



Laparoscopic-Endoscopic Cooperative Surgery for Gastric Gastrointestinal Stromal Tumors

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Abstract

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors originating in the gastrointestinal tract. Laparoscopic endoscopic cooperative surgery (LECS), consist of endoscopic surgery in the form of endoscopic mucosal incision and laparoscopic surgery, is an important advantage over conventional laparoscopic wedge resection(LWR) for local resection of gastric gastrointestinal stromal tumors (GIST). The first LECS method was reported by Hiki in 2008, which was named “classical LECS” to distinguish from subsequent modified methods, for example, laparoscopic assisted endoscopic full-thickness resection (LAEFR), inverted LECS and a combination of laparoscopic and endoscopic approaches to neoplasia with a non-exposure technique (CLEAN-NET) and non-exposed endoscopic wall-inversion surgery (NEWS). Each of these procedures has advantages and disadvantages. So we have reviewed these techniques, identify the difference between them, define their indications and elaborate their characteristics. And in conclusion, as a relative safe, feasible, and beneficial procedure, classical LECS technique, along with subsequent modified methods substantially promote the development of surgical treatment for gastrointestinal neoplasms especially for GISTs. Moreover, further studies such as large sample prospective clinical trials are also required to confirm the feasibility and stability of these treatment methods, especially with regard to safe and long-term outcomes.

Keywords: Laparoscopic-endoscopic cooperative surgery; Laparoscopic wedge resection; Gastrointestinal stromal tumors

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors originating in the gastrointestinal tract, which usually occur in the stomach (60%) or small intestine (30%) [1]. GISTs range in size from less than 1 cm to very large lesions measuring upwards of 35 cm. Large tumors frequently present with hemorrhage, necrosis, and cystic degeneration. Size, mitosis, primary site and rupture of tumor are considered the four most important risk factors for prognosis of GISTs, which guide the selection of patients who may require adjuvant therapy [2].

Due to the high potential for malignancy of GIST, the first-line treatment of localised GISTs is complete surgical excision of the lesion without residual tumor cells (R0) or tumor rupture, and systematic locoregional lymph node dissection is usually unnecessary. For complete resection, pseudocapsule should not be damaged during manipulation of the tumor and macroscopically negative margin as well as adequate safety margin should be spared. Tumors >20 mm or growing tumors should be surgically resected, because, if diagnosed as GIST, will imply a higher risk. The preferred resection margin is 10-20 mm grossly. Since GISTs rarely metastasizes to local or regional lymph nodes, lymphadenectomy is warranted only if metastasis is suspected, such as when enlarged lymph nodes are noted.

Compared with open surgery, laparoscopic surgery has similar outcomes for GIST patients in terms of oncologic prognosis with several advantages, such as less pain, less invasiveness, early recovery, and better cosmetic results [2]. Some studies and consensus have indicated that laparoscopic surgery can only be safely performed for GISTs that are 5 cm or smaller in favorable locations [3,4], while things were changed with the development of medical practice and technology. Besides, laparoscopic-assisted surgery may also be recommended because of its good safety and short operation time [3]. LWR has been used to treat GISTs for decades [5], many studies demonstrate that LWR is feasible and safe with all the benefits of minimally invasive surgery even for GISTs that are larger than 2 cm. However, determining the appropriate incision line is difficult from the outside of the stomach when these lesions are intraluminal, which might result in transformation

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Table 1: Comparison of various LECS procedure.

	Classical LECS	LAEFR	Inverted LECS	CLEAN - NET	NEWS
Tumor location	No limitation	No limitation	No limitation	Except EGJ or pyloric ring	Except EGJ or pyloric ring
Recommended tumor size (SMT)	≤5cm	≤5cm	≤5cm	≤3cm	≤3cm
Intentional gastric Perforation	Yes	Yes	Yes	No	No
Suturing technique	Linear stapler	Hand-suturing	Linear stapler	Linear stapler	Hand-suturing
Retrieval route	Transabdominal	Transroral or Transabdominal	Transroral	Transabdominal	Transroral
Estimated procedure time (min)	120-182	181-389	120-180	120-240	180-300
Advantage	Accurate determination of the resection line, rational combination of endoscopy and laparoscopy	Minimal invasive endoscopic resection, expose of lesion assist by laparoscopy	Diminishes the risk of spillage and contamination, accurate determination of the resection line	No transluminal communication	No transluminal Communication, accurate determination of the resection line
Limitation	Risk of spillage and contamination Not adapted for early gastric cancer	Requires advanced endoscopy skills, time-consuming	Not adapted for early gastric cancer	difficult to determine the resection line, restriction in the tumor size and location	restriction in the tumor size and location, time-consuming

CLEAN-NET: Combination of Laparoscopic and Endoscopic Approaches to Neoplasia with a Non-exposure Technique; EFTR: Endoscopic Full Thickness Resection; EGJ: Esophagogastric Junction; LECS: Laparoscopic and Endoscopic Cooperative Surgery; NEWS: Non-exposed Endoscopic Wall-inversion Surgery

of the stomach with consequent gastric stasis at food uptake. Besides, it's hard to ensure negative margins of large tumors and tumors located at the esophagogastric junction (EGJ), near the pylorus, or on the posterior gastric with LWR method. So laparoscopic endoscopic rendezvous surgery has been described to determine the appropriate incision line for local resection of the stomach [6,7], then the formal concept of classical laparoscopic endoscopic cooperative surgery (LECS) was first reported to treat GISTs by Hike in 2008 [8], consisting of endoscopic surgery in the form of endoscopic mucosal incision and laparoscopic surgery, which is an important advantage over conventional laparoscopic wedge resection using linear staplers. However LECS has some inherent risks such as peritoneal infection and cancer cell seeding due to the necessity for gastric perforation, so many attempts have been made to improve the reliability and feasibility of this technique.

With the development of the original LECS procedure or "classical LECS", a number of modified LECS procedures have been investigated by numerous researchers, for example, laparoscopic assisted endoscopic full thickness resection (LAEFR) [9], inverted LECS, combination of laparoscopic and endoscopic approaches to neoplasia with a non-exposure technique(CLEAN-NET) [10] and non-exposed endoscopic wall inversion surgery (NEWS) [11,12]. These techniques are advantageous because a more precise resection area can be determined using intraluminal endoscopy, thus minimizing the resection area. This will result in less deformity and better surgical margins.

Here we review the application of classical and further modified LECS techniques, identify and classify the different techniques described, define their indications and elaborate their characteristics (Table 1).

Classical LECS

Laparoscopic wedge resection is safe and feasible treatment for gastric submucosal tumors, while a major difficulty with this type of tumor resection lies in determining the appropriate resection line. In order to solve this problem, Hiki et al. [8] first report the classical laparoscopic and endoscopic cooperative surgery (LECS) for gastric wedge resection, which is applicable for submucosal tumor resection independent of tumor location and size.

The LECS procedure combines gastrointestinal endoscopy and laparoscopy: the lesion is located and partially dissected by Endoscopic Submucosal Dissection (ESD) and the resection is completed by laparoscopy.

First, the setup for laparoscopic surgery is similar with standard LWR method, including the position of surgeons and operative ports. Then the tumor location is confirmed by intraluminal endoscopy, besides, the tumor location of laparoscopic image is confirmed by maneuvered the stomach wall with biopsy forceps from the mucosal side. Ultrasonically activated device and Ligasure are used to manipulate blood vessels periphery of the lesion. Then endoscopic submucosal resection around the tumor is manipulated. An Argon plasma coagulation is used to mark the periphery of the tumor and 10% glycerin is injected into the submucosal layer, then a small initial incision is made with a standard needle knife and the tip of the insulation-tipped diathermic electro-surgical (IT) knife inserted into the submucosal layer, three-fourths of the marked area was cut circumferentially using the IT knife. An artificial perforation is performed with the needle knife which allow the insertion of the tip of the ultrasonically activated device, thus further seromuscular layer is dissected along the incision line using the Ligasure vascular sealing system. The tumor is turned over toward the abdominal cavity after seromuscular three-fourths of the circumference around the tumor had been dissected. At last, the tumor (non resected part) and the edge of the incision line then was lifted up, and the closure of gastric wall is performed by laparoscopic stapling device or a laparoscopic hand sewn suture technique.

Many studies demonstrated the feasibility and satisfactory outcome of LECS for GIST, including minimizes the surgical specimen and providing a sufficient surgical margin to successfully cure gastric GIST [13-17]. Furthermore, the classical LECS procedure is believed not affected by tumor location or size [16,18].

However, as classical LECS needs to open the gastric wall during the dissection, the artificial perforation might result in spillage of gastric contents and lead to bacterial contamination of peritoneal cavity and dissemination of peritoneal tumor cells. After all, classical LECS is a feasible technique for the treatment of tumors including GIST if the tumor is unable to seed elsewhere.

Laparoscopy-Assisted Endoscopic Full-Thickness Resection (LAEFR)

As LWR may lead to excessive normal tissue removal, Abe et al. [9] proposed a concept of modified LECS technique, which known as laparoscopy-assisted endoscopic full-thickness resection (LAEFR). This technique is performed under the same principles of LECS except the endoscopic full thickness resection around the tumor. The standard LAEFR consists of four major steps: 1) a circumferential incision as deep as the submucosal layer around the lesion by the ESD technique; 2) endoscopic full-thickness (from the muscle layer to the serosal layer) incision around the three-fourths or two-thirds circumference on the submucosal incision under laparoscopic supervision; 3) laparoscopic full-thickness incision around the remaining one-fourth or one-third circumference from inside the peritoneal cavity; 4) hand sewn closure of the gastric-wall defect. At last the specimen is retrieved either per orally or protected in a plastic bag through a port site.

The LAEFR method consist of Endoscopic full-thickness resection (EFTR) and laparoscopic hand sewn closure of the gastric wall defect, the combination of these 2 procedures makes the full-thickness resection more accurate and as small as possible [19]. An increasing number of studies have focused on this technique [20-22], specifically Hirohito Mori et al. [23] believed that for GISTs that do not require lymphadenectomy and can be cured by radical tumor enucleation, LAEFR is a safe and established surgical endoscopy procedure. However compared to classical LECS, the complicated procedure of LAEFR may leads to longer operation time and learning curve.

Inverted LECS

As described above, LECS may leads to peritoneal infection or cancer cell seeding due to the necessity for gastric perforation. So in order to reduce the risk of these complications, Souya Nunobe et al. [24] developed a new modified LECS technique named "inverted LECS".

The procedures of inverted LECS are identical to classical LECS before laparoscopic seromuscular dissection and formation of artificial perforation. To prevent contact between the tumor and the visceral tissue, the tumor is inverted to face the intragastric cavity using the traction of the stitch at the edge of the resected specimen, and the resection line of the stomach is also pulled up by these stitches. Then the tumor is resected into the gastric cavity and collected via the per-oral route, the edge of the incision line was closed temporarily using hand sewn sutures. At last a laparoscopic stapling device is used to close the incision line as the conventional method of the classical LECS procedure.

With inverted LECS procedure, the lesion is kept inside the stomach, thus the direct contact between tumor and the perigastric viscera is prevented effectively. However, there is still risk of gastric content contamination and tumor cells seeding as artificial perforation of gastric wall and instruments contact are inevitable [25,26].

Clean-Net

CLEAN-NET, which is known as a combined laparoscopic and endoscopic approach for non-exposure full thickness gastric wall resection, was first described by Inoue et al. [10] in 2012 to completely prevent the risk of cancer cell dissemination. This technique preserves the continuity of the mucosa as a barrier (a clean net) by using a seromuscular incision. Then the mucosal tissue is pulled out toward

the outside of the stomach, thus maintains a sufficient epithelial margin around the cancer tissue, in this way can keep a minimal defect of stomach wall.

First, endoscopic markings are made approximately 5 mm from the lesion margin on the mucosa with an electrocautery knife. Then fix the mucosal layer to the seromuscular layer with full-layer stitches using 4 stay sutures under the guidance of laparoscope and endoscope. Next 4 stitches are pulled upward with laparoscopic forceps, a selective seromuscular dissection along the outside of the 4 stitches is performed using an laparoscopic electrocautery knife, and the mucosal layer maintains its continuity in this method which prevents gastric contents from flowing out into the peritoneal cavity. A full-layer specimen with sufficient lateral mucosal margin is cut and taken out with a laparoscopic stapling device.

After all, CLEAN-NET allows full-layer gastric wall resection to be completed with minimal risk of contamination of abdominal cavity from gastric content. However, as the mucosal layer must maintains its continuity when be pulled out toward the outside of the stomach, then specimen size is limited to avoid mucosal laceration. Besides, the appropriate mucosal incision might be difficult to determine for the incision line is determined from the serosal side [26].

News

Non-exposed endoscopic wall in version surgery (NEWS) was first performed in 2011 in an *ex vivo* porcine model by Osamu Goto et al. [11]. This non-exposure technique enables full-thickness resection of the gastric wall without transmural communication, thus preventing tumor dissemination into the abdominal space. Interestingly, the procedures of NEWS also resemble "inverted" kind of CLEAN-NET to some extent.

The NEWS method can be manipulated as following steps: First, markings of lesion are made with endoscope, then inject 0.9% normal saline with indigo carmine into the sub mucosa around the markings. Second, a circumferential sero-muscular incision is made from the outside with an electrocautery knife, guided by the color of the sub mucosal injection and intragastric navigation with the endoscope. Third, the muscle layer is linearly sutured with the lesion inverted into the inside. Finally, a circumferential muco-submucosal incision is made with an electrocautery knife employed with the endoscope and the tumor is retrieved per orally [11].

The method was originally performed for 3 lesions, including 1 anterior wall, 1 lesser curve and 1 posterior wall of the gastric body, all lesions were resected successfully with no apparent complications occurred such as air leakage or perforation, thereby proving NEWS is effective as a minimally invasive, and minimal-size surgery for gastric submucosal tumors, which also reflected by several other studies [12,27,28]. However, as tumors are retrieved per orally, so its application is limited by tumor size. Besides, compared to CLEAN-NET, the seromuscular hand suturing and circumferential mucosal incision process are time consuming. At last, it's complicate to determine proper mucosal incision, which may result in a relatively large resection area.

Discussion

Compared with open surgery, laparoscopic surgery has similar outcomes for GIST patients in terms of oncologic prognosis with several advantages, such as less pain, less invasiveness, early recovery, and better cosmetic results. Although tumors with an extra gastric

growth pattern can be easily treated using conventional laparoscopic wedge resection, laparoscopic methods alone have some limitations for the resection of GISTs. Laparoscopy is less efficient than open surgery in removing small tumors and tumors located in the posterior gastric wall and lesser curvature of the stomach. In addition, the removal of large tumors and those located near the cardia or pylorus can result in post-operative complications, such as stenosis or damage to the cardia or pylorus. Furthermore, for single laparoscopic technique, it's difficult to determine the appropriate incision line for intraluminal lesions from the outside of the stomach. Therefore Hike et al proposed the concept of "Laparoscopic-endoscopic cooperative surgery" (classical LECS) in 2008 [8], which indicates that endoscopic support is crucial for reducing complications, such as bleeding, stenosis or damage to the cardia or pylorus, especially for the tumors that are located in the gastric fundus or antrum, besides, with direct intraluminal visualization, the tumor can be totally removed with accurate incision line. However, classical LECS procedure still has some inherent disadvantages, for example, tumor cell seeding and bacterial contamination of the abdominal cavity. So many attempts have been made to improve the reliability and feasibility of this technique.

In order to prevent excessive normal tissue removal, Abe et al. [9] invented the LAEFR technique, which familiar to LECS but instead of a full thickness endoscopic resection. The combination of EFTR and laparoscopic hand sewn closure of the gastric wall defect makes the full-thickness resection more accurate and as small as possible. As for Inverted LECS, the lesion is kept inside the stomach, thus the direct contact between tumor and the perigastric viscera is prevented effectively. While these 2 techniques have some common disadvantages, for example, inevitable artificial gastric perforation, which may lead to abdominal contamination and tumor cell seeding, even its morbidity is extremely low according to present studies. So how to solve this "inevitable" problem? Thereafter, "non-exposure" techniques have been developed to further refine LECS methods.

CLEAN-NET and NEWS, which both known as combined laparoscopic and endoscopic approach for non-exposure full thickness gastric wall resection, preserve the continuity of the mucosa as a barrier and thus allow a minimal risk of contamination of abdominal cavity from gastric content. Besides, NEWS can also achieve accurate resection line for tumors. While for multiple reasons describe above, both CLEAN-NET and NEWS techniques are not appropriate for resection of tumors with big size or in difficult locations, such as close to the EGJ or pyloric ring.

For now, all the main techniques base on LECS have some disadvantages that prevent their further application. Thus new attempts have been made to improve the feasibility and stability of LECS technique and expand its application. For example, Eri Maeda et al. [29] reported the first case of multiple gastric GISTs treated by LECS with no intraoperative or postoperative complications, therefore indicates that this procedure is feasible and safe as a GIST treatment even in cases of multiple lesions. YE YAN et al. [30] reported an innovative procedure of laparoscope combined with endoscopy for GIST resection and cholecystectomy, which demonstrated that LECS is feasible and would be an ideal choice for invisible abdominal scar surgery, in particular for multi-visceral resection. Besides, LECS is now also applied as a safe and useful procedure to other organs such as the duodenum and colon [31-33].

Conclusion

As a relative safe, feasible, and beneficial procedure, classical LECS technique, along with subsequent modified methods substantially promote the development of surgical treatment for gastrointestinal neoplasms especially for GISTs. Moreover, further studies such as large sample prospective clinical trials are required to confirm the feasibility and stability of these treatment methods, especially with regard to safe and long-term outcomes.

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