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Endoscopic resection in combination with ligation for the treatment of duodenal subepithelial lesions: a single-center experience

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A list of abbreviations

SELs, subepithelial lesions; ER-L, endoscopic resection after ligation; GISTs, gastrointestinal stromal tumors; EUS, endoscopic ultrasonography; ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection; CT, Computed tomography.

Abstract

Duodenal subepithelial lesions (SELs) are increasingly detected during an endoscopic examination. However, no feasible and safe methods are available for removing duodenal SELs. In the present study, we aimed to assess the feasibility and safety of endoscopic resection in combination with ligation (ER-L) in removing the duodenal SELs. A total of 101 patients with duodenal SELs received ER-L from February 2010 to February 2020. The primary outcomes were complete resection, en

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bloc resection, and R0 resection. The secondary outcomes included procedure duration, bleeding, perforation, and residual lesions. A total of 101 patients with 101 duodenal SELs (ranged from 8.4 mm to 20.2 mm in size) were included in this study. Most of the SELs (95.1%) originated from the submucosal layer and were successfully removed using ER-L. The rates of complete resection, en bloc resection, and R0 resection were 100%, 96.0%, and 88.1%, respectively. The median procedure duration was 8 min. There was no severe complication, except for four patients who developed post-procedure bleeding (4.0%) and recovered after conservative treatment. Furthermore, no residual lesions were detected during the follow-up period (median of 36 months). Indeed, logistic regression analysis showed that the size of duodenal SELs was an independent factor for R0 resection during the ER-L procedure. Conclusively, ER-L was feasible and safe to remove the duodenal SELs that originated from the submucosal layer and were less than 20 mm. However, the feasibility and safety of the ER-L should be further confirmed when removing the duodenal SELs that originated from the muscularis propria (MP) layer and were larger than 20 mm in diameter.

Keywords: Duodenal subepithelial lesions. Endoscopic resection. Endoloop ligation.

Introduction

Duodenal subepithelial lesions (SELs) are increasingly detected in patients during endoscopic screening, most of which are asymptomatic and clinically insignificant lesions and covered by normal mucosa[1]. Furthermore, most SELs consist of Brunner’ s adenomas, lipomas, and cysts, which are often benign[2], whereas some lesions are neuroendocrine tumors and gastrointestinal stromal tumors (GISTs) with overt and potential malignancy[3, 4]. Although it is recommended that patients with SELs less than 2 cm can be followed up through endoscopy or endoscopic ultrasonography (EUS), it may delay the diagnosis of malignancy[5]. Meanwhile, previous studies have shown that lesions less than 2 cm can still metastasize in some cases[6, 7].

Endoscopic resection (ER) can not only treat the duodenal SELs but also achieve appropriate histopathological diagnoses. ER for SEL removal is composed of endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and surgical resection. Compared with the lesions in other parts of the gastrointestinal tract, duodenal SELs are difficult to resect because of the duodenal anatomic feature[8, 9]. Therefore, feasible, safe, and viable methods for the removal of duodenal SELs have not yet been established. For instance, EMR can effectively remove the duodenal SELs, whereas it is associated with a low R0 resection rate and a high adverse event rate[10]. Although ESD has a satisfactory R0 resection rate, the risk of perforation is dramatically high[11, 12]. Indeed, surgical resection is complex, invasive, and susceptible, resulting in serious complications[13, 14]. Herein, we would like to share our experiences in the treatment of duodenal SELs using ER in combination with an endoloop ligation (ER-L) within 10 years in our clinical center.

Patients and methods

A total of 112 consecutive patients, who had duodenal SELs and were treated with ER-L in the Second Clinical Medicine College (Shenzhen People's Hospital) of Jinan University from February 2010 to February 2020. Eleven patients were excluded due to the loss to follow-up. Therefore, 101 patients were retrospectively enrolled in the present study. Patients who were lost during follow-up after the ER-L procedure were excluded (Figure 1). The size and origin of the duodenal SELs were confirmed using EUS and computed tomography (CT). This study was approved by the Ethics Committee of Shenzhen People's Hospital. Written informed consent was obtained from all patients.

ER-L procedure

ER-L procedure was performed by four senior endoscopists (L-S W, Z-L X, B-H W, and D-G Z). The patients were anesthetized using midazolam (0.5 mg) and pethidine hydrochloride (50 mg). The steps of ER-L were briefly described as follows. (1) Marking dots for incision lines were placed in the SELs (Figure 2A and Figure 2B). (2) A submucosal bleb was created by injecting saline containing 0.3 % indigo carmine beneath the marking dots to lift the mucosa (Figure 2C). (3) A cross-sectional incision was performed as deep as the submucosa layer around the marking dots using Hook

Knife (Endocut mode, 30 W, effect 3, ERBE, Germany) (Figure 2D). (4) The endoscope was removed, and an endoloop and ligation (OLYMPUS, Japan) device was assembled (Figure 2E). (5) The SELs were suctioned into the cap (OLYMPUS, Japan), and then the endoloop was deployed (Figure 2F). (6) The SELs were removed using a snare above the endoloop (Figure 2G). (7) Another endoloop was used to close the defect (Figure 2H).

All patients were hospitalized and fasted after the ER-L procedure for one night. Moreover, all patients were intravenously administered with prophylactic proton pump inhibitors (PPIs). All patients with no evidence of complications were discharged, and they were advised to follow a soft diet for 2 weeks and prescribed PPIs (Omeprazole, 20 mg, once a day) for 2 weeks.

Outcomes

The primary outcomes included complete resection, En bloc resection, and R0 resection of ER-L. The complete resection was defined as no residual lesion fragment on endoscopic views at the resection site. En bloc resection was defined as single piece resection without remnant lesions on endoscopic views. R0 resection was defined as en bloc resection with a free pathological margin.

The secondary outcomes included procedure duration, bleeding, perforation, and residual lesions. The procedure duration was defined as the time from the start of marking dots to the defect closure of SEL resection. Bleeding consisted of intra-procedure and post-procedure bleeding. Intra-procedure bleeding was defined as the requirement of endoscopic hemostasis during the procedure, while post-procedure bleeding was defined as overt bleeding, including hematemesis, melena, or a reduction in the hemoglobin level of more than 2 g/dL after the procedure. Perforation also consisted of intra-procedure and post-procedure perforation. Intra-procedure perforation was defined as that the extra-duodenal structure was visualized during the procedure, while post-procedure perforation was defined as the evidence of diffuse gas or intestinal fluid localized in the peritoneum.

Follow-up

Surveillance endoscopy was performed to evaluate the wound healing and residual lesions at 3, 6, and 12 months and once yearly thereafter.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR, 25%-75%), while categorical variables were expressed as percentages. Logistic regression was used to identify possible factors associated with R0 resection. *P* values < 0.05 were considered statistically significant.

Results

Clinical characteristics

There were 52 males and 49 females in the present study. The median age of these patients was 55 years (ranging from 48.5 to 63.5 years). Of these 101 patients, 78 patients complained of gastrointestinal symptoms, and others underwent early gastric cancer examination. Table 1 lists the detailed information.

A total of 101 duodenal SELs were removed with ER-L. In the 101 SELs, the median diameter was 10.1 mm (ranging from 8.4 mm to 20.2 mm). Of these 101 SELs, 44 SELs (43.6%) were located in the first part, 46 SELs (45.5%) were located in the second part, and the others were located in the third part. Most of the SELs originated from the submucosal layer (N=96, 95.1%), while others originated from the muscularis propria (MP) layer (N=5, 4.9%). Moreover, the histopathological examination revealed that there were 51 cases of Brunner's gland hyperplasia, 19 cases of lipoma, 17 cases of heterotopic pancreas, 13 cases of well-differentiated neuroendocrine tumor (WDNET), and one case of very low-risk GIST (Table 1).

ER-L procedure outcomes

Complete resection was achieved in all SELs (100%), whereas en bloc resection and R0 resection were achieved in 97 SELs (96.0%) and 89 SELs (88.1%), respectively (Table 2).

The average duration of the ER-L procedure was 6.5 min (±3.2 min). There was no case of perforation and intra-procedure bleeding, whereas four patients developed post-procedure bleeding. However, these four patients recovered smoothly after the conservative treatment (Table 2).

Factors associated with en bloc resection and R0 resection

The univariate and multivariate logistic regressions were used to determine the correlations between the factors, such as sex, age, lesion size, lesion origination, and

lesion location, and en bloc resection. We found that sex, age, lesion origination, and lesion location were not associated with the en bloc resection, while the lesion size was an independent factor of the en bloc resection (Table 3). Similarly, the lesion size was associated with the R0 resection rate by logistic regression (Table 4).

Follow-up

All patients received follow-up, and the median period was 36 months (ranging from 3 to 120 months). Moreover, no residual lesions and distant metastasis were detected. Although there were five cases of Brunner's gland hyperplasia, four cases of heterotopic pancreas, two cases of WDNET, and one case of lipoma in 12 SELs, which did not achieve R0 resection, no residual tissues were macroscopically detected at the resection site. There were two patients with WDNET, they did not experience additional surgical resection, and no recurrence of WDNET was detected during 36 months of follow-up.

Discussion

To the best of our knowledge, we, for the first time, assessed the feasibility and safety of ER-L for patients with duodenal SELs. Our results showed that the complete resection rate was 100%, whereas the en bloc resection rate and R0 resection rate were 96.0% and 88.1%, respectively. Furthermore, no patients experienced severe complications. Although four patients developed post-procedure bleeding, they all recovered smoothly with the conservative treatment. Indeed, there was no residual SEL during the follow-up period. Therefore, ER-L was a feasible and safe modality for the removal of duodenal SELs.

Kim *et al.* have found that the complete resection rate and en bloc resection rate are 100% and 96.9% for EMR of duodenal SELs, respectively, which is similar to our results[11]. Meanwhile, no residual lesions are detected between EMR and ER-L. Although the procedure duration of EMR is less than that of ER-L (3 min vs. 9 min), the complication rate of EMR is dramatically higher compared with ER-L (11% vs. 4.0%)[11]. Ye *et al.* have reported that EMR is effective in the removal of duodenal SELs with wound closure using clips and an endoloop. The complete resection rate is 100%, while the complication rate is nearly 7.4%, which is higher than our results (7.4% vs. 4.5%)[15]. Therefore, we considered that ER-L might be superior to EMR for

the removal of duodenal SELs.

When ESD is used to remove duodenal SELs, it has been disclosed that the R0 resection rate is 100%, while the complication of perforation is 37.5%, which is somewhat higher than our results (37.5% vs. 0%)[11]. Several anatomical features of the duodenum contribute to the challenge with ESD in treating duodenal SELs. For instance, the wall of the duodenum is stiff, leading to poor mucosal lift[16, 17]. Moreover, the deep muscle layer of the duodenum is relatively thin, which increases the risk of perforation[18]. Indeed, the duodenum has abundant blood vessels with a dual bleeding supply system, resulting in frequent bleeding during the ESD procedure[18]. However, ER-L can successfully sweep these challenges and be easily manipulated. Therefore, we considered that ER-L was superior to ESD for the treatment of duodenal SELs.

Ren *et al*. have shared their experience in removing 32 duodenal lesions that originate from the MP layer using endoscopic full-thickness resection (eFTR) without laparoscopic assistance[19]. Their results demonstrate that the complete resection rate is 100% with a low incidence of complication (3.1%) when the endoloop and metallic clips are used to suture the defect[19]. However, this technique is difficult to manage for inexperienced endoscopists. Moreover, Kappelle *et al*. have shared their experience of using eFTR to remove the duodenal SELs by a new flat-based over-the-scope clip and found that the technical success rate is 85%, while the observed adverse event rate is 83.3%[20]. Therefore, they consider that this technique needs further refinement to improve the safety of the resection of duodenal SELs. In the present study, most of the SELs originated from the submucosal layer, and whether ER-L was feasible to remove the lesion in the MP layer needed to be further confirmed. Kappelle WFW *et al*. have reported that eFTR with this new flat-based OTS clip is feasible and effective for the removal of duodenal SELs (< 20 mm) with a favorable en bloc resection rate and R0 resection[20]. However, the multivariate regression analysis showed that the size of duodenal SELs was an independent factor of the en bloc resection rate and R0 resection rate in this study.

There were some key options and considerations, which should be taken into account during the ER-L procedure. First, when the SELs were suctioned into the

endoloop, it was appropriate to cover the integral SELs, which could increase the en bloc resection and R0 resection rate. Second, to avoid mechanical excision, the endoloop was slowly tightened. Third, after removing the SELs, another endoloop was used to reinforce the defect, which could effectively reduce the bleeding and perforation.

However, there were some limitations in this study. First, this was a single-center and retrospective study. Second, most of the duodenal SELs originated from the submucosal layer in this study, and it was necessary to further confirm the feasibility and safety of the ER-L when removing the lesions that originated from the MP layer. Third, all of the SELs were less than 20 mm in this study, whereas ER-L lacked experience in resecting lesions larger than 20 mm. Indeed, the logistic regression revealed that the lesion size was an independent factor for the en bloc resection rate and R0 resection rate. Therefore, whether the ER-L is feasible and safe to remove large SELs (>20 mm) should be confirmed in future studies. Fourth, there was no control group in this study. Therefore, a randomized controlled trial (RCT) should be designed to compare the feasibility and safety between the ER-L and EMR for the treatment of duodenal SELs.

Collectively, this is the first study and largest case series to investigate the feasibility and safety of the ER-L for the removal of the duodenal SELs. We found that ER-L was a feasible and safe technique to resect the duodenal SELs that originated from the submucosal layer and were less than 20 mm in diameter. However, we should further confirm the feasibility and safety of the ER-L for the removal of duodenal SELs that originated from the MP layer and were larger than 20 mm in diameter.

Conflict of Interest

The authors declare no conflict of interest.

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Table 1 Clinical characteristics

Patients	
Gender, n(%)	
Male	52(51.5%)
Female	49(48.5%)
Age (years)	55(48.5-63.5)
Indications, n (%)	
Gastrointestinal symptoms	78(77.2%)
Early Gastric cancer examination	23(22.8%)
Duodenal SELs	
Median size (mm)	10.1(8.4-20.2)

Location, n (%)	
First part	44(43.6%)
Second part	46(45.5%)
Third part	11(10.9%)
Origination, n (%)	
Submucosal layer	96(95.0%)
Muscularis propria layer	5(5.0%)
Histology diagnosis, n (%)	
Brunner’ s glands hyperplasia	51(50.5%)
Lipoma	19(18.8%)
Heterotopic pancreas	17(16.8%)
Well-differentiated neuroendocrine tumor	13(12.9%)
Very low risk gastrointestinal stromal tumors	1(1.0%)

Note: SELs, subepithelial lesions

Table 2 Outcomes and adverse events

Outcomes, n (%)	
Complete resection	101(100%)
En bloc resection	97 (96.0%)
R0 resection	89(88.1%)
Procedure duration (min), mean (SD)	6.5±3.2
Adverse events, n (%)	
Intra-procedure bleeding	0
Post-procedure bleeding	4 (4.0%)
Intra-procedure perforation	0
Post-procedure perforation	0

Note: SD, Standard Deviation.

Table 3 Logistic regression analysis associated the factors with En bloc resection

	Univariate analysis	Multivariate analysis

	OR	95% CI	p-value	OR	95% CI	p-value
Gender						
Male	Reference			Reference		
Female	3.3	0.3 to 33.1	0.3	2.5	0.6 to 10.4	0.6
Age	1.1	0.9 to 1.2	0.2	1.1	0.9 to 1.3	0.2
Size	0.6	0.4 to 0.9	0.08	0.4	0.2 to 0.8	0.02
Histology	1.4	0.6 to 2.9	0.4	2.2	0.6 to 8.5	0.3
Origination	1.0	0.99 to 1	1.0	1.0	0.99 to 1	1.0
Location	1.6	0.3 to 8.1	0.6	2.4	0.5 to 12.8	0.1

Note: OR, Odds ratio; CI, confidence interval.

Table 4 Logistic regression analysis associated the factors with R0 resection

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Gender						
Male	Reference			Reference		
Female	1.6	0.5 to 5.3	0.5	6.5	0.2 to 17.7	0.3
Age	1.0	0.9 to 1.1	0.4	1.0	0.8 to 1.2	0.9
Size	0.2	0.1 to 0.8	0.02	0.2	0.03 to 0.9	0.04
Histology	1.0	0.7 to 1.4	0.8	1.8	1.1 to 7.2	0.5
Origination	1.0	0.99 to 1.0	1.0	1.0	0.99 to 1.0	1.0
Location	0.7	0.3 to 1.6	0.4	2.1	0.9 to 11.9	0.2

Note: OR, Odds ratio; CI, confidence interval.

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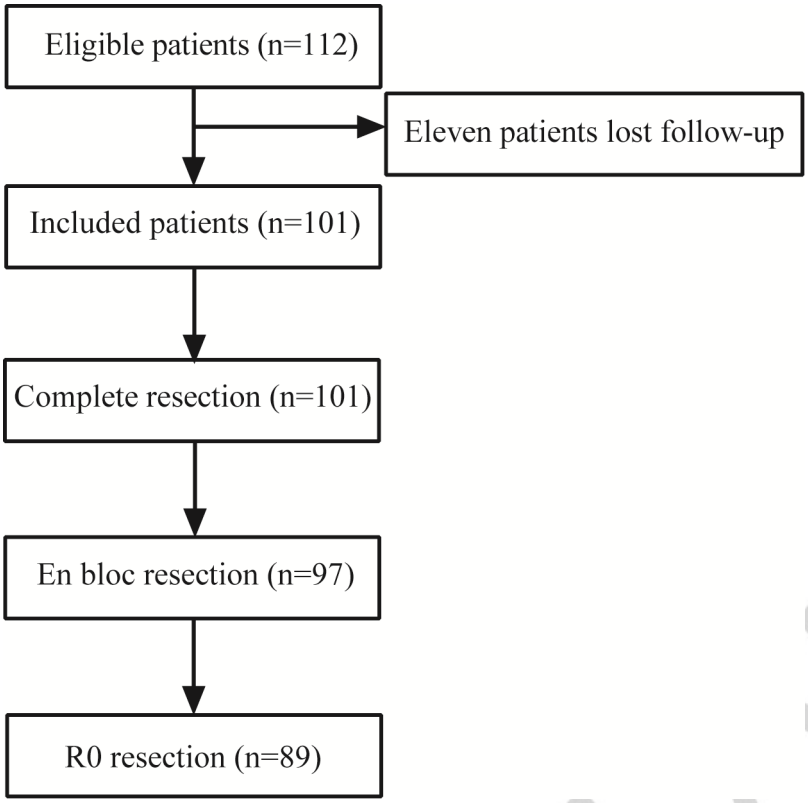

Figure 1: Flow chart.

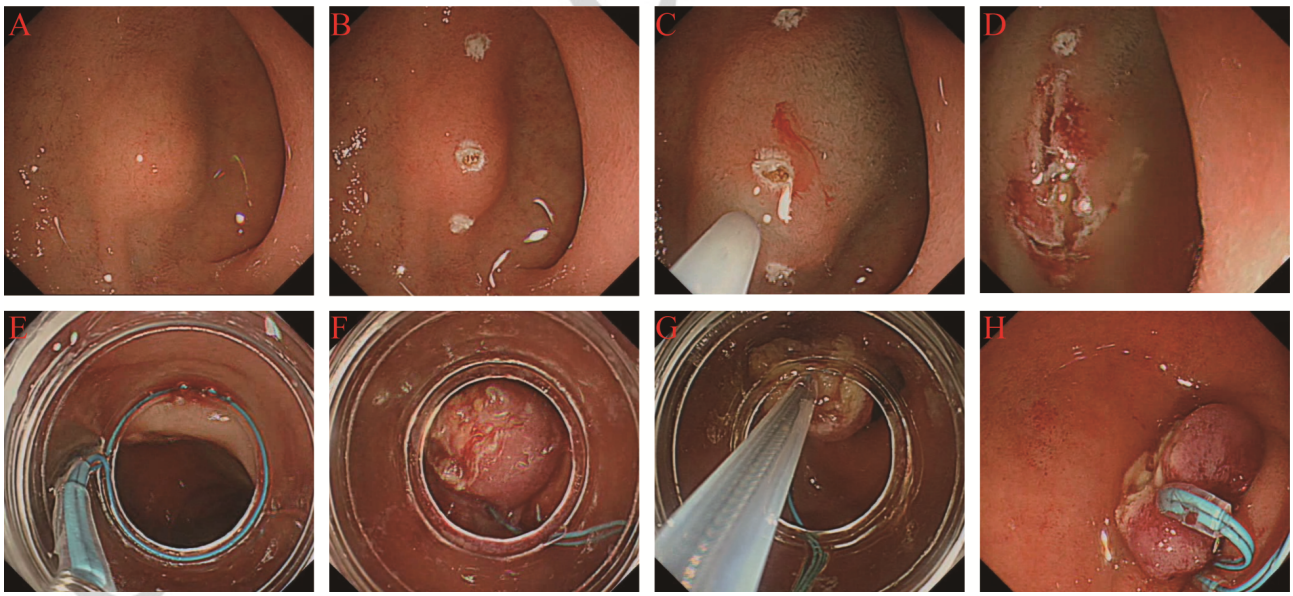

Figure 2: A, Duodenal SEL; B, Marking dots; C, Submucosal injection; D, A vertical cross incision; E, Assembling endoloop and ligation device; F, Ligation of SEL; G, Removing SEL; H, Closing the defect.

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