Original research

Endoscopic papillectomy versus surgical ampullectomy for adenomas and early cancers of the papilla: a retrospective Pancreas2000/European Pancreatic Club analysis

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ABSTRACT

Objective Ampullary neoplastic lesions can be resected by endoscopic papillectomy (EP) or transduodenal surgical ampullectomy (TSA) while pancreaticoduodenectomy is reserved for more advanced lesions. We present the largest retrospective comparative study analysing EP and TSA.

Design Of all patients in the database, lesions with prior interventions, benign histology advanced malignancy (T2 and more), patients with hereditary syndromes and those undergoing pancreatoduodenectomy were excluded. All remaining cases as well as a subgroup of them, after propensity-score matching (nearest-neighbour-method) based on age, gender, anthropometrics, comorbidities, size and histological subtype, were analysed. The median follow-up was 21 months (IQR 10–47) after the primary intervention. Primary outcomes were rates of complete

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Ampullary lesions, in particular ampullary adenoma, are a rare disease with a potential for a malignant transformation and should be completely resected. Whether to choose an endoscopic or surgical technique is unclear.

WHAT THIS STUDY ADDS

⇒ In this retrospective database, we compared endoscopic papillectomy (EP) with transduodenal surgical ampullectomy. The rates of inappropriate indications (non-neoplastic lesions, advanced cancers) were still high. For the remaining cases, both procedures were safe, but EP showed lower rates of R0 resection in the whole cohort. In a matched cohort analysis, we found EP non-inferior to the surgical counterpart with regard to overall survival, but recurrences and retreatments appeared to be higher.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In selected patients, EP could be considered first, when R0 resection appears feasible. Case selection and step-up approaches should be studied further.

resection (R0) and complications. Groups were compared by Fisher's exact or χ^2 test, Mann-Whitney-U-test and log-rank test for survival.
Results Of 1673 patients in the database, 1422 underwent EP and 251 TSA. Of them, 23.2% were excluded for missing or inconclusive data and 19.8% of patients for prior interventions or hereditary syndromes. Final histology showed in 24.2% of EP and 14.8% of TSA patients a histology other than adenoma or adenocarcinoma while advanced cancers were recorded in 10.9% of EP and 36.6% of TSA patients. Finally, 569 EP and 63 TSA were included in the overall analysis, with a higher rate of more advanced cases and higher R0 resection rates in the TSA groups (90.5% vs 73.1%; p<0.01), with additional ablation in the EP group in 14.4%. Severe adverse event rates were 3.2% (TSA) vs 1.9% (EP). Recurrence after histological R0 resection was 16% (EP) vs 3.2% (TSA; p=0.01), and additional therapy for R1 resection was applied in 67% of the 159 cases. Propensity-score-based matching identified 62 pairs of EP/TSA patients with comparable baseline patient and lesion characteristics. The initial R0-rate was 72.6% (EP) compared with 90.3% (TSA, p=0.02) with recurrences found in 8% (EP) vs 3.2% (TSA; p=0.07); reinterventions were more frequent in the EP group. Overall survival was comparable.
Conclusions The rate of patients with poor indications due to non-neoplastic disease or advanced cancer is still high for both EP and TSA; multiple retreatments were necessary for EP. Although EP can be considered an appropriate primary therapy for certain ampullary adenomas, case selection for both therapies (especially with regard to the best step-up approach) should be studied further.

INTRODUCTION

Ampullary neoplastic lesions are rare, with a prevalence of 0.1% and account for 10% of all periampullary lesions.[1 2] About 90% of them are histologically classified as adenoma or adenocarcinoma, but also neuroendocrine and mesenchymal lesions or other rare subtypes can be found.[3] Ampullary adenoma is considered as premalignant lesion which follows an adenoma-to-carcinoma sequence.[4 5] Of note, the ampulla of Vater is a transitional region leading to cancers with distinct molecular subtypes (mostly intestinal, pancreaticobiliary or mixed subtype).[6]

Historically, the treatment of ampullary lesions has included transduodenal surgical ampullectomy (TSA)[7] and pancreaticoduodenectomy (PDD).[8] However, substantial morbidity and mortality associated with these procedures[9–11] led to the development of endoscopic techniques. The first case of an endoscopic papillectomy (EP) was described by Suzuki[12] in 1983 and the first large case series was published in 1993.[13] Since initial results were not satisfying, subsequent improvements in patient selection and technical advances were reported.[14] Therefore, the current guideline of the European Society of Gastrointestinal Endoscopy (ESGE) recommends this technique as the first choice treatment for ampullary adenoma up to 30 mm in diameter.[15]

However, mostly single-centre series comparing EP and surgical procedures have been published and the quality of evidence is limited.[15] A recent meta-analysis revealed a pooled rate of complete resection (R0) of 76.6% for EP compared with more than 95% for surgical procedures. However, the heterogeneity between the studies was high.[16 17] Furthermore, TSA and PDD have different indications, so generally patients with more advanced lesions undergo the more extensive procedure. We, therefore, analysed outcomes and complications of local resection techniques (EP and TSA) for ampullary lesions included in a large multicentric retrospective database and used a propensity score matching to compare both procedures in a subgroup of cases.

PATIENTS AND METHODS

Patients

We used the database of the ESAP study (Endoscopic Papillectomy vs Surgical Ampullectomy vs Pancreaticoduodenectomy for ampullary neoplasm), which was developed in the framework of a multinational multicentre retrospective study (online supplemental file 2).[18] In the ESAP study data of patients with EP, TSA and PDD were collected between January 2007 and September 2020 from 58 participating centres. All centres had to provide at least 10 patients in the mentioned period. All adult patients with a histologically confirmed ampullary neoplasm based on endoscopic biopsy who underwent an endoscopic or surgical resection were eligible for inclusion, but the present analysis only includes ampullary adenoma and early cancers after EP and TSA interventions. Neuroendocrine and other rare lesions have been previously published.[19 20] In addition, lesions of the minor papilla were excluded and analysed in a prior study.[21] Patients with prior interventions were excluded and also patients with laterally spreading lesions including duodenal mucosa or treated in palliative intentions were not considered in this analysis.

A minimum follow-up of 12 months or until death after the first intervention with clinical, endoscopic and/or cross-sectional imaging after resection was required. All collected data underwent a data quality check including analysis of plausibility, completeness of data and missing outcomes or reinterventions. All centres included consecutive patients (online supplemental figure 1) but monitoring of missing cases, that is, cases not included during the study period for various reasons, was not possible.

Histological subtypes of the resected ampullary specimen were classified as non-neoplastic (including hyperplastic, inflammatory lesions and chronic papillitis), low-grade dysplasia (LGD), high-grade dysplasia (HGD), invasive cancer or rare lesions (neuroendocrine lesions, gastrointestinal stroma tumour, paraganglioma) but only adenoma and early adenocarcinoma were considered for the outcome analysis. Paris classification was used for morphological classification of lesions.[22] Data on the primary biopsy results before therapy were not analysed in this study. The treatment of recurrences was not the primary outcome of this study and analysed in another project of the ESAP cohort.[23]

Furthermore, local legal and regulatory authorities as well as the medical secrecy and the Federal Data Protection Act

followed. The Strengthening the Reporting of Observational Studies in Epidemiology guidelines were followed.[24]

Outcomes

Primary outcome was the rate of complete resection (R0 determined by histology, initial treatment success) achieved by the first endoscopic or surgical intervention. Possible additional ablative measures in the endoscopic group were recorded; since in a retrospective study, precise reasons cannot be given, we assumed that examiners thought that there was residual tissue visible which had to be abladed (R2 resection); preventive ablation as in colon EMR is not standard in EP. Secondary outcomes were R0-rates when including repeated interventions for incomplete resections, recurrences and complications. Outcomes were analysed for whole cohorts and matched patients (see below). Recurrences were defined as new lesions after completed resection and at least one normal follow-up on endoscopic surveillance.

Follow-up

Surveillance of patients was based on the usual follow-up protocols of the participating centres. All centres policies are detailed in online supplemental figure 1. In the vast majority of cases, an endoscopic follow-up was conducted after 3–6 months (all), 12 months (85%) and then annually (75%) after EP and TSA. If a stent was placed at the initial EP, it was then removed. Follow-up started after the first intervention and continued for at least 12 months or until death. Follow-up may have included repeated therapies during the period. Individual data about adherence to the protocols with regard to completeness and a number of examinations are not available.

Datasets

The following medical information was extracted from the ESAP study database if available: age at diagnosis, gender, anthropometrics, comorbidities, anticoagulation, concomitant hereditary polyposis syndrome (exclusion criterion), clinical presentation, size, morphology and histology of the lesion (only definitive histology of the resected specimen were considered to avoid a possible sampling error of biopsy). Specific information regarding the interventional procedures (duration, rate of en bloc and complete resection, repeated interventions, additional ablative therapy, recurrence, specific complications and others) was also asked for. For EP, the following items were extracted: sphincterotomy, submucosal injection, stenting and complementary treatment. In addition, the type of surgery, drains and margins were specified for TSA. Procedure-related adverse events (AEs) were stratified according to the American Society of Gastrointestinal Endoscopy (ASGE) complication scale[25 26] for EP, and according to the Clavien-Dindo classification[27] for surgical procedures. Postinterventional acute pancreatitis was stratified according to the Revised Atlanta Classification.[28] Bleeding and pancreatic fistula were graded according to the International Study Group of Pancreatic Surgery definition.[29] Only severe AEs were reported, and only for the neoplastic cases included in this final analysis (ie, not for non-neoplastic lesions).

Selection process

To compare endoscopic and surgical procedures, a strict primary selection process of datasets was performed (figure 1). We excluded all patients with polyposis syndromes as such patients might differ from sporadic lesions. In addition, all cases with missing data, especially regarding matching criteria (see below) as well as interventions for palliation

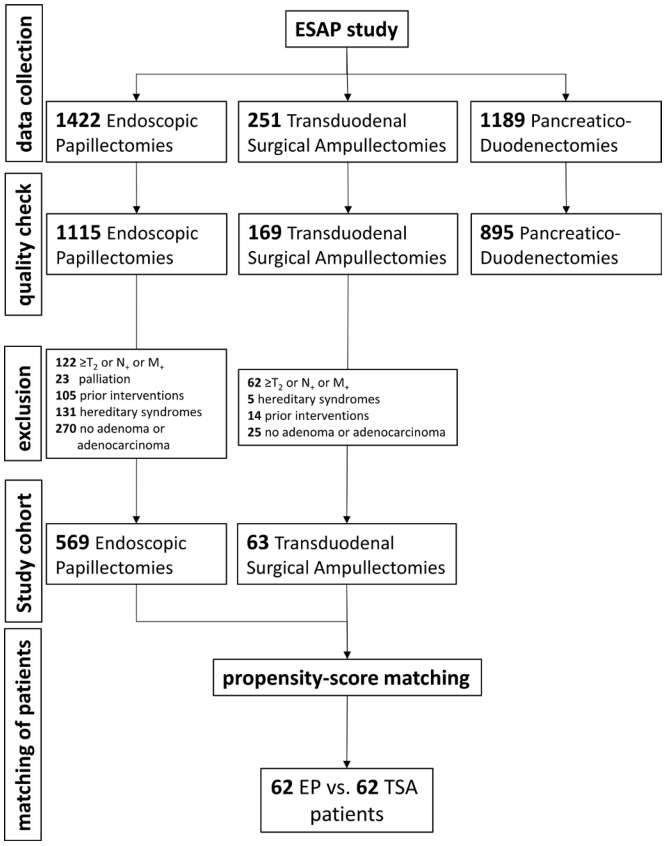

Figure 1 Flow chart of patient selection. The whole ESAP study database was screened for eligible patients. The following datasets were excluded: histopathological detection of ampullary carcinoma with stage T_2, T_3, T_4, nodal or distant metastasis; histology other than adenoma or adenocarcinoma, missing values for propensity-score matching and missing outcomes, polyposis syndromes, palliative treatment or prior interventions. Some patients had more than one exclusion criterion. ESAP, Endoscopic Papillectomy vs Surgical Ampullectomy vs Pancreaticoduodenectomy for ampullary neoplasm; TSA, transduodenal surgical ampullectomy.

were excluded. Only adenoma and early cancers (T_1) were included. Invasive cancers of the papilla with a tumour stage of T_2 or higher as well as lymph node or distant metastasis were also excluded as such patients are no candidates for local resections despite being performed and primarily included. Patients with complementary interventions such as radiofrequency ablation (RFA) or argon plasma coagulation (APC) were included in the total cohort. However, these patients were not considered in the matched cohorts if the ablation was performed during the initial EP to reduce variability as primary additional ablation does not reflect so far the standard of care in EP. We included patients treated with RFA or APC into the matching process if performed in later interventions as 'adjuvant' therapy to treat R1 resections. In EPs with R1 status, only cases with additional treatment attempts were considered. If ablation techniques were used as additional therapy, a complete resection was confirmed by endoscopic follow-up with negative biopsies. Finally, 569 EP and 63 TSA cases were selected (figure 1). Analysis of excluded patients shows that they were comparable to patients available for propensity score matching regarding age, gender, comorbidities and size of the lesion.

Propensity-score matching

Propensity-score-based matching was used as the populations (EP, TSA) showed distinct heterogeneity in baseline criteria, size and subtype of the resected lesions. Matched parameters were age, gender, body mass index (BMI), ASA physical status classification system (ASA score), size and histological subtype of the lesion. In addition, data of complete resection and R0 status as well as the report of complications were mandatory. A multiple logistic regression analysis was applied to generate a propensity score for each dataset. The 'nearest-neighbour-matching'-method (pairing a given point with another, 'closest' point) was used to achieve a 1:1 matching with a calliper of 0.2 without replacement (recommended calliper should be 0.2 or less[30]). Post hoc balance diagnostics were calculated by using mean standardised differences.[31] Finally, 124 (62 vs 62) matched EP/TSA patients were identified. The graphical results of the matching process can be found in figure 2. The p value for the overall balance test was 0.89. The L1 imbalance test after matching was 0.88.[32]

Statistical analysis

All statistical analyses were performed by using SPSS (V.22.0.0.0, released 2013, IBM). For propensity-score matching, R (V.2.15.3) with R library digest, optmatch, RItools, SparseM and xtable extensions with SPSS R essentials were used. Imbalances in covariates after matching were calculated by the overall balance test from Hansen and Bowers and the L1 relative imbalance test by Lacus, King and Porro.[32] For the overall balance test, a t-test was used to calculate a p value (no significance if covariates are balanced) and in the L1 imbalance test values near 1.0 are often the result of multiple covariates.[33] Data are presented as counts with percentages for categorical variables and median with interquartile range (25%–75%) for continuous variables. χ^2 or Fisher's exact test was applied to analyse categorical variables. The non-parametric Mann-Whitney U test was used to compare continuous variables. Overall survival was calculated by using the Kaplan-Meier log-rank test. Following the recommendations for survival analyses of matched cohorts, stratified log-rank tests were performed for matching parameters.[34] All tests were two tailed and p values <0.05 were considered statistically significant. The graphical abstract was designed by means of BioRender (Toronto, Canada). Sample size calculations were performed with GPower (V.3.1, University of Düsseldorf, Germany).

RESULTS

Descriptive parameters and selection of the entire study group

Patient selection is shown in figure 1. The 2862 patients of the whole ESAP study database were included from 58 participating centres during a study period of 14.75 years (177 months). The contribution of centres and the period of inclusion of cases is shown in online supplemental figure 1. Cases with PDD were primarily excluded from this analysis (n=1189).

Of the remaining 1673 patients in the database, 1422 had undergone EP and 251 TSA. Data were then checked for missing or inconclusive data (in particular missing outcomes or missing values in matching parameters), leading to the exclusion of a further 23.2% of datasets. Of the remaining 1284 patients (1115 EP, 169 TSA), 652 cases (546 EP and 106 TSA) patients were not considered in this study for the following reasons; some cases had more than one exclusion criterion:

1. 255 patients (19.8%) were dismissed for prior interventions or hereditary syndromes.

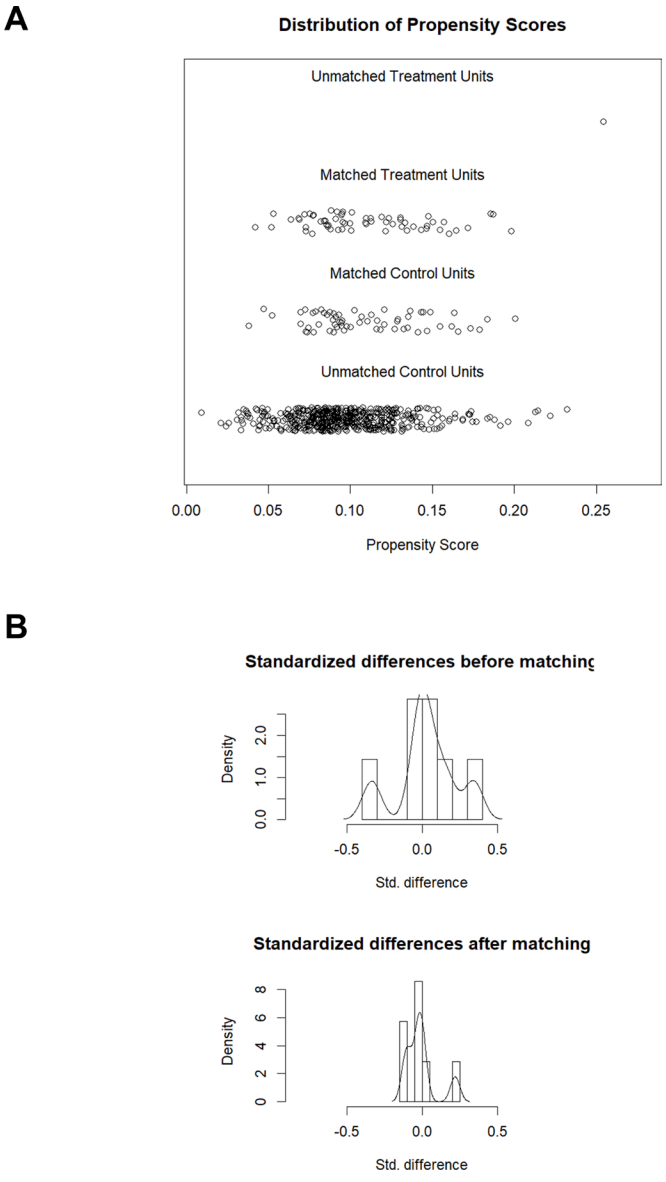

Figure 2 Propensity-score matching The propensity-score matching was performed to identify patient pairs of EP/TSA patients with age, gender, body mass index, size and histology of lesion, ASA score and previous treatment as cofactors. (A) Graphical presentation of propensity-score matching and (B) reduction in mean differences after matching. ASA, American Society of Anesthesiologists; EP, endoscopic papillectomy; TSA, transduodenal surgical ampullectomy.

2. Non-neoplastic histology: a final histology other than adenoma or adenocarcinoma was found in 23.0% of cases (270 EP (24.2%) and 25 TSA cases (14.8%), mainly hyperplastic or chronic inflammation).
3. Advanced malignancy (stage T_2 or higher, nodal involvement): these were 122 EP (10.9%) and 62 TSA (36.6%) patients most of whom underwent secondary PDD. 23 cases (2%) in the EP group were done with palliative intention.

The final EP cohort included 569 patients (40.0% of all database cases) and the TSA cohort 63 patients (25.1%).

Baseline criteria of EP and TSA cohorts

The baseline criteria of the entire study cohorts are detailed in table 1. These data showed statistically some significant different characteristics between the two cohorts of patients. TSA patients

Table 1 Baseline characteristics of entire EP and TSA cohorts

	EP (569)	TSA (63)	P value
Age (year, median, IQR)	67, 57–75	68, 57–74	0.95
Male gender (%)	305 (53.6)	34 (54.0)	0.36
BMI (kg/m^2, median, IQR)	25.5, 23.0–28.4	24.4, 20.9–27.3	*0.03*
ASA score			*<0.001*
1–2	486 (85.4)	52 (82.5)	
3–4	84 (14.8)	11 (17.5)	
Comorbidities (%)			
Overall at least one	285 (50.1)	29 (46.0)	0.59
Coronary artery disease	75 (13.2)	4 (6.3)	*0.04*
Diabetes	91 (16.0)	9 (14.3)	0.49
COPD	39 (6.8)	3 (4.8)	0.12
Renal failure	26 (4.6)	3 (4.8)	0.16
Liver disease	18 (3.2)	0 (0)	*0.04*
Clinical presentation (%)			
Asymptomatic	275 (48.3)	20 (29.0)	0.08
Obstructive jaundice	91 (16.0)	7 (11.1)	0.47
Abdominal pain	152 (26.7)	16 (25.4)	0.69
Bleeding	16 (2.8)	0 (0)	0.32
Acute pancreatitis	26 (4.6)	6 (9.5)	0.19
Acute cholangitis	39 (6.9)	11 (17.5)	*0.01*
Elevated liver tests	135 (23.7)	26 (41.3)	*0.004*
Weigth loss	22 (3.9)	4 (6.3)	0.26
Antiplatelets/anticoagulation (%)			*<0.001*
No	472 (82.9)	43 (68.3)	
Withheld	75 (13.2)	7 (11.1)	
Continued	22 (3.9)	13 (18.8)	
Type of antiplatelets/anticoagulation (%)			*<0.001*
Aspirin mono	43 (7.6)	4 (6.3)	
P2Y12 mono	11 (1.9)	0 (0)	
Dual antiplatelet therapy	4 (0.7)	0 (0)	
Warfarin	17 (3.0)	2 (3.2)	
DOAC	6 (1.1)	0 (0)	
LMWH	16 (2.8)	14 (22.2)	

Italic values indicate statistical significance.
ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulants; EP, endoscopic papillectomy; LMWH, low-molecular-weight heparin; TSA, transduodenal surgical ampullectomy.

revealed a higher ASA score for comorbidities but lower BMI (median 24.4 vs 25.5 kg/m^2). More elevated liver tests and less acute cholangitis were found in TSA patients. In the TSA group, also more patients had anticoagulants and/or antiplatelets (29.9% vs 17.1%, p<0.001) or continued the medication during the intervention.

Detailed characterisation of the resected lesions and outcomes of the procedures is presented in table 2. More patients showed an intraductal extension of the ampullary lesion in preinterventional imaging but this was not analysed in every resected specimen. Dilation of bile and pancreatic duct was more often found in the TSA group (44.4 vs 33.2% and 22.2% vs 16%, p<0.001, respectively). The median size of the lesion was higher in the EP group (18 mm vs 15 mm, p=0.04) and more advanced lesions were found in the TSA group (HGD+cancer: 58.8% vs 42.2%, p=0.001).

Main outcomes including AE in the entire group

The median follow-up of the entire group was 21 months (IQR 10–47) after the first intervention. Details of outcomes and complications for all patients (adenoma and adenocarcinoma) are presented in table 2. In the EP group (n=569), the overall initial R0 resection rate was 73.1% compared with 90.5% in the TSA group (p=0.001). For both, adenoma and adenocarcinoma, the length of the procedure and length of hospital stay was significantly longer in the TSA group. Overall survival between entire EP and TSA cohort was not significantly different (figure 3A, p=0.10). Recurrence in R0-treated patients was 16% (82/512) in the EP group and 3.2% (2/63) in the TSA group (p=0.01). Of the 569 EPs and 63 TSA, severe complications were very rare and recorded in 11 patients in the EP (1.9%) and 2 in the TSA cohort (3.2%, p=0.38). However, there was one procedure-related death reported in the TSA cohort. There were no differences between the adenoma and the cancer groups. Details of procedures and complications can be found in online supplemental table 2.

Resection outcomes of entire group in ampullary adenoma

EP group

For adenoma, the initial R0-rate was 80.2% (386/481) in the EP group, but this included additional measures such as ablation during the first session in 14.4% (69 cases, 3 RFA and 66 APC, table 2). Thus, the primary success rate (R0) of EP in procedures without ablation was 76.9% (317/412). If the 69 cases with ablation were included as probably R2 resections requiring additional ablative treatment, the primary success rate (R0) of EP alone of all 481 cases would be 65.9% (317/481).

Of the 95 adenoma patients with a histological R1 status after EP, 42 did not undergo a retherapy for various reasons. In 40 patients a second endoscopic intervention was performed using ablation alone with APC (n=7) or RFA (n=11) or re-EP with ablation (n=22). Five R1-cases with adenomas received a secondary TSA and eight patients a secondary PDD. Surgery resulted in complete resection in all cases.

In 17 out of the 40 patients (42.5%) with endoscopic retherapy, an incomplete resection was observed on the first follow-up thereafter and a second retreatment was performed (5 EP with APC, 7 EP with RFA, 9 EP alone, 2 pancreaticoduodenectomies). In 12 of the remaining 15 endoscopic cases (80%) a third reintervention was necessary (5 EP with APC, 3 EP with RFA and 4 EP alone) that all finally resulted in a negative follow-up endoscopy with negative biopsies. However, after at least one negative follow-up, the rate of recurrence was 65/481 (13.5%).

TSA group

In the TSA group, the initial R0 resection rate for adenoma was 92.9% (53/57) and thus significantly higher than the EP group (p=0.01). Recurrence after R0 resection was 3.5% (2/57). All four patients with incomplete resection underwent an endoscopic retreatment (three EP with APC and one EP with RFA). Two of them had to be retreated with additional EP with APC that resulted in negative follow-up endoscopy with negative biopsies. However, after at least one negative follow-up, two recurrences were seen.

Resection outcomes of entire group in ampullary adenocarcinoma

EP group

In the EP group, there were 88 invasive cancers (15.5% of patients, 62.5% male gender, median 72 years), 75 of them

Table 2 Procedural data and outcomes of entire EP and TSA cohorts

	EP (569 patients)	TSA (63 patients)	P value
Intrabiliary extension imaging (%)	33 (5.8)	13 (20.6)	*<0.001*
Intrabiliary extension histology (%)	15 (2.6)	0 (0)	0.13
Intrapancreatic extension imaging (%)	6 (1.0)	0 (0)	*0.007*
Intrapancreatic extension histology (%)	7 (1.2)	0 (0)	0.31
Bile duct dilation (%)	189 (33.2)	28 (44.4)	*<0.001*
Pancreatic duct dilation (%)	91 (16.0)	14 (22.2)	*<0.001*
Size (mm, median, IQR)	18, 11–28	15, 7–25	*0.04*
Histology (%)			*0.001*
LGD	329 (57.8)	26 (41.2)	
HGD	152 (26.7)	31 (49.2)	
Invasive cancer	88 (15.5)	6 (9.6)	
T1a	75/88	5/6	
T1b	13/88	1/6	
Initial R0 (%)	416/569 (73.1)	57/63 (90.5)	*0.001*
R0 for adenoma	386/481 (80.2)	53/57 (92.9)	*0.01*
R0 for carcinoma	30/88 (34.1)	4/6 (66.6)	0.12
Concomitant therapy during resection (%)			
APC (%)	83 (14.6)	–	–
RFA (%)	3 (0.5)	–	–
Retherapy for R1-treated patients (%)	100/153 (65.4)	6/6 (100)	
Repeated intervention			
(Repeated) EP 1×	25	1	
(Repeated) EP 1x+APC	10	3	
(Repeated) EP 1×+RFA	14	1	
(Repeated) EP 2×±ablation	18	2	
(Repeated) EP 3×±ablation	13	–	
TSA	5	–	
PDD	37	1	
PDD after EP	2	–	
Chemotherapy	4	–	
BSC	5	–	
R0 after first endoscopic retreatment (%)	29/49 (59.2)	3/5 (60)	
R0 after second endoscopic retreatment (%)	5/18 (27.8)	2/2 (100)	
R0 after third endoscopic retreatment (%)	13/13 (100)	–	
Recurrence in R0-treated patients (%)	82/512 (16.0)	2/63 (3.2)	*0.01*
Local	74	2	
Nodal	4	0	
Distant	4	0	
Complications (%)			0.38
Severe (ASGE≥severe, Clavien-Dindo ≥4)	11 (1.9)	2 (3.2)	
Including deaths	0 (0)	1 (1.6)	
Duration of procedure (min, median, IQR)	30, 14–53	227.50, 183.75–267.75	*<0.001*
Lenght of hospital stay (days, median, IQR)	3, 2–5	14, 9.75–21	*<0.001*
Follow-up (months, median, IQR)	20, 9–46	38, 15–61	*0.003*

Italic values indicate statistical significance.
APC, argon plasma coagulation; ASGE, American Society of Gastrointestinal Endoscopy; BSC, best supportive care; EP, endoscopic papillectomy; HGD, high-grade dysplasia; LGD, low-grade dysplasia; PDD, pancreaticoduodenectomy; RFA, radiofrequency ablation; TSA, transduodenal surgical ampullectomy.

T_{1a} and 13 T_{1b}. Histological R0-rate was 34.1% (30/88), 17 patients received a concomitant APC during the initial EP. In 11 of the 58 patients (18.9%) with incomplete resection, no retreatment was performed for various reasons. Nine patients received additional EP (3 with APC, 3 with RFA and 3 EP alone), 27 underwent PDD, 4 received chemotherapy and 5 best supportive care. Of the nine endoscopically retreated patients, three (33%) were R1 and received additional EP (one with APC). One of them was R1 and underwent a third retreatment with EP and RFA and was finally negative on the first follow-up endoscopy with negative biopsies. Thus, endotherapy alone, even if in several sessions, was successful in 45.3% (34/75) of the T_{1a} and 38.5% (5/13) of the T_{1b} cancers. Of the 27 patients who underwent PDD as retreatment, 11.1% (3/27) were R1, 2 received additional resection and chemotherapy, 1 best supportive care. In 6 of the 27 surgically retreated patients an adjuvant chemotherapy was administered. In 25.8%

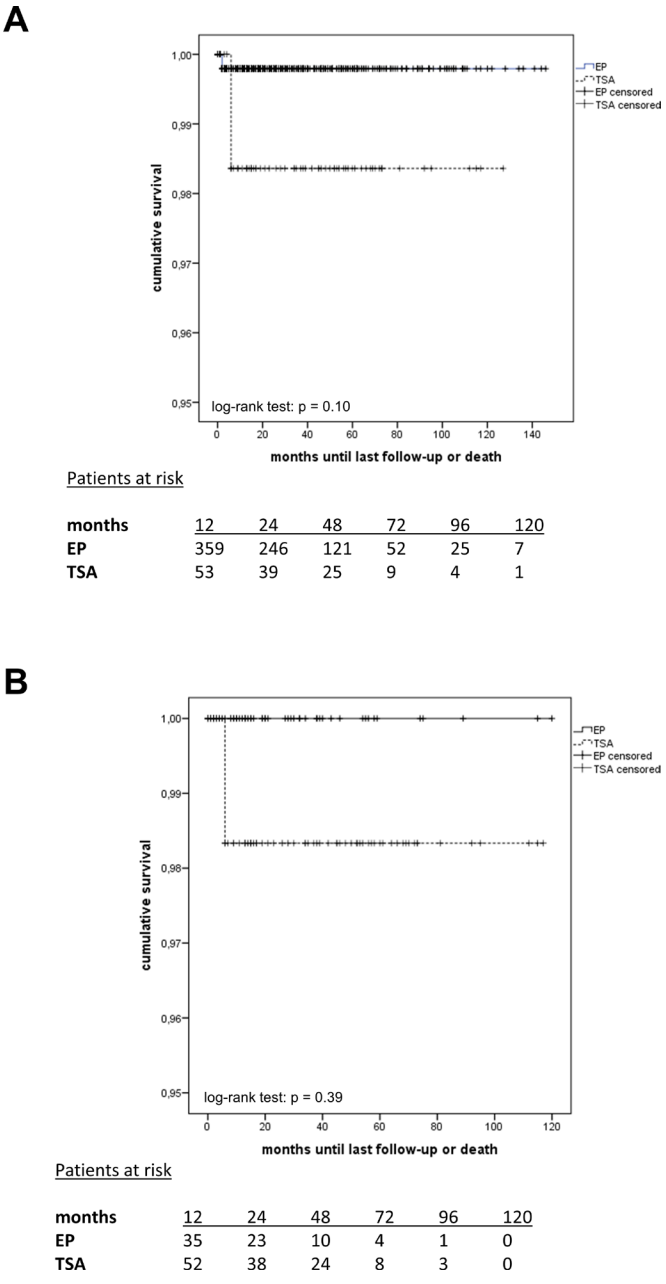

Figure 3 Survival analysis Kaplan-Meier curves for overall survival of EP/TSA patients (A) and matched EP/TSA cohorts (B) with corresponding log-rank test. EP, endoscopic papillectomy; TSA, transduodenal surgical ampullectomy.

(17/66) of the final R0-treated patients a recurrence was detected.

TSA group

In the TSA group, six early cancers were included, five T_{1a} and 1 T_{1b}, R0-rate was 66.6% (4/6). One of the R1-treated patients underwent an EP without ablation and one patient a PDD. Both patients showed a negative follow-up. There were no recurrences in the six TSA patients.

Results of propensity-score matching for EP and TSA

In order to make patient cohorts more comparable regarding baseline characteristics and lesions, a propensity-score-based matching was performed. After propensity-score matching, we could identify 62 EP/TSA pairs of patients. For one TSA patient, no corresponding EP case could be identified (figure 2A). The matched cohorts represent 4.4% and 24.7% of the original dataset and 10.9% and 98.4% of the corrected case numbers (see figure 1). The baseline characteristics (table 3) were comparable regarding age, gender, BMI and comorbidities. In both groups, ampullary lesions were mainly an incidental finding not causing any symptoms (more often in EP). In symptomatic patients, elevated liver tests were more frequent in the EP group. The use of antiplatelets or anticoagulants was comparable between both cohorts but low-molecular-weight heparin was more often administered to TSA patients.

Table 3 Baseline characteristics of matched EP and TSA patients

	EP (62 patients)	TSA (62 patients)	P value
Age (year, median, IQR)	66, 59–76	68, 57–74	0.94
Male gender (%)	30 (48.4)	34 (54.8)	0.47
BMI (kg/m^2, median, IQR)	23.8, 20.7–26.8	24.5, 22.1–27.3	0.73
ASA score (%)			0.34
1–2	54 (87.1)	51 (82.2)	
3–4	8 (12.9)	11 (17.8)	
Comorbidities (%)			
Overall at least one	31 (50.0)	29 (46.8)	0.41
Coronary artery disease	10 (16.1)	4 (6.5)	0.08
Diabetes	6 (9.7)	9 (14.5)	0.27
COPD	6 (9.7)	3 (4.8)	0.2
Renal failure	1 (1.6)	3 (4.8)	0.22
Liver disease	6 (9.7)	0 (0)	*0.01*
Clinical presentation (%)			
Asymptomatic	32 (51.6)	20 (32.3)	*0.04*
Obstructive jaundice	10 (16.1)	6 (9.7)	0.33
Abdominal pain	17 (27.4)	16 (25.8)	0.58
Bleeding	1 (1.6)	0 (2.4)	0.50
Acute pancreatitis	5 (8.1)	6 (9.7)	0.58
Acute cholangitis	5 (8.1)	10 (16.1)	0.25
Elevated liver tests	15 (24.2)	25 (40.3)	0.06
Weigth loss	5 (8.1)	4 (6.5)	0.31
Antiplatelets/anticoagulation (%)			0.13
No	49 (79.0)	42 (67.7)	
Withheld	9 (14.5)	7 (11.3)	
Continued	4 (6.5)	13 (21.0)	
Type of antiplatelets/anticoagulation (%)			*0.03*
Aspirin mono	6 (9.7)	4 (6.5)	
P2Y12 mono	1 (1.6)	0 (0)	
Dual antiplatelet therapy	1 (1.6)	0 (0)	
Warfarin	2 (3.2)	2 (3.2)	
DOAC	1 (1.6)	0 (0)	
LMWH	1 (1.6)	14 (22.6)	

Italic values indicate statistical significance.
ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulants; EP, endoscopic papillectomy; LMWH, low-molecular-weight heparin; TSA, transduodenal surgical ampullectomy.

Outcome of matched EP and TSA cohorts

Comparisons of procedural data and main outcomes between EP and TSA are presented in table 4. There were more lesions with intraductal extension in preinterventional imaging but not in histological evaluation and slightly more dilation of

Table 4 Procedural data and outcomes of matched EP and TSA patients

	EP (62 patients)	TSA (62 patients)	P value
Intrabiliary extension imaging (%)	5 (8.1)	13 (21)	*0.01*
Intrabiliary extension histology (%)	2 (3.2)	0 (0)	0.19
Intrapancreatic extension imaging (%)	0 (0)	0 (0)	–
Intrapancreatic extension histology (%)	0 (0)	0 (0)	–
Bile duct dilation (%)	19 (30.6)	28 (45.2)	*0.001*
Pancreatic duct dilation (%)	8 (12.9)	14 (22.6)	*0.02*
Size (mm, median, IQR)	15, 10–20	15, 7–21.3	0.62
Histology (%)			0.08
LGD	34 (54.8)	26 (41.9)	
HGD	14 (22.6)	30 (48.4)	
Invasive cancer	14 (22.6)	6 (9.7)	
T1a	13/14	5/6	
T1b	1/14	1/6	
Initial R0 (%)	45 (72.6)	56 (90.3)	*0.02*
Retherapy for R1-treated patients (%)	17/17 (100)	6/6 (100)	
Repeated intervention			
(Repeated) EP 1×	5	1	
(Repeated) EP 1×+APC	6	3	
(repeated) EP 1×+RFA	6	1	
(repeated) EP 2×±ablation	4	2	
(repeated) EP 3×±ablation	1	–	
PDD	–	1	
R0 after first endoscopic retreatment (%)	13/17 (76.5)	3/5 (60)	
R0 after second endoscopic retreatment (%)	3/4 (75)	2/2 (100)	
R0 after third endoscopic retreatment (%)	1/1 (100)	–	
Recurrence in R0-treated patients (%)	5 (8.0)	2 (3.2)	0.07
Local	5 (100)	2 (100)	
Nodal	0 (0)	0 (0)	
Distant	0 (0)	0 (0)	
Complications (%)			1.0
Severe (ASGE≥severe, Clavien-Dindo≥4)	1 (1.6)	2 (3.2)	
Including deaths	0	1	
Duration of procedure (min, median, IQR)	36, 15.25–50	225, 182.50–266	*<0.001*
Lenght of hospital stay (days, median, IQR)	3, 2–6	14, 9.5–21	*<0.001*
Follow-up (months, median, IQR)	15.5, 5.75–38.25	37.5, 15–60.25	*0.006*

Italic values indicate statistical significance.
APC, argon plasma coagulation; ASGE, American Society of Gastrointestinal Endoscopy; EP, endoscopic papillectomy; HGD, high-grade dysplasia; LGD, low-grade dysplasia; RFA, radiofrequency ablation; TSA, transduodenal surgical ampullectomy.

bile and pancreatic duct in the TSA group. The size of the lesions was comparable in both groups with a median value of 15 mm (p=0.62) and also the distribution of the histological subtype was comparable after matching (mainly LGD and HGD). We found 14 invasive cancers in the EP and 6 cancers in the TSA cohort, mostly of T_{1a} stage.

The rate of complete resection (R0) during the initial intervention was significantly higher in the TSA group (90.3% vs 72.6%, p=0.02). All R1-treated patients underwent additional interventions. In the EP group, of the 17 patients with incomplete resection, 6 received EP with APC, 6 EP with RFA and 5 EP alone. Of the 17 retreated patients 13 (76.5%) were R0, the remaining 4 patients underwent additional endoscopic therapy (2 EP with APC and 2 with RFA). Of these four patients, three were R0 and 1 patient received a third reintervention with EP and APC that finally resulted in follow-up endoscopy without any evidence for adenoma or carcinoma and negative histology. The reinterventions for the six incomplete resected TSA patients are described above (see results for entire group).

Reported recurrences were low in both groups (8% vs 3.2%, p=0.07) and only local. Severe complications, defined as ≥ 'severe' by scoring scale of the ASGE or ≥ '4' by Clavien-Dindo-classification were not significantly different between EP and TSA treatment. However, there was one procedure-related death after TSA. Procedural times were significantly longer in the TSA group (median 36 vs 225 min, p<0.001) and the median length of hospital stay was 14 days after TSA compared with 3 days after EP (p<0.001). Technical details of each procedure and complications can be found in online supplemental table 2.

Patients in the TSA group had a longer median follow-up (37.5 vs 15.5 months, p=0.006). The overall survival is illustrated in figure 3B. The log-rank test revealed no significant differences in patient survival between both groups.

DISCUSSION

The management of ampullary lesions has been a challenge because of the decision-making between less invasive EP versus surgery, either limited to using the transduodenal technique with TSA or extended using PDD with curative intention. Meta-analyses of non-comparative trials still demonstrate an inferior R0 resection-rate of EP but also lower AE rate.[16 17 35] These publications may have limited case numbers, reveal a very high

heterogeneity as well as the risk of a selection bias and thus have to be interpreted with caution.

The first interesting aspect of our study has to do with the exclusion of cases, namely those with normal histology and cancer: First, it has to be stressed that we were focusing on the final histology results of the resection specimens and did not include the primary biopsy results. Discrepancies are well known from the literature: One study showed a limited preinterventional overall accuracy of only 69% for a single initial biopsy.[36] In another study on ampullary adenoma, the accuracy was 81.8% (3.6% missed malignancies) and only 66.7% for adenocarcinoma.[37 38] Second, and of quite some clinical relevance, it is remarkable, that in a substantial number of cases—almost 25% in the EP and 15% in the TSA group—final histology showed non-neoplastic tissue while it has to be assumed that resection was planned on the basis of a preinterventional biopsy positive for neoplasia. Conversely, the rate of advanced malignancy was 10.9% for EP and 36.6% for TSA. Also here, it can be speculated that preprocedural planning might have been insufficient, but both facts represent real-life evidence. Thus, one important conclusion from our study is that preprocedural assessment has to be improved, by either repeating endoscopy and possibly biopsy when patients are referred or having biopsy samples reassessed by expert pathologists in a second opinion procedure. To improve the diagnostic accuracy of preinterventional staging, in particular histological evaluation of biopsy, the use molecular markers such as KRAS expression might be helpful to discriminate adenoma from adenocarcinoma.[39] However, these data were not available in our study population. Whether refined imaging using MRCP or EUS may help, is currently unclear.

The results of our larger cohort comparing EP and TSA revealed an overall R0 for EP of 73.1% that was significantly lower compared with TSA (90.5%, p=0.001). However, when including endoscopic retreatment, success is likely to be increased, although at the cost of several reinterventions. In addition, recurrences can only be reliably excluded by careful endoscopy with routine biopsy even if macroscopically negative. In large retrospective databases like ours, these detailed data are usually not available. Thus, later recurrences cannot be excluded. Also, our reported recurrence rate of 16% after histologically confirmed R0 resection should be used to interpret complete resection with caution. It is likely, that further follow-up with possible further retreatment is necessary, especially in the EP group. In the TSA group, 3.2% recurrences were found after R0 resection, and R1 recurrences were also retreated using a variety of techniques, endoscopically and surgically, with seemingly good results.

Comparison of rates of AE showed no significant differences, with numerically higher AE rates in surgery (3.2% vs 1.9%). Such differences could be higher or become significant with (much) larger case numbers, and retrospective databases have well-known limitations with regard to scrutiny and completeness. A recent meta-analysis of the complication results of control groups in randomised trials looking at post-ERCP complications revealed a constantly higher rate[40] than usually reported in retrospective database studies.[41] To overcome such limitations, we asked for endoscopic and surgical complications in detail (see online supplemental table 2). However, this topic can only be clarified by larger and ideally prospective studies focusing on AE. Additionally, we analysed long-term survival and found no statistically significant difference between EP and TSA groups, neither in the entire group nor in matched cohorts. However, our study was not designed to analyse survival and this possibly will be addressed by future projects of the ESAP study group.[18]

As the entire cohort revealed significant differences between both resection techniques in terms of baseline characteristics of both patients and lesions, we performed a propensity-score matching. A propensity-score-based matching is an accepted alternative to prospective randomised controlled trials (RCTs)[31] that would be hard to perform for AL. By virtue of this method, a substantial number of patients are not included in the comparison. In the matched cohorts, R0-rates increased and recurrences substantially decreased in the EP cohort. We think that our study comprises a representative patient cohort in comparison to the published case series.[16] These results also showed EP to be effective when including retreatments. Here, our data are in line with recent publications indicating a rate of complete resection for EP ranging from 49.2%[42] to 96.4%[43] if only series with at least 50 cases were considered. The largest cohort by Yamamoto *et al*[38] found a R0-rate of 76.6% that corresponds with the results of current meta-analyses[16 17] as well as our database analysis. Another recent publication including more than 100 EP showed a rate for complete resection of 78.2%.[44] However, much more relevant for clinical implication is the possibility to achieve a complete resection when performing additional interventions related to the risk of AEs in surgical approaches. In this regard, our results show that a repeated endoscopic therapy may finally improve results. Thus, the benefits and risks of repeated endoscopic interventions (possibly even long term) vs likely reduced morbidity of EP have to be weighed against each other.

In addition, lesion size may also play a role in selecting the appropriate therapy: In our study, most ampullary lesions were below 30 mm in diameter. This is in line with recent recommendations of the ESGE[15] and also highlights that our data reflect daily practice. From our propensity score matched dataset we are not able to evaluate lesions beyond 30 mm in size as these were not available in sufficient numbers in the matched cohorts. Another potential concern involves the issue of submucosal injection. In our matched cohorts, in 24.2% of EP patients submucosal injection was applied during EP. However, submucosal injection is no longer recommended by the ESGE guideline. Evidence from the literature is contradictory,[42 45] perhaps submucosal injection only in the distal part of the papilla may result in comparable rates of complete resection but less periprocedural bleeding and pancreatitis.[46] The inclusion of EPs with submucosal injection is a result of the initial criteria of the ESAP study database. In this dataset, procedures dating back more than 10 years were eligible for inclusion. Although such cases with submucosal injection could therefore have influenced the EP results, limitations of a retrospective analysis prevent reliable conclusions.

Regarding recurrences, we found lower ratees in the TSA group (3.2% in both entire and matched cohort) compared with the EP group (16% entire cohort, 8% matched cohort). This probably reflects the deeper resection of TSA (ampullectomy) as compared with EP (papillectomy). Recurrence much depends on the scrutiny of follow-up, both endoscopically as well as with regard to biopsy policy (eg, taking biopsies when macroscopy is deemed normal). Results of a large retrospective database are naturally limited in this respect. This is reflected in the very wide range of reported recurrences in the literature, ranging from 0%[38 47] to 73%[48] with a mean recurrence of 13% in a previous meta-analysis.[16] However, the heterogeneity between the included studies was 91.3%, and therefore, a distinct evidence-based calculation of recurrences after EP is limited. Even when focusing on cohort studies including more than 100 EPs, the recurrence is still between 0% and 15%.[16] Due to methodological limitations, this issue cannot fully be clarified by our study either. In general, it is comprehensible that more advanced

lesions result in a higher number of recurrences and the rate of recurrent lesions relies both on the lesion size and histology as well as the performance quality of the respective procedure. Both procedures had comparable outcomes when looking at final results including retreatment (which however was more frequent in the EP group) and especially survival. While due to the limited invasiveness of EP, this procedure should probably be given preference in lesions up to 3 cm as in our study, treatment of the residual/recurrent neoplasia as well as mode of step-up approaches have to be systematically studied further. Also, the relevance of small residual/recurrent adenoma in an elderly and otherwise frail patient has to be taken into account, too.

Results in ampullary cancers are of some interest, although we report only a limited number of 94 cases. However, other series are much smaller. Petrone *et al* found recurrence after EP in 8 out of 14 patients (57%) with T_1 ampullary carcinoma[49] while Will *et al* showed a recurrence only in 2 out of 12 patients (16.6%) with T_1 carcinoma treated by EP.[50] In another study, 1 local and 1 metastatic recurrence was found in 14 patients (14.3%) with T_1 carcinoma after EP with no additional surgery.[51] Woo *et al* showed a local recurrence in 3 (5.3%) and a metastatic disease in 1 (1.7%) out of 57 T1 ampullary cancers after EP.[52] These data also highlight the remarkable heterogeneity between the published case series and our study data could be seen within an acceptable range regarding recurrences, especially with regard to patients' general condition and risk factors. These data also underline the need to distinguish between T_{1a} and T_{1b} adenocarcinoma that carry a significantly different risk of nodal metastasis. In addition, the therapeutic management of recurrences was not the main outcome of this study and was analysed in another project of our study group.[23]

Patients in the surgical group more often showed dilated bile or pancreatic ducts and a greater intraductal extension of the ALs as judged by pretreatment imaging. In general, an intraductal extension of less than 10 mm is considered amenable to endoscopic resection, although in particular in AL below 20 mm, histological staging of intraductal extension often is challenging.[53] When combining EP with ablation therapy, endoscopic treatment might also be acceptable for intraductal extensions up to 20 mm.[54 55] However, these data need to be confirmed by larger cohorts.

Our study has some limitations. First this is a retrospective study and by nature of this study type a selection bias and/or missing data cannot be definitively excluded. This risk of a selection bias may be reduced when all participating centres include consecutive interventions and do not dismiss patients due to incomplete data, which we tried to ascertain. Of course, a formal study monitoring was outside the scope of this database due to limited resources. This was one reason why we analysed thoroughly matched patients to overcome this possible limitation of our study and prior cohort series.[56] Based on our inclusion criteria, both low-volume and high-volume centres were included in the whole ESAP database. Not all centres provided data on all three procedures (EP, TSA, PDD) but this was not a prerequisite and also does not reflect daily practice. Of course, some centres included more than 100 cases, others less. However, to include also low-volume centres will more adequately reflect daily practice and prevents limiting our results only to expert centres. We did not analyse a possible centre-volume in our study. In addition, the exclusion of patients with missing data could also harbour the risk of a selection bias. However, an exclusion analysis showed that patients who were excluded because of missing data were comparable to patients available for the propensity score matching.

Our results could ideally be confirmed by an RCT. Such an RCT would undoubtedly provide the highest level of evidence but is unlikely to be performed for several reasons, most likely due to the well-known difficulty to randomise patients between endoscopy and surgery, which might exclude the majority of eligible patients. Sample-size calculations of a two-armed trial comparing EP and TSA reveal 190 patients (95 per group) who will need to be randomised (alpha-error 0.05, power 0.95, ratio 1:1, effect size 0.5). Given the fact that only non-invasive adenoma and T_1-cancers will be able to undergo randomisation, we estimate a dropout out at least 30% leading to a screening population of 315 patients with ampullary lesions. Such a trial will be unrealistic to perform even on an international level. In addition, one could argue that TSA is not broadly available and a lot of surgical centres do not have experience with TSA.[57]

In summary, our results support the recommendation that ampullary adenoma and perhaps early-stage ampullary cancers, for example, T_{1a}, should preferably be treated by EP up to a certain size (eg, 3 cm), if R0-resection with an adequate pathology analysis is feasible. TSA should be proposed if EP cannot lead to R0 resection or for lesions with advanced intraductal extension. Further management details, for example, whether to repeat endoscopic therapy and how often versus a step-up approach from EP to TSA should be the subject of further studies.

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