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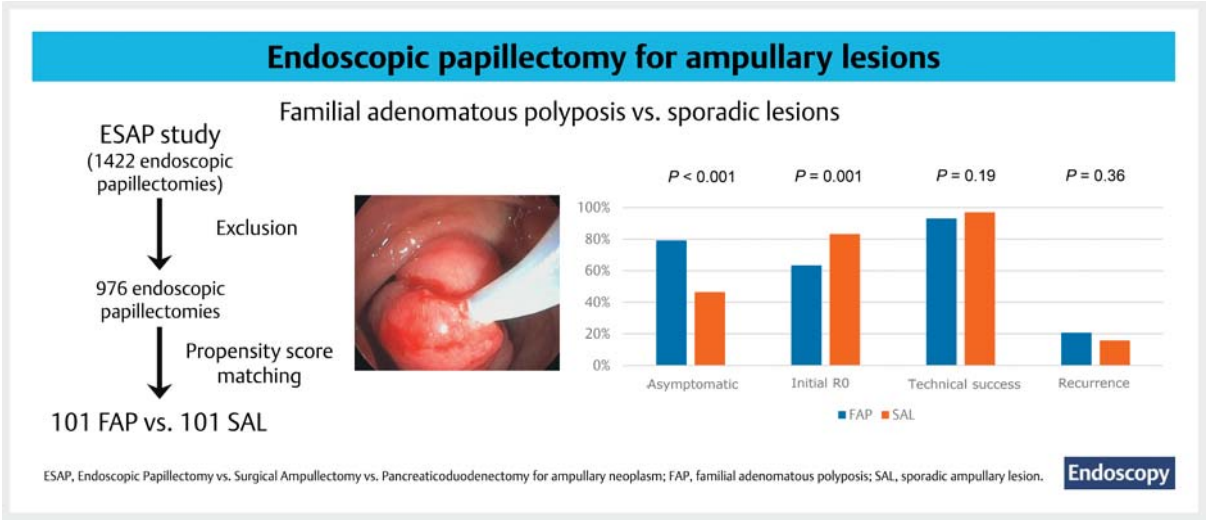
# Endoscopic papillectomy for ampullary lesions in patients with familial adenomatous polyposis compared with sporadic lesions: a propensity score-matched cohort

## GRAPHICAL ABSTRACT

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## ABSTRACT

**Background** Familial adenomatous polyposis (FAP) is a rare inherited syndrome that predisposes the patient to cancer. Treatment of FAP-related ampullary lesions is challenging and the role of endoscopic papillectomy has not been elucidated. We retrospectively analyzed the outcomes of endoscopic papillectomy in matched cohorts of FAP-related and sporadic ampullary lesions (SALs).

**Methods** This retrospective multicenter study included 1422 endoscopic papillectomy procedures. Propensity score matching including age, sex, comorbidity, histologic subtype, and size was performed. Main outcomes were complete resection (R0), technical success, complications, and recurrence.

**Results** Propensity score matching identified 202 patients (101 FAP, 101 SAL) with comparable baseline characteristics. FAP patients were mainly asymptomatic (79.2 % [95 %CI 71.2–87.3] vs. 46.5 % [95 %CI 36.6–56.4]); $P<0.001$). The initial R0 rate was significantly lower in FAP patients (63.4 % [95 %CI 53.8–72.9] vs. 83.2 % [95 %CI 75.8–90.6]; $P=0.001$). After repeated interventions (mean 1.30 per patient), R0 was comparable (FAP 93.1 % [95 %CI 88.0–98.1] vs. SAL 97.0 % [95 %CI 93.7–100]; $P=0.19$). Adverse events occurred in 28.7 %. Pancreatitis and bleeding were the most common adverse events in both groups. Severe adverse events were rare (3.5 %). Overall, 21 FAP patients (20.8 % [95 %CI 12.7–28.8]) and 16 SAL patients (15.8 % [95 %CI 8.6–23.1]; $P=0.36$) had recurrence. Recurrences occurred later in FAP patients (25 [95 %CI 18.3–31.7] vs. 2 [95 %CI CI 0.06–3.9] months).

**Conclusions** Endoscopic papillectomy was safe and effective in FAP-related ampullary lesions. Criteria for endoscopic resection of ampullary lesions can be extended to FAP patients. FAP patients have a lifetime risk of relapse even after complete resection, and require long-time surveillance.

## Introduction

Ampullary lesions represent a rare group of neoplasms of the papilla, with a prevalence of 0.1 % and an incidence of less than 1 per 100 000 per year [1, 2]. The most common subtypes are ampullary adenoma in about 90 % of cases [3]. These lesions can develop either sporadically or can be less frequently associated with genetic syndromes such as familial adenomatous polyposis (FAP). FAP is an autosomal dominant inherited disease showing a mutation in the adenomatous polyposis coli gene (*APC*), which predisposes to the development of adenocarcinoma in the gastrointestinal tract [4]. In patients with FAP who undergo proctocolectomy, the main region at risk for precancerous lesions is the ampulla of Vater [5]. Thus, an evaluation of the ampulla is recommended in the surveillance of patients with FAP [6]. In addition to the risk for malignant transformation, ampullary lesions can cause jaundice, cholangitis, or acute pancreatitis and should therefore be resected [7].

Treatment options for ampullary lesions have evolved in recent decades and now comprise both endoscopic (endoscopic papillectomy) and surgical (transduodenal surgical ampullectomy, pancreas-preserving duodenectomy, and pancreaticoduodenectomy) techniques [8, 9]. Surgical interventions are effective even in invasive cancers of the ampulla but show significant rates of adverse events [10–13]. In contrast, endoscopic papillectomy in selected patients has shown a lower morbidity and mortality than surgery but is limited to noninvasive lesions and early cancers without risk of lymph node metastasis [14, 15]. Therefore, the recent guidelines of the European Society of Gastrointestinal Endoscopy (ESGE) and the Japan Gastroenterological Endoscopy Society recommend endoscopic papillectomy as the first-choice treatment for ampullary adenoma up to 20–30 mm in diameter [16, 17].

However, data on endoscopic papillectomy in patients with FAP are limited to cohort studies with low patient numbers, and have revealed, at least in part, inconclusive results regarding R0 rate (64 %–70.2 %), adverse events (12.5 %–41 %), and recurrence (0–66.7 %) (see **Table 1 s** in the online-only Supplementary material) compared with sporadic ampullary lesions (SALs) [18–23]. In a large multicenter study, we retrospectively evaluated the clinical outcomes of endoscopic papillectomy in patients with FAP. We aimed to compare the efficacy and safety of endoscopic papillectomy for patients with FAP and patients with SAL who were matched by propensity score matching.

## Methods

### Patients

This study assessed endoscopic papillectomy outcomes in patients with FAP compared with those in patients with SAL based on propensity score matching. We used the database of the Endoscopic Papillectomy vs. Surgical Ampullectomy vs. Pancreaticoduodenectomy for ampullary neoplasm (ESAP) study. The ESAP study was a multinational multicenter retrospective study and included data of 1422 endoscopic papillectomies, 251 transduodenal surgical ampullectomies, and 1189 pancreaticoduodenectomies from 58 participating centers [24]. All adult patients who underwent endoscopic resection for an ampullary lesion were considered. Patients with peri-ampullary lesions and advanced ampullary adenocarcinoma staged T2 or higher or with nodal or distant metastasis were excluded.

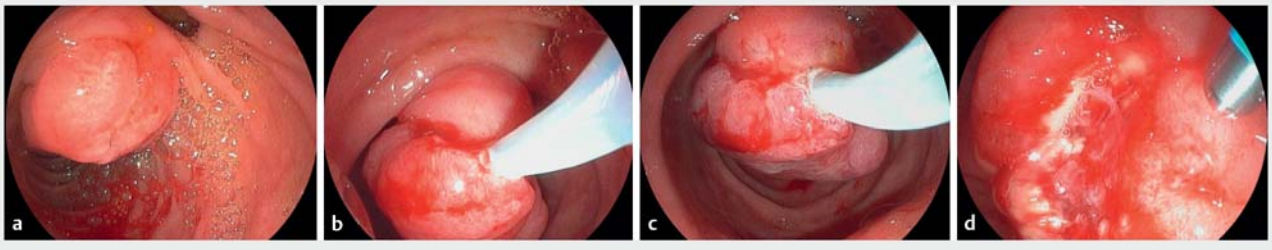
The final study protocol was approved by the ethics committee of the Medical Faculty of the University of Leipzig (455/18-ek) in accordance with the declaration of Helsinki, the "Medical Association's Professional Code of Conduct" and the principles of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice (issued in June 1996, ISO14155 from 2012). Furthermore, local legal and regulatory authorities, as well as the medical secrecy and the Federal Data Protection Act were followed. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed [25]. No patients were included in previous publications.

### Endoscopic papillectomy

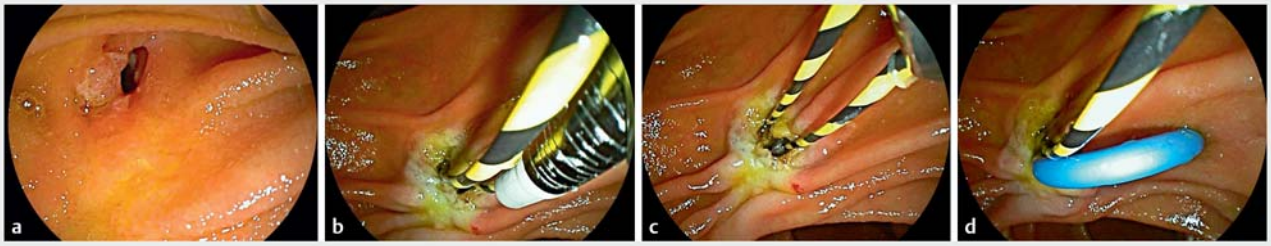
Endoscopic papillectomy was performed by experienced endoscopists as described previously [26, 27]. The use of endoscopic ultrasound or cross-sectional imaging prior to endoscopic retrograde cholangiopancreatography was at the discretion of the treating physician and endoscopist. Procedures were done under conscious sedation or general anesthesia. By using a side-viewing therapeutic duodenoscope, a snare resection of the ampullary lesion was attempted for complete lesion removal (en bloc resection). The use of submucosal injection, settings for electrocautery resection, injection of methylene blue to the pancreatic duct, and the use of radiofrequency ablation (RFA) or argon plasma coagulation (APC) were at the discretion of the endoscopist. If en bloc resection could not be achieved, a piecemeal resection technique was attempted. After resection, a pancreatic duct and/or bile duct stent was placed if possible. The choice of stent and management of bleeding complications were at the endoscopist's discretion. Representative images of an endoscopic papillectomy and endoscopic papillectomy with RFA are shown in ▶ **Fig. 1** and ▶ **Fig. 2**.

### Surveillance

After endoscopic papillectomy, all patients were monitored until the following day and received a routine laboratory test. The first surveillance endoscopy was usually performed 4–6 weeks after endoscopic papillectomy. If a stent had been placed during the initial endoscopic papillectomy procedure, it was removed. For lesions that were suspicious for residual lesion, another endoscopic papillectomy was directly performed or a




▶ **Fig. 1** Papillectomy of a patient with familial adenomatous polyposis. **a** Adenoma of the papilla. **b** Positioning of the snare. **c** Electrical resection. **d** Result of the papillectomy.




▶ **Fig. 2** Radiofrequency ablation (RFA) of adenoma recurrence. **a** Adenoma recurrence after papillectomy. **b** RFA with ablation probe. **c** Result of the RFA. **d** Pancreatic duct stent placement.

biopsy was done to confirm the presence of residual lesion before resection.

After complete resection and no evidence of residual lesions at the first endoscopic follow-up, surveillance endoscopy was performed within 3–6 months and 12 months after resection. Thereafter, patients underwent annual endoscopy but further surveillance was based on individual protocols of the included centers.

## Datasets

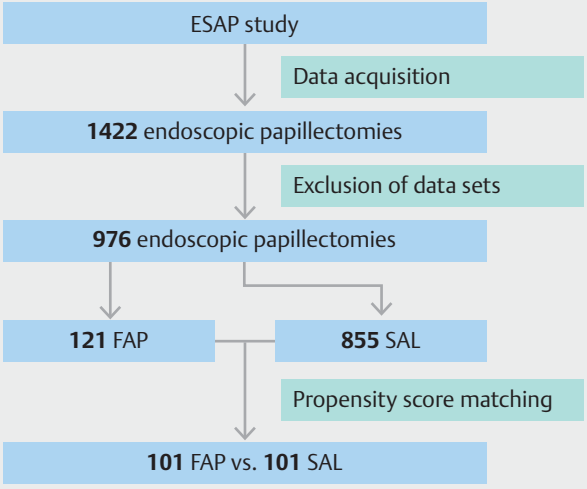
We collected medical information from the ESAP study database. Data included age at intervention, sex, comorbidities, concomitant hereditary polyposis syndrome, clinical presentation, size, morphology, and histology of the lesion. Specific information regarding the interventional procedures (sphincterotomy, submucosal injection, stenting, complementary treatment, duration, rates of en bloc and complete resection, repeated interventions, recurrence, specific complications, and others) was also collected.

Technical success was defined as complete removal (histologically confirmed) of the lesion including multiple endoscopic interventions. Procedure-related adverse events were stratified according to the American Society for Gastrointestinal Endoscopy [28, 29].

Recurrence was defined as local lesion observed in an endoscopy after initial inconspicuous papilla in the first surveillance examination. Disease-free survival was defined as the time between primary endoscopic papillectomy and the first evidence of recurrence. Overall survival was defined as the time between primary resection and death or end of follow-up (January 2021).

## Selection process and propensity-score matching

▶ **Fig. 3** shows the selection process. We excluded all patients with missing information for the matching criteria (see below). Patients with incomplete data on resection status were also excluded. Patient with ablative therapy (APC or RFA) in the initial endoscopic papillectomy were also excluded as this is not the current standard of care. However, APC and RFA were allowed for repeat interventions for R1 resections. Complete resection was evaluated by histologic evaluation and by follow-up endoscopy. A total of 976 endoscopic papillectomies were incorporated into the matching process.




▶ **Fig. 3** Flow chart of patient selection.

We performed propensity score matching for patients with FAP and SAL based on age, sex, comorbidity (American Society of Anesthesiologists [ASA] Physical Status score), histology, and size of the ampullary lesion. A propensity score was calculated by using a multiple logistic regression analysis. The "nearest-neighbor-matching" method was used to obtain 1:1 matching without replacement. For the post hoc balance diagnostics, we used mean standardized differences [30]. The *P* value for the overall balance test was 0.781. Finally, 202 matched patients were identified.

## Statistical analysis

All statistical analyses were performed using SPSS version 26.0.0.0 (released 2019; IBM Corp., Armonk, New York, USA). R language version 4.1.2 (released 2021; R Foundation for Statistical Computing, Vienna, Austria) was used for propensity score matching. Python version 3.11.0 (released 2022; Python Software Foundation, Wilmington, Delaware, USA) was utilized to visualize Kaplan–Meier analysis and scatter plot. Data are presented as count with percentage for categorical variables, and as median with range for continuous variables. In addition, we described bivariate variables by using simple proportion

with 95 %CIs. For comparing FAP and SAL groups, chi-squared or Fisher's exact test were applied to analyze categorial variables, and the nonparametric Mann–Whitney *U* test was performed for continuous variables. Disease-free survival was calculated by using the Kaplan–Meier method. All tests were two tailed. Given the multiple end points, we used an adapted level of significance. Therefore, *P* values of < 0.01 were considered statistically significant for chi-squared, Fisher's exact, and Mann–Whitney *U* tests.

# Results

## Patient characteristics

We identified 140 patients with FAP-related ampullary lesions out of the whole ESAP database. A total of 121 underwent endoscopic papillectomy and 19 underwent surgery (not reported). By using propensity scoring, we could match 101 patients with FAP to 101 patients with SAL. The matching characteristics are shown in ▶ **Table 1**.

Age, sex, ASA score, lesion size, and histology were not significantly different between the two groups. Ampullary lesions were mainly asymptomatic in the FAP group (79.2 % vs. 46.5 %; *P* < 0.001). In symptomatic cases, SAL patients presented most often with abdominal pain. In addition, we could exclude any possible selection bias regarding the matching of patients from low-volume and high-volume centers (**Table 2 s**).

▶ **Table 1** Matching characteristics.

| | FAP, n = 101 | SAL, n = 101 | *P* value[1] |
|---|---|---|---|
| Age, median (range), years | 48 (18–81) | 50 (20–79) | 0.16 |
| Male sex, n (%) [95 %CI] | 49 (48.5) [38.5–58.4] | 54 (53.5) [43.5–63.3] | 0.48 |
| ASA score, n (%) [95 %CI] | | | 0.76 |
| ▪ 1–2 | 95 (94.1) [89.4–98.8] | 94 (93.1) [88.0–98.1] | |
| ▪ 3–4 | 6 (5.9) [1.3–10.6] | 7 (6.9) [1.9–12.0] | |
| Lesion size, median (range), mm | 15 (2–104) | 15 (5–100) | 0.80 |
| Histology, n (%) | | | 0.59 |
| ▪ Hyperplastic | 7 (6.9) | 8 (7.9) | |
| ▪ LGD | 67 (66.3) | 60 (59.4) | |
| ▪ HGD | 25 (24.8) | 28 (27.7) | |
| ▪ invasive cancer | 2 (2.0) | 5 (5.0) | |
| ▪ T1a | 2 (100) | 4 (80.0) | |

FAP, familial adenomatous polyposis; SAL, sporadic ampullary lesion; ASA, American Society of Anesthesiologists; LGD, low grade dysplasia; HGD, high grade dysplasia.
[1] *P* values < 0.01 were considered statistically significant.

## Procedural outcome

▶ **Table 2** summarizes the procedural data and outcomes of both groups. There were no significant differences in the intrabiliary and intrapancreatic extension. More patients had bile duct dilation in the SAL group (5.0 % vs. 15.8 %; *P* = 0.01). The median ampullary lesion size was 15 mm and was comparable between groups (*P* = 0.80). The histological findings of resected specimens showed mostly adenomas with low and high grade dysplasia, with equal distribution between the two groups (▶ **Table 1**). Hyperplastic lesions were infrequent in both cohorts (FAP 6.9 % vs. SAL 7.9 %). Invasive cancers were found in seven patients (FAP 2 vs. SAL 5). In the FAP group, only T1a can-

▶ **Table 2** Procedural data and outcomes of matched patients.

| | FAP, n = 101 | SAL, n = 101 | *P* value[1] |
|---|---|---|---|
| Comorbidities, n (%) [95 %CI] | 13 (12.9) [6.2–19.5] | 18 (17.8) [10.2–25.4] | 0.33 |
| ▪ Coronary artery disease | 4 (4.0) | 3 (3.0) | |
| ▪ Diabetes | 7 (6.9) | 11 (10.9) | |
| ▪ COPD | 1 (1.0) | 4 (4.0) | |
| ▪ Renal failure | 4 (4.0) | 4 (4.0) | |
| ▪ Liver disease | 1 (1.0) | 2 (2.0) | |
| Clinical presentation (%, 95 % CI) | | | |
| ▪ Asymptomatic | 80 (79.2) [71.2–87.3] | 47 (46.5) [36.6–56.4] | < 0.001 |
| ▪ Obstructive jaundice | 2 (2.0) | 6 (5.9) | |
| ▪ Abdominal pain | 4 (4.0) | 31 (30.7) | |
| ▪ Bleeding | 0 (0.0) | 1 (1.0) | |
| ▪ Acute pancreatitis | 3 (3.0) | 8 (7.9) | |
| ▪ Acute cholangitis | 0 (0.0) | 1 (1.0) | |
| ▪ Elevated liver tests | 10 (9.9) | 17 (16.8) | |
| ▪ Weight loss | 2 (2.0) | 1 (1.0) | |
| Intrabiliary extension imaging, n (%) [95 % CI] | 3 (3.0) [0.0–6.3] | 4 (4.0) [0.0–7.8] | 0.70 |
| Intrapancreatic extension imaging, n (%) [95 %CI] | 3 (3.0) [0.0–6.3] | 1 (1.0) [0.0–3.0] | 0.31 |
| Bile duct dilation, n (%) [95 %CI] | 5 (5.0) [1.0–9.3] | 16 (15.8) [8.6–23.1] | 0.01 |
| Pancreatic duct dilation, n (%) [95 %CI] | 3 (3.0) [0.0–6.4] | 7 (6.9) [1.9–12.0] | 0.19 |
| LSL, n (%) [95 %CI] | 18 (17.8) [10.2–25.4] | 7 (6.9) [1.9–12.0] | 0.02 |

▶ **Table 2** (Continuation)

| | FAP, n = 101 | SAL, n = 101 | *P* value[1] |
|---|---|---|---|
| Initial R0, n (%) [95 %CI] | 64 (63.4) [53.8–72.9] | 84 (83.2) [75.8–90.6] | 0.001 |
| Repeated interventions, n/N (%) [95 %CI] | 30/37 (81.1) [67.8–94.3] | 14/17 (82.4) [62.1–100] | 0.91 |
| ▪ Endoscopic papillectomy | 20/30 (66.7) | 9/14 (64.3) | |
| ▪ RFA | 4/30 (13.3) | 1/14 (7.1) | |
| ▪ APC | 6/30 (20.0) | 4/14 (28.6) | |
| Technical success, n/N (%) [95 %CI] | 94/101 (93.1) [88.0–98.1] | 98/101 (97.0) [93.7–100] | 0.19 |
| Recurrence in R0 treated patients, n (%) [95 %CI] | 21 (20.8) [12.7–28.8] | 16 (15.8) [8.6–23.1] | 0.36 |
| En bloc, n (%) [95 %CI] | 69 (68.3) [59.1–77.5] | 82 (81.2) [73.4–88.9] | 0.04 |
| Submucosal injection, n (%) [95 %CI] | 48 (47.5) [37.6–57.4] | 33 (32.7) [23.4–42.0] | 0.03 |
| Adverse events, n (%) [95 %CI] | 30 (29.7) [20.6–38.8] | 28 (27.7) [18.8–36.6] | 0.76 |
| ▪ Bleeding | 13 (12.9) | 13 (12.9) | |
| ▪ Pancreatitis | 17 (16.8) | 15 (14.9) | |
| ▪ Cholangitis | 0 (0) | 2 (2.0) | |
| ▪ Perforation | 3 (3.0) | 3 (3.0) | |
| ▪ Cardiovascular | 1 (1.0) | 1 (1.0) | |
| ASGE ≥ severe adverse events, n (%) [95 %CI] | 5 (5.0) [0.6–9.3] | 2 (2.0) [0.0–4.7] | 0.25 |
| Duration of procedure, median (range), minutes | 44 (1–141) | 34 (2–200) | 0.04 |
| Length of hospital stay, median (range), days | 2.5 (0–79) | 2.5 (0–29) | 0.67 |
| Follow-up, median (range), months | 39 (0–153) | 27 (0–146) | 0.09 |

FAP, familial adenomatous polyposis; SAL, sporadic ampullary lesion; COPD, chronic obstructive pulmonary disease; LSL, laterally spreading lesion; RFA, radiofrequency ablation; APC, argon plasma coagulation; ASGE, American Society for Gastrointestinal Endoscopy.
[1] *P* values <0.01 were considered statistically significant.

cers were found compared with one case of T1b and four cases of T1a in the SAL group.

After initial intervention, the rate of complete resection (R0) was significantly higher in the SAL group than in the FAP group (83.2 % vs. 63.4 %; *P* = 0.001). Most patients with incomplete resection underwent an additional intervention with APC (n = 10), RFA (n = 5), or repeat endoscopic papillectomy (n = 29). The mean number of additional interventions was 1.30 per patient. For patients who underwent APC or RFA, the follow-up endoscopy evaluated completeness of resection or recurrence. By summarizing initial intervention and repeated intervention, the technical success was 93.1 % in the FAP group and 97.0 % in the SAL group (*P* = 0.19). However, the en bloc resection rate was higher in patients with SAL (81.2 %) compared with those with FAP (68.3 %; *P* = 0.04), and patients with FAP received more submucosal injection (47.5 % vs. 32.7 %; *P* = 0.03). The endoscopic procedure including endoscopic papillectomy and diagnostic evaluation lasted longer in the FAP group than in the SAL group (44 minutes [range 1–141] vs. 34 minutes [range 2–200]; *P* = 0.04), although this may be related to the intensive inspection of the whole duodenum during surveillance in patients with FAP. Based on the adapted level of significance (*P* < 0.01), these differences were not considered statistically significant.

### Adverse events

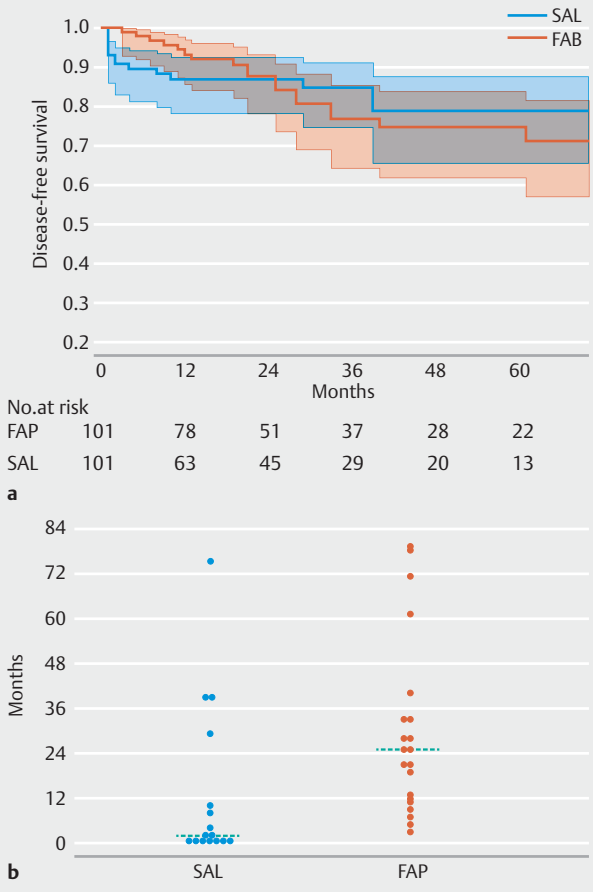
Overall, adverse events were reported in 28.7 % of all patients. There was no significant difference in adverse events between patients with FAP and patients with SAL (FAP 29.7 % vs. SAL 27.7 %; *P* = 0.76). Pancreatitis (FAP 16.8 % vs. SAL 14.9 %) and bleeding (12.9 % in both groups) were the most common adverse events. Cholangitis (FAP 0 % vs. SAL 2.0 %), perforation (3.0 % in both groups), and cardiovascular complications (1.0 % in both groups) were rare and were not significantly different between the two groups. No procedure-related deaths occurred. The length of hospital stay was comparable (FAP 2.5 days [range 0–79] vs. SAL 2.5 days [range 0–29]; *P* = 0.67).

### Follow-up

The median follow-up was 39 months (range 0–153) in the FAP group and 27 months (range 0–146) in the SAL group (*P* = 0.09). ▶ **Fig. 4a** shows the disease-free survival of both groups. The 1– and 3-year disease-free survival rates were 93.3 % (95 %CI 87.6–99.1) and 76.8 % (95 %CI 66.6–87.0), respectively, in the FAP group, and 87.0 % (95 %CI 78.6–93.5) and 84.8 % (95 %CI 75.2–92.4), respectively, in the SAL group. A log-rank test was not performed as the curves crossed. A total of 37 recurrences were recorded after complete resection: 21 in the FAP group (20.8 %) and 16 in the SAL group (15.8 %; *P* = 0.36). ▶ **Fig. 4b** demonstrates the time to recurrence in these patients during follow-up. Patients with FAP relapsed after a median of 25 months (95 %CI 18.3–31.7), and in patients with SAL, median time to recurrence was 2 months (95 %CI 0.06–3.9). Most recurrences were treated endoscopically. Three patients in the FAP group received pancreaticoduodenectomy as secondary surgery. In the SAL group, one patient with a recurrence underwent transduodenal surgical ampullectomy and eight underwent resection by pancreaticoduodenectomy.

## Discussion

In FAP, the ampulla of Vater appears to be a predilection site for adenomatous lesions [4]. Endoscopic papillectomy is a minimally invasive treatment for ampullary lesions but only a few




▶ **Fig. 4** Disease-free survival and time to recurrence following endoscopic papillectomy in patients with familial adenomatous polyposis and sporadic ampullary lesions. **a** Kaplan–Meier analysis with 95 %CI estimating disease-free survival. **b** Recurrence time in relapsed patients, with median. SAL, sporadic ampullary lesion; FAP, familial adenomatous polyposis.

cohort studies to date have analyzed endoscopic papillectomy in FAP-related ampullary lesions. The current study compared outcomes and adverse events of endoscopic papillectomy for ampullary lesions between patients with FAP and those with SAL in thoroughly matched cohorts.

To the best of our knowledge, this study is the largest series of endoscopic papillectomy for patients with FAP. Our data show a rate of complete resection (R0) after initial endoscopic papillectomy of 63.4 % in the FAP group and 83.2 % in the SAL group ($P$ = 0.001). However, repeated interventions increased the technical success in the FAP group to the level of the SAL group. The initial lower rate of complete resection in patients with FAP could be a result of different resection techniques used in the multinational ESAP study database. Therefore, we also analyzed submucosal injection for endoscopic papillectomy. More patients in the FAP group received submucosal injection compared with the SAL group (47.5 % vs. 32.7 %), without statistical significance. However, submucosal injection is no longer recommended in the current ESGE guideline [16, 31]. These high rates of submucosal injection in our study are a result of inclusion criteria of the ESAP study database dating back more than 10 years [24]. In addition, recurrences and remnant lesions were not significantly different when using submucosal injection in a prospective trial [32]. More recently, a modified technique of submucosal injection only in the distal part of the papilla resulted in comparable rates of complete resection but less periprocedural bleeding and pancreatitis [33, 34]. Therefore, the use of submucosal injection is still a matter of debate and submucosal injection alone is not an adequate explanation for the lower R0 rate in the FAP group.

The R0 rate in patients with FAP in our study seems to be lower than in previously published trials (**Table 1 s**). A systematic review from Ramai et al. reported a “technical success” of 90.3 % in a pooled analyses in patients with FAP [35]. However, there are methodological differences that have to be considered, and the term “technical success” was not defined as R0 but included en bloc resection, endoscopic or histologic evaluation of complete resection, and additional interventions [22]. Cecinato et al. compared the technical success between patients with FAP and patients with SAL. The authors reported a higher success rate in the FAP group (95.2 %) compared with the SAL group (65.8 %; $P$ = 0.03) [22]. Conversely, Catalano et al. showed a higher success rate in patients with sporadic lesions (86 %) compared with patients with FAP (68 %; $P$ = 0.02) [23].

Given the abovementioned definition of technical success, our data showed a technical success of 93.1 % in patients with FAP and 97.0 % in patients with SAL when including repeated interventions ($P$ = 0.19). This analysis also included eight patients who were lost to follow-up after R1 resection (six FAP, two SAL). However, when considering the results with the high rate of technical success, we do not believe that this limitation could have biased our results substantially.

By using propensity score matching, age was comparable between the cohorts. Previous data indicate that ampullary lesions occur in patients with FAP at a younger age and become obvious due to the specific endoscopic screening of the upper gastrointestinal tract in FAP [6]. In the study of Cecinato et al. that showed different results from those in our cohorts, the authors found that patients with FAP were significantly younger than patients with SAL (48.0 years vs. 67.6 years; $P$<0.001). More importantly, ampullary lesions were significantly smaller in size in the FAP group (15.3 mm vs. 21.49 mm; $P$ = 0.04), representing a huge limitation for the interpretation of these results [22]. In contrast, our patients were thoroughly matched for age and lesion size, and there was no significant difference between patients in the two groups. The majority of ampullary lesions were below 30 mm (94.1 %) and our interventions are therefore in line with the current recommendations of the ESGE to perform endoscopic papillectomy for ampullary lesions up to 20–30 mm in size [16]. Thus, our data provide evidence that ESGE criteria for SAL can be extended to FAP-related ampullary lesions.

The adverse event rate associated with endoscopic papillectomy was 28.7 % for all cases. The most common adverse events were pancreatitis (FAP 16.8 %, SAL 14.9 %) and bleeding (FAP

12.9 %, SAL 12.9 %). Perforation and cholangitis occurred less frequently. There was no significant difference in the adverse events between patients with FAP and patients with SAL. Overall, severe adverse events were rare, and there were no endoscopic papillectomy-related deaths. Small FAP series have reported adverse events such as pancreatitis (19 %–20 %) and bleeding (4 %–13 %), which are in line with our results [18, 20]. Roos et al. showed an adverse event rate of 41 %, which was understandable given that most lesions were ≥ 10 mm in size [21]. A recent analysis including more than 100 endoscopic papillectomies in patients with SAL also reported that pancreatitis and bleeding were the most common endoscopic papillectomy-related adverse events [36].

In our study, patients with FAP were mostly asymptomatic (79.2 % vs. 46.5 %; $P<0.001$). A possible explanation could be the regular screening of patients with FAP for adenoma of the upper gastrointestinal tract. The current ESGE guideline recommends starting endoscopic duodenal and ampullary surveillance at the age of 25 years in patients with FAP [37]. Therefore, the fact that ampullary lesions did not cause symptoms in the majority of patients with FAP is understandable. Regarding the histological classification of the resected specimens, most lesions were ampullary adenoma and were equally distributed in the two groups. In seven cases we found invasive cancers (six T1a and one T1b). Patients with T2 cancers or nodal or distant metastasis were excluded, as these patients are not candidates for endoscopic papillectomy.

Recurrence rates after complete resection were higher in the FAP group compared with the SAL group (21 patients [20.8 %] vs. 16 patients [15.8 %]), but the difference was not significant ($P=0.36$). Interestingly, patients with FAP relapsed later than patients with SAL (median 25 months vs. 2 months). Prior reports also observed the tendency of a late relapse of ampullary lesions in patients with FAP [20, 22, 38]. Ma et al. reported a recurrence rate of 58.3 % in patients with FAP over a mean follow-up of 84 months [20], and in the study by Gluck et al., 67 % of the patients showed recurrence during a follow-up of 7.2 years [18]. In the current study, one patient with FAP relapsed after 79 months. In contrast, in the study by Catalano et al., all patients with sporadic lesions relapsed within 1 year after endoscopic papillectomy [23]. Regarding the definition of recurrence, it is important to know that patients with FAP have a high risk of developing new FAP-related lesions in the whole gastrointestinal tract [39]. Thus, new lesions of the ampulla of Vater after complete resection via endoscopic papillectomy were defined as recurrence although this might also have included some new neoplasms. However, we still consider defining such lesions as recurrences. The authors also refer to the definition of residual/recurrent adenoma rate. Residual/recurrent adenoma rate is more frequently accepted as a quality indicator for colonoscopy but the discrimination of a residual lesion from a recurrence is not always possible by surveillance endoscopy [40]. In summary, our data are in line with the published literature and underline that there is a lifetime risk of recurrence of ampullary lesions particularly in patients with FAP. Thus, adequate long-term surveillance is necessary.

The strengths of our study are the large number of patients included and the use of the propensity score-matched method. This matching method is a common accepted procedure to obtain patient groups with comparable baseline characteristics [30]. Although 20 patients with FAP could not have been considered in the matching process owing to a lack of matching partners in the SAL group, their exclusion did not impact our outcomes. As patients with FAP were regularly screened for neoplastic lesions of the upper gastrointestinal tract, patients with FAP-related ampullary lesions are often younger than patients with SAL [6]. Thus, we were not able to find a perfect "age match" for 20 patients with FAP. Limitations of this study originate from the retrospective design, and selection bias could be introduced due to missing data. Furthermore, data were collected over a period dating back more than a decade and a minor influence of technical improvements in endoscopic papillectomy or a selection bias cannot be excluded. We tried to overcome these limitations by using clearly defined inclusion criteria and a rigorous matching method. In addition, a multicenter long-term prospective study for ampullary lesions in patients with FAP would be difficult to perform and therefore unlikely.

In conclusion, endoscopic papillectomy was a safe and effective therapy for ampullary lesions in both FAP and SAL. The criteria for endoscopic resection of ampullary lesions in patients with SAL can therefore be extended to patients with FAP. However, even after complete resection, there is a need for adequate long-time surveillance, especially in patients with FAP.

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### Competing Interests

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