Surg Endosc (2016) 30:3357–3361
DOI 10.1007/s00464-015-4612-0

A comparison of the efficacy and safety of endoscopic full-thickness resection and laparoscopic-assisted surgery for small gastrointestinal stromal tumors

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Received: 17 July 2015 / Accepted: 30 September 2015 / Published online: 23 October 2015

Abstract
Background and aim Laparoscopic-assisted surgery (LAC) is an alternative to open surgery for gastrointestinal stromal tumors (GISTs). Endoscopic full-thickness resection (EFTR), a recently developed procedure, is increasingly used to resect GISTs originated from the muscularis propria. In this retrospective study, we aimed to compare EFTR with LAC as minimally invasive treatments for GISTs, especially those with a diameter <2 cm, originating from the muscularis propria. Moreover, we evaluated the clinical efficacy, safety, and feasibility of EFTR for GISTs.
Methods The study included 68 patients with GISTs originating from the muscularis propria (35 patients who underwent EFTR, and 33 who underwent LAC) who were treated at the Affiliated Hospital of Guangdong Medical University (Zhanjiang, China) between January 2011 and December 2013. The therapeutic outcomes of EFTR and LAC were reviewed retrospectively.
Results In the EFTR group, the mean tumor size was 13 ± 5 mm, the mean procedure time was 91 ± 63 min, and the complete resection rate was 100 %. There were 35 "artificial" perforations and four cases of intraoperative bleeding; all complications were successfully managed endoscopically without emergency surgery. In the LAC group, the mean tumor size was 16 ± 4 mm, the mean operation time was 155 ± 37 min, and complications included three wound infections and one anastomotic leakage.
Conclusions EFTR was associated with a lower complication rate than LAC, with favorable en bloc and sufficient tumor tissue for histological diagnosis. EFTR seems to be an efficacious, relatively safe, and minimally invasive treatment for GISTs and could replace LAC surgical resection in cases where the tumor is smaller than 2 cm in diameter.

Keywords Gastrointestinal stromal tumors · Endoscopic full-thickness resection · Laparoscopic-assisted surgery

Gastrointestinal stromal tumors (GISTs) are the most common gastrointestinal tumors. They can emerge in any part of the gastrointestinal tract; however, they generally occur in the stomach and small intestine [1, 2] and originate from the muscularis propria. GISTs are thought to have malignant potential [3], but rarely metastasize to the lymph glands [4, 5]. Radiation therapy and chemical therapy are invalid treatment options for GISTs, and therefore, complete resection is the primary treatment for non-metastatic GISTs. In the past, open or laparoscopic wedge resection was usually selected to treat GISTs; however, surgical resection could result in different degrees of injury [6, 7].

More recently, with the development of endoscopy techniques and instruments, endoscopic submucosal dissection (ESD) evolved as a new technique to achieve en bloc resection for mucosal or even submucosal lesions, such as early malignancy, premalignancy, and submucosal tumor (SMT) [8, 9]. With increasing experience of ESD, studies have shown that endoscopic full-thickness resection (EFTR), a technique developed from ESD, could be used

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as an effective treatment for GISTs that originated from the muscularis propria or have close relation to serosa [10]. However, the feasibility and safety of laparoscopic-assisted surgery (LAC) and EFTR in the management of these neoplasms have not been compared, and therefore, it remains unknown which therapeutic method is more appropriate for gastric GISTs.

In this retrospective study, we compared the efficacy and safety of these two minimally invasive methods for treating gastric GISTs.

Patients and methods

Patients

The study included 68 patients who underwent curative resection for gastric GISTs by either EFTR or LAC between January 2011 and December 2013 at the Affiliated Hospital of Guangdong medical university (Zhanjiang, China). Among them, 35 patients underwent EFTR and 33 patients underwent LAC treatment. The general data and clinical characteristics of the patients are shown in Table 1. All patients were selected according to the following criteria: (1) each patient had only one lesion, in the stomach, as evidenced by gastroscopy (GIF-260; Olympus); (2) the submucosal tumor originated from the muscularis propria as determined by endoscopic ultrasound (EUS) (UM-2R, 12 MHz, UM-3R, 20 MHz; Olympus Optical Co, Ltd, Tokyo, Japan); (3) the tumor was no more than 5 cm in size; (4) there was no metastasis as determined by computerized tomography (CT); and (5) the lesion was not located in the esophagus or duodenum. Blood pressure, prothrombin time, and electrocardiograms were examined. Signed informed consent was obtained from all patients after a detailed conversation about each procedure and the possible risks. The surgical approach (LAC or EFTR) was selected according to patient preference.

Table 1 Demographics and clinical data of the patients

	LAC	EFTR
Patients	33	35
Age, years, mean ± SD	56 ± 14	55 ± 14
Sex		
Male	20	25
Female	13	10
Clinical symptoms		
Epigastric pain	10	16
Heartburn	8	3
Abdominal bloating	3	8
Asymptomatic	7	8
Tumor location		
Fundus	12	10
Body		
High body	3	5
Mid-body	5	6
Low body	2	4
Antrum	11	10

Technique and procedure of EFTR

All patients were anesthetized by tracheal intubation with propofol during the procedure. EFTR was performed with a standard single-accessory-channel endoscope (GIF-H260; Olympus) or a dual-channel endoscope (GIF-2T240; Olympus) fitted with a transparent hood (D-201-1074; Olympus) to its head. Other equipment used for the EFTR procedure included injection needles (NET 2522-G4; Endo-Flex GmbH, Voerde, Germany), snares (NOE 342,217-G; Endo-Flex GmbH, Germany), a hook knife (KD-620LR; Olympus), an insulated-tip (IT) knife (KD-610L; Olympus), hemostatic forceps (FD-410LR; Olympus), hot biopsy forceps (NE6122-G; Endo-Flex GmbH), clips (HX-600-135L, HX-610-90; Olympus), a high-frequency generator (ICC-200; ERBE, Tübingen, Germany), and an argon plasma coagulation unit (APC300; ERBE). In addition, a CO_2 regulator (Gas Regulator, Crown, Model FR-IIS-P; Yutaka Engineering, Tokyo, Japan) was used during the endoscopic procedure [11]. All EFTR procedures were performed using the following steps. (1) "Marking," several marking dots were placed by an argon plasma coagulation unit around the edge of the gastric stromal tumor. (2) "Submucosal injection," a salt solution (containing 100 ml saline, 5 ml indicarminum, and 1 ml epinephrine) was injected into the submucosa at the lateral edge of the marks. (3) "Mucosal incision," a needle knife or IT knife was used to incise the mucosa and submucosa around the marked points, and then a snare was used to dissect the overlying mucosa of the tumor exposing the lesion clearly. (4) "Full-thickness resection," where the tumor was so close to adhere with the serous membrane, the serous membrane around the tumor was completely resected with the snare. Sometimes, a dual-channel endoscope was used with forceps grasping the tumor to prevent the tumor being displaced into the peritoneal cavity when the tumor was removed with the snare. If the diameter of the tumor was less than 1.0 cm, the tumor was pressure suctioned into the transparent cap and then completely resected with the snare. During the resection procedure, the gastric fluid must be sucked away to prevent gastric acid from flowing into the abdominal cavity which would cause acute peritonitis, and CO_2 insufflation was used to prevent patients from suffering abdominal discomfort [11]. (5) "Clipping the artificial perforation," titanium clips were

used for closure of perforations without stitching; larger wounds could be managed using a nylon band together with clips [12].

Technique of LAC

After examination by gastrointestinal endoscopy, EUS, and CT, which were helpful in displaying intraluminal lesions, extraluminal involvement, and metastasis, the patients were treated with LAC. Patients underwent with gastric resection (wedge resection) by endoscopic linear cutting anastomat (Endo—GLA) directly under tracheal intubation general anesthesia. The trocar incisions position and quantity were determined according to the surgeon's appropriate judgment and the location of the stomach neoplasm. The cut edge from the tumor was larger than 2 cm. During the procedure, the most important point was protecting the surrounding tissue and the integrity of the tumor in order to avoid causing any abdominal cavity or surrounding tissue metastasis.

Specimen handling

The resected specimens were fixed by 10 % formalin solution for histopathological evaluation. Immunohistostaining analysis of CD117, CD34, Dog-1, S-100, and smooth muscle actin (SMA) was performed in all cases.

Follow-up methods

All patients were scheduled for regular follow-up (1 week and 1, 6, and 12 months posttreatment and yearly thereafter) by gastroscopy to observe the healing of the wound and eliminate cases of residual tumor or recurrence. If local recurrence was suspected, EUS was performed.

Statistical analysis

Experimental results are expressed as mean values ± standard error. Statistical analyses were performed with Student's *t* test for two groups using SPSS software, v15.0 (International Business Machines Corporation). $P < 0.05$ was considered significant.

Results

Therapeutic outcomes and complications

Of the 68 patients included in this study, 35 had GISTs that were treated by EFTR and 33 had GISTs that were treated by LAC. The mean procedure time (mean ± standard deviation [SD]) for the EFTR procedure was 91 ± 63 min, and that for the LAC procedure was 155 ± 37 min; the difference was significant ($P < 0.05$). The median time for which postoperative eating time was restricted after each procedure was 2 days in the EFTR group (range 1–4 days) and 3 days in the LAC group (range 2–5 days). The median overall hospital stay in the two groups was 7 days (range 5–7 days) and 8 days (range 7–10 days), respectively (Table 2); the difference between the two groups was significant ($P < 0.05$). Intraoperative bleeding was significantly less in the EFTR group than in the LAC group ($P < 0.05$) (Table 2). The mean tumor diameter (mean ± SD) in the EFTR group was 13 ± 5 mm, which was smaller than that in the LAC group (16 ± 4 mm) ($P > 0.05$). In the EFTR group, there were 35 "artificial" perforations and four cases of intraoperative bleeding. All complications were successfully managed by endoscopy without emergency surgery, and the complete resection rate of EFTR was 100 %. In the LAC group, all tumors were resected by LAC, but emergent endoscopic identification of the GIST was required in 12 cases of LAC. Complications included three wound infections, all managed with antibiotics, and one case of anastomotic leakage which was managed by avoiding oral intake (Table 2).

Pathological characteristics and risk classification

Retrospective immunohistochemistry staining revealed that CD117 and CD34 were positive in every patient and that S-100 was negative in all cases. As for the level of risk, 68 patients were at very low risk and one patient was at low risk, without intermediate risk or malignant potential (Table 3).

Follow-up outcomes

All patients were followed up for 1–72 months by gastroscopy or EUS. No local recurrence was observed.

Discussion

Generally, GISTs originate from the muscularis propria and have non-specific clinical symptoms in the early stage. Usually, they are found incidentally during gastroscopy or other upper abdominal inspections. The tumor's characteristics of smooth apophysis lesions are only visible under gastroscopy, and it is difficult to determine the origin and nature of the tumor by conventional biopsy. Although the origin, size, and nature of the tumor can be identified by EUS, it is difficult to distinguish between GISTs and leiomyomas or a benign lesion and a malignant lesion using EUS alone. According to recent guidelines of the

Table 2 Results of endoscopic full-thickness resection (EFR) or laparoscopic-assisted surgery (LAC) for gastrointestinal stromal tumors ($GIST_s$) in 68 patients

	LAC	EFTR	t	*P* value
Procedure time, min, mean ± SD	155 ± 37	91 ± 63	5.124	<0.05
Intraoperative bleeding (ml)	25 ± 11	0.60 ± 1.70	12.260	<0.05
Postoperative eating time (day)	3.12 ± 1.11	2.54 ± 0.92	2.332	<0.05
Postoperative hospital stay (day)	7.79 ± 1.29	6.74 ± 0.85	3.910	<0.05
Anastomosis leakage (*n*)	1			NA
Perforation (*n*)		35		NA
Wound infection (*n*)	3			NA
Tumor size, mm, mean ± SD	16 ± 4	13 ± 5		NS

NS not significant, *NA* not available

Table 3 Pathological characteristics and risk classification

Patients	LAC (*n*)	EFTR (*n*)
Mitotic index <5/50 HPF	33	35
Risk classification		
Very low risk	32	35
Low risk	1	0

HPF high-power fields

National Comprehensive Cancer Network, all GISTs larger than 2 cm should be resected, and the treatment options for incidental tumors smaller than 2 cm are resection or surveillance [13]. However, the interval of follow-up for GISTs has no clear regulations which means that for patients with gastric stromal tumors smaller than 2 cm, the indefinite follow-up examinations may cause an enormous psychological burden and lifetime suffering; therefore, most patients would choose to undergo lesion resection as soon as possible if there was a minimally invasive treatment option. Generally, all GISTs are considered to be potentially malignant irrelevant of their size [14, 15]. For this reason, at present, it is important to look for a relatively safe and effective method, especially for stromal tumors smaller than 2 cm.

In the past, given the low morbidity, short hospital stays, and low recurrence rates, studies have suggested that laparoscopic wedge resection is a preferable option for patients with the gastric SMTs originating from the muscularis propria [16, 17]. However, with the development of minimally invasive ESD technology and the rapid advances in endoscopic instruments, EFTR without laparoscopic assistance has evolved as a new approach for treating GISTs [10]. What type of treatment method is more suitable for patients with stromal tumors smaller than 2 cm? Currently, few data are available for the comparison. Our study was a retrospective study that compares EFTR with LAC in order to find a safe and effective treatment.

In our study, in the EFTR group, full-thickness resection of the tumor including the serosa was successfully performed in all 35 patients, without laparoscopic assistance. A total of 33 patients were involved in the LAC group, and 21 of them were successfully treated by LAC; however, 12 cases required emergency intraoperative endoscopy because laparoscopy was unable to identify the precise lesion area. If the tumors are located behind the stomach or near the esophageal gastric junction, laparoscopic surgery is difficult to perform. For intraluminal growing lesions smaller than 2 cm, laparoscopy is unable to locate the tumors from outside the gastric serosa. Difficulty in determining the lesion is sometimes a technical flaw of laparoscopic surgery, which provides further evidence that EFTR procedure may be more convenient than LAC.

In this study, the EFTR treatment time was significantly shorter than that in the LAC group ($P < 0.001$). In terms of intraoperative bleed loss, compared with LAC procedures, the loss in EFTR procedures was typically lower (mean = 2 ml). Moreover, the postoperative hospital stay and the time of food intake in the EFTR groups were shorter than those of the LAC group. Although, there were 35 "artificial" perforations in the EFTR group (100 % of cases), they were successfully treated endoscopically by clipping or nylon loop suturing, and no wound leakage was found on roentgenography after the procedure. Furthermore, the complication rate for EFTR was also lower than that of LAC. Finally, patients who underwent laparoscopy would be left with an abdominal wound, but this was not the case with EFTR. Data showed that abdominal wound metastasis might be a rare complication of LAC [18]. In conclusion, on comparing the data for the EFTR and LAC groups, our study suggests that EFTR is a safe treatment and provides excellent pathological diagnosis for GISTs smaller than 2 cm.

Although EFTR was developed from ESD, the EFTR procedure differs in some aspects. It is more difficult and has higher technical requirements compared with ESD that involves relying on skillful hands; therefore, in our study, EFTR was performed by an experienced

endoscopist. The key to the EFTR procedure is the successful treatment of complications of the resection procedure to prevent further surgery. Before removal of the lesion, the gastric fluid in the stomach should be sucked away in order to reduce postoperative peritoneal infection, and then all the "artificial" perforations should be successfully sutured by clipping or nylon loop. As for intraoperative bleeding, small vessels in the submucous layer should be directly coagulated with electrosurgical dual-knife or argon plasma coagulation (APC), while larger vessels should be treated by hot hemostatic clip. If necessary, minute vessels on the surface of the wound should be treated by APC after removal of the tumor. In this study, intraoperative bleeding occurred in four patients and successful hemostasis was completed under endoscopy in each case. During the period of hospitalization, there was no postoperative bleeding.

In conclusion, we have described the safety and curative resection rates of EFTR compared to those of the LAC procedure. EFTR represents a feasible, minimally invasive treatment for GISTs smaller than 2 cm. However, the present study has some disadvantages. For example, it was a retrospective study that compared EFTR with LAC in a single medical institution, and the number of cases was few. Furthermore, the follow-up time was short. Therefore, further research into the long-term efficacy of these procedures is necessary.

Acknowledgments The authors are grateful to the help of Department of Gastrointestinal Surgery, the Affiliated Hospital of Guangdong Medical University, Zhanjiang, Guangdong Province, China.

Compliance with ethical standards

Disclosures Hao Wang, Xiao Feng, Shicai Ye, Jie Wang, Jian Liang, Shao Mai, Meifen Lai, Huayang Feng, Guo Wang, and Yu Zhou declare that they have no conflict of interests.

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