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## Endoscopic resection in subepithelial lesions of the upper gastrointestinal tract; experience of a tertiary referral hospital in The Netherlands.

Cynthia Verloop, Lieke Hol, Marco Bruno, Lydi Van Driel, Arjun D Koch.

Affiliations below.

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### Abstract:

#### Objectives

Histological confirmation of subepithelial lesions (SELs) in the upper gastrointestinal tract remains challenging. Endoscopic resection of SELs is increasingly used for its excellent diagnostic yield and opportunity to do away with continued surveillance. In this study, we aimed to evaluate the indications, success-rates and complications of different endoscopic resections techniques for SELs in a large, tertiary referral hospital in Rotterdam, The Netherlands.

#### Methods

Data between October 2013 and December 2021 were retrospectively collected and analyzed. Main outcomes are R0-resection rate, en bloc resection rate, recurrence rate and procedure-related adverse events (Clavien-Dindo). Secondary outcomes are procedure time, need for surgical intervention and clinical impact on patient management.

#### Results

A total of 58 patients were referred for endoscopic resection of upper gastro-intestinal SELs. The median diameter of lesions was 20 mm (range 7-100mm). Median follow-up time was 5 months (range 0.4-75.7). Forty-eight (83%) procedures were completed successfully leading to en bloc resection in 85% and R0-resection in 63%. Procedure-related adverse events occurred in 6 patients (13%). Severe complications (CD grade 3a) were seen in 3 patients. Local recurrence rate for (pre)malignant diagnosis was 2%. Additional surgical intervention was needed in 7 patients (15%). A total of 32 patients (67%) could be discharged from further surveillance after endoscopic resection.

#### Conclusions

Endoscopic resection is a safe and effective treatment for SELs and offers valuable information in undetermined SELs in which repeated sampling attempts have failed to provide adequate tissue for diagnosis.

### Corresponding Author:

Cynthia Verloop, Erasmus Medical Center, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands, verloopc@maasstadziekenhuis.nl

### Affiliations:

Cynthia Verloop, Erasmus Medical Center, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands

Cynthia Verloop, Maasstad Hospital, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands

Lieke Hol, Maasstad Hospital, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands

[...]

Arjun D Koch, Erasmus Medical Center, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands

## Tables

<b>Clinical and patient demographics of 58 patients referred for endoscopic resection of upper gastrointestinal SELs.</b>	
<b>Gender, male (n, %)</b>	27 (47%)
<b>Age (median, range)</b>	58 (20-81)
<b>Incidental findings (n, %)</b>	27 (47%)
<b>Indication for endoscopic resection (n, %)</b>	
<i>Suspected or proven (pre)malignant SEL</i>	34 (59%)
<i>Symptomatic lesion</i>	10 (17%)
<i>Undetermined SEL and patient-preference</i>	12 (21%)
<i>Previous incomplete endoscopic resection</i>	2 (3%)
<b>Tumor diameter in mm (median, range)</b>	20 (7-100)
<b>Tumor location</b>	
<i>Oesophagus</i>	8 (14%)
<i>Stomach</i>	42 (72%)
<i>Duodenum</i>	8 (14%)
<b>Pre-procedural determined layer of origin</b>	
<i>Muscularis mucosae</i>	9 (16%)
<i>Submucosa</i>	19 (33%)
<i>Muscularis propria</i>	27 (47%)
<i>Muscularis propria with extraluminal growth</i>	3 (5%)
<b>Follow-up, months (median, range)</b>	4,9 (0.4-75.7)

Table 1 Clinical and patient demographics. SEL = subepithelial lesion, mm = millimeters.

<b>Histopathological diagnosis in total study population</b>	
Brunner's glands	1
Calcifying fibrous polyp	1
GIST (low-risk)	21
Hamartoma	1
Heterotopic pancreas	7
Inflammatory fibroid polyp	3
Leiomyoma	7
Leiomyosarcoma	2
Lipoma	3
Neuroendocrine tumor	
<i>Low-grade (1)</i>	6
<i>Intermediate-grade (2)</i>	2
Pyloric gland adenoma	1
Reactive cells	1
Unknown because of unsuccessful endoscopic resection	2

Table 2 Overview of histopathological diagnosis of included patients. GIST = gastrointestinal stromal tumor.

<b>Overview of primary and secondary outcomes of endoscopic resection procedures</b>			
	<b>EFTR</b>	<b>ESD</b>	<b>STER</b>
<b>Total number of procedures</b>	22	28	8
<b>Tumor diameter, mm (median, range)</b>	15 (9-25)	21.5 (7-100)	35 (10-60)
<b>Technical success (n, %)</b>	17 (77)	25 (89)	6 (75)
<b>En bloc resection (n, %)</b>	12 (71)	23 (92)	6 (100)
<b>R0-resection (n, %)</b>	13 (76)	13 (52)	4 (67)
<b>R1-resection in premalignant diagnosis (n, %)</b>	3 (18)	8 (29)	1 (17)
<b>Local recurrence (n, %)</b>	1 (6)	1 (4)	-
<b>Procedure time, min (median, range)</b>	35.5 (19-120)	72 (9-240)	138.5 (44-487)
<b>Additional surgical intervention (n, %)</b>	2 (9)	5 (18)	-
<b>Post-procedural complications (n, %)</b>	2 (9)	4 (14)	1 (13)

Table 3 Overview of primary and secondary outcomes of endoscopic resection procedures. EFTR = Endoscopic Full Thickness Resection. ESD = Endoscopic submucosal dissection. STER = Submucosal Tunneling Endoscopic Resection. R0 = pathological radical resection. R1 = pathological irradical resection.

<b>Overview of procedure-related complications</b>				
<b>Clavien-Dindo classification</b>	<b>EFTR</b>	<b>ESD</b>	<b>STER</b>	<b>Total</b>
No complications (n, %)	20 (91)	24 (86)	7 (88)	51 (88)
1 (n, %)	1 (5) <i>Post-ERCP pancreatitis</i>	2 (7) <i>Nausea and pain</i>	-	3 (5)
2 (n, %)	-	-	-	-
3 (n, %)	1 (5) - <i>Obstruction of common bile duct due to OTS-clip</i>	2 (7) <i>Additional endoscopy for bleeding</i>	1 (13) <i>Additional endoscopy for pain after dehiscence of mucosal access</i>	4 (7)
4 (n, %)	-	-	-	-
5 (n, %)	-	-	-	-

Table 4 Overview of procedure-related complications. EFTR = Endoscopic Full Thickness Resection. ESD = Endoscopic submucosal dissection. STER = Submucosal Tunneling Endoscopic Resection. OTS-clip = over the scope clip. ERCP = Endoscopic retrograde cholangiopancreatography.

# 1 Introduction

2 Subepithelial lesions (SELs) appear as a mass or bulge covered by normal-appearing mucosa and  
3 originate from the gastrointestinal wall [1]. Only 10-15% are (pre)malignant and require follow-up or  
4 even endoscopic or surgical resection [2].

5 As SELs are covered by normal-appearing mucosa, conventional endoscopy with biopsies are usually  
6 insufficient to obtain a definite diagnosis. Endoscopic ultrasonography (EUS) is the preferred primary  
7 diagnostic modality because of its ability to determine the lesion and the ability to obtain a tissue  
8 diagnosis by means of EUS-guided fine needle aspiration (EUS-FNA) or biopsy (EUS-FNB) [3, 4]. The  
9 reported diagnostic accuracy for EUS-FNA/B, however, varies widely.

10 Endoscopic resection can be used as diagnostic tool as well as a treatment for small SELs [2].  
11 Different methods for endoscopic resection have been described including endoscopic mucosal  
12 resection (EMR), submucosal tunneling endoscopic resection (STER), endoscopic submucosal  
13 dissection (ESD) and endoscopic full-thickness resection (EFTR). Compared with surgery, endoscopic  
14 resection is less invasive, has short recovery time, and preserves the normal anatomy and function  
15 of the digestive tract [5].

16 Choice and success rate of the different endoscopic resection methods depends on the layer of  
17 origin, the location of a lesion and the experience of the endoscopist. The rates for complete  
18 resection vary between 85% and 98%, with reported adverse event rates around 5-10% [5-7]. Data  
19 on efficacy and complications of endoscopic en bloc resection limited and mainly derives from Asian  
20 countries [8].

21 Therefore, this retrospective study aims to evaluate the indications, success rates and complications  
22 of different endoscopic resection techniques in SELs in a large academic hospital in The Netherlands.

## 23 Methods

### 24 Patients and data collection

25 This study was approved by the Medical Research Ethics Committees United (MEC-U). Data of  
26 patients who underwent endoscopic resections for a SEL in the upper gastrointestinal tract at the  
27 Erasmus MC Cancer Institute (University Medical Center Rotterdam, The Netherlands) between  
28 October 2013 and December 2021 were analyzed. All consecutive adult (>18 years old) patients that  
29 underwent endoscopic resection for a SEL during this time period were included.

30 The following data were collected: patient demographics, lesion characteristics, such as size (mm),  
31 determined by EUS or endoscopy when available, procedure-related outcomes, histological data and  
32 follow-up data.

### 33 Outcome parameters

34 The main outcomes of this study are technical success rate of endoscopic resection, en bloc  
35 resection rate, pathological radical (R0) resection rate, procedure-related adverse events and  
36 recurrence rate. Technical success rate is defined as the percentage of procedures in which the  
37 intended endoscopic resection technique was completed successfully, without early termination of  
38 the procedure or the need for conversion to another technique or surgical intervention. En bloc  
39 resection rate is defined as number of lesions that are macroscopically completely and intact  
40 removed as described by the endoscopist. R0 resection indicates a microscopically margin-negative  
41 resection determined by the pathologist. Secondary outcomes are procedure time, need for surgical  
42 intervention and the clinical impact of endoscopic resection on patient management. The clinical  
43 significance of endoscopic resection is defined by the number of patients who can be discharged  
44 from further surveillance following a successfully completed procedure. Adverse events are graded  
45 according to the Clavien-Dindo scoring system [9].

### 46 Procedures and follow-up

47 The endoscopic resections described in this study were performed by two experienced endoscopists  
48 from the gastroenterology department with a colonic FTRD. The endoscopist determined the type of  
49 endoscopic resection based on lesion characteristics such as location, size and previous imaging.

50 After all endoscopic procedures, patients were observed in the recovery unit. When there were no  
51 signs of delayed complications, the patients were discharged on the same day. The patients are  
52 prescribed high dose proton pump inhibitors orally (40mg twice daily for at least four weeks) and  
53 advised to keep a clear liquid diet for 12-24 hours as per local protocol.

54 All patients returned to visit the outpatient department within one to three weeks after the  
55 procedure for follow-up. Dependent of clinical and histopathological outcomes, patients were  
56 discharged from further follow-up or entered a surveillance program. When the histopathological  
57 diagnosis was GIST, NET or another malignant outcome, the decision for further management was  
58 discussed in a multidisciplinary sarcoma or neuro-endocrine tumor team considering features of the  
59 lesion such as size and histopathological risk assessment and comorbidities of the patient.

## 60 Results

61 A total of 58 patients with 67 SELs in the upper gastrointestinal tract were referred for endoscopic  
62 resection in the study period and included in this study.

63 Clinical and patient demographics are shown in Table 1.

64 The indications for endoscopic resection were distributed over 3 major groups; referral because of  
65 suspected or proven (pre)malignant diagnosis (e.g. GIST or NET) (n=34), a symptomatic lesion (n=10)  
66 or uncertain diagnosis despite previous attempts for tissue acquisition and preference of the patient  
67 for removal of the lesion instead of surveillance (n=12).

68 A total of 58 procedures were initiated, including 22 EFTRs, 28 ESDs, and 8 STER-procedures. The  
69 median diameter of all lesions was 20mm (range 7-100mm). Forty-eight out of 58 procedures (83%)  
70 could be successfully completed. En bloc resection was achieved in 41/48 patients (85%) and  
71 pathological radical (R0) resection in 30/48 patients (63%). Procedure-related adverse events were  
72 seen in 7 patients (12%). The overall local recurrence-rate after en bloc endoscopic resection was 4%  
73 (n=2) during a median follow-up of 5 months (range 0.4-75.7), one inflammatory polyp and one NET.  
74 Additional complementary surgical intervention was needed in 7 patients (12%).

75 Twenty-seven patients (47%) had benign histopathological outcome. Most of these patients (10/27,  
76 37%) were referred for resection because a (pre)malignant diagnosis was suspected, followed by  
77 uncertain diagnosis despite previous attempts for histology as reason for resection (9/27, 33%). For  
78 this reason, benign lesions as heterotopic pancreas were resected.

79 A total of 31 patients (31/58, 53%) had definitive (pre)malignant histopathological diagnosis (GIST,  
80 NET or leiomyosarcoma) (table 2). Fifteen out of these 31 (48.4%) patients had prior histology with a  
81 (pre)malignant histopathological outcome. The other 16 patients were referred because a GIST or  
82 NET was suspected based on EUS-features or radiologic imaging. All confirmed GIST lesions were  
83 deemed very low to low risk based on mitotic count. Five out of 8 NETs were radically resected (R0,  
84 62.5%). Of the 19 endoscopically resected GISTs, 10 were R0-resected (52.6%).

85 An overview of the outcomes for endoscopic resection are shown in table 3. An overview of  
86 procedure-related complications according to Clavien-Dindo classification is shown in table 4.

## 87 **EFTR**

88 The EFTR was successful in 17/22 patients (77%) with a median lesion size of 15mm (range 9-25).  
89 Most EFTR were performed in the stomach (n=14), the other 8 were performed in duodenum.  
90 Endoscopic en bloc resection was accomplished in 12 out of 17 procedures (71%) [Supplementary  
91 material: Figure I]. Three (18%) of the lesions that were not radically resected (R1) concerned a NET  
92 (n=3) (grade 1-2), but none recurred during a median follow-up time of 8 months (range 0.3-75.7).

93 In 5/22 patients EFTR was unsuccessful, because the lesion could not be pulled into the cap based on  
94 size or rigidity. Eventually, 2/5 patients with incomplete procedures were referred for surgical wedge



95 excision of the lesions as there was a high suspicion of a malignant diagnosis, 2/5 patients were  
96 rescheduled for ESD leading to successful resection of GIST and 1 patient remains in surveillance to  
97 date (47 months follow-up).

98 Two patients (9%) experienced procedure-related complications. In both cases, the (pre)malignant  
99 lesions were located in duodenum, near the ampulla of Vater. Given the patients' comorbidities,  
100 surgical intervention was not viable and endoscopic resection was deemed to be the second best  
101 option. One patient developed a mild post-ERCP pancreatitis after pre-procedural placement of a  
102 protective stent in the common bile duct (Clavien-Dindo 1). Another patient developed obstruction  
103 of the common bile duct due to the position of the OTS-clip. Later, the OTCS-clip was removed.  
104 (Clavien-Dindo 3a).

## 105 **ESD**

106 Of 28 initiated ESD-procedures, 25 (89%) procedures were successful [Supplementary Material:  
107 Figure II] in lesions with a median size of 21.5 (range 7-100) . All ESD were performed in stomach.  
108 Three procedures were unsuccessful due to extraluminal growth (n=2) or because the lesion was too  
109 large to resect endoscopically (n=1). En bloc resection rate was 92% (23/25), the R0 resection rate  
110 was 52% (13/25). In patients with R1-resection, 8/12 lesions (29%) were low-risk GIST, other lesions  
111 were heterotopic pancreas (n=3/12) and an inflammatory polyp (n=1/12). Despite R1-resection of  
112 GIST, 5/8 patients were discharged because of benign characteristics and en bloc resection of the  
113 lesion. Local recurrence after ESD developed in one patient during a median follow-up time of 7  
114 months (range 0.4-69.3), this was a grade I NET.

115 In one frail elderly patient, a symptomatic GIST was too large (60mm) to be removed after ESD  
116 through the mouth. Consequently, the tumor was left in the stomach following dissection, making  
117 the assessment of resection margins unfeasible. Resection margins could therefore not be  
118 evaluated. Surgical intervention was not considered an option for the patient. A follow-up visit was  
119 occurred two months after the intervention. The symptoms subsided and the patient remained in  
120 good health. Therefore, further monitoring was deemed unnecessary.

121 As shown in Table 4, 4 patients experienced post-procedural complications. Two patients presented  
122 with melena and needed additional endoscopy to treat the post-procedural bleeding (Clavien-Dindo  
123 3a). Two patients needed hospitalization for observation of symptoms such as nausea or pain  
124 (Clavien-Dindo 1).

125 Additional surgery (n=5) was successfully performed in four patients with an unsuccessful  
126 endoscopic resection, resulting in radical resection of 3 GISTs and 1 leiomyoma, and in 1 patient with  
127 an R1- resection of a GIST.

## 128 **STER**

129 All patients underwent STER because the lesion was located in the esophagus. The lesions had a  
130 median size of 35mm (range 10-60mm). Of 8 procedures, 6 were successful (75%) and en bloc  
131 resection was achieved [Supplementary material: figure III]. Despite circumferential dissection, one  
132 lesion could not be removed because of fibrosis. The supplying blood vessels were transected and  
133 the lesion was left in situ. Per-procedural biopsies showed leiomyoma. After three months the lesion  
134 decreased in size and the patient reported resolvment of dysphagia.

135 The lesions with irradical resection margins were all leiomyomas. However, radical resection could  
136 not be determined in one patient due to damaging of the lesion when passing through the upper  
137 esophageal sphincter. This was a low-grade leiomyosarcoma for which surveillance was advised in  
138 the referring hospital.

139 One patient was hospitalized after the procedure because of progressive thoracic pain caused by a  
140 post-procedural dehiscence of the mucosal access with spill into the submucosal tunnel. This  
141 dehiscence was closed by clipping a mucosal flap over the defect. The patient recovered swiftly with  
142 additional antibiotics (Clavien-Dindo 3a).

## 143 **Clinical impact on patient management**

144 An overview of the clinical impact of the endoscopic resections in this study is shown in figure 1.

145 Of 48 completed procedures, 32 patients (67%) were discharged from further surveillance after the  
146 procedure. The majority of these patients (20/32) had R0-resection of a histopathological benign  
147 lesion (n = 13) or low-risk (pre)malignant diagnosis (n = 7). In addition, 12 patients with R1-resections  
148 could also be discharged from further follow-up because of benign histopathological outcome (n=7),  
149 a diagnosis of low-risk GIST in a patient with severe comorbidities (n=1) or benign characteristics in  
150 the histopathological sample in combination with en bloc resection of the lesion (n=3). One  
151 discharged patient with R1-resection of low-risk GIST achieved additional surgical wedge excision  
152 showing no residual malignant cells in the histopathological sample. No local recurrence is known to  
153 have occurred in these patients during a median follow up time of 1 month (range 0.3-69.3).

154 A total of 16 patients (33%) entered a surveillance program. Three patients had irradical resection  
155 margins of GISTs, 3 other patients had low-grade NETs. The other 10 patients had radical resection  
156 margins, but the histopathological diagnosis (e.g. NET (n=6), large, recurrent or multiple GIST (n=3)  
157 or leiomyosarcoma (n=1)) entailed that the patient had to enter a surveillance program. During a  
158 median follow-up period of 7 months (range 0.4-69.3), one patient developed a local recurrence of a  
159 neuroendocrine tumor (NET) after undergoing ESD and one patient had local recurrence of a  
160 symptomatic inflammatory fibroid polyp after EFTR.

## 161 Discussion

162 Adequate tissue sampling is essential to achieve a diagnosis that distinguishes between  
163 (pre)malignant lesions requiring follow-up or resection, and non-neoplastic lesions, which require no  
164 additional surveillance. In addition, histological diagnosis is important for risk stratification and  
165 subsequent management of a NET and a GIST. Current tissue acquisition methods, however, have  
166 their limitations and optimal management strategy remains unclear, especially in small SELs [10].  
167 This retrospective clinical data study in 58 patients with SELs demonstrates endoscopic resection  
168 could provide a safe and effective treatment with a technical success-rate of 83%, and adverse event  
169 rate of 12%, achieving en bloc resection and R0-resection in 85% and 63% respectively. In addition,  
170 in only 12% additional surgery was needed and 67% of patients could subsequently be discharged  
171 from further surveillance after successful endoscopic resection.

172 Guidelines suggest obtaining tissue with EUS-guided fine needle aspiration (EUS-FNA), fine needle  
173 biopsy (EUS-FNB) or mucosal incision-assisted biopsy (MIAB) [2, 10, 11]. In clinical practice, EUS-FNA  
174 and EUS-FNB are the most widely used but have a poor diagnostic yield especially in lesions  
175 <20mm[12-14]. Current literature suggests that MIAB-techniques result in higher diagnostic yield.  
176 [15-17]. However, the reported diagnostic yield of these techniques is limited in small (<20mm)  
177 lesions (47–79%) [12-14] and all available MIAB-techniques can result in local fibrosis, which may  
178 hamper future attempts of endoscopic resection using for instance submucosal tunneling [18-20].  
179 This study indicates that endoscopic resection can be considered an effective diagnostic tool for  
180 small SELs with 36 out of 58 (62%) SELs being <20mm (range 7-100) [15, 16, 21].

181 Undiagnosed SELs often require intensive surveillance [2, 10], which may lead to a significant burden  
182 especially in young patients. In addition, previous data showed a low compliance (44.6%) for the  
183 recommended surveillance strategy [22]. In the most recent ESGE-guideline for the management of  
184 SELs, it is therefore suggested that resection is an option for undetermined SELs of < 20mm to avoid  
185 the need for intensive follow-up [10].

186 The challenge remains in setting correct eligibility criteria for choosing endoscopic resection. Since  
187 the current study was performed with clinical data from a tertiary referral hospital, specialized in  
188 GIST and NET treatment, most patients (59%) were referred for endoscopic resection because of a  
189 high suspicion or proven (pre)malignant SEL. Twelve patients (21%) were referred for endoscopic  
190 resection because of an undetermined SEL for which the patient expressed a preference to resection  
191 instead of surveillance. In this group with a median diameter of SEL of 18.5 mm (range 9-30 mm),  
192 the technical success-rate was 91.7% (11/12 procedures) with pathological (R0) resection rate of  
193 54.5% (6/11 procedures). Long-term surveillance could be prevented in 8/11 patients because of

194 benign histopathological outcome (n=6) or R0-resection of low-risk premalignant lesion (n=2). These  
195 results suggest that even though a R0-resection is not achieved, endoscopic resection can be safe  
196 and effective in managing small, undetermined SELs, as the majority are benign.

197 When considering the clinical impact of successful endoscopic resection, this study showed out of 48  
198 successful endoscopic resections, 32 (67%) patients could be discharged from follow-up. There are  
199 no direct comparisons between a follow-up strategy and direct diagnostic excision strategy.  
200 However, the findings in this study might indicate that endoscopic treatment can contribute in  
201 preventing the patient from unnecessary diagnostic and therapeutic procedures through diagnosing  
202 an undetermined lesion or curation of a malignant lesion.

203 Surgical wedge excision is considered to be the gold standard in Western guidelines for treatment of  
204 (malignant) SELs. In agreement with previous studies the choice for an endoscopic resection  
205 technique was dependent on the diameter and location of the lesion, and local expertise [7, 23].  
206 There are no previous studies directly comparing the different endoscopic resection techniques. In  
207 the current study, adverse events were seen in 12% (7/58 procedures), but these were only severe  
208 (CD  $\geq$  3) in 7% (4/58 procedures) and could be quickly resolved. These rates are consistent with  
209 previously reported adverse event rates, which range from 5-15% [7, 24]. The adverse event rates of  
210 endoscopic resection are comparable to laparoscopic resection techniques [25, 26]. Endoscopic  
211 resection can therefore be considered a safe, less invasive alternative for providing both diagnosis  
212 and treatment in SELs, with less procedure time, less blood loss and length of hospital stay [25, 27].

213 The optimal treatment of small GISTs still remains controversial. For intraluminal GISTs smaller than  
214 20 mm, resection and surveillance are both acceptable alternatives. For lesions up to 35 mm,  
215 endoscopic resection may be an alternative to laparoscopic wedge excision [10, 28]. The current  
216 study shows high technical success rates for EFTR (77%), ESD (89%) and STER (75%), with en bloc  
217 resection rate of 71%, 92% and 100% respectively. These outcomes for ESD are in concordance with  
218 previous literature, but higher successful resection rates are reported for EFTR and STER [7, 29, 30].  
219 A possible explanation for this could be that the average diameter of resected lesions in this study  
220 was relatively large which might have hampered successful performance of the EFTR- and STER-  
221 procedures. However, subgroup analysis demonstrated only an improved success rate for STER in  
222 lesions with diameter  $\leq$ 30mm (n=4; 100%). Good visibility and the ability to successfully resect the  
223 lesion in EFTR and STER is limited by the maximum diameter of the cap size for EFTR and the upper  
224 esophageal sphincter in STER. Also, some SELs are fixed to the surrounding gastro-intestinal wall  
225 making it difficult to be captured into the cap. Reported complete resection rates in literature ranges  
226 from 74- 100%, with higher rates reported for lesions originating from the third wall layer and

227 smaller of size [31, 32]. In ESD, the resection margin is close-fitted to the SEL and evaluation of the  
228 pathological margin is more difficult, which might explain the lower reported pathological resection  
229 rate of 52% found in the current study. However, no local recurrence was seen in the R1-resected  
230 lesions. Local recurrence rate for premalignant diagnosis in this study was only 2% during follow-up.  
231 In addition, it is implied R1-resection in GIST is not associated with a higher risk of local recurrence or  
232 lower survival outcome as long as an en bloc resection is achieved [33].

233 Although the present results support the feasibility and effectiveness of endoscopic treatment in  
234 SEL, it is appropriate to recognize several limitations of the study. The study is a retrospective  
235 evaluation of clinical data of an experienced referral tertiary center. Important data or nuances  
236 could be missed when these were not documented in the electronic health records. Even though  
237 most patients were discharged from further surveillance, the follow-up time in the remaining  
238 patients was modest. The possibility of long-term recurrence therefore cannot be completely ruled  
239 out. In addition, because the procedures were performed by experienced endoscopists in a tertiary,  
240 referral center, data cannot be transposed to smaller, regional centers with less experience for this  
241 specific indication.

242 In conclusion, endoscopic resection is an effective treatment for SELs and offers valuable information  
243 in undetermined SEL in a field with a low diagnostic accuracy of current techniques. In addition, in  
244 the current study two-third of the referred patients could be discharged from surveillance and  
245 unnecessary follow-up procedures were prevented. Eligibility criteria and the long-term recurrence  
246 rate for endoscopic resection are not yet well-established and need further investigation.

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<b>Figure 1</b>	Clinical impact of endoscopic resections. GIST = gastro-intestinal stromal tumor. NET = neuro-endocrine tumor. R0 = pathological radical resection. R1 = pathological irradical resection.
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<b>Supplementary Figure I</b>	EFTR-procedure for a gastric neuro-endocrine tumor <b>A.</b> Marked nodule lesser curvature. <b>B.</b> Resection surface above the above the deployed over-the-scope clip (OTSC) <b>C.</b> Full thickness resection of the lesion pinned down on foamboard.
<b>Supplementary Figure II</b>	ESD-procedure for a gastro-intestinal stromal tumor <b>A.</b> Gastric subepithelial lesion <b>B.</b> Submucosal dissection of the lesion. <b>C.</b> Resection surface. <b>D.</b> View of en bloc resection lesion.
<b>Supplementary Figure III</b>	STER-procedure of a leiomyoma <b>A.</b> View of subepithelial lesion in oesophagus <b>B.</b> Submucosal tunneling <b>C.</b> Dissection of lesion out of tunnel <b>D.</b> View of tunnel before closing the entry.

256 **Figure Legends**

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