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Clinicopathological features and management strategy for superficial nonampullary duodenal tumors: a multi-center retrospective study

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Purpose: We investigated the clinicopathological features and management for superficial nonampullary duodenal tumors (SNADTs). The safety and feasibility of laparoscopic management, especially laparoscopic endoscopic cooperative surgery (LECS), were evaluated.
Methods: A total of 59 patients with SNADTs who underwent operations from January 2009 to December 2018 at all 8 institutions of the Catholic Medical Center were identified in our comprehensive multi-institutional database. Clinicopathological and surgical data on the 4 anatomical regions of the duodenum were collected and compared. Characteristics of conventional laparoscopic procedure (laparoscopy-only) and LECS procedures were also compared.
Results: There were significantly more asymptomatic patients with tumors in the first and second *vs*. third and fourth duodenal regions. Gastrointestinal stromal tumors (GISTs), carcinoids, and ectopic pancreatic tumors were identified in 32, 12, and 5 cases, respectively. Forty-two patients (71.2%) underwent laparoscopy. Of patients undergoing laparoscopy, the LECS group exhibited significantly more endophytic features and smaller tumor sizes ($P < 0.001$ and $P < 0.001$, respectively). Although no significant difference in the wedge resection or postoperative complication rate was seen between the 2 groups ($P = 0.096$ and $P = 0.227$, respectively), the wedge resection rate was higher, and the complication rate lower, in the LECS group than the conventional laparoscopic surgery group.
Conclusion: Most of the SNADTs located in proximal duodenum were detected incidentally. GISTs were the most common diagnoses of SNADTs in all locations. In treating these tumors, laparoscopic resection is safe and feasible. Especially, LECS may be ideal for treating small endophytic tumors, minimizing over-resection and postoperative complications.
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Key Words: Duodenal neoplasm, Endoscopy, Laparoscopy, Surgery

INTRODUCTION

Superficial nonampullary duodenal tumors (SNADTs) have traditionally been considered unlikely to be malignant [1]. Recently, routine endoscopic screening and development of imaging tools can detect duodenal tumors (adenomas, adenocarcinomas, and neuroendocrine tumors) at a higher rate than before [2]. Previously, the pathological features of SNADTs were unclear prior to resection. Several treatment options are available, including tumor removal via endoscopic or surgical resection [3-6]. However, no consensus has been achieved regarding management because the tumors are rare, confined

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to the duodenum, and difficult to treat. Although endoscopic diagnosis and treatment are effective [5,6]. Endoscopic treatment is more difficult for duodenal lesions than other gastrointestinal lesions. The surgical anatomy is complex, and bile and pancreatic juice often induce hemorrhage and perforation [7,8]. Surgically complete *en bloc* resection with a negative surgical margin is the standard approach; this does not require lymph node dissection when treating low-risk tumors of the duodenum (mucosal cancers, adenomas, and submucosal tumors) [9]. Although open surgery has traditionally been the standard approach, minimally invasive laparoscopic, robotic, and hybrid surgery are emerging as the new standards [9]. Laparoscopic resection may adequately treat SNADTs. However, difficulty in determining tumor location may lead to unnecessary laparoscopic duodenal resection [10]. Laparoscopic endoscopic cooperative surgery (LECS), which exploits the advantages and minimizes the disadvantages of endoscopic and laparoscopic treatments, may be appropriate [9-13].

Given the rarity of SNADTs and the lack of standard surgical strategies for tumors that differ both in terms of location and pathological features, further studies are required. Herein, we describe the clinicopathological features and challenges associated with treatment of SNADTs based on surgical experience accumulated in our multi-center institution. In addition, we compare the safety and feasibility of conventional laparoscopic surgery and LECS for patients with low-risk SNADTs.

METHODS

This study was performed in accordance with the Declaration of Helsinki and written informed consent was waived due to its retrospective nature. This study was approved by the Institutional Review Board of the College of Medicine, The Catholic University of Korea (No. XC20RIDI0149).

Patients

Patients who were operated on to treat SNADTs from January 2009 to December 2018, in all 8 institutions of the Catholic Upper Gastrointestinal Surgery Study Group, were identified in our comprehensive, multi-institutional surgical database. We excluded patients with adenocarcinomas. In total, 59 patients were enrolled, and clinical, surgical, pathological, and survival data were collected.

Patient grouping by anatomical tumor location

The patients were divided into 4 groups by tumor location (first, second, third, and fourth region of the duodenum). The first region of the duodenum runs from the pylorus to the corner of the superior duodenal flexure. The second region runs from the superior duodenal flexure to just before the inferior duodenal flexure. The third region begins at the inferior duodenal flexure and runs transversely to the left. The fourth region includes the ascending portion and duodenojejunal flexure [14].

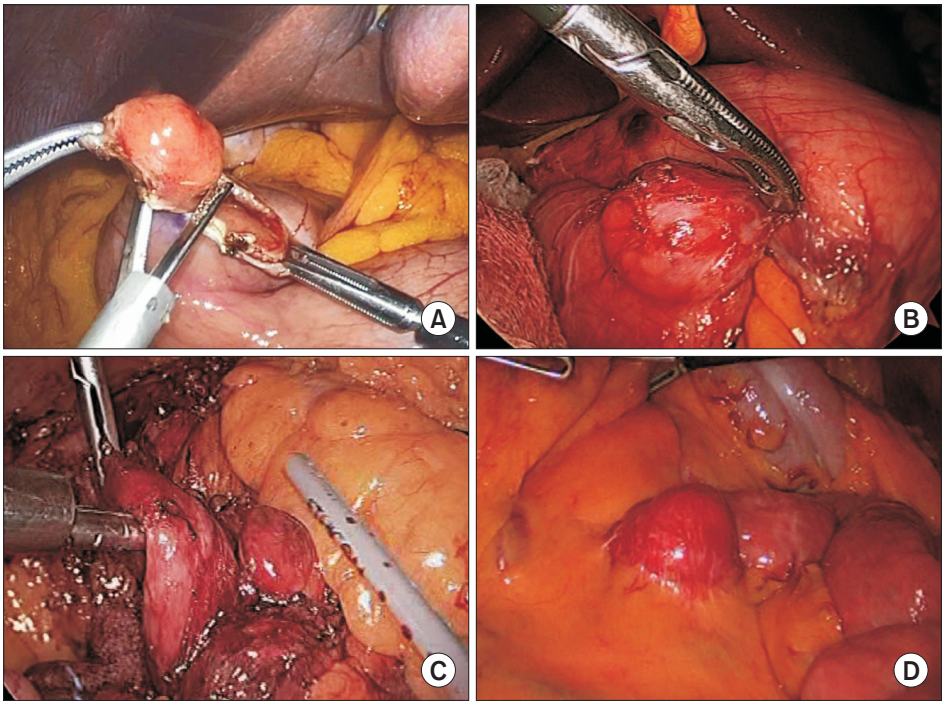

Fig. 1. (A) Tumor located in the first duodenal region. (B) Tumor located in the second region. (C) Tumor located in the third region. (D) Tumor located in the fourth region.

Definition of patient groups based on surgical procedures

All patients were classified into laparoscopy and laparotomy groups according to approach methods. Subsequently, the laparoscopy group was classified into LECS and conventional laparoscopic surgery (laparoscopy-only) groups based on the use of endoscopic guidance or dissection during surgery.

Under general anesthesia, a carbon dioxide pneumoperitoneum was created via a 12-mm laparoscopic port inserted through the umbilicus. Additional trocars were then inserted at the discretion of the surgeon. Tumors located in the first region were located and underwent simple wedge resection (Fig. 1A). If a tumor was located in the second region, the laparoscopic Kocher maneuver was performed until the anterior wall of the second region was well-exposed; this exposed structures in the retroperitoneum behind the duodenum and pancreas (Fig. 1B). When the tumor was located in the third region, the transverse colon and mesentery were retracted in the cephalic direction with the patient in the Trendelenburg position. The operator then dissected the posterior aspect of the mesentery to expose the tumor (Fig. 1C). When the tumor was located in the fourth region, the ligament of Treitz and several jejunal vessels were ligated and resected to secure the proximal resection margin (Fig. 1D). After resection, a luminal stricture or discontinuity was evident in most patients with third- and fourth-region tumors. Therefore, additional bypass surgery was performed. The LECS group underwent intraluminal endoscopy to mark the tumor, or endoscopic resection during laparoscopic intraabdominal tumor resection (Fig. 2). The laparoscopy-only group underwent laparoscopic tumor resection without any endoscopic procedure.

Gastrointestinal stromal tumor risk groups

Using the modified National Institutes of Health (NIH) grading system [15], the 32 gastrointestinal stromal tumor (GIST) patients were divided into very low-, low-, intermediate-, and high-risk groups.

Statistical analysis

Continuous and categorical variables were compared using the independent t-test and chi-square test, respectively. A P-value of <0.05 was taken to indicate significance. All statistical analyses were performed using IBM SPSS Statistics ver. 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Clinicopathological characteristics by duodenal anatomy

Patient characteristics are listed in Table 1. Seventy-eight percent of patients had no symptoms; the tumors were detected incidentally. The male:female ratio was 49.2:50.8. Initial symptoms differed significantly by tumor location ($P = 0.015$). There were significantly more asymptomatic patients with tumors in the first and second *vs.* third and fourth duodenal regions. Age, sex, and the American Society of Anesthesiologists physical status classification did not differ significantly among the groups ($P = 0.266$, $P = 0.129$, and $P = 0.081$, respectively).

Surgical outcomes by duodenal anatomy

The surgical results are listed in Tables 2 and 3. There were 32, 12, and 5 cases of GIST, carcinoids, and ectopic pancreas, respectively. Eighteen and 9 patients, respectively, were

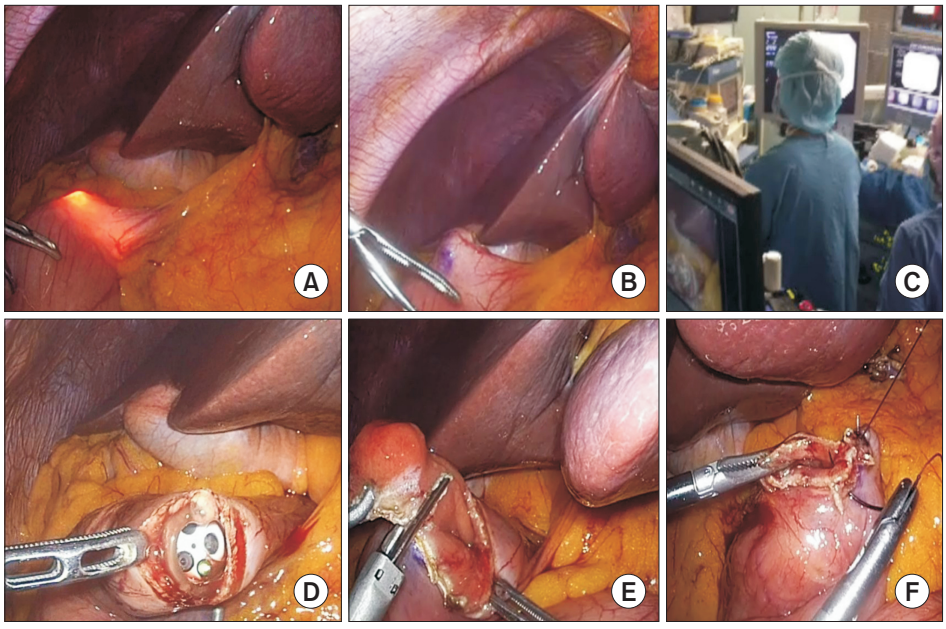

Fig. 2. (A) Tumor location was confirmed laparoscopically and by intraluminal endoscopic illumination. (B–D) Endoscopists performed full-thickness resections. (E) After the tumor had been fully exposed by the surgeon, it was resected using an energy device. (F) The edge of the incision line on the duodenum was closed after tumor resection using hand-sewn sutures or the endovascular gastrointestinal anastomosis (Endo-GIA) stapler.

Table 1. Baseline characteristics of all enrolled patients according to duodenal tumor locations

Characteristic	Total	First	Second	Third	Fourth	P-value
No. of patients	59	24	21	6	8	
Age (yr)	58.3 ± 12.8	56.0 ± 11.8	57.6 ± 12.2	58.5 ± 18.8	66.4 ± 11.4	0.266
Sex						0.129
Male	29 (49.2)	14 (58.3)	6 (28.6)	4 (66.7)	5 (62.5)	
Female	30 (50.8)	10 (41.7)	15 (71.4)	2 (33.3)	3 (37.5)	
ASA PS classification						0.081
I	32 (54.2)	15 (62.5)	12 (57.1)	4 (66.7)	1 (12.5)	
II	27 (45.8)	9 (37.5)	9 (42.9)	2 (33.3)	7 (87.5)	
Symptom at first						0.015
None	46 (78.0)	22 (91.7)	17 (81.0)	4 (66.7)	3 (37.5)	
Melena	8 (13.6)	2 (8.3)	3 (14.3)	1 (16.7)	2 (25.0)	
Abdominal pain	4 (6.7)	0 (0)	0 (0)	1 (16.7)	3 (37.5)	
Dyspepsia	1 (1.7)	0 (0)	1 (4.7)	0 (0)	0 (0)	

Values are presented as number only, mean ± standard deviation, or number (%).
ASA, American Society of Anesthesiologists; PS, physical status.

Table 2. Pathological findings according to duodenal tumor locations

Pathological diagnosis	No. of cases	Duodenal tumor location			
		First (n = 24)	Second (n = 21)	Third (n = 6)	Fourth (n = 8)
GIST	32	9 (37.5)	13 (61.9)	3 (50.0)	7 (87.5)
GIST risk according to modified NIH					
Very low		4	1	0	0
Low		4	8	3	3
Intermediate		0	0	0	0
High		1	4	0	4
Carcinoid	12	8 (33.3)	3 (14.3)	1 (16.7)	0 (0)
Ectopic pancreas	5	3 (12.5)	2 (9.5)	0 (0)	0 (0)
Hamartoma	6	4 (16.7)	2 (9.5)	0 (0)	0 (0)
Leiomyoma	3	0 (0)	1 (4.8)	1 (16.7)	1 (12.5)
Paraganglioma	1	0 (0)	0 (0)	1 (16.7)	0 (0)

Values are presented as number only or number (%).
GIST, gastrointestinal stromal tumor; NIH, National Institutes of Health.
P = 0.069.

diagnosed with low- and high-risk GISTs using the modified NIH classification. When compared the incidence according to duodenal anatomy, GIST was the most common diagnosis in all locations. GIST most often occurred in the second duodenal region. And carcinoid, ectopic pancreas, and hamartoma most often occurred in the first duodenal region (Table 2, Fig. 3).

Of 59 patients with duodenal tumors, 42 (71.2%) underwent laparoscopy (LECS, n = 19 [45.2%]; laparoscopy-only, n = 23 [54.8%]). The overall endophytic:exophytic tumor ratio was 50.8:49.2. More patients with tumors in the first and second duodenal regions underwent laparoscopy than laparotomy; this trend was reversed in those with tumors in the third and fourth regions (P = 0.011). Tumors in the first and second regions were more commonly endophytic than endophytic lesions (P = 0.008). Tumors in the first and second regions underwent wedge resection more commonly than segmental resection (P < 0.001). Eleven cases (18.6%) developed complications. Leakage occurred in 1 case (1.7%) with a tumor in the second region, and a stricture developed in 1 case (1.7%) with a tumor in the third region. The complication rate was higher in patients who underwent laparotomy rather than laparoscopy (35.3% *vs.* 11.9%) (Table 3).

Clinicopathological characteristics and surgical outcomes: comparison between laparoscopic endoscopic cooperative surgery and laparoscopy-only

In the LECS group, the number of endophytic features and proportion of carcinoids were significantly higher, and the tumor size was significantly smaller than in the laparoscopy-

Table 3. Operative findings of all enrolled patients according to tumor location

Variable	Total (n = 59)	First (n = 24)	Second (n = 21)	Third (n = 6)	Fourth (n = 8)	P-value
Approach						0.011
Laparotomy	17 (28.8)	2 (11.8)	7 (41.2)	4 (23.5)	4 (23.5)	
Laparoscopy	42 (71.2)	22 (52.4)	14 (33.3)	2 (4.8)	4 (9.5)	
Conversion	4 (6.8)	2	2	0	0	
Tumor gross feature						0.008
Endophytic	30 (50.8)	16 (53.3)	12 (40.0)	2 (6.7)	0 (0)	
Exophytic	29 (49.2)	8 (27.6)	9 (31.0)	4 (13.8)	8 (27.6)	
Resection						<0.001
Wedge	49 (83.1)	24 (49.0)	20 (40.8)	5 (10.2)	0 (0)	
Bypass[a]	2 (3.4)	1	1	0	0	
Segmental	10 (16.9)	0 (0)	1 (10.0)	1 (10.0)	8 (80.0)	
Complication						0.220
Absentce	48 (81.4)	22 (45.8)	17 (35.4)	4 (8.3)	5 (10.4)	
Presence	11 (18.6)	2 (18.2)	4 (36.4)	2 (18.2)	3 (27.3)	
Leakage	1 (1.7)	0	1	0	0	
Stricture	1 (1.7)	0	0	1	0	
Complication according to approach[b]						
In laparotomy	6 (35.3)	1	2	2	1	
Stricture	1 (5.9)	0	0	1	0	
In laparoscopy	5 (11.9)	1	2	0	2	
Leakage	1 (2.4)	0	1	0	0	

Values are presented as number only or number (%).
[a]Among the wedge resection cases, one each patient was required bypass surgery due to its luminal stricture possibility in the first and second sections. [b]Total number is included in presence of complication (n = 11) and percentage is calculated to rate in each approach method.

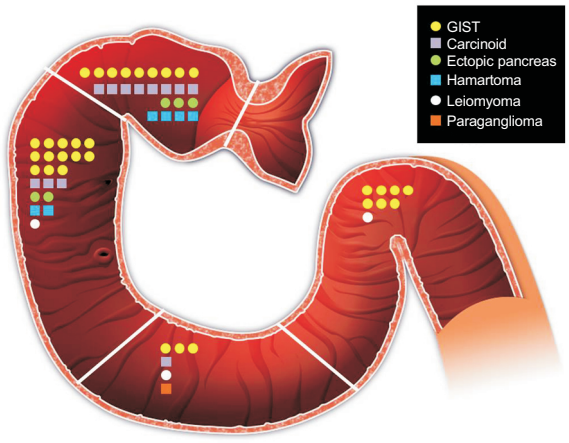

Fig. 3. Schematic illustration of the relationship between tumor location and pathological diagnosis. GIST, gastrointestinal stromal tumor.

only group (P < 0.001, P = 0.001, and P < 0.001). However, the LECS proportion did not differ by tumor location (P = 0.119). In addition, operation time, hospital stay, and conversion rate did not differ significantly between the 2 groups (P = 0.622, P = 0.299, and P = 0.841, respectively). The wedge resection rate showed a trend toward being higher in the LECS than in the laparoscopy-only group (P = 0.096). The postoperative complication rate was higher in the laparoscopy-only group compared with the LECS group, although the difference was not significant (17.4 *vs.* 5.3%, P = 0.227) (Table 4).

DISCUSSION

We investigated the features of patients operated on for duodenal tumors in various locations and described the unique clinicopathological features of SNADTs. Patients with endophytic and proximal duodenal tumors were asymptomatic on admission. Most distal tumors were treated via laparotomy. In the present study, we demonstrated that laparoscopic management has a lower complication rate compared with laparotomy. Especially, LECS was feasible and safe, and showed good performance in terms of operation time, hospital stay, and the conversion, wedge resection and complication rates compared with laparoscopy-only management.

To the best of our knowledge, this is the first Korean study on duodenal tumors based on a comprehensive, multi-institutional surgical database, and the first to classify SNADT patients into 4 groups by anatomical tumor location prior to analysis of clinicopathological features and to prove that LECS is superior to with conventional laparoscopic surgery in treating SNADT.

Previously, Matsueda et al. [16] studied SNADTs on the oral and anal side of the ampulla of Vater. The mucin phenotype

Table 4. Clinicopathologic characteristics and surgical outcomes of LECS patients

Characteristic	LECS (n = 19)	Conventional laparoscopy (n = 23)	P-value
Age (yr)	55.4 ± 14.4	58.8 ± 9.7	0.361
Sex			0.711
Male	11 (47.8)	12 (52.2)	
Female	8 (42.1)	11 (57.9)	
Body mass index (kg/m^2)	23.8 ± 3.3	24.6 ± 3.4	0.449
Location			0.119
First	10 (54.5)	12 (45.5)	
Second	7 (50.0)	7 (50.0)	
Third	2 (100)	0 (0)	
Fourth	0 (0)	4 (100)	
Resection			0.096
Wedge	19 (51.4)	18 (48.6)	
Segmental	0 (0)	4 (100)	
Tumor gross feature			<0.001
Endophytic	17 (76.0)	6 (24.0)	
Exophytic	0 (0)	17 (100)	
Pathologic diagnosis			0.001
GIST	2 (12.5)	14 (87.5)	
Carcinoid	11 (91.7)	1 (8.3)	
Ectopic pancreas	2 (40.0)	3 (60.0)	
Hamartoma	3 (50.0)	3 (50.0)	
Leiomyoma	1 (33.3)	2 (66.7)	
Paraganglioma	0 (0)	0 (0)	
Operation time	134.5 ± 42.5	150.8 ± 138.0	0.622
Hospital stay (day)	7.3 ± 5.8	9.0 ± 5.2	0.299
Size (cm)	1.3 ± 0.6	3.4 ± 1.9	<0.001
Mitosis (/50 HPF)	1.3 ± 0.7	2.3 ± 2.2	0.063
Conversion	2 (10.5)	2 (8.7)	0.841
Complication	1 (5.3)	4 (17.4)	0.227
Leakage	1 (5.3)	0 (0)	

Values are presented as mean ± standard deviation or number (%).

differed significantly among the groups, as did clinical symptoms and the optimal operation type. In both this study and that of Matsueda et al. [16], significant macroscopic differences were found by tumor location. However, they did not exclude adenocarcinomas, and classified tumors macroscopically type using different criteria. Matsueda et al. [16] reported that the duodenal tumor incidence on the anal side of the ampulla of Vater was 56.8%; in our study, the rate was lower (23.7%). In our study, the low incidence may have been due to the fact that only patients with large tumors developed symptoms and underwent operations. Distal tumors are difficult to detect incidentally, i.e., on regular endoscopic examination, as the endoscope is relatively short. Thus, alternative novel imaging tools for early detection of distal duodenal tumors could be necessary. In addition, as our data shows, because the most common pathologic diagnosis of distal duodenal tumors is GIST, an intensive surgical approach for distal tumors would be required.

Until now, few studies have compared LECS and laparoscopy-only groups for duodenal tumors, and most were single-arm confirmatory trials, case reports, or offered only technical tips regarding LECS [9,10,12,13]. As a comparative study, Ojima et al. [11] concluded that LECS was an ideal alternative to endoscopic resection for low-risk duodenal tumors in terms of complication and curative resection rates. Although the present study has something in common with that study in that it compared the short-term outcomes, the present study has a difference in that it compared LECS and laparoscopy in terms of wedge resection and complication rates [11].

In treating noncancerous SNADTs, complete *en bloc* resection with negative margins is the standard treatment that can be used in endoscopic, laparoscopic, or open surgical approaches [3,4,7,8,17-19]. First of all, endoscopic resection seems adequate for treating endophytic SNADTs [3,4,8]. However, as the duodenal wall is thin, complications of duodenal endoscopic resection may arise, including exposure to bile and pancreatic juice, and difficult access to the narrow lumen. As the risks of perforation and bleeding are high, endoscopists may be

reluctant to perform the procedure [20]. In addition, endoscopic resection does not guarantee adequate deep margins. On the contrary, surgical resection provides better margins for deep tumors than endoscopic resection. In particular, laparoscopic wedge resection (among various surgical approaches) is easy to perform for exophytic duodenal tumors with or without endoscopic guidance. However, for endophytic and small duodenal tumors, it is very difficult to determine the extent of excision via laparoscopic-only approach. Similarly, the laparoscopy-only group exhibited significantly more exophytic features and larger tumors than the LECS group in our study. This may reflect the fact that large protruding tumors do not require LECS because LECS affords no advantages when used to treat large exophytic tumors. In other words, LECS would be a better option to treat small and endophytic duodenal tumors, as shown in other studies for gastric tumors [21,22].

In summary, LECS overcomes the difficulty in determining tumor location and eliminates the risk of unnecessary duodenal resection associated with the conventional laparoscopic approach. We found that the wedge resection rate was higher during LECS than during laparoscopy-only, although not significantly. However, some institutions are not possible to use intraoperative endoscopy for LECS in the clinical setting. According to experiences for gastric tumors due to its rarity of duodenal reports, tattooing using dye or blood, preoperative endoscopic clipping (combining with intraoperative portable abdominal radiography, intraoperative laparoscopic ultrasonography or preoperative 3-dimensional CT reconstruction measurements), fluorescence imaging with indocyanine green could be challenging but alterative solutions [23-25]. Compared with these methods, LECS has advantages in easy detection of tumors and direct detection of postanastomotic complications, although it is required need of endoscopic instruments and endoscopists [24].

There were several limitations in the present study. First, this is a retrospective study. Retrospective studies are at risk of various forms of bias. In our study, the operative and endoscopic methods were heterogeneous because we collected data from many surgeons over a long period of time, because the incidence of duodenal tumor is low. However, surgical decision-making and performance were of a high standard; all of our centers employ well-trained surgeons. As noted above, a prospective study is needed to validate our findings and further future study is required to evaluate the indication which has advantages for applying LECS in duodenal tumors. Second, our data included 5 patients who underwent surgery for ectopic pancreas. Although the ectopic pancreas is benign nature, pancreatitis or pancreatic cancer has also been reported in ectopic pancreas, it would be better to resect the ectopic pancreas completely during operation [26,27]. Fortunately, all 5 patients in our study completed the operation with simple wedge resection.

In conclusion, most of the SNADTs located in proximal duodenum were detected incidentally. GISTs were the most common diagnoses of SNADTs in all locations. In treating these tumors, laparoscopic management has shown lower complication rate compared with laparotomic resection. In laparoscopic surgery, LECS is feasible and safe, and yielded good short-term outcomes in terms of complication rate and prevention of unnecessary duodenal resection for low-risk duodenal tumors with small and endophytic features compared with conventional laparoscopic surgery.

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Conflict of Interest

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

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