of the tumour site during surgery was achieved with the PINPOINT® endoscopic fluorescence imaging system, which was developed using a SPYTM small-vessel image data-processing system. During laparoscopic surgery, tumour sites were observed with the help of visible and fluorescent light.<sup>17</sup> Wanatanabe made indocyanine green injections undergoing preoperative colonoscopy for early colon cancer or colon adenoma. During subsequent laparotomy, the colon was first observed with the naked eye, and then using a prototype machine with a charge-coupled device (CCD) video camera equipped with a cut-off filter and a LED at a wavelength of 760 nm as the light source.<sup>18</sup> Different method was presented by Barberio et al. They used the fluorescent coating material (near-infrared coating of equipment: NICE) which was synthesized by combining a biocompatible polymer poly(methyl methacrylate) (PMMA) with a specifically engineered fluorescent dye. This fluorescent paint can coat medical instruments using direct immersion or a paintbrush. In six pigs, they made tattoos using 0.05 mg/mL of Indocyanine Green and marked regions using the novel fluorescently coated clips. Simultaneously, NIR laparoscopy was executed. During laparoscopy, fluorescence intensity was assessed. In one human cadaver, FOSC was used to mark a site on the stomach and on the sigmoid colon, respectively. Intraoperative detection during NIR laparoscopy was assessed.<sup>19</sup> Choi et al used the fluorescent clips which were placed on the mucosal surface of a porcine colon and stomach, and the operator then attempted to identify the fluorescent clips from the outer serosal side of the colon and stomach. Then were used 532-nm diode laser and filter glass for visualizing the fluorescence signals through the colonic tissue. A 650-nm diode laser and a digital charge-coupled device (CCD) camera equipped with a band pass emission filter were used for the imaging of the fluorescent clips through the thick stomach tissue.<sup>20</sup> Nomikava used preoperative placement of endoscopic marking clips equipped with resin-conjugated fluorescent indocyanine green to determine the resection margin in eight patients with gastrointestinal cancer. During laparoscopic surgery, a dedicated laparoscopic system with a xenon light source was used to detect fluorescence. The evaluation determined whether the fluorescent from the clips was visualized during laparoscopic surgery.<sup>21</sup> Ryu et al evaluated the intraoperative visibility of the Zeoclip FS using a VISERA ELITE 2 and the short-term outcomes of 37 cancer patients who underwent preoperative fluorescent clip marking. Thirty-three patients exhibited clear fluorescent clip marking and easily determined transection lines. Fluorescence was not observed only in one sigmoid colon cancer patient, who required a colonic stent for preoperative obstruction. Three patients required additional procedures for fluorescence visualization. Kawaguchi

used indocyanine green fluorescent imaging to detected the point of perforation in common bile duct. ICG-fluorescence imaging was used to detect grossly unidentifiable bile leak associated with a small perforation caused during the ERCP procedure. The intrabiliary route was selected for ICG administration because the ENBD tube had already been placed and intravenous injection could have decreased contrast between leaking bile and surrounding structures.<sup>23</sup>

## Conclusion

In all of the studies mentioned, tattooing using this LED-activated fluorescence imaging technique and using novel fluorescently clips is a new concept for marking lesions and is useful, without any side effects, for identifying the location of a tumor in the perioperative period. The differential diagnosis of diseases of the oral mucosa should include the performance of other additional tests: bacteriological and mycological tests, viral cultures, allergy tests, serological tests, immunohistochemistry and immunofluorescence, as well as radiological tests (overview and intraoral radiography, panoramic dental tomography, radiovisiography, sialography), arthrography, angiography) and other imaging techniques such as: axial computed tomography, magnetic resonance, ultrasound and scintigraphy.

## References

1. ECIS – European Cancer Information System. Colorectal cancer burden in EU-27. [https://ecis.jrc.ec.europa.eu/pdf/Colorectal\\_cancer\\_factsheet-Mar\\_2021.pdf](https://ecis.jrc.ec.europa.eu/pdf/Colorectal_cancer_factsheet-Mar_2021.pdf). Accessed: 07.06.2021.
2. Cunningham D, Atkin W, Lenz HJ, et al. Colorectal cancer. *Lancet*. 2010;375(9719):1030-1047.
3. Lin OS, Kozarek RA, Cha JM. Impact of sigmoidoscopy and colonoscopy on colorectal cancer incidence and mortality: an evidence-based review of published prospective and retrospective studies. *Intest Res*. 2014;12:268-274.
4. Kim S, Milsom J, Church J, et al. Perioperative tumor localization for laparoscopic colorectal surgery. *Surg Endosc*. 1997;11:1013-1016.
5. Feingold DL, Addona T, Forde KA, et al. Safety and reliability of tattooing colorectal neoplasms prior to laparoscopic resection. *J Gastrointest Surg*. 2004;8(5):543-546.
6. Sauntry JP, Knudtson KP. A technique for marking the mucosa of the gastrointestinal tract after polypectomy. *Cancer*. 1958;11:607-610.
7. Ponsky JL, King JF. Endoscopic marking of colonic lesions. *Gastrointest Endosc*. 1975;22:42-43.
8. Yang M, Pepe D, Schlachta CM, Alkhamesi NA. Endoscopic tattoo: the importance and need for standardised guidelines and protocol. *J R Soc Med*. 2017;110(7):287-291.
9. Shatz BA, Weinstock LB, Swanson PE, Thyssen EP. Long-term safety of India ink tattoos in the colon. *Gastrointest Endosc*. 1997;45(2):153-156.

10. Hyman N, Wayne JD. Endoscopic four quadrant tattoo for the identification of colonic lesions at surgery. *Gastrointest Endosc.* 1991;37(1):56-58.
11. Fu KI, Fujii T, Kato S, Sano Y, Koba I, Mera K. A new endoscopic tattooing technique for identifying the location of colonic lesions during laparoscopic surgery: a comparison with the conventional technique. *Endoscopy.* 2001;33:687-669.
12. Nahid MAK, Shrestha AK, Imtiaz MR, Basnyat PS. Endoscopic tattooing for colorectal lesions: impact on quality of care and patient outcomes. *Ann Royal Coll Surg Engl.* 2020;102:8:594-597.
13. Reinhart MB, Huntington CR, Blair LJ, Heniford BT, Augenstein VA. Indocyanine Green. *Surgical Innovation.* *Surg Innov.* 2016;23(2):166-175.
14. Ushimaru Y, Omori T, Fujiwara Y, et al. The Feasibility and Safety of Preoperative Fluorescence Marking with Indocyanine Green (ICG) in Laparoscopic Gastrectomy for Gastric Cancer. *J Gastrointest Surg.* 2019;23(3):468-476.
15. Tanaka C, Kanda M, Funasaka K, et al. Detection of indocyanine green fluorescence to determine tumor location during laparoscopic gastrectomy for gastric cancer: Results of a prospective study. *Asian J Endosc Surg.* 2020;13(2):160-167.
16. Nagata J, Fukunaga Y, Akiyoshi T, et al. Colonic marking with near-infrared, light-emitting, diode-activated indocyanine green for laparoscopic colorectal surgery. *Dis Colon Rectum.* 2016;59:e14-e18.
17. Ozawa Y, Murakami M, Watanabe M, et al. Preoperative colonic cancer tattooing using the near-infrared fluorescence laparoscopic imaging system. *Asian J Endosc Surg.* 2016;9(4):340-343.
18. Watanabe M, Tsunoda A, Narita K, Kusano M, Miwa M. Colonic tattooing using fluorescence imaging with light-emitting diode-activated indocyanine green: A feasibility study. *Surg Today.* 2009;39:214-218.
19. Barberio M, Pizzicannella M, Spota A, et al. Preoperative endoscopic marking of the gastrointestinal tract using fluorescence imaging: submucosal indocyanine green tattooing versus a novel fluorescent over-the-scope clip in a survival experimental study. *Surg Endosc.* 2020. doi: 10.1007/s00464-020-07999-2
20. Choi Y, Kim KG, Kim JK. A novel endoscopic fluorescent clip for the localization of gastrointestinal tumors. *Surg Endosc.* 2011;25:2372-2377.
21. Namikawa T, Iwabu J, Hashiba M, et al. Novel endoscopic marking clip equipped with resin-conjugated fluorescent indocyanine green during laparoscopic surgery for gastrointestinal cancer. *Langenbecks Arch Surg.* 2020;405(4):503-508.
22. Ryu S, Okamoto A, Nakashima K, et al. Usefulness of Preoperative Endoscopic Fluorescent Clip Marking in Laparoscopic Gastrointestinal Surgery. *Anticancer Res.* 2020;20(11):6517-6523.
23. Kawaguchi Y, Ishizawa T, Harada Y, et al. Intraoperative Identification of Bile Duct Perforation Following ERCP Using Indocyanine Green-Fluorescence Imaging. *Dig Dis Sci.* 2014;59:1063-1065.