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Review Article

Recent development of innovative resection methods for gastric neoplasms using hybrid natural orifice transluminal endoscopic surgery approach

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ABSTRACT

There have been an evolutionary development with respect to the resection modality for the treatment of the gastric neoplasms such as gastric subepithelial tumors (SETs) or early gastric cancers (EGCs). Hybrid natural orifice transluminal endoscopic surgery (hybrid NOTES) played a central role in the process of development. In the earlier period, the non-exposure type hybrid NOTES such as laparoscopy and endoscopy cooperative surgery (LECS), endoscope-assisted wedge resection (EAWR), and laparoscopy-assisted endoscopic full-thickness resection (LAEFTR) has been introduced by several investigators. However, a concern about a spillage of gastric content including the tumor cells has been continuously raised among the clinicians. Accordingly, the non-exposure type hybrid NOTES such as combination of laparoscopic and endoscopic approaches to neoplasia with a non-exposure technique (CLEAN-NET), non-exposed endoscopic wall-inversion surgery (NEWS), and hybrid neo-endoscopic full-thickness resection (hybrid neo-EFTR) have been developed to the clinicians. Although most of studies about hybrid NOTES for the treatment of the gastric neoplasms have a small number of patients and require further validations, those are enough to receive our attention. Here, we describe and summarize the development process of the innovative resection methods for gastric neoplasms using hybrid NOTES approach.

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Keywords: Endoscopy; Gastric neoplasms; Laparoscopy; Natural orifice transluminal endoscopic surgery

Introduction

There has been an outstanding development in the minimally invasive treatment of gastric neoplasms in recent decades. Many innovative resection methods have been suggested on the strength of the new developing operative tools.¹ The same goal of them is the precise resection of the primary gastric neoplasms adhering to oncologic principle and minimizing unnecessary resection of the normal tissue around the neoplasms.

Hybrid approach using both laparoscopic and endoscopic devices is closest to achieving the above-mentioned goal in the resection of the gastric neoplasms. The strength of endoscopic inspection lies in the definite visualization of the tumor's margin. With the aid of laparoscopic approach, the compact closure and essential support to the endoscopic resection are possible. Finally, the simultaneous manipulations of laparoscopic and endoscopic devices enables the treatment team to gain optimal resection than the manipulation with only one of them.

This review article will describe the recent process of development of emerging resection methods using endoscopic and laparoscopic cooperative approach for the gastric neoplasms and compare the differences of them. I will describe in order of the exposure type and the non-exposure type as shown in Table 1.

Exposure Type Hybrid Natural Orifice Transluminal Endoscopic Surgery (Hybrid NOTES)

Laparoscopy and endoscopy cooperative surgery (LECS)

Hiki et al² introduced LECS method to resect gastric subepithelial tumors for the first time. This method is consisted of tumor localization, laparoscopic blood vessel preparation in the excision area, endoscopic submucosal resection around the tumor, and finally laparoscopic seromuscular dissection. LECS has been demonstrated to be feasible and safe in the subsequent studies. In a retrospective study performed by Qiu et al,³ 69 patients with gas-

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Table 1 The Newly Developed Resection Methods for the Gastric Tumors Using Hybrid NOTES

Type	Resection methods
A. Exposure type	LECS EAWR LAEFTR
B. Non-exposure type	CLEAN-NET NEWS Hybrid neo-EFTR

NOTES, natural orifice transluminal endoscopic surgery; LECS, laparoscopy and endoscopy cooperative surgery; EAWR, endoscope-assisted wedge resection; LAEFTR, laparoscopy-assisted endoscopic full-thickness resection; CLEAN-NET, combination of laparoscopic and endoscopic approaches to neoplasia with a non-exposure technique; NEWS, non-exposed endoscopic wall-inversion surgery; Hybrid neo-EFTR, hybrid neo-endoscopic full-thickness resection.

gastric gastrointestinal stromal tumors underwent LECS (laparoscope-assisted endoscopic resection [LAER] in 5 patients, endoscope-assisted wedge resection [EAWR] in 64 patients), with a median follow-up of 35 months. The mean operating times in the two methods were 81.6 minutes and 86.3 minutes, respectively ($P = 0.776$). There were two complications after surgery, a leakage along the suture line in one patient and an intraluminal bleeding in another patient which were resolved by endoscopic and conservative treatment. During follow-up, all enrolled patients were disease-free and postoperative mortality did not occur. More recently, a multicenter retrospective study with a large number of patients was published. LECSs were carried out for 126 patients with gastric subepithelial tumors (SETs) in eight medical centers at Japan. The mean operation time was 190.2 minutes. The procedure was converted to open surgery in two patients, because there were intra-abdominal adhesions or stenosis (1.6%). Leakage and gastric stasis occurred in 1 and 1 patient, respectively. And, there was no major bleeding. This study showed that the results were excellent and the LECS procedure could be successfully implanted in a real clinical circumstance.⁴ For the gastric SETs located at esophagogastric junction, it was reported that the LECS could be performed without significant problems. Hoteya et al⁵ reported the results of LECS performed for 25 patients, in which 5 patients with esophagogastric junction tumors were included. There were no significant difference in outcomes between esophagogastric junction neoplasms and the others.

Although LECS have been proved to prevent an excessive resection of the stomach with tumors, whether the gastric motility would be preserved has not been well-known. In a single center study carried out Waseda et al,⁶ two of 22 patients who underwent LECS experienced a clinically relevant gastric dysmotility, which was evaluated by endoscopy and a new onset of symptoms. Importantly, the tumors of these two patient were located in lesser curvature. The authors explained that this result could be explained by the innervation of vagus nerve at the lesser curvature of the stomach. However, there have been few reports to investigate the motility of residual stomach by an objective measurement such as manometry or gastric emptying study after the LECS procedure. The objective estimation of gastric motility after LECS remains to be determined in the future prospective studies.

Several studies about comparison of the LECS to the conventional laparoscopic resection were published.^{7,8} They have reported that the mean operation time of the LECS was significantly longer than conventional laparoscopic resection and the amount of blood loss was lower than conventional laparoscopic resection.

Importantly, the feasibility and safety of the LECS was kept when it was performed for the gastric SETs less than 5 cm.

The cases of single port laparoscopic approach for the LECS were introduced in previous studies.^{9,10} However, laparoscopic manipulation only with a single port is not easy and could not be adequate when the tumors are located at difficult sites to be approached from laparoscopic insertion sites such as the posterior wall or the remote sites from the laparoscopy. The additional studies to resolve these problems should be needed for clinical application.

EAWR

EAWR is a similar resection method with the LECS, except an endoscopy has only supportive roles including the identification of the tumor location and complications after the surgery and the assistance to laparoscopic resection. As for the LECS, EAWR was reported to be feasible and safe in previous studies.¹¹⁻¹³ Because the laparoscopic seromuscular dissection and suturing in the LECS is a time-consuming step, EAWR could be selected for the gastric neoplasms which are easy to access and resected without the endoscopic resection modalities.

Laparoscopy-assisted endoscopic full-thickness resection (LAEFTR)

LAEFTR has a great difference from the previously mentioned exposure type hybrid NOTES in that LAEFTR is finished by laparoscopic suturing, not by stapler. In addition, the role of an endoscopist is more important than the two techniques, because the partial full-thickness resection of the gastric wall should be performed by an endoscopists. In 2008 and 2009, Abe et al^{14,15} reported the two publications about LAEFTR for the patients with gastric SETs and early gastric cancers (EGCs). By LAEFTR, more meticulous resection was possible with a strength of endoscopic manipulation. The following studies demonstrated that LAEFTR was feasible and safe and it could be a excellent option as an alternative therapy for the gastric neoplasms.¹⁶⁻¹⁸ Although the role of an endoscopist was increased compared with previous exposure type methods, the learning and adaptation to this method was not difficult to an endoscopist. For an skilled therapeutic endoscopist, LAEFTR is accessible to learn and apply in a clinical circumstance.

Non-Exposure Type Hybrid NOTES

Non-exposure type resection methods for the gastric neoplasms have been introduced in recent decades; combination of laparoscopic and endoscopic approaches to neoplasia with a non-exposure technique (CLEAN-NET), non-exposed endoscopic wall-inversion surgery (NEWS), and hybrid neo-endoscopic full-thickness resection (hybrid neo-EFTR). The above-mentioned resection techniques can't help opening the inner side of the stomach into the peritoneal cavity, which could theoretically increase the risk of peritoneal seeding of the tumor cells, even if the cases with peritoneal seeding or intraperitoneal metastasis due to these resection methods have not been yet. Therefore, several investigators developed the non-exposure type resection techniques for the gastric neoplasms including epithelial and SETs.

CLEAN-NET

The CLEAN-NET is composed of several steps as follows; (A) endoscopic localization and marking of the tumor, (B) laparoscopic localization of the tumor, (C) laparoscopic seromuscular

dissection of the tumor, (D) laparoscopic retraction of the tumor and stapling at the outside of the seromuscular dissection line, (E) cutting of the tumor with stapler, and then (F) completely resected lesion with nodes.^{19,20} The CLEAN-NET was the first method that enabled to resect the stomach without exposure of the tumor to a peritoneal cavity. However, the range of resection made by a stapler inevitably becomes wider than the laparoscopic seromuscular dissection area created along the endoscopic marking spots, which always induce an unnecessary resection around the tumors. Therefore, the CLEAN-NET is hard to apply to the gastric neoplasms located in the antrum or the esophagogastric junction area.

NEWS

A new non-exposure resection method was introduced with an *ex vivo* porcine stomach model, which was called as the NEWS.²¹ After endoscopic marking for an imaginary tumor, a seromuscular dissection was performed laparoscopically. And then, laparoscopic suturing of muscular layer was done while inner dissected tumor was inverted into gastric lumen. At last, the tumor was resected by an endoscopic muco-submucosal incision.

Mitsui et al²² published a case series of the NEWS procedure for six patients diagnosed as gastric SETs for the first time. In first three cases, perforation occurred during the procedure and conversion to open surgery was done in one patient. And, the mean operation time were quite long (296 minutes; range, 140–397 minutes).

The NEWS is similar with the CLEAN-NET in that laparoscopic seromuscular dissection should be done before the tumor is resected. However, in the NEWS, the tumor is finally resected by endoscopic dissection with endoscopic knives, that is the greatest difference from the CLEAN-NET procedure. This shows that the NEWS is superior to the CLEAN-NET with respect to the optimal resection without an unnecessary resection of normal gastric structure around the tumors. Because the resection by endoscopic knives under endoscopic view is the method to give the most-delicate resection margin.

At first, the NEWS was tried to the patients with gastric SETs. After several years, Goto et al²³ reported a first case of applying the NEWS with sentinel node basin dissection to a patient diag-

nosed as EGC. Because a theoretical background about sentinel node navigation around the stomach has been made by several prospective studies, the NEWS to EGCs is anticipated to be more actively applied to the patients with EGCs in the near future.

Hybrid neo-EFTR

Kim et al²⁴ suggested another new method using *in vivo* pig model, which was a kind of non-exposure endolaparoscopic full-thickness resection. The most important difference of this technique from CLEAN-NET or NEWS was that laparoscopic seromuscular suturing was performed without laparoscopic seromuscular dissection. After seromuscular suturing on serosal side with a barbed suturethread (V-Loc), the endoscopic full-thickness resection using conventional endoscopic knives was done at an inverted gastric wall including an imaginary tumor. Finally, this procedure was terminated by an endoscopic mucosal suture with endoloops and clips.

This resection modality deserves to receive attention, because it has more advantageous points than other non-exposure techniques. First, this method is simple and easy. Laparoscopic seromuscular dissection and suturing using in the process of CLEAN-NET and NEWS techniques are time-consuming and difficult steps. A mean operation time of NEWS technique was more than 3 hours, which was quite longer than the time for this method (137.0 ± 28.2 minutes). Second, this method has little risk of perforation, compared with the other techniques. However, several limitations should be overcome. A number of procedures was very small, and the procedure was performed in the same location (body of the stomach). A long-term morbidity was not sufficiently evaluated. Finally, clips and endoloops are quite consumed than the other resection methods. The feasibility and efficacy should be investigated in a further prospective study with a setting of multicenter.

Conclusion: The Future and Perspective of Hybrid NOTES in the Treatment of Gastric Neoplasms

Until now, innovative surgeons and therapeutic endoscopists have been developing a various types of resection modalities for the gastric neoplasms, of which the characteristics were sum-

Table 2 The Comparison of Detailed Steps among the Newly Developed Resection Methods

Name of method	Inspection of the tumor	Endoscopic manipulation	Laparoscopic manipulation	Closure	Resection margin
LECS	Endoscopy & laparoscopy	Submucosal dissection	Seromuscular dissection	Stapler	Along stapler and submucosal dissection lining
EAWR	Endoscopy & laparoscopy	Only supportive	Full-thickness resection by stapler		Along stapler
LAEFTR	Endoscopy & laparoscopy	Submucosal dissection followed by partial full-thickness resection	Partial full-thickness resection	Suture after resection	Along submucosal dissection lining
CLEAN-NET	Endoscopy & laparoscopy	Submucosal injection and localization	Seromuscular dissection and full-thickness resection by stapler		Outside of seromuscular dissection lining
NEWS	Endoscopy & laparoscopy	Muco-submucosal resection of an inverted tumor	Seromuscular dissection followed by suturing	Suture before resection	Along submucosal resection lining
Hybrid neo-EFTR	Endoscopy & laparoscopy	Submucosal dissection followed by full-thickness resection	Suturing of seromuscular layer	Endoscopically and laparoscopically	Along submucosal dissection lining

LECS, laparoscopy and endoscopy cooperative surgery; EAWR, endoscope-assisted wedge resection; LAEFTR, laparoscopy-assisted endoscopic full-thickness resection; CLEAN-NET, combination of laparoscopic and endoscopic approaches to neoplasia with a non-exposure technique; NEWS, non-exposed endoscopic wall-inversion surgery; Hybrid neo-EFTR, hybrid neo-endoscopic full-thickness resection.

marized in Table 2. The goal of these modalities is to achieve the optimal resection; minimizing the normal gastric structure around the tumor, preserving the function of the stomach, and keeping the oncologic safety. Apart from the other malignancies, the neoplasms of gastrointestinal tracts could be treated by both endoscopic and surgical approach. Especially, the gastric neoplasms could be more accessible with these manners than the neoplasms of the other gastrointestinal tracts. When we look back the history of development in the innovative resection modalities for the gastric neoplasms, the role of endoscopists has been reinforced to identify the exact resection margin and to resect partially or totally the gastric wall around the tumor. Sometimes, conflicts about which modality would be more appropriate might occur between endoscopists and surgeons. Hybrid NOTES will definitely resolve the uncertainty about therapeutic choice between surgical and endoscopic approach.

In the future, because the need for minimal invasive surgery is accordingly increasing, the hybrid NOTES will be focused as an important alternative for the gastric neoplasms. The non-exposure type resection methods would be regarded as more reasonable option than the exposure type resection methods. However, several limitations remain to be determined in all of these modalities; the longer resection times, the need of both endoscopist and surgeon, the coverage of insurance, lack of long-term morbidity and oncologic follow-up results, and the suggestion of education. Regardless of these limitations, both endoscopists and surgeons should pay more attention to the treatment with hybrid NOTES approach, because they are one of the closest options to the optimal treatment of the gastric neoplasms.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

References

- Ntourakis D, Mavrogenis G. Cooperative laparoscopic endoscopic and hybrid laparoscopic surgery for upper gastrointestinal tumors: current status. *World J Gastroenterol.* 2015;21:12482-97.
- Hiki N, Yamamoto Y, Fukunaga T, Yamaguchi T, Nunobe S, Tokunaga M, et al. Laparoscopic and endoscopic cooperative surgery for gastrointestinal stromal tumor dissection. *Surg Endosc.* 2008;22:1729-35.
- Qiu WQ, Zhuang J, Wang M, Liu H, Shen ZY, Xue HB, et al. Minimally invasive treatment of laparoscopic and endoscopic cooperative surgery for patients with gastric gastrointestinal stromal tumors. *J Dig Dis.* 2013;14:469-73.
- Matsuda T, Nunobe S, Kosuga T, Kawahira H, Inaki N, Kitashiro S, et al; Society for the Study of Laparoscopy and Endoscopy Cooperative Surgery. Laparoscopic and luminal endoscopic cooperative surgery can be a standard treatment for submucosal tumors of the stomach: a retrospective multicenter study. *Endoscopy.* 2017;49:476-83.
- Hoteya S, Haruta S, Shinohara H, Yamada A, Furuhashi T, Yamashita S, et al. Feasibility and safety of laparoscopic and endoscopic cooperative surgery for gastric submucosal tumors, including esophagogastric junction tumors. *Dig Endosc.* 2014;26:538-44.
- Waseda Y, Doyama H, Inaki N, Nakanishi H, Yoshida N, Tsuji S, et al. Does laparoscopic and endoscopic cooperative surgery for gastric submucosal tumors preserve residual gastric motility? Results of a retrospective single-center study. *PLoS One.* 2014;9:e101337.
- Namikawa T, Hanazaki K. Laparoscopic endoscopic cooperative surgery as a minimally invasive treatment for gastric submucosal tumor. *World J Gastrointest Endosc.* 2015;7:1150-6.
- Kawahira H, Hayashi H, Natsume T, Akai T, Uesato M, Horibe D, et al. Surgical advantages of gastric SMTs by laparoscopy and endoscopy cooperative surgery. *Hepatogastroenterology.* 2012;59:415-7.
- Obuchi T, Sasaki A, Baba S, Nitta H, Otsuka K, Wakabayashi G. Single-port laparoscopic and endoscopic cooperative surgery for a gastric gastrointestinal stromal tumor: report of a case. *Surg Today.* 2015;45:641-6.
- Sasaki A, Koeda K, Nakajima J, Obuchi T, Baba S, Wakabayashi G. Single-incision laparoscopic gastric resection for submucosal tumors: report of three cases. *Surg Today.* 2011;41:133-6.
- Kang WM, Yu JC, Ma ZQ, Zhao ZR, Meng QB, Ye X. Laparoscopic-endoscopic cooperative surgery for gastric submucosal tumors. *World J Gastroenterol.* 2013;19:5720-6.
- Privette A, McCahill L, Borrazzo E, Single RM, Zubarik R. Laparoscopic approaches to resection of suspected gastric gastrointestinal stromal tumors based on tumor location. *Surg Endosc.* 2008;22:487-94.
- Novitsky YW, Kercher KW, Sing RF, Heniford BT. Long-term outcomes of laparoscopic resection of gastric gastrointestinal stromal tumors. *Ann Surg.* 2006;243:738-45; discussion 745-7.
- Abe N, Takeuchi H, Yanagida O, Masaki T, Mori T, Sugiyama M, et al. Endoscopic full-thickness resection with laparoscopic assistance as hybrid NOTES for gastric submucosal tumor. *Surg Endosc.* 2009;23:1908-13.
- Abe N, Mori T, Takeuchi H, Ueki H, Yanagida O, Masaki T, et al. Successful treatment of early stage gastric cancer by laparoscopy-assisted endoscopic full-thickness resection with lymphadenectomy. *Gastrointest Endosc.* 2008;68:1220-4.
- Cho WY, Kim YJ, Cho JY, Bok GH, Jin SY, Lee TH, et al. Hybrid natural orifice transluminal endoscopic surgery: endoscopic full-thickness resection of early gastric cancer and laparoscopic regional lymph node dissection—14 human cases. *Endoscopy.* 2011;43:134-9.
- Hur H, Lim SG, Byun C, Kang JK, Shin SJ, Lee KM, et al. Laparoscopy-assisted endoscopic full-thickness resection with basin lymphadenectomy based on sentinel lymph nodes for early gastric cancer. *J Am Coll Surg.* 2014;219:e29-37.
- Lim SG, Hur H, Han SU, Lee KM, Kang JK, Shin SJ, et al. Laparoscopy-assisted endoscopic full-thickness resection for gastric subepithelial tumors originated from the muscularis propria layer: a pilot study with literature review. *Scand J Gastroenterol.* 2017;52:257-63.
- Inoue H, Ikeda H, Hosoya T, Yoshida A, Onimaru M, Suzuki M, et al. Endoscopic mucosal resection, endoscopic submucosal dissection, and beyond: full-layer resection for gastric cancer with nonexposure technique (CLEAN-NET). *Surg Oncol Clin N Am.* 2012;21:129-40.
- Shiwaku H, Inoue H, Minami H, Satodate H, Kudo SE. M1605: clinical experience of full-thickness resection (CLEAN-NET: combination of laparoscopic and endoscopic approaches to neoplasia with non-exposure technique) for early gastric cancer with severe scar. *Gastrointest Endosc.* 2010;71:AB265.
- Goto O, Mitsui T, Fujishiro M, Wada I, Shimizu N, Seto Y, et al. New method of endoscopic full-thickness resection: a pilot study of non-exposed endoscopic wall-inversion surgery in an ex vivo porcine model. *Gastric Cancer.* 2011;14:183-7.
- Mitsui T, Niimi K, Yamashita H, Goto O, Aikou S, Hatao F, et al. Non-exposed endoscopic wall-inversion surgery as a novel partial gastrectomy technique. *Gastric Cancer.* 2014;17:594-9.
- Goto O, Takeuchi H, Kawakubo H, Sasaki M, Matsuda T, Matsuda S, et al. First case of non-exposed endoscopic wall-inversion surgery with sentinel node basin dissection for early gastric cancer. *Gastric Cancer.* 2015;18:434-9.
- Kim CG, Yoon HM, Lee JY, Cho SJ, Kook MC, Eom BW, et al. Nonexposure endoscopic full-thickness resection with simple suturing technique. *Endoscopy.* 2015;47:1171-4.