Research Article

A Valuable Endoscopic Tattooing Method for Early Gastric Cancer Localization before Laparoscopic Surgery

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Abstract

Background and Aims: Laparoscopic surgery for gastric cancer has become popular in recent years and preoperative localization is required as surgeons are unable to identify small tumors through tactile sensation during the surgery. Thus we would like to evaluate our novel endoscopic method using tattooing with SPOT for early gastric cancer localization preoperatively.

Methods: 78 patients had tattooing with SPOT, with or without metal clip. We categorized these patients into two groups according to whether metal clips were used, and analyzed patients' characteristics, pathological features and surgical outcomes. Furthermore, we classified patients into whether they underwent subtotal gastrectomy or pylorus-preserving segmentectomy and analyzed if our tattooing method could be feasible in both types of surgeries. We also evaluated the risk factors of insufficient safety margins to improve our tattooing method in the future.

Results: 78 patients underwent endoscopic tattooing and 15 patients combined with metal clips. The patients' characteristics, pathological features and

surgical outcomes had no clinical significance between two groups. Additionally, subtotal gastrectomy and pylorus-preserving segmentectomy with preoperatively tattooing had similar outcomes except the duration of surgery is significantly shorter in the later. The analysis for risk factors of insufficient safety margin showed that only tumor size in specimens, especially above 2 cm, had clinical significance.

Conclusions: Our method is feasible even without metal clips used and we suggest the location of tattooing or resection margin should be modified if the tumor size is more than 2 cm due to a higher rate of insufficient safety margin.

Keywords: Early gastric cancer; Endoscopic tattooing; Laparoscopic surgery

1. Introduction

Gastric cancer remains high in incidence as the fifth most common cancer and the third most common cause of cancer death worldwide. The incidence is even higher in Asia and may be attributable to *Helicobacter pylori* infection, age, high salt intake, and diets low in fruit and vegetables [1, 2]. Early gastric cancer is mainly treated through Endoscopic Submucosal Dissection (ESD) or Endoscopic Mucosal Resection (EMR) with criteria including cT1a, without ulceration, and a tumor diameter of ≤2-cm that is histologically diagnosed as differentiated-type adenocarcinoma, according to The Japanese Gastric Cancer Association (4th edition) treatment guidelines [3-5]. The depth of cancer invasion and whether the lymph node has metastasis may impact the prognosis of endoscopic therapy. Inoue et al. reported that the 5-year survival rate is 100% in patients with tumor limited to mucosa and 90% in those with submucosal invasion. Furthermore, their study revealed that lymph node metastasis may have an effect on prognosis with overall survival rate at 99% if no regional lymph node metastasis, to 73% if 1~2 group of lymph nodes metastasis [6]. Endoscopic treatment is unable to dissect regional lymph nodes as the evaluation of lymph node metastasis based on imaging is not reliable. Therefore, laparoscopic surgery or open surgery may be an alternative choice in selective cases to achieve complete resection. Laparoscopy-assisted gastrectomy was first described in 1991 by Kitano et al. for early gastric cancer [7]. With advances in technology and improvements in technique, minimally invasive procedures with laparoscopic surgery have become popularized worldwide due to reduced hospital days, decreased need for painkillers, and better cosmetic results. Three phase III trials comparing open surgery with laparoscopic surgery conducted in Japan and Korea presented satisfactory short-term and long-term outcomes in the later [8-10]. However, due to the complexity of lymph node dissection and the involvement of surrounding vasculature and organs in advanced gastric cancer, laparoscopic surgery is mainly limited to early gastric cancer. Some meta-analyses and cohort studies have found favorable outcomes, however, there is a lack of prospective studies [11-14]. The decision on which type of laparoscopic surgery to perform is dependent on tumor location. Laparoscopic total gastrectomy is suggested for proximal gastric cancer with T1N0 and laparoscopic distal gastrectomy for distal gastric cancer with T1~2N0 [15]. Many attempts had been made to perform function-preserving gastrectomy in order to improve postoperative quality of life, especially in early-stage patients of low recurrence. Thus, pylorus-preserving gastrectomy is recommended for tumors in the middle portion of the stomach with the distal tumor border at least 4 cm proximal to the pylorus. Segmental gastrectomy or local resection under sentinel navigation is also

feasible but still regarded as investigational treatments [3]. The lack of tactile feedback during laparoscopy in early gastric cancer unable resection lines with adequate margins, especially in distal gastrectomy, as it is often difficult to identify, particularly when the tumor is located close to the upper third of the stomach. Thus preoperative localization had been proposed as an essential method to localize. There are nine methods for localization before or during laparoscopic gastric surgery and three of them are most used in clinical practice in the past decades [16]. Endoscopic tattooing is the first method and is very convenient as it can be done within three days prior to laparoscopic surgery [17]. Another method is using endoscopy-assisted gastric resection during laparoscopic surgery reported by Matsui et al. which also showed a favorable result [18]. However, an additional workforce including one endoscopist and multiple technicians with expensive endoscopic equipment is required in the operative room. In addition, the method of intraoperative endoscopic localization of the lesion requires full air insufflation of the stomach which will interfere with the process of the surgery. The third method uses endoscopic metal clips before laparoscopic surgery for localization in early gastric cancer [19, 20]. Kim et al. conducted a retrospective study with 80 patients with preoperative endoscopic localization with metal clips for early gastric cancer and all patients had tumor-free resection margin without any complications [21]. However, in totally laparoscopic gastrectomy, the clips can only be visualized by fluoroscopy and may prolong operative time in surgery.

Endoscopic tattooing with dye before surgery is still commonly used for colonic lesions at present because of safety and convenience [22, 23]. To the best of our knowledge, there-are only two studies that discuss the effectiveness of endoscopic tattooing combined with clipping in early gastric cancer. Yamazaki et al. used India ink injection along with metal clips at tumor margins preoperatively and their result revealed that all patients had R0 resection but 11.1% had widespread stains during the surgery [24]. Another prospective study conducted by Tokuhara et al. also used the same method and there were no complications after surgery with all margin free resection [17]. They used the metal clips for two aims, to guide the application of the India ink injection and for portable radiographing if the marked site is unclear or too wide spread during the operation. However, SPOT is the only FDA proved dye used for localization [25]. We previously conducted a retrospective study to present endoscopic tattooing with SPOT as a reliable method for gastric subepithelial tumor localization before laparoscopic resection[26]. Therefore, we would like to evaluate if this method could be feasible in early gastric cancer localization preoperatively.

2. Materials and Methods

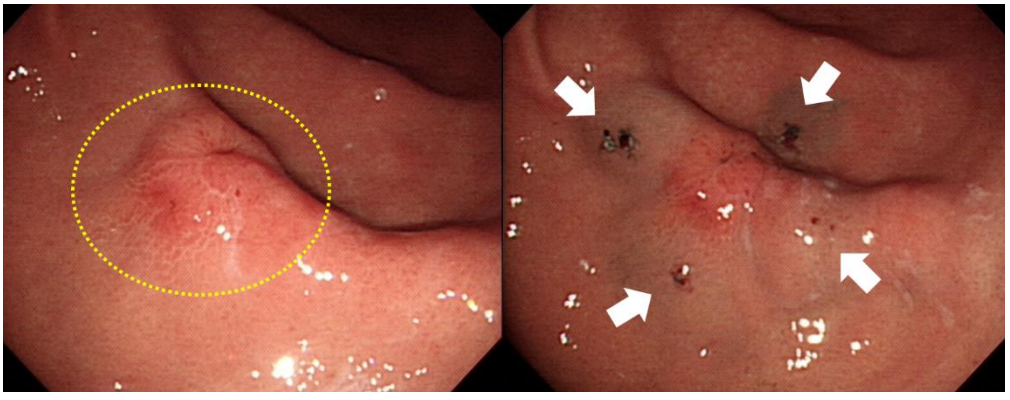
2.1. Patient

This retrospective cohort study enrolled patients with early gastric cancer and tattooing done followed by laparoscopic gastrectomy from January 2017 to June 2021 at Chang Gung Memorial hospital in Taiwan. We retrieved data from our prospectively registered database in the therapeutic endoscopic center. During this period, 81 patients had endoscopic tattooing for early gastric cancer and we excluded 3 patients that had tattooing during the surgery. A total of 78 patients enrolled in our study for analysis. Among them, 15 patients had endoscopic tattooing with metal clips and the others had tattooing only. These patients were all diagnosed as gastric adenocarcinoma by endoscopy with histological confirmation. Computed Tomography (CT) scan

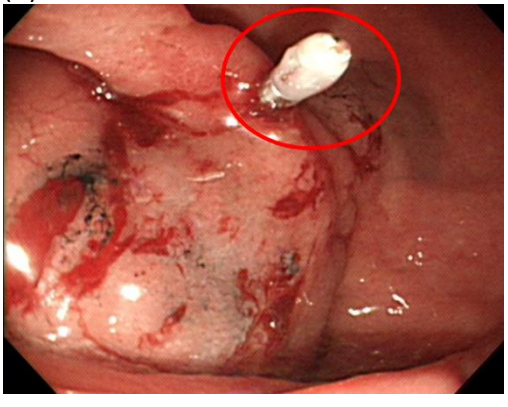
revealed negative or only locoregional disease without distant metastasis. As the patients do not qualify for the criteria of ESD/EMR according to image and histology, these patients were suggested to have laparoscopic surgery and referred to our therapeutic endoscopic center for preoperative tattooing based on surgeons' evaluations before the surgery. The patients' data included characteristics (age, gender), preoperative data (tumor size under endoscopy, location under endoscopy, tattooing time to surgery, duration of endoscopy, Paris Classification under endoscopy), type of surgery (subtotal gastrectomy, total gastrectomy or pylorus preserving segmentectomy) and whether adjuvant chemotherapy was used. Pathological features, including pathological diagnosis, distance from tumor margin, as well as the proportion of adequate distance from the tumor margin, which the distance needs to be more than 2 cm in pT1 and more than 3 cm in pT2~T4 [3], were collected. The distance from the tumor margin is pathologically defined as the shortest distance between the resection margin and nearest edge of the malignant lesion. Perioperative course and outcome (operative time, hospital days, complication and estimated blood loss) were also recruited. To recognize if metal clips were needed for localization, we then categorized these patients into two groups including with or without metal clip usage and analyzed the relevance to the safety margin as well as surgical outcome. Additionally, we were interested in investigating whether preoperative endoscopic tattooing could facilitate the procedure even in different types of surgery, thus we classified patients into two groups by surgery with subtotal gastrectomy and pylorus preserving segmental gastrectomy. However, only one patient had total gastrectomy, therefore the patient was excluded due to the small sample for analysis.

2.2. Localization method

Endoscopic tattooing was done within two days prior surgery as we previously published [26]. In brief, the patients laid in the left lateral position under mild sedation with fentanyl and midazolam. We inspected the location and margin of the gastric cancers under white light (from Olympus company, CV-260) (Figure 1A). There are two methods for endoscopic localization in this study, first, we only performed tattooing with a carbon particle containing solution, SPOT (GI Supply, Camp Hill, PA.) without dilution using the 23 Gauge injection needle (Olympus, product number: NM-400L-0423, Tokyo, Japan). We punctured perpendicularly at four quadrants near the tumors margin deep into the muscle layer with 0.1 mL SPOT injected in each quadrant after insufflation of the stomach with carbon dioxide (Figure 1B) and the procedure was shown as vedio. Second, we used metal clips to mark the lesions followed by tattooing with SPOT 0.1 mL injection near every clip and the number of clips applied would be adjusted based on the different type of surgery (Figure 1C).



(A) (B)



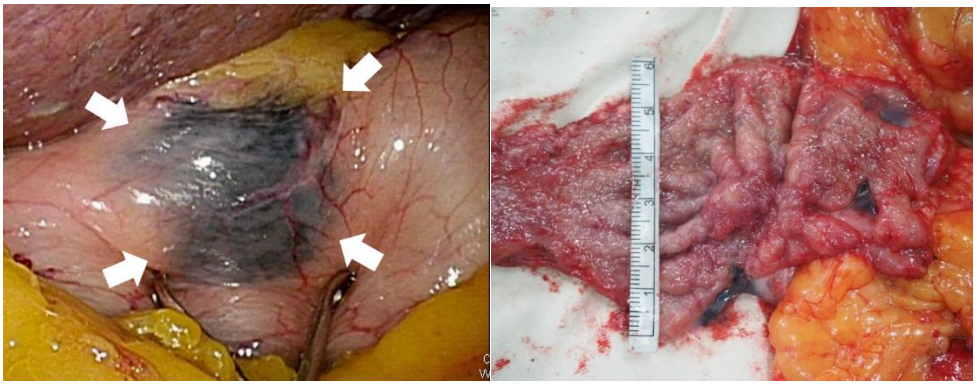
(C)

Figure 1: The gastric cancer and its margin cound be inspected (yellow dashed line) under white light by endoscopy (A). The first method uses endosocpic tattooing method with SPOT 0.1 mL injected at four quadrants (white arrows) 1 cm from margin of the gastric cancer (B). The second method uses both metal clip (red circle) to mark 1 cm from the margin of the lesion followed by tattooing(C).

2.3. Surgery

The operative method was decided by the surgeon according to tumor location and the depth of tumor invasion. Patients underwent totally laparoscopic radical subtotal, total, or pylorus-preserving central gastrectomy followed by gastrojejunostomy, esophagojejunostomy or gastrogastrostomy. A four-port technique was adopted. The video port was created through a 2.0-cm peri-umbilical incision and a commercially available access port was inserted (EZ Access; Hakko, Nagano, Japan). Then a pneumoperitoneum was established using carbon dioxide insufflation at a pressure of approximately 10–12 mmHg. The working and assistant ports were created over the left para-umbilical area and the upper quadrant of the left or right abdomen, respectively under laparoscopy. After identifying the targeted lesion (tattooing made by the endoscopist with blue dye over the subserosa) (Figure 2A), division of the greater/lesser omentum and vessels as well as lymphadenectomy (D1, D1+ or D2) were performed using an energy device (Ligasure^{TM} or Harmonic^{TM}). Then the stomach, including the lesion, was transected by endoscopic linear staplers with at least 2cm margins from tattooing marks to ensure

safe margins followed by intracorporeal alimentary reconstruction (Figure 2B).



(A) (B)

Figure 2: The blue dye at subserosa was visualized during the laparoscopic surgery (white arrows) (A). The stomach including the lesion was transected by endoscopic linear staplers with at least 2 cm margins from tattooing marks (B).

2.4. Statistical analysis

The univariate analysis was done using Chi-square test for categorical variables and the independent sample *t* test for continuous variables. A *p* value less than 0.05 was considered significant. Variables are expressed as mean plus range. All statistical analyses were performed using the Statistical Product and Service Solutions, SPSS, version 26 (IBM, Armonk, NY, USA).

2.5. Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Chang Gung Medical Foundation Institutional Review Board (protocol code 202101143B0 and approval on 2021/7/5). Chang Gung Medical Foundation Institutional Review Board is the IRB which reviewed and approved all the human studies conducting in Chang Gung Memorial Hospital and Chang Gung university and we confirmed that patients' consent obtained is proved via IRB.

3. Results

Total 78 patients were enrolled, with mean age of 59.5 years old and females predominant (Female: 61.5%). Most gastric cancers (N=72, 92%) located at mid body to antrum except 6 patients with tumors located at high body. EUS was only performed in 15 patients to estimate the possibility for ESD but none of them fit the criteria. CT was done for all patients preoperatively but most tumors (N=63, 80.8%) could not be inspected due to small size. There was no evidence of distant metastasis under CT. Endoscopic tattooing was done within two days before surgery. The average time from tattooing to surgery is 8.3 hours, ranging from 1 to 48 hours. The average duration of the endoscopy for tattooing is 11.7 minutes, ranging from 5 to 27 minutes. 30 patients (38.5%) had overlying superficial ulcers and most gastric cancers (N=45, 57.7%) were classified as type 0-IIc based on Paris Classification. 12 patients underwent pylorus preserving segmentectomy, 63 underwent subtotal gastrectomy and 3 patients had total gastrectomy. The choice of which surgery was

at the surgeon's discretion. All patients had negative resection margins according to pathological reports and no recurrence was found during follow up (18.5±13.2 months). Adjuvant chemotherapy was applied in 6 patients because of locoregional lymph node metastasis found in the specimens with stages more than pT2 as Japanese gastric cancer treatment guideline 2014 suggested [3]. All patients' characteristics are shown as (Table 1). We categorized patients into tattooing with clip (N=15) and without clip (N=63). The duration of endoscopy, tumor size by endoscopy, time from tattooing to surgery, distance from margin to cancer edge, and proportion of adequate margin achieved all had no clinical significance between the two groups (Table 1 and Table 2). Perioperative outcome including the duration of surgery, blood loss, hospitalized days, time to intake, and complications all had no clinical significance between the two groups (Table 3). Among the patients with complications, severity of fever and wound infection was mild and improved after antibiotic use in 1 week. But the patient with internal bleeding had a second laparoscopic surgery for hemostasis in 48 hours and this episode prolonged hospitalization and delayed time to intake although he discharged eventually without any discomfort during OPD follow up. The effect of tattooing in different types of surgery between pylorus preserving sementectomy (N=12) and subtotal gastrectomy (N=63) is revealed as Table 4. The duration of surgery is significantly shorter with pylorus preserving sementectomy than subtotal gastrectomy (p=0.04). There is no clinical significance in perioperative outcome, distance from margin, and proportion of adequate margin achieved between the two groups. Risk factors of insufficient safety margins from the tumor, including tumor size under endoscopy, superficial ulcer, Paris Classification, tumor size in specimen, pT stage and Lauren's classification were also analyzed (Table 5). The only variable that had clinical significance is tumor size in specimen and it seems that tumors more than 2 cm may increase possibility of insufficient safety margins from tumor.

	Total	**With clip**	**Without clip**	**p value**
	(N=78)	(N=15)	(N=63)	
Age	59.5±13.4	56.4±14.6	60.2±13.4	0.611
Gender				0.345
Male	30(38.5%)	3(20%)	27(42.9%)	
Female	48(61.5%)	12(80%)	36(57.1%)	
Tumor location by endoscopy				0.58
High-body	6(7.7%)	0(0%)	6(9.5%)	
Mid-body	24(30.8%)	6(40%)	18(28.6%)	
Low-body	30(38.5%)	3(20%)	27(42.9%)	
Antrum	18(23.1%)	6(40%)	12(19.0%)	
Time to surgery (hour)	8.3±11.7	6.9±10.2	8.7±12.3	0.76
Endoscopic finding				
Duration of procedure (minutes)	11.7±5.6	12.6±4.2	11.5±6.0	0.71
Tumor size	2.0±1.3	1.8±0.8	2.1±1.4	0.369
Superficial ulcer				0.345
Yes	30(38.5%)	3(20%)	27(42.9%)	
No	48(61.5%)	12(80%)	36(57.1%)	

Paris type				0.687
0-Is	6(7.7%)	0(0%)	6(9.5%)	
0-Ip	0(0.0%)	0(0%)	0(0%)	
0-IIa	0(0.0%)	0(0%)	0(0%)	
0-IIb	24(30.8%)	3(20%)	21(33.3%)	
0-IIc	45(57.7%)	12(80%)	33(52.4%)	
0-III	3(3.8%)	0(0%)	3(4.8%)	
Type of surgery				0.85
Subtotal gastrectomy	63(80.8%)	12(80%)	51(81.0%)	
Total gastrectomy	3(3.8%)	0(0%)	3(4.8%)	
Pylorus preserving segmental gastrectomy	12(15.4%)	3(20%)	9(14.3%)	
Adjuvant chemotherapy				0.473
Yes	6(7.7%)	0(0%)	6(9.5%)	
No	72(92.3%)	15(100%)	57(90.5%)	

Table 1: Patient characteristics

	With clip	**Without clip**	**p value**
	(N=15)	(N=63)	
T stage			0.761
T1a	12(80%)	36(57.1%)	
T1b	3(20%)	18(28.6%)	
T2	0(0%)	6(9.5%)	
T3	0(0%)	3(4.8%)	
Lauren class			0.619
Intestinal type	6(40%)	18(28.6%)	
Diffuse type	9(60%)	45(71.4%)	
Distance from margin	3.0±1.5	3.2±2.0	0.798
Sufficient margin[1]			0.856
Yes	12(80%)	48(76.2%)	
No	3(20%)	15(23.8%)	
[1] T1: distance from margin ≥ 2 cm, T2~T4: distance from margin ≥ 3 cm			

Table 2: Pathologic features.

	With clip	**Without clip**	**p value**
	(N=15)	(N=63)	
Duration of surgery (minute)	286±46.7	322.4±101.6	0.447
Blood loss (mL)	60±38.1	56.2±105.8	0.938
Hospital days	11.6±1.8	16.0±24.0	0.687
Time to intake (day)	6.6±1.9	9.6±13.1	0.623
complication			0.915
No	12(80%)	45(71.4%)	
Fever	3(20%)	12(19%)	
Wound infection	0(0%)	3(4.8%)	
Internal bleeding	0(0%)	3(4.8%)	
Recurrence			1
Yes	0(0%)	0(0%)	
No	15(100%)	63(100%)	

Table 3: Surgical outcome.

	Pylorus preserving segmentectomy	**Subtotal gastrectomy**	**p value**
	(N=12)	(N=63)	
Duration of surgery (minute)	225±30.0	326.2±90.7	0.040*
Blood loss (mL)	37.5±41.4	61.0±105.5	0.67
Hospital days	13.3±5.0	15.5±24.0	0.858
Time to intake (day)	9.3±4.3	8.9±13.1	0.965
complication			0.236
No	6(50%)	51(81%)	
Fever	6(50%)	6(9.5%)	
Wound infection	0(0%)	3(4.8%)	
Internal bleeding	0(0%)	3(4.8%)	
Recurrence			1
Yes	0(0%)	0(0%)	
No	12(100%)	63(100%)	
Specimen			
Distance from margin	3.1±2.9	3.1±1.6	0.986
Stomach diameter	11.2±3.8	12.7±4.4	0.52
Tumor diameter	1.3±0.5	2.1±1.7	0.37
Tumor/stomach ratio	0.12±0.06	0.19±0.18	0.451
Sufficient margin[1]			0.184
Yes	6(50%)	51(81%)	
No	6(50%)	12(19%)	
[1] T1: distance from margin ≥2 cm, T2~T4: distance from margin ≥3 cm			

Table 4: Different type of surgery.

	Sufficient margin	Insufficient margin	p value
	(N=60)	(N=18)	
Endoscopy finding			
Tumor size under endoscopy	1.8±1.1	2.9±1.7	0.06
Tumor size>2 cm	24(40%)	12(66.7%)	0.25
Tumor size<2 cm	36(60%)	6(33.3%)	
Superficial ulcer			0.211
Yes	27(45%)	3(16.7%)	
No	33(55%)	15(83.3%)	
Paris type			0.061
0-Is	3(5%)	3(16.7%)	
0-Ip	0(0%)	0(0%)	
0-IIa	0(0%)	0(0%)	
0-IIb	15(25%)	9(50%)	
0-IIc	42(70%)	3(16.7%)	
0-III	0(0%)	3(16.7%)	
Pathologic features			
Tumor size	1.4±0.7	3.4±2.7	0.005*
Tumor size>2 cm	9(15%)	12(66.7%)	0.012*
Tumor size<2 cm	51(85%)	6(33.3%)	
T stage			0.693
T1a	36(60%)	12(66.7%)	
T1b	18(30%)	3(16.7%)	
T2	3(5%)	3(16.7%)	
T3	3(5%)	0(0%)	
Lauren class			0.877
Intestinal type	18(30%)	6(33.3%)	
Diffuse type	42(70%)	12(66.7%)	
*p value<0.05 considered as clinical significance			

Table 5: Factors influence sufficient negative margin.

4. Discussion

Based on our results, all the variables had no clinical significance between tattooing with or without metal clips. All patients had margin free resection. 76% patients (48/63) had adequate safety margins even without the use of clips. This validates that our endoscopic tattooing method is efficient enough for tumor localization preoperatively even without clips used. We also speculate that our endoscopic tattooing method may be able to facilitate laparoscopic surgery with pylorus preserving segmentectomy as there is no clinical significance in perioperative outcome, distance from margin, and proportion of adequate margin achieved between the two groups. However, interpretation was careful due to limited number of patients and the lower proportion of adequate margin

achieved in pylorus preserving segmentectomy compared to subtotal gastrectomy (50% vs. 81%) though no clinical significance was found. Furthermore, 15 patients had metal clips but none of them used intraoperative fluoroscopy due to negative resection margins by frozen section or by inspection from surgeon. This showed that the use of metal clip is not required for localization in early gastric cancer and does not depend on the type of laparoscopic surgery performed. It is also cost-effective for patients because of fees from metal clips during endoscopy. Safety is the most important issue in this invasive procedure. 21 patients had complications that include fever, wound infection and internal bleeding after the surgery though none are related to endoscopic tattooing. Previous studies had reported the most common and disturbing adverse effect after the tattooing being peritoneal staining, when unintended transmural injection occurs which may induce peritonitis and could obscure the surgical dissection planes, making surgery more dangerous and challenging [27, 28]. No obvious dye spillage was found during the operations in our study. However, India ink, mainly for colonic lesions, was used in previous studies, which is different to our method in the stomach [29, 30]. We used SPOT as the dye for tattooing, which is similar to India ink but has less inflammatory effects and is the only U.S. Food and Drug Administration (FDA) certified product for tattooing [25]. Another possible reason we had no adverse effects is that the gastric wall is thicker than the colon's thus reducing the chance of transmural injection. We also avoided dye dilution by saline and pre-injection with saline, which is the submucosal injection method used in previous studies [17]. Due to geographic variation in gastric cancer's incidence, different approaches are noted in different countries. More than 70% of cases occur in developing countries including Central and Eastern Europe, South America and Eastern Asia, mainly in China [31]. Gastric cancer in western countries are more advanced with locations more proximal and with a higher proportion of diffuse type histologically. After debating for decades about treatment and surveillance protocol between East and West countries, there is recent consensus in treating gastric cancers based on two systems of guidelines which include the Japanese Gastric Cancer Association (JGCA) and the Union for International Cancer Control (UICC/TNM) [3, 32-34]. Increased detection in earlier stages of the disease, which results in better prognosis, is attributable to extensive screening with esophagogastrodudenoscopy (EGD) done in Japan due to the high incidence of gastric cancer. Therefore, laparoscopic surgery for early gastric cancers developed rapidly in recent years in Japan and Korea but much slower in Western countries [35, 36]. However, preoperative localization is usually needed due to the lack of tactile feedback during surgery. Recently, Yamazaki et al reported a study using metal clips along with tattooing with India ink for early gastric cancer localization. They applied two metal clips over the oral site of the lesions, injected 2 mL of normal saline into the submucosal layer, 0.1 mL of India ink, and 1 mL of saline injected near the clips. Additionally, some cases had biopsy performed to ensure negative margins in their study. Although all patients had R0 resection, 11.1% patients had widespread-stains [24]. Different from their practice, we only injected 0.1 mL of SPOT directly without dilution at four quadrants of the target lesion and no cases had peritoneal staining intraoperatively. In addition, we did not do any negative biopsy during endoscopic tattooing and all patients had negative resection margins. Another study conducted by Kim et al used two or three metal clips proximal to the tumor for preoperative localization [21]. All patients in their study had

margin free resection with a mean proximal margin length of 3.42 ± 2.02 cm, which is similar to our patients that underwent endoscopic tattooing without clips (mean distance from margin: 3.2±2.0 cm). However, C-arm fluoroscopy should be used to localize the metal clip in the operation room and the extra radiation would be exposed to the surgeon.

According to our study, 80% of patients had sufficient safety margin resections from the tumor whether clips were used. In other words, around 20% patients may have had a risk of recurrence. We also found that 50% of patients had insufficient safety margins in the group of pylorus preserving gastrectomy. Thus we would like to figure out whether there are any risk factors that could predict insufficient safety margins during endoscopic tattooing. Previous study mentioned that surgeons can only decide the resection margin depending on the marking the endoscopist located preoperatively, especially in early gastric cancer [21]. It implied that the location we marked at from the tumor is important although the surgeon may resect at least 2cm distant from the tattooing for safety margin. However, this could be affected by submucosal spreading or the histological feature of poorly differentiated adenocarcinoma. Kumazu et al. enrolled 2757 patients that underwent gastrectomy for gastric cancer and evaluated risk factors of microscopic positive resection margins [37]. They found that remnant gastric cancer (odds ratio [OR] 4.7), esophageal invasion (OR 6.3), tumor size ≥80 mm (OR 3.9), and a histopathological diagnosis of undifferentiated type (OR 3.6), macroscopic type 4 (OR 3.7), or pT4 disease (OR 4.6) had correlation to R1 resection. We also analyzed these possible risk factors and only tumor size in specimen had clinical significance, particularly tumor size above 2 cm. In addition, previous studies also showed a tumor size>2 cm implied a more advanced stage [5]. Regarding the tumor size under endoscopy, we can only observe the trend that larger size under endoscopy is more likely to have insufficient safety margin. One third of tumors with sizes more than 2 cm had insufficient resection margin, compared to 14% in tumor sizes less than 2 cm. However, no clinical significance was found under statistical analysis. Therefore, we suggest that the location of tattooing from the tumor edge or the transection line from the center of the tattoo could be more distant if the size of tumor is more than 2 cm under endoscopy or CT image.

5. Conclusion

Our novel method with SPOT at four-quadrants in early gastric cancer before laparoscopic subtotal gastrectomy is a feasible and safe method even without metal clips used. It is feasible in pylorus preserving segmentectomy as no statistical difference was found in surgical outcomes and pathological features compared to subtotal gastrectomy with limited patients in our study. 18(23%) patients had insufficient safety margins although no tumor recurrence was found when followed up (for how long in this 6 patients group). In addition, our analysis showed that tumor size, particularly above 2 cm, is a risk factor for insufficient safety margins using this method of endoscopic tattooing localization. Thus the markings could be located more distant from the tumor's edge or the surgeon could modify the resection margin in high risk patients. There are some limitations with our study. First, this is a retrospective and single-centered study. Second, the limited number of patients may cause outcomes to not be as convincible. Third, EUS features could not be evaluated as only part of patients had done EUS preoperatively.

Declaration

Ethical Approval and Consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Chang Gung Medical Foundation Institutional Review Board (protocol code 202101143B0 and approval on 2021/7/5). Consent was obtained from all subjects involved in the study.

Consent for publication

not required

Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Competing interests

None of the authors of this study has any financial interest or conflict with industries or parties

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Authors' contributions

Conceptualization, S.-F.W. and K.-F.S.; methodology, K.-F.S. and C.-H.L.; software, J.-T.H.; validation, J.-T.H., C.-H.W. and M.-H.L.; formal analysis, S.-F.W.; investigation, C.-J.L.; resources, K.-F.S.; data curation, S.-F.W.; writing—original draft preparation, S.-F.W.; writing—review and editing, K.-F.S.; visualization, C.-J.L.; supervision, K.-F.S. and T.-S.Y.; project administration, S.-F.W.; funding acquisition, S.-F.W. All authors have read and agreed to the published version of the manuscript.

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