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How to Approach a Patient With Ampullary Lesion

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Tumors involving the major duodenal papilla are rare in the general population with reported prevalence rates from autopsy series of 0.04%–0.12%,[1] occurring most commonly in patients of 50–70 years of age. Nevertheless, sporadic papillary tumors are more frequently diagnosed with aging population and increasing use of upper gastrointestinal endoscopy, mostly incidentally in early asymptomatic stages, although they can cause typical symptoms owing to their location, such as obstructive jaundice and pancreatitis. Most of these papillary tumors are of neoplastic origin, with a majority of adenomas, following the adenoma to carcinoma sequence similar to colorectal adenocarcinoma.[2] In addition, other neoplastic, nonadenomatous lesions such as neuroendocrine tumors, adenomyomas, or gangliocytic paragangliomas occur in this region as well.[3]

Treatment Options

Owing to the potential cancer progression of most of these papillary lesions, with an estimated incidence of malignant transformation ranging from 26% to 65% for sporadic adenomas,[4] therapy is mandatory in most cases, especially if symptoms are present. As with all neoplasms, patient-, lesion- and procedure-related factors like age, comorbidities, anticipated life expectancy, tumor stage (especially risk of lymph node metastases [LNM]) and procedure related risk need to be considered, determining the individualized therapeutic approach for each patient.

For early, noninvasive tumors, endoscopic resection, also known as endoscopic papillectomy (EP), is an effective and safe therapeutic option, showing long-term cure rates of approximately 80% with recurrence rates of about 33% and low morbidity and mortality rates (9.7%–20% and 0.09%–0.3%, respectively),[3–6] making it a viable alternative therapy to surgery. In comparison, the 2 surgical procedures, the transduodenal ampullectomy, which also can leave behind residual adenomatous tissue in 13%–100% of cases, and the more radical pancreaticoduodenectomy, carry high rates of morbidity (transduodenal ampullectomy, 20%–30%; pancreaticoduodenectomy, 25%–50%) and mortality (transduodenal ampullectomy, 0%–6%; pancreaticoduodenectomy, 3%–9%).[6] Despite the overall good results of the endoscopic approach, relevant procedure-related adverse events (AEs) occur in approximately 20%–35%, even in specialized centers.[6,7] Thus, to ensure the greatest efficacy and safety for the patient, EP should be performed in tertiary centers by endoscopists trained in advanced endoscopic retrograde cholangiopancreatography—and endoscopic resection—techniques. In addition, for the appropriate management of AEs, ready access to the full spectrum of pancreaticobiliary surgery and interventional radiology support should be granted.[8]

Preprocedural Assessment

A thorough pretherapeutic assessment is necessary to identify patients who are likely to benefit from the endoscopic approach. Therefore, the estimated risk of LNM must be negligible and the entire lesion accessible to resection. Lesions with low-grade and high-grade dysplasia with an intraductal tumor extension (ITE) of $<$10 mm are regarded as suitable for EP.[5,9,10] Even if the lesion is largely spreading to the duodenal wall, between 40 and 60 mm in diameter, named laterally spreading tumors of the papilla (LST-P; Figure 5*A*), cure can be achieved by endoscopic treatment (EP combined with endoscopic mucosal resection [EMR]) at rates comparable with lesions confined to the papilla.[11] If malignancy is expected, patients usually should be referred to surgery, even in early T1 cancers (tumor limited to Vater's ampulla or sphincter of Oddi), owing to high rates of lymphovascular invasion (LVI; 56.7%) with coexisting LNM (18%).[6,12] Otherwise, endoscopic cure of selected low-risk T1 carcinomas is feasible and has been demonstrated in small series.[13–16] If complete resection (R0) was achievable and tumors were well-differentiated without evidence of submucosal invasion (SMI), or LVI, EP was curative in 100% of cases.[14]

For patients with advanced age or major comorbidities, who do not suffer from tumor-related symptoms like jaundice with itching or pancreatitis, observation alone may be appropriate because the majority of papillary tumors are slowly progressive and the procedure-related risk

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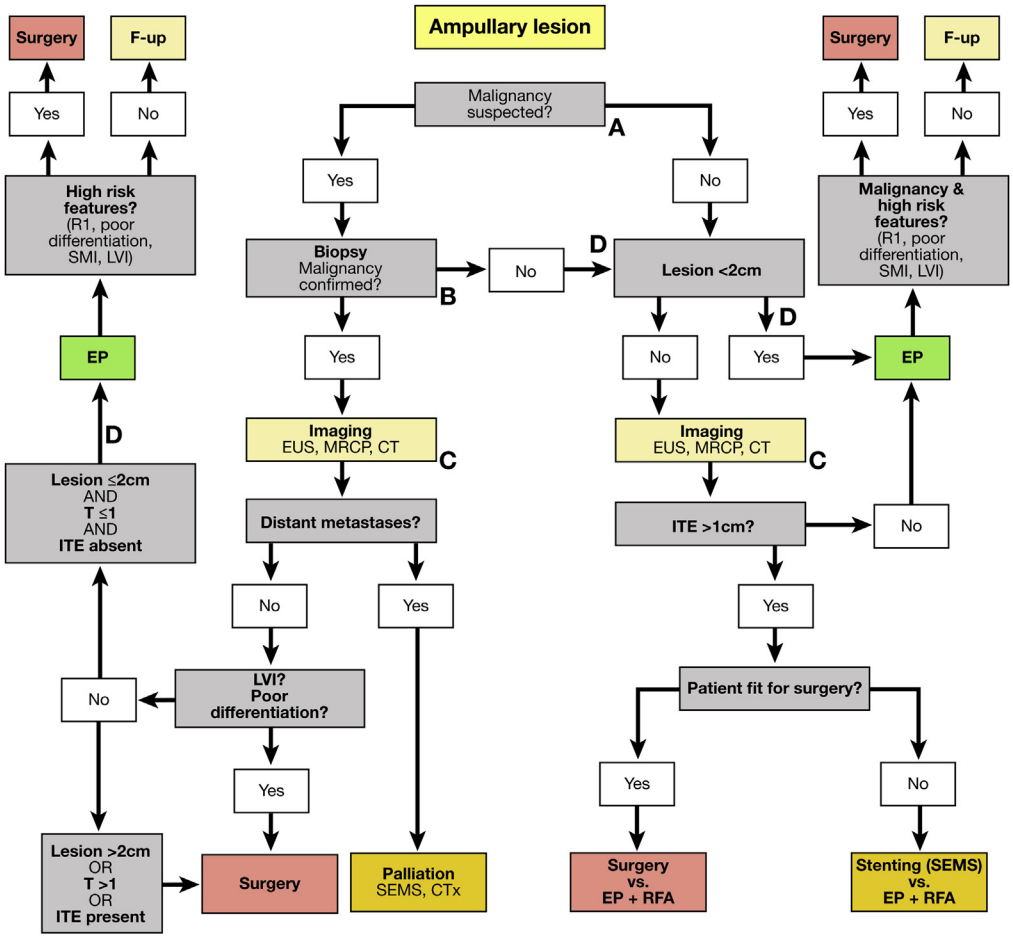

Figure 1. Algorithmic approach to a patient with ampullary lesion. CT, contrast-enhanced multidetector computed tomography; CTx, chemotherapy; EP, endoscopic papillectomy; EUS, endoscopic ultrasound; F-up, follow-up; ITE, intraductal tumor extension; LVI, lymphovascular invasion; MRCP, magnetic resonance cholangiopancreatography; R1, histologically confirmed incomplete resection; RFA, radiofrequency ablation; SEMS, self-expandable metal stent; SMI, submucosal invasion.

substantial. Figure 1 gives an overview of the management algorithm for patients with ampullary lesions.

Role of Endoscopy

An ampullary lesion is best assessed endoscopically with a side-viewing duodenoscope for optimal visualization of the papilla. But how to distinguish adenomas and low-risk T1 carcinomas from advanced carcinomas? There are no well-established endoscopic criteria predicting early neoplasia of the papilla like in other regions of the gastrointestinal tract such as Kudo- or JNET-classification for characterization of early colorectal neoplasia. Magnification and optical enhancements like narrow band imaging (NBI) may be helpful to delineate the lesions extent, especially for LST-P, and to estimate the histologic grade[17,18]; however, this method has not been widely adopted. If the lesion is slightly elevated or sessile with regular surface appearance, soft, movable and non-ulcerated, benign disease seems likely (Figure 2*A*, Figure 3*A*). If the lesion is firm, not movable and/or ulcerated with spontaneous bleeding, malignancy appears to be obvious (Figure 4*B*). In case of doubt, biopsies should be taken (Figure 1*B*) or even EP as diagnostic-therapeutic step be performed (Figure 1*D*).

Role of Biopsies

Biopsies have a limited diagnostic accuracy of between 45% and 80%, with a high rate of false-negative results (16%–60%)[3] and carry the risk of inducing pancreatitis.[19] Therefore, only in cases suspicious for cancer, biopsy sampling is recommended (Figure 1*B*), because poor differentiation or LVI might lead to surgery. To minimize the risk of pancreatitis in these selected cases, biopsies should be taken from the 9 to 1 o'clock area, far away from the pancreatic orifice. If suspected malignancy cannot be confirmed by biopsy, and EP is considered to be feasible and safe, resection as a diagnostic-therapeutic step is appropriate (Figure 1*D*).

Role of Imaging

Preinterventional imaging is not obligatory, especially for small lesions (<2 cm), but advantageous to assess ITE, the presence of pancreatic duct anatomic variants, such as pancreas divisum, and in cases suspicious for cancer, for local tumor and nodal staging. Because the only main predictor of invasion in ampullary adenomas is size,[20] imaging is recommended for lesions ≥2 cm or those suspicious for cancer[3] (Figure 1*C*). For this purpose, endoscopic ultrasound imaging, magnetic resonance imaging/magnetic resonance cholangiopancreatography

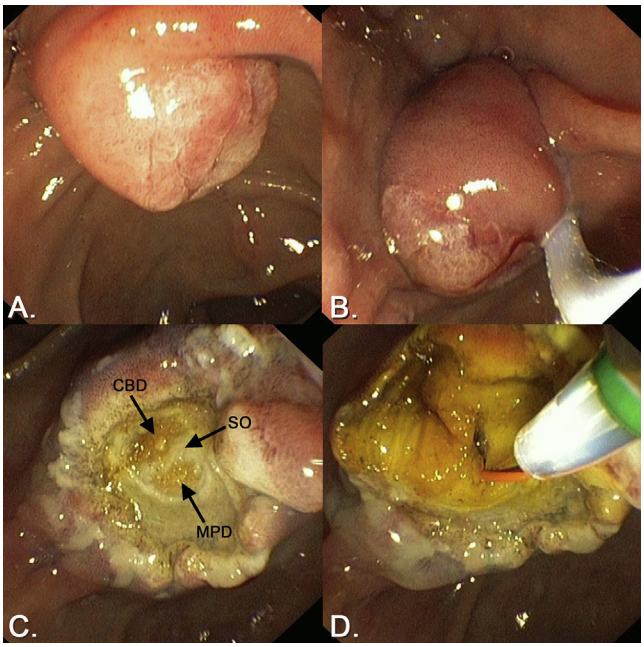

Figure 2. Endoscopic simple snare papillectomy. *A*, Endoscopic view of an adenoma limited to the major duodenal papilla. *B*, Resection with a standard polypectomy snare without prior submucosal injection. *C*, Endoscopic view of the resection site with the orifices of common bile duct (CDB) at 11 o'clock and main pancreatic duct (MPD) at 5 o'clock, surrounded by fibers of sphincter of Oddi (SO). *D*, Guidewire inside the MPD for stent placement.

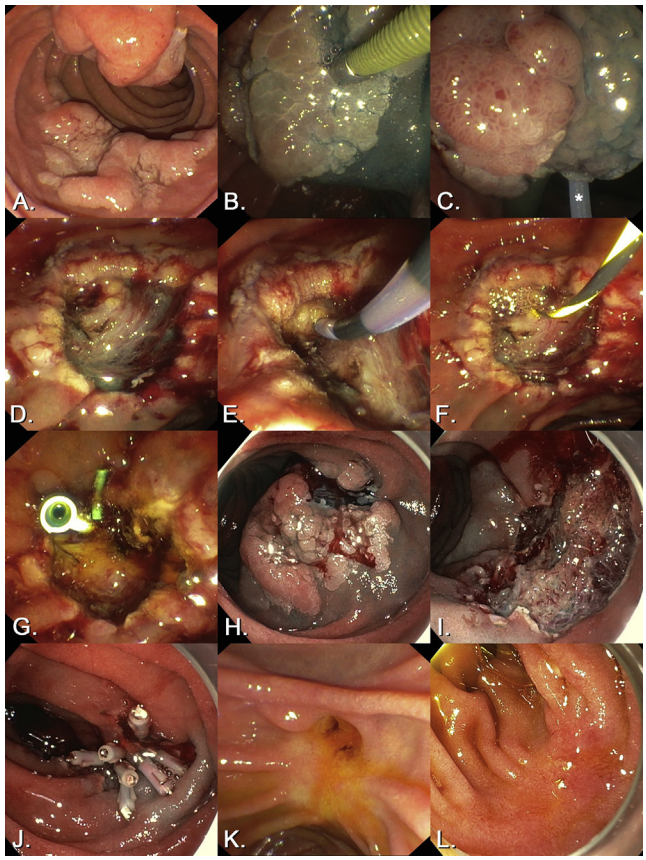

Figure 3. Endoscopic papillectomy (EP) of ampullary adenoma (*A*–*G*) and endoscopic mucosal resection (EMR) of oppositely located duodenal adenoma (*H*–*J*). Procedure (*A*–*J*) and long-term results (*K*, *L*). *A*, Endoscopic view of a papillary lesion in the upper part of the picture with a large vertical extension and only small laterally spreading component. In the lower part, a slightly elevated (Paris 0-IIa) laterally spreading adenoma. *B*, Selective submucosal injection of the extrapapillary component. *C*, En bloc resection of the entire lesion with a polypectomy snare (white starlet). *D*, Endoscopic view of the resection area. *E*, Cannulation of the pancreatic orifice with a standard catheter. *F*, Pancreatic guidewire in place. *G*,. Plastic 10F biliary and 5F pancreatic stents have been placed. *H*, Duodenal adenoma with submucosal injection and partial resection of the lateral portion. *I*, Completed EMR with mild ongoing bleeding. *J*, Several clips have been placed. *K*, *L*., Surveillance endoscopy at 4 years. Bland scar of the papilla (*K*) and the opposite duodenal wall (*L*) with no recurrence.

and contrast-enhanced multidetector computed tomography, endoscopic retrograde cholangiopancreatography, and intraductal ultrasound imaging are used complementarily, because no test has proven to be definitive. Despite the high diagnostic accuracy concerning T staging and ITE,[21,22] the application of intraductal ultrasound imaging is limited in clinical practice owing to its limited availability, expense and the linked risks (eg, pancreatitis).

Tables 1–3 provide an overview of the role of endoscopic ultrasound, computed tomography, magnetic resonance imaging, endoscopic retrograde cholangiopancreatography, and intraductal ultrasonography in preinterventional imaging, with corresponding overall accuracies. Table 4 shows recommended imaging modalities according to clinical situations.

Role of EP as Diagnostic-Therapeutic Step

In uncertain borderline cases, in which no definitive diagnosis or prediction of curative resectability is possible by endoscopy, biopsy, and imaging, and en bloc resection seems to be feasible and safe, EP can provide accurate histology, as well as grading, T and LVI staging in cases of malignancy. If high-risk features for LNM like SMI, LVI, or poor differentiation are encountered, subsequent surgical management is not hampered by prior EP (Figure 4). Lesions considered to be eligible for this approach are $\leq$20 mm in diameter and feature $\leq$10 mm lateral extension, because these conditions enable en bloc resection with a low procedure-related risk.[25]

How to Perform EP

With EP, neoplastic tissue from the papilla, more precisely the mucosa and submucosa of the duodenal wall, can be removed endoscopically, and therefore the term "endoscopic papillectomy" is a more appropriate term than "endoscopic ampullectomy," although the two often are used interchangeably in clinical practice. Ampullectomy refers to the surgical removal of the entire ampulla of Vater and consists of circumferential resection of the papilla with reinsertion of the common bile duct and the main pancreatic duct into the duodenal wall, which necessitates longitudinal duodenotomy and partial resection of pancreatic head tissue.[26]

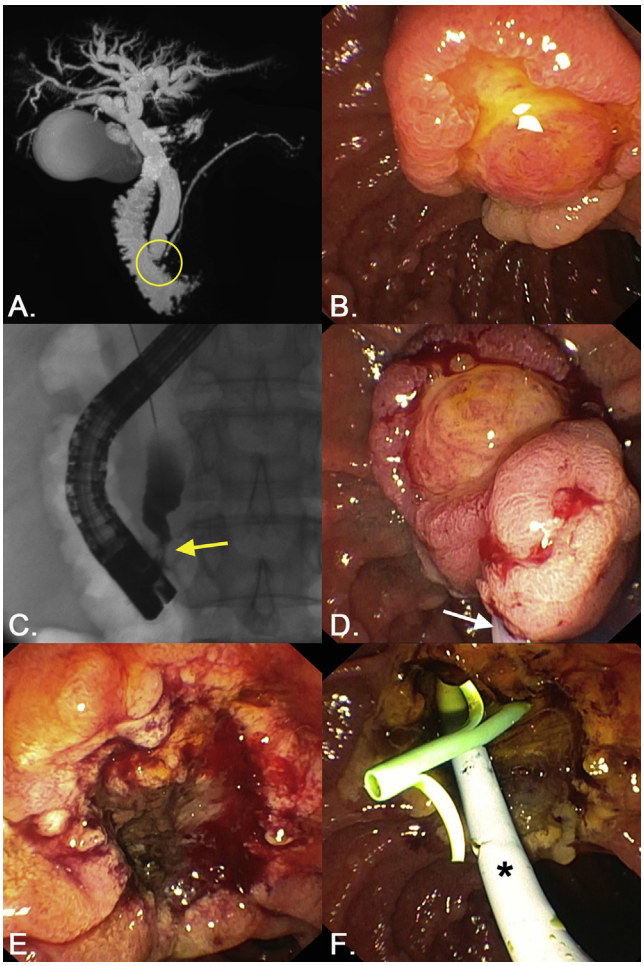

Figure 4. Endoscopic papillectomy (EP) of ampullary T1 carcinoma as diagnostic-therapeutic step. *A*, Magnetic resonance cholangiopancreatography of a patient with painless jaundice and assumed small filling defect (yellow circle) at the distal common bile duct (CDB), suspicious for intraductal tumor extension (ITE) of <1 cm. *B*, Endoscopic view of an ulcerated tumor arising from the major duodenal papilla. Biopsy revealed well-differentiated adenocarcinoma without lymphovascular invasion (LVI). Imaging (endoscopic ultrasound, computed tomography) showed T1 stage and no ITE, lymph node (LNM), or distant metastases (not shown). *C*, Endoscopic retrograde cholangiography excluded ITE (yellow arrow). *D*, En bloc resection of the tumor with a polypectomy snare (white arrow) without prior submucosal injection. *E*, Endoscopic view of the resection site. *F*, Plastic 5F straight stent inside main pancreatic duct and 10F pigtail stent (black starlet) inside the CDB. Histology revealed submucosal and lymphovascular invasion. The patient was referred to surgery, pancreaticoduodenectomy was performed without detection of residual carcinoma but 1 LNM; therefore, adjuvant chemotherapy was conducted.

Cholangiography and Pancreatography

After thorough endoscopic inspection of the lesion concerning extent and malignancy and before resection, fluoroscopic evaluation of the distal common bile duct and main pancreatic duct is recommended, with particular attention paid to filling defects that may suggest ITE or coexisting neoplastic changes of the ducts (Figure 4*C*). Furthermore,

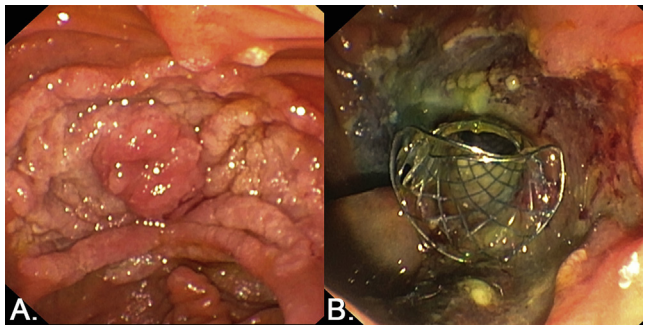

Figure 5. Endoscopic papillectomy (EP) and endoscopic mucosal resection (EMR) of a large laterally spreading tumor of the papilla (LST-P). *A*, Late recurrence of LST-P in an elderly patient after surgical ampullectomy, presenting with obstructive jaundice, unfit for repeat surgery. *B*, Resection area with a biliary fully covered self-expandable metal stent (FC-SEMS) in place.

locating the pancreatic orifice for stent placement after resection can be facilitated by adding methylene blue to contrast medium, minimizing the risk for post-EP pancreatitis.[27] Occasionally, cannulation may be difficult or even impossible, especially with large lesions, because the tumor may obscure the ductal orifices. In this case, especially if a magnetic resonance cholangiopancreatography has been done, excessive attempts at cannulation should be avoided to minimize the risk of post-EP pancreatitis.[28,29] For this reason, rectal nonsteroidal anti-inflammatory drugs, like indomethacin or diclofenac, should be applied before EP, as well.[3,28] In cases of failed cannulation before resection, cholangiogram and pancreatogram should be obtained after EP.

Resection

To minimize the risk of recurrence and enable accurate histologic assessment, complete en bloc resection of the entire lesion should be the goal and is usually feasible for lesions ≤20 mm in diameter and ≤ 10mm lateral extension.[6,25,30] For these kind of lesions, EP without prior submucosal injection (simple snare papillectomy [SSP]; Figure 2) may be a simpler and primarily recommendable technique, as submucosal injection papillectomy (SIP) showed no advantage over SSP in terms of achieving complete resection (SIP 50% vs SSP 81%) or decreasing the frequency of postpapillectomy AEs, such as bleeding (SIP 36% vs SSP 27%) and pancreatitis (SIP 25% vs SSP 15%), although the recurrence rate was similar (SSP 12% vs SIP 10%).[31] To capture the lesion, the tip of a snare is anchored above the superior part of the papilla. As the snare is carefully opened, it is drawn down over the lesion, while the tip of the snare maintains its contact with the mucosa and the duodenoscope is gently pushed inferiorly into the duodenum. This maneuver has been termed the "fulcrum technique"[8] (Figure 2*B*). The snare is closed maximally and the mobility of the papilla is assessed. If the entrapped tissue is independently mobile relative to the duodenal wall, it is transected by application of electrocautery (Endocut Q,

Table 1. Evaluation of Intraductal Tumor Extension

	Endoscopic Ultrasound	Endoscopic Retrograde Cholangiopancreatography	Intraductal Ultrasonography
Accuracy	91%[23]	84%[23]	90%[22]

effect 3, ERBE VIO 300D, Tübingen, Germany). Standard braided polypectomy snares, as well as thin wire snares can be used, because there is no evidence of superiority of 1 type of snare over another.[3] However, some authors recommend the use of thin wire snares, because they may maximize current density for swift transection, probably minimizing inadvertent injury to the pancreatic orifice, increasing the risk of late stenosis.[25] The first concern after successful resection is to retrieve the specimen to prevent distal migration. For this purpose, the snare should be used to lift the specimen above the papilla to drop into the duodenal bulb.

In lesions with a large vertical extension and only a small laterally spreading component, selective submucosal injection should be used only to elevate the extrapapillary component with the goal to perform en bloc resection of the entire lesion[25] (Figure 3). In case of LST-P (Figure 5, Video 1), standard duodenal endoscopic mucosal resection techniques are used to remove the laterally spreading component, first aiming to isolate the papilla for en bloc resection at the end.[6] In this case, submucosal injection of the adjacent mucosa should be performed cautiously, to avoid a papilla, buried between the lifted mucosa.

Pancreatic Stenting

As a second priority after resection, pancreatic stent placement should be performed if possible, because it may decrease the risk of post-EP pancreatitis (PEP).[27,32] Patients with complete pancreas divisum on magnetic resonance cholangiopancreatography are of course excluded from this recommendation. The pancreatic orifice is usually identified at the 5 o'clock position of the papillectomy site and should be cannulated wire guided[28] (Figure 2*C*, *D*). If methylene blue has been added to contrast medium before resection, identification of the pancreatic orifice might be facilitated.[27] However, whether or not pancreatic stent placement can decrease the rate of PEP remains controversial, because some studies have shown no significant benefit.[33] In case of difficult pancreatic duct cannulation after EP, excessive attempts at cannulation should be avoided because it increases the risk of post EP pancreatitis.[29] For this reason, rectal nonsteroidal anti-inflammatory drugs should be applied before EP as mentioned.[28]

Biliary Stenting/Sphincterotomy

Routine biliary stenting and sphincterotomy are generally not necessary; the evidence for this approach is weak and cholangitis as well as papillary stenosis after EP are rare.[3,6] In patients with EP and extensive piecemeal resections of LST-P and, thus, a high risk for delayed bleeding with consecutive ascending cholangitis from haemobilia as well as papillary stenosis, prophylactic biliary stenting is recommended.[11] If the bile duct is not dilated, plastic stents are appropriate.[6] Fully covered self-expandable metal stents (Figure 5*B*) may have some beneficial effects, theoretically, regarding the closure of unanticipated microperforations at the resection site, prevention of delayed bleeding, and dilation therapy of the distal common bile duct, which may facilitate subsequent direct endoscopic assessment and treatment of residual tissue in case of ITE. However, evidence for these indications is lacking.[8]

Ablative Therapies

Limited data suggest that EP and intraductal ablative therapies like radiofrequency ablation may effectively treat ITE of ampullary neoplasms, even >1 cm and, therefore, may be appropriate in selected patients, particularly when the main treatment alternative is surgery.[10,34] For final recommendations concerning this matter, prospective, randomized controlled trials are needed.

AEs

Procedure-related AEs occur in approximately 20%–35% and mainly include, with decreasing incidence, pancreatitis (4%–20%), bleeding (2%–30%), perforation (0%–4%), and cholangitis (1%–2%) as early complications and papillary stenosis (1%–2%) as a late complication.[6] Almost all of these complications can be managed endoscopically/conservatively, and even selected cases of perforation, which is usually retroperitoneal, do not require surgical intervention and may be managed with gut rest,

Table 2. T Staging

	Endoscopic Ultrasound	Computed Tomography	Magnetic Resonance Imaging	Intraductal Ultrasonography
Accuracy	63%–90%[22–24]	26.1%[24]	53.8%[24]	78%–88.9%[21,22]

Table 3. N Staging

	Endoscopic Ultrasound	Computed Tomography	Magnetic Resonance Imaging
Accuracy	66.7%[24]	43.5%[24]	76.9%[24]

antibiotics, and close surgical involvement.[35] The management of EP-associated complications has been described in detail elsewhere.[8,25]

Postprocedural Care and Follow-up

Owing to the frequency and possible severity of procedure related risks,[7] we perform all our EP procedures as an inpatient procedure, which is in accordance with American Society for Gastrointestinal Endoscopy guidelines.[3] After EP, patients remain fasting for 3–4 hours and then receive first clear and later nonclear liquids, usually for 3–4 days. Furthermore, all patients receive intravenously proton pump inhibitors twice a day.

Pancreatic stent removal should be carried out within 2 weeks after EP to minimize the risk of ductal injuries and is mostly undertaken 3 days after EP in our unit. This timing offers the chance to evaluate the resection site before patient discharge. Endoscopic surveillance of the resection area with a side viewing duodenoscope (Figure 3*K*) is performed at 3-month intervals for 1 year. If residual adenoma is found, it is usually easily excised or ablated. After this, subsequent follow-up endoscopies are repeated every 6 months for another year and then annually for 3 years. However, endpoints for surveillance in these patients have not yet been established.[3]

Conclusion

Sporadic ampullary lesions are rare but more frequently diagnosed and feature substantial progression to cancer, which necessitates therapy in most cases. For this purpose, EP is a highly effective albeit complex procedure with relevant procedure-related risks, although relatively low when compared with surgery. A thoroughly multimodal pretherapeutic assessment is required to identify the individualized approach for each patient, especially because most affected patients are elderly, often with relevant comorbidities, and the majority of papillary tumors are slowly progressive.

Table 4. Recommendations for the Use of Preinterventional Imaging Modalities

Situation	Recommendation	Rationale
No malignancy suspected, tumor <2 cm	No imaging	No risk for invasion or ITE
No malignancy suspected, tumor ≥2 cm	EUS (IDUS)	No risk for invasion but ITE
Malignancy suspected	EUS, MRI/MRCP, CT	Risk for invasion, ITE, and metastases

CT, computed tomography; EUS, endoscopic ultrasound; IDUS, intraductal ultrasound; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.11.010.

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Conflicts of interest
The authors disclose no conflicts.