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Retrospective Study

16

Comparison of endoscopic and laparoscopic resection of gastric gastrointestinal stromal tumors: A propensity score-matched study

Endoscopic *vs* laparoscopic resection

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Abstract

BACKGROUND

Endoscopic resection (ER) and laparoscopic resection (LR) have been widely used for the treatment of non-metastatic gastric gastrointestinal stromal tumors (gGISTs) (2-5 cm), but there are no selection criteria for their application.

AIM

We Compared the outcomes of ER and LR for 2-5 cm gGISTs, to provide a reference for standardized treatment strategies.

METHODS

Clinical baseline characteristics, histopathological results, and short- and long-term outcomes of patients who treated with ER or LR for gGISTs of 2-5 cm in Taizhou Hospital of Zhejiang Province from January 2014 to August 2022 were retrospectively reviewed. Propensity score matching (PSM) was employed to achieve balance in baseline characteristics.

RESULTS

Among 206 patients (135 in the ER group and 71 in the LR group), the ER group had significantly smaller tumors (3.5cm [3.0-4.0] vs. 4.2cm [3.3-5.0], $P < 0.001$) and different tumor locations ($P = 0.048$). After PSM, 59 pairs of patients were balanced. After matching, the baseline characteristics of the ER and LR groups did not differ significantly from each other. Compared with LR, ER had faster recovery of diet ($P = 0.046$) and fewer postoperative symptoms ($P = 0.040$). LR achieved a higher complete resection rate ($P < 0.001$) and shorter operation time ($P < 0.001$). No significant differences were observed in postoperative hospital stay ($P = 0.478$), hospital costs ($P = 0.469$), complication rates ($P > 0.999$), pathological features (mitosis, $P = 0.262$; NIH risk Classification, $P = 0.145$), recurrence rates ($P = 0.476$), or mortality rates ($P = 0.611$).

CONCLUSION

Both ER and LR are safe and effective treatments for gGISTs. ER has less postoperative pain and faster recovery, while LR has a higher rate of complete resection.

Key Words: Gastrointestinal stromal tumor (GIST); Endoscopic resection; Laparoscopic resection; Propensity score matching; Prognosis; Complete resection

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Core Tip: We aimed to compare the outcomes of endoscopic resection (ER) and laparoscopic resection (LR) for 2-5 cm gastric gastrointestinal stromal tumors, with the ultimate goal of informing the development of standardized treatment strategies. Propensity score matching was used to minimize selection bias. Notably, ER was associated with reduced postoperative pain and accelerated recovery, positioning it as a favorable option in cases where cosmetic outcomes or organ function preservation are paramount. Conversely, LR demonstrated a superior rate of complete resection, making it the preferred approach for larger tumors.

INTRODUCTION

Gastrointestinal stromal tumors (GISTs), representing the foremost mesenchymal neoplasms encountered within the gastrointestinal tract[1], arise from the interstitial cells of Cajal and possess the potential for malignancy[2]. The annual incidence rate of GISTs has been estimated to a range from 10 to 20 cases per million individuals, with the stomach being the most prevalent site of occurrence[3]. The primary mechanisms of metastasis in GISTs encompass transperitoneal dissemination and hematogenous dissemination, with regional lymph node involvement being an uncommon occurrence[4,5]. Thus, the management of primary GISTs often necessitates local

resection as opposed to comprehensive organ resection and lymph node dissection[6]. Both the Chinese Society of Clinical Oncology guidelines and National Comprehensive Cancer Network recommend active follow-up for GISTs < 2 cm in diameter that lack a high risk of malignancy on endoscopic ultrasound, while surgical excision of lesions is recommended for localized gGISTs \geq 2 cm in diameter[7,8].

With the popularization and application of laparoscopic technology, laparoscopic wedge resection has become a popular alternative to conventional open surgery for gGIST[9-11]. Laparoscopic surgery offers various advantages over open surgery, including less postoperative pain, achieving faster recovery, shorter hospitalization, and less blood loss[12, 13]. The *laparoscopic approach may be considered for selected GISTs in favorable anatomical locations, such as the anterior wall of the stomach*[8]. Another hotspot in the treatment of GISTs is the use of endoscopic resection (ER). ER, which has the advantages of maintaining organ integrity, low invasion, and good cosmetic results, has become a new treatment option for GISTs in clinical practice[14]. ER, which encompasses endoscopic mucosal resection (EMR), ¹¹ submucosal tunnel endoscopic resection (STER), and endoscopic submucosal dissection (ESD), is extensively utilized for the management of gastric submucosal tumors[15,16]. Conversely, for GISTs with a tumor diameter larger than 5 cm, surgical intervention, either in an open or laparoscopic surgery, is the recommended primary therapeutic approach. For GISTs with a diameter of 2-5 cm, ER or laparoscopic resection (LR) should be considered[17].

However, there is no selection criteria for specific applications, and the comparison of outcomes between ER and LR is inconsistent across studies[6,18]. For gastric GISTs (gGISTs) of 2-5 cm, Lei *et al*[14] showed that the incidence rate of complications and reoperation ¹⁵ were higher in the ER group than in the LR group; therefore, laparoscopic surgery was recommended, and Dong *et al*[6] concluded that LR is better than ER because of its lower complication rates and shorter hospital stay. However, some studies have shown that ER has ¹⁴ advantages of a shorter operation time, less intraoperative bleeding, shorter postoperative hospital stay, lower hospitalization costs, and lower incidence of surgical complications than LR with no marked difference in the

rate of long-term recurrence, suggesting that ER of select small gGISTs (≤ 5 cm) is feasible, safe, and has good intraoperative outcomes[18-20].

Based on this background, we retrospectively collected data on LR and ER of GISTs with diameter of 2–5 cm at Taizhou Hospital in Zhejiang Province from January 2014 to August 2022. This study provides an updated reference for the standardization of treatment of 2- to 5-cm gGISTs.

MATERIALS AND METHODS

Patients

The ethics committee of the Taizhou Hospital of Zhejiang Province, Wenzhou Medical University approved this retrospective study (K20220788). We reviewed and compiled information on patients with gGISTs who underwent ER or LR at our hospital from January 2014 to August 2022. Patient inclusion criteria were as follows: (1) age > 18 years old; (2) longest tumor diameter of 2–5 cm as measured using excised specimens; (3) a diagnosis of gGIST confirmed by postoperative pathological evaluation and immunohistochemical findings; (4) surgery performed by experienced attending surgeons or endoscopists; and (5) surgical method of ER or LR. The exclusion criteria were as follows: (1) failure to complete surgery; (2) adjacent organ invasion; and (3) duodenal and small intestinal stromal tumors.

Patient clinicopathological data

Data were collected on the patient general condition (age, sex), tumor (lesion location, size, pathological characteristics, operation data (operation method, operation duration, presence of en bloc resection, complete resection, cutting edge, surgical complications [e.g. infection, bleeding, anastomotic leakage, and perforation]), postoperative recovery (time to liquid diet, postoperative hospital stay, postoperative symptoms), hospital cost, and postoperative follow-up (follow-up time, survival, recurrence). The tumor size was defined as the maximum tumor diameter. The operation duration was defined as the period from the initiation of anesthesia to the end of anesthesia. En bloc resection refers

to the excision of the tumor in its entirety as a single piece, whereas complete resection is defined as an en bloc resection with histologically negative margins, ensuring no residual tumor tissue at the resection site. The definition of postoperative infection is a fever occurring after surgery, despite the use of antibiotics, with a body temperature higher than 38 °C persisting for more than 48 hours. Bleeding included intraoperative bleeding (intraoperative blood loss > 100 mL) and postoperative bleeding (postoperative symptoms, such as hematemesis and melena that required endoscopic hemostasis or surgical hemostasis). Perforation was rigorously defined as other extraluminal fat, organs, or extraluminal space outside the muscle layer that could be observed through endoscopy during ER [21]. However, perforations that did not necessitate surgical intervention and were amenable to closure *via* endoscopic techniques were not categorized as complications in this context[22]. Anastomotic leakage was defined as the postoperative endoscopic examination revealing a leakage or postoperative upper gastrointestinal imaging showing contrast agent leakage.

ER

ER was carried out by highly experienced endoscopists under the administration of general anesthesia. The primary methods were ESD, endoscopic full-thickness resection (EFTR), endoscopic submucosal excavation (ESE), and STER. The electrosurgical generator used in ER was an AVIO 200D (ERBE, Tübingen, Germany).

First, the tumor lesion margins of 3-5 mm were marked by electrocoagulation (KD-650Q; Olympus, Tokyo, Japan), Submucosal injection (NM400 L0625 [Olympus]; 0.9% normal saline + methylene blue + 0.01% epinephrine) was then performed at the edge of the lesion to lift the mucosa. The lesion was exposed by dissecting the mucosal layer and submucosa along the marker points with gradual dissection of the exposed tumor in the submucosa. A cross or circumferential mucosal incision was then made using a knife (KD-650Q; KD-611 L, IT2; or KD-620 LR; Olympus) to reveal the lesion. For tumor excision, snare resection (SD-230U-20; Olympus) was performed to achieve complete excision of the lesion following resection of three-quarters of the tumor's circumference.

Finally, the wound was closed. After full hemostasis was achieved, titanium clips (HX-600-135 [Olympus] or ROCC-D-26-195-C [Micro-Tech Co., Ltd., Nanjing, China], a ligation device (loop-20B0/30B0/40B0; LEOMED, Jiangsu, China), and an over-the-scope clip system (12/6 t-type; Ovesco Endoscopy AG, Tubingen, Germany) were used to close the wound according to the wound condition. Hot biopsy forceps (HBF-23/1600; Micro-Tech Co., Ltd.) were used to achieve intraoperative hemostasis.

ESE is a derivative technology based on ESD that gradually peels the submucosa and part of the muscularis propria at the base of the tumor.

EFTR is a method similar to traditional ESD, which uses new endoscopic suture techniques to close gastrointestinal wall defects. The muscularis propria was dissected to the serosa layer along the edge of the lesion, and the serosa was cut to form an "artificial perforation," with the lesion completely removed. To prevent the removed tumor from falling into the abdominal cavity, a trap or grasping forceps are used to fix and remove the lesion, and full-thickness excision of the lesion site and wound closure after resection can be performed. Depending on the size of the wound, the wound was closed by endoscopic titanium clamp closure, endoscopic purse sutures, and an over-the-scope clip.

LR

There are many methods available for performing LR for gGISTs, depending on the location, size, and growth pattern of the tumor. The main methods of laparoscopic surgery are wedge resection, subtotal gastrectomy (including proximal and distal gastrectomy), and total gastrectomy.

Regarding the main steps of the operation, after general anesthesia, a 1-cm incision was made in the skin of the umbilical margin, and a pneumoperitoneum needle was inserted to induce carbon dioxide pneumoperitoneum. Incisions were also made under the left and right collarbone midline costal margin and midpoint umbilical cords and under the left and right collarbone midline rib arch, each about 0.5, 0.5, 1.0, and 0.5 cm long, respectively. An ultrasound knife, intestinal forceps, and other instruments were

placed under laparoscopic monitoring. The size, location, and metastasis of the tumor were investigated, and appropriate surgical methods were selected depending on the location and size of the tumor. For example, for GISTs > 2 cm located in the greater curvature or anterior wall of the stomach, local or wedge surgery was performed. The mass was excised, placed in a specimen recovery bag, and removed from the incision.

Follow-up

All patients underwent regular postoperative follow-up with an endoscopic examination and CT. Follow-up data were acquired *via* telephone interviews or outpatient follow-up after surgery. The follow-up time was defined as the period from the date of surgery to the last follow-up (August 2022) or death. All patients were followed up for over a year, except for deceased patients.

Propensity score (PS) matching

In order to address the issue of selection bias, we used propensity scores to match the patients in the LR group to those in the ER group. We conducted a 1: 1 PSM analysis utilizing four covariates: Age, sex, tumor size, and tumor location. A caliper width of 0.1 was employed to ensure precise matching, and this approach simulated the conditions of randomization in observational studies. In total, 135 patients were treated with ER, and 71 patients were treated with LR, resulting in 59 pairs of balanced matches.

Statistical analysis

The statistical analyses were conducted using the SPSS software program (version 26.0, SPSS, Chicago, IL, USA). The sample size was estimated using G*Power software (Version 3.1.9.2). Quantitative data with a normal distribution were presented as mean \pm standard deviation, and we used an independent samples *t*-test for comparisons. For quantitative data with a skewed distribution, we expressed the results as medians and quartile spacing, and used the Mann-Whitney *U* test for comparisons. Qualitative data

were presented as the frequency (%), and we compared the characteristics between the groups either the χ^2 test or Fisher's exact test. We considered $P < 0.05$ on both sides to be significant.

RESULTS

Patient baseline characteristics

The power analysis was conducted using G*Power 3.1.9.2 with an alpha level of 0.05, a power of 0.80, and an effect size of 0.5. The analysis indicated that the sample size was adequate, with a required sample size of $n = 53$ for each group. From January 2014 to August 2022, 206 patients with 2- to 5-cm gGISTs participated in this study, with 135 in the ER group and 71 in the LR group.

Table 1 presents the baseline characteristics of the study cohort. Before PS matching, the tumor size in the ER group was significantly smaller (3.5 [3.0-4.0] cm) compared to the LR group (4.2 [3.3-5.0] cm; $P < 0.001$). The distribution of tumor locations differed between the groups ($P = 0.048$). In the LR group, 63.4% of patients had tumors located in the gastric body, and 0.0%, 28.2%, and 8.4% of the tumors were located in the gastric cardia, gastric body, and gastric antrum, respectively. In contrast, 48.9%, 3.7%, 42.2%, and 5.2% of the tumors in the ER group were located in the gastric body, cardia, fundus, and antrum, respectively. We performed a PS-matched analysis to eliminate the impact of confounding factors and enhance the credibility of the findings. After PS matching, 59 patients from each group were selected and included in the subsequent analysis. Post-matching, there were no significant differences between the two groups in terms of these factors (Table 1).

Short-term outcomes

Before and after PS matching, the ER group had longer operative times than the LR group (both $P < 0.001$), but the median postoperative time to liquid diet was significantly shorter in the ER group than in the LR group ($P = 0.008$ and $P = 0.046$, respectively). After PS matching, the ER group had significantly fewer postoperative

symptoms than the LR group ($P = 0.040$). However, there was no significant difference in the postoperative hospital stay or hospital costs between the groups (both $P > 0.05$) (Table 2).

The intraoperative and postoperative complications in both groups are summarized in Table 2. There was no significant difference in surgery-related complications between the two groups before or after PS matching ($P = 0.863$ and $P = 0.999$, respectively). After PS matching, bleeding occurred in 3 patients (5.1%) in the ER group and was successfully treated with conservative treatment or endoscopic hemostasis. Anastomotic fistula occurred in one case (1.7%) in the LR group postoperatively and improved after fasting, adequate drainage, and anti-infection. With regard to postoperative infection, 5 cases (8.5%) were found in the ER group compared with 8 (13.6%) in the LR group, and there was no significant difference in the incidence of postoperative infections between the groups ($P = 0.378$). According to the Clavien-Dindo classification scale[23], the ER group reported 5 cases of grade I, 2 cases of grade II, and 1 case of grade III, while the LR group reported 5 cases of grade I and 2 cases of grade II. En bloc resection was achieved in all tumors in both groups (100%). In the ER group, 107 (79.3%) and 43 (72.9%) tumors received en bloc removal from the stomach and complete resection before and after PS matching, respectively. The remaining 28 (20.7%) and 16 (27.1%) tumors were temporarily attached to the stomach using clips and then removed en bloc with the help of an endoscopic lithotripter the following day before and after PS matching, respectively. In the LR group, only one tumor did not achieve complete resection due to fragmentation. Thus, the rates of complete resection were higher in the LR group than in the ER group (both $P < 0.001$). There were no significant differences in the tumor mitotic count or pathological report risk between the groups.

Long-term outcomes

The median follow-up in the LR group was 54.0 (34.8–92.4) months, significantly longer than the 51.1 (28.7–74.2) months in the ER group, but this difference was not statistically

significant ($P = 0.173$). Prior to the last follow-up, GIST recurrence occurred in 3 patients in the ER group (2.2%, 3/135) and 2 in the LR group (2.8%, 2/69), but the difference was not found to be significant ($P > 0.999$). After PS matching, there were no occurrences of GIST recurrence in the ER group (0%, 0/59) and 2 occurrences in the LR group (3.4%, 2/59), with no significant difference ($P = 0.476$). All patients with high-risk gGISTs were treated with imatinib mesylate. No metastases were observed during the follow-up period. During follow-up, there was no significant difference in mortality between the two patient groups before (4.4% vs. 4.2%, $P > 0.999$) or after matching (1.7% vs. 5.1%, $P = 0.611$). A total of nine patients died in both groups, with one in the LR group dying of GIST recurrence and the remaining eight dying of other GIST-resection-unrelated diseases.

DISCUSSION

GISTs have malignant potential, and surgery is the standard treatment for non-metastatic GISTs > 2 cm in diameter[8]. For tumors 2-5 cm in size, ER and LR are safe and feasible treatments for localized GISTs over the past few years[20]. However, there is still disagreement as to which is the better choice.

In our cohort of 206 patients with a tumor size of 2-5 cm, we compared baseline characteristics, surgical outcomes, pathologic results, and surgical complications between the ER and LR groups. As expected, the tumor diameters in the LR group were significantly larger than those in the ER group, and the location of lesions also differed significantly between the two groups, with the ER group demonstrating a higher proportion of cases in the cardia and fundus compared to the LR group. This finding is in line with previous studies that have shown an advantage of ER in managing lesions located at these anatomical sites[18,24]. To overcome selection bias, we used the PS to match patients in the LR group with those in the ER group, resulting in 59 pairs of balanced matches.

In terms of complications, scholars have differing opinions. Some have suggested that complications (intraoperative bleeding, fistula, perforation) are significantly more

frequent with ER than with LR[6,14]. However, Pang *et al.* concluded that ER had significantly fewer complications than LR and found that intraoperative major bleeding and infection rates were lower in the former than in the latter[18]. In addition, a meta-analysis of 10 clinical studies showed no marked difference in surgical complications between the groups[20], which is consistent with our findings. In the present study, both ER and LR showed satisfactory safety profiles. Surgical complications occurred in only 16 patients (11.9%) in the ER group and 9 (12.7%) in the LR group. Delayed postoperative hemorrhaging occurred in four cases in the ER group, all of which were successfully treated with conservative treatment or endoscopic hemostasis, and no intraoperative or postoperative hemorrhaging occurred in the LR group. Postoperative anastomotic fistula occurred in one case of laparoscopy, which improved after fasting, adequate drainage, and anti-infection. After matching, the postoperative infection rates were 8.5% and 13.6% in the ER and LR groups, respectively, mainly manifesting as upper respiratory tract infection, lung infection, and localized peritonitis. In this study, no perforations requiring surgical intervention were observed. However, it should be noted that 18 cases of GISTs originating from the muscularis propria and closely adhering to the serosal layer were completely removed by "active perforation" of the gastric wall using EFTR. The wound was successfully repaired using endoscopic suturing techniques, which we did not include as complications. According to the Clavien-Dindo classification, complications in both groups of this study were primarily classified as grade I, which were clinically significant and require attention and management from healthcare professionals. However, it is important to note that the definitions of complications may differ across studies, leading to variability in analysis results and a lack of convergence.

Previous studies have shown that ER shortens the operation duration and postoperative hospital stay, reduces hospital costs compared with LR, and has advantages of early resumption of a liquid diet and fewer postoperative symptoms[14,18,19]. In the present study, the ER group had a longer operation time and no advantage in terms of postoperative hospital stay and hospital costs compared

to the LR group. This may be because of the large tumors in this study and the low seniority of some endoscopists. Consistent with previous studies, the ER group had preserved organ integrity and better cosmetic results than the LR group, and patients resumed a liquid diet earlier after surgery and had fewer postoperative symptoms, thereby reducing postoperative pain.

It is widely acknowledged that R1 resection is associated with a poor prognosis for malignant tumors. A multicenter study involving 112 hospitals across 12 countries demonstrated a significant difference in overall survival (OS) between patients undergoing R1 and R0 resections. However, excluding tumor rupture, the difference in OS between R1 and R0 resections disappeared[25]. This finding suggests that endoscopists should avoid intraoperative tumor rupture to improve patients' overall survival rate. The complete resection rate was significantly lower in the ER group than in the LR group. The reason for this was that the tumor diameter in this study was relatively large, with 53 cases (49.3%) of tumors > 4 cm in the ER group. Exceeding 4 cm in diameter, tumor resection *via* endoscopy is hindered by limited cardia and esophageal space, which makes it difficult to remove the tumor en bloc[22]. In this study, the en bloc resection rate in the ER group was 100%. During the initial surgery, when it was not possible to remove the tumor from the stomach, the doctors used several clips to attach the tumor to the stomach wall. This allowed them to remove the tumor from the stomach the next day. It's important to note that the outer membrane of the tumor had been eroded by stomach acid, which can potentially lead to the tumor spreading within the gastrointestinal tract. This method of tumor removal also has an impact on the pathological assessment of the tumor. Nevertheless, there was no marked difference in the prognosis between the two groups, which is similar to the findings reported in some studies[26,27]. Furthermore, in previous studies at our center, patients who underwent this tumor resection method did not show any residual tumor or recurrence during follow-up[28].

Based on a thorough review of existing literature, guidelines, and clinical expertise, we have found that tumor diameter and location play a crucial role in determining the

most suitable surgical approach, which consequently influence operation duration, postoperative recovery, and ultimately, the prognosis of the patient's condition[29, 30]. This study improved the reliability of the results by performing a PS-matched analysis to minimize potential selection biases. Many studies have compared the effects of the two surgical methods, but most did not match the tumor size and location, resulting in significant selection bias. To our knowledge, only a few scholars have performed a PS-matched analysis, but different scholars have different views. For example, Dong *et al*[6] concluded that LR was better than ER, whereas other studies concluded that ER is safer and more economical than LR[18,30,31]. The present study posits that ER is associated with reduced postoperative pain and a faster recovery, whereas LR demonstrates a shorter operation time and a higher complete resection rate, which is not entirely consistent with findings reported in prior research endeavors. Therefore, the results of the present study may serve as a reference for clinicians.

⁹ However, it is pertinent to acknowledge several limitations inherent to the current study. First, it was a single-center retrospective study, which may have resulted in some selection bias. For gGISTs with a diameter of 2-5 cm without lymph node or distant metastasis, the choice of surgical method mainly depends on two factors: (1) the patient's preference; and (2) the department where the patient consults, endoscopic resection if consulting gastroenterology, or surgical resection if consulting gastrointestinal surgery. Second, the sample size was relatively small. Third, of the 206 patients, follow-up was discontinued in 8 due to unrelated deaths. Therefore, a randomized, controlled, and multicenter clinical trial is warranted to further validate and substantiate the observations made in this study.

In this retrospective study, the baseline clinical data were unevenly distributed between the two groups of patients. After PS ¹⁰ matching, no statistically significant differences were identified between the two groups in terms of the age, sex, tumor size, and tumor location. The matched ER group showed significantly better outcomes than the LR group in terms of the resumption of a liquid diet and postoperative symptoms. The LR group had an advantage over the ER group in terms of the complete resection

rate. ¹ There were no statistically significant differences between the two groups in terms of either the incidence of complications or the long-term postoperative outcomes.

CONCLUSION

Both ER and LR are safe and effective treatments for gGISTs. ER is associated with less postoperative pain and faster recovery, and is particularly suitable for cases where cosmetic results or preservation of organ function are desired. In contrast, LR is strongly recommended for large tumors (> 4 cm) due to its high rate of complete resection.

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