



Combination of laparoscopic and endoscopic approaches for neoplasia with non-exposure technique (CLEAN-NET) for gastric submucosal tumors: updated advantages and limitations

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Abstract: Laparoscopic and endoscopic cooperative surgery (LECS) for gastric submucosal tumors (SMTs) has been developed under the concept of resecting gastric tumors with both complete curability and preserving organ functions. Precise resection is obtained by classical LECS, however, concerns regarding intraoperative bacterial infection and dissemination of the tumor cells into the abdominal cavity by LECS with exposure technique still remain. To prevent these concerns, several LECS-related procedures with non-exposure techniques, such as combination of laparoscopic and endoscopic approaches for neoplasia with non-exposure technique (CLEAN-NET) and non-exposed endoscopic wall-inversion surgery (NEWS), have been reported to be safe and feasible. Classical LECS, CLEAN-NET, and NEWS have the same concept, however, each has its own different characteristic procedures; exposure or non-exposure technique, inversion of the tumor into or outer the lumen, retrieval of tumor per oral or through the abdominal cavity, and dominance in the role of the endoscopist or the laparoscopic surgeon. Familiarization with these procedure details is important to understand their indications, advantages and limitations, resulting in providing a tailored minimally invasive surgery for patients. The main scope of this review article is to introduce readers to the clinical application, procedure, and results of CLEAN-NET, both from previous literatures and from our experience, as well as to offer a closer look at its advantages and limitations while comparing with other LECS procedures from the viewpoint of introducing CLEAN-NET first.

Keywords: Laparoscopic and endoscopic cooperative surgery (LECS); combination of laparoscopic and endoscopic approaches for neoplasia with non-exposure technique (CLEAN-NET); non-exposed endoscopic wall-inversion surgery (NEWS); gastric submucosal tumors (SMTs)

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Introduction

Complete surgical resection is currently considered the first choice of treatment for patients with resectable gastric submucosal tumors (SMTs) including gastrointestinal stromal tumors (GISTs) (1-3). For complete surgical *en bloc* resection of gastric SMTs, an adequate safety margin should be secured without injuring the pseudocapsule of the SMTs during resection (1). Laparoscopic gastric surgery has been advanced and standardized worldwide. Furthermore, laparoscopic wedge resection for gastric SMTs has also been reported to be safe, oncologically feasible, and with a decrease in the length of hospital stay and blood loss (4-6). For SMTs with extraluminal growth, laparoscopic wedge resection is easier to detect, however, when they grow in the intra-lumen, identification and determination of appropriate free margin of the SMT from the outside of the stomach is difficult, sometimes resulting in postoperative gastroparesis due to excessive resection, deformity or stenosis of the stomach.

In order to overcome these concerns, Hiki *et al.* first reported laparoscopic and endoscopic cooperative surgery (LECS), currently named classical LECS, for gastric GISTs in 2008 (7). The procedure of classical LECS is as follows: (I) determination of accurate incision line from the endoscopic view; (II) endoscopic submucosal resection around the tumor; (III) artificial perforation of the stomach by endoscopic device along the resection line; (IV) seromuscular dissection by endoscopic or laparoscopic device, (V) removal of the tumor from the abdominal cavity; and (VI) closure of the opened gastric wall with hand-sewn sutures or laparoscopic stapling device (*Figure 1A*). This technique produces an appropriate margin, which is keeping an oncological enough distance from the tumor with minimizing resected stomach. Classical LECS has been reported to be safe and with excellent results (7-13), however, there have been concerns regarding the risks of scattering and seeding of bacterial contamination or tumor cells into the abdominal cavity due to the perforation of the gastric wall.

To avoid these concerns, several modified LECS techniques without exposure of the gastric mucosa were reported. Combination of laparoscopic and endoscopic approaches for neoplasia with non-exposure technique (CLEAN-NET) (14) and Non-exposed endoscopic wall-inversion surgery (NEWS) (15-17) were among the representatives of non-exposure techniques (*Figure 1B,C*). Since we developed the first CLEAN-NET in 2012 (14), only a few reports regarding the results of CLEAN-NET

have been published so far (18-21).

The main scope of this review article is to introduce readers to the clinical application, procedure, and results of the CLEAN-NET, both from previous literatures and from our experience, as well as to offer a closer look at its advantages and limitations while comparing with other LECS procedures, classical LECS, and NEWS.

Procedures of CLEAN-NET

CLEAN-NET is a technique of non-exposure full-thickness gastric wall resection performed under the combination of laparoscopic and endoscopic approaches. The procedure of CLEAN-NET for SMTs is as follows: (I) endoscopic marking around the tumor from the intra-lumen of the stomach; (II) laparoscopic marking around the tumor on the serosa under the assistance of the endoscopic confirmation of the resection line; (III) laparoscopic seromuscular dissection around the tumor along to the resection line; (IV) lifting the tumor toward the abdominal cavity for obtaining definite margin-free resection; (V) full-layer resection with a laparoscopic linear stapling device; (VI) transabdominal retrieval of the specimen wrapped with a collecting bag; and (VII) checking by intraoperative endoscopy after resection (14) [*Figure 1C* (upper); *Figure 2*]. Fujishima *et al.* and Kanehira *et al.* reported a further modified CLEAN-NET technique, altering the final cut-and-closure procedure from stapling full-layer cut-and-closure to stapling only the mucosal layer and adding seromuscular closure by hand-sewn suturing (19,21) [*Figure 1C* (below)].

Outcomes of CLEAN-NET

Published data of the outcomes of the original/modified CLEAN-NET for gastric SMTs are shown in *Table 1*. Previous reports on CLEAN-NET are relatively few, with only a small number of patients included. The total number of patients was 75. The average tumor size was approximately 35 mm. The maximum tumor size was 90 mm, since Kanehira *et al.* included patients who were selected for modified CLEAN-NET even when the tumor was larger than 5cm, or when the base of the tumor included in the gastric wall was less than 5 cm and the tumor was exophytic. The location of the tumors was widely distributed in the stomach including lesions adjacent to esophagogastric junction (EGJ) or the pyloric ring, however, in a report of the largest series, SMTs located adjacent

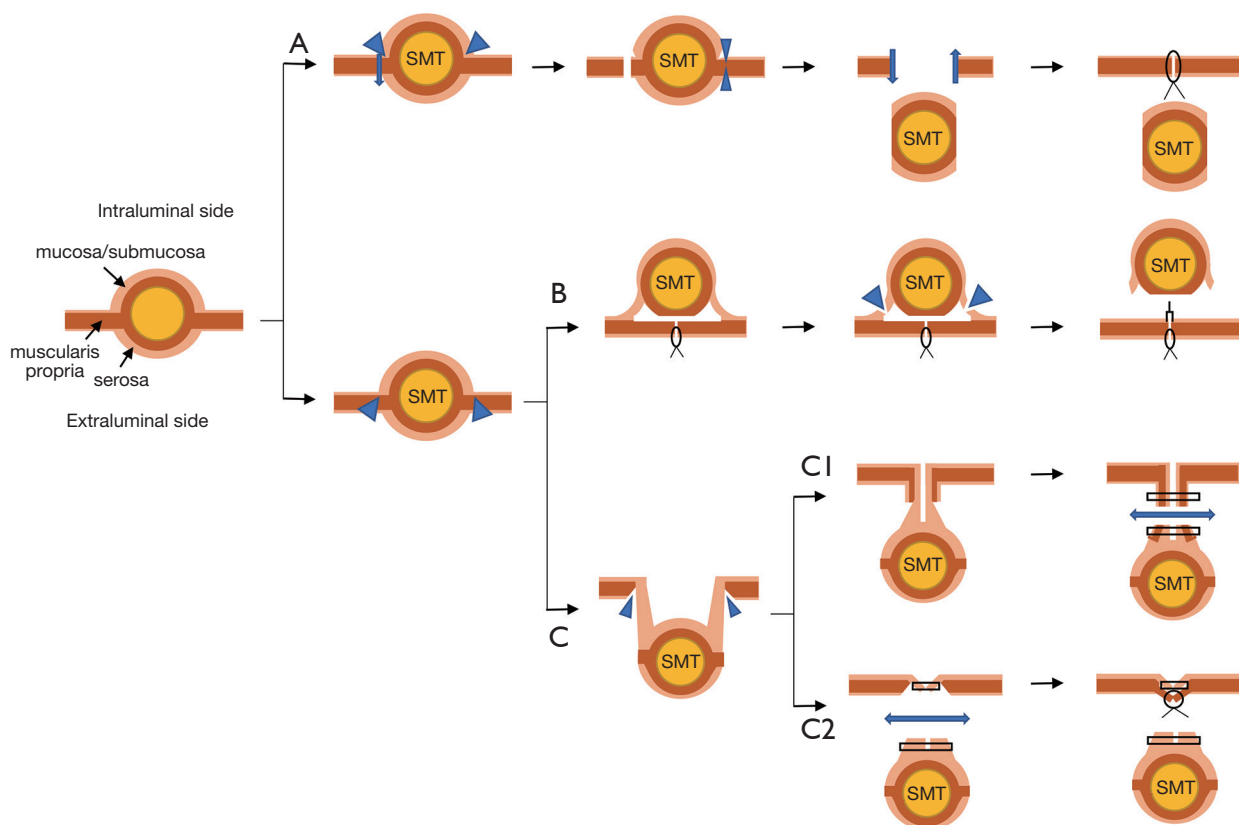


Figure 1 Schema of the procedures: (A) classical LECS (B) NEWS (C1) CLEAN-NET and (C2) modified CLEAN-NET. LECS, laparoscopic and endoscopic cooperative surgery; NEWS, non-exposed endoscopic wall-inversion surgery; CLEAN-NET, combination of laparoscopic and endoscopic approaches for neoplasia with non-exposure technique.

to EGJ were excluded from the indicated criteria (21). The operation time, blood loss, and the length of hospitalization were approximately 120 minutes, 7–8 g, and 6.0 days, respectively. Only 1 case (1.3%), wherein the tumor was located on the posterior wall of the middle stomach, was reported to have a postoperative complication of stenosis (19). Importantly, 50 cases out of a total of 75 cases were GISTs, and all were completely resected and were reported without any recurrences.

Our clinical results of the original CLEAN-NET for gastric SMTs were also shown in *Figure 3* and *Table 2*. These 36 cases included 8 cases from our first published report (14), and had almost the same results as the published results so far. In one patient, postoperative gastroparesis, which needed reoperation (distal gastrectomy), was observed. In this case, the tumor was located on the posterior gastric angle with a 40 mm size and resected with a minimum tumor-free margin by the original CLEAN-NET. Intraoperative endoscopic examination confirmed that the

staple line was distant enough from the pyloric ring and the remnant stomach had a minimal deformity without difficulty in passing the endoscope through the pyloric ring. However, two months after CLEAN-NET, the patient had symptoms of gastroparesis. Postoperative endoscopic examination revealed a delay in the shortening of the distance from the staple line to the pyloric ring caused the poor outflow passage of the stomach (*Figure 4*).

Discussion

The concept of LECS is to resect gastric tumors with both complete curability and preserving organ functions. Similar to classical LECS and NEWS, previous literatures and our series revealed that CLEAN-NET is also a safe and feasible technique while maintaining the concept of LECS. These techniques have the same concept, however, each technique has different and unique manipulations; exposure or non-exposure technique, inversion of the tumor into or outer the

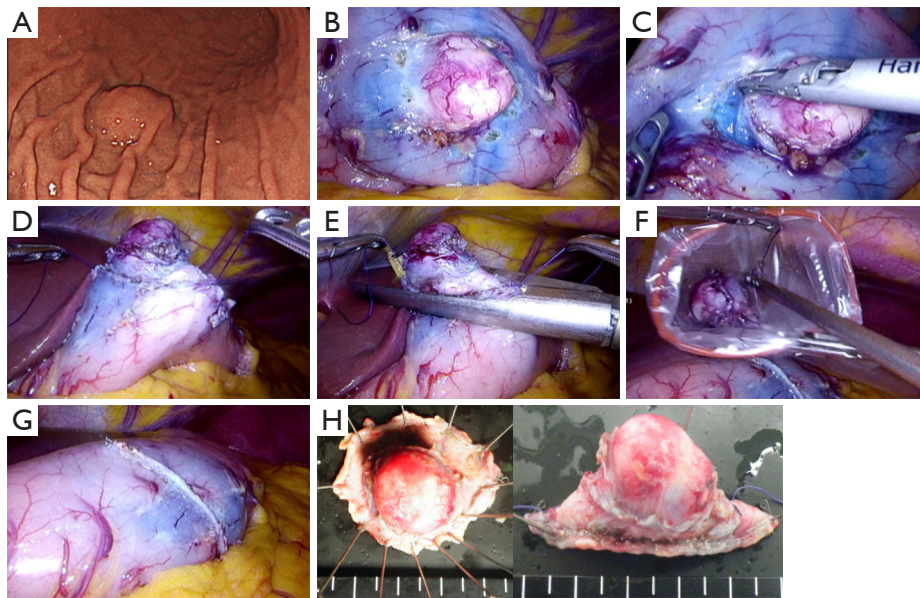


Figure 2 Procedure of CLEAN-NET: (A) preoperative endoscopy showed a 30 mm SMT with intraluminal growth at the greater curvature in the middle stomach; (B) laparoscopic marking around the tumor on the serosa under the assistance of the endoscopic confirmation of the resection line; (C) laparoscopic seromuscular dissection around the tumor along the resection line; (D) lifting the tumor toward the abdominal cavity for obtaining definite margin-free resection; (E) full-layer resection with a laparoscopic linear stapling device; (F) transabdominal retrieval of the specimen wrapped with a collecting bag; (G) checking by intraoperative endoscopy after resection; (H) resected specimen diagnosed as schwannoma having a 23 mm × 20 mm × 18 mm size with free-margin from the tumor. CLEAN-NET, combination of laparoscopic and endoscopic approaches for neoplasia with non-exposure technique; SMT, submucosal tumor.

lumen, retrieval of tumor per oral or through the abdominal cavity, and dominance in the role of the endoscopist or the laparoscopic surgeon.

We herein review and discuss the advantages and limitations of CLEAN-NET in comparison with the characteristics of classical LECS and NEWS.

Patient characteristics

In these series, CLEAN-NET was performed safely on patients over 80 years old or with comorbidities. The operation time, blood loss, and length of hospitalization were acceptable, and no operation-related systemic adverse events occurred. Therefore, it has been concluded that CLEAN-NET is also a minimally invasive and safe procedure similar to classical LECS and NEWS.

Tumor size

Laparoscopic resection of gastric GISTs smaller than 5 cm was reported to be safe when performed by experts (22-24).

In most of these reports, a tumor size of >5 cm was excluded from the indication criteria. Considering the tumor was retrieved per orally, tumor size was limited to <3 cm in NEWS. Meanwhile, since the tumor was retrieved transabdominally in CLEAN-NET, there was no limitation in tumor size. Interestingly, Kanehira *et al.* resected a tumor with 90 mm size and reported that a tumor size of >5 cm is possible to be resected safely if the tumor base included in the gastric wall is <5 cm (21). However, when the size of the resected specimen is >5 cm, even though CLEAN-NET is completed safely, deformity of the remnant stomach may highly occur, leading to postoperative stenosis or gastroparesis. As shown in *Figure 5*, this case was excluded from the indication of CLEAN-NET due to its tumor size and performing of distal gastrectomy (*Figure 5*). Furthermore, from the oncological view, NCCN guidelines and Japanese guidelines state that laparoscopic resection of GISTs >5 cm or GISTs <5 cm with malignant character is not recommended (2,25,26). Therefore, CLEAN-NET can be applied technically for any size of gastric SMTs, however, CLEAN-NET for SMTs >5 cm should be carefully applied

Table 1 Published data of original/modified CLEAN-NET for gastric SMTs

Author & year	No	Tumor size (mm)	Tumor location	Operation time (min)	Growth pattern	Blood loss (g)	Delle (+)	Complete resection rate (%)	Complication	Histology (n)	Length of hospitalization (days)	Recurrence
Inoue <i>et al.</i> 2012 (14)	8	N/A	N/A	N/A	N/A	N/A	N/A	100	N/A	GIST 8	N/A	0
Nabeshima <i>et al.</i> 2015 (18)	2	40	U	202 [†]	N/A	29	2/2	100	0	GIST 2	8	0
Fujishima <i>et al.</i> 2017 (19)	13	37 [¶]	U [‡] 5; M Ant 1; Post 2; Less 1; L 4	128	N/A	16	N/A	100	Stenosis 1	GIST 13	10 [¶]	0
Hajar <i>et al.</i> 2018 (20)	2	45	L, Post	180	Intra	N/A	N/A	100	0	GIST 2	10	0
Kanehira <i>et al.</i> 2019 (21)	50	34.7 [¶]	M Ant 7; Gre 9; Post 6; Less 4; L Ant 7; Gre 8; Post 5; Less 4	105.4 [¶]	N/A	7.5 [¶]	4/50	100	0	GIST 25; leiomyoma 6; schwannoma 10; ectopic pancreas 3; granuloma 3; carcinoid 1; cyst 1	N/A	0

[†], including cholecystectomy; [‡], 4 cases are located <2 cm to EGJ; [§], 2 cases are located <2 cm to pyloric ring; [¶], average. CLEAN-NET, combination of laparoscopic and endoscopic approaches for neoplasia with non-exposure technique; SMTs, submucosal tumors; N/A, not available; U, upper stomach; M, middle stomach; L, lower stomach; Ant, anterior; Gre, greater curvature; Post, posterior; Less, lesser curvature; Intra, intraluminal growth; Extra, extraluminal growth.

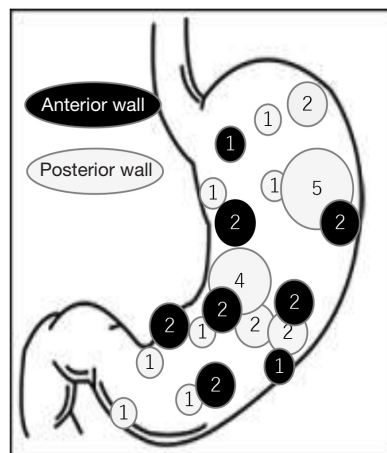


Figure 3 Location of the SMTs performed CLEAN-NET: SMTs were distributed in any lesions of the stomach. Black circle, white circle, and numerals in the circle represented locations on the anterior wall, locations on the posterior wall, and numbers of patients, respectively. CLEAN-NET, combination of laparoscopic and endoscopic approaches for neoplasia with non-exposure technique; SMT, submucosal tumor.

in the view of postoperative dysfunction and oncology.

Location of the tumor

Gastric SMTs located adjacent to EGJ and the pyloric ring, or on the lesser curvature are sometimes technically demanding since it is easier to result in postoperative stenosis in these locations. Classical LECS was reported to be applied for SMTs in these lesions since classical LECS can obtain precise control of the incision line from the inside of the stomach (10). On the other hand, CLEAN-NET for SMTs within a 1cm distance from the EGJ or the pyloric ring might be challenging, since closing the incised seromuscular line by laparoscopic linear stapling device has the potential of excessive loss of the stomach. As mentioned above in the Procedures of CLEAN-NET, Fujishima and Kanehira modified the original CLEAN-NET. Fujishima *et al.* reported that this modified CLEAN-NET, termed serosal and muscular layers incision technique (SAMIT), could resect 6 cases of the gastric SMTs within 2 cm distance from the EGJ or the pyloric ring without any stenosis or stasis (19). By using this modified technique, CLEAN-NET might be applied for SMTs in any lesions. Moreover, in lesions found on the lesser curvature, cut-and-close by using a linear stapling device may sometimes

Table 2 Patients' demographics and clinical results of CLEAN-NET for gastric SMTs (N=36)

Variables	Results
Gender (male/female)	21/15
Age (average, min–max)	59.9 [25–87]
ASA physical status classification (I/II/III/IV/V/VI)	15/21/0/0/0/0
Growth pattern (intraluminal/extraluminal)	33/3
Tumor size (average, min–max)	31.3 [15–63] mm
Dell (+/–)	9/27
Tumor location	Shown in <i>Figure 3</i>
Operation time (average, min–max)	112.7 (30–198) min
Blood loss (average, min–max)	8.7 (0–135) g
Margin negative	36 (100%)
Pathological diagnosis (n)	GIST: 27; schwannoma: 5; aberrant pancreas: 2; leiomyoma: 1; hamartoma: 1
Postoperative complications	1 (2.8%) gastroparesis
Recurrence	0 (0%)
Follow-up period (days)	1,387 [33–3,294]

CLEAN-NET, combination of laparoscopic and endoscopic approaches for neoplasia with non-exposure technique; SMTs, submucosal tumors.

cause severe deformity or damage to the Latarjet branch of the vagal nerve, leading to a delay in gastric emptying. Therefore, when a large-sized tumor is located on the lesser curvature, minimal area of blood vessel manipulation and closure by hand-sewn suturing might solve these concerns.

Tumor location also directly affects the accessibility to the tumor. When the tumor is located on the posterior wall, the laparoscopic approach is somewhat more challenging. Similarly, when the tumor is located in the fornix, procedures which include endoscopic submucosal resection such as classical LECS and NEWS may sometimes be technically demanding.

Delle/ulceration

It is still controversial whether there are risks of bacterial infection and tumor dissemination when gastric content is exposed into the abdominal cavity during manipulation. Mori

et al. reported the possibility of bacterial infection and reduction effect by preoperative saline lavage of the stomach (27), in comparison to a report by Ikehara *et al.* stating that perforation associated with EMR and ESD did not lead to peritoneal dissemination (28). As of present, SMTs with delle/ulceration are considered better to be resected with non-exposure technique.

Growth pattern

When the tumor grows extraluminally, the tumor base on the gastric wall is usually small. In these lesions, laparoscopic simple wedge resection with the linear stapling device has minimal risks of postoperative deformity, and it is easier to perform hence shortening the time of the procedure. Therefore, LECS and LECS-related techniques are not necessary to be applied to SMTs with extraluminal growth. On the contrary, these should be applied to the SMTs with intraluminal growth.

Cost

Both endoscopic dissecting devices and laparoscopic devices are needed for Classical LECS and NEWS, while CLEAN-NET can be completed only by using laparoscopic devices. However, linear stapling devices, which are cost-consuming, must be used for the cut-and-closing procedure in CLEAN-NET, while classical LECS and NEWS can be closed by hand-sewn suturing. When the situations of the tumor are allowed, reducing cost might be a benefit for patients and should be considered.

Technical issue

CLEAN-NET was developed based on the concept that minimizing the resected seromuscular area, not mucosal area, of the stomach may contribute to the minimization of deformity. This concept was the reason why most of the approaches were done from the outside of the stomach (seromuscular dissection, cutting, and closing), and the process of lifting-up the lesion, which allows minimum resection of the seromuscular area with a wide mucosal tumor-free margin, reflects this concept.

The procedure of cut-and-closing by linear stapling device in CLEAN-NET results easier and reduced procedure time compared to other techniques. In addition, other LECS and LECS-related procedures require endoscopists to be familiar with the endoscopic treatment

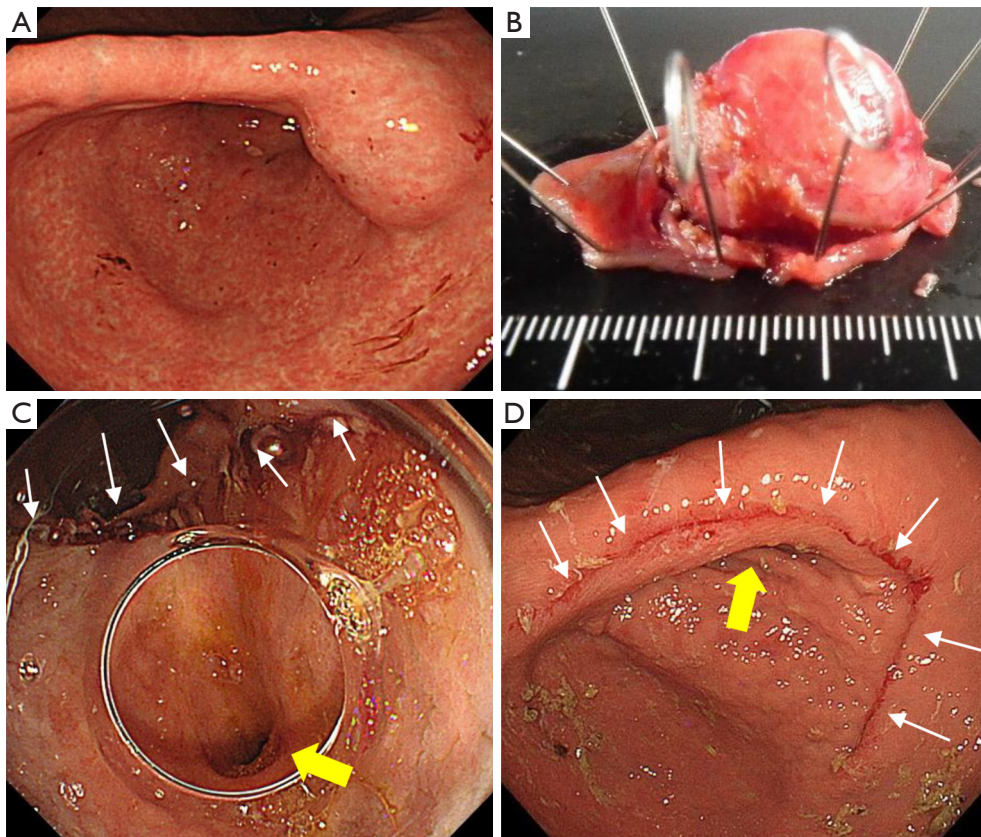


Figure 4 A case of postoperative gastroparesis after CLEAN-NET: (A) A 40 mm × 40 mm size intraluminal growth GIST was located on the posterior gastric angle; (B) GIST was resected with a minimum tumor-free margin by CLEAN-NET; (C) intraoperative endoscopy confirmed that the staple line (white arrow) was distant enough from the pyloric ring (yellow arrow) and remnant stomach had minimal deformity; (D) endoscopic examination after 2 months revealed a delayed shortening of the distance from staple line (white arrow) to the pyloric ring (yellow arrow), leading to postoperative gastroparesis. CLEAN-NET, combination of laparoscopic and endoscopic approaches for neoplasia with non-exposure technique; GIST, gastrointestinal stromal tumor.



Figure 5 A case of SMT excluded from the indication criteria of CLEAN-NET: (A) Endoscopic view showed a large 70 mm SMT, located at the lower stomach with delle; (B) CT scan also showed a large 70 mm SMT with intraluminal growth; (C) distal gastrectomy was selected to avoid strong deformity after CLEAN-NET. Pathological diagnosis was schwannoma. SMT, submucosal tumor; CLEAN-NET, combination of laparoscopic and endoscopic approaches for neoplasia with non-exposure technique.

Table 3 Characteristics of laparoscopic simple wedge resection, classical LECS, NEWS and CLEAN-NET

Variables	Factors	Laparoscopic Simple wedge resection	Classical LECS	CLEAN-NET (modified CLEAN-NET)	NEWS
Procedures	Operators' role	Lap only	End = Lap	Endo < Lap	Endo ≥ Lap
	Artificial perforation of the gastric wall	Not required	Required	Not required	Not required
	Resection	Excessive resection of the mucosa and serosa	Accurate and minimum	Excessive resection of the mucosa	Accurate and minimum
	Closing technique	Linear stapler	Linear stapler or hand-sewed suturing	Linear stapler (+ hand-sewed suturing)	Hand-sewed suturing and Endoscopic closure
	Removal route	Transabdominal	Transabdominal	Transabdominal	Transoral
	Complexity of procedures	Very simple	A little complicated	Simple	Complicated
	Procedure of time	Very short	Short – moderate	Short	Longer
	Cost/Manpower	Small	Indispensable	Indispensable	Indispensable
Indications	Tumor size	≤50 mm	≤50 mm	≤50 mm	≤30 mm
	Tumor location	Any lesion	Any lesion	Except EGJ or pyloric ring (any lesion)	Any lesion
	Delle/ulceration	Applicable	Not applicable	Applicable	Applicable
	Tumor growth pattern	Extraluminal	Intraluminal	Intraluminal	Intraluminal
	Indications for cancers	Yes	No	Yes	Yes

Lap, laparoscopists; End, endoscopists; LECS, laparoscopic and endoscopic cooperative surgery; NEWS, non-exposed endoscopic wall-inversion surgery; CLEAN-NET, combination of laparoscopic and endoscopic approaches for neoplasia with non-exposure technique.

including submucosal resection (ESD), therefore, CLEAN-NET may be easier for the introduction and standardization of LECS procedures.

Summary of characteristics of classical LECS, NEWS, and CLEAN-NET were shown in *Table 3*.

A further direction of CLEAN-NET

For gastric cancers, regardless of the improvement of the ESD technique, there still remains lesions which are technically difficult to complete ESD due to the tumor locations or non-lifting lesions with severe scars. When the lesions meet the inclusion criteria of ESD, LECS with non-exposure technique is applied in some limited institutions. Inoue *et al.* (14) and Goto *et al.* (29) reported the results and possibility of applying CLEAN-NET and NEWS for early gastric cancers, respectively. In the recent years, favorable results of minimally invasive function-preserving gastrectomy with sentinel lymph node navigation surgery have been reported (30-34). Perhaps in

the near future, sentinel lymph node navigation surgery may be established, and a tailored minimally invasive surgery can be provided.

Conclusions

CLEAN-NET is one of the safe and feasible LECS-related procedures with a non-exposure technique for gastric SMTs. In selecting a procedure, familiarization with the characteristics (indications, procedural pitfalls, advantages and limitations) of each procedure is important to secure the curability and postoperative function, and it may provide further applications of LECS procedures.

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Footnote

Conflicts of Interest: H Inoue is an advisor of Olympus Corporation and Top Corporation. He has also received educational grants from Olympus Corp., and Takeda Pharmaceutical Co. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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