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Endoscopic Submucosal Dissection in Europe: Results of 1000 Neoplastic Lesions From the German Endoscopic Submucosal Dissection Registry

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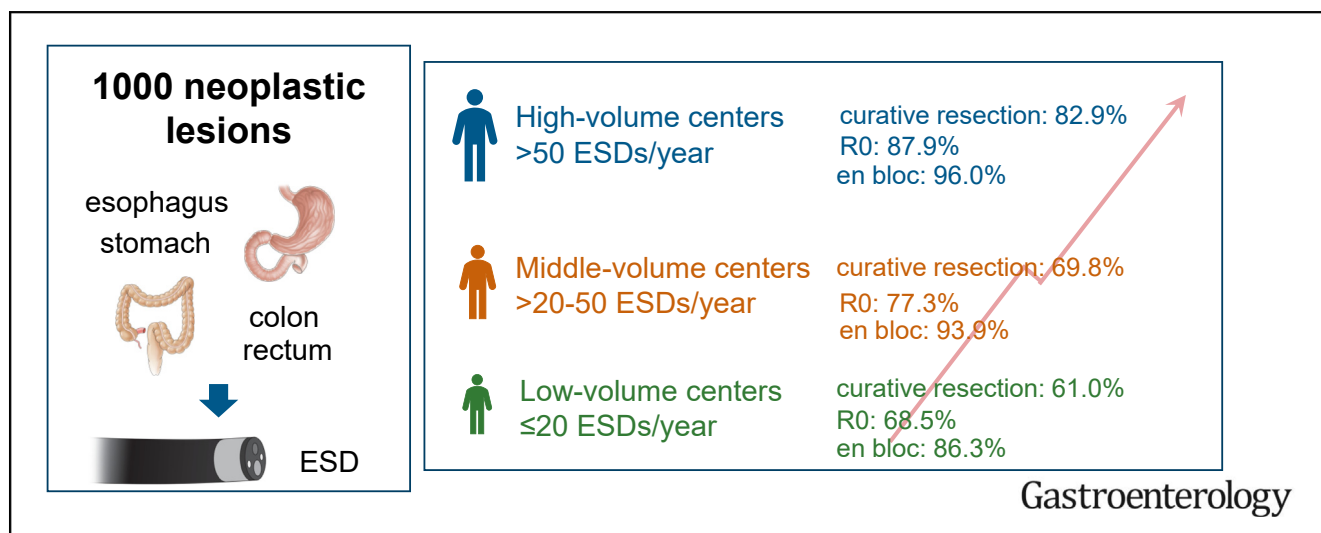
BACKGROUND AND AIMS: Endoscopic submucosal dissection (ESD) enables the curative resection of early malignant lesions and is associated with reduced recurrence risk. Due to the lack of comprehensive ESD data in the West, the German ESD registry was set up to evaluate relevant outcomes of ESD. **METHODS:** The German ESD registry is a prospective uncontrolled multicenter study. During a 35-month period, 20 centers included 1000 ESDs of neoplastic lesions. The results were evaluated in terms of en bloc, R0, curative resection rates, and recurrence rate after a 3-month and 12-month follow-up. Additionally, participating centers were grouped into low-volume (≤20 ESDs/y), middle-volume (20–50/y), and high-volume centers (>50/y). A multivariate analysis investigating risk factors for noncurative resection was performed. **RESULTS:** Overall, en bloc, R0, and curative resection rates of 92.4% (95% confidence interval [CI], 0.90–0.94), 78.8% (95% CI, 0.76–0.81), and 72.3% (95% CI, 0.69-0.75) were achieved, respectively. The overall complication rate was 8.3% (95% CI, 0.067–0.102), whereas the recurrence rate after 12 months was 2.1%. High-volume centers had significantly higher en bloc, R0, curative resection rates, and recurrence rates and lower complication rates than middle- or low-volume centers. The lesion size, hybrid ESD, age, stage T1b carcinoma, and treatment outside high-volume centers were identified as risk factors for non-curative ESD. **CONCLUSION:** In Germany, ESD achieves excellent en bloc resection rates but only modest curative resection rates. ESD requires a high level of expertise, and results vary significantly depending on the center's yearly case volume.

Over the past few years, endoscopic submucosal dissection (ESD) has become a well-established treatment option for premalignant lesions and early cancer (EC) of the gastrointestinal tract.[1,2] Compared with endoscopic mucosal resection, ESD has higher R0 resection rates, a more accurate histopathologic assessment, and a reduced recurrence risk, especially for lesions larger than 20 mm.[3] Initially established for the stomach, ESD is now performed in the entire gastrointestinal tract.[4]

ESD requires a high level of skill and expertise, training is time-consuming, and learning curves have been long and tedious.[5] Although ESD has become more common, data from the West still show lower en bloc, R0, and curative resection rates, and higher recurrence and complication rates compared with data from Asian countries.[6]

In Europe, ESD data are mostly limited to single-center studies or small case series.[7–9] Therefore, the German ESD registry was set up to evaluate and assess the technical success, curative resection rates, long-term outcomes, and economic aspects of ESD procedures performed in Germany. In this article, we present the first results of the German ESD registry, including en bloc, R0, curative resection rates, and complication and recurrence rate in 1000 procedures.

Patients and Methods

The German ESD registry is a prospective uncontrolled multicenter study. All German centers performing ESD were invited to participate. Data were collected anonymously via electronic case report form and managed in a centralized database at the University Hospital of Augsburg. Ethics approval was granted by the ethics committee of the Ludwig-Maximilian-University Munich, Germany (study ID: DRKS00011781). In addition, all other participating centers received approval from their local institutional review boards.

Patient inclusion commenced on January 1, 2017. This first evaluation is based on patients included from January 1, 2017–November 30, 2019.

Participating centers agreed to report all ESDs performed during the study period. Patient and lesion characteristics (eg, date of ESD, age, sex, and location), procedure characteristics (eg, hybrid ESD, conventional or standard ESD, and piecemeal resection), complications, histopathologic assessment (eg, invasion depth, curative resection rate, and size of the resected specimen), and follow-up data, material costs, and costs of hospital-stay (eg, medication, equipment, personal costs, and intensive care unit monitoring) were reported. All authors had access to the study data and reviewed and approved the final manuscript.

Definitions and Follow-up

ESD was performed as a standard ESD procedure or a hybrid ESD (snare resection after circumferential incision with or without partial submucosal dissection). En bloc resection was classified as a resection of the target lesion in 1 piece. R0-resection was diagnosed when the histopathologic

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

A multicenter registry was established to determine the overall quality of endoscopic submucosal dissection (ESD) in Germany.

NEW FINDINGS

ESD outcomes depend on the case volume of procedures being performed in a center. With a case volume of >20 ESDs/y, acceptable results can be achieved.

LIMITATIONS

Not all follow-up data are available, there was inclusion of hybrid ESD procedures, and the experience level of individual endoscopists was not registered.

IMPACT

The data collected reflect the status of ESD in Europe and allow comparison with the results of large Asian ESD studies.

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assessment confirmed the horizontal and the vertical margins to be free of neoplasia. R0 resection was classified as curative in all benign lesions (low-grade dysplasia [LGD] and high-grade dysplasia [HGD]). If histopathologic assessment showed EC with low-risk criteria (depth of submucosal invasion: esophageal squamous cell carcinoma $\leq 200\ \mu m$, absence of lymphatic and vascular invasion, well differentiated; esophageal or gastric adenocarcinoma $\leq 500\ \mu m$, colorectal adenocarcinoma $\leq 1000\ \mu m$; absence of lymphatic and vascular invasion; well or moderately differentiated), the resection was also judged to be curative.[1] When R0 resection could not be confirmed histopathologically, or ECs did not fulfill low-risk criteria, resections were classified as noncurative. The definition of R0 resection in Barrett's esophagus was considered for the histologic entity in question. For example, for Barrett's carcinoma and HGD, R0 was accepted, even if lateral margins showed LGD or nondysplastic Barrett's. For LGD, R0 resection was accepted even if the lateral margins showed nondysplastic Barrett's mucosa. Recurrence was considered when carcinoma or HGD was detected histopathologically in the resected area after initial resection of a carcinoma or HGD. The same procedure was followed for lesions with LGD.

Follow-up endoscopic examinations were performed 3 and 12 months after the ESD procedure. Recurrence was diagnosed when neoplasia was confirmed histopathologically after an initial R0-situation. For Barrett's esophagus, recurrence was considered when carcinoma was detected within the resected area after initial resection of a carcinoma; analogous procedures were applied to cases with HGD and LGD.

Adapted from the results of the Nagano ESD study group, centers were subgrouped into the following[10]: low-volume centers: <21 ESDs/y (n = 14); middle-volume centers: 21–50 ESDs/y (n = 5); and high-volume centers: >50 ESDs/y (n = 1).

Complications

Predefined complications included perforation, bleeding, and stricture formation. Bleeding was defined as a hemoglobin decrease >2 g/dL or clinical signs of bleeding.[11] It was categorized as intraprocedural when it led to the termination of the procedure or as delayed when it occurred later. Perforation was defined as a transmural injury leading to intraprocedural or delayed endoscopic or surgical treatment. Stricture formation was considered as a complication if it was clinically symptomatic. Additionally, all reported complications were grouped according to the grading system of the American Society for Gastrointestinal Endoscopy.[11]

Statistical Analysis

For proportions, exact binomial confidence intervals (CIs) were calculated. Associations between categorical variables were analyzed using chi-square tests, except for recurrence, where Fisher exact test was used. $P < .05$ was considered to be statistically significant. All calculations were performed using the software package R (R Foundation for Statistical Computing 2020). For the multivariate analysis, all dependent variables were coded to be dichotomous. Due to the low case number of American Society of Anesthesiology (ASA) grade 4 (n = 8), the ASA grade 3 and 4 categories were grouped together. The multivariate analysis was performed using binomial logistic regression. The importance of influencing variables was assessed via Wald-type test statistics, the odds ratio, and its 95% CI.

Results

Patient and Lesion Characteristics

During a 35-month period (January 2017–November 2019), 1170 patients from 20 participating centers were included. Only neoplastic lesions (n = 1000) were included for further evaluation. Figure 1 gives an overview of the number of patients included by each center.

The number of patients included per center ranged between 5 and 397 cases. ESD was performed in the esophagus, stomach, duodenum, colon, and rectum. Due to the low number of duodenal ESDs (17 procedures in 6 centers), these cases are reported separately. All groups were comparable concerning median patient age, sex, and ASA status. Also, 92.9% of lesions were treatment-naïve. The average lesion size was 42 x 32mm. Table 1 shows an overview of patient and lesion characteristics.

Procedure Characteristics

Table 2 summarizes all procedure characteristics.

All lesions. Standard ESD was performed in 885/1000 cases (88.5%), and a hybrid ESD in 115/1000 cases (11.5%). The overall en bloc resection rate was 924/1000 cases (92.4%); 76 procedures were completed with endoscopic mucosal resection (7.6%). R0-resection was achieved in 788/1000 cases (78.8%); curative resection was performed in 723/1000 cases (72.3%). Resection was non-curative in 277/1000 lesions (27.7%), of which 74 cases were benign lesions, and 203 cases were carcinomas (R1 n = 126; high-risk situation n = 77).

The median procedure time was defined as the time from insertion of the endoscope to completion of the examination (removal of the endoscope). The overall median procedure time was 85 minutes (range, 15–540 minutes); the median procedure time in the esophagus was 90 minutes (range, 15–335 minutes), in the stomach, 90 minutes (range, 15–540 minutes), in the colon 85 minutes (range, 20–310 minutes), and in the rectum, 85 minutes (range, 15–480 minutes).

All patients were routinely admitted after ESD for observation. The median hospital stay was 4 days (range, 1–29). If no complications occurred, the median hospital stay was 4 days (range, 1–24). In the subgroup with 83 complications, the median hospital stay was 4 days (range, 1–29).

Duodenum. A total of 17 duodenal ESDs were performed in 6 centers, including 6 cases in high-volume, 1 case in middle-volume, and 10 cases in low-volume centers. None of the lesions were pretreated. Eleven cases were neoplastic (6 adenomas with HGD, 3 adenomas with LGD, and 2 were neuroendocrine tumors [NET]). The en bloc resection rate of duodenal neoplastic lesions was 81.8% (n = 8/11), whereas the R0 resection rate was 54.5% (n = 6/11). Curative resection was achieved in 5 cases (45.4%). Bleeding occurred in 18.1% of cases (n = 2/11), including intraprocedural bleeding (n = 1) and 1 case of delayed bleeding on the first postinterventional day.

Esophagus. Three hundred six esophageal lesions were included.

Regarding Barrett's-related neoplasia, a total of 252/306 esophageal lesions (82.4%) were related to Barrett's dysplasia, of which 232 lesions were treatment-naïve (94.0%). Two lesions were located in the upper, 11 in the middle, and 239 in the distal esophagus. The 252 lesions are subgrouped into 234 adenocarcinomas (G1 n = 132; G2 n = 78; G3 n = 23; G4 n = 1), 10 lesions with HGD, and 8 lesions with LGD. En bloc rate was 243/252 cases (96.4%), R0- rate was 193/252 cases (76.6%), and curative resection rate was 182/252 cases (71.2%).

Regarding squamous cell neoplasia, a total of 54 squamous cell neoplasias were resected in the esophagus, and their distribution is as follows: 20 lesions in the upper, 27 lesions in the middle, and 7 lesions in the distal esophagus. Forty-nine lesions were treatment-naive (90.7%). The histopathologic assessment showed 51 squamous cell carcinomas (G1 n = 12; G2 n = 28; G3 n = 11), 2 lesions with HGD, and 1 lesion with LGD. En bloc rate was 98.1% (53/54), R0 rate was 81.5% (44/54), and curative resection rate was 46.2% (25/54).

Stomach. Two hundred thirty-six gastric lesions were treated using ESD: 48 in the proximal, 61 in the middle, and 127 in the distal stomach. Also, 218/236 lesions were resected en bloc (92.4%) with an R0-rate of 190/236 (80.5%). In 170/236 cases, resection was curative (72.0%).
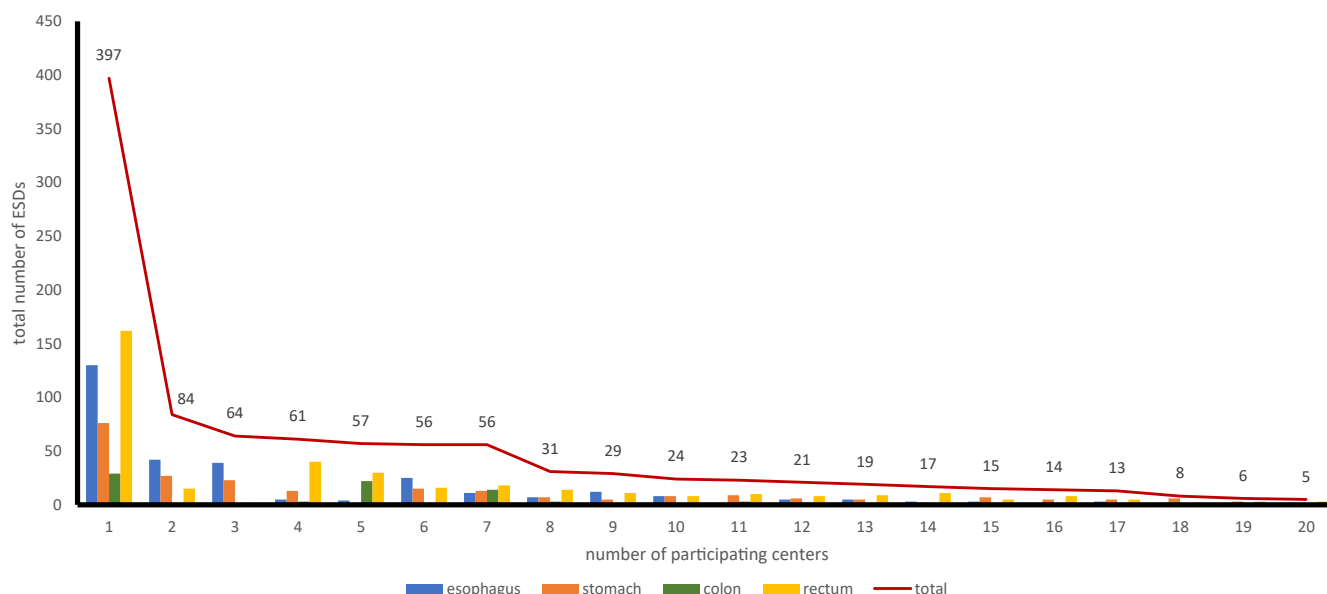
Figure 1. ESDs from 20 participating centers.

Histopathologic findings showed 167 adenocarcinomas (G1 n = 84; G2 n = 61; G3 n = 22), 12 cases of HGD, 43 cases of LGD, and 14 NETs.

Colon. Seventy-eight lesions were located in the colon (cecum n = 12; ascending colon n = 18; transverse colon n = 8; descending colon n = 7; and sigmoid colon n = 33). En bloc resection was performed in 66/78 cases (84.6%) with an R0 rate of 56/78 cases (71.8%) and a curative resection rate of 53/78 cases (67.9%). The histopathologic assessment showed 10 adenocarcinomas (G1 n = 4; G2 n = 6), 24 cases of HGD, and 44 cases of LGD.

Rectum. A total of 380 lesions were resected in the rectum. En bloc resection was achieved in 344/380 cases (90.5%), R0-resection in 305/380 cases (80.3%), and curative resection in 293/380 cases (77.1%). Histopathology showed 57 adenocarcinomas (G1 n = 15; G2 n = 41; G3 n = 1), 194 cases of HGD, 121 cases of LGD, and 8 NETs.

Complications

Complications occurred in 83/1000 ESD procedures (8.3%; Table 2). The delayed bleeding rate was 2.6% (8/306) after esophageal, 5.9% after gastric (14/236), and 1.0% after rectal ESD (4/380). No delayed bleeding occurred after colonic ESD. Eight patients required blood transfusion after delayed bleeding (3 after esophageal and 5 after gastric ESD). Bleeding was successfully treated by clipping, coagulation, or combination of both. All bleedings were moderate adverse events.

Perforation was reported in 42 cases (4.2%); perforation rate was 2.6% in the esophagus (8/306), 4.2% in the stomach (10/236), 14.1% after colonic ESD (11/78), and 3.4% after rectal ESD (13/380). None of the esophageal perforations needed surgical treatment; 6 perforations were treated with through-the-scope-clips (TTSC), 1 perforation was treated with an over-the-scope clip (OTSC, OVESCO, Tübingen, Germany), and 1 perforation was managed with antibiotic treatment and a nil-per-os diet. Nine of 10

Table 1. Patient and Lesion Characteristics

	All	Esophagus	Stomach	Colon	Rectum
n	1000	306	236	78	380
Age, median (range), y	69 (29–94)	69 (29–90)	69 (34–89)	68 (35–88)	69 (30–94)
Sex, n (%)					
Male	703 (70.3)	246 (80.4)	154 (65.3)	53 (77.9)	250 (65.8)
Female	297 (29.7)	60 (19.6)	82 (34.7)	25 (32.1)	130 (34.2)
ASA grade 1/2/3/4	340/493/159/8	79/167/57/3	57/121/57/1	30/40/8/0	174/165/37/4
Specimen size, median (mm)	42 x 32	40 x 29	38 x 29	35 x 28	47 x 37
Treatment-naive lesion (%)	930 (93.0)	281 (91.8)	228 (96.6)	74 (94.9)	347 (91.3)

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Table 2. Procedure Characteristics

	All	Esophagus	Stomach	Colon	Rectum
N	1000	306	236	78	380
En bloc resection, n (proportion, 95% CI)	924 (0.92, 0.90–0.94)	296 (0.97, 0.94–0.98)	218 (0.92, 0.88–0.95)	66 (0.85, 0.75–0.92)	344 (0.90, 0.87–0.93)
R0 resection, n (proportion, 95% CI)	788 (0.79, 0.76–0.81)	237 (0.77, 0.72 – 0.82)	190 (0.80, 0.75–0.85)	56 (0.72, 0.60–0.81)	305 (0.80, 0.76–0.84)
Curative resection rate, n (proportion, 95% CI)	723 (0.72, 0.69–0.75)	207 (0.67, 0.62–0.73)	170 (0.72, 0.66–0.78)	53 (0.68, 0.56–0.78)	293 (0.77, 0.73–0.81)
Complications, n, (proportion, 95% CI)	83 (0.083, 0.067–0.102)	31 (0.37, 0.27–0.49)	24 (0.29, 0.19–0.39)	11 (0.13, 0.07–0.22)	17 (0.20, 0.12–0.31)
Delayed bleeding, n (%)	26 (2.6)	8 (2.6)	14 (5.9)	0 (0)	4 (1.0)
Perforation, n (%)	42 (4.2)	8 (2.6)	10 (4.2)	11 (14.1)	13 (3.4)
Intraprocedural perforation (%)	31(3.1)	2 (0.6)	9 (3.8)	11(14.1)	9 (2.4)
Delayed perforation (%)	11 (1.1)	6 (1.9)	1 (0.4)	0 (0)	4 (1.0)
Stricture formation (%)	15 (1.5)	15 (4.9)	0 (0)	0 (0)	0 (0)

stomach perforations were managed endoscopically, 2x via OTSC, 7x via TTSC, and 1 patient underwent surgery. The highest perforation rate was documented in the colon, in 11/78 cases (14.1%). Six perforations were treated with standard TTSC and 3 with an OTSC. Two patients with perforation who could not be managed endoscopically underwent surgery (1x partial colectomy, 1x right-sided hemicolectomy). Two of 13 rectal perforations underwent surgery; 1 patient needed partial colectomy, and another developed fever and abdominal pain on the sixth post-procedural day. This was caused by a retroperitoneal abscess that was treated using trans-anal surgery and drainage of the abscess. The remaining 11 rectal perforations were managed endoscopically, 8x with conventional TTSC, in 1 case via endoscopic vacuum sponge therapy and 2x via OTSC. Perforations were graded as mild (n = 36), severe (n = 5), and moderate (n = 1).

Fifteen cases of esophageal stricture formation were reported. In 1 case, stricture formation occurred, although less than one third of the circumference was resected. Nine cases of esophageal stricture formation were reported after ESD of at least two thirds of the circumference. Esophageal stricture occurred in 5 of 15 cases after circumferential ESD. All esophageal stricture formations were moderate complications.
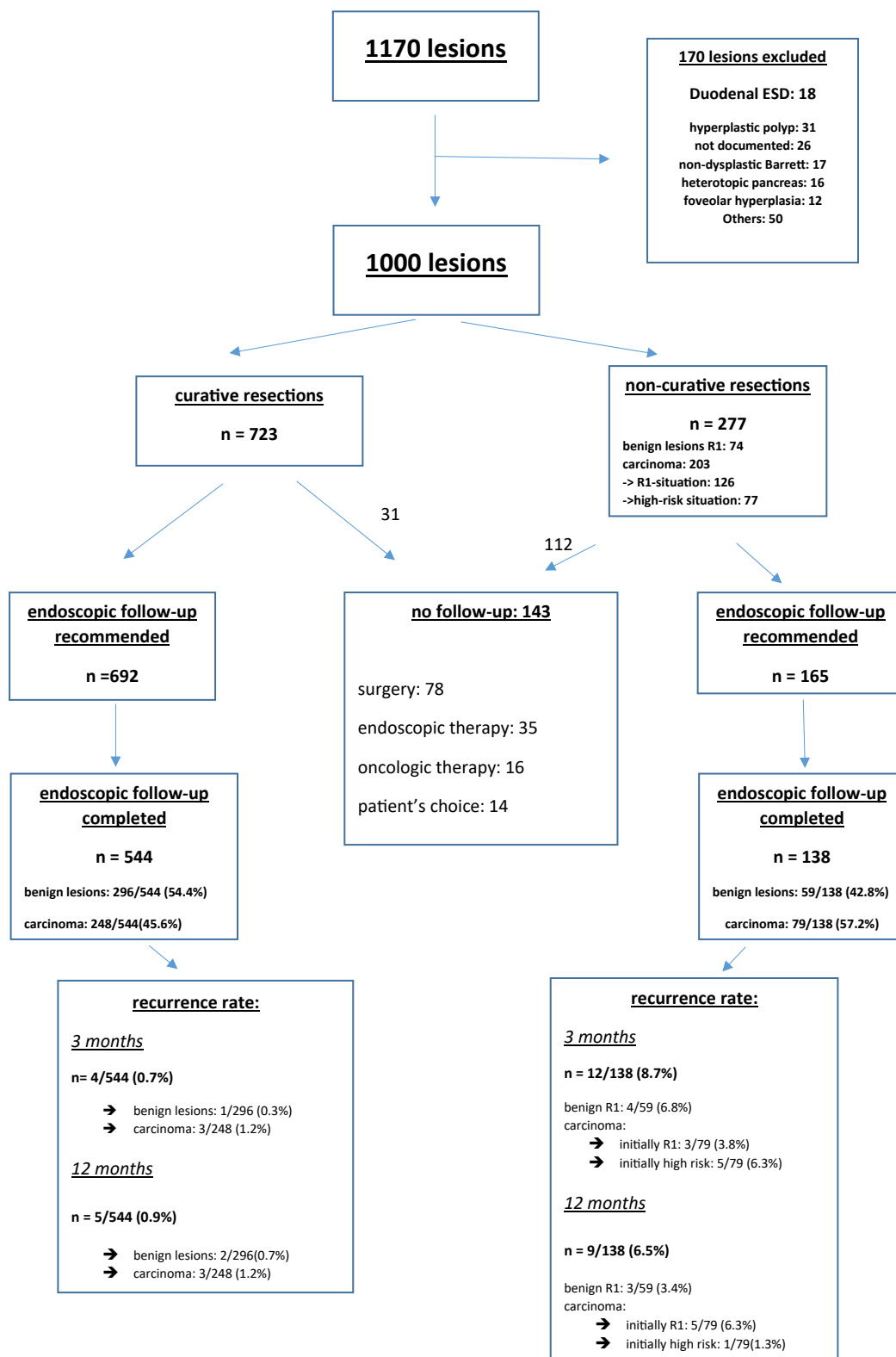
Recurrence Rate

Endoscopic follow-up was recommended for 857 patients, in 692 cases after curative resection and in 165 cases after noncurative resection.

Follow-up after 3 months. Follow-up endoscopy after 3 months was documented in 682/857 cases (79.6%). Local recurrence was diagnosed in 16/682 cases (2.3%). Seven local recurrences occurred in the esophagus (2.8%), 4 in the stomach (2.3%), 1 in the colon (3.0%), and 4 cases in the rectum (1.8%). In 4 cases, recurrence occurred after curative resection, once after resection of an HGD, whereas 3 lesions were carcinomas. In 12 cases, a recurrence after noncurative resection was documented; of these, 4 lesions were benign, but there was an R1 situation, whereas 8 lesions were carcinomas. These had undergone R1 resection in 3 cases, whereas 5 were with high-risk histologic criteria.

Follow-up after 12 months. Follow-up endoscopy at 12 months was documented in 660/857 cases (77.0%). Local recurrence was diagnosed in 14/660 cases (2.1%). Seven local recurrences occurred in the esophagus (2.8%), 5 in the stomach (3.2%), 1 in the colon (2.4%), and 1 case was reported in the rectum (0.5%). In 5 cases, a recurrence occurred after curative resection, once after resection of an LGD, and once after resection of an HGD, whereas 3 lesions were carcinomas. In 9 cases, a recurrence after noncurative resection was documented; of these, 3 lesions were benign, but there was an R1 situation, whereas 6 lesions were carcinomas. These had undergone R1 resection in 5 cases, whereas 1 case was with high-risk histologic criteria.

Figure 2 gives an overview of the follow-up data and recurrences.

1170 lesions

170 lesions excluded

Duodenal ESD: 18

hyperplastic polyp: 31
not documented: 26
non-dysplastic Barrett: 17
heterotopic pancreas: 16
foveolar hyperplasia: 12
Others: 50

1000 lesions

curative resections

n = 723

non-curative resections

n = 277
benign lesions R1: 74
carcinoma: 203
-> R1-situation: 126
->high-risk situation: 77

31

112

endoscopic follow-up recommended

n =692

no follow-up: 143

surgery: 78

endoscopic therapy: 35

oncologic therapy: 16

patient's choice: 14

endoscopic follow-up recommended

n = 165

endoscopic follow-up completed

n = 544

benign lesions: 296/544 (54.4%)

carcinoma: 248/544(45.6%)

endoscopic follow-up completed

n = 138

benign lesions: 59/138 (42.8%)

carcinoma: 79/138 (57.2%)

recurrence rate:

3 months

n= 4/544 (0.7%)

➔ benign lesions: 1/296 (0.3%)
➔ carcinoma: 3/248 (1.2%)

12 months

n = 5/544 (0.9%)

➔ benign lesions: 2/296(0.7%)
➔ carcinoma: 3/248 (1.2%)

recurrence rate:

3 months

n = 12/138 (8.7%)

benign R1: 4/59 (6.8%)
carcinoma:
➔ initially R1: 3/79 (3.8%)
➔ initially high risk: 5/79 (6.3%)

12 months

n = 9/138 (6.5%)

benign R1: 3/59 (3.4%)
carcinoma:
➔ initially R1: 5/79 (6.3%)
➔ initially high risk: 1/79(1.3%)

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Figure 2. Endoscopic follow-up and recurrence; oncologic therapy included radiation, chemotherapy, or combination of both.

Outcome According to ESD Caseload per Year

Figure 3 shows the case volume per year of participating centers.

Procedure Characteristics

Procedure time varied from 80 minutes (median, range 15–480) in the high-volume center to 85 minutes (median,
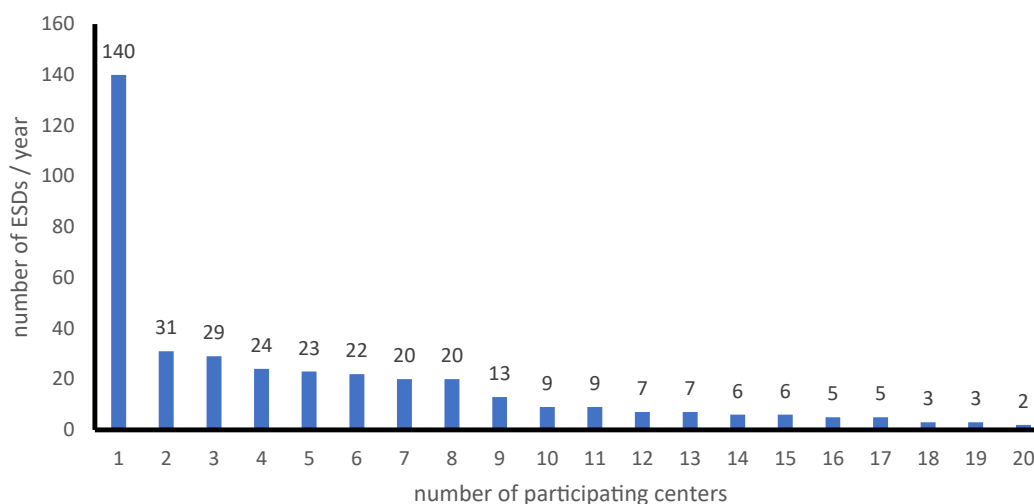
Figure 3. Centers and numbers of ESD/y.

range 25–540) in middle-volume and 87.5 minutes (median, range 20–355) in low-volume centers. Concerning en bloc resection, the high-volume center achieved the highest rate with 96.0%, followed by middle-volume (93.9%) and low-volume centers (86.3%). The high-volume center achieved the highest R0-resection rate with 87.9%. The R0-resection rate decreased from 77.3%, in middle-volume centers, to 68.5% in low-volume centers. The curative resection rate was 82.9% in the high-volume center, followed by 69.8% in middle-volume centers and 61.0% in low-volume centers (Table 3).

Regarding standard ESD versus hybrid ESD according to case volume, the highest number of standard ESDs was performed in the high-volume center with 371/397 cases (93.5%). Here, en bloc resection was achieved in 367/371 cases (98.9%), R0 resection in 337/371 cases (90.8%), and curative resection in 317/371 cases (85.4%). A total of 26/397 ESDs in the high-volume center was performed as hybrid procedures (6.5%) with an en bloc rate of 14/26 cases (53.8%), R0 rate of 12/26 cases (46.1%), and curative resection rate of 12/26 cases (46.1%).

Middle-volume centers performed standard ESD in 272/295 cases (92.2%); for standard ESDs, an en bloc rate of 97.7% was achieved (266/272 cases), an R0 rate of 80.8% (220/272 cases), and a curative resection rate of 72.3% (198/272 cases). Hybrid ESDs were performed in 23/295

Table 3. Comparison Caseloads per Year

ESD volume/y	n ≤ 20/y	n > 20–50/y	n > 50/y	P
Centers (n)	14	5	1	
Number of ESDs/y	115	129	140	
Number of ESDs (total)	308	295	397	
Specimen size, median (mm)	39 x 31	40 x 30	45 x 35	
Location (esophagus/stomach/colon/rectum)	74/91/23/120	102/69/26/98	130/76/29/162	.0071
En bloc rate (%)	266 (86.3)	277 (93.9)	381 (96.0)	<.00001
R0 (%)	211 (68.5)	228 (77.3)	349 (87.9)	<.00001
Curative resection rate (n%)	188 (61.0)	206 (69.8)	329 (82.9)	<.00001
Complications (n%)	33 (10.7)	38 (12.9)	12 (3.0)	<.00001
Postprocedural endoscopic follow-up recommended (%)	260 (84.4)	238 (80.6)	359 (90.4)	.0010
Follow-up 3 mo documented (n%)	198 (76.1)	144 (60.5)	340 (94.7)	<.00001
Recurrence after 3 mo (n%)	4 (2.0)	6 (4.1)	6 (1.7)	.81
Follow-up 12 mo documented (n%)	169 (65.0)	211 (88.6)	280 (78.0)	<.00001
Recurrence after 12 mo (n%)	11 (6.5)	3 (1.4)	0 (0)	<.00001

cases (7.8%), with an en bloc rate of 47.8% (11/23 cases) and R0 and curative resection rate of 34.7% (8/23 cases), respectively.

In low-volume centers, the proportion of standard ESDs was 242/308 cases (78.6%). En bloc rate was 236/242 cases (97.5%), R0 rate was 184/242 cases (76.0%), and curative resection rate was 161/242 cases (66.5%). Thus, the highest amount hybrid ESDs with 66/308 ESDs (21.4%) was performed in low-volume centers, with an en bloc resection rate of 45.4% (30/66 cases), an R0 resection rate of 40.9% (27/66 cases), and a curative resection rate of 40.9% (27/66 cases).

Complications according to case volume. The highest complication rate was reported in middle-volume centers with 38 documented complications (12.9%): 13 episodes of delayed bleeding, 18 perforations (all managed endoscopically), and 7 strictures. In low-volume centers, 33 complications (10.7%) were documented: 5 cases of delayed bleeding, 20 perforations with 2 subsequent surgeries, as well as 8 documented strictures. In the high-volume center, 12 complications were documented (3.0%): 8 cases of delayed bleeding and 4 perforations, 3 of which needed further surgical treatment. No stricture was documented (Table 3).

Recurrence. Regarding follow-up after 3 months, in low-volume centers, follow-up data were available for 198/260 patients (76.1%). Four of 198 cases developed local recurrence after 3 months (2.9%). Middle-volume centers reported 6 local recurrent lesions in 144 follow-up endoscopic examinations (4.1%). In the high-volume centers, 6/340 recurrent lesions were documented (1.7%; Table 3).

Regarding follow-up after 12 months, in low-volume centers, follow-up data were available for 169/260 patients (65.0%). Eleven of 169 cases developed local recurrence after 3 months (6.5%). Middle-volume centers reported 3/211 recurrent lesions (1.4%). In the high-volume study cohort, no recurrent lesion was documented (Table 3).

Variables Influencing Favorable Outcome: A Multivariate Analysis

In this section, possible variables influencing the achievement of en bloc, R0, and curative resection were investigated. It was also investigated which variables increase the risk of complications as well as recurrences. Analyzed parameters included: age, sex, ASA status, lesion size, standard vs hybrid ESD, location, histopathologic findings (LGD, HDG, and carcinoma T1 vs carcinoma T1b), and caseload. All figures of the multivariate analysis can be found in the supplementary file.

The en bloc resection rate was significantly influenced by lesion size ($P = .008$; odds ratio [OR], 0.97; 95% CI, 0.94–0.99) as well as by performing a standard ESD ($P < .01$; OR, 58.73; 95% CI, 28.32–121.81; Supplementary Figure 1).

Patient age ($P = .041$; OR, 0.98; 95% CI, 0.06–0.99) and lesion size ($P = .001$; OR, 0.97; 95% CI, 0.96–0.99) significantly influenced R0 resection rates positively. In addition, an R0 situation was significantly more frequently achieved

after performing standard ESD ($P < .01$; OR, 8.70; 95% CI, 5.38–14.08). Resection of a LGD ($P < .01$; OR, 3.02; 95% CI, 1.69–5.38), HGD ($P < .01$; OR, 4.88; 95% CI, 2.63–9.05) and a T1a carcinoma ($P = .001$; OR, 2.34; 95% CI, 1.40–3.92) is associated with a higher likelihood of an R0 situation compared with T1b carcinomas. Also, performing ESD at high-volume centers makes R0 resection statistically more likely ($P < .01$; OR, 2.63; 95% CI, 1.68–4.14; Supplementary Figure 2).

Influential variables making achievement of curative resection more likely were lesion size ($P = .013$; OR, 0.98; 95% CI, 0.97–0.99) and performance of standard ESD ($P < .01$; OR, 5.0; 95% CI, 3.07–8.14). Resection of an LGD ($P < .01$; OR, 17.29; 95% CI, 9.50–31.41), HGD ($P < .01$; OR, 24.87; 95% CI, 13.27–46.16) and T1a carcinoma ($P < .01$; OR, 8.55; 95% CI, 5.17–14.14) is significantly more often associated with R0 resection compared with T1b carcinomas. Treatment at a high-volume center also makes R0 resection statistically more likely ($P < .01$; OR, 2.19; 95% CI, 1.43–3.35; Supplementary Figure 3).

Compared with complications after rectal ESD, complications of squamous cell neoplasia ($P = .019$; OR, 5.69; 95% CI, 2.14–15.15), gastric lesions ($P = .018$; OR, 2.63; 95% CI, 1.17–5.91), and lesions in the colon ($P < .01$; OR, 2.95; 95% CI, 1.19–7.33) occurred significantly more frequently. Performing a standard ESD ($P < .029$; OR, 0.48; 95% CI, 0.25–0.93) as well as treatment at a high-volume center ($P < 0.01$; OR, 1.21; 95% CI, 0.711–2.06) reduced the risk of complications (Supplementary Figure 4).

Squamous cell neoplasia ($P < .004$; OR, 28.62; 95% CI, 2.97–275.43) resulted in a statistically higher recurrence rate at 3 months compared with rectal lesions. All other variables studied showed no statistical significance concerning recurrence rate at 3 months (Supplementary Figure 5).

The risk of recurrence at 12 months was increased for squamous cell neoplasia ($P = .025$; OR, 24.69; 95% CI, 1.48–109.65). Treatment in high-volume ($P = .047$; OR, 0.15; 95% CI, 0.07–0.65) and middle-volume centers ($P = .025$; OR, 0.20; 95% CI, 0.05–0.81) is associated with a lower risk of recurrence compared with low-volume centers (Supplementary Figure 6).

Discussion

ESD is a technically demanding resection technique. Although comprehensive data exist from Asian countries, ESD data from the Western world are primarily from retrospective, single-center studies.[8,9,12] Current ESD quality standards in the West are based mainly on prospective studies from Asian countries with high case numbers and excellent study outcomes.[13] Therefore, the German ESD registry was established to evaluate the use and the quality of ESD in Germany and to create a broader scientific database for Western settings.

In this study, we present the first results of the German ESD registry, including en bloc, R0, curative resection rates, complication, and recurrence rates. A satisfactory overall en bloc resection rate of 92.4% (95% CI, 0.90–0.94) was

achieved; however, when compared with Asian data, the R0 and curative resection rates were considerably lower with 78.8% (95% CI, 0.76–0.81) and 72.3% (95% CI, 0.69–0.75), respectively. Only 70 (7.0%) of the lesions were pretreated. A possible explanation may be that ESD has gained importance as a treatment modality and a primary intervention option in Europe over the last years.

In a prospective national survey from France, results from 16 centers with 288 ESDs were evaluated. The en bloc rate was 91.7%, the R0 rate was 72.9%, and the complication rate was 14.1%.[14] The results were compared with a 2011 study of the same study group. A significant increase in the en bloc rate from 77.1% to 91.7% and a decrease in the complication rate from 29.2% to 14.1% were shown; the R0 rate did not change significantly.[15] Although the German ESD registry results are better than the results from the French survey, they still fall short of the outcomes from Asian studies where en bloc, R0, and curative resection rates of above 97%, 91%, and 89%, respectively, have been reported.[13,16,17]

Effect of Lesion Location

Unlike in most published studies, the results presented here refer to ESDs performed in different organs, which may have had a considerable effect on study outcomes. The highest en bloc rate of 96.7% in the esophagus (95% CI, 0.94–0.98) contrasts with an en bloc rate of 84.6% (95% CI, 0.75–0.92) in the colon. The highest R0 rate of 80.5% (95% CI, 0.75–0.85) was in the stomach, and the lowest rate with 71.7% (95% CI, 0.60–0.81) was in the colon. The highest curative resection rate of 77.1% (95% CI, 0.73–0.81) was in the rectum, whereas the lowest was in the esophagus with 67.6% (95% CI, 0.62–0.73). A retrospective Italian self-report survey yielded similar results.[18]

Comparing ESD in the esophagus with published data from other European centers, no differences in en bloc resection, R0 resection, and curative resection rate were found.[19,20] For gastric lesions, European single-center studies reported en bloc resection rates ranging from 90%–100% and R0 resection rates of 64.3%–92.8%.[9,21,22] The present study results with an en bloc rate of 92.3% (95% CI, .88–0.95) and an R0 resection rate of 80.5% (95% CI, 0.75–0.85) are similar to these data.

In 2016, Sauer et al published a case series of 182 colorectal ESDs >20 mm. Most of the lesions were located proximal to the rectum. A high en bloc rate of 88.4% was achieved, the R0 resection rate was 62.6%, and the perforation rate was 9.3%.[12] In our study, comparable en bloc, R0 resection, and perforation rates are demonstrated for colonic lesions. Nevertheless, there is still a lack of comprehensive and broad-based data for colonic ESD in Europe.

For rectal ESD, numerous European publications have shown en bloc and R0 resection rates between 72.7%–96% and 67.2%–84.8%, respectively.[7,8,23,24] In the German ESD registry, rectal ESD data showed a high en bloc resection rate of 90.5% (95% CI, 0.87–0.93) and R0 resection rate of 80.2% (95% CI, 0.76–0.84).

In a cohort of patients who underwent follow-up after 3 months, a total of 16 recurrences (2.3%) was documented. In the second follow-up documented after 12 months, 14 recurrences were registered (2.1%). This is within the range of the data published from Japan.[25] It is worth mentioning that only 4 of the 16 recurrences after 3 months and 5 of the 14 recurrences after 12 months occurred after curative resection. However, it could be possible that the 12 recurrences after 3 months and the 9 recurrences after 12 months, and after initial noncurative resection, were metachronous lesions and not true recurrences.

Effect of Case Volume

The Nagano ESD study group published a retrospective multicenter study in which they investigated the outcome after ESD for gastric neoplasia. The authors divided the participating centers into high-volume (>30 ESDs/y) and low-volume centers (<30 ESDs/y). A significant difference in outcome between high-volume and low-volume centers could not be demonstrated.[10]

Based on our data, the ESD landscape in Germany proved to be more heterogeneous, with a predominant number of centers performing <20 ESDs/y. In contrast to the Nagano ESD study group, which included only gastric ESDs, our analysis of all lesions showed significant differences in the en bloc resection rate ($P < .00001$), the R0 resection rate ($P < .00001$), and the curative resection rate ($P < .00001$). Also, complications occurred significantly less frequently in the high-volume centers than in the other 2 groups ($P < .00001$).

To date, there are no studies from the western world that report on the influence of the ESD caseload per year on

Table 4. Hospital Volume and ESD Complications

Reference	Patients (n)	Study design	Localization	Center definitions ESDs/y	Complication rate (%)
Odagiri et al[26]	12,899	Retrospective cohort study	Esophageal	VLVHs ≤8 LVHs 9–17 HVHs 18–38 VVHVs ≥39	3.3
Murata et al[27]	27,385	Retrospective cohort study	Gastric	LVHs <50 MVHs 50–100 HVHs >100	3.5
Odagiri et al[28]	7567	Retrospective cohort study	Colorectal	VLVHs ≤18 LVHs 19–35 HVHs 36–58 VHVs ≥59	4.6

HVHs, high-volume hospitals; LVHs, low-volume hospitals; MVHs, middle-volume hospitals; VHVs, very high-volume hospitals; VLVHs, very low-volume hospitals.

patients' outcomes. Retrospective Japanese studies with a high number of patients assessed the impact of hospital volume per year on complications after ESD in the esophagus, stomach, and colorectum (Table 4). It was shown that low-volume hospitals had significantly more complications after esophageal ESD.[26] Murata et al[27] showed that ESDs in the upper gastric body had significantly fewer complications than low-volume and middle-volume hospitals. In a further retrospective study, the lower occurrence of complications in colorectal ESD and its significant association with higher hospital volume was reported.[28]

Concerning the recurrence rate after 3 months, no significant difference was shown in our data among the 3 groups ($P = 0.81$) except for the recurrence rate after 12 months ($P < .00001$).

Risk Factors for Failed Curative ESD

Prediction models and risk analyses for noncurative ESD exist predominantly for gastric ESDs. Risk factors for noncurative ESD have been postulated to be, for example, age, gender, lesion size, advanced histology, and location in the upper gastric body.[29,30] We identified lesion size and hybrid ESD as risk factors for failed en bloc resection. Lesion size, age, and hybrid ESD were shown to be risk factors for R1 resection, in addition to the presence of a T1b stage and treatment outside of high-volume centers. Risk factors for noncurative resection were hybrid ESD and T1b stage and treatment outside high-volume centers. The complication risk is higher for squamous neoplasms, gastric lesions, and colonic lesions than for rectal lesions. Within the parameters studied, only squamous cell neoplasia could be identified as a predictor of increased risk of recurrence. After 12 months, an increased risk of recurrence is present for treatment in low-volume centers in addition to squamous neoplasia. For this reason, treatment by hybrid ESD should be avoided, lesion selection should be made carefully, and patients should be treated in high-volume centers.

Limitations of this study include the fact that, although a total of 20 centers have included patients to the ESD registry, it remains questionable whether this represents the entire ESD landscape in Germany. Also, not all follow-up examinations were recommended or performed, which may have influenced the reported recurrence rate. In addition, the results may have been inferior in terms of en bloc and R0 resection due to the evaluation of hybrid ESDs. Finally, individual endoscopist experience was not analyzed, and it is unclear how many endoscopists at what level of expertise were involved in the ESD procedures.

In summary, this study provides current data on ESD in Germany. Satisfactory en bloc and R0 resection rates contrast to a curative resection rate that needs to be improved. Acceptable en bloc and R0 values can be achieved with a case volume of >20 ESDs/y. However, R0 and curative resection rates >80% were only achieved in the high-volume center. The data presented here suggest that ESD is an efficient treatment method that experts should perform with an appropriate yearly caseload. Further prospective multicenter studies should follow to optimize and establish ESD in the West.

Supplementary Material

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