

ORIGINAL ARTICLE

Novel treatment for gastric intestinal metaplasia, a precursor to cancer

Shiu Kum Lam^{*,†} and George Lau^{*,†,‡}

^{*}Humanity & Health GI & Liver Centre, Humanity & Health Medical Group, Hong Kong SAR, [†]Humanity & Health Clinical Trial Centre, Humanity & Health Medical Group, Hong Kong SAR and [‡]Liver Diseases & Transplant Centre, The Fifth Medical Centre of Chinese PLA General Hospital, Beijing, China

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Correspondence

Shiu Kum Lam, Humanity & Health GI & Liver Centre, Humanity & Health Medical Group, Unit 2101, No. 9 Queen's Road Central, Hong Kong. Email: carecare.lam@gmail.com

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Introduction

Gastric intestinal metaplasia (GIM) has a worldwide prevalence of 25% according to a meta-analysis of 107 studies involving 30 960 subjects,¹ and prevalence varies between eastern and western countries, being 24–84% in east Asia^{2–6} and 7–25% in the United States and Europe.^{7–10} GIM is a precursor to gastric cancer, with a pooled odds ratio (OR) of 3.6 in a meta-analysis of 21 studies comprising 402 636 participants¹¹ and an OR of 29.3 in rural China.¹² Annual progression from GIM to cancer also differs, being 600×10^{-5} in China¹³ and 129×10^{-5} in Sweden.¹⁴ GIM is not reversible.^{15–17} It is often extensive, affecting major areas of the stomach,¹⁸ and extensiveness is associated with increased cancer risk.^{19,20}

Helicobacter pylori is known to start a cascade of chronic gastritis, gastric atrophy, GIM, and gastric cancer.²¹ In a meta-analysis of 24 studies involving 48 064 individuals, eradication of

Abstract

Background and Aim: Gastric intestinal metaplasia (GIM) is precancerous with a worldwide prevalence of 25%. Eradicating *Helicobacter pylori* prevented about half of gastric cancers; failure to prevent the rest was attributed to GIM. GIM is irreversible and often extensive. There is no treatment. Existing endoscopic mucosal resection (EMR) is designed to treat early gastric cancer of usually <2 cm. We designed a two-endoscope technique of EMR for extensive lesions such as GIM.

Methods: Forty patients with histologically confirmed moderate to severe GIM (operative link on GIM [OLGIM] classification) received the treatment in a daycare center. Chromoendoscopy with methylene blue was first performed to indicate the GIM. Submucosal saline injections were used to lift the stained mucosa to form multiple safety cushions, which were transformed into artificial polyps by suction and ligation, using a cap familiar to gastroenterologists for ligation of esophageal varices. EMRs were then achieved by snare polypectomy. By rotating two gastroscopes, one was designated to perform lift and snare and the other to perform suction and ligation; cycles of lift–ligate–snare were performed until all stained mucosa was removed. Assessment chromoendoscopy with \geq seven biopsies was performed at 6 months.

Results: A total of 227 EMRs were performed, with a median of 3.5 per patient. Bleeding was uncommon and minimal. Gastric perforation ascribable to loss of a safety cushion occurred in one patient. Chromoendoscopy at 6 months in 36 willing patients showed no recurrence of GIM.

Conclusion: The two-endoscope technique of EMR for GIM was essentially safe and effective, with no recurrence at 6 months. It could be performed by endoscopists with standard skills.

H. pylori reduced the consequence of cancer by 54%²²; the failure in the rest was attributed to pre-existing GIM,^{23,24} confirmed by a meta-analysis of 16 studies involving 52 363 subjects.²⁵ Attempts to treat GIM with long-term antioxidative supplements²⁶ or selective COX-2 inhibitors²⁷ failed. There is no treatment for GIM.

GIM is asymptomatic.²⁸ Time to develop cancer has been reported to be 4.6–7 years.^{23,29,30} A European guideline in 2019 recommends regular surveillance for early cancer as the main management for GIM.³¹ In Asia, screening for early gastric cancer remains a prevalent approach.³² An American guideline suggests against routine use of endoscopic surveillance except in situations at high risk for cancer such as incomplete or extensive GIM, and family history of gastric cancer.³³

Existing techniques of endoscopic mucosal resection (EMR) are designed for small lesions such as early gastric cancer, usually measuring less than 2 cm.³⁴ Past developments of endoscopic technique have been focused on the

use of *one* endoscope. We have designed a *two*-endoscope technique of EMR for extensive lesions, and we report the first experience of its application to treat GIM.

Methods

Operative link on GIM system. Moderate to severe GIM of operative link on GIM (OLGIM) was used as the starting point of treatment. Moderate to severe GIM has been shown to be associated with cancer development.³¹ OLGIM has an almost perfect interobserver agreement at 0.9 and has superseded the operative link on gastritis assessment (OLGA) system, which is based on the assessment of atrophic gastritis, for which the interobserver agreement was low.³⁵ Because of its simplicity and practicality, OLGIM has also superseded the complete and incomplete classification of GIM³⁶; while no study is available to correlate the two systems, moderate to severe GIM most probably correlates with incomplete GIM as both are associated with cancer development.^{30,31} OLGIM is also preferred to classification by dysplasia,³⁷ which is the ultimate stage before cancer, but is known to be associated with synchronous cancer,³⁸ and interobserver variability on dysplasia is inevitable.^{39,40}

Patients. Forty consecutive patients were studied (including 20 males, mean age $62.3 \pm SE 2.9$ years and 20 females, mean age $58.6 \pm SE 2.4$ years). They were recruited during the period from January 2015 to December 2018 from 152 patients who presented with dyspepsia. A prior gastroscopy with five biopsies, as recommended by the updated Sydney classification of gastritis,⁴¹ plus two prepyloric biopsies confirmed the presence of moderate to severe GIM using the OLGIM system. Informed and signed consent was obtained from all.

Instruments and materials. Two standard gastroscopes (Olympus GIF-HQ290) were used, one fitted with a cap for band ligation of esophageal varices (caps with up to 10 bands are available from Boston Scientific or Wilson Cook) and the other uncapped (Fig. 1); endoscopic cannula, injection needle and snare, normal saline, and chromoendoscopy solutions⁴¹ including n-acetyl choline and methylene blue at 1:1 dilution mixed with adrenaline at 1:10 000 were used. Methylene blue is known for its safety.⁴²

Procedure. After an overnight fast, patients underwent the procedure in a daycare center under monitored anesthetic care

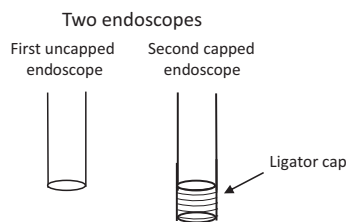


Figure 1 Schematic drawings of two standard endoscopes, one with a cap for band ligation of esophageal varices attached to its end and the other without any cap.

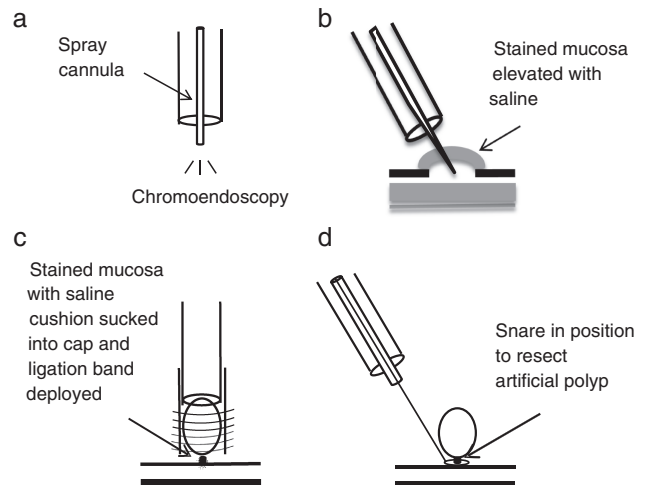


Figure 2 Schematic drawings of the two-endoscope technique of endoscopic mucosal resection for intestinal metaplasia. (a) Endoscope with a spray cannula inserted through the biopsy channel for chromoendoscopy. (b) Injection needle inserted through the stained mucosa into the submucosa and saline injected to raise the mucosa, forming a safety cushion. (c) Because of the safety cushion, only the stained mucosa and not the deeper layers would be sucked into the ligator cap and banded; the banded cushion would become an artificial polyp. (d) Snare resection of the artificial polyp would remove the stained mucosa.

with propofol for sedation. Chromoendoscopy was first performed with the uncapped endoscope using a cannula to spray the entire stomach with n-acetyl choline to remove any mucus, followed by methylene blue to stain and demonstrate the GIM (Figs 2a, 3, and 4a). Three minutes were allowed for the stain to take hold, followed by vigorous flushing with water to remove the stain and frequent suction of the solutions to prevent esophageal reflux and bronchial aspiration. Persistently stained mucosa indicated GIM.⁴²

This uncapped endoscope was then used for the insertion of a needle through the stained mucosa into the submucosa. A total of 10–50 ml of normal saline was injected to elevate the stained mucosa to form a cushion; multiple injections could be carried out to form multiple cushions (Figs 2b and 4b).

The endoscope was withdrawn and replaced with the capped endoscope immediately to minimize the diffusion of saline to the neighboring tissue, thereby losing the safety cushions. The capped endoscope was positioned over the elevated cushion of stained mucosa; suction was applied to draw the mucosa into the cap; and a band was deployed to ligate the mucosa, transforming it to an artificial polyp containing saline (Figs 2c and 4b). In one sitting, multiple artificial polyps could be constructed.

This capped endoscope was then withdrawn, and the uncapped endoscope was reinserted to perform snare polypectomy of the artificial polyps (Figs 2d and 4c). All resected specimens were retrieved, usually with a basket, for pathological examination to confirm GIM and to detect the presence of any dysplasia and/or malignancy.

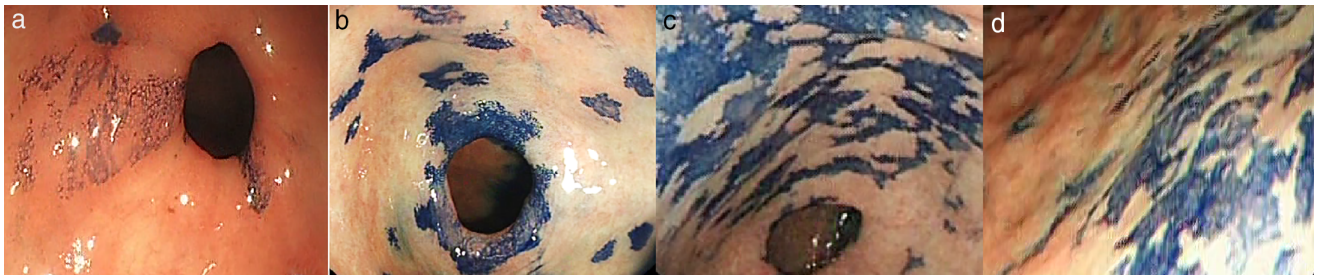


Figure 3 Chromoendoscopy with methylene blue, revealing gastric intestinal metaplasia of: (a) distal half of antrum, (b) entire antrum, and (c) entire antrum extending to (d) distal gastric body.

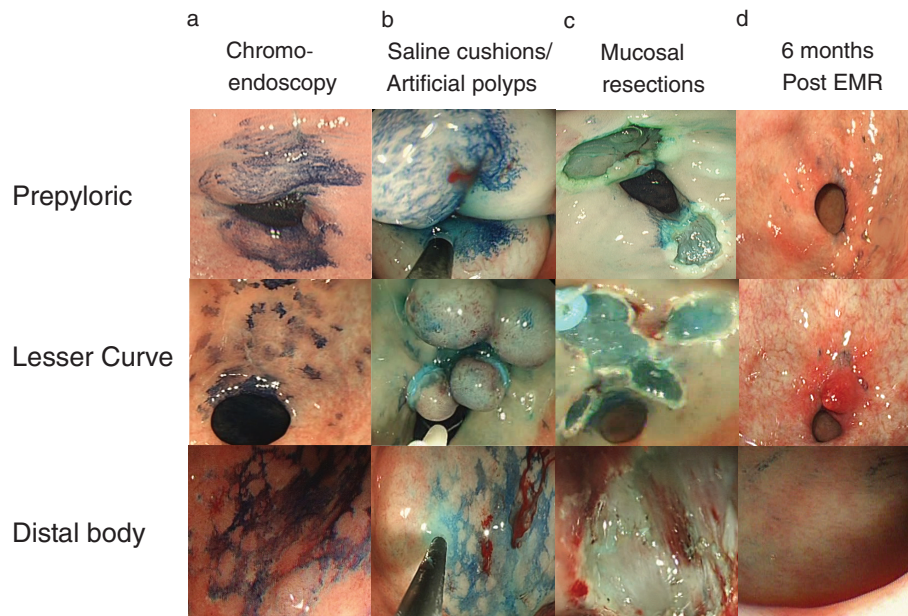


Figure 4 Chromoendoscopy and two-endoscope technique of endoscopic mucosal resection (EMR) for gastric intestinal metaplasia (GIM). First column: chromoendoscopy using the first uncapped endoscope, indicating GIM, second column: safety cushions formed by submucosal saline injections and artificial polyps constructed by suction and ligation, third column: EMRs completed after snare resections of artificial polyps, fourth column: chromoendoscopy at 6 months; remnant stains could be removed with hot biopsy forceps.

Cycles of endoscope exchanges were carried out until all stained mucosa had been resected (Fig. 4c). The EMR wounds could be clipped, but this was generally not necessary as

practically all wounds were superficial. Small residual spots of stained mucosa, usually 2–5 mm, could be destroyed by electrocoagulation and retrieved using hot biopsy forceps. Patients were discharged after the procedure with a proton-pump inhibitor and sucralfate.

Table 1 Endoscopic mucosal resections (EMRs) performed, by gender and site, and cycles of endoscope exchanges per patient

	Patients	EMRs performed		
		Male	Female	Total
	<i>n</i>	20	20	40
Distal half of antrum	20	25	23	48
Entire antrum	10	43	18	61
Entire antrum + distal body	10	71	47	118
Total	40	139	88	227

Follow up. Follow up was scheduled at 1 and 4 weeks and every 4–12 weeks thereafter. Thirty-six patients agreed to have repeat chromoendoscopy and biopsies (total seven, *vide supra*, irrespective of staining) at 6 months.

This study was approved by the Hong Kong Clinical Research Ethics Committee (no. 012019001).

Results

In this consecutive series, chromoendoscopy showed that GIM was patchy and affected the distal half of the antrum in all

40 patients, extending proximally to involve the whole antrum in 10 patients and further to the distal gastric body in another 10 (Table 1, Fig. 3).

A total of 227 EMRs were performed with a median of 3.5 per patient. All patients had the procedure performed in one session, except two, both with GIM involving the entire antrum and distal body, with one requiring two and the other three sessions, approximately 8 weeks apart. Bleeding was uncommon and minimal and could be readily controlled by electrocoagulation. No patient had major gastrointestinal bleeding in the form of hematemesis or melena. In the patient who required three sessions, one EMR at the second session resulted in perforation, which was discovered during the procedure; laparoscopic repair of the perforation was performed. The patient returned on a later date to have the EMRs (total 31) completed. No patient had aspiration pneumonia. There was no mortality. All specimens were retrieved for pathological examination; no malignancy or dysplasia was present.

Median follow up was 52 weeks. At 1 week, 62.5% of patients reported no complains; the others reported minor epigastric or chest discomfort in the first 2 days. No patient phoned up for an immediate appointment because of postoperative discomfort.

In the 36 patients who agreed to have repeat chromoendoscopy and multiple biopsies at 6 months (Fig. 4d, chromoendoscopy was negative in all except six patients, in whom fewer than ten 2–5 mm spots of persistent staining were present; these were most likely remnants of previous EMR and were removed by hot biopsy, which demonstrated mild GIM. All other biopsies indicated no GIM.

Discussion

The advantages of the two-endoscope technique of EMR include: (i) the ability to resect gastric lesions larger than the conventional limit of 2 cm,³² as is often the case in GIM¹³; (ii) simplicity—chromoendoscopy, needle injection of saline to elevate mucosa, ligation, and snare resection are all familiar to endoscopists with standard skills; (iii) readily available standard endoscopes, instruments, and materials; (iv) safety—mucosal elevation to form safety cushions before band ligation and snare resection avoids perforation and bleeding; (v) low costs—routine setting of an endoscopy center; and (vi) convenience—daycare environment and home discharge afterward.

The disadvantages include (i) the need for multiple endoscope insertions and withdrawals with possible minor injury to throat, although this can generally be avoided with well-lubricated endoscopes or the use of a throat guard (which we found unnecessary), and (ii) perforation, as occurred in one of the 40 patients. In retrospect, this was related to the loss of a safety cushion, which could occur when a significant portion of its saline diffused to neighbor tissue so that subsequent suction and ligation trapped all layers of the stomach, leading to perforation when snare resection was applied. This complication is preventable by ensuring that all safety cushions are adequately and generously filled with saline before applying suction and ligation. New devices and techniques have become available for endoscopic closure of gastrointestinal perforations.⁴³

This technique avoids the use of specially designed caps for EMR, which are generally more expensive than the caps for ligation of esophageal varices.⁴⁴ The use of specially designed EMR caps limits EMR to one site at a time, in a piecemeal manner. While this would be laborious, if not impossible, when large areas of IM are present, it also increases the chance of solution leakage through an adjacent wound, posing danger to subsequent resections.

Endoscopic submucosal dissection (ESD), while designed for small lesions such as early gastric cancer, can in theory be extended to treat extensive IM; it is typically performed by endoscopists with experience in the technique itself. ESD carries a significantly higher risk of perforation (3.2%) than EMR (1.2%), as shown in a meta-analysis study.⁴⁵

In this study, 36 patients agreed to a repeat chromoendoscopy and biopsies at 6 months; this confirmed the loss of IM, indicating that the treatment was effective and that there was no recurrence.

As indicated earlier, eradication of *H. pylori* reduced gastric cancer risk by only about half (17), and the failure in the other half could be attributed to pre-existing GIM (18–20). It is hoped that this technique will pave the way for the ultimate prevention of gastric cancer through future controlled trials.

In summary, the two-endoscope technique of EMR can be applied to treat GIM, which is precancerous, often extensive, and for which there is no established treatment. It is essentially free from complications and can be readily performed by endoscopists with standard skills.

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