

Endoscopic tattooing of colorectal lesions: Is it a risk-free procedure?

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Abstract

Endoscopic tattooing is one of the most useful tools for the localization of small colorectal lesions especially in the laparoscopic setting. This is a minimally invasive endoscopic procedure without risk of major complications. However, many studies have revealed complications resulting from this procedure. In this article, several topics are reviewed including the accuracy, substance preparation, injected techniques and complications related to this procedure.

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Key words: Colorectal cancer; Complication; Endoscopic tattooing; Preoperative localization

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in the US population^[1]. In 2007, the incidence was 52.7 per 100 000 population and 53 219 people died from this disease, making it the second leading cause of cancer-related death in the United States^[2]. CRC screening is recommended in people older than 50 years because 90% of CRC cases are diagnosed in this age range^[3] with an increasing incidence of CRC over time^[4]. Family history of CRC is one of the most important risk factors. A meta-analysis showed that the relative risk of a first-degree relative of a CRC patient was 2.24. Moreover, the risk increased to 3.97 if two or more first-degree relatives were affected^[1,5]. There are several other risk factors for CRC, such as personal history of adenoma, sessile serrated polyps or chronic inflammatory bowel disease, which are not covered in detail in this review.

Endoscopy, including flexible sigmoidoscopy and colonoscopy, is one of the CRC screening tools in addition to fecal occult blood test, stool DNA test, double contrast enema, and computed tomography colonography. Thirty to 50% of individuals older than 50 years were discovered to have one or more polyps with all screening methods^[6]. From these findings, the prevalence of malignant polyps ranges from 0.2% to 11%^[7]. Currently, most of the lesions can be removed endoscopically as a result of improving skills with more advanced endoscopic techniques. Unfortunately, some patients still need subsequent surgical resection, due to a high risk of lymph node metastases or positive resected margins.

The intraoperative localization of small lesions or a

previous polypectomy site is often challenging, especially during the laparoscopic approach. Therefore, without precise preoperative localization, it is possible to remove an incorrect segment of intestine. Currently, various methods are widely used for preoperative localization. Double-contrast barium enema is an effective method for identifying large tumors, whereas small lesions are frequently missed^[8]. Approximately 10%-20% of tumor locations identified from colonoscopy are inconsistent with the intraoperative tumor site^[9-11]. Adding a secondary intervention to colonoscopy, such as endoscopic tattooing, seems to be less invasive and a more common approach for preoperative localization. Indications, techniques, and complications of endoscopic tattooing are reviewed in this article.

ENDOSCOPIC TATTOOING

In 1958, Sauntry *et al.*^[12] first reported the technique of tattooing using blue dye at the base of the polyps. Subsequently, Knoernschild^[13] reported on a series of 190 patients who underwent endoscopic tattooing. In 1975, Ponsky *et al.*^[14] initially proposed the endoscopic tattooing of colonic lesions for intraoperative localization. After that, tattooing under endoscopic procedures became more common due to high accuracy with minimal risk of complications. The accuracy, failure rate and complications of this technique are summarized in Table 1.

From our investigations, the accuracy of endoscopic tattooing for localization varies from 70% to 100%. False positive and invisible lesions at the time of surgery ranged from 1.6% to 7% and 1.6% to 15%, respectively. Most of the invisible cases required intraoperative colonoscopy to identify the lesions. The reasons for invisibility may be the result of superficial injection or an injection into the mesenteric side. The rate of dye spillage into the intraperitoneal cavity varies from 2.4%-13%. No clinical infections were detected in these patients. The details of these complications will be discussed later.

The indirect benefit of endoscopic tattooing is an improvement in the adequacy of lymph node dissection from pathological analysis in terms of the number of lymph nodes harvested from the surgical specimens as a result of likely staining in the lymphatic system. One retrospective study demonstrated a significantly higher mean number of lymph nodes examined in tattooed specimens than in non-tattooed specimens (23 *vs* 19, $P = 0.03$). In addition, the proportion of adequate lymph nodes examined (≥ 12 nodes) in the tattooed group was significant greater than that in the non-tattooed group (87.1% *vs* 72.3%, $P = 0.02$)^[22].

Endoscopic tattooing also allows identification of the site of locally advanced rectal cancer after neoadjuvant chemoradiation^[23]. With regard to the disadvantages of tattooing a rectal lesion, the plane of dissection may be obscured if transmural injection and spillage of dye occurs. Moreover, transmural injection can cause inflammatory-related changes in the pathological segment.

Therefore, the role of tattooing in rectal lesions is still a controversial issue.

SUBSTANCES

In 1989, Hammond *et al.*^[24] reported on the use of eight different dyes, including methylene blue, indigo carmine, toluidine blue, lymphazurine, hematoxylin, eosin, indocyanine green (ICG), and India ink injected into dog colon. Only India ink and hematoxylin produced adverse tissue reaction. Mucosal ulceration was found in hematoxylin-injected specimens, whereas India ink produced marked inflammation. This inflammation can be the result of the composition of substances within India ink, including ethylene glycol, phenol, shellac, and animal products (i.e., gelatin)^[25].

Spot (GI Supply, Camp Hill, PA, United States) is a sterile suspension of highly purified and very fine carbon particles. This is a non-India ink permanent marker for endoscopic tattooing. Spot is the only substance that has been approved by the US Food and Drug Administration for endoscopic tattooing. Askin *et al.*^[26] reported on the safety and efficacy of Spot in 113 patients who underwent endoscopic tattooing. None of the patients developed symptoms or signs of inflammation after the procedure. The stain remained for up to 1 year in this study.

Historically, ICG was used for the evaluation of cardiac output and hepatic function with a high level of safety. In 1993, Hammond *et al.*^[27] reported on the injection of ICG as a dye for colonic tattooing in 12 patients (15 colonic lesions), 1 d prior to surgery. ICG remained at the site for at least 36 h. Only one patient developed subclinical local inflammation at the site of injection. Miyoshi *et al.*^[21] reported on the injection of a solution of ICG in 40 cases, who subsequently underwent surgical resection. ICG solution contains 25 mg of powdered ICG in 2 mL sterilized water, and this solution was prepared by the manufacturer. The accuracy of ICG staining was 100% in the group who underwent surgery within 8 d and 92.7% in the later group.

PREPARATION AND STERILIZATION

During the early period of using India ink for endoscopic tattooing, non-sterile India ink was used in approximately 42% of all procedures^[28]. This may have been the possible cause of adverse effects following the tattooing technique, causing an inflammatory reaction due to too-high concentrations of the substance. Subsequently, several studies proposed preparation and sterilization techniques. Salomon *et al.*^[29] recommended the preparation of India ink with 0.9% normal saline of 1:100 dilution. The ink was then sterilized by autoclaving for 20 min at 110°C to 121°C before storage. The American Society for Gastrointestinal Endoscopy^[25] later approved this technique as the standard recommended preparation. Another proposed technique was the passage through a bacteriostatic

Table 1 Summary of the accuracy, false positive and spillage rates of endoscopic tattooing for localization before surgery from previously published reports

Authors	n	Substances	Techniques	Mean interval	Accuracy (%)	False positive (%)	Invisible (%)	Spillage (%)
Cho <i>et al</i> ^[9]	96	India ink	NA	6 d	97.9	0	2.1	6.3
Fu <i>et al</i> ^[15]	36	India ink	0.2 mL injected directly	30.8 d	86	0	14	8.3
	55	India ink	0.2 mL injected after 3 mL injection of saline solution	17.6 d	98	0	2	1.8
Arteaga-González <i>et al</i> ^[16]	21	India ink	Total 0.2-0.5 mL of 90% India ink injected after 3 mL injection of saline solution	NA	100	0	0	14.3
Park <i>et al</i> ^[17]	63	Spot	1-1.5 mL injected after 1 mL injection of saline solution	1 d (all)	96.8	1.6	1.6	9.5
Feingold <i>et al</i> ^[18]	50	Spot	1-4 mL tangentially injected into multiple sites distal to the lesions	1 d (60%)	88	0	12	NA
Conaghan <i>et al</i> ^[19]	54	Spot	NA	NA	70	7	15	NA
Hwang <i>et al</i> ^[20]	20	Spot	0.5 mL injected after 0.5 mL injection of saline solution, 3 sites at 1 cm distal to the lesions	3 d	90	0	10	5
Miyoshi <i>et al</i> ^[21]	41	Indocyanine green	1 mL injected after 2 mL injection of saline solution	4 d	92.7 (100, ≤ 8 d)	0	7.3 (> 9 d)	2.4

NA: Not available.

Millipore filter (0.22 μm)^[28,29].

TECHNIQUES

Depth of injection is one of the crucial points in endoscopic tattooing. An optimal technique is needed to prevent possible complications due to transmural or too deep injections and invisible lesions from superficial injections. In addition, superficial injections, another possible explanation for invisible lesions, results from injection into the mesenteric or retroperitoneal side of the intestine. To prevent this adverse event, Hyman *et al*^[30] recommended a “four quadrant” circumferential tattooing technique to improve intraoperative visualization. The technique which involves the injection of 0.2-0.5 mL of India ink, raising a bleb, into the colonic wall 1 cm distal of the tumor was suggested. The needle should be inserted tangentially to prevent transmural injection^[31].

Sawaki *et al*^[32] proposed a two-step marking method with a first injection of 0.5 mL of saline solution into the submucosal space to create the bleb. India ink was subsequently injected into the saline-blebs. One study compared the two tattooing techniques in 91 patients, 55 patients underwent the two-step approach and 36 patients underwent the conventional method. The results showed that the saline injection technique provided better tumor visualization ($P = 0.034$). The rate of complications was slightly lower in patients who underwent the two-step approach (1.8% *vs* 8.3%, $P = 0.297$)^[15]. However, the spillage rate due to transmural injection was up to 14.3% in the saline injection group. Therefore, only one method is not the answer to eliminate overall complications. The important issue is awareness of possible complications at every step.

In our unit, we prefer to use the “four quadrant” technique by the one step approach with a 1:100 solution

of India ink and normal saline because of the cost and availability. The solution is injected tangentially into the colonic wall at 0.5-1 cm distal to the lesion. The volume per injection is 0.2-0.5 mL. The total volume of the injected solution is about 10-20 mL. After endoscopic tattooing, the patient will undergo surgery within the next couple of days.

COMPLICATIONS

Several studies have proved that endoscopic tattooing is a safe technique. According to a large review of 447 cases by Nizam *et al*^[28], the risk of clinical complications was only 0.22%. McArthur *et al*^[33] reported a small number of complications in a study of 195 patients who underwent endoscopic tattooing. None of the patients in this study had any overt complications. In addition, a prospective study of endoscopic tattooing using India ink in 55 patients by Shatz *et al*^[34] showed no clinical short-term complications. Moreover, we reviewed the long-term safety of India ink tattoos in the colon. None of 280 patients had endoscopic abnormalities over a mean follow-up period of 36 mo. Of these, biopsies from the tattoo sites revealed mild chronic inflammation in 8 patients (2.9%) and only one patient had hyperplastic changes at the biopsy site.

The number of complications following endoscopic tattooing is relatively small but not limited, and most are related to transmural injection. From our investigations, the spillage rate of transmural injections varies from 2.4% to 13% (Table 1). Most of these cases did not have any symptoms resulting from those complications. Case reports and case series of the adverse effects of endoscopic tattooing, including focal peritonitis^[35,36], infected hematoma and/or abscess formation^[36-38], inflammatory pseudotumor^[39], idiopathic inflammatory bowel dis-

Table 2 Summary of complications of endoscopic tattooing for colorectal lesion localization from previously published reports

Authors	Location	Interval time	Material	Amount	Instrument	Complications
Yano <i>et al</i> ^[41]	NA	NA	India ink	0.7 mL undiluted	NA	Post-op adhesion
Bahadursingh <i>et al</i> ^[43]	Sigmoid	NA	India ink	NA	NA	Transmural injection to small bowel
Singh <i>et al</i> ^[35]	Rectosigmoid	NA	India ink	NA	NA	Transmural injection, focal peritonitis
Park <i>et al</i> ^[36]	Descending	18 h	India ink	0.5 mL diluted 1:10	Sclerotherapy needle	Colonic abscess with focal peritonitis
Gopal <i>et al</i> ^[40]	70, 85 cm from Anal verge	No surgery	India ink	4 mL undiluted	NA	Idiopathic inflammatory bowel disease
Tutticci <i>et al</i> ^[42]	Rectum	75 d	Spot	2 mL (0.5 mL each)	25G endoscopic needle	Pigmentation peritoneal adenocarcinoma (tumor inoculation)
Marques <i>et al</i> ^[37]	Sigmoid	3 d	Spot	4 mL (0.5 mL each)	NA	Infected intramural hematoma
Alba <i>et al</i> ^[38]	Sigmoid	10 d	India ink	1 mL diluted 1:10	Sclerotherapy needle	Rectus muscle hematoma and abscess
Coman <i>et al</i> ^[39]	Sigmoid	5 d	India ink	2 mL (0.5 mL each) diluted 1:1	NA	Inflammatory pseudotumor
	Sigmoid	14 d	India ink	2 mL (0.5 mL each) diluted 1:1	NA	Inflammatory pseudotumor
Cappell <i>et al</i> ^[44]	Cecum	7 d	India ink	4 mL total	Sclerotherapy needle	Transmural injection Spillage of dye into peritoneal cavity
	Cecum	13 d	India ink	4 mL total	Sclerotherapy needle	Transmural injection Spillage of dye into peritoneal cavity

NA: Not available.

ease^[40], post-operative adhesions^[41], and tumor inoculation^[42] have been published. A summary of the complications of endoscopic tattooing from previously published reports is shown in Table 2.

One of most the common preparations from the standard recommendation is the concentration of India ink for injection, which consists of undiluted, 1:1, or 1:10 dilution solutions. These solutions might be one of the possible reasons for the adverse results seen when using this technique. Another technical concern is the intraperitoneal scatter of dye from transmural injection. Consequently, this can lead to a number of complications including infection and inflammatory reaction. Moreover, a major concern, although there is only one case report of needle tract inoculation that might be contaminated with cancer cells from the intraluminal area to the intraperitoneal cavity, was reported by Tutticci *et al*^[42]. This interesting case report is a concern and questions whether all the scattered dye in the peritoneal cavity should be examined or removed at the time of surgery. Unfortunately, there are no recent data to answer this question. Further study is needed.

CONCLUSION

CRC screening is recommended in the US population for individuals older than 50 years. As a result, 30%-50% of all subjects were found to have polyps and 0.2%-11% had a malignancy. Some polyps can be removed endoscopically, but some require further surgical intervention. Therefore, localization of the lesion is crucial to prevent false segment resection, especially for the laparoscopic approach.

Endoscopic tattooing is one of the most common preoperative localization techniques. From this review,

the accuracy of endoscopic tattooing is high and varies from 70% to 100%. The false positive rate is 1.6%-7% and the incidence of intra-operative invisible lesions is 1.6%-15%. The number of complications is small but not limited, and most are related to transmural injection. The spillage rate varied from 2.4% to 13%, but most patients with dye spillage were asymptomatic. Following the standard recommendation, including the preparation of substances and injection techniques can prevent unanticipated events.

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