Original Article

Endoscopic Resection of Gastric Submucosal Tumors: A Comparison of Endoscopic Nontunneling with Tunneling Resection and a Systematic Review

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ABSTRACT

Background/Aim: Endoscopic tunneling resection is a relatively novel endoscopic technology for removing gastric submucosal tumors. Our study aimed to compare the differences between tunneling and nontunneling resection for gastric submucosal tumors. **Materials and Methods:** Resections of gastric submucosal tumors (n = 97) performed from 2010 to 2015 at our endoscopy center were reviewed, and PubMed was searched for clinical studies on gastric submucosal tumor resection by endoscopic nontunneling and tunneling techniques. **Results:** At our endoscopy center, nontunneling (Group 1) and tunneling resection (Group 2) were performed for 78 and 19 submucosal tumors, respectively; median tumor diameters were 15 and 20 mm (P = 0.086), median procedural times were 50 and 75 min (P = 0.017), successful resection rates were 94.9% (74/78) and 89.5% (17/19) (P = 0.334), and en bloc resection rates were 95.9% (71/74) and 94.1% (16/17) (P = 0.569) in the Groups 1 and 2, respectively. Postoperative fever, delayed hemorrhage and perforation, hospitalization time, and hospitalization expense were statistically similar between the 2 groups. A literature review on gastric submucosal tumor resection suggested that the en bloc resection rates of the two methods for tumors with a median diameter of 15–30 mm were also high, and there were no relapses during the follow-up period. **Conclusions:** Both endoscopic nontunneling and tunneling resection seem to be effective and safe methods for removing relatively small gastric submucosal tumors. Compared with endoscopic nontunneling, tunneling resection does not seem to have distinct advantages for gastric submucosal tumors, and has a longer mean operative time.

Key Words: Endoscopic full-thickness resection, endoscopic submucosal dissection, endoscopic submucosal tunnel dissection, gastric submucosal tumor, submucosal tunneling endoscopic resection

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To date, studies[1,2] on successful endoscopic resection of gastric submucosal tumors have been reported, suggesting that endoscopic resection of gastric submucosal tumors with relatively small size seems to be feasible. Ye *et al.*[1] retrospectively analyzed 773 cases of submucosal tumors resected endoscopically. The median diameter of submucosal tumors was 1.7 (1.0–4.0) cm, en bloc resection rate was 97.1% without severe complications, and no recurrence occurred during a median follow-up period of 28 months. Another study[2] was from Korea, which indicated that it was feasible to selectively resect gastrointestinal stromal tumors by endoscopic methods and the recurrence rate was low during the 4-year follow-up period. With the development of endoscopic technology, endoscopic resection of gastric submucosal tumors may be gradually recognized and accepted.

At present, the main methods for resecting submucosal tumors are endoscopic submucosal dissection (ESD) and

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endoscopic full-thickness resection (EFTR), and they are considered endoscopic as nontunneling resections. A relatively new method for removing submucosal tumors is endoscopic tunneling resection, which was first reported by Inoue *et al*.[3] and initially used for the tumors of the esophagus and cardia. In contrast to endoscopic nontunneling resection (ESD and EFTR), tunneling resection is performed to resect a tumor through a tunnel created in the submucosal layer, and maintains the structural integrity of the mucosa, which facilitates postoperative recovery.[4] The main difference between endoscopic nontunneling and tunneling resection is that a tunnel is needed in the latter technique. For tunneling resection, the same method as in ESD or EFTR is used to resect the tumor after creating a submucosal tunnel. A recent study compared tunneling resection with endoscopic excavation for treating submucosal tumors of the esophagus and cardia, and concluded that tunneling resection was the better choice for submucosal tumor sizes of >10 mm.[5] However, there have been no comparative studies of nontunneling and tunneling resection for gastric submucosal tumors.

To compare the differences between the two endoscopic methods, we retrospectively analyzed the cases of gastric submucosal tumors resected at our endoscopy center, and systematically reviewed the published studies on the endoscopic resection of gastric submucosal tumors.

MATERIALS AND METHODS

Retrospective analysis of submucosal tumor cases at our endoscopy center

Case selection

We retrospectively reviewed the case histories of submucosal tumor patients who underwent endoscopic nontunneling or tunneling resection from 2010 to 2015 at our digestive endoscopy center, Nanfang Hospital, Southern Medical University, Guangzhou, China. The submucosal tumors in these patients mainly consisted of gastric stromal tumor, leiomyoma, or lipoma. Prior to resection, these patients underwent endoscopic ultrasonography examinations to evaluate the indications for endoscopic treatment. All patients gave signed informed consent for endoscopic treatment as well as for the study. The study protocol was approved by the institute's ethics committee on human research. All the submucosal tumors were resected by endoscopy physicians who had plenty of experience on ESD, peroral endoscopic myotomy (POEM), and tunneling resection.

Endoscopic method and pathological assessment

Our protocols for resecting tumors were in accordance with those reported in the literature for endoscopic nontunneling (ESD[6-8] and EFTR[9,10]) and tunneling resection.[11] Tumors were subjected to pathological examination after resection, and were independently reviewed by two pathologists. En bloc resection was defined as complete resection of a submucosal tumor in a single piece.

Collection of basic information on the cases at our endoscopy center

Detailed information on the cases included age, gender, tumor size, location, origin of tumor in the submucosa or muscularis propria, resection method, operative time, complications during resection, successful and complete resection, postoperative fever, severe abdominal pain (requiring analgesic drugs in the clinic), and postoperative complications.

Statistical analysis

All data were analyzed using the Statistical Package for the Social Sciences version 19.0 software. Quantitative data with a normal distribution were expressed as mean ± standard deviation (SD) and analyzed by *t*-test; quantitative data with a non-normal distribution were expressed as median (interquartile range) and analyzed using the Mann–Whitney U test. Classifiable variables were tested by Chi-square analysis. When the expected frequency in more than 20% frames of R×C contingency table was <5 or the expected frequency in any frame was <1 , Fisher's exact probability test was used to analyze the data. $P < 0.05$ in a two-sided hypothesis test was considered to be a significant difference.

Literature review of submucosal tumor resection by endoscopic nontunneling (endoscopic submucosal dissection and endoscopic full-thickness resection) and tunneling resection

The PubMed database was searched for clinical studies regarding endoscopic nontunneling and tunneling resection of tumors. The search terms were (gastric OR stomach) and (submucosal neoplasm OR submucosal lesion OR submucosal tumor) and (stromal tumor OR stromal neoplasm). The retrieval fields were titles and abstracts.

All selected studies conformed to the following criteria: Resection of submucosal tumors were performed by endoscopic nontunneling (ESD and EFTR) or tunneling resection, including endoscopic submucosal tunnel dissection (ESTD) and submucosal tunneling endoscopic resection (STER); all the information required for our study could be extracted from the original research. Excluded from the present study were case reports, reviews, and meta-analyses, or unavailable full paper text. We summarized and analyzed the following data: Resected tumor size, location, and origin of tumor from the submucosa or muscularis propria, pathological type, operative time, complications, rate of complete resection, and follow-up information.

RESULTS

Retrospective analysis of submucosal tumor cases at our endoscopy center

Characteristics of gastric submucosal tumors

Data of 97 submucosal tumors were collected in our retrospective study. Of these, 78 were resected by endoscopic nontunneling (Group 1) and 19 were resected by tunneling (Group 2). As shown in Table 1, the median tumor sizes for the 2 groups were 15 mm and 20 mm (P = 0.086), respectively. The 2 groups were statistically similar in the distribution of pathological types of submucosal tumors (P = 0.744); the proportions of stromal tumor, leiomyoma, and lipoma were 43.8%, 31.5%, and 16.4% in Group 1; and 43.8%, 43.8%, and 12.5% in Group 2, respectively. The tumor locations of the two groups were not significantly different (P = 0.174); in Groups 1 and 2, there were 30 (38.5%) and 11 (57.9%), respectively, in the fundus; 23 (29.5%) and 2 (10.5%), respectively, in the gastric body; and 25 (32.1%) and 6 (31.6%), respectively, in the gastric antrum. In addition, the two groups were similar in the proportions of tumors originating from the submucosa and muscularis propria (P = 0.071).

Table 1: Resection-related parameters and histopathologic evaluation of gastric submucosal tumors removed by endoscopic nontunneling and tunneling resection at our endoscopy center

	Nontunneling resection (*n*=78)	Tunneling resection (*n*=19)	*P*
Age (Years) (mean±SD)	49.53±10.15	47.16±7.855	0.345
Male/female	31/47	9/10	0.545*
Size (mm) [Median (interquartile range)]	15 (8)	20 (10)	0.086
Size (mm)			
≤20	63/76 (82.9%)	13/19 (68.4%)	0.200†
>20	13/76 (17.1%)	6/19 (31.6%)	
Size (mm)			
≤20	63/76 (82.9%)	13/19 (68.4%)	0.282†
20-30	5/76 (6.6%)	3/19 (15.8%)	
>30	8/76 (10.5%)	3/19 (15.8%)	
Tumor location			
Gastric fundus	30/78 (38.5%)	11/19 (57.9%)	0.174
Gastric body	23/78 (29.5%)	2/19 (10.5%)	
Gastric antrum	25/78 (32.1%)	6/19 (31.6%)	
Tumor layer on endoscopic ultrasonography			
Muscularis propria layer	52/77 (67.5%)	16/18 (88.9%)	0.071*
Submucosal layer	25/77 (32.5%)	2/18 (11.1%)	
Perforation during resection	21/78 (26.9%)	7/19 (36.8%)	0.392*
Endoclip	19/21 (90.5%)	/	
Endoclip + nylon loop	1/21 (4.8%)	/	
Endoclip + omentum	1/21 (4.8%)	/	
Successful resection (Yes/No)	74/4	17/2	0.334†
Time for resection (minutes) [Median (interquartile range)]	50 (46)	75 (65)	0.017
En bloc resection	71/74 (95.9%)	16/17 (94.1%)	0.569†
Tumor shape (round/irregular)	58/12	15/3	1.0†
Histopathologic evaluation			
Gastrointestinal stromal tumor	32/73 (43.8%)	7/16 (43.8%)	0.744†
Leiomyoma	23/73 (31.5%)	7/16 (43.8%)	
Lipoma	12/73 (16.4%)	2/16 (12.5%)	
Others (carcinoid, neurilemmoma, etc.)	6/73 (8.2%)	0	

*Pearson's Chi-square test; †Fisher's exact test

Feasibility evaluation of endoscopic resection of submucosal tumors

The median operative times for the nontunneling and tunneling resection were 50 (46) min and 75 (65) min (P = 0.017), respectively. The rates of successful resection of tumors in the nontunneling resection and tunneling groups were 94.9% (74/78) and 89.5% (17/19; P = 0.334), and the rates of complete resection were 95.9% (71/74) and 94.1% (16/17; P = 0.569), respectively. The perforation rates in the two groups were 26.9% (21/78) and 36.8% (7/19; P = 0.392) respectively, and all the perforations were successfully closed in both groups. For example, a submucosal tumor was successfully resected by nontunneling resection, and the other by tunneling resection, as shown in Figures 1 and 2, respectively. Perforations that occurred during nontunneling and tunneling resection were successfully closed with endoclips combined with endoloops or by endoclips alone.

Postoperative conditions

As shown in Table 2, some cases of fever was reported in patients with resected submucosal tumors developed on the first day after resection. The proportions of patients with fever in the nontunneling and tunneling groups were similar (P = 0.10): 29.4% (20/68) and 50% (9/18), respectively. Most of these patients had low-grade fever: 12 (70.6%) in the nontunneling group and 6 (85.7%) in the tunneling group. No patient in either group experienced postoperative perforation. In the nontunneling and tunneling groups, 11 and 4 patients had obvious abdominal pain after resection (P = 0.731), respectively.

In the nontunneling and tunneling groups, the total hospitalization days were 9.14 ± 2.8 and 9.33 ± 2.4, respectively (P = 0.796), and the total hospitalization costs were 25503 ± 9802 Chinese yuan (CNY) and 29240 ± 8865 CNY (P = 0.163), respectively.

Table 2: Clinical information on patients with gastric submucosal tumors resected by endoscopic nontunneling and tunneling resection at our endoscopy center

	Non-tunneling resection (*n*=78)	Tunneling resection (*n*=19)	*P*
Coagulation parameters before procedure			
PT (seconds) (mean±SD)	12.013±1.098	11.941±0.951	0.806
INR (mean±SD)	1.046±0.094	1.052±0.079	0.810
Blood platelets (10^9/L) (mean±SD)	230±66	252±45	0.203
Fever after procedure (No/Yes)	48/20	9/9	0.10‡
Time of fever onset after procedure [Median (interquartile range)]	1 (0)	1 (1)	0.044
Temperature after procedure			0.629§
37.4∽38°C	12/17 (70.6%)	6/7 (85.7%)	
38.1∽39°C	5/17 (29.4%)	1/7 (14.3%)	
39.1°C∽	0	0	
Usage of antibiotics after procedure			
Time of antibiotic use [Median (interquartile range)]	0 (0)	0 (0)	0.716
Days of antibiotics use [Median (interquartile range)]	3 (3)	5 (2)	0.151
Delayed bleeding after procedure (No/Yes)	63/1	18/0	1.0§
Delayed perforation after procedure (No/Yes)	64/0	18/0	1.0§
Severe abdominal pain after procedure (No/Yes)	53/11	14/4	0.731§
Hospital stay (mean±SD)	9.14±2.8	9.33±2.4	0.796
Total cost of hospitalization (mean±SD) (CNY)	25,503±9802	29,240±8865	0.163

CNY Chinese Yuan; ‡Pearson's Chi-square test; §Fisher's exact test

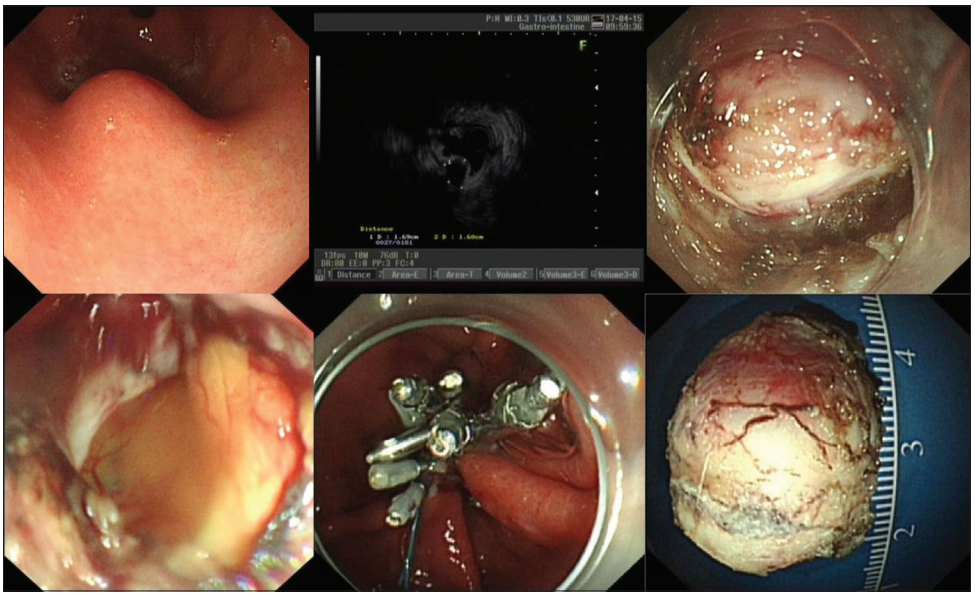

Figure 1: A submucosal tumor was successfully resected by endoscopic nontunneling resection

Summary and analysis of reported studies on resection of gastric submucosal tumors by endoscopic nontunneling or tunneling resection

As shown in Figure 3, the search of the PubMed database yielded 8 (294 tumors), 5 (166 tumors), and 2 (51 tumors) studies on gastric submucosal tumors resected by endoscopic non-tunneling (ESD[6-8,12-16] and EFTR[9,10,17-19]) and tunneling resection,[11,20] respectively. Related information was extracted from each study (Supplemental data). To better understand the feasibility of each method, the information was summarized and analyzed [Table 3].

Endoscopic submucosal dissection

In the selected studies,[6-8,12-16] the average diameter of gastric submucosal tumors resected by ESD was 15.14–29 mm, with 11% originating from the submucosa (32/294) and 89%

Table 3: Summary of published clinical studies on gastric submucosal tumor resection by endoscopic nontunneling (ESD, EFTR) and tunneling resection

Characteristics	Nontunneling resection		Tunneling resection [11,20]
	ESD[6-8,12-16]	EFTR[9,10,17-19]	
Article number (lesions)	8 (294)	5 (166)	2 (51)
Diameter range (mm)	3-60	5-54	8-50
Average diameter range (mm)	15.14-29	15.9-28.3	21,23
Layer	SM: 32/294 (11%) MP: 262/294 (89%)	MP: 100%‖	MP: 100%
Location	Cardia: 38/294 (13%) Fundus: 118/294 (40%) Body: 105/294 (36%) Antrum: 33/294 (11%)	Fundus: 88/166 (53%) Body: 73/166 (44%) Antrum: 5/166 (3%)	Fundus: 22/51 (43%) Body: 18/51 (35%) Antrum: 11/51 (22%)
Type	GIST: 169/294 (57%) Leiomyoma: 99/294 (34%) Others: 26/294 (9%)	GIST: 133/166 (80%) Leiomyoma: 21/166 (13%) Others: 12/166 (7%)	GIST: 24/51 (47%) Leiomyoma: 24/51 (47%) Others: 3/51 (6%)
Average operative time (minutes)	32.29-119.1	59.72-271	51.8, 75.1
Average operative time (minutes)††	<51.8: 32.29[13] 51.8-75.1: 52, 60.9, 63.41[8,14,16] >75.1: 81, 90, 110, 119.1[6,7,12,15]	51.8-75.1: 59.72[18] >75.1: 78.82, 90, 105, 271[9,10,17,19]	51.8, 75.1
Complete resection Rate (%)	≧90%:90-94.4%[7,8,12,14,15,] <90%:81.1,74.3,75%[6,13,16]	100%	100%
Severe infection after procedure	0	0	0
Death due to procedure	0	0	0
Number of surgeries	12	0	0
Average Follow-up (months)	6.13-24.2	6-8**	5,28
Follow-up (months)	1-51	0-24**	2-32
Recurrence/metastasis	no	no	No

MP: Muscularis propria; SM: Submucosa; ESD: Endoscopic submucosal dissection; EFTR: Endoscopic full thickness resection; GIST: Gastrointestinal stromal tumor; Others included schwannoma, ectopic pancreas, myofibroblastic tumor, glomus tumor, nerve sheath tumor, lipoma, granular cell tumor, carcinoid tumor, neurogenic tumors, ectopic spleen, fibroepithelioma, hamartoma, and others. ‖Three articles reported the layers of the tumors, while 2 did not; **Data were extracted from only 3 of the 5 articles included; ††Average operative time for endoscopic tunneling resection as a reference for comparison

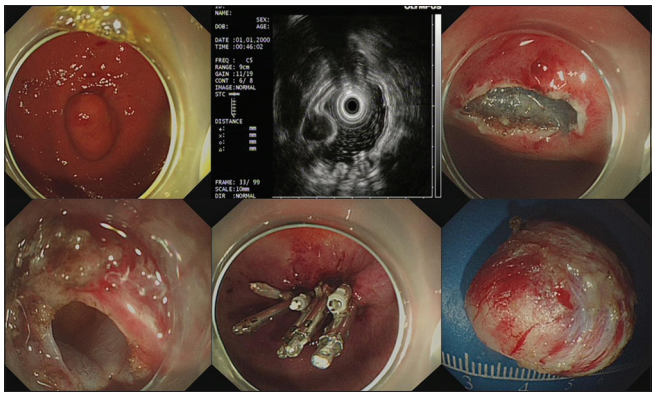

Figure 2: A submucosal tumor was successfully resected by endoscopic tunneling resection

from the muscularis propria (262/294). Tumors were mostly located in the fundus (118/294, 40%). Pathological types mainly included stromal tumor, leiomyoma, and lipoma, with gastric stromal tumor accounting for the highest proportion at 57% (169/294). Rates of complete resection mostly ranged from 90 to 94.4%,[7,8,12,14,15] and only 3 studies reported complete resection rates of 81.1%, 74.3%, and 75%.[6,13,16] No severe infection or death occurred in any successfully resected cases. No relapse or metastasis occurred in the follow-up period of 1–51 months.

Endoscopic full-thickness resection

The average diameter of submucosal tumors resected by EFTR was 15.9–28.3 mm. Most tumors were located in the fundus (88/166, 53%). The pathological types mainly included stromal tumor, leiomyoma, and lipoma. Gastric stromal tumor accounted for the highest proportion at 80% (133/166). The rates of complete resection were 100%. No severe infection or death occurred after the procedure. The follow-up time ranged from 0 to 24 months in 3 studies,[9,10,18] and there were no reports of relapse or metastasis.

Endoscopic tunneling resection

The average diameters of gastric submucosal tumors resected by tunneling were 21 mm and 23 mm in 2 studies.[11,20] All tumors originated from the muscularis propria. Most tumors

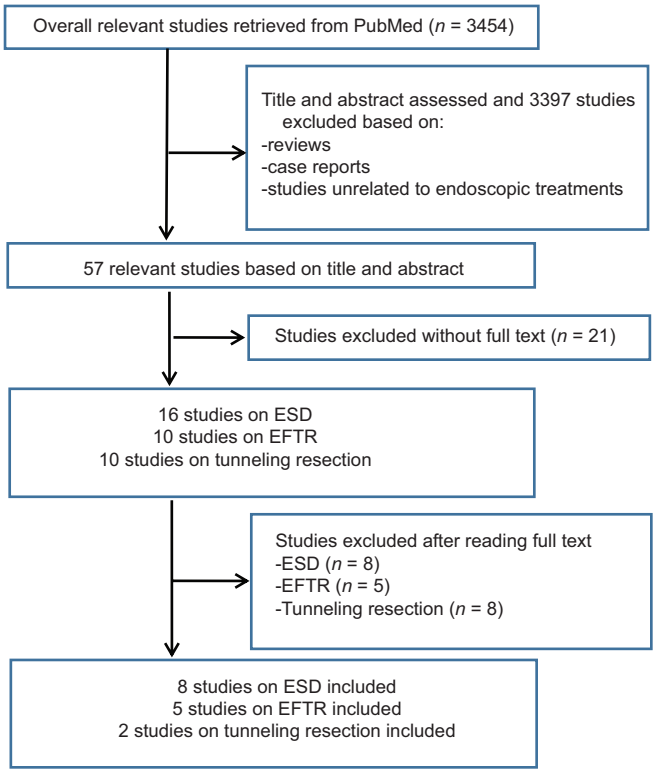

Figure 3: Study selection flow diagram

were located in the fundus (22/51, 43%). The pathological types mainly included stromal tumor, leiomyoma, and lipoma. Gastric stromal tumor and leiomyoma accounted for the highest proportion of tumors at 47% (24/51) and 47% (24/51), respectively. The rates of complete resection were 100%. No severe infection or death occurred after the procedure. The follow-up time ranged from 2 to 32 months and there was no relapse or metastasis.

DISCUSSION

In our study, the differences between endoscopic nontunneling and tunneling resection for gastric submucosal tumors were systematically analyzed and compared. Our study showed that they seem to be effective and safe for resecting some tumors; compared with nontunneling, tunneling resection as a novel endoscopic technique does not seem to have distinct advantages for resecting gastric submucosal tumors.

At our endoscopy center, the median diameters of gastric submucosal tumors resected by endoscopic nontunneling and tunneling were 15 mm and 20 mm, respectively. Published studies reported average diameters of tumors resected by non-tunneling ranged from 15.1 to 29 mm,[6-10,12-19] and the tumors resected by tunneling were 21–23 mm.[11,20] Thus, the average sizes of tumors resected by the two methods showed no obvious difference. In addition to tumor size, tumor location is also an important factor that should be considered to select an appropriate resection method. Normally, endoscopic nontunneling resection is not limited by tumor location. Unlike the esophagus, the gastric cavity is large and curved, and the tunneling procedure may be limited by tumor location; thus, only some gastric submucosal tumors are easily resected. Li *et al*. suggested that gastric submucosal tumors located close to the cardia in the lesser curvature of the gastric corpus and in the greater curvature of the gastric antrum are usually optimal indications for the tunneling method.[11] Thus, endoscopic nontunneling resection seems to be more widely used than tunneling resection for gastric submucosal tumors located in different parts of the stomach.

For gastric submucosal tumors, the complete endoscopic resection rate is an important index of the efficacy of endoscopic resection. Most studies[7-10,12,14,15,17-19] reported a high complete resection rate for nontunneling resection ranging from 90% to 100%. For tunneling, the complete resection rate was 94.1% at our endoscopy center, and two studies[11,20] reported complete resection rates of 100% for tumors from the muscularis propria. Consequently, both methods seem to be effective for the complete resection of gastric submucosal tumors. In addition, perforation is a major concern for tumor resection. At our endoscopy center, the perforation rates for nontunneling and tunneling resection during surgery were 26.9% and 36.8%, respectively. All perforations were closed successfully by endoscopic clips or nylon loops or by blocking the tunneling opening. In general, perforation during tunneling resection can be easily closed by blocking the tunnel opening; however, perforation during nontunneling resection can also be effectively closed with endoclips.[6-10,12-19] Further, to evaluate the efficacy of tumor resection, long-term follow-up is needed. In published studies, the proportions of gastric stromal tumors resected by endoscopic nontunneling[6-10,12-19] and tunneling resection[11,20] were 57–80% and 47%, respectively, and there were no cases of relapse or metastasis after average follow-up periods of 0–51 and 2–32 months, respectively.

In our study, the median operative time for endoscopic tunneling resection was significantly longer than that for nontunneling resection; thus, tunneling resection did not seem to be simpler and easier than nontunneling resection. The construction of a submucosal tunnel could contribute to the long operative time. In addition, other parameters such as postoperative fever, delayed hemorrhage and perforation, hospitalization time, and hospitalization expense were similar for both methods. In published studies of gastric submucosal tumors resected by the two methods,[6-20] no severe infections occurred after resection. In our study, the rates of postoperative fever in the patients with endoscopic surgery were relatively high, however, most of the patients

had only a low-grade fever. The studies[21,22] reported that the rates of fever ranged from 12% to 41.3%, however, most of postoperative fevers were low-grade and transient. Old patients and patients with large size tumors were considered to be risk factors of postoperative fever.[23]

There were several limitations to this study. First, this was a retrospective study, which is itself a limitation. Second, we tried to compare nontunneling with tunneling resection of gastric submucosal tumors. The sample size of the tunneling resection group in our study was relatively small, which may add to the difficulty of determining which method was better. Third, Joensuu *et al.*[24] suggested that most patients who underwent stromal tumor resection had a relapse within the first 5 years of follow-up. However, most of the studies in our analysis had a median follow-up of 2 years. Thus, longer follow-up time may be needed.

CONCLUSION

In conclusion, both endoscopic nontunneling and tunneling resection seem to be effective and safe methods for removing gastric submucosal tumors. We found no significant differences between the two methods, except for the longer operative time in tunneling resection; hence, it appears that endoscopic tunneling resection does not have distinct advantages for gastric submucosal tumors. The number of cases of tunneling resection in this comparative study was relatively small, and a prospective study with a larger sample size may be needed.

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Conflicts of interest
There are no conflicts of interest.

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