

# Methods and outcome of the endoscopic treatment of ampullary tumors

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**Abstract:** Ampullary tumors are rare neoplasms but increasingly encountered due to an increase in diagnostic procedures, mainly upper gastrointestinal endoscopy. Diagnosis, staging, and treatment of these tumors are described and recommendations given based on the most recent literature.

**Keywords:** ampullary tumors, ERCP, EUS

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## Introduction

Ampullary tumors (AT) arise from the ampulla of Vater itself, distal to the bifurcation of the distal common bile duct (CBD) and the pancreatic duct (PD). They are rare neoplasms, accounting for less than 0.5% of all gastrointestinal neoplasms,<sup>1</sup> but their incidence has increased in the last years due to improved diagnostic endoscopic and radiological methods.<sup>2</sup> Although they can be benign (like lipomas), more than 95% are premalignant (like adenomas) or malignant (like adenocarcinomas).<sup>3</sup> Adenomas follow the adenoma to carcinoma sequence similar to colorectal adenocarcinoma.<sup>4,5</sup>

If sporadic, ampullary neoplasms are often incidentally diagnosed during the sixth to seventh decade of life on upper endoscopy or cross-sectional imaging performed for another reason. Nonetheless, they can course with symptoms in relation to a mass effect of the neoplasm compressing and obstructing biliary and pancreatic outflow.

As most of these AT are of neoplastic origin, their removal is recommended in most cases, especially if symptoms are present. Age, comorbidities, anticipated life expectancy, tumor stage, and procedure-related risks have to be considered to personalize the best therapeutic approach for each case. Three options can be offered for the treatment of AT: pancreaticoduodenectomy (Whipple's

procedure), surgical local excision (transduodenal surgical ampullectomy), and endoscopic ampullectomy (EA). Pancreaticoduodenectomy or local surgical resection have been traditionally considered the treatment choices for AT. Nonetheless, the perioperative mortality occurs in 4–15% and morbidity in up to 50% of cases<sup>6–8</sup> in Whipple's procedure and in 19–25% morbidity rate with recurrence rate up to 32% at 5 years after local resection.<sup>9</sup> In the last years, EA, a minimally invasive therapy with lower morbidity, mortality, and recurrence rates than surgery, has become the first line of treatment of superficial AT and will be the subject of this article.

## Diagnosis and staging

A correct preoperative diagnosis and staging of AT is crucial for determining the prognosis and the best therapeutic strategy. Endoscopic appearance, histology, Endoscopic ultrasound (EUS), and Endoscopic retrograde cholangiopancreatography (ERCP) at the time of ampullectomy are needed to evaluate the type and extent of the lesion, including evidence of submucosal invasion, lymph node metastasis, and degree of intraductal invasion.

An endoscopic evaluation using a high-definition white light side-viewing endoscope is the best approach to evaluate the ampulla of Vater.<sup>10</sup>

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Several appearances have been described for an AT: an intramural protrusion, as a prominence underneath a normal-appearing papilla; an exposed protrusion, as a neoplastic-appearing tissue extending out from an abnormal-appearing papilla; or an ulcerative lesion.<sup>11</sup> Features suggesting a benign disease comprise regular margins, absence of ulceration or spontaneous bleeding, and soft consistency. However, the macroscopic distinction of an AT can be difficult.<sup>12</sup> Biopsies, taken from the 10–12 O'clock position of the ampulla to avoid the PD orifice, confirm the presence of adenoma with a sensitivity of more than 90%. Nonetheless, there is a high rate of discrepancy for pathologic results before and after resection, ranging from 25% to 60%,<sup>13,14</sup> with up to 30% of the cases with adenocarcinoma being missed.<sup>13</sup> Additional techniques can be used to enhance the accuracy of biopsies, such as increasing the number of biopsies for at least 6,<sup>15</sup> performing biopsies after 6–10 days of the sphincterotomy,<sup>16</sup> and adding chromoendoscopy to the procedure, for example, with narrow-band imaging which can also predict histology.<sup>17</sup> At the end, complete excision of the AT is mandatory to truly confirm diagnosis.

As already mentioned, sphincterotomy improves the yield for malignancy in endoscopy biopsies and its yield is the highest after 6–10 days of the sphincterotomy, after diathermy artifact has cleared. ERCP also enables assessment of intraductal extension. Brush cytology may also help in selected cases of suspected ampullary malignancy.<sup>18</sup> Given the risks and the limited benefit, ERCP should not be routinely performed as a diagnostic or staging technique, but only for resection and drainage.

EUS is better than computed tomography (CT), magnetic resonance imaging (MRI), and transabdominal ultrasound for detecting small AT<sup>19</sup> and can diagnose invasive carcinoma not recognized in other procedures. It can evaluate the relation with periampullary structures,<sup>20,21</sup> determine extension into the pancreaticobiliary ducts,<sup>22</sup> and assess the T and N staging for ampullary neoplasms.<sup>20,23</sup> Accuracy of T staging can be improved with contrast-enhanced EUS.<sup>24</sup> EUS can also be performed to sample the papilla, periampullary region, and regional lymph nodes, to confirm the diagnosis and plan the best treatment. The sensitivity, specificity, and positive and negative predictive values of EUS-guided tissue sampling for AT are 82%, 100%, 100%, and

76.9%, respectively.<sup>25</sup> EUS assessment should be considered for larger lesions or those where there is concern for invasive cancer.

CT scan and MRI are mostly useful for detection of distant metastases.

In addition, a screening colonoscopy should be performed before considering endoscopic resection to exclude colonic polyps.<sup>26</sup>

## EA

With the introduction of EA by Suzuki and colleagues,<sup>27</sup> treatment of AT has shifted toward a minimal invasive endoscopic resection<sup>28</sup> and is currently regarded as preferable to surgery when feasible.<sup>29,30</sup>

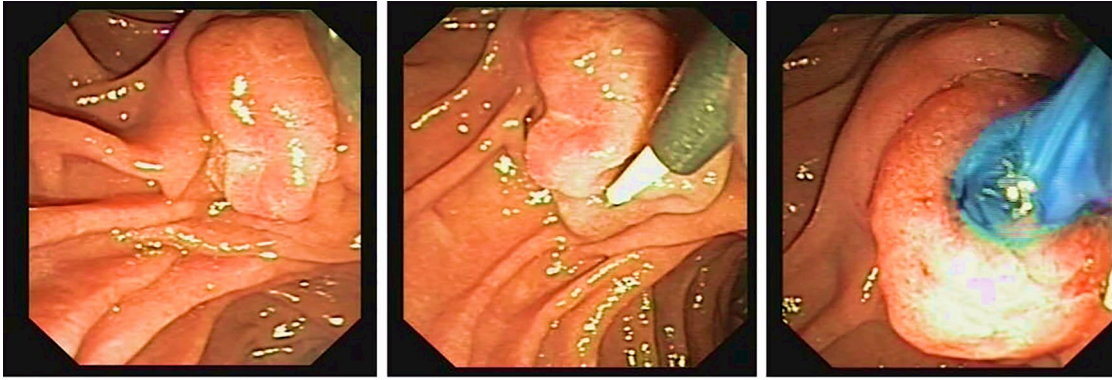
### Indications

For performing an EA, the lesion must fulfill the following accepted criteria: endoscopic benign features, benign histology, and intraductal extension <1 cm inside the CBD or the PD.<sup>6,28,31–34</sup> Size in itself is, in experienced hands, not considered to be a determinant of endoscopic resectability since, as reviewed below, also larger lesions can successfully be removed endoscopically. Lesions not satisfying these parameters, as with proven or suspected malignancy in a patient fit for surgery or tumor intraductal growth beyond 1 cm, are traditionally considered for surgery.

### General principles

EA is performed with a duodenoscope, under conscious sedation, deep (propofol) sedation, or anesthesia. The step-by-step technique and necessary equipment are explained hereafter.

*Sedation/anesthesia.* Depending on pre-existing medical conditions and consequent risk of sedation, EA can be performed with different depth of sedation. If the patient has no risk factors for sedation, a narcotic-benzodiazepine combination, with or without an adjunctive agent (as diphenhydramine, promethazine, or droperidol), can be used. Deeper sedation should be considered in the presence of a prolonged therapeutic procedure, for example, a piecemeal resection of a large AT; intolerance to standard sedatives; increased risk for adverse events because of severe medical comorbidities, although, as always, risks and benefits of the procedure need to be carefully taken



**Figure 1.** Blue methylene injection.

into consideration; or increased risk for airway obstruction due to an anatomic variant.

*Carbon dioxide.* Carbon dioxide is increasingly used in endoscopy for luminal insufflation. It is rapidly absorbed through the bowel mucosa, causing less luminal distension and less abdominal pain and bloating at the end of the procedure. If a duodenal perforation occurs during EA, the use of CO<sub>2</sub> insufflation quickly reabsorbs the escaped gas, reduces transmural pressure, and probably decreases the risk of tension pneumoperitoneum.<sup>35</sup>

*PD cannulation plus methylene blue.* Some authors advocate primary pancreatography with the injection of small volume of diluted methylene blue to outline PD orifice and facilitate identification and cannulation after resection<sup>36</sup> (Figure 1). Secretin can also be administered after resection in case of no PD cannulation.

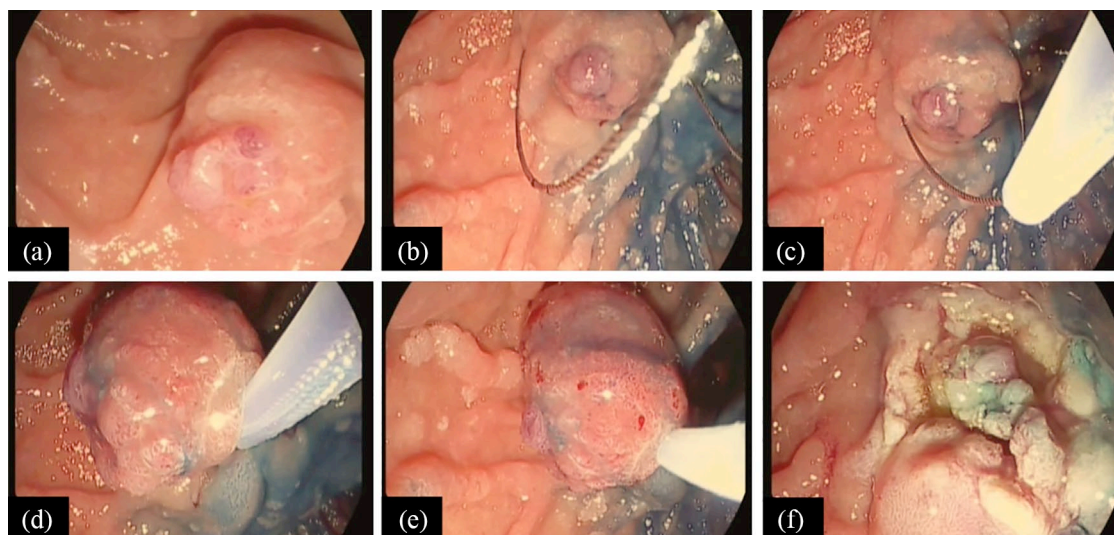
*CBD cannulation.* CBD cannulation is only intended when intraductal extension needs to be evaluated or there is a proven obstruction of the CBD (with cholestasis, jaundice).

*Submucosal injection.* Submucosal injection lifts tumors from the wall and it is thought to yield wider resection margins and to prevent perforation and bleeding. As such, it is performed routinely in cases of endoscopic mucosal resection or endoscopic submucosal dissection. However, the ampulla complex is different from the rest of the gastrointestinal wall, for example, in the colon, as it combines different structures (duodenum, CBD, and PD) that are not lifted with injection (as CBD and PD orifices are fixed to the sphincter of Oddi muscle complex). It can possibly lift

tumors confined to the duodenal surface, but intra-ampullary tumors or involving the walls of the distal ends of the PD and CBD cannot be lifted and would rather be hidden behind the swollen periampullary tissue. Moreover, it could blur the margins of the tumor and make it difficult to grasp the entire tumor tissue with a snare. As such, submucosal lifting is not mandatory and often counterproductive when en bloc resection of an adenoma confined to the papilla is attempted.<sup>37</sup> In cases of minimal extrapapillary extension, careful lifting of the caudal and lateral parts can however be helpful. A recent study compared the clinical outcomes of endoscopic papillectomy with and without submucosal injection and concluded that routine submucosal injection is associated with more frequent residual tumor and shorter recurrence-free survival, without reducing post-procedural adverse events.<sup>38</sup>

*Polypectomy snares.* No superiority has either been proven between different materials for polypectomy snares, although in most reports, standard braided stainless steel wire have been used. There are no comparisons of snare shapes for ampullary resection. In our practice, standard materials are used, among which a large, flexible oval snare (Acusnare, Cook Medical) and a stiff hexagonal snare (Captivator, Boston Scientific).<sup>39</sup> The size of the snare has to be adapted to the size of the lesion. An electrocautery needle knife can be used to make a circumferential incision around the lesion, in order to facilitate the snare capture.<sup>33</sup>

*Electrocautery settings.* Both pure cutting and blended currents have been used. Pure cutting minimizes edema and the cautery effect caused by coagulation. Blended current enables cutting according to the properties of the tissue. In our



**Figure 2.** Ensnaresment and resection of ampullary lesion: (a) ampullary lesion; (b-e) ensnaresment; (f) resection.

practice, for snare resection, “ENDO CUT Q” mode is used with standard setting for polypectomy: effect 3, cut duration 1, and cutting interval 6 (VIO200D, ERBE, Tübingen, Germany).<sup>39</sup>

*Resection technique.* After careful endoscopic assessment of the lesion, an endoscopic resection plan is formulated. For en bloc resections of bulky lesions, we use the fulcrum technique. The snare is fully, or almost fully, opened, partially inside the working channel and anchored proximal/cranial of the lesion. The snare is then pushed out of the working channel while slowly opening the elevator and carefully pushing the scope more distally in alignment with the axis of the ampullary complex and infundibulum. Once all tissue that should be resected is in the snare, it should be closed slowly while maintaining its position parallel to the duodenal wall. After closing it, the papilla mobility is checked. The entrapped papilla should be independently mobile relative to the duodenal wall behind. The specimen can now be resected using settings as described above. Figure 2 summarizes this step.

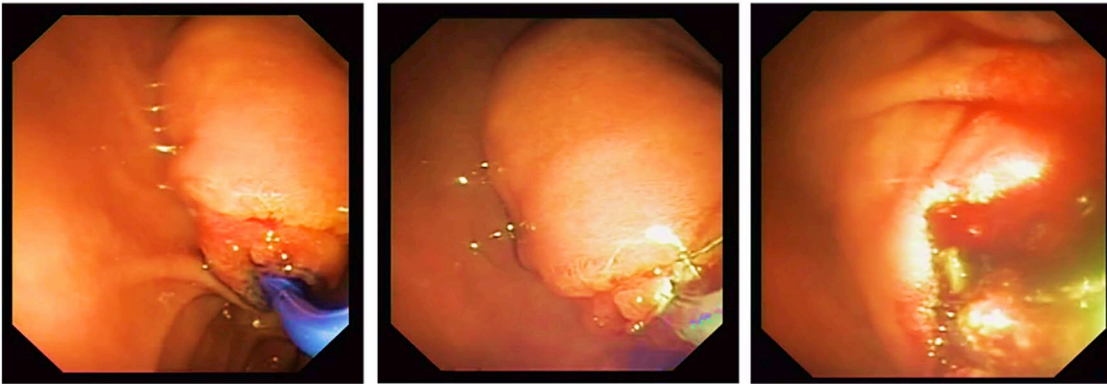
Whenever possible, en bloc resection should be aimed, as it reduces the time of the procedure, the need of cautery, and it provides a complete tissue acquisition enabling complete histopathology evaluation and minimizing the likelihood of residual neoplasia. For lesions smaller than 20mm, this should be considered standard of care; for lesions 20–30mm without extension > 1 cm beyond the papillary mound, it should be attempted.

Balloon-catheter-assisted EA has been reported to facilitate en bloc resection mainly of flat papillary tumors.<sup>40,41</sup> A balloon catheter linked to a snare is inserted into the bile duct via the accessory channel of a duodenoscope, and a snare resection is easily performed after pulling the expanded balloon toward the duodenal lumen.

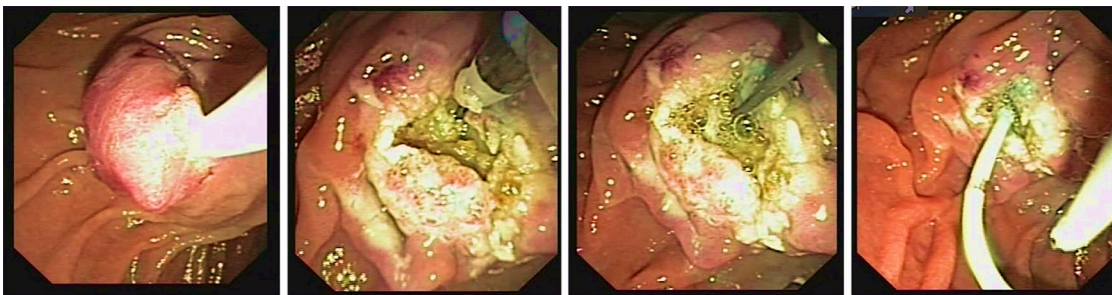
Careful inspection should be performed immediately after the resection to ensure complete resection and exclude deep injury.

*Recovery of resected specimen.* Prior to the resection, an anti-peristaltic agent, such as glucagon 1 mg or buscopan, should be given to prevent distal migration. Immediately after the excision, the specimen shall be retrieved, with retrieval net or a snare. Endoscopic suction of the resected specimen can also help preventing tissue migration, but caution shall be given not to aspirate it, as it could break the specimen. If the specimen is larger than 15mm, it should be flattened on a polystyrene block and their margins pinned to prevent curling of the tissue within the formalin and to aid orientation and facilitate margin analysis.

*Adjunctive therapies.* Argon plasma coagulation (APC) (7Fr diameter device with a setting of 50–60W) can be used as an adjunctive therapy to control immediate bleeding, prevent post-procedural bleeding, or treat suspected residual or recurrent adenomatous tissue that is not amenable for resection. Comparing to no ablation, APC has shown to be potentially beneficial preventing



**Figure 3.** Bleeding in sphincterotomy.



**Figure 4.** PD cannulation and stenting.

bleeding events without harmful effects; nonetheless, the recurrence rate of the AT seems to be similar.<sup>42</sup>

More recently, intraductal radiofrequency ablation (RFA) was introduced as an option to treat post-ampullectomy neoplastic tissue extending from the ampullary orifice into the CBD or into the PD. After ampullary resection and sphincterotomy, the intraductal extension of the adenomatous lesion is exposed and its removal can be attempted.<sup>32,41</sup> If resection is not successful, RFA has been shown to be a feasible and effective alternative. In the first multicenter prospective trial recently published, 70% of histologically proven remnant endobiliary adenomas had been eradicated at 12 months after a single RFA session.<sup>42</sup> Drawbacks of these treatments are biliary stenosis and pancreatitis, and so, prophylactically, biliary and pancreatic stents are usually placed.

Despite potential advantages of these techniques, no tissue for histology can be obtained with none of these techniques.

*Biliary and pancreatic sphincterotomy.* Performing sphincterotomy in the context of EA is controversial. It can be performed to increase the technical success, helping in the pancreaticobiliary drainage after ampullectomy. Nonetheless, it can limit the en bloc resection due to scarring, may hamper complete pathologic assessment due to thermal injury, and increase the risks of perforation, bleeding (Figure 3), and tumor seeding.

*Pancreatic stenting.* Pancreatic stenting (Figure 4) is crucial after ampullectomy in order to reduce the incidence and severity of pancreatitis, reduce the risk of papillary stenosis, and provide safer usage of adjunctive coagulative therapies.<sup>43–45</sup> The length, diameter, shape, and optimal duration of the stenting are still controversial. In our clinical practice,<sup>39</sup> we routinely place a 4 or 5 Fr unflanged single pig-tail stent after completion of the ampullectomy. A plain abdominal film is obtained within 2 weeks to check for spontaneous stent migration. If a stent is still present, it should be removed at gastroscopy.

*Prophylactic NSAIDs.* Nonsteroidal anti-inflammatory drugs (NSAIDs) (100 mg diclofenac or

indomethacin) are administered rectally before or after the procedure to prevent pancreatitis in concordance with the European Society of Gastrointestinal Endoscopy (ESGE) guideline on prevention of post-ERCP pancreatitis.<sup>46,47</sup>

*Biliary stenting.* Acute cholangitis after EA is uncommon and routine biliary stenting is not recommended. Biliary stenting is only indicated if no complete biliary drainage is achieved, there is concern for microperforation, to ensure correct bile drainage, or to prevent ascending cholangitis if a significant bleeding occurs or if intraductal therapy is performed, as the risk of biliary obstruction is higher.

*EUS-ERCP in a single session.* As previously discussed, AT is one of the indications for both EUS and ERCP. Combining both in the same session has shown to be effective and safe<sup>48,49</sup> and is, unquestionably, clinical and economically cost-effective, as it reduces hospital stay and improves patient comfort.

#### *Specific situations*

*Lateral spreading tumors of the papilla.* A relatively uncommon subgroup of AT is termed laterally spreading tumor (LST-P) arbitrarily defined as extension of the adenomatous tissue of more than 10 mm into the duodenal wall beyond the papilla. For practical purposes, a more subjective definition can be given by defining LSTs as extension that precludes en bloc resection. These tumors grow laterally, typically flat, along the luminal circumference and obtain a large size before exhibiting vertical growth or invasive behavior. Although traditionally considered an indication for surgery, endoscopic resection of LST-P has been suggested as a feasible, effective, and safe treatment option, with immediate and long-term outcomes comparable to standard ampullectomy, despite a higher risk of bleeding.<sup>39,50</sup>

Some specific technical aspects must be taken into consideration while approaching LST-P, namely the submucosal lifting and resection steps. In this case, tumor components spreading out of the ampullary complex (extra-papillary portion) are better removed after submucosal injection,<sup>50</sup> while tumor components within the papilla can and probably should be removed without injection. Submucosal injection includes a dye and a fluid. Both 0.9% saline and

succinylated gelatin (gelofusine) can be infused, but gelofusine seems to have a more sustained lifting effect and improve technical outcomes in colonic Endoscopic mucosal resection,<sup>51</sup> although there is no evidence in the duodenum. The blue dyes indigo carmine and methylene blue can be used to enhance endoscopic visualization of the margins of the adenoma, to delineate the extent of the submucosal cushion, and to confirm that one is working in the correct tissue plane. Dilute epinephrine in a concentration of 1:100,000 can also be added in the solution to help minimizing intraprocedural bleeding and prolonging the time that the mucosa is lifted. Figure 5 depicts an ampullectomy of a LST-P.

Hopper and colleagues<sup>52</sup> described different techniques according to the type of LST-P:

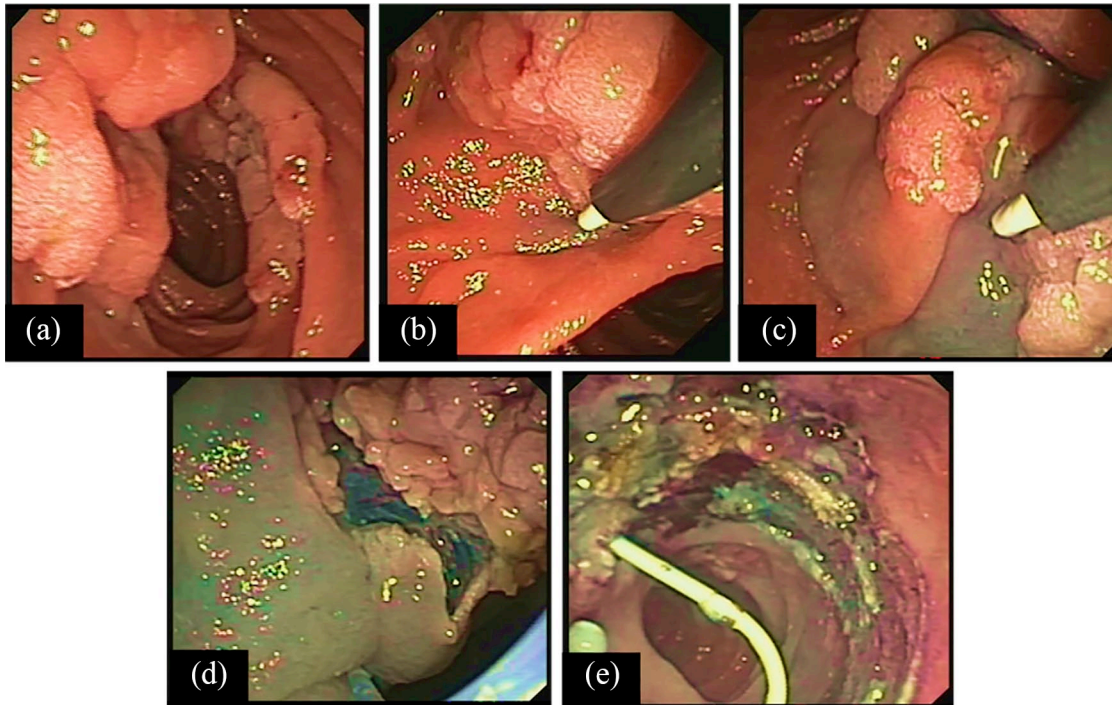
- LST-P with a predominant vertical extra-papillary extension (Paris classification 0-Is + IIa) should be treated by initial maximal ampullectomy, followed by resection of residual adenomatous tissue with endoscopic mucosal resection;
- LST-P with a predominant lateral extra-papillary extension (Paris classification 0-IIa + Is) should be approached with a submucosal injection and endoscopic mucosal resection at one edge, working sequentially from the distal aspect on one side and then the other to isolate the papilla, allowing subsequent en bloc papillectomy.

The key aspect is achieving en bloc resection of the papilla.

Piecemeal resection is usually required if the lesion measures more than 2 cm. Its drawbacks are related to possible repeated procedures to remove the entire lesion and incomplete histopathological evaluation, due to electrocautery-related injury to tissue fragments. Despite these, a recent study described good results for piecemeal resection for LST-P, with a high rate of success with one single treatment session and a total resection rate of 100%, with outcomes not inferior to the en bloc resection group.<sup>53</sup>

Resected pieces of the adenoma can be positioned in either bulb or stomach and retrieved at the end of the procedure.

The steps following the resection are the same as previously described.



**Figure 5.** LST-P ampullectomy. (a) LST-P appearance, (b) and (c) submucosal injection mixture of gelofusine and blue methylene, (d) resection, and (e) pancreatic stenting.

*Lesions with intraductal extension.* As already mentioned, endoscopic resection can be attempted in lesions with intraductal extension as long as it occurs in a very short segment (<1 cm). Particular considerations should be taken if intraductal extension is suspected or demonstrated on EUS or cholangio/pancreatography: cannulation and sphincterotomy of the involved duct should be performed after resecting the duodenal/exterior part of the lesion; with exposition of the intraductal extension of the adenomatous lesion, its removal can be attempted;<sup>33,44</sup> if resection is not successful, RFA has been shown to be a feasible and effective alternative. In the first multicenter prospective trial recently published, 70% of histologically proven remnant endobiliary adenomas had been eradicated at 12 months after a single RFA session.<sup>54</sup> As already mentioned, drawbacks of these treatments are biliary stenosis and pancreatitis, and so, prophylactically, biliary and pancreatic stents are usually placed.

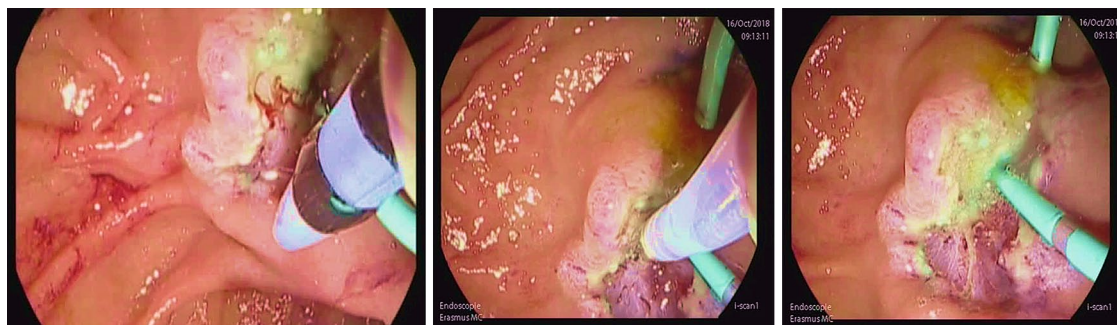
*Minor papilla.* There are few case reports in the literature regarding tumors of the minor papilla, varying from adenomas to malignant lesions. Endoscopic minor ampullectomy, following the same steps as previously described for major

papilla, has been reported as technically achievable, safe, and effective.<sup>55</sup>

*Ampullary carcinoma.* The good results in EA have justified an attempt to expand its role in early ampullary carcinomas. EA has, indeed, been suggested to be a curative treatment in early stages of adenocarcinoma (Tis and T1) that are well-differentiated, with clear margins of resection and without lymphovascular invasion.<sup>40,56-62</sup> Despite these reports, there is still no sufficient evidence for considering it a standardized therapeutic option in these cases. As always, when performing a planned endoscopic resection of a presumed early ampullary cancer or an incidental finding of cancer after resection of a presumed benign lesion, risks and benefits of additional surgery (pancreaticoduodenectomy) versus watchful waiting should be carefully balanced and tailored to the specific situation of the patient.

#### *Post-procedural care*

No clear guidelines exist on direct post-procedural care after performing ampullary resection. Given the relatively high risk of complications in our unit, these patients are routinely admitted overnight while on a liquid diet. Proton



**Figure 6.** Bleeding treated with hemostatic forceps.

pump inhibitors are started for 4 weeks. If no signs of complications are present the next day, patients are discharged.

### Complications

Several studies have confirmed a decreased rate of overall complications for EA in comparison to surgical resection, albeit still considerable (up to 30%).<sup>32,33,63</sup> In our cohort, 25.3% of patients had a procedure-related complication.<sup>39</sup> Bleeding, perforation, and pancreatitis account for immediate complications, while duodenal luminal stenosis and papillary stenosis occur later in the follow-up. EA-related mortality is very rare, occurring in 0.3%.

**Pancreatitis.** Iatrogenic pancreatitis is the most frequent complication after EA, occurring in around 8–19% of cases.<sup>32,33,44,52,64</sup> Post-EA pancreatitis is typically mild to moderate in terms of severity in the era of routine NSAID administration and prophylactic pancreatic stenting.<sup>47</sup> Risk factors for iatrogenic pancreatitis are electrocautery, sphincterotomy, stenting, and ablation. As already described, prophylactic pancreatic stenting is effective in reducing the risk of pancreatitis, especially severe and should therefore always be attempted unless there is a pancreas divisum. In case of a minor ampullectomy, pancreatic stenting is only necessary in the setting of (in)complete pancreas divisum. A different strategy is the use of a PD wire-guided resection technique.<sup>65,66</sup> Although conceptually attractive, the uptake of this technique thus far has been limited mainly due to decreased maneuverability especially for the resection of LSTs.

**Bleeding.** Bleeding is a relatively common complication, with a median risk of 8.5%,<sup>67</sup> most likely due to the high vascularization of the

duodenal wall. Intraductal extension adenoma and LST-P have been reported to be risk factors for bleeding.<sup>44,52,63</sup> Bleeding can occur either peri-procedurally or late (usually in the first 12 h after resection but occasionally much later, like in colonic resections).

Peri-procedural bleeds can virtually always be managed endoscopically although the use of all commonly used accessories for bleedings is more challenging when using a duodenoscope (especially clips). Furthermore, the use of extensive adrenaline injection or clips can possibly interfere with the ongoing resection in case of lateral spreading tumors. We therefore typically use a coagrasper hemostatic forceps to control bleeding as a first step (Figure 6). In those rare cases of severe bleeding and endoscopic hemostatic failure, arterial embolization and surgery may be needed.

The risk of delayed bleeding is very much associated with the size of the resection. Especially in case of very large (>4–5 cm) LSTs, some degree of bleeding is virtually always present and often due to diffuse oozing, more than from a specific bleeding site/vessel. We, therefore, in these cases and in the absence of hemodynamic instability, typically refrain from performing an endoscopy but treat symptomatically.

To reduce the risk of bleeding complications, antiplatelets and anticoagulants must be discontinued prior to the procedure, as recommended by international guidelines with the exception of acetylsalicylic acid that can be continued.

**Perforation.** Perforation is an uncommon, but potentially serious, adverse event. It can be related to sphincterotomy (if performed) or to the resection. In either case, due to the retroperitoneal location, these can almost always be managed



conservatively. If detected during the endoscopy, antibiotics should be given peri-procedurally. As already mentioned, carbon dioxide insufflation should be used to reduce the risk of pneumoperitoneum. A careful inspection of the resection plane and the fluoroscopy images at the end of the procedure is important to increase peri-procedural detection of perforations. Further management of retroperitoneal perforations is beyond the scope of this article but can be found in ESGE guidelines regarding iatrogenic endoscopic perforations.<sup>68</sup>

*Duodenal luminal stenosis.* This rare, late complication is only seen after resections of LST-P with extensive duodenal circumferential or longitudinal involvement. Typically, these strictures respond well to balloon dilation.

*Papillary and biliary stenosis.* Rare late papillary stenosis occurs with an incidence of 2.9–8% and may be prevented with pancreatic stent placement.<sup>32,69–71</sup> Biliary stricture causing obstructive jaundice has been reported in up to 3%.<sup>72</sup> It can be treated with biliary sphincterotomy, dilation, and stent placement.

### Outcome

Endoscopic success of an EA, defined as complete excision of the lesion disregarding the number of sessions required and absence of recurrence during the follow-up period, ranges from 46%<sup>44</sup> and 92%.<sup>28</sup> The wide range of success rates is due to differences in the inclusion criteria of EA (as tumor size or extent of the tumor) and several other parameters (e.g. endoscopist experience, length, and method of follow-up) between published series. Two recent large-scale studies found a 78.2–89.4% endoscopic success.<sup>64,73</sup> We found similar curative rates after revising the last 14 years of our clinical practice (87.5% of patient with an adenoma confined to the ampulla and 85% in patients with LST-P).<sup>39</sup> Cure is achieved in the presence of free lateral and in-depth resection margins and no occult adenocarcinoma. Radicality is not assessable by the pathologist if a piecemeal resection is taken.

Limiting factors for EA as a curative procedure are incomplete resection and recurrence. Recurrence, opposed to residual lesion, occurs when there is at least one endoscopy with biopsies showing no residual tissue and a 3-month interval between the end of the treatment and the diagnosis of recurrence. Jaundice at presentation, occult

adenocarcinoma in the resected specimen, and intraductal involvement seem to be related to a lower rate of complete resection, whereas en bloc ampullectomy increases the odds of complete endoscopic resection. Despite complete resection in the index procedure, recurrence has been described in up to 15% cases.<sup>63</sup> It has been reported in up to 5 years after resection but is more frequent in the first 14 months.<sup>32,69</sup> Some risk factors have been implied, such as young age (less than 48 years old), female sex, polyposis syndrome, large lesions (more than 24 mm), high-grade dysplasia, and intraductal adenoma growth/ductal dilation.

### Surveillance

Due to the risk of recurrence and residual disease, some sort of surveillance after EA is obligatory, although a standardized protocol, outside the setting of Familial adenomatous polyposis, is not available. Typically, it is not necessary to routinely perform a cholangio- or pancreaticogram and careful inspection with a duodenoscope with biopsies of scar and suspected adenomatous tissue is sufficient. In our unit, we typically perform surveillance at 3, 12, 24, and 48 months after the initial resection and in case of negative findings.

### Conclusion

EA is currently the first-line curative treatment for AT of major papilla without extensive ductal extension or duodenal involvement, replacing surgical interventions. Even when an endoscopically resected specimen has a well-differentiated intramucosal cancer with clear margins and neither vascular nor lymphatic invasion, subsequent radical surgery may not be necessary. Its morbidity and mortality rates are much lower than compared to surgery. It has a successful tumor eradication rate around 85% of patients with ampullary adenomas. An accurate diagnosis and staging of AT is crucial to select the appropriate candidates for this therapy. A meticulous technique and experience with management of complications are crucial to ensure a safe and adequate EA. Despite its substantial risk and complications, these are usually mild to moderate and conservatively managed. The ideal surveillance protocol has yet to be established, but should be routinely performed, to better approach eventual recurrence. Collaborative, prospective, randomized, long-term studies among referral centers are essential to better standardize the EA technique and optimize the associated outcomes.

### Authors' note

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