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Predictors of Therapeutic Success and Adverse Events in Endoscopic Ampullectomy: A Multicenter Retrospective Study

Maria Teresa Magalhães Guedes Novais

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Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

Estudante

Maria Teresa Magalhães Guedes Novais

Estudante do 6ºano do Mestrado Integrado em Medicina do Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

Endereço de correio eletrónico: mariateresa88@outlook.pt

Orientador

Professor Doutor Paulo Sérgio Durão Salgueiro

Assistente Hospitalar Graduado, Serviço de Gastrenterologia, Unidade Local de Saúde de Santo António (ULSSA)

Professor Associado Convidado, Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

Endereço eletrónico: paulosalgueiro@gmail.com

Coorientadora

Drª Sandra Inês Ribeiro Correia

Interna de Formação Específica em Gastrenterologia, Serviço de Gastrenterologia, Unidade Local de Saúde de Santo António (ULSSA)

Endereço eletrónico: sandraribeirocorreia@chporto.min-saude.pt

Coorientadora

Drª Andreia Isabel Cruz Rei

Assistente Hospitalar, Serviço de Gastrenterologia, Unidade Local de Saúde de Santo António (ULSSA)

Endereço eletrónico: aicrei@hotmail.com

Porto, Junho 2025

Estudante

Maria Teresa Magalhães Guedes Novais

Maria Teresa Magalhães Guedes Novais

Orientador

Assinado por: Paulo Sérgio Durão Salgueiro
Num. de Identificação: BI12422301
Data: 07-06-2025 15:06:37 +01:00

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Professor Doutor Paulo Sérgio Durão Salgueiro

Coorientadora

Assinado por: **SANDRA INÊS RIBEIRO CORREIA**
Num. de Identificação: 15061459
Data: 2025.06.07 14:16:36 +0100

CHAVE MÓVEL

Dr.ª Sandra Inês Ribeiro Correia

Coorientadora

Assinado por: Andreia Isabel Cruz Rei
Identificação: BI12320056
Data: 2025-06-07 às 13:40:08

Dr.ª Andreia Isabel Cruz Rei

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Resumo

Enquadramento: Os adenomas da papila de Vater são lesões raras, pré-malignas, que têm sido tradicionalmente tratadas cirurgicamente. A ampulectomia endoscópica (AE) surgiu como uma alternativa minimamente invasiva em casos selecionados. Todavia, os preditores de sucesso clínico, recorrência e eventos adversos ainda não se encontram bem estabelecidos. A baixa incidência destas lesões e a escassez de dados provenientes de estudos multicêntricos têm condicionado a definição de orientações clínicas baseadas na evidência.

Objetivos: O objetivo primário do estudo foi identificar preditores de eficácia e segurança após ampulectomia endoscópica, nomeadamente o sucesso endoscópico, a taxa de recorrência e a ocorrência de eventos adversos. Os objetivos secundários foram avaliar o impacto do volume de procedimentos por centro, da concordância histológica, das características da lesão, e da técnica de ressecção, nos resultados da ampulectomia endoscópica.

Metodologia: Estudo de coorte retrospectivo e multicêntrico, realizado em 12 centros hospitalares portugueses, incluindo 187 doentes submetidos a ampulectomia endoscópica por adenomas da papila de Vater entre janeiro de 2019 e dezembro de 2023. Procedeu-se à recolha de dados demográficos, clínicos, relativos aos procedimentos técnicos e às caracteristicas das lesões, através de um modelo padronizado. Foi realizada análise de regressão logística univariada e multivariada para identificação de preditores independentes de sucesso endoscópico, recorrência e eventos adversos.

Resultados: Obteve-se sucesso endoscópico em 96.3% dos casos. A taxa de recorrência foi de 18,9%, sendo maioritariamente detetada na primeira endoscopia de vigilância (71,4%) e tratada por abordagem endoscópica em 84,4% dos casos. Os eventos adversos mais comuns foram pancreatite aguda pós-procedimento (20,3%) e hemorragia (intraprocedimento: 18,2%; tardia: 12,9%). A análise multivariada identificou como preditores independentes de recorrência: idade (OR=0,948; p=0,008), extensão intraductal (OR=17,88; p=0,022), injeção da submucosa (OR=2,60; p=0,037) e hemorragia intraprocedimento (OR=3,55; p=0,011). A hemorragia tardia associou-se de forma independente à injeção da submucosa (OR=2,96; p=0,025) e à colocação de prótese pancreática (OR=5,05; p=0,036). Nenhuma variável se associou de forma independente à ocorrência de pancreatite aguda pós-procedimento ou colangite aguda. O volume dos centros associou-se significativamente com a recorrência da lesão e hemorragia tardia, com taxas superiores de recorrências nos centros com baixo volume de procedimentos.

Conclusões: A ampulectomia endoscópica é uma intervenção eficaz e segura no tratamento de lesões ampulares. A recorrência de lesão associou-se às características da lesão e a procedimentos técnicos. Os melhores resultados (em termos de eficácia e em segurança foram obtidos em centros com maior volume de procedimentos. Estes resultados reforçam a importância de realizar este procedimento endoscópico avançado em centros com maior treino e experiência

Palavras-chave: Adenoma ampular; Ampulectomia endoscópica; Colangiopancreatografia Retrógrada Endoscópica; Resultados clínicos; Eventos adversos

Abstract

Background: Ampullary adenomas are rare and premalignant lesions that have historically been managed surgically. Endoscopic ampullectomy (EA) has emerged as a minimally invasive alternative for selected cases, however predictors of clinical success, recurrence and adverse events remain poorly defined. The low incidence of ampullary tumors and scarcity of multicenter data have limited the definition of evidence-based guidelines.

Objectives: The primary objective is to identify predictors of efficacy and safety following endoscopic ampullectomy, including endoscopic success, recurrence rate, adverse events. The secondary objective is to evaluate the impact of patient center volume, histological concordance, lesion characteristics and resection technique on clinical outcomes.

Methods: This was a multicenter, retrospective cohort study conducted across 12 Portuguese tertiary centers, including 187 patients who underwent endoscopic ampullectomy for ampullary adenomas between January 2019 and December 2023. Demographic, clinical, procedural, and lesion-related data were collected using a standardized template. Univariate and multivariate logistic regression analyses was performed to identify independent predictors of endoscopic success, recurrence and adverse events.

Results: Endoscopic success was achieved in 96.3% of patients. Recurrence occurred in 18.9%, most commonly detected at first surveillance (71.4%), and managed endoscopically in 84.4% of cases. The most common adverse events were post-procedural pancreatitis (20.3%) and bleeding (intraoperative: 18.2%; delayed: 12.9%). Multivariate analysis identified age (OR=0.948, p=0.008), intraductal extension (OR=17.88, p=0.022), submucosal injection (OR=2.60, p=0.037), and intraprocedural bleeding (OR=3.55, p=0.011) as independent predictors of recurrence. Delayed bleeding was independently associated with submucosal injection (OR=2.96, p=0.025) and pancreatic stent placement (OR=5.05, p=0.036). No variable was independently predictive of post-ERCP pancreatitis and cholangitis. Center volume was significantly associated with recurrence and delayed bleeding, with higher rates observed in low-volume centers.

Conclusions: Endoscopic ampullectomy is effective and safe for ampullary adenomas. Recurrence correlates with lesion features and technical procedures, while outcomes improve in high-volume centers, highlighting the value of centralization and personalized strategies.

Keywords: Ampullary adenoma; Endoscopic ampullectomy; Endoscopic Retrograde Cholangiopancreatography; Clinical Outcomes; Adverse events;

List of Abbreviations

AA – Ampullary Adenoma

ASA – Acetylsalicylic Acid

AE – Ampulectomia Endoscópica

ALP – Alkaline Phosphatase

BMI – Body Mass Index

CKD – Chronic Kidney Disease

CPRE - Colangiopancreatografia Retrógrada Endoscópica

CRP – C-Reactive Protein

CT – Computed Tomography

DOAC – Direct Oral Anticoagulants

EA – Endoscopic Ampullectomy

ERCP – Endoscopic Retrograde Cholangiopancreatography

ESGE – European Society of Gastrointestinal Endoscopy

EUS – Endoscopic Ultrasound

FAP – Familial Adenomatous Polyposis

GGT – Gamma-Glutamyl Transferase

HGD – High-Grade Dysplasia

LGD – Low-Grade Dysplasia

LST – Laterally Spreading Tumor

MRCP – Magnetic Resonance Cholangiopancreatography

OR – Odds Ratio

PD – Pancreaticoduodenectomy

PEP – Previous ERCP Pancreatitis

SA – Surgical Ampullectomy

SPSS – Statistical Package for the Social Sciences

ULS – Unidade Local de Saúde

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Introduction

Ampullary tumors arise from the ampulla of Vater, distally to the bifurcation of the pancreatic duct and the distal common bile duct. They are rare with an incidence of less than 1 per 100 000 per year, representing only 0.6-0.8% of all cancers. Nevertheless, their incidence has increased in the last years due to improved endoscopic and radiological diagnostic methods. The mean age of diagnosis occurs in the sixth to seventh decade with a male to female sex ratio of 1.5[1].

Even though the majority of ampullary tumors are considered sporadic, a diagnosis at a younger age should raise suspicion of hereditary polyposis syndromes, particularly familial adenomatous polyposis (FAP) as this is the most commonly inherited syndrome associated with ampullary neoplasms [2].

Most noninvasive ampullary tumors of the major papilla are asymptomatic and an incidental finding detected during conventional upper endoscopy performed for a non-related indication. Nonetheless, they can present with symptoms such as jaundice (16.6%), pain (14.4%), bile duct stones (38%), acute pancreatitis (4.1%) and/or cholangitis (1%)[1].

Biopsies taken during endoscopy followed by histological examination are mandatory for the diagnosis of ampullary tumors. However, endoscopic biopsy of ampullary tumors carries a 30% false-negative rate and diagnostic discrepancy of pathologic results, reported as 25%-50%[3].

Ampullary adenomas (AA) are considered premalignant lesions following the adenoma to carcinoma sequence similar to colorectal adenocarcinoma. Due to their malignant potential, adenomas should be removed in most cases [1,4]. For all stages combined, disease-specific survival without resection at 1 and 5 years is reported to range from 71.7% to 89% and from 38.8% to 47.2%, respectively. This outcome is significantly better compared with carcinomas located in the duodenum, distal bile duct, and pancreatic head. Tumors present at stage 1 in up to a third of cases which was one of the most relevant independent predictive factors of survival[1].

Regarding the treatment of ampullary tumors there are three recommended procedures: pancreaticoduodenectomy (PD), transduodenal surgical ampullectomy (SA) and endoscopic ampullectomy (EA). Historically, the management of ampullary lesions has primarily relied on surgical interventions[5-6]. While surgery offers lower recurrence rates, it is also associated with significant risks, including elevated rates of adverse events, prolonged hospitalization, substantial

morbidity, and potential mortality [6-7]. Advancements in endoscopic techniques, particularly endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP), have revolutionized diagnostic and therapeutic approaches [2,6,8]. Endoscopic resection procedures are associated with reduced morbidity while maintaining high rates of efficacy [3,4,6]. As a result, for patients with small (20-50mm), benign lesions or those who are poor surgical candidates, endoscopic treatment serves as a safe and effective alternative [3,4,6].

In addition to its therapeutic role, EA can provide “macrobiopsies” that aid in tumor staging, particularly when resection margins are compromised [3,8]. This function is critical given the previously mentioned limitations of endoscopic biopsy for accurate pre-procedural diagnosis. In fact, studies indicate an accuracy of 81.8% for ampullary biopsies, with 3.6 % of malignancies being undetected, and only 66.7 % accuracy for adenocarcinomas, even when endoscopic ultrasound (EUS) is employed[9].

Endoscopic ampullectomy (EA) was first introduced by Suzuki et al. in 1983, with the first extensive case series documented by Binmoeller et al. in 1993 [10,11].

In subsequent years, numerous studies have reported favorable outcomes, demonstrating low morbidity and mortality associated with endoscopic intervention [3,4,6].

Currently, there is no clear consensus or standardized guidelines for the use of EA. However, EA is common practice for smaller lesions (20–50 mm) that meet specific criteria, including the absence of invasive carcinoma, clear margins, soft tissue composition and no signs of ulceration [1,3,6].

Recent advancements have broadened these criteria, with studies showing the feasibility of performing "piecemeal" EA even for larger, laterally spreading lesions, cases with deep ductal invasion, and presumed node-negative T1 adenocarcinomas [3,7,12].

Nevertheless, endoscopic ampullectomy is an advanced endoscopic approach that ideally should be performed in specialized referral centers [1,3,12].

Patients undergo the procedure in the left lateral decubitus position using therapeutic duodenoscopes with conscious sedation or general anesthesia as needed. Initial steps should include detailed inspection of the ampulla, looking for endoscopic signs of invasive neoplasia. Standard polypectomy with monopolar diathermic snares and blended electrosurgical current are used. *En bloc* resection is prioritized. If immediate bleeding occurs it can be endoscopically managed. Prophylaxis of acute pancreatitis should include rectal indomethacin and/or hyper-hydration and pancreatic stent placement. Specimens are carefully retrieved for

histopathology, avoiding fragmentation. After the procedure, patients should be carefully monitored for adverse events for at least 48h [3,13,14].

The average R0 resection rates typically show significant variation among treatment approaches, with endoscopic ampullectomy (EA) achieving 76.6%, surgical ampullectomy (SA) 94.4%, and pancreaticoduodenectomy (PD) 98.9% [3,7,15].

A comprehensive systematic review and meta-analysis by Garg et al. (2023) including 1763 patients, found that EA and SA have comparable long-term recurrence rates at 1, 2, 3, and 5 years of follow-up, supporting the role of EA as a safe and effective treatment option for benign ampullary adenomas. The adverse events rate escalates from 24.7% for EA to 28.3% for SA and peak at 44.7% for PD [17].

In the context of EA, the most frequently observed adverse events (AEs) are post-procedural pancreatitis (11.9%) and bleeding (10.6%), and less commonly perforation (3.1%) and cholangitis (2.7%) [3,13]. Long-term adverse events, including papillary stenosis, are reported in 2.4% of cases, with a low procedural mortality rate of 0.3%. [3,4] Despite the typically mild nature of most AEs, their potential to negatively affect patient outcomes underscores the importance of meticulous assessment and management [13,14].

To mitigate the risk of adverse events associated with endoscopic papillectomy, the European Society of Gastrointestinal Endoscopy (ESGE) recommends the routine rectal administration of 100 mg of diclofenac or indomethacin before the procedure in patients without contraindications to non-steroidal anti-inflammatory drugs [14]. Additionally, prophylactic pancreatic duct stenting is advised to minimize the incidence of post-procedural pancreatitis. When stenting is not feasible, alternative measures, such as high-volume hydration with lactated Ringer's solution, may be employed to reduce the risk of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis [13,14].

In cases of post-ampullectomy bleeding, ESGE advocates the use of standard endoscopic hemostatic techniques, including epinephrine injection, electrocoagulation, endoscopic clip placement, noncontact hemostatic methods, and argon plasma coagulation [14] . For cases of severe bleeding that are refractory to endoscopic intervention, angiographic embolization should be considered [14].

Recurrence following endoscopic procedures remains a considerable challenge, with rates reaching up to 33%. About two-thirds of recurrences are detected during the initial follow-up

evaluation. Recurrences or persistent ampullary adenomas require additional therapeutic interventions or definitive surgical management [3,18].

Early recurrence has been significantly associated with advanced age (>65 years), tumor size exceeding 1.5 cm, and findings on EUS such as intraductal extension, submucosal invasion, irregular or enlarged papilla, ductal dilatation, lymph node involvement, as well as positive or uncertain resection margins [3,19]. Conversely, late recurrence has been correlated with the presence of clinical symptoms and piecemeal resection. A multi-center study analyzing 106 patients found that piecemeal resection significantly increased the risk of recurrence and was a significant risk factor for non-curative resection, underscoring the importance of *en bloc* resection for durable outcomes [19].

Non-curative resection has demonstrated a strong association with elevated body mass index (BMI), symptomatic presentation, and piecemeal resection [12]. Importantly, piecemeal resection is linked to markedly higher recurrence rates compared to *en bloc* resection, although this does not result in a corresponding increase in adverse event rates [3,12].

Due to the recurrence risk, the ESGE underscores the need for long-term monitoring following resection. ESGE recommends systematic follow-up using duodenoscopy with biopsies of the scar tissue and any abnormal areas [1]. This surveillance protocol should be conducted within the first three months post-procedure, followed by evaluations at six and twelve months, and subsequently on an annual basis for a minimum duration of five years [1] . Notwithstanding the recurrence risk, benign residual or recurrent lesions can often be effectively addressed through additional endoscopic interventions [3,4].

In summary, ESGE recommends endoscopic ampullectomy as the preferred approach for eligible patients due to its favorable safety profile, lower morbidity, and comparable recurrence rates to surgery [1]. With complete resection rates of 94% and curative outcomes in 87% of cases, EA represents a valuable minimally invasive approach [6]. Future studies should focus on refining patient selection criteria, improving procedural techniques, and minimizing recurrence to further optimize outcomes. However, it's imperative for clinicians to carefully weigh the benefits and risks of each therapeutic approach, considering factors such as lesion size, location, and patient comorbidities, to determine the most appropriate clinical decision for optimal patient outcomes [3].

Despite significant advancements in endoscopic techniques and the increasing adoption of endoscopic ampullectomy (EA) for the treatment of ampullary lesions, substantial gaps remain in the literature regarding the precise definition of factors influencing procedural success and safety. The low incidence of ampullary tumors poses a major challenge to conducting large-scale prospective clinical trials, relying on retrospective studies and expert consensus to inform current management strategies [3,16] .

Moreover, most published evidence to date is based on small, single-center case series, which inherently limit the generalizability of findings and preclude comprehensive analysis of predictive variables for clinical outcomes and adverse events. In light of these limitations, there is a compelling need to conduct a multicenter study that consolidates data across institutions and populations. Such an approach would significantly contribute to strengthening the existing evidence, enabling a more accurate definition of selection criteria, therapeutic efficacy, and surveillance protocols for patients undergoing endoscopic ampullectomy.

Thus, the aim of our study is to investigate the predictors of therapeutic success, adverse events, and recurrence after endoscopic ampullectomy.

Objectives

The primary objective is to investigate the predictors of efficacy (endoscopic success and recurrence) and safety (post-ERCP pancreatitis, delayed bleeding, perforation, cholangitis), in order to determine their impact on short- and long-term clinical outcomes.

The secondary objectives include assessing the influence of patient center volume on treatment efficacy and safety profiles, as well as evaluating histopathological concordance between initial biopsy and final resection specimens, diagnostic accuracy and the impact of lesion size in the resection technique.

Methods

An observational, multicentric, retrospective cohort study, conducted at the Gastroenterology Department of Unidade Local de Saúde (ULS) de Santo António (coordinator center), ULS de Coimbra, Fundação Champalimaud, ULS Lisboa Ocidental, ULS de São João, ULS de Braga, ULS de Santa Maria, ULS de São José, ULS Guimarães, ULS de Trás-os-Montes e Alto Douro, ULS Amadora /Sintra, Hospital Divino Espírito Santo, Ponta Delgada e ULS da Arrábida.

The study included patients submitted to endoscopic resection of an ampullary adenoma between January 1st, 2019, and December 31th, 2023.

The inclusion criteria were all adult patients (≥18 years), presenting with an ampullary adenoma with the following characteristics: lesions up to 30 mm (including with a laterally spreading component), low-grade dysplasia (LGD) or high-grade dysplasia (HGD) on preprocedural histology, no evidence of invasive malignancy on endoscopic assessment (including endoscopic features such as hard consistency, friable or ulcerative surface, and spontaneous bleeding), and a minimum follow-up period of one year after endoscopic ampullary resection.

Exclusion criteria included lesions exhibiting evidence of invasive malignancy, other non-adenomatous lesions, previous endoscopic resection or surgical ampullectomy , and those with less than one year of follow-up after endoscopic ampullary resection.

Clinical, demographic, lesion-related, and procedural data were retrospectively collected from electronic medical records at each participating center using a standardised data collection template to ensure consistency across centers. To address potential sources of bias, particularly selection and information bias, all eligible patients who met the inclusion criteria during the defined study period were included consecutively.

All data were anonymized and stored in a secure database on the investigators´ hardware workplace equipment. Each participating center had access only to their own patient records. The proponent investigation team, after signing a collaboration agreement, had access and merged all the information in a unique database to perform the statistical data analysis.

In order to identify predictor factors for adverse events, endoscopic success and recurrence, a dataset was compiled, encompassing variables pertaining to patient-related, lesion-related and procedure-related factors.

Patient-related factors included: gender; age; active smoking; alcohol use; use of anticoagulants [direct oral anticoagulants (DOACs); Vitamin K antagonist]; use of antiplatelet drugs [acetylsalicylic acid (ASA), clopidogrel, other P2Y12 receptor - ticlopidine, ticagrelor, prasugrel – dual antiplatelet; liver cirrhosis; inherited bleeding disorders.

The reported lesion-related factors were: lesion type (ampullary lesion; ampullary with laterally spreading component); lesion size (<10mm; ≥10 and <20mm; ≥ 20 and < 30mm); lesion high risk features (hard consistency, friable or ulcerative surface and spontaneous bleeding); preprocedural pathology (biopsies: normal intestinal mucosa; adenoma – villous, tubular or tubulovillous; neuroendocrine tumor; inflammatory), preprocedural dysplasia [no dysplasia; low-grade dysplasia (LGD); high grade dysplasia (HGD); invasive carcinoma]; post procedural pathology (adenoma – villous, tubular or tubulovillous; neuroendocrine tumor; inflammatory; normal intestinal mucosa), postprocedural dysplasia (no dysplasia; LGD; HGD; invasive carcinoma); resection specimen size (<10mm; ≥10 and <20mm; ≥ 20 and < 30mm).

Procedure-related factors were subdivided into preprocedural, procedural and outcomes.

Preprocedural-related factors included: the background diagnosis of ampullary lesion (incidental finding; surveillance; clinical symptoms); the context of ampullary lesion (sporadic ampullary lesion; FAP-related ampullary lesion); the presence of clinical symptoms (jaundice, abdominal pain, abnormal liver enzymes, others); preprocedural imaging assessment [duodenoscopy; Magnetic resonance cholangiopancreatography (MRCP); Endoscopic ultrasound (EUS); Computed tomography (CT scan) abdominal; combination of imaging modalities] as well as additional imaging findings (bile duct dilation; pancreatic duct dilation).

The considered procedure-related factors were: the type of resection (*en bloc*; piecemeal); intraductal extension (length); technical aspects (sphincterotomy performed; difficult bile duct cannulation; cholangiography performed; pancreatography performed; procedure time), pancreatitis prophylaxis (pancreatic duct stenting, hyperhydration, rectal indomethacin); management of pancreatic duct stenting (radiography, endoscopic removal at 5-10 days, no stent removal).

Main outcomes were efficacy outcomes and safety outcomes.

Efficacy outcomes included: endoscopic success (complete endoscopic resection of the ampullary lesion with absence of endoscopically visible residual lesion); long-term therapeutic success (absence of endoscopically visible and histologically proven residual lesion at one year of follow-up); procedure-related mortality (rate); performed endoscopic follow-up (at 3, 6 and 12 months); recurrence of ampullary adenoma (endoscopic or histological evidence of adenomatous tissue at the resection site on 1-year surveillance endoscopy, without initial histologically proven residual lesion at the first follow-up endoscopy); time to recurrence (early: within 3-6 months after endoscopic ampullectomy; late: >6 months after endoscopic ampullectomy); recurrence management (endoscopic or surgical); total follow-up time (≤ 5 years; >5 years).

Safety outcomes were assessed based on the presence of post-ampullectomy adverse events namely intraprocedural bleeding (defined by persistent oozing or spurting bleeding occurring during the procedure that did not stop spontaneously and that required endoscopic hemostasis); early bleeding (clinically significant overt bleeding (manifested as hematemesis and/or melena) or hemoglobin drop >2 g/dL, requiring endoscopic evaluation during the postprocedural surveillance (first 24-48h); delayed bleeding (clinically significant overt bleeding [hematemesis and/or melena] or hemoglobin drop >2 g/dL, occurring 2-14 days after the postprocedural surveillance period, requiring visit to emergency department, endoscopic evaluation or re-hospitalization); bleeding management (thermal, epinephrine injection, hemostatic clip, stenting, others).

Other adverse events considered included: acute pancreatitis (the diagnosis was established following Atlanta criteria: typical abdominal pain; serum amylase and/or lipase greater than 3 times the upper limit of normal; and/or characteristic abdominal imaging findings and its severity [mild: characterized by the absence of organ failure and local or systemic complications; moderately severe: characterized by transient organ failure (resolves within 48 hours) and/or local or systemic complications without persistent organ failure (>48 hours); severe: characterized by persistent organ failure that may involve one or multiple organs]; acute cholangitis [following Tokyo 2018 guidelines, characteristic clinical features of Charcot's triad, evidence of systemic inflammation (i.e., leukocytosis, high C-reactive protein CRP) and evidence of cholestasis (e.g., elevated direct bilirubin, gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP)) and/or imaging with biliary dilation or evidence of the underlying etiology (eg, a stricture, stone, or stent); perforation (presence of a transmural defect or evidence of free retroperitoneal or intraperitoneal air and/or luminal contents determined by imaging or on follow-up endoscopy), perforation type (Stapfer classification: type I: free duodenal wall perforation; type II: retroperitoneal duodenal perforation secondary to periampullary injury; type III: Perforation of the pancreatic or bile duct; type IV: retroperitoneal air alone); perforation management (conservative management with antibiotics; endoscopic stenting; surgery); ampullary stricture and its management (conservative management; endoscopic dilation; surgery).

The study was registered on ClinicalTrials.gov under the identifier NCT06648746.

Statistical Analysis

All patients´data were collected into an anonymized database which included demographic, clinical, histopathological and procedural characteristics.

Due to the observational and retrospective nature of the study, some missing data from medical records is expected, which could introduce bias in the analysis. To minimize this, we focused on categorical variables that are relevant and specific for the study aims and usually available in the regular clinical reports.

A descriptive analysis was conducted: categorical variables were reported as absolute frequencies and relative frequencies, n (%) and compared using the Pearson Chi-square test (with Fisher correction when needed) and expressed as a relative risk with a corresponding 95% confidence interval.

Continuous variables were reported as means with standard deviations or median with interquartile ranges (P25 to P75) depending on their distribution characteristic (normal or non-normal, respectively). Differences in continuous variables were compared using a Student's t-test or Mann-Whitney U test. Data distribution was tested using Kolmogorov-Smirnov and Shapiro-Wilk tests.

Univariate analyses were conducted to examine associations between clinical and procedural variables and the outcomes of post-ERCP pancreatitis, delayed bleeding, perforation, cholangitis, endoscopic success, and recurrence. Categorical variables were assessed using the Chi-square test or Fisher's exact test when expected counts were low, while continuous variables were analyzed using the Student's *t*-test. Variables showing a statistically significant association ($p < 0.05$) in the univariate analysis were subsequently entered into a multivariable logistic regression model to identify potential predictors of endoscopic success, adverse events, and recurrence. Results were expressed as odds ratios (ORs) with corresponding confidence intervals.

The impact of the volume of patients in different centers on key clinical outcomes—namely adverse events, recurrence, and endoscopic success—was evaluated across three categories of procedural volume: low-volume centers (<15 patients), medium-volume centers (15–24 patients), and high-volume centers (≥25 patients).

A *p* value of <0.05 was considered statistically significant. All data analysis was performed using IBM® SPSS® Statistics version 30.0 (IBM Corp. Armonk, New York, USA).

Ethical considerations and dissemination

The study was submitted and approved by the ethics committee of each participating center. Data transfer to the proponent investigators was approved by each center and legal responsibilities shared via a collaboration agreement.

Due to the retrospective multicenter cohort nature of the study, only clinical record data was retrieved, thus, patients did not in any case participate directly in the study. Therefore, there was assurance that no direct physical, emotional or material harm was imposed on patients. Thus, obtaining informed consent from the patients is not an appropriate requirement. However, written informed consent for the endoscopic ampullectomy procedure was obtained from all patients as a prerequisite before the procedure.

All the collected data was pseudonymised and handled in accordance with EU General Data Protection Regulation 2016/679 (GDPR). Only pseudonymised data was transferred between the participants of this study. Patient identifiers were kept at each local center and were not shared nor sent to another institution or otherwise made available to anyone other than the participants of the local center. Thus, researchers will not be able to identify the subjects during the processing of pooled datasets.

Only the data essential for the purposes of this study in accordance with the data minimization principle were processed.

The final database will be retained for two years after the study and will be deleted after this period.

Results

Descriptive statistics

In this multicentric study, a total of 215 patients were initially assessed for eligibility. Twenty eight patients were excluded for: evidence of invasive malignancy (n=6), non-adenomatous histology (n=3), previous endoscopic or surgical ampullectomy (n = 5), loss of follow-up (n = 4) and follow-up duration of less than one year following endoscopic ampullary resection (n = 10). The final cohort included 187 patients and is shown in table I.

The mean age of the cohort was 62.64 years (±13.41), ranging from 25 to 86 years. Fifty nine percent (*n*=112) patients were male. Fourteen percent (n=22) patients were active smokers. Relevant comorbidities included chronic kidney disease in 3.2% (*n*=6), liver cirrhosis in 2.2% (*n*=4), PEP in 0.5% (n=1) of the patients.

Regarding pharmacological therapy, 12.0% (*n*=22) of individuals were receiving antiplatelet agents, 6.5% (*n*=12) were under anticoagulation therapy and 0.5% (*n*=1) were taking both.

As demonstrated in table II, sporadic ampullary lesion was the primary indication for endoscopic ampullectomy in 81.3% (*n*=152) of the patients, followed by lesions associated with familial adenomatous polyposis (FAP), in 23.0% (*n*=43) of the patients. In addition, incidental findings prompted the procedure in 75.3% (*n*=140) of the cases, while symptomatic presentation was documented in 24.7% (*n*=46). The most commonly reported clinical manifestations were abdominal pain (29.5%; *n*=13), jaundice (18.2%; *n*=8), acute pancreatitis (6.8%; *n*=3), cholangitis (4.5%; *n*=2), abnormal liver enzyme levels (4.5%; *n*=2), and gastrointestinal bleeding (2.3%; *n*=1). Other symptoms were documented in 34.1% (*n*=15) of the patients.

Preprocedural imaging was used to assist in lesion characterization and procedural planning and is represented in table III. The most frequently employed modalities included duodenoscopy plus EUS (35.7%; *n*=65), followed by duodenoscopy only (25.3%; *n*=46) and EUS only (17.0%; *n*=31). MRCP was performed in 11.5% (*n*=21) of cases, while a combination of duodenoscopy and MRCP was conducted in 8.8% (*n*=16). Abdominal CT was used as the sole imaging method in 1.6% (*n*=3) of the patients. Intraductal extension of the lesion was documented in 2.2% (*n*=4) of the patients. Pancreatic duct dilation was present in 4.9% (*n*=9), and bile duct dilation was observed in 19.0% (*n*=35).

Histological evaluation prior to resection showed low-grade dysplasia (LGD) in 85.9% (*n*=152) of the patients and high-grade dysplasia (HGD) in 9.6% (*n*=17).

Concerning lesion size, 62.9% (*n*=117) measured between 10 and < 20 mm, 20.4% (*n*=38) measured between 20 and 30 mm, while lesions smaller than 10 mm accounted for 16.7% (*n*=31). Laterally spreading tumors (LSTs) were identified in 15.5% (*n* = 29) of cases, as demonstrated in table IV.

As provided in table V, regarding the resection technique, *en bloc* resection was successfully performed in 73.8% (*n*=138) of cases, whereas piecemeal resection was conducted in 26.2% (*n*=49).

A cross-tabulation analysis between lesion size and resection type revealed a clear trend: smaller lesions (<10 mm) were predominantly treated with *en bloc* resection (87.1%; *n* = 27), while larger lesions (20–30 mm) were more frequently resected in piecemeal technique (60.5%; *n=23).* Medium-sized lesions (10–<20 mm) were most commonly resected *en bloc* (81.2%; *n*=95), although a proportion required piecemeal resection (18.8%; *n*=22), as reflected in table VI.

Sphincterotomy was not performed in the majority of cases (73.8%) (*n*=138), whereas submucosal lifting was applied in 26.3% (*n*=49) of the patients to facilitate margin delineation. Difficult cannulation was reported in 16.8% (*n*=31) of the procedures. Pancreatography was carried out in 27.4% (*n*=51) of cases, while cholangiography was performed in 29.0% (*n*=54), as shown in table V.

As demonstrated in table VII, prophylactic strategies to prevent acute pancreatitis were implemented in 95.2% (*n*=178) of the patients, including rectal administration of indomethacin in 93.0% (*n*=172), aggressive intravenous hydration in 77.8% (*n*=144) and pancreatic stent placement in 71.9% (*n*=133). Among those who received a pancreatic stent, stent removal was performed in 50.8% (*n*=67) of cases. Of these, 31.3% (*n*=41) were removed during the first follow-up endoscopy, while 20.6% (*n*=27) underwent removal within 5 to 10 days following the procedure. The stent was not removed in 46.6% (*n*=61) of the patients, as represented in table VIII. Biliary stenting was performed in 20.0% of the patients (*n*=37).

Post-resection histopathology showed LGD in 66.3% (*n*=122) of the patients, no dysplasia in 16.8% (*n*=31) and HGD in 14.7% (*n*=27) as shown in table IV. Negative resection margins were achieved in 75.1% (*n*=139) of the patients, while 24.9% (*n*=46) had either positive or uncertain margins (table V).

Endoscopic success was achieved in 96.3% (*n*=180) of the patients (table IX)

As demonstrated in table IX, the mean follow-up period after endoscopic resection was 32.8 months (±18.7), while the average hospitalization stay was 4.78 days (±5.74). During the follow-up period, recurrence was observed in 18.9% (*n*=35) of the patients, with 71.4% (*n*=25) of cases being identified at the first surveillance endoscopy. The majority of recurrences (84.4%;

n=27) were managed endoscopically, while surgical intervention was necessary in 15.6% (*n*=5). Re-recurrence occurred in 5.1% (*n*=8) of cases. The mean adenoma-free survival period was 21.6 months (± 31.6).

Adverse events were documented in 35.3% (*n*=66) of the patients (table X). The most prevalent complication was post-procedural pancreatitis, reported in 20.3% (*n*=38) of cases; among these, 76.9% (*n*=30) were classified as mild and 23.1% (*n*=8) as severe. Intraoperative bleeding occurred in 18.2% (*n*=34) of the patients, whereas delayed bleeding was identified in 12.9% (*n*=24). Hemostatic clips were applied in 41.2% (*n*=14) of intraoperative bleeding cases, and epinephrine injection was administered in 35.3% (*n*=12). The majority of delayed bleeding episodes (70.6%; *n*=12) were successfully managed through endoscopic intervention, 23.5% (*n*=4) required blood transfusion. Perforation occurred in 4.8% (*n*=9) of the patients; all were managed conservatively.

Other adverse events included cholangitis, reported in 4.8% (*n*=9) of cases, as well as multiple forms of stenosis: ampullary (4.8%; *n*=9), and biliary (2.2%; *n*=4). Among individuals who developed stenosis, 77.8% (*n*=7) underwent endoscopic dilation, while the remaining 22.2% (*n*=2) required surgical management. No procedure-related deaths were observed within this cohort (table X).

Univariate analysis

Univariate analyses were performed to examine the association between clinical and procedural variables and six outcomes: endoscopic success, recurrence, post-ERCP pancreatitis, delayed bleeding, perforation and cholangitis. Categorical variables were assessed using the Chi-square test or Fisher's exact test when the number of events was low. Continuous variables were analyzed using the independent samples *t*-test. A p-value < 0.05 was considered statistically significant.

I) Endoscopic Success Outcome

As shown in table XI, FAP was significantly associated with less endoscopic success (X^2=4.789; p=0.029)

Lesion-related characteristics such as lesion size, LST (p=0.297), intraductal extension (p=1.000), pre-procedural pathology (p=0.703) , post-procedural pathology (p=0.153) were not significantly associated with endoscopic success.

Procedure-related factors, specifically resection type (p=0.885), submucosal injection (p=1.000), sphincterotomy (p=0.575) and intraprocedural bleeding (p=0.468) did not demonstrate a significant association with endoscopic success.

Presence of adverse events (p=1.000) and center volume (p=0.368) were not significantly associated with endoscopic success.

II) Recurrence Outcome

As demonstrated in table XII, the diagnosis of FAP was not significantly associated with recurrence. In contrast, age was significantly associated with recurrence, with advanced age being a predictive factor for recurrence (t=2.976; p=0.006).

Lesion related-factors such as lesion size (X^2=10.439; p=0.005), LST (X^2=15.049; p<0.001) and intraductal extension (X^2=8.254; p=0.004) demonstrated a significant association with recurrence. In contrast, post-resection pathology was not associated with this outcome (p=0.303).

Procedure-related factors, namely submucosal injection (X^2=10.649; p=0.001), sphincterotomy (X^2=6.315; p=0.043) and intraprocedural bleeding (X^2=5.440; p=0.020) were significantly associated with recurrence. An uncertain/positive resection margin (X^2=9.738; p=0.002) and resection type (X^2=5.941; p=0.015), specifically piecemeal resection technique demonstrated a significant association with recurrence.

Conversely, endoscopic success and presence of adverse events did not show a significant association with this outcome.

The center patient volume showed a significant association with recurrence (X^2=6.167; p=0.046); lesions removed in low volume centers (<15 procedures) were more likely to recur.

III) Post-ERCP Acute Pancreatitis Outcome

As demonstrated in table XIII, none of the variables examined showed a statistically significant association with post-ERCP acute pancreatitis.

Age (p=0.457), PEP (p=0.203) and lesion-related factors such as lesion size (p=0.203), laterally spreading lesions (p=0.578) and intraductal extension (p=1.000) were not significantly associated with post-ERCP pancreatitis.

Procedural-related aspects such as submucosal injection (p=0.214), difficult cannulation (p=0.426), sphincterotomy (p=0.716), pancreatography (p=0.324), and resection type (*en bloc vs* piecemeal) (*p* = 0.986) were not predictive of this complication.

Among the prophylactic measures, pancreatic stenting (*p* =0.593), rectal indomethacin (*p*=0.474), and hyperhydration (*p* =0.800) were not significantly associated with pancreatitis risk. The time of removal of the pancreatic stent also was not associated with post-ERCP pancreatitis (p=0.223).

Center patient volume was not significantly associated with this outcome (p=0.976).

IV) Delayed Bleeding Outcome

As provided in table XIV, patient-related factors such as age (p=0.135), FAP (p=0.203), CKD (p=0.569), cirrhosis (p=0.429) and medication (p=0.070) were not significantly associated with delayed bleeding.

Lesion related factors, namely LST (p=0.545) and intraductal extension (p=1.000) were also not associated with delayed bleeding. In contrast, tumor size (p=0.011) was significantly associated with delayed bleeding, showing a higher bleeding risk for bigger lesions (≥10 mm), with a likelihood ratio of 9.099.

Procedure-related factors such as sphincterotomy (p=0.478), difficult cannulation (p=0.771), resection type (p=0.068) and intraprocedural bleeding (p=1.000) were not significantly associated with this outcome.

Conversely, submucosal injection (X^2= 5.301; p=0.021), was significantly associated with a higher risk of delayed bleeding.

In addition, pancreatic stent was significantly associated with a higher risk of delayed bleeding (X^2=5.406 ; p=0.020).

A statistically significant association was observed between the center and the occurrence of delayed bleeding. Specifically, with lower-volume centers (< 25 procedures) reporting higher rates of delayed bleeding.

V) Perforation Outcome

As represented in table XV, patient-related factors such as age (p=0.508) were not significantly associated with perforation.

Lesion-related factors such as lesion size (X^2=7.800; p=0.020) and presence of LST (X^2=11.573; p<0.001), were significantly associated with higher risk of perforation. In contrast, intraductal extension (p=1.000) did not show a significant association with this outcome.

Submucosal lifting (X^2=4.15; p=0.041) showed a significant association with this outcome. In contrast, resection type (p=0.244), difficult cannulation (p=0.648) and sphincterotomy (p=0.315) were not significantly associated with perforation. Center patient volume was not significantly associated with perforation (p=0.241).

VI) Cholangitis Outcome

As shown in table XVI, patient-related factors such as age (p=0.765) and cirrhosis (p=0.181), did not demonstrate a significant association with cholangitis.

Lesion-related variables namely lesion size (p=0.627), LST (p=1.000) and intraductal extension (p=0.183) were not significantly associated with cholangitis.

Procedure-related factors such as resection type (p=1.000), submucosal lifting (p=0.449), difficult cannulation (p=0.649), sphincterotomy (p=0.312) and biliary stenting (p=0.690) did not show a significant association with this outcome.

Ampullary stenosis (p=1.000) and center patient volume (p=0.700) also did not demonstrate a significant association with this outcome.

Multivariate analysis

Prior to conducting the multivariate logistic regression for the outcome of lesion recurrence, multicollinearity among the significant variables on univariate analysis was assessed using tolerance and Variance Inflation Factor (VIF) statistics. All variables presented VIF values below 2.0 and tolerance values above 0.6, indicating an acceptable level of collinearity and no evidence of multicollinearity that would compromise the reliability of the regression estimates. Therefore, all variables were retained for multivariate analysis.

I) Endoscopic Success Outcome

Since only FAP was statistically significant in the univariate analysis, multivariate binary logistic regression was not conducted for this outcome.

II) Recurrence Outcome

As shown in table XII, in the multivariate analysis, age (OR= 0.948, 95%CI 0.912-0.986, p=0.008), intraductal extension (OR= 17.887, 95%CI 1.506-212.425, p=0.022), intraprocedural bleeding (OR= 3.553, 95%CI 1.344-9.393, p=0.011) and submucosal injection (OR=2.602, 95% CI 1.057-6.401, p=0.037), remained significant.

In contrast, lesion size (p=0.205), LST (p=0.085), sphincterotomy (p=0.788), resection type (p=0.825), resection margin (p=0.079) and center volume (p=0.124), did not reach statistical significance.

III) Post-ERCP Acute Pancreatitis and Cholangitis Outcome

As none of the variables assessed demonstrated a statistically significant association with post-ERCP acute pancreatitis and cholangitis in the univariate analysis, a multivariate logistic regression model was not constructed for these outcomes. This decision was based on standard statistical practice to include only variables with preliminary univariate significance in multivariable modeling.

IV) Delayed Bleeding Outcome

As provided in table XIV, multivariate binary logistic regression was conducted to evaluate independent predictors of delayed bleeding following endoscopic ampullectomy. Submucosal injection (OR= 2.959, 95%CI 1.145-7.649, p=0.025), and pancreatic stent (OR=5.050, 95%CI 1.110-22.968, p=0.036), remained predictive factors of delayed bleeding. In contrast, lesion size was not significant (p=0.998).

V) Perforation Outcome

In the multivariate binary logistic regression, neither lesion size (p=0.585), LST (p=0.153), nor submucosal lifting (p= 0.379) remained statistically significant (table XV).

Discussion

Our study sought to contribute to this evolving field by evaluating predictors of endoscopic success, recurrence, and adverse events in the largest national multicenter cohort.

We aimed to identify clinically relevant risk factors that could support clinical decision-making and improve patient outcomes in the context of EA.

I) Efficacy Outcomes

A) Endoscopic Success

In our cohort, endoscopic success was achieved in 96.3% of patients, a rate that lies at the upper limit of published literature, with success rates typically ranging from 70% to 95% [3,6,19]. This high success rate reflects not only technical proficiency across participating centers but also advances in technical skills, imaging, and peri-procedural protocols that have evolved over the past years [8,21,24].

Negative resection margins were obtained in 75.1% of cases, while 24.9% had positive or uncertain margins, which is consistent with literature [3]. This finding may guide clinical decision-making regarding the need for close follow-up or adjunctive therapy [12,16,19].

A significant association was found between FAP and lower endoscopic success rates. This may be attributed to the increased difficulty in managing FAP-associated adenomas, which are often larger, multifocal and anatomically more complex. These features impair clear margin delineation and frequently require piecemeal rather than *en bloc* resection, the latter being more effective in preventing recurrence. Moreover, FAP-related ampulomas are inherently more prone to recur [25].

B) Recurrence

In our cohort, recurrence occurred in 18.9% of patients, in accordance with the reported range in the literature between 7% and 30% [3,16,18].

Interestingly, 71.6% of recurrences in our study were detected during the first surveillance endoscopy, indicating that a significant proportion may represent residual adenomatous tissue rather than true *de novo* recurrence. This aligns with prior data reporting residual lesions in up to 28.4% of patients at initial follow-up [18,19]. The majority of recurrences (84.4%) were successfully managed endoscopically, underscoring the feasibility of reintervention [3,18,19]. However, 15.6% required surgical management, reinforcing the need for close monitoring and early detection to

maximize the chances of minimally invasive retreatment [7,16,18]. Re-recurrence was relatively rare, presenting in only 5.1% of the patients. The mean adenoma-free survival time was 21.6 months (± 31.6), which was comparable to the median time to recurrence of 29 months reported in larger series [3,16,18]. Although late recurrences beyond five years have been described—particularly in patients with familial adenomatous polyposis (FAP)— it surpassed the scope of our study, and also our follow-up duration was not sufficient to address this question matter [2,16,19].

Despite the well-established association between FAP and higher recurrence risk following endoscopic papillectomy, our study did not demonstrate a statistically significant correlation between FAP status and recurrence [25]. This may be attributed to the structured and intensive surveillance protocols that FAP patients typically undergo. These protocols often allow earlier detection of residual or recurrent lesions, enabling timely therapeutic intervention. Additionally, FAP patients are frequently treated in specialized high-volume centers with expertise in hereditary gastrointestinal syndromes, potentially improving resection technique and follow-up care. Indeed, the majority of FAP patients in our cohort were treated in medium and high-volume centers (95.35%), supporting this hypothesis.

In contrast, increasing age was identified as a statistically significant predictor of recurrence, an association scarcely documented in existing literature. Potential explanations include age-related physiological changes in tissue or the adoption of more conservative procedural strategies in elderly patients.

Lesion size, lateral spreading tumor (LST) and intraductal extension were associated with recurrence. These features have been previously linked to technical difficulty, higher likelihood of piecemeal resection, and increased risk of incomplete resection. For instance, a single-center retrospective cohort study by van der Wiel et al. [26] reported a markedly lower rate of curative endoscopic resection (9.1%) in cases involving intraductal growth.

Submucosal injection was significantly associated with recurrence. While some authors advocate for its use—particularly in LST-type ampullomas—to delineate lateral margins and prevent bleeding and deep thermal injury [1], this technique may be less suitable in non-LST lesions. Unlike colonic polyps, ampullary lesions are anchored by the bile and pancreatic ducts, making them less amenable to lifting. This may create a "dome effect" that can make *en bloc* resection more challenging [1].

In our cohort, this submucosal approach may have contributed to the recurrence rate: 65.31% of patients who received submucosal injection did not have LST, while 41.38% of LST patients did not undergo this injection. These data highlight the need for clearer and selective evidence-based guidance on the use of submucosal injection in ampullary lesions.

Intraprocedural bleeding also showed a significant association with recurrence. This finding is consistent with existent literature since bleeding may impair endoscopic visibility, limiting complete (R0) resection. Additionally, thermal coagulation used to control bleeding may cause tissue distortion, complicating histopathological evaluation [1,28].

Sphincterotomy was significantly associated with recurrence. This may be explained by the inherent thermal injury from the procedure, which impairs histological margin evaluation. Prior studies have reported challenges in assessing resection margins due to coagulative artifacts from prior sphincterotomy [27].

A positive or uncertain resection margin was a strong predictor of recurrence. This likely reflects the presence of residual microscopic disease and the challenges of assessing margins in cauterized tissue [3,16,28].

Piecemeal resection was also significantly associated with recurrence, as expected from previous literature on endoscopic resection of GI lesions. Compared to *en bloc* resection, piecemeal techniques increase the likelihood of incomplete excision, make margin assessment more difficult, and may leave residual neoplastic tissue, thereby raising the risk of recurrence [3,18,25,28].

Center procedural volume was significantly associated with recurrence, with higher recurrence in low-volume centers (<15 procedures). This finding supports existing literature showing that high-volume centers benefit from greater technical expertise and better access to imaging and patients treated in low-volume centers may possibly be at higher risk of suboptimal resection and less consistent follow-up, contributing to elevated recurrence rates [16,28].

In multivariate analysis, only the following factors remained independently associated with recurrence: age, intraductal extension, intraprocedural bleeding and submucosal injection. Variables such as lesion size, LST, sphincterotomy, resection type, resection margin and center volume did not retain statistical significance. This might be explained by confounding and collinearity between predictors. In addition, some variables, such as intraductal extension, were

present in only a small proportion (2.2%, *n*=4) of cases, which may have limited the statistical power to detect independent effects for other variables [17] .

II) Safety Outcomes

In our multicentric cohort, adverse events occurred in 35.3% of patients, slightly higher than those reported in several prior studies, where overall complication rates for EA have ranged from 24.9% to 30% [4,6,13]. The most prevalent complication in our series was post-procedural pancreatitis in 20.3% of patients, which exceeds the 11.9% reported in the literature [13]. However, the majority of these cases (76.9%) were classified as mild; those presenting as severe (23.1%) were all managed nonoperatively.

Intraoperative bleeding occurred in 18.2% of cases and delayed bleeding in 12.9%, both higher than the average rates of approximately 10.6% described in previous studies [3,17]. Nonetheless, most bleeding events were effectively managed endoscopically using hemostatic clips (41.2%) and epinephrine injection (35.3%), with only 2.1% requiring blood transfusion and none demanding surgical intervention. This demonstrates the feasibility of non-invasive management, even for high-risk adverse events [22].

Perforation was identified in 4.8% of patients—slightly above the 3.1% reported in the literature [6,17]—but in our cohort all were managed conservatively. Cholangitis occurred in 4.8% of cases, compared to 2.7% reported in other series [4,14]. Complications, such as ampullary (4.8%), and biliary (2.2%) stenosis, were observed at very low rates and were primarily managed by endoscopic dilation (77.8%), with surgical intervention required in a few (22.2%) [8,19,24].

Importantly, no procedure-related mortality was reported, reinforcing the overall safety of endoscopic ampullectomy when performed in experienced centers [3,6,17]. While the incidence of adverse events in our study was higher than previously reported, their effective endoscopic management without the need for surgery supports the role of ampullectomy as a less invasive alternative to surgical resection in appropriately selected patients [1,17,19].

A) Post-procedural pancreatitis and prophylaxis

In our cohort, post-procedural pancreatitis was the most frequent adverse event, occurring in 20.3% of patients. Among these, 76.9% were classified as mild, and 23.1% as severe, reflecting the spectrum of inflammatory response typically seen after ampullectomy. This incidence is notably higher than the 11–15% range commonly reported in the literature for

endoscopic ampullectomy, despite the universal use of prophylactic measures in our cohort [6,13,14].

Prophylactic strategies were implemented in 95.2% of patients and included pancreatic stent placement (71.9%), rectal indomethacin administration (93%), and aggressive intravenous hydration (77.8%), consistent with current best-practice guidelines [13,14].

In our cohort, none of the variables examined showed a statistically significant association with post-ERCP acute pancreatitis. It is possible that the non-significant findings stem from inadequate statistical power, driven by a low event rate and an imbalance in the distribution of certain lesion characteristics as for instance, intraductal extension (*n*=4), PEP (n=1).

Despite being typically considered potential risk factors, difficult cannulation, pancreatography and the resection technique were not significantly associated with post-procedure pancreatitis. This may be explained by consistent technical performance and widespread use of risk-reduction strategies [14,24].

Among the prophylactic measures, pancreatic stenting, rectal indomethacin and hyperhydration were not significantly associated with pancreatitis risk. These findings suggest that although prophylactic measures are widely used, their individual effectiveness in preventing pancreatitis may be limited or influenced by specific clinical contexts. In complex ampullectomy cases, anatomical challenges and procedural factors may diminish the impact of standard preventive strategies [13,14].

Although ESGE suggests pancreatic stenting as a standard prophylaxis in endoscopic ampullectomy, and, if not possible, the use of rectal indomethacin, and several studies supporting its protective effect, its effectiveness in preventing post-procedural pancreatitis remains controversial [1,29]. Previous studies have reported conflicting results regarding its utility [3,13,14]. Some have suggested that pancreatic stent placement reduces the incidence of pancreatitis by facilitating ductal drainage and preventing transient pancreatic duct obstruction or stenosis [13,14,24]. Conversely, other studies have found no protective effect, and some have even proposed a potential increase in pancreatitis risk, possibly due to repeated cannulation and mechanical irritation of the pancreatic duct [3,13].

In our cohort, no statistically significant association was found between pancreatic stenting and the occurrence of post-ampullectomy pancreatitis. These findings contribute to the

ongoing debate and underscore the need for prospective, well-powered studies to clarify their role and identify which patient subgroups may derive the greatest benefit [13,14,24].

To investigate whether the timing of pancreatic stent removal affects the risk of post-procedural pancreatitis, we analyzed outcomes between early removal, delayed removal, and non-removal groups. Despite the lack of statistically significant associations ($p = 0.223$), the absence of a clear effect challenges the assumption that early stent removal is uniformly preferable and suggests a more complex interaction between ductal drainage, mucosal repair, and inflammation [24,26].

Center patient volume did not demonstrate a significant association with post-procedure pancreatitis ($p = 0.976$). This lack of correlation may be indicative of increasing procedural uniformity across institutions, likely facilitated by the widespread adoption of standardized techniques and quality benchmarks outlined in ESGE guidelines.

B) Predictors of Delayed Bleeding

In the univariate analysis, only tumor size ≥10 mm, submucosal injection, and pancreatic stent placement were significantly associated with an increased risk of delayed bleeding. Larger lesions appeared to carry a higher bleeding risk, likely due to the broader resection area and greater mucosal disruption [28].

However, in the multivariate binary logistic regression, lesion size lost statistical significance, suggesting its association was likely confounded by procedural factors. In contrast, both submucosal injection and pancreatic stent placement remained independent predictors of delayed bleeding. Submucosal injection, while intended to lift the lesion and facilitate safer resection, may inadvertently distend and stretch submucosal vessels, increasing their vulnerability to injury. Additionally, the injected fluid can alter tissue planes, making it more difficult to visualize bleeding points intraprocedure, thereby contributing to delayed post-procedural bleeding [24].

Similarly, the use of pancreatic stents, as a foreign body, may also act as a local irritant, exacerbating inflammatory responses and increasing the risk of delayed bleeding through mechanical trauma or interference with mucosal healing [30].

In this cohort, lesion-related factors such as laterally spreading tumors (LST) and intraductal extension were not significantly associated with delayed bleeding. This may be

explained by the low event rate, which limits the statistical power to detect significant associations [28].

Likewise, procedure-related factors, including sphincterotomy, difficult cannulation, resection type, and intraprocedural bleeding, were not significantly associated with delayed bleeding. These findings likely reflect the standardization of endoscopic techniques and the consistent application of prophylactic measures, which help to minimize procedural variability and mitigate the risk of adverse events [1,24].

The absence of significant associations between delayed bleeding and patient-related factors—such as age, familial adenomatous polyposis (FAP), chronic kidney disease (CKD), cirrhosis, and medication use—may also be attributed to the low overall incidence of this variables, which reduces the ability to detect differences. Moreover, some of these conditions, such as CKD and cirrhosis, may influence overall procedural risk rather than specifically increasing the risk of delayed bleeding, especially when hepatic function and coagulation parameters are well managed [19,28].

Finally, it is important to consider that several of these factors may act indirectly or synergistically, and their effects may not be fully captured in univariate or multivariate analyses that assess variables in isolation [17].

A statistically significant association was found between treatment center volume and delayed bleeding, with higher rates observed in centers performing fewer than 25 procedures. This likely reflects the impact of limited operator experience in low-volume settings, given the technical demands and learning curve associated with endoscopic papillectomy. These findings emphasize the importance of specialized training and the potential benefit of centralizing complex procedures to high-volume centers [3].

C) Predictors of Perforation

Perforation occurred in 4.8% of patients, which is slightly higher than the 3.1% incidence reported in prior studies [6,17]. Importantly, all cases were managed conservatively, with no requirement for surgical intervention.

In the univariate analysis, lesion size and the presence of laterally spreading tumors (LSTs) were significantly associated with the outcome. These findings are consistent with previous

literature, which indicates that larger lesions and LSTs are typically associated with an increased risk of perforation [17,28,31].

Submucosal lifting was also associated with an increased risk of perforation. This finding may appear counterintuitive, as submucosal lifting is typically performed in lesions with LSTs to reduce the risk of perforation [24]. Therefore, its apparent association with increased perforation risk likely reflects a selection bias, since submucosal lifting is more commonly employed in LSTs—lesions that are inherently at higher risk for perforation [21,24,27].

Additionally, the low incidence of perforation in our cohort may have limited our ability to detect a statistically significant protective effect of the submucosal lifting technique [22].

While these variables demonstrated significant associations with perforation in the univariate analysis, their loss of significance in the multivariate regression likely reflects the complex interplay between lesion characteristics and procedural decisions. Submucosal lifting, for example, is preferentially used in larger LSTs, which themselves are high-risk. This clustering of risk factors may dilute the independent predictive value of each variable when analyzed simultaneously. Additionally, the relatively small number of perforations in our cohort limits the statistical power to detect independent effects [22,24,27].

However, intraductal extension, resection type, difficult cannulation, sphincterotomy and age did not show a significant association with this outcome, which is consistent with prior findings by Jiang et al. 2021, who also reported no statistically significant correlation between intraductal extension and procedural complications in a 76 patient retrospective analysis [22].

Center patient volume was not significantly associated with perforation ($p = 0.241$), consistent with findings from a large multicenter cohort study by Fritzsche et al. 2021, which found no significant difference in perforation rates between high- and low-volume centers [3].

D) Predictors of Cholangitis

In the univariate analysis, no variable showed a statistically significant association with cholangitis. This included patient-related factors such as age, cirrhosis, and chronic kidney disease, as well as lesion characteristics like lesion size, LSTs, and intraductal extension. Procedural variables—including resection type, submucosal lifting, difficult cannulation, sphincterotomy, and biliary stenting—were also not significantly associated. Neither ampullary stenosis nor center volume demonstrated a significant effect.

While some of these findings are consistent with previously published data [22], the absence of significant predictors in our analysis may also be attributed to the low incidence of cholangitis, which was observed in only 4.8% of cases (n = 9). Moreover, the low prevalence of relevant comorbidities—including chronic kidney disease in 3.2% (n = 6) and liver cirrhosis in 2.2% (n = 4)—may have further limited the statistical power to detect associations [22].

III) Effect of Center Volume on safety and efficacy outcomes

The association between center volume and clinical outcomes remains a critical consideration in the context of endoscopic papillectomy. While center patient volume was not significantly associated with outcomes such as endoscopic success ($p = 0.368$), perforation ($p = 0.241$), post-procedural pancreatitis ($p = 0.976$), or cholangitis ($p = 0.700$), a statistically significant association was observed for both recurrence ($\chi^2 = 6.167$; $p = 0.046$) and delayed bleeding, particularly in lower-volume centers (<15 and <25 procedures, respectively).

These findings suggest that lower-volume centers may have less experienced endoscopists performing papillectomies or may lack extensive practice managing complex lesions and adverse events. This can contribute to technical errors, incomplete resections, or suboptimal hemostatic techniques, all of which are known risk factors for recurrence and delayed bleeding. These observations are consistent with existing literature, where procedural experience and case volume have been shown to correlate with improved outcomes in overall ERCP [3].

Furthermore, high-volume centers are often equipped with advanced technology and have multidisciplinary support, including interventional radiology and surgical backup. These institutional resources facilitate enhanced procedural safety and more effective management of intra- and post-procedural adverse events. In addition, high-volume institutions frequently adopt standardized protocols (e.g., regarding submucosal injection and biliary drainage), which promote procedural consistency and reduce inter-operator variability.

Conversely, the lack of association between center volume and outcomes such as perforation and cholangitis may be explained by the low event rates of these complications, limiting the statistical power to detect meaningful differences [22].

The absence of a volume-outcome effect for post-ERCP pancreatitis may reflect the widespread adoption of prophylactic strategies, such as pancreatic duct stenting and rectal indomethacin, which helped to standardize care across centers.

Similarly, the non-significant association between center volume and endoscopic success may be due to the high overall success rate (96.3%) and a potential ceiling effect, along with sample size limitations and operator heterogeneity [3,13,24].

Despite managing a disproportionately higher number of complex or genetically predisposed cases—such as those with familial adenomatous polyposis (FAP), of whom 95.3% were treated in medium- and high-volume centers—high-volume institutions consistently achieved high therapeutic success rates and maintained favorable safety profiles [2,3,7]. To ensure equitable standards and robust outcome comparisons across centers, future studies should employ risk-adjusted analytical models that account for key confounding variables, including FAP status, lesion morphology, resection margin status, and follow-up intensity [3,12,16].

IV) Histological Concordance and Diagnostic Accuracy

Our study revealed a substantial discordance between pre-procedural biopsy and final histological diagnosis, with overestimation of histological grade in 66.2%, no dysplasia found in 16.8% and an underestimation of histological grade in 33.8% of cases. This result is clinically significant, as it challenges the reliability of forceps biopsy in evaluating ampullary lesions [9]. Previous studies have similarly reported discrepancies, attributing them to sampling limitations, tissue acquisition and the heterogeneous architecture of ampullary lesions [21]. Overestimation of histological grade may lead to unnecessary interventions and patient anxiety, while underestimation may result in incomplete resections or missed malignancies. This observation corroborates the importance of incorporating additional diagnostic modalities including endoscopic ultrasound-guided fine-needle aspiration/biopsy (EUS-FNA/B) [20].

V) Impact of Lesion Size on Resection Technique

In our cohort, *en bloc* resection was achieved in 73.8% of cases, whereas piecemeal resection was required in 26.2%. An inverse correlation was observed between lesion size and the likelihood of *en bloc* resection. Specifically, smaller lesions were predominantly managed with *en bloc* resection, while larger or laterally spreading lesions more often required a piecemeal technique.

This finding is consistent with established clinical practice. *En bloc* resection is the preferred technique for endoscopic ampullectomy when feasible, since it enables complete excision of the lesion, allows accurate histological margin assessment, and has been associated with lower recurrence rates [1,3,12]. However, in cases involving large or anatomically complex lesions, *en bloc* removal may carry higher risks of complications such as bleeding or duodenal perforation [17,22,23]. In such scenarios, piecemeal resection provides a safer alternative, despite some limitations in histological assessment and higher recurrence risk [17,22,23].

VI) Strengths

This study presents several notable strengths that enhance the validity and clinical relevance of its findings. First, the multicenter design draws from a diverse set of institutions, increasing the external validity of the results. Despite its limitations, this study represents the largest national multicenter cohort to date evaluating predictors of therapeutic success and adverse events in endoscopic ampullectomy (EP)—an area that remains relatively underexplored. Our findings therefore contribute valuable data to guide future research and improve procedural outcomes.

The use of robust statistical methods, including both univariate and multivariate logistic regression, allowed for the identification of independent risk and protective factors, while accounting for key confounders. Importantly, we confirmed the association between piecemeal resection and higher recurrence risk, reinforcing current concerns regarding margin assessment and long-term outcomes in larger or complex lesions.

Few previous studies have systematically explored the relationship between center procedural volume and clinical outcomes across multiple endpoints in endoscopic ampullectomy. The present study identifies significant associations between low-volume centers and increased rates of recurrence and delayed bleeding, suggesting a potential learning curve effect for this technically demanding intervention. These findings provide clinically actionable insights for the centralization of complex endoscopic procedures and the design of targeted training programs for therapeutic endoscopists.

The inclusion of case-mix variables—notably familial adenomatous polyposis (FAP) and center volume—allowed for a contextual interpretation of efficacy and recurrence rates, highlighting the importance of risk-adjusted analysis in outcome comparisons. Finally, the high rate of endoscopic therapeutic success (96.3%), along with the effective management of most

adverse events without surgery, supports the role of endoscopic ampullectomy as a safe and effective minimally invasive alternative in appropriately selected patients.

Moreover, we incorporated grading of adverse event severity, allowing for a more detailed understanding of post-EP adverse events. Notably, despite the presence of complications, the majority (60.7%) were mild, supporting the notion that EP is overall a safe and reliable therapeutic option, particularly in expert centers. This distinction is essential, as previous studies often reported adverse event rates without stratifying by severity.

VII) Limitations

This study has several important limitations that warrant consideration.

First, the retrospective nature of the analysis inherently introduces, despite the efforts, potential biases, including selection bias, information bias, and variability in data quality, owing to the reliance on medical records that were not originally designed for research purposes. In particular, incomplete or inconsistent documentation may have influenced the accuracy of clinical, procedural, and outcome data.

Second, the lack of centralized pathological review may have affected the uniformity and reliability of histological classifications. Inter-observer variability among pathologists at different centers may have led to discrepancies in diagnostic interpretation, especially for borderline or dysplastic lesions.

Third, although the study was conducted across multiple centers, procedural techniques were not standardized, and clinical decision-making (e.g., resection modality, surveillance intervals, or adjunctive treatments) varied according to local practices. This heterogeneity may have introduced confounding factors that impacted comparability of outcomes across centers.

Fourth, while the overall cohort size was relatively large for this procedure type, subgroup analyses—particularly those involving rare events or specific procedural subtypes—were limited by smaller sample sizes, reducing the statistical power and stability of multivariable models.

In addition, although the mean follow-up duration was 32.8 months, follow-up data were not available for 4 patients, primarily due to loss of follow-up. The variability in follow-up intervals and strategies across institutions may also have influenced the detection and reporting of long-term outcomes such as recurrence.

Furthermore, center volume was categorized post hoc, without access to operator-specific experience data. More detailed volume metrics, such as annual procedure numbers or individual endoscopist caseloads, would allow for a more precise assessment of volume–outcome associations.

Finally, as a retrospective observational study, causal inferences cannot be definitively established, and unmeasured confounders may still exist. To overcome these limitations, future research should focus on prospective multicenter registries and establish personalized treatment strategies for ampullary lesions.

VIII) Clinical Implications

The findings of this study offer several actionable insights with potential to inform clinical practice and procedural strategies in endoscopic ampullectomy.

First, our finding of a 66.2% rate of histological overestimation and 33.8% underestimation between initial forceps biopsy and final post-resection pathology underscores the diagnostic limitations of pre-resection biopsy in ampullary lesions. These data reinforce current guideline recommendations advocating for resection-based diagnosis, and highlight the potential value of adjunctive diagnostic modalities such as endoscopic ultrasound-guided fine-needle aspiration/biopsy (EUS-FNA/B) to improve diagnostic accuracy in this context.

The identification of piecemeal resection, positive or uncertain resection margins, and intraprocedural bleeding as significant predictors of recurrence underscores the importance of achieving *en bloc* resection whenever technically feasible and safe. This approach enhances margin assessment and may reduce the risk of residual adenomatous tissue. In instances where piecemeal resection is unavoidable—typically due to lesion size or complexity—closely timed and intensified surveillance should be implemented to facilitate early detection and management of recurrence.

Although submucosal injection is frequently advocated to elevate lesions and mitigate the risk of perforation, particularly in laterally spreading tumors (LSTs), it was independently associated with both recurrence and delayed bleeding in this study. These findings suggest that its routine use—especially in non-LST lesions—may be suboptimal or even detrimental. As such, the application of submucosal injection should be selectively tailored to lesion morphology, emphasizing individualized procedural planning over generalized protocols.

In addition, while prophylactic measures such as pancreatic stenting and rectal indomethacin remain widely implemented, their limited effectiveness in preventing post-procedural pancreatitis in this cohort highlights the need for more individualized approaches to risk stratification and prophylaxis. Factors such as lesion complexity, ductal anatomy, and patient-specific inflammatory risk should be considered in tailoring preventive strategies. In patients where pancreatic duct cannulation is shown to be technically difficult, it may be more prudent to avoid prophylactic pancreatic stent placement, as repeated cannulation attempts are an established risk factor for post-ERCP pancreatitis [32].

Finally, our results underscore the importance of structured and standardized post-procedural surveillance protocols. The majority of recurrences were detected at the first surveillance endoscopy and were still amenable to endoscopic treatment, supporting that timely detection can often preclude the need for surgical intervention. Developing consensus guidelines for follow-up intervals and imaging modalities may optimize recurrence management and improve long-term outcomes.

Conclusion

This study represents the largest national multicentric retrospective to date focused on endoscopic ampullectomy (EA) for ampullary adenomas, consolidating data from 12 Portuguese institutions and reflecting clinical practice across diverse healthcare settings. The results provide solid evidence that EA is not only a technically feasible and therapeutically effective intervention, but also a safe and long-lasting therapeutic option when performed in appropriately selected patients.

The high rate of endoscopic success observed in this cohort (96.3%) surpasses that reported in most existing literature, underscoring the quality of procedural expertise and institutional experience across centers. Importantly, this study identifies clinically meaningful predictors of therapeutic success and recurrence — including patient age, lesion morphology (such as laterally spreading tumors and intraductal extension), and procedural factors like submucosal injection — that may serve as critical variables for individualized treatment planning.

By filling critical gaps in the literature — namely, the lack of large, multicenter datasets with detailed procedural and outcome data — this study enhances the feasibility of endoscopic management of ampullary lesions. These findings have the potential to contribute to future clinical guidelines, refine patient selection criteria, and improve peri-procedural strategies aiming to enhance endoscopic success, mitigate adverse events and recurrence rates.

To conclude, this study highlights the role of endoscopic ampullectomy as a highly effective, minimally invasive therapy for ampullary adenomas and confirms it as a standard-of-care procedure for these cases. The recognition of relevant predictors moves the field closer to a more personalized and evidence-based endoscopic approach. Prospective validation of these findings in larger, standardized cohorts will be essential to further consolidate the role of endoscopic ampullectomy in clinical practice.

Appendix

Table I -Baseline characteristics of patients

Variable	**Total (*n*)**	**Frequencies (%)**	**Mean (±SD)**
Number of patients	215		
Final cohort	187		
Gender			
Male	112	59.9%	
Female	75	40.1	
Age			62.64 (±13.41)
Active smokers	22	14	
CKD	6	3.2	
Cirrhosis	4	2.2	
PEP	1	0.5	
Pharmacological therapy			
Antiplatelet	22	12	
Anticoagulation	12	6.5	
Both	1	0.5	

Table II - Presentation at diagnosis

Variable	**Total (n)**	**Frequencies (%)**
Sporadic	152	81.3
FAP - related	43	23
Incidental	140	75.3
Symptomatic	46	24.7
Symptoms		
Abdominal pain	13	29.5
Jaundice	8	18.2
Pancreatitis	3	6.8
Cholangitis	2	4.5
Abnormal liver enzyme levels	2	4.5
Gastrointestinal bleeding	1	2.3
Other symptoms	15	34.1

Table III- Preprocedural assessment

Variable	**Total (n)**	**Frequencies (%)**
Duodenoscopy + EUS	65	35.7%
Duodenoscopy	46	25.3
EUS	31	17.0
MRCP	21	11.5
Duodenoscopy + MRCP	16	8.8
Abdominal CT	3	1.6

Table IV - Baseline characteristics of lesions

Variable	**Total (*n*)**	**Frequencies (%)**
Lesion size		
<10mm	31	16.7
≥ 10-<20mm	117	62.9
≥ 20-30mm	38	20.4
Intraductal extension	4	2.2
LST	29	15.5
Preprocedural pathology		
LGD	152	85.9
HGD	17	9.6
Post resection pathology		
No dysplasia	31	16.8
LGD	122	66.3
HGD	27	14.7

Table V - Baseline characteristics of procedure

Variable	**Total (*n*)**	**Frequencies (%)**
Resection type		
En bloc	138	73.8
Piecemeal	49	26.2
Resection margin		
Negative	139	75.1
Uncertain/Positive	46	24.9
Sphincterotomy		
Intraprocedural	30	16.0
Previous	19	10.2
None	138	73.8
Pancreatography	51	27.4
Cholangiogram	54	29

Table VI - Cross Tabulation between lesion size and resection type

Lesion Size	En Bloc Resection	Piecemeal Resection	Total (n)
< 10 mm	27 (87.1%)	4 (12.9%)	31
10–<20 mm	95 (81.2%)	22 (18.8%)	117
20–30 mm	15 (39.5%)	23 (60.5%)	38
Total	**137 (73.3%)**	**49 (26.2%)**	**187**

Table VII - Prophylactic strategies to prevent post-procedural pancreatitis

Variable	**Total (*n*)**	**Frequencies (%)**
Prophylaxis	178	95.2
Rectal indomethacin	172	93.0
Pancreatic stent	133	71.9
Aggressive intravenous hydration	144	77.8

Table VIII- Time of removal of pancreatic stent

Variable	**Total (*n*)**	**Frequencies (%)**
First 5-10 days	27	20.6
First follow-up endoscopy	41	31.3
Not removed	61	46.6

Table IX - Efficacy outcomes

Variable	**Total (n)**	**Frequencies (%)**	**Mean (±SD)**
Endoscopic success	180	96.3	
Recurrence	35	18.9	
Management of recurrence			
Endoscopic	27	84.4	
Surgical	5	15.6	
Follow-up time (months)			32.8 months (±18.7)
Hospitalization stay (days)			4.78 days (±5.74)
Adenoma-free period (months)			21.6 months (± 31.6)

Table X- Safety outcomes

Variable	**Total (*n*)**	**Frequencies (%)**
Adverse events	66	35.3
Post-procedural pancreatitis	38	20.3
Mild	30	76.9
Severe	8	23.1
Intraprocedural bleeding	34	18.2
Delayed bleeding	24	12.9
Perforation	9	4.8
Cholangitis	9	4.8
Stenosis	13	7.0
Ampullary	9	4.8
Biliary	4	2.2
Mortality	0	0.0

Table XI-Univariate and multivariate analysis of Endoscopic Success outcome

Variables	**Univariate**			**Multivariate**		
	Test	**95%CI**	**p value**	**OR**	**95%CI**	**p value**
FAP	X^2=4.789		0.029			0.105
Lesion size	X^2=0.299		0.861			
LST	Fisher		0.297			
Intraductal	Fisher		1.000			
Pre procedural pathology	Likelihood ratio= 2.179		0.703			
Submucosal injection	Fisher		1.000			
Sphincterotomy	X^2=1.107		0.575			
Resection type	x2=0.021		0.885			
Intraprocedural bleeding	x2=0.528		0.468			
Post procedural pathology	Likelihood ratio = 6.690		0.153			
Adverse events	Fisher		1.000			
Center volume	Likelihood ratio 0.811		0.368			

Table XII- Univariate and multivariate analysis of Recurrence outcome

Variables	Univariate			Multivariate		
	Test	95% CI	p value	OR	95%CI	p value
FAP	X^2=1.873		0.171			
Age	t=2.796	2.05-11.88	0.006	0.948	0.912-0.986	0.008
Lesion size	X^2=10.439		0.005			0.205
LST	X^2=15.049		<0.001			0.085
Intraductal	X^2=8.254		0.004	17.887	1.506-212.425	0.022
Post pathology	Likelihood ratio=4.853		0.303			
Submucosal injection	X^2=10.649		0.001	2.602	1.057-6.401	0.037
Sphincterotomy	X^2=6.315		0.043			0.788
Resection type	X^2=5.941		0.015			0.825
Intraprocedural bleeding	X^2=5.440		0.020	3.553	1.344-9.393	0.011
Endoscopic success	Fisher		0.126			
Resection margin	X^2=9.738		0.002			0.079
Adverse events	X^2=0.124		0.725			
Center volume	X^2=6.167		0.046			0.124

Table XIII- Univariate and multivariate analysis of post-procedure Pancreatitis outcome

Variables	**Univariate**			**Multivariate**		
	Test	**95%CI**	**p value**	**OR**	**95%CI**	**p value**
Age	t-test	-6.67-3.01	0.457			
PEP	Fisher		0.203			
Lesion size	X^2=0.761		0.684			
LST	X^2= 0.309		0.578			
Intraductal extension	Fisher		1.00			
Submucosal injection	X^2= 1.545		0.214			
Difficult cannulation	X^2=0.633		0.426			
Sphincterotomy	X^2=0.669		0.716			
Pancreatography	X^2=0.973		0.324			
Rectal indomethacin	Fisher		0.474			
Hyperhydration	X^2=0.064		0.800			
Pancreatic stent	X^2=0.285		0.593			
Removal of pancreatic stent	X^2=0.275		0.600			
Time of removal	Fisher		0.223			
Center volume	X^2=0.048		0.976			
Resection type	X^2=0.000		0.986			

Table XIV -Univariate and multivariate analysis of Delayed bleeding outcome

Variables	**Univariate**			**Multivariate**		
	Test	**95% CI**	**p value**	**OR**	**95%CI**	**p value**
Age	t=-1.501		0.135			
FAP	X^2=1.618		0.203			
CKD	Fisher		0.569			
Cirrhosis	Fisher		0.429			
Lesion size	Likelihood ratio = 9.099		0.011	0.000	0.000	0.998
LST	Fisher		0.545			
Intraductal	Fisher		1.000			
Sphincterotomy	Fisher		0.478			
Intraprocedural bleeding	Fisher		1.000			
Submucosal lifting	X^2=5.301		0.021	2.959	1.145-7.649	0.025
Difficult cannulation	Fisher		0.771			
Pancreatic stent	X^2=5.406		0.020	5.050	1.110-22.968	0.036
Resection type	X^2=3.334		0.068			
Medication	Likelihood ratio =7.074		0.070			
Center volume	X^2=6.910		0.032			

Table XV Univariate and multivariate analysis of Perforation outcome

Variable	Univariate			Multivariate		
	Test	**95%CI**	**p value**	**OR**	**95%CI**	**p value**
Age	t=0.664	-12.162,-6.040	0.508			
Lesion size	Likelihood ratio = 7.800		0.020			0.585
LST	Likelihood ratio = 11.573		<0.001			0.153
Intraductal	Fisher		1.000			
Resection type	Fisher		0.244			
Submucosal lifting	X^2=4.159		0.041			0.379
Difficult cannulation	Fisher		0.648			
Sphincterotomy	Likelihood ratio		0.315			
Center volume	Likelihood ratio		0.241			

Table XVI-Univariate and multivariate analysis of Cholangitis outcome

Variable	Univariate			Multivariate		
	Test	**95%CI**	**p value**	**OR**	**95%CI**	**p value**
Age	t =0.299		0.765			
Cirrhosis	Fisher		0.181			
Lesion size	X^2= 0.932		0.627			
LST	Fisher		1.000			
Intraductal	Fisher		0.183			
Biliary stenting	Fisher		0.690			
Resection type	Fisher		1.000			
Submucosal lifting	Fisher		0.449			
Difficult cannulation	Fisher		0.649			
Sphincterotomy	Likelihood ratio		0.312			
Ampullary stenosis	Fisher		1.000			
Center volume	X^2=0.714		0.700			

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