

## Nonexposed wall-inversion surgery as a novel local resection method for neoplasms in the gastrointestinal tract

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### ABSTRACT

Nonexposed wall-inversion surgery was invented for the treatment of node-negative gastrointestinal tumors that are difficult to be resected using the endoluminal approach alone. The advantages of this surgery include 1. full-thickness resection procedure of gastrointestinal wall with minimum necessary tumor-negative margins and 2. less risk of bacterial contamination and tumor seeding into the abdominal cavity. We conducted a PubMed search to select relevant articles published until the end of October 2019 for pooled case analyses using the keyword “nonexposed wall-inversion surgery;” Based on our search, we enrolled the data of 88 gastric lesions and 1 duodenal lesion retrieved from 7 case report articles and 4 original articles of clinical cases. The gastric lesions consisted of 59 gastrointestinal stromal tumors, 7 ectopic pancreases, 5 leiomyomas, 3 early gastric cancers, and 14 others, with a mean maximal tumor diameter of 25.0 mm. In 5 lesions (5.7%), intraoperative perforation was performed, and 2 lesions (2.3%) were retrieved by the transabdominal route. All 4 major postoperative complications (4.5%) were managed without resurgical interventions. The duodenal case, neuroendocrine tumor, measuring 13 mm in size, was curatively resected without complications. Nonexposed wall-inversion surgery appears to be an acceptable treatment for node-negative gastric and duodenal tumors; however, further accumulation of cases is necessary to confirm the feasibility.

**Keywords:** laparoscopy and endoscopy cooperative surgery, submucosal tumor, early gastrointestinal neoplasm, full-thickness resection, local resection

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### INTRODUCTION

According to the National Database (NDB) released by the Ministry of Health, Labor and Welfare, the number of esophagogastroduodenoscopies (EGDs) performed under the coverage of national medical insurance is approximately 9 million per year in Japan.<sup>1</sup> Opportunistic screening of diseases in the upper gastrointestinal (GI) tract by EGD has been well accepted as a medical checkup for decades, and, additionally, EGD was introduced as a measure of population-based mass screening of gastric cancer in 2016 in our country. These easy accessibilities to EGD

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enable the detection of upper GI tumors at a very early stage in the majority of cases. Under these circumstances, novel endoscopic resection (ER) methods such as polypectomy, endoscopic mucosal resection, and endoscopic submucosal dissection (ESD) were introduced for treating gastric tumors in Japan that spread gradually for treating other GI organs and also across the world to avoid radical surgery.

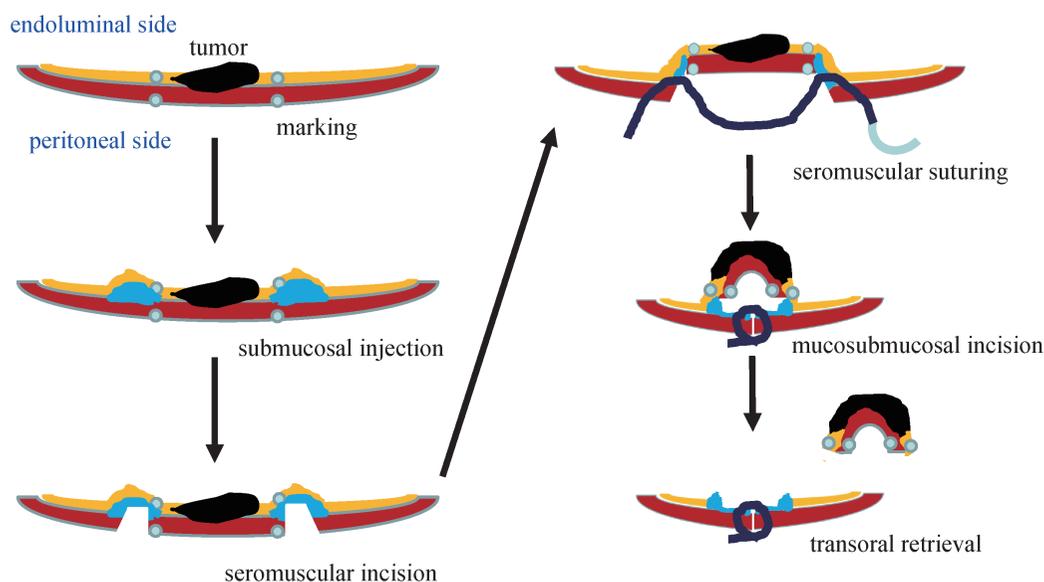
In principle, ER can be applied as a minimal invasive and organ-preserving treatment for GI tumors with the negligible risk of lymph node metastases. However, in a substantial number of these tumors, we have to give up performing ER due to technical difficulty and select surgical resection (SR), especially for subepithelial tumors such as gastrointestinal stromal tumors (GISTs). In this situation, tumors with a large amount of non-neoplastic surrounding tissue are commonly resected, such as by distal gastrectomy, according to the judgment of the operators, because of the lack of an established standard surgical method for local resection. To bridge the huge gap between ER and SR in terms of invasiveness and postoperative quality of life, laparoscopic and endoscopic cooperative surgery (LECS) was recently innovated as a novel treatment for gastric tumors and is currently applied to tumors in other GI organs.<sup>2</sup>

Although “LECS” reminds us of any type of abdominal treatments that use laparoscopy and endoluminal endoscopy, this approach essentially stands for local full-thickness resection of GI wall, which combines the techniques of laparoscopic surgery and ESD. As of 2019, 5 representative LECS procedures are established as shown Table 1.<sup>2-6</sup>

Among those LECS procedures, the nonexposed endoscopic wall-inversion surgery (NEWS) was reported by one of the authors (M.F.) and his colleagues as a novel full-thickness resection procedure with minimum necessary tumor-negative margins and less risk of bacterial contamination and tumor seeding into the abdominal cavity.<sup>3</sup> The specific procedure is described herein. After marking the mucosal and serosal side, circumferential seromuscular incisions are made laparoscopically. The seromuscular layers are linearly sutured, with the lesion inverted inward the stomach. Then, circumferential muco-submucosal incisions are made by using endoluminal endoscope. Finally, the specimen is retrieved perorally (Figure 1). In this article, we summarize the outcomes of NEWS as a systemic review of literature.

**Table 1** Representative LECS procedures

Procedure	Authors	Year	Lesion size in short axis	Intentional perforation	Retrieval route	Suturing
Classical LECS <sup>1)</sup>	Hiki et al	2008	< 5 cm	Present	Trans abdominal	Mechanical suturing device or Hand suturing
NEWS <sup>2)</sup>	Goto et al	2011	< 3 cm	Absent	Trans oral	Hand suturing
CLEAN-NET <sup>3)</sup>	Inoue et al	2012	< 3 cm	Absent	Trans abdominal	Mechanical suturing device
Inverted LECS <sup>4)</sup>	Nunobe et al	2012	< 5 cm	Present	Either trans abdominal or oral	Mechanical suturing device or Hand suturing
Closed LECS <sup>5)</sup>	Kikuchi et al	2017	< 3 cm	Absent	Trans oral	Hand suturing



**Fig. 1** Schema of NEWS procedure

## METHODS

PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) was used to conduct electronic searches of the literature. The search included all English language entries published until the end of October 2019. The following keyword was used in all fields: “nonexposed wall-inversion surgery.” One reviewer (M.F.) selected the relevant articles according to the following criteria: whether they enrolled patients who underwent NEWS and whether they reported the efficacy or safety of NEWS, irrespective of the study’s country of origin. Case report articles were also selected when the lesion characteristics and the treatment outcomes were clearly described. Full text of the selected articles was carefully assessed to determine whether they were eligible for inclusion in this review. When the same cases from a single research group were reported in multiple publications and could be identified individually, duplicated cases were enrolled once in the analyses. When it is impossible to identify the cases individually, only the study involving the largest cohort was included in the analysis.

The following data were extracted from the eligible articles: the country of origin; age and gender of patients; location, size, and histology of lesions; completeness of the NEWS procedure; operation time; intraoperative and postoperative complications; and hospital stay. Accordingly, the efficacy and safety of the pooled cases that underwent NEWS were investigated.

## RESULTS

A total of 26 articles were selected automatically by the PubMed search using the keyword “nonexposed wall-inversion surgery,” which were categorized as 7 case report articles (4 Japan, 2 Thailand, and 1 South Korea), 4 original articles of clinical cases (3 Japan and 1 Czech Republic), 2 original articles of porcine models, 12 review articles, and 1 non-English article after reading the abstracts.

**Table 2** Characteristics of 89 lesions in 88 patients with non-exposed endoscopic wall-inversion surgery

Age (years), mean (range)		61.6 (17–85)	
Sex, n (%) *			
	Male	49 (55.7)	
	Female	39 (44.3)	
Country of origin, n (%)			
	Japan	76 (85.4)	
	Czech republic	10 (11.2)	
	Thailand	2 (2.2)	
	South Korea	1 (1.1)	
Lesion location: n (%)			
	Upper third	54 (60.7)	
	Middle third	24 (27.0)	
	Lower third	10 (11.2)	
	Duodenum	1 (1.1)	
Circumference, n (%)			
	Anterior wall	30 (33.7)	
	Posterior wall	30 (33.7)	
	Greater curvature	15 (16.9)	
	Lesser curvature	10 (11.2)	
	Unknown	4 (4.5)	
Tumor size (mm), mean (range)		24.9 (10–70)	
Tumor histology, n (%)			
	GIST	59 (66.3)	
		Very low grade	17 (19.1)
		Low grade	31 (34.8)
		Intermediate grade	3 (3.4)
		High grade	4 (4.5)
		Unknown	4 (4.5)
	Ectopic pancreas	7 (7.9)	
	Leiomyoma	5 (5.6)	
	Neurinoma	3 (3.4)	
	Early gastric cancer	3 (3.4)	
	Neuroendocrine tumor	2 (2.2)	
	Schwannoma	2 (2.2)	
	Granuloma	2 (2.2)	
	Hemangioma	1 (1.1)	
	Gastritis cystica profunda	1 (1.1)	
	Desmoid fibromatosis	1 (1.1)	
	Lipoma	1 (1.1)	
	Vanek's tumor	1 (1.1)	
	Glomus tumor	1 (1.1)	

\* 88 in total

Therefore, the 7 case report articles<sup>7-13</sup> and the 4 original articles of clinical cases<sup>14-17</sup> were enrolled as relevant articles for full-text assessment. Because two original articles were reported from a single research group with some duplicated cases,<sup>14,15</sup> the duplication was carefully assessed and avoided double count.

Based on the results, 89 lesions in 88 patients were enrolled for a pooled analysis. Table 2 shows the characteristics of the 89 lesions in 88 patients who underwent NEWS. The lesions were primarily located in the anterior or posterior side of the upper third of the stomach. The majority of lesions were GISTs, but subepithelial tumors without possible malignancy and epithelial tumors such as early gastric cancers were enrolled.

In terms of technical outcomes, although intraoperative perforation was observed in 5 lesions (5.6%), technical success defined as transoral retrieval after the completion of the procedure was obtained in 98% (87/89) of lesions. The largest tumor was a lipoma measuring 70 mm in size, but transoral retrieval was possible due to the soft nature and the short axis would measure <30 mm.<sup>17</sup>

Postoperative clinical courses were fair in general. Postoperative complications such as infected liver hematoma, resection line bleeding, a fever of unknown origin, and pneumonia were experienced in 4 patients.

In two studies of Mitsui et al and Aoyama et al, the authors reported a median operation time of 184 and 198 min in 28 GISTs and 43 submucosal tumors, respectively.<sup>15,16</sup> Aoyama et al also reported a median hospital stay of 7.0 days in their case series of submucosal tumors.<sup>16</sup>

In another study, Goto O et al reported successful curative resection of early gastric cancer in a combination of NEWS and sentinel node basin dissection conducted within 270 min without intraoperative complications. The patient was uneventfully discharged 10 days after the procedure without any late complications.<sup>7</sup> Hejer et al also reported two early gastric cancers removed by NEWS with regional lymph node dissection. The operation times were 70 and 105 min, respectively, with no complications experienced in both cases.<sup>17</sup>

## DISCUSSION

In addition to ER methods, LECS procedures were introduced for treating gastric tumors in Japan that further spread for treating other GI organs and into other countries as well. As the merits of these procedures became well recognized in several years after development, LECS for gastric tumors was covered by the national medical insurance in Japan from 2014 onward. The NDB revealed that 1312 LECS procedures for treating gastric tumors were performed in 2017 in our country.<sup>1</sup> Among them, some cases were treated by NEWS, but there were no accessible public data to indicate the breakdown of LECS procedures into subcategories. In fact, only 76 Japanese cases have been reported in the literature as shown in this review. The reported cases were primarily from two research groups where NEWS was invented and innovated. This implies that the outcomes may be better than those in other hospitals. In addition, how to indicate the different LECS procedures still remains an open question, and it is speculated that the procedures are primarily selected by the operator preference and experiences. In Japan, we have a nationwide surgical database termed as the National Clinical Database<sup>18</sup> and a nationwide endoscopy database termed as the Japan Endoscopy Database,<sup>19</sup> led by Japan Surgical Society and Japan Gastroenterological Endoscopy Society, respectively. In both databases, we could break down the LECS procedures into subcategories such as NEWS. Although the accessibility to the collected data is strictly controlled by the societies, it would be possible to use the data after permission. To elucidate the clinical impact of NEWS, it is necessary to analyze real-world data,

including unpublished cases, using these databases as the next agenda.

In terms of spread to other countries, this review identified only 13 cases from 3 countries (Thailand, South Korea, and Czech Republic) reported in the literature. The major reason for the very low permeability to the rest of the world could be the difficulty to have both well-trained endoscopist and laparoscopist who are interested in NEWS in one unit. The endoscopist must be good at performing ESD for successful NEWS, because the endoluminal process of NEWS is a similar complex technique as ESD. To promote NEWS worldwide, it is also necessary to cultivate more endoscopists who could perform ESD in each region and country.

In terms of target lesions, this review revealed that the majority were subepithelial tumors, especially GISTs. The largest shortcoming of NEWS compared with other LECS procedures must be the limited maximum size in the shortest axis of the target lesions. Considering the peroral retrieval of the resected tumor, the shortest axis should be <3 cm in size. To increase the case volume for NEWS, it is also important to further promote the earlier detection of target lesions smaller in size. In addition to subepithelial tumors, some early gastric cancers without little probability of lymph node metastasis were treated by NEWS. The best indication of NEWS would be a differentiated-type intramucosal cancer measuring <3 cm in size with deep ulcer findings or scar formation due to previous ER (involvement of the proper muscle layer). In some submucosal invasive cancers subclassified as EB-virus-positive cancer<sup>20</sup> or gastric adenocarcinoma of the fundic gland type,<sup>21</sup> the risks of lymph node metastases have been reported to be significantly lower than those of routine cases, which would be promising candidates of NEWS. When sentinel node basin dissection was combined with NEWS, the indication of NEWS would expand more for submucosal invasive cancers with negative sentinel node metastases.<sup>22</sup>

Although theoretically available, there has been no report of performing NEWS in the colon. The major reason would be the much less need for local resection with minimum necessary tumor-negative margins than the stomach or the duodenum when considering the complexness of the procedure and the quality of life after colectomy. However, after the innovation of NEWS to simpler and easier procedures in the future, the concept of NEWS would be applied in the managements of colonic lesions.

In conclusion, this review of recent literature revealed that NEWS has been slowly but steadily accepted as a local resection procedure with minimum necessary tumor-negative margins in the stomach, especially in Japan. However, further accumulation of cases from inside and outside of Japan published in the literature or real-world data analyses are necessary to demonstrate the clinical impact of NEWS.

#### DISCLOSURE OF POTENTIAL CONFLICT OF INTEREST

Nothing to declare.

#### RESEARCH INVOLVING HUMAN PARTICIPANTS AND /OR ANIMALS

We did not enroll human participants and/or animals for this review article.

#### INFORMED CONSENT

Informed consent is not necessary because no human subjects were enrolled for this review article.

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