



Application of endoscopic tattooing in intraoperative localization of colon tumours and sentinel lymph nodes

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Abstract

Introduction. Minimally invasive techniques in colorectal surgery have become increasingly popular and are considered a standard of care in most surgical centres. Locating the tumour during laparoscopic procedure can be technically challenging. Incorrect localization of the primary lesion may lead to a non-radical resection margin. The technique of endoscopic tattooing (ET) prior to surgery or endoscopic treatment is considered a useful tool. Various dyes can be used for this purpose, such as: Indian ink, methylene blue, indigocarmine, toluidine blue, isosulfan blue, haematoxylin and eosin, indoxin green. This procedure is recommended by international scientific societies (ASGE and ESGE).

Objective. The purpose of the study is to review the current literature on the use of ET in large intestine tumour lesions.

Materials and method. A MEDLINE literature search of English language articles addressing the use of ET to enable intraoperative tumour localization in colorectal surgery was performed to evaluate and summarize the feasibility of this technique.

Results. The use of ET enables the easy and safe localization of colorectal tumours during minimally invasive colorectal procedures. The percentage of complications is insignificant.

Conclusions. The available literature proves the safety and benefits of using the ET prior to surgical or endoscopic treatment. ASGE and ESGE recommend the use of ET in marking tumours before surgical treatment, and the area after endoscopic resection for further evaluation.

Key words

colorectal cancer, surgical treatment, Endoscopy, endoscopic tattoo

INTRODUCTION

Minimally invasive techniques in colorectal surgery have become increasingly popular and are considered a standard of care in most surgical centres. The introduction of laparoscopic and robotic techniques to common use allows achievement better outcomes [1]. However, the intraoperative localization of small colorectal tumours still remains technically challenging. Difficulties in locating the lesion may lead to an inappropriate range of intestinal resection. One of the ways to facilitate accurate tumour localization is to perform an endoscopic tattooing (ET) procedure prior to surgery. This technique was first described in 1975 by Ponsky et al. [2]. In their recent guidelines the European Society of Gastrointestinal Endoscopy (ESGE) recommends marking the lesion prior to surgical or endoscopic treatment [3]. The use of endoscopic tattooing enables the staining of the tumour area and lymph nodes. Other imaging methods allow for staging the disease and for the treatment of qualification. The endoscopic tattoo affects the type of surgery, the extent of the bowel resection and the use of sparing treatment, and increases the intraoperative comfort of the surgeon and

the safety of the patient. However, several studies indicate that ET are not always effective [1, 4, 5]. According to this data, ET may be inaccurate in about 7% of patients [3, 4] or even not visible in 15–31% of cases [1, 4]. According to several studies, during the post-operative histopathological examination, the presence of dye in the tumour area has been confirmed in only 76% of patients after ET [1, 4, 5]. Various substances can be used for ET, such as: Indian ink, methylene blue, indigocarmine, indocyan green (ICG), toluidine blue, isosulfan blue, haematoxylin and eosin. Some of these dyes may be additionally used for identification of the lymphatic system, including the identification of guard lymph nodes, which is essential to achieve radicality of the resection.

OBJECTIVE

The aim of the review is to evaluate the current literature on endoscopic tattooing. A MEDLINE literature search of English language articles addressing the use of ET to enable intraoperative tumour localization in colorectal surgery was performed to evaluate and summarize the feasibility of this technique. Key words such as ‘endoscopic tattoo’, ‘endoscopic dyes’ and the names of each dye were searched for. Data up to May 2019 was analysed.

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MATERIALS AND METHOD

Application technique. Recommendations from ESGE and the American Society of Gastrointestinal Endoscopy (ASGE) indicate that performing an ET prior to surgical or endoscopic treatment is an important aspect of the treatment. The ESGE experts recommend the use of ET for any lesion that may undergo surgery or be endoscopically controlled in the future. According to the ASGE guidelines, it is recommended to administer the dye using the ‘four-quadrant injection’ technique. This is important especially in the determination of colon lesions. In most cases, 0.5–1.0 ml of the substance is injected in each of the four quadrants of the primary lesion [6]. On the other hand, ESGE recommendations advise the administration of dye by 2–3 injections into the region of the tumour. The injection should be made about 3 cm from the distal side. One injection should be performed in the lesion line and the other on the opposite side [3]. There are two methods of marker administration: conventional and with submucosal bubble formation. In the conventional method, the injection needle should be directed obliquely into the intestinal wall for submucosal dye administration. The technique of marker administration is the ‘saline injection test’, in which the submucosal layer is determined by means a saline injection by the formation of a submucosal follicle. The saline syringe is then replaced by an ink syringe and the dye is injected. Finally, the saline is re-injected to empty the ink contained in the injection needle. In the study by Fu et al., [7], where this technique was used in 55 patient, identification of the intra-operative lesion was more effective than in the conventional technique (98% vs 86.1%, $p=0.034$). The efficacy and safety of this method of administration was also demonstrated in studies for Spot dye [6, 7]. A two-stage variant of this technique is also describe, in which a salt solution is first injected to form a submucosal bubble. This is followed by separate puncture of the bubble with a needle containing Indian ink, and the injection of a small amount of dye [8]. Injection of a small amount of marker at the puncture site results in smaller and more precise tattoos without wide staining of surrounding tissues.

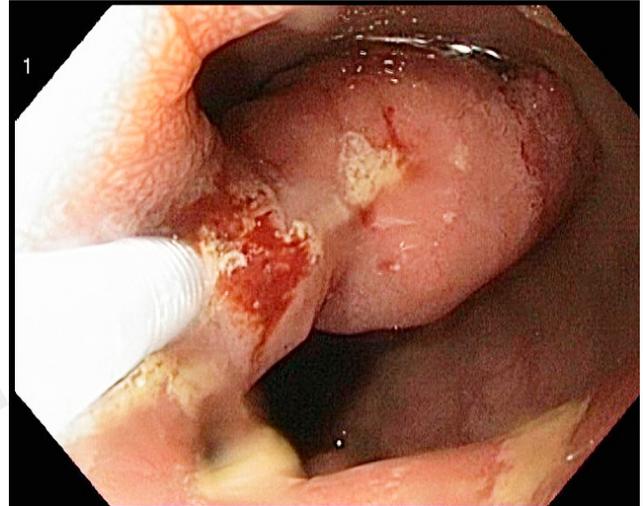


Figure 2. Endoscopic injection of dye

Dyes. Various dyes can be used to perform an endoscopic tattoo. The most commonly used are: Indian ink, methylene blue, indigocarmine, toluidine blue, isosulfan blue, haematoxylin and eosin or indocian green.

Indian ink. This dye is in use since the 1970s [9] and is one of the most popular for endoscopic tattooing. It consists of a colloidal suspension of carbon particle in the solution of organic or non-organic substances. It may contain additional substances such as: ethylene glycol, phenol or gelatin. Although these compounds may cause inflammatory reactions [6] no serious complications in the form of fever, infection or histopathological changes in the collected tissue material have been observed [10]. The marker can be identified intraoperatively more than 48 hours after endoscopic injection [6,11]. It is usually used to mark neoplastic colorectal tumours or adenomatous polyps before surgical treatment. Indian ink, together with indocyanine green, is also used for preoperative determination of pancreatic proliferative changes, including small neuroendocrine tumours. Dye injections are performed

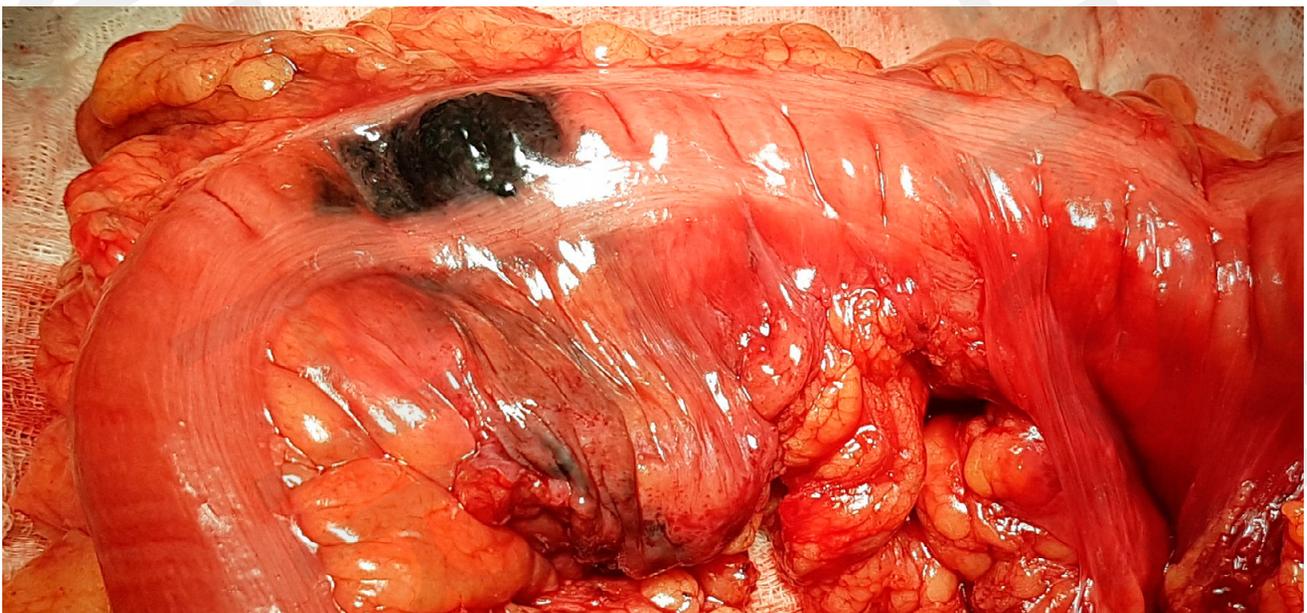


Figure 1. Intraoperative localization of tumor

under the guidance of endoscopic ultrasonography (EUS) [6, 12–14]. It is worth mentioning that before using Indian ink, it should be sterilized.

Methylene blue. Methylene blue is an organic dye and a thiazine derivative, first synthesized in 1876 by the German chemist Heinrich Caro [15]. It is often used in injections with saline or adrenaline in endoscopic procedures, such as polypectomy (EP), mucosectomy (EMR) and submucosal dissection (ESD). After injecting into the submucosal layer, it enables the correct identification of intestinal wall layers, which reduces the risk of perforation and enables safe removal of a larger piece of tissue. In chromoendoscopy it is used to detect dysplastic changes or other pre-cancerous conditions. It can also be used to detect sentinel lymph nodes [16, 17]. After endoscopic administration, it is absorbed within 24 h.

Indigocarmin. An organic blue compound which is also a dye commonly used in medicine. It is used for endoscopic determination and distinction of flat mucous membrane lesions, such as: unspooled polyps, shallow epithelial defects or irregularity of mucous membrane surface. It is also used to highlight areas of Barrett's oesophagus before endoscopic biopsy, as well as to detect dysplastic changes and early forms of malignant tumours. Indigocarmin is routinely used in hereditary non-polypoid colorectal cancer (HNPCC), for the detection of flat polyps and in control tests, among others, in the course of inflammatory bowel diseases (IBD) and coeliac disease. One of the dangerous complications of this dye may be increased arterial pressure [18].

Toluidine blue. An organic thiazin dye, also used as a diagnostic dye in chromoendoscopy. Toluidine blue dye intensively colours the cells with increased DNA synthesis: malignant cells, erosions, ulcers and inflammatory cells [19].

Isosulfan blue. A synthetic lymphatic imaging agent. The dye is injected into the periphery of the tumour. Isosulfan blue is used to locate the lymphatic system and helps to identify sentinel lymph nodes that are coloured blue during surgery. In the study by Rivet et al., it was used to map lymph nodes in laparoscopic resection in patients with colorectal cancer [20]. Another study proposed the use of isosulfan blue as a safe method for intraoperative lymphatic mapping in patients with colorectal cancer metastases to the liver [21].

Haematoxylin and eosin. These are basic dyes used in histology. Haematoxylin is a blue dye which has a high affinity for DNA phosphate groups, which makes it possible to colour-and-violet alkaline structures (e.g. cell nuclei). Eosin is a yellowish dye that colours acid-absorbent structures (e.g. cytoplasmic proteins) pink. It is also used in the diagnosis of *Helicobacter pylori* infection, and in the case of endoscopic biopsies of mucosal discolouration [22].

Indocyanine green (ICG). A cyanine fluorescent dye, developed as a dye in photography and first tested in 1957 in the Mayo Clinic for clinical use. Today, ICG has many applications, such as determining cardiac output and liver function. It is also used in angiography, lymph node mapping, lymphatic drainage, detection of early cancer in Barrett's oesophagus, and to assess tissue perfusion and blood supply to gastrointestinal anastomoses [23]. Iodine allergy is a

contraindication to ICG [6]. An additional impediment to this imaging method is the need for an infrared camera with a laparoscopic set, to enable detection.

Radioisotope markers. The use of radioisotopes, developed in the 1990s, is one of the modalities of mapping lymph nodes. The most common isotope used is technetium-99 (^{99m}Tc) in combination with dye. This radioisotope is injected one day before the operation. During the operation, lymph nodes are detected with a gamma probe. This procedure involves transporting the patient to a nuclear medicine facility where the patients are exposed to radiation during the preoperative period.

Spot marker. This is a new commercial product available on the market. The most important ingredient of the dye is a sterile suspension containing fine carbon particles, developed for endoscopic tattooing, approved by the American Food and Drug Administration (FDA). In addition, the marker contains: water, glycerol, polysorbate 80, benzyl alcohol, simetone and very fine, high purity carbon molecules. Unlike Indian ink, it does not contain such substances as phenol, shellac or ammonia, which reduces the risk of inflammatory reactions. Additionally, it does not require sterilization before endoscopic administration. The use of this marker for endoscopic tattooing is recommended by the ESGE and ASGE [3, 6].

Sienna + *. The main component of this dye is superparamagnetic iron oxide. After administration to the surrounding area, the primary tumour is identified with the Sentimag probe, both in the lesion and in the sentinel lymph nodes. The identification is expressed by sound and numerical values, which show the amount of marker in the examined tissues. Until now, this marker has been used in breast, endometrial, colorectal and prostate cancer [24–33]. Currently, studies are being conducted on the use of this compound for endoscopic tattooing in patients with stomach and colorectal cancer *in vivo*.

Complications. There are not many reports of complications after endoscopic tattooing. Studies show that this method is safe. Most of the complications are associated with improperly deep intramural injection outside the digestive tract. So far, single cases of abdominal and abdominal wall abscesses [34–37], focal peritonitis [34, 38], liver abscess [39], and haematoma [40] have been reported. There have also been cases of gastrointestinal bleeding in the form of haematemesis [34], formation of inflammatory pseudotumours [34, 41–42], idiopathic enteritis [34, 43], masked enteric infarction [34, 44], intestinal perforation [34, 45], and mesentery air embolism [34, 46]. Previously reported complications connected with ET techniques are summarized in Table 1.

DISCUSSION

ET was developed to better locate tumours of the gastrointestinal tract and numerous studies confirm its clinical effectiveness [6, 48–54]. Scientific societies (ASGE and ESGE) recommend the routine use of this procedure [3, 6]. The results of tests in the evaluation of lymph node detection after the application of the tattoo, however, are ambiguous [49, 50, 55–60]. Correct

Table 1. Studies reporting complications after using endoscopic tattooing technique

Year	Author	Dye	Application	Complications
2017	Gonzalez-Tallon et al. ³⁴	Spot [®]	Stomach	Gastric laceration
2017	Awsaj et al. ³⁹	Spot [®]	Colon	Liver abscess
2014	Bang et al. ³⁶	Indian ink	Colon	Colonic abscess
2012	Chen et al. ⁴⁶	Indian ink	Small intestine	Mesenteric air embolism
2011	Marques et al. ⁴⁰	Spot [®]	Rectum	Rectal intramural hematoma
2006	Singh et al. ³⁸	Indian ink	Colon	Peritonitis
2003	Gianom et al. ⁴⁵	Indian ink	Colon	Retroperitoneal perforation
2003	Bahadursingh et al. ⁴⁴	Indian ink	Colon	Inadvertent transmural tattoo simulating infarction of small bowel
2000	Alba et al. ³⁷	Indian ink	Colon	Rectus muscle abscess
1999	Dell'Abate et al. ⁴¹	Indian ink	Colon	Inflammatory pseudotumour
1999	Gopal et al. ⁴³	Indian ink	Colon	Idiopathic inflammatory bowel disease
1991	Park et al. ⁴⁷	Indian ink	Colon	Colonic abscess and peritonitis
1991	Coman et al. ⁴²	Indian ink	Colon	Adipose tissue necrosis and inflammatory pseudotumour

identification of a large number of LN makes it possible to detect potential metastases. Many studies have shown an increased number of LN after application of the tattoo. Bartels demonstrated the effectiveness of endoscopic tattoos for the evaluation of lymph nodes [49], results that were confirmed in a study by Aldecoa [50]. Keller's retrospective review confirmed the effectiveness of tattoo rectal lesions. In 5–8% of probably benign polyps, the presence of invasive cancer was reported. Without performing an endoscopic tattoo, there is no other possibility of licking the place of polypectomy of a given change? [61].

Endoscopic tattoo is a safe method with a low percentage of complications.

CONCLUSIONS

Studies confirm the benefits and safety of the ET procedure. Severe adverse events and complications have not been described as common. Many dyes are currently available, and the most commonly used and recommended are: Indian ink, Spot[®] dye, indocyanine green, methylene blue and indigocarmine. The administration of certain dyes, such as indocyanine green, can be used for intraoperative evaluation of lymphatic drainage and sentinel lymph nodes. The use of endoscopic tattooing is a technique recommended by many scientific societies, and is gradually becoming a standard procedure before a planned endoscopic or surgical treatment.

Conflict of interest

The authors declare no conflict of interest.

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