Endoscopic Papillectomy

Sara Teles de Campos, MD[a], Marco J. Bruno, MD, PhD[b,*]

KEYWORDS

- Ampullary lesions • Endoscopic ultrasound
- Endoscopic retrograde cholangiopancreatography • Endoscopic papillectomy
- Radiofrequency ablation

KEY POINTS

- Endoscopic papillectomy is the first-line treatment for histology-proven ampullary lesions of the major papilla up to 20 to 30 mm in diameter, with benign endoscopic characteristics and with up to 20 mm intraductal extension.
- Initial diagnostic evaluation comprises side-viewing endoscopy with biopsies, EUS, and/or MRCP.
- Endoscopic papillectomy is a complex procedure that requires ample endoscopic expertise and skills, proper equipment, and qualified support staff.
- Complications can occur but are most often mild to moderate and usually treated conservatively.
- There is a risk of recurrence and long-term follow-up after EP with a minimum of 5 years is recommended.

Video content accompanies this article at http://www.giendo.theclinics.com

INTRODUCTION

Ampullary lesions (ALs) arise from the ampulla of Vater. Although considered to be rare with an incidence of less than 1 per 100,000 persons per year, representing only 0.6% to 0.8% of the digestive cancers[1,2] and 6% to 10% of lesions arising in the periampullary region,[3] they account for 20% of all tumor-related obstructions of the common bile duct (CBD).[4] The incidence of AL has remained stable in old age groups, but is increasing among young adults (<45 years).[5]

Most ALs are sporadic, involve the major papilla, and are premalignant (eg, adenomas).[6] Adenomatous precursor lesions arise from intestinal-type mucosa or pancreatic duct–type ampullary mucosa.[7] The intestinal-type AL follows the well-known

[a] Department of Gastroenterology, Digestive Unit, Champalimaud Foundation, Avenida de Brasília, Lisbon 1400-038, Portugal; [b] Department of Gastroenterology & Hepatology, Erasmus University Medical Center, Dr. Molewaterplein 40, Rotterdam 3015 GD, the Netherlands
* Corresponding author.
E-mail address: m.bruno@erasmusmc.nl

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adenoma-carcinoma sequence similar to colorectal adenocarcinoma.[8] AL may therefore also present as an adenocarcinoma. Occasionally, an AL may prove to be a neuroendocrine tumor.[9]

The diagnosis of AL is often incidental when patients, in their sixth to seventh decade of life, undergo an upper endoscopy or cross-sectional imaging for another clinical motive. They can also manifest clinically due to biliary and pancreatic outflow compression secondary to a mass effect of the neoplasm.

As most ALs are of neoplastic origin, resection is generally recommended. Factors such as age, comorbidities, anticipated life expectancy, tumor stage, and procedure-related risks have to be taken into account when managing these patients. Endoscopic papillectomy (EP), introduced by Suzuki and colleagues,[10] is an intervention associated with low morbidity and mortality and has become the preferred treatment over surgery for benign AL.

PRERESECTION EVALUATION

Careful evaluation of an AL is crucial to guide and ensure optimal management. This evaluation includes an endoscopic appraisal together with a staging investigation according to the TNM classification[11] for which endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP)[12] are appropriate investigational tools.

Role of Endoscopy

Endoscopy, using high-definition white light and dye-based or virtual chromoendoscopy, can help differentiate benign from malignant lesions and identify lesions with advanced histology that may be unsuitable for endoscopic resection.[13] When the major papilla is not correctly identified by standard gastroscopy, one option would be to perform cap-assisted endoscopy. Side-viewing duodenoscopy, however, is much preferred to evaluate AL and assess the opportunity for endoscopic resection.[12] Endoscopically, AL may be confined to the ampullary mound or can have an extrapapillary component and/or intraductal extension (IDE).[14] If the extrapapillary part involving the duodenal wall is greater than the size of the papillary adenoma, or there is a laterally spreading ampullary tumor with $\geq$10 mm extension beyond the ampullary mound, it is defined as a lateral spreading lesion of the papilla (LSL-P).[12] LSL-P are usually Paris type 0-IIa+Is.

Endoscopic features suggesting a benign AL include regular surface/margins, soft appearance, and mobility,[15] whereas ulceration, rigidity, friability, a depressed component, and nonlifting of LSL-P suggest local invasion.[16] Endoscopic biopsies and histologic examination may further increase the diagnostic accuracy of AL and are recommended before considering treatment.[12] They should be taken from 10- to 12-o'clock position of the ampulla to avoid the pancreatic orifice and the development of acute pancreatitis. Biopsies have a very high positive predictive value, but the negative predictive value is limited. They are particularly useful to confirm the presence of adenoma (with a sensitivity of more than 90%), but a diagnosis of adenocarcinoma can be missed in up to 30% of cases.[17] In addition, there are some rare inflammatory ("papillitis")[18] and tumor-like lesions, like hamartomatous lesions, adenomyomas, or adenomyomatous hyperplasia,[19] that should be differentiated from a dysplastic lesion. Diagnostic accuracy increases with more biopsies (at least 6) or repeating biopsies at least 1 week after sphincterotomy,[20,21] but complete removal and pathologic appraisal of the AL is crucial to confirm the diagnosis.

Role of EUS, CT, and MRI/MRCP

EUS and MRCP are recommended for helping in the diagnosis and staging of AL.[12] Both methods are important to specifically obtain/assess:

- histology of AL through EUS-guided tissue sampling, when standard histologic biopsies are not diagnostic[12];
- the presence and extent of IDE for which EUS appraisal is as good as ERCP[22];
- the presence of pancreas divisum for which EUS and MRCP are both appropriate modalities[23];
- local staging of ampullary cancers. EUS, sometimes combined with EUS-guided tissue sampling, can be of help to stage AL. For T staging, EUS has significantly higher accuracy compared with CT, and comparable or slightly but not significantly higher accuracy compared with MRCP.[24] A recent meta-analysis evaluated the performance of EUS and showed a pooled sensitivity and specificity of 77% (95% confidence interval [CI], 69% to 83%) and 78% (95% CI, 72% to 84%), respectively, for the diagnosis of a T1 tumor.[25] For N staging, MRCP is the best option, but the difference was not significantly different as compared with EUS or CT.[24] EUS has a statistically higher sensitivity for malignant lymph node diagnosis compared with CT.[22] The pooled sensitivity and specificity of morphologic criteria for lymph node involvement in EUS were 70% (95% CI, 62% to 77%) and 74% (95% CI, 67% to 80%), respectively.
- distant metastases by means of cross-sectional imaging investigations (CT and MRI).

Combining EUS with EP/ERCP in the same session has shown to be effective and safe,[26] increases patient comfort and reduces costs.

Role of ERCP

Although potentially useful to increase the accuracy of biopsies after having performed a biliary sphincterotomy and to be able to obtain brush cytology[27] or to evaluate the CBD with IDE to assess IDE, the risks involved and limited additional diagnostic value preclude the use of ERCP as a standard diagnostic staging technique.

Role of Colonoscopy

All patients with AL, regardless if they are sporadic or in the context of familial adenomatous polyposis (FAP), should be offered a screening colonoscopy before considering endoscopic ampullary resection to exclude colonic polyps as these patients have an increased risk for development of colorectal neoplasia.[28]

INDICATIONS FOR EP

EP is generally indicated for resection of histology-proven AL up to 20 to 30 mm in diameter, with benign endoscopic characteristics and with up to 20 mm IDE. Surgery should be considered in cases considered not feasible for endoscopic resection including the presence of a periampullary diverticulum, size > 4 cm, endoscopic features of malignancy, IDE of greater than 20 mm, or malignant AL of stage T1 or higher.[12] AL of 3 to 4 cm in size should be considered on a case-by-case basis.

TECHNIQUE

Equipment

EP is performed using a duodenoscope for optimal viewing of the ampullary region and optimal manipulation of instruments with the help of the elevator. Luminal

insufflation is preferably achieved with carbon dioxide because it causes less luminal distension, less abdominal pain and bloating at the end of the procedure. Moreover, if there is a duodenal perforation, CO_2 insufflation potentially reduces the risk of tension pneumoperitoneum and the degree of extramural contamination.[29,30]

An electrosurgical generator with the possibility of providing alternating cycles of high-frequency short pulse cutting current and coagulation current is required. Both pure cutting and blended currents have been used. In our practice, we advocate the use of the endocut mode with standard settings for polypectomy (eg, Endocut Q, effect 3, cut duration 1, cutting interval 6; ERBE VIO 200D, Tübingen, Germany) for tissue transection and reduce intraprocedural and early postprocedural bleeding.[12,31]

Equipment that should always be readily available includes sphincterotomes, hydrophilic guidewires, injection catheters, polypectomy snares, coagulation forceps, endoscopic clips, biliary stents (short plastic 10Fr and fully-covered metal stents 8 and 10 mm diameter), pancreatic stents (short 5Fr with no internal flange but with a flange or a pigtail on the duodenal side[32]), retrieval nets, fluids and dyes, and diluted epinephrine for submucosal injection.

No superiority has been shown of a specific polypectomy snare although in most reports standard braided stainless steel wires have been used. No comparisons between snare shapes have been made either. In our practice, depending on the local situation, we tend to use either a large, flexible, oval snare (AcuSnare, Cook Medical) or a stiff hexagonal snare (Captivator, Boston Scientific).[14,31]

For submucosal lifting, ESGE suggests the use of injectates that are more viscous than normal saline and whose safety has been proven such as succinylated gelatin (gelofusine), hydroxyethyl starch, or glycerol.[33] The blue dyes indigo carmine and methylene blue can be used to enhance endoscopic demarcation of the margins of the AL, to define the extent of the submucosal cushion, and to check that one is cutting in the correct tissue plane. Diluted epinephrine (1:100.000) can be added to the submucosal solution to help reduce intraprocedural bleeding and to prolong the lifting time of the mucosa.

Sedation/Anesthesia

The type and depth of sedation (conscious sedation, deep sedation, or anesthesia) depend on patient's comorbidities, and type and extent of the AL. If a prolonged therapeutic procedure is anticipated in case of resection of a large AL, a deeper sedation (propofol) is preferable.

Endoscopic Technique

The duodenoscope should be inserted and placed in a stable position facing the ampulla. Margins and feasibility for en-bloc resection should be well assessed.

Despite lack of clear evidence, some endoscopists, especially when an EUS or MRCP was not performed, obtain a cholangiogram and a pancreatogram before EP, to rule out deep IDE.

For lesions confined to the papillary mound, no submucosal injection is indicated as it might hamper the resection: the center of the AL may not lift and is tethered down by the biliary and pancreatic ducts (**Fig. 1** and Video 1). Injection may create a "dome" effect, hinder snare placement and en-bloc resection[34]; and the risk of postresection pancreatitis may increase.[12] Moreover, it is not proven that it reduces the depth of thermal injury to the duodenal wall.[35]

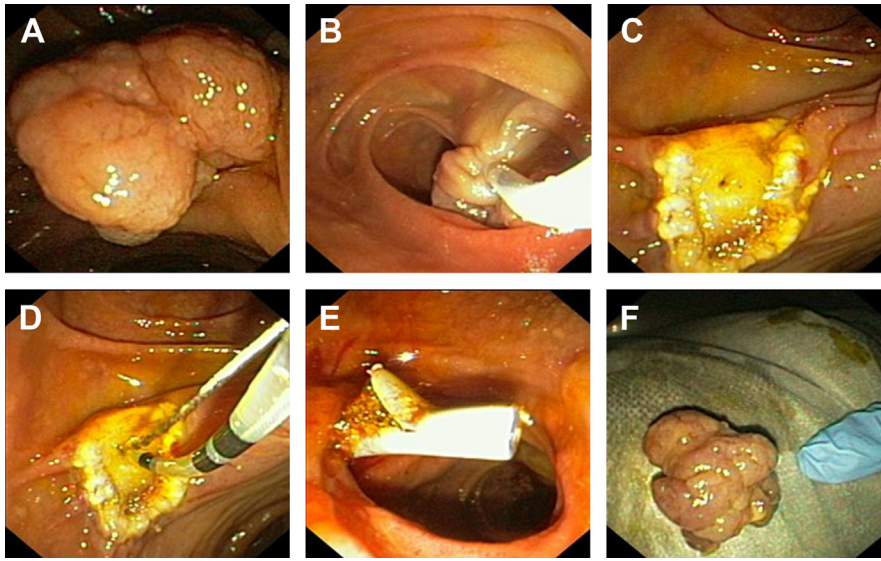

Fig. 1. (*A*) Papillary adenoma. (*B*) En-bloc snare resection of an ampullary adenoma without submucosal lifting. (*C*) Resection plane immediately after papillectomy. (*D*) Selective cannulation of the pancreatic duct. (*E*) Placement of a protective stent in the pancreatic duct. (*F*) Captured resection specimen to be sent off for pathologic evaluation.

En-bloc resection should be achieved in lesions up to 20 mm and may be attempted in lesions with 20–30 mm, if the adenoma does not extend > 1 cm beyond the papillary mound.[12]

For en-bloc resections, we use the wildly adopted fulcrum technique,[31] which consists of the following steps:

1. Open fully, or almost fully, the snare partially inside the working channel;
2. Anchor the tip of the snare proximal/cranial of the lesion and align it slightly to the right of the long axis of the infundibulum for better snare control and to avoid snare disimpaction;
3. Slowly push the snare out of the working channel and position it to fully grasp the papilla;
4 .Gently push the duodenoscope distally and slowly open the elevator slowly, while at the same time, apply a gentle force to keep the snare tip impacted in the duodenal wall above;
5. Slowly close the snare while maintaining its position parallel to the duodenal wall. When the snare is completely closed, the papilla/lesion should move independently of the duodenal wall. To confirm it, the snare should be moved back and forth with the elevator open;
6 .After completing these steps and ensuring there is no invasive disease and no deeper tissues are captured, the resection is performed by closing the snare with the elevator opened;

Balloon-catheter–assisted EP has been described to assist en-bloc resection mainly of flat papillary tumors.[36] A balloon catheter linked to a snare is inserted into the bile duct via the accessory channel of the duodenoscope and a snare resection is performed after pulling the inflated balloon toward the duodenal lumen.

After resection, the specimen should be captured for pathology, either using the snare or a retrieval net. An antiperistaltic agent, such as glucagon 1 mg or buscopan 10 to 20 mg i.v., can be administered before the ampullectomy to prevent distal migration of the specimen after resection. The specimen should ideally be pinned on a cork board to allow better histology assessment for lateral and deep margins, especially if larger than 15 mm.

Immediately after resection, the duodenoscope is reinserted for inspection to ensure hemostasis, complete resection, and exclude deep injury.

Pancreatic and Biliary Sphincterotomy and Stenting

Sphincterotomy before resection is generally not recommended. It does not confer any advantage for successful post-EP cannulation or stenting rates, may lower the rate of en-bloc and single-session resection due to scarring,[37] may hamper complete pathologic assessment due to thermal injury, and may even increase the risk of adverse events.[38]

After the specimen has been retrieved and the resection plane is inspected, the pancreatic duct (PD) should be cannulated and stented to reduce the risk of iatrogenic pancreatitis, papillary stricture formation, and offer safer usage of adjunctive coagulative therapies in case of postprocedural bleeding during follow-up.[39,40] The PD is visualized as a slit-like opening at the 5- to 6-o'clock position (**Fig. 2**). To facilitate PD identification after resection, some endoscopists prefer to inject a small amount of methylene blue into the PD before resection.[31] After resection also secretin can be administrated in case of difficult PD identification.[31]

Within 5 to 10 days after PD stent placement, patients should undergo a plain abdominal radiograph according to guidelines.[32] Retained stents should be removed promptly.

Usually, the rate of post-EP cholangitis is very low, and biliary cannulation, sphincterotomy, and stenting should only be attempted in case of a suspicion of delayed biliary drainage, intraprocedural bleeding or high risk of early postprocedural bleeding,

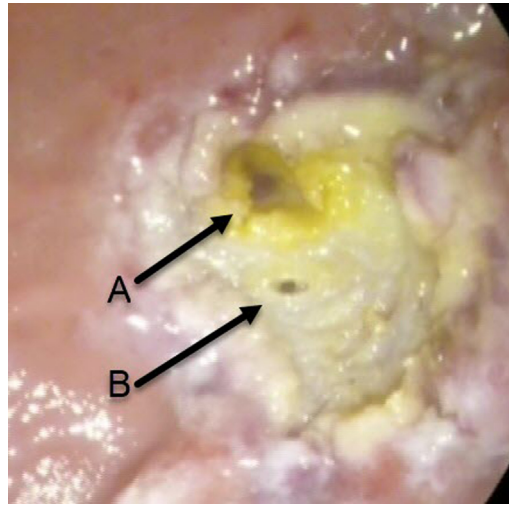

Fig. 2. Postpapillectomy anatomy showing the common bile duct orifice (A) and the pancreatic duct orifice (B).

biliary IDE (irrespective of having undergone treatment or not), or small perforations at the level of the papillectomy.[12] In case of bleeding or perforation, we prefer to insert a fully-covered metal stent. In case of IDE that is potentially amenable to endoscopic resection, an extended biliary sphincterotomy should be performed to facilitate complete resection using a smaller snare or argon plasma coagulation (APC).

Special Situations

Lateral spreading lesions of the papilla

In case of treating LSL-P endoscopically, some particular technical aspects must be considered.

We start approaching the lateral spreading component of the adjacent duodenal wall first by performing endoscopic mucosal resection (EMR) using submucosal injection in line with the recommendation for EMR in the gastrointestinal tract. Subsequently, the papilla is isolated, allowing en-bloc EP (**Fig. 3**).

Piecemeal resection is usually required for lesions measuring more than 2 cm. Major drawbacks of this technique are incomplete pathologic assessment and a higher risk for recurrence.

ALs with IDE

Classically, ALs with IDE were referred for surgery because of a significantly low rate of curative endoscopic resection and a high rate of rescue surgery.[41] Nonetheless, complementary endoscopic techniques, such as thermal ablation by cystotome or intraductal radiofrequency ablation (RFA), have been developed and are a feasible option for cases with an AL $\leq$ 20-mm IDE.[12]

Intraductal thermal ablation by a wire-guided cystotome (6Fr to 10Fr), using soft coagulation (effect 4–5) or forced coagulation (effect 3, 80W) is safe and has been successfully used to treat AL with IDE.[42]

More recently, RFA has been introduced as an ancillary technique to eradicate remnant endobiliary adenomatous tissue.[43] A recent study by Tringali and colleagues[44] prospectively evaluated patients with IDE of adenomatous ALs. They reported a technical success of 100% with 67% of patients free of recurrence after a median follow-up of 21 months. Another study by Hoon Choi and colleagues,[45] with a median follow-up period of 253 days, showed a 10% risk of recurrence needing additional surgery.

Biliary strictures and pancreatitis are common (up to 30%) after RFA for IDE[43–45] for which reason both temporary biliary and pancreatic stents should be placed prophylactically.[12]

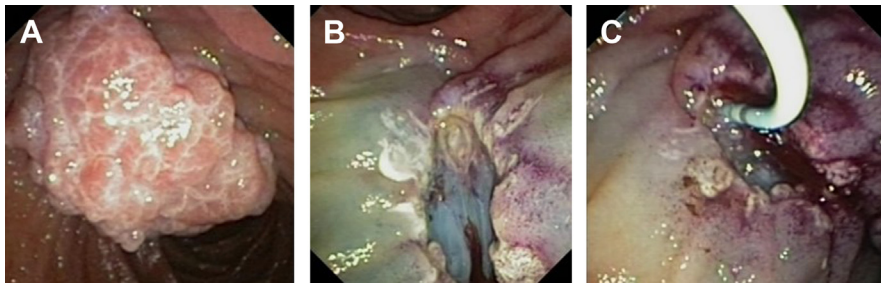

Fig. 3. (*A*) papillary adenoma with distal extension along the duodenal wall. (*B*) Resection plane after papillectomy and resection of the distal extension of the adenoma after submucosal lifting with saline and methylene blue (note the blue-stained submucosal plane). (*C*) Placement of a protective pancreatic stent.

Ampullary carcinoma

Several studies have reported that EP can be curative in case of early stages of adenocarcinoma (Tis and T1) that are well-differentiated, with clear margins of resection and without lymphovascular invasion.[46–48] Nonetheless, to date there is insufficient evidence to recommend EP as the preferred therapy for T1 tumors although EP is regarded as a viable option for TisN0M0 lesions according to recent guidelines.[12]

Postprocedure Instructions

No clear guidelines exist on the immediate postprocedural care after EP. Given the risks associated with EP, in our unit, patients are admitted overnight and are kept nil by mouth for at least 6 hours before starting clear fluids. We should administer intravenous proton pump inhibitors for 24 hours, followed by oral PPI twice daily for a minimum of 4 weeks. If there are no symptoms or signs suggesting a complication, patients are discharged.

A plain abdominal film needs to be obtained 5 to 10 days after the procedure to document spontaneous PD stent migration. If the PD stent has not migrated spontaneously, it must be removed promptly by regular gastroduodenoscopy. A CBD stent can be removed at the first surveillance endoscopy 3 months after EP.

SPECIFIC CONSIDERATIONS IN THE FAP POPULATION

Although the majority of AL is sporadic, a genetic predisposition in the setting of adenomatous polyposis syndromes, including FAP and MUTYH-associated polyposis, must be suspected in case of diagnosis at a younger age. FAP represents the strongest hereditary predisposition with a 120-fold increased relative risk of ampullary adenocarcinoma and a 300-fold risk of duodenal adenocarcinoma compared with the general population,[49] with an absolute lifetime risk of developing duodenal adenocarcinoma or ampullary carcinoma of about 5%.[50] Duodenal and periampullary cancers have become a leading cause of death for FAP patients since prophylactic colectomy became the standard of care.[51] Fortunately, screening and early resection of AL have become more widespread. ESGE suggests starting endoscopic duodenal surveillance at age 25 years and continuing at intervals determined by the characteristics of previously found polyps[52] and the Spigelman score.[53] Spigelman score assesses the severity of duodenal polyposis according to number, size, histology, and grade of dysplasia of duodenal adenomas (**Table 1**). The surveillance interval should be based on both Spigelman stage and separate judgment of the ampulla (**Table 2**).

Table 1
Assessment of Spigelman score based on findings at duodenoscopy and pathologic examination

Findings at Duodenoscopy	1 Point	2 Points	3 Points
Number of adenomas	1–4	5–20	>20
Size, mm	1–4	5–10	>10
Histology[a]	Tubular	Tubulovillous	Villous
Dysplasia[a]	Low grade	NA	High grade

[a] Based on pathology obtained for complete removal of duodenal polyps or prior pathology results.

Table 2
Determination of the surveillance interval based on Spigelman score and stage

Spigelman Score	Spigelman Stage	Surveillance Score[a]
0 point	0	5 y
1–4 points	I	5 y
5–6 points	II	3 y
7–8 points	III	1 y
9–12 points	IV	6 mo, consider (endoscopic or surgical) treatment

[a] Additional adjustment based on inspection of the ampullary region: normal ampulla, surveillance interval of 5 y; adenomatous change less than 10 mm in the ampulla, 3 y; if $\geq$ 10 mm, 1 y is proposed for endoscopic surveillance interval or treatment (preferred).

Biopsies should only be taken if the AL seems not amenable to endoscopic removal because of size or suspicion of invasive growth.

In patients with ampullary adenomas associated with FAP, low-risk lesions are often monitored without immediate resection. This differs from the approach in sporadic AL and is based on the assumption that AL in FAP is less aggressive, although it is not clear whether the duration of progression from adenoma to advanced adenoma is truly longer.[54] It is hypothesized that specific histologic features and differences in the adenoma-carcinoma sequence, compared with sporadic lesions, lead to a slower progression.[54] Another consideration is the presence of multiple duodenal lesions in FAP, making it impossible to completely eradicate all the adenomatous tissue with only high-grade dysplastic lesions being removed in such cases. ESGE suggests treatment only for patients with ampullary adenomas $\geq$ 10 mm, showing excessive growth or suspicion of invasive growth.[52] The modality of treatment (endoscopic vs surgical) follows the same prerequisites as for sporadic AL. Although feasible and safe, there is a higher recurrence rate, partially explained by their underlying genetic predisposition.[54] The benefit of endoscopic management in patients with FAP is that it avoids additional surgery in patients who have likely undergone previous abdominal surgery, decreasing the risk of postoperative short-term and long-term adverse events including the development of a mesenteric desmoid tumor.[54]

Three small observational studies[55–57] have studied the effect of endoscopic ampullectomy in FAP patients: complication rates were high (19%–20% pancreatitis, 4%–13% bleeding, 8% abdominal pain) and recurrence occurred in up to 67% of the cases after a follow-up ranging from 53 to 85 months with no evidence of ampullary cancer. In one of the studies,[55] 2 patients (13%) needed surgery after several repeated endoscopic resections.

EXPERT TIPS ON MINIMIZING COMPLICATIONS AND THEN MANAGING COMPLICATIONS

Literature reports suggest a reduced rate of overall complications with EP compared with surgical treatment. Nevertheless, also after EP, the complication rate is significant. In our experience, 25.3% of patients suffered a procedure-related complication.[14] A recent systematic review reported an overall adverse event rate of 24.9% (95% CI, 21.2% to 29%).[16] Fortunately, complications are usually mild to moderate and can be treated conservatively. They can be divided into early complications including pancreatitis, bleeding and perforation, and delayed complications, such

as papillary and biliary stenosis or duodenal luminal stenosis. EP-related mortality is rare and reported to be 0.3%.

Postprocedural Pancreatitis

Postprocedural pancreatitis is caused by temporary edema of the pancreatic orifice and obstruction as a result from the electrocautery and reported to be the most common adverse event occurring in 11.9% of cases (95% CI, 10.5% to 13.6%). Preventive measures include administration of 100 mg rectal indomethacin or diclofenac immediately before EP in all patients without a contraindication.[12,32] PD stent placement is recommended to reduce the pancreatitis risk,[12,58] except in cases of complete pancreas divisum. In case of minor ampullectomy, PD stent placement is only indicated in the setting of (in-)complete pancreas divisum. Despite the absence of sound scientific evidence, it is considered reasonable to place a PD stent after ID-RFA[43] or APC.[41] When prophylactic PD stenting is not possible after EP, high volume hydration using lactated Ringer's solution can be considered to reduce the risk of post-ERCP pancreatitis.[12] Management of postampullectomy pancreatitis follows the same recommendations for treating acute pancreatitis of other etiologies. Of interest, a PD wire-guided resection technique[59,60] has been developed to secure PD stenting to prevent postprocedural pancreatitis. For this, the PD is cannulated with a guidewire first, after which a snare loop is passed over that guidewire to capture the EL. Immediately after snare resection, a PD stent is placed over the indwelling guidewire. Although conceptually attractive, this technique is limited in its use because of decreased endoscopic maneuverability.

Bleeding

Bleeding is the second most frequent complication (10.6%; 95% CI, 5.2% to 13.6%) and is a significant adverse event in case of LSL-P,[61] because of high vascularization of the duodenal wall. Bleeding can present intraprocedural or delayed, usually in the first 12 hours after resection, but sporadically much later, as in colonic resections. The size of the lesion/resection is one of the most important risk factors for delayed bleeding. In case of intraprocedural bleeding, soft coagulation (80 W, effect 4) with the tip of snare or with coagulation forceps can be attempted. APC (with a 7Fr diameter device and a setting of 50–60W) can also be used safely, not only for immediate bleeding control but also for preventing postprocedure bleeding.[62] In case of a delayed bleeding presenting with melena in a hemodynamically stable patient, a conservative approach can be attempted, with admission and supportive care, as the bleeding usually settles spontaneously. If hematemesis or hematochezia occurs in an unstable patient, urgent endoscopy is indicated. Standard hemostasis techniques, such as epinephrine injection, electrocoagulation or clipping, noncontact hemostatic techniques, and APC, preferably using a duodenoscope, should be attempted to control the bleed. One study reported successful endoscopic hemostasis using fibrin glue in refractory bleeding.[63] Before applying these techniques, it is important to identify the PD orifice and ideally place a prophylactic PD stent in order to protect it from inadvertent closure (**Fig. 4**).

In Case of an Uncontrolled Major Bleeding, Angiographic Embolization and/or Surgery Is Indicated

Perforation

Perforation, an adverse effect related to electrocautery, is reported after EP in 3.1% of cases (95% CI, 2.2% to 4.2%). Careful inspection of the defect, endoscopically and fluoroscopically, is crucial to detect deep tissue injury. Owing to retroperitoneal

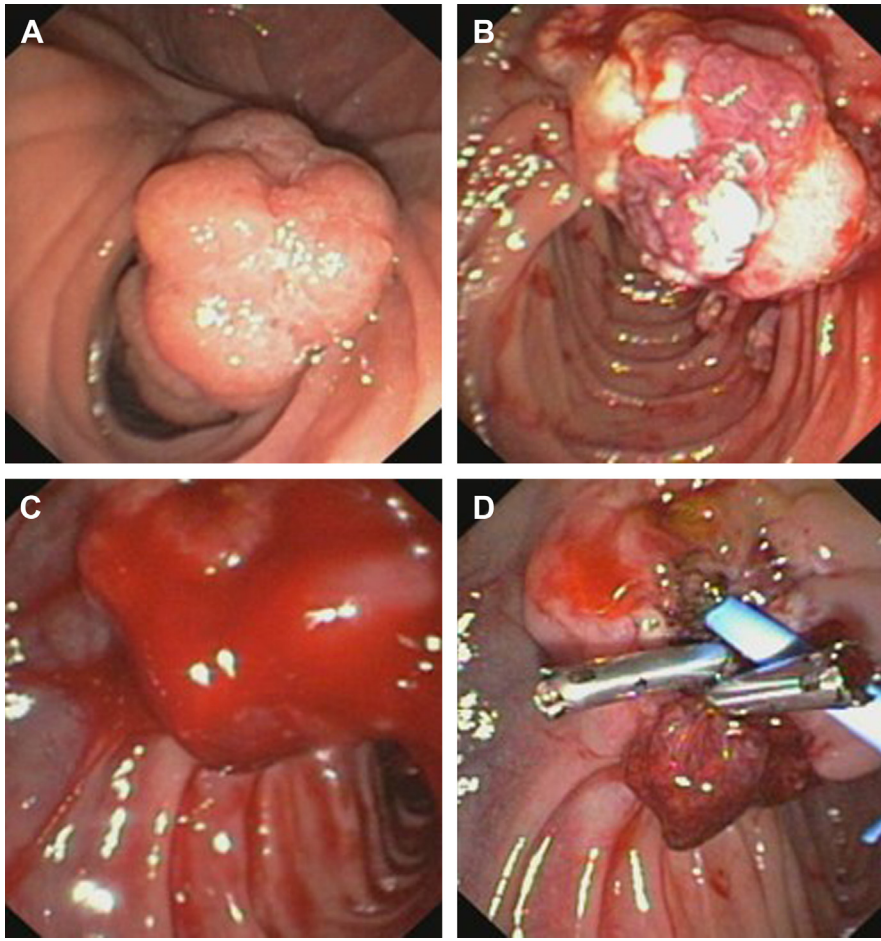

Fig. 4. (*A*) Papillary adenoma. (*B*) Immediately after papillectomy with specimen that needs to be retrieved without signs of a postpapillectomy bleeding. (*C*) Reintroduction of endoscope, however, shows an (arterial) postpapillectomy bleed. (*D*) Successful clipping of the bleeding spot AFTER securing pancreatic duct patency and drainage with a pancreatic stent.

location, it can almost always be managed conservatively. If diagnosed during the procedure, apart from administrating intravenous antibiotics, an attempt to close it with endoclips and biliary stenting with a fully covered self-expandable metallic stent should be performed. To avoid accidental clipping of the PD orifice, it is pivotal to assure a good anatomic overview or, even better, to place a protective pancreatic stent before closing the perforation. The patient should be kept NPO and admitted for clinical observation. If a suspicion of perforation develops after the procedure, an abdominal CT scan should be performed.

Cholangitis

Cholangitis is reported to occur in 2.7% of cases (95% CI, 1.9% to 4%).[16] It can be caused by bacterial translocation, which usually resolves quickly by the administration of antibiotics. In some cases, intraductal remnant adenoma or a blood clot causes ductal outflow obstruction requiring re-ERCP.

Duodenal Luminal Stenosis

Duodenal luminal stenosis occurs only after resection of LSL-P with extensive duodenal circumferential or longitudinal involvement. These cases can be managed with early pre-emptive dilation starting 3 to 4 weeks after the resection.[64]

Biliary and Pancreatic Orifice Stenosis

Biliary and pancreatic orifice stenosis occur in 2.4% of cases (95% CI, 1.6% to 3.4%). PD stent placement can prevent pancreatic stricture formation.[65] Sphincterotomy, balloon dilation, and serial stent placement result in stricture resolution in most of the cases.

OUTCOMES

In a systematic review, it is reported that complete endoscopic resection (or technical success), defined as the absence of any adenomatous remnant from the resection margins at the end of the procedure, was achieved in 94.2% of cases (95% CI, 90.5% to 96.5%).[16] Curative endoscopic resection was achieved in 87.1% of cases (95% CI, 90.5% to 96.5%). The only predictive factor of a curative resection was en-bloc resection, which was achieved in 82.4% of cases (95% CI, 74.7% to 88.1%). EP is considered to be curative if there are no histologic features of locoregional persistence and pathology confirms AL with low-grade dysplasia or high-grade dysplasia with free lateral and in-depth margins (R0).[12] If resection margins are positive (R+), complementary techniques such as APC or EMR need to be considered. Tis ampullary cancer with free margins after EP can be considered curative.[12] If pathology after EP reveals a malignant lesion of the ampulla including stage T1, pancreaticoduodenectomy (including lymphadenectomy) is recommended as the preferred treatment because the risk of lymph node metastasis is significant.[12]

Regarding LSL-P, endoscopic treatment has shown comparable outcomes regarding endoscopic curative resection and recurrence rate to those for adenoma confined to the ampulla,[14,61,66] but the risk of bleeding should be taken into consideration.[12]

Well-designed, prospective studies comparing EP and surgical treatment (either pancreaticoduodenectomy or transduodenal ampullectomy) of AL are not available.

FOLLOW-UP

Long-term endoscopic follow-up is recommended and should be performed using a duodenoscope with biopsies of the scar and any abnormal areas, at 3, 6, and 12 months, are thereafter yearly for at least 5 years (**Fig. 5**).[12] As aforementioned, in case of very large, circumferential LSL-P, earlier follow-up, at 3 to 4 weeks, is advised to evaluate for duodenal stricture and early treatment with balloon dilation when indicated.

Despite complete endoscopic resection at the index procedure, recurrence has been reported in 11.8% of cases (95% CI 8.4% to 16.5%).[16] Recurrence is defined as the discovery of a lesion after at least one surveillance endoscopy with biopsies showing no residual adenomatous tissue.[67] It is more frequently reported in the first 14 months of FU.[68] Younger age (<48 years), female sex, polyposis syndrome, larger lesions (>24 mm), high-grade dysplasia, and IDE have been implied as risk factors for recurrence. A small number of patients have shown delayed recurrence and adenocarcinoma even after 5 years, which questions whether certain patients should be followed up lifelong, but specific data guiding proper patient selection are lacking.[14,69,70]

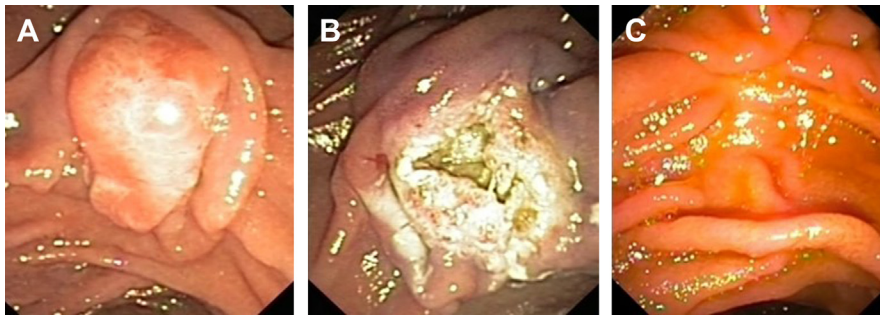

Fig. 5. (*A*) Papillary adenoma. (*B*) Immediately after papillectomy. (*C*) Follow-up endoscopy after 2 years showing no signs of recurrence.

Any recurrence should be carefully assessed before retreatment. Usually, recurrence is relatively minor and can be treated with snare excision or cold avulsion followed by snare tip soft coagulation or other ablation techniques.[12] In a systematic review, complete excision of the AL regardless of number of sessions and including recurrent lesions was achieved in 80.9% of cases (95% CI, 73% to 87%).[16]

SUMMARY

ALs are rare but responsible for 20% of all rumor-related obstructions of CBD. The incidence of AL has remained stable in old age groups, but is increasing among young adults. Most ALs are sporadic but a genetic predisposition, namely FAP, should be suspected if diagnosed at a younger age (<50 years).

EP is regarded as the first-line curative treatment for sporadic-proven AL of the major papilla with up to 20 to 30 mm in diameter, with benign endoscopic characteristics, and with up to 20 mm IDE. AL sized between 3 and 4 cm should be considered on a case-by-case basis. In the FAP population, endoscopic treatment is only indicated for ampullary adenomas $\geq$ 10 mm.

Preresection endoscopic evaluation of AL is pivotal for selecting the appropriate candidates for EA and improving outcome and generally includes side-viewing endoscopy, biopsies, EUS, and/or MRCP.

EP is an advanced procedure that requires specific endoscopic expertise and skills, appropriate equipment, and an experienced support team. The optimal technique of EP depends on the characteristics of the lesion, its size, the presence and extent of IDE, and the presence and extent of extrapapillary extension along the duodenal wall.

Complete endoscopic resection and curative resection rates are very high.

Complications can occur in up to a quarter of cases but are usually mild to moderate and can usually be managed conservatively. The most frequent early adverse events are postprocedural pancreatitis and bleeding.

Long-term monitoring after EP up to 5 years is recommended due to risk of recurrence.

CLINICS CARE POINTS

- Preresection evaluation of an AL involves a primary evaluation with standard gastroscopy, complemented with a side-viewing *duodenoscopy* and *biopsies.* Endoscopic biopsies should be taken from 10- to 12-o'clock position of the ampulla to avoid the pancreatic orifice.

- *EUS* and *MRCP* are complementary procedures useful for staging, namely to evaluate possible IDE and the presence of pancreas divisum or perform a local staging in case of ampullary cancer. EUS tissue sampling can also be performed if standard biopsies are inconclusive.
- All patients with AL should perform a *colonoscopy* before considering endoscopic resection, to exclude colonic polyps.
- EP is the first-line treatment for histology-proven ampullary lesions of the major papilla up to 20 to 30 mm in diameter, with benign endoscopic characteristics and with up to 20 mm IDE. Surgery should be considered in cases considered not feasible for endoscopic resection including the presence of a periampullary diverticulum, size > 4 cm, endoscopic features of malignancy, IDE of greater than 20 mm or malignant AL of stage T1 or higher. AL of 3 to 4 cm in size should be considered on a case-by-case basis.
- The following *equipment* should be available to perform EP: duodenoscope, CO_2 insufflation, electrosurgical generator with the possibility of providing alternating cycles of high-frequency short pulse cutting current and coagulation current, sphincterotomes, hydrophilic guidewires, injection catheters, polypectomy snares (no superiority has shown between different snares), coagulation forceps, endoscopic clips, biliary stents (short plastic 10Fr and fully-covered metal stents 8 and 10 mm diameter), pancreatic stents (short 5Fr with no internal flange but with a flange or a pigtail on the duodenal side), and submucosal lifting solutions (with injectates, blue dyes, diluted epinephrine).
- EP should be done under sedation and, for lesions confined to the papillary mound, en-bloc resection should be attempted by resecting with a snare without mucosal injection and by using the fulcrum *technique.* Variations of this technique will depend on the specific characteristics of the AL (eg, LST of the papilla).
- *Acute pancreatitis* is the most common complication. Its risk can be reduced by the administration of 100 mg rectal indomethacin or diclofenac immediately before EP when there is no contraindication and the placement of prophylactic pancreatic duct stenting whenever there is no pancreas divisum.
- *Bleeding* is the second most frequent adverse event and can generally be managed with standard endoscopic hemostasis techniques.
- EP has very good outcomes. Nonetheless, as there is a risk of recurrence, long-term *monitoring* after EP is advised. It should be based on duodenoscopy evaluation with biopsies of the scare and of any abnormality. The reevaluation should be done at regularly basis (first 3 months, at 6 and 12 months, and after, in a yearly basis for a minimum of 5 years).

DISCLOSURE

M.J. Bruno is a consultant for, and the recipient of industry-initiated and investigator-initiated studies from Boston Scientific, Cook Medical, and Pentax Medical and the recipient of support for investigator-initiated studies from Mylan and ChiRoStim.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.giec.2022.01.005.

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