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Endoscopic management of adenomatous ampullary lesions

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Abstract

Lesions of the ampulla of Vater represent an uncommon group of gastrointestinal malignancies. The majority of lesions of the ampulla of Vater are either adenomas or adenocarcinomas. Ampullary lesions are often incidental findings. Accurate preoperative diagnosis and staging of ampullary tumors is imperative for predicting prognosis and determining the most appropriate therapeutic approach. Endoscopic ampullectomy is a safe and efficacious therapeutic procedure that can obviate the need for potentially major surgical intervention. This review will provide the framework for the diagnosis and management of ampullary lesions from the perspective of the practicing gastroenterologist. Strategies for safe and successful endoscopic ampullectomy with a focus on accurate preoperative diagnosis and staging, resection technique, and management of complications are presented.

Key words: Ampullary adenoma; Papillary tumors; Endoscopic ampullectomy; Endoscopic ultrasound; Pancreatitis

Core tip: Adenomatous ampullary lesions are rare. Endoscopic retrograde cholangiopancreatography and endoscopic ultrasound (EUS) have changed the management of patients with these lesions. Endoscopic ampullectomy is a technique that has revolutionized the treatment of these lesions avoiding potential complications of surgery. We herein discuss the epidemiology, the role of EUS in the local staging and the role of endoscopy in the treatment of the adenomatous ampullary neoplasms.

INTRODUCTION

The anatomy of the ampulla of Vater is complex. Ampullary adenomas are an uncommon group of gastrointestinal malignances. With the advances in esophagogastroduodenoscopy and ultrasonography, detection of ampullary neoplasms has increased. Most periampullary lesions are malignant tumors appearing from the ampulla, duodenum, or pancreas. Benign neoplasms entail in this region only < 10% of neoplasms[1-3]. Advances in endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS) have changed the clinical management of these patients. Endoscopic ampullectomy may be considered in patients with smaller lesions that do not contain invasive carcinoma, and in patients who are poor surgical candidates[4-6]. Many series have reported low morbidity and mortality with endoscopic therapy[4,7-19]. Detailed preoperative assessment and staging is needed in other to decide on the best therapeutic option. We review the epidemiology, the role of EUS, ERCP and endoscopy in the approach of ampullary neoplasms.

EPIDEMIOLOGY

Ampullary neoplasms comprise several lesions: adenoma, adenocarcinoma, adenoendocrine carcinoma, small cell carcinoma, adenosquamous carcinoma, and undifferentiated carcinoma[20]. Adenomas or adenocarcinomas representing > 95% of these lesions[21,22]. Ampullary adenomas (AA) are benign lesions but, can potencially develop into ampullary carcinomas in a comparable progression to that of colorectal cancer[2,3,23-29]. Ampullary adenomas can be sporadic or in the context of a familial polyposis syndromes [*e.g.*, familial adenomatous polyposis (FAP)]. FAP is a risk factor; 80 percent of affected patients develop duodenal adenomas, which are often multiple[30]. In this polyposis syndrome, the lifetime incidence of peri-ampullary adenomas is 50%-100%. The prevalence of AA has increased in the last years with the extensive availability of endoscopy.

CLINICAL MANIFESTATIONS

Ampullary lesions are often found incidentally on cross-sectional imaging or by endoscopic examination. Presenting symptoms are usually non-specific, reflecting biliary or pancreatic obstruction. The most common presentation is with painless jaundice, which is present in 50%-75% of patients[21,31-34]. Cholangitis or acute pancreatitis are rare manifestations[35-38]. Nausea, vomiting, biliary colic, and weight loss may also occur[21,33].

ACCURATE PREOPERATIVE DIAGNOSIS AND STAGING

Accurate preoperative diagnosis and staging is critical to decide on the best treatment option and establish a prognosis.

Endoscopy

The best endoscopic examination of the papilla of Vater is performed with a side-viewing endoscope[20]. This endoscope allows an adequate assessment of the morphological features of the lesion. Thus the following features are suggestive of benign disease: (1) a regular margin; (2) absence of ulceration or spontaneous bleeding; and (3) a soft consistency[39]. Furthermore, the side-viewing endoscope enables an easy acquisition of tissue by biopsy, at the time of procedure. However, on this respect, we know that sensitivity with forceps biopsies for demonstrating the presence of adenoma is > 90%; this is lower for adenocarcinoma, and there is up to 30% of miss diagnosis[11,40-42]. Thus, a negative histological diagnosis of carcinoma on endoscopic biopsy of an ampullary adenoma does not exclude a possible focus of adenocarcinoma[42-47]. The accuracy of endoscopic biopsies can be enhanced when additional techniques are employed. Thus, taking biopsies several days after sphincterotomy[48], and taking at least six biopsies, minimizes the chance of false negative results[49] . Despite its gaps, endoscopic forceps biopsy is the mainstay of pre-excisional histological assessment in lesions of the ampulla. However, we ought to remember that resection of all ampullary adenomas might be the best approach for excluding the presence of carcinoma.

Endoscopic retrograde cholangiopancreatography

ERCP has a central role in the staging and management of obstructive jaundice in ampullary adenomas. Adenoma ingrowth into the pancreatic or biliary ducts does not always indicate malignancy, but may hinder endoscopic excision and considerably decreases the chance of complete endoscopic resection. ERCP at the time of endoscopic papillectomy permits: (1) evaluate the intraductal extension; (2) the placement of a pancreatic stent in order to reduce the risk of pancreatitis; and (3) deploy, if required, a biliary duct stent for the palliation of obstructive jaundice.

Endoscopic ultrasound

EUS, in conjunction with ERCP, allows to assess for infiltration of the periampullary wall layers and pancreatobiliary ducts but, it does not have to be universally incorpored into the diagnostic evaluation of an ampullary adenoma[45,50-57]. The use of EUS in the assessment of ampullary adenomas is undefined. There is no consensus on the requirement or not for EUS prior to consideration of treatment on all patients with ampullary adenomas. It has been suggested by some experts that EUS is not required if the lesion is less than 1 cm in diameter or there are no endoscopic signs to suggest malignancy[58]. Others claim that, if accessible, EUS testing ought to be taken into consideration prior to endoscopic or surgical resection[59]. EUS has been reported to be of help in recognizing non-invasive lesions amenable to local resection, but as yet there are no preoperative test which are as accurate as clinical judgment and intraoperative pathological diagnosis[45,60]. A recent retrospective review concluded that EUS is useful in predicting the depth of mucosal invasion in the preoperative evaluation of suspected peri-ampullary and duodenal adenomas (specificity: 88%; negative predictive value: 90%)[53]. However, EUS is an invasive technique, operator dependent, with different rates of over-diagnosis and under-diagnosis. In this context, peritumoral inflammatory changes can lead to over-staging and likewise focal pancreatic infiltration to under-staging[61,62]. A recent meta-analisis of 14 studies and a systematic review, concluded that the results obtained by EUS were comparable to the histological results with moderate strength of agreement in the following: preoperative staging of papillary neoplasm, predicting lymph node involvement and tumor invasion[63]. The modest EUS sensitivity (77%) and specificity

(78%) in predicting T1 neoplasms makes it not optimal in choosing the right patients for endoscopic papillectomy. EUS sensitivity and specificity for detecting nodal invasion was 70% and 74%, respectively. We believe, as other authors that if the clinical suspicion for invasive carcinoma is low (*e.g.*, absence of jaundice, endoscopic features of noncancerous lesion), and the lesion appears amenable to endoscopic resection, then EUS may not impact the endoscopist's decision to stage the lesion *via* ampullectomy. Few studies have been reported comparing efficacy of EUS and intraductal ultrasound (IDUS) for ampullary neoplasms[54,60,64]. IDUS was superior to EUS in terms of tumor visualization and staging (staging accuracy: 78%-93%). Therefore, IDUS can be particularly appropriate in deciding which patients should undergo endoscopic ampullectomy. However, the availability of this technique is limited and therefore the number of patients undergoing IDUS is small.

Magnetic resonance imaging and computed tomography

Magnetic resonance imaging (MRI) and computed tomography (CT) use is limited to staging of know ampullary cancers, for nodal staging and metastatic evaluation. CT is less precise than EUS for T staging of ampullary cancer[56,65].

ENDOSCOPIC AMPULLECTOMY

Patients diagnosed with an ampullary adenoma have three treatment options: pancreaticoduodenectomy (Whipple procedure), surgical local excision (surgical ampullectomy), or endoscopic ampullectomy. There are no clear guidelines about the surgical or endoscopic management of ampullary adenomas and, if they should undergo postprocedure surveillance[66]. Surgical excision is typically recommended for patients with larger lesions, lesions that contain carcinoma, lesions with lymph node involvement on preprocedure imaging, or for patients who do not have access to an experienced endoscopist in ampullectomy. Pancreaticoduodenectomy is more likely to achieve complete excision compared with local excision, but it is associated with higher operative morbidity and mortality rates (25%-65% and 0%-10%, respectively)[67,68]. Perioperative mortality rates were lowest (< 4%) in centers with a high procedure volume. Surgical ampullectomy has lower morbidity and mortality,

but has the disadvantage of having more recurrence rate. Randomized trials comparing surgical ampullectomy with pancreaticoduodenectomy have not been performed. Endoscopic ampullectomy was first described in 1983 by Suzuki *et al*[59] and ten years later Binmoeller *et al*[4] described a considerable case series. More recently, many other series have reported low morbidity and mortality with endoscopic therapy[7-19]. However, the role of endoscopic ampullectomy is still debatable and it is largely performed only in reference hospitals with skill in therapeutic endoscopy. Endoscopic ampullectomy may be considered in smaller lesions (< 30 mm) that do not contain carcinoma and in patients with severe diseases. Lesions with endoscopic characteristics suggestive of posible malignancy (*e.g.*, nonlifting, firmness, ulceration, friability) should be offered surgical resection[6].

ENDOSCOPIC AMPULLECTOMY TECHNIQUE

General principles

Endoscopic ampullectomy is a therapeutic modality which must be undertaken by an endoscopist with enough training and expertise. The goal with ampullary adenomas is for total *en-bloc* removal of the neoplasm. Initially, the endoscopist must determine whether resection of the entire lesion in one piece ("*en bloc*") is feasible and locate the margins of the lesion. This method has several advantages: (1) it increases the likelihood of complete removal; (2) it provides clear margins for histopathologic evaluation; and (3) it reduces the procedure time. However, en bloc excision may not be technically feasible if the adenoma is of a large size, and/or there is a limited endoscopic accessibility. Piecemeal excision is usually reserved for these cases, frequently with adjuvant ablative therapy[69]. It has been postulated that this technique can reduce recurrence rates, bleeding and perforation. However, comparative trials are lacking[13] (Figure 1).

Submucosal lifting

The role of submucosal injection of saline, which may be combined with epinephrine or methylene blue before ampullectomy, is controversial[6,62,66]. Epinephrine and methylene blue may help minimize bleeding and enhance endoscopic visualization

of the lesions margins, respectively[13]. Local saline injection may increase technical success and decrease complications similar to mucosectomy[13,70]. However, this technique is not recommended by other authors because submucosal saline injection may involve certain disadvantages: (1) the ampullary lesion may not lift due to tethering by the biliary and pancreatic ducts; (2) The dome effect created by submucosal injection may cause difficulty in the placement of the snare for effective en bloc resection[13,70-72]; and (3) increased risk of postresection pancreatitis has been reported. Currently, the evidence to support submucosal injection before ampullectomy is not significant. A possible indication may be adenomas with lateral extraampullary spread[72].

Endoscopic resection

There is no specific type of snare for endoscopic ampullectomy. For the majority of usual adenomas both hexagonal or oval snares of 3 cm are recommended. Standard braided polypectomy snares are typically used. The use of a thin wire snare is advised by some authors, limiting dispersion of the energy and risk of injury to the pancreatic orifice[72]. Occasionally, a peripheral circumferential incision to the adenoma with a needle knife device may make easier the snare capture[6]. To resect the lesion, the tip of the snare is placed on the top of adenoma; then, the snare is closed maximally and, after previously checking for papilla mobility, the lesion is sectioned by continuous application of current.

Optimal current

There is no general recommendation regarding the optimal current and power output for endoscopic ampulectomy. Some investigators recommend pure-cutting current for this purpose[4,15,73] to preclude the edema originated by the coagulation mode, although, a pure cutting current has been related to bleeding. Others, using a blended electrosurgical current[4,6,9] or alternating cut/coagulation modes[6,62,74]. Power output oscillates between 30 W and 150 W[6,9,13,73,75]. Most experts, advocate a blended current[76]. We prefer to use Erbe electrosurgical generators (Endocut, effect 2)[77].

Retrieval of resected specimen

Retrieval of the specimen is essential for total evaluation and detection of small malignant foci. An anti-peristaltic agent administration (*e.g.*, glucagon or hyoscine butylbromide) to avoid intestinal migration is recommended. Retrieval should be performed immediately after excision since there is a tendency for the excised specimen to migrate distally into the jejunum. For this purpose, the snare that was used for the excision or a retrieval net is ideal. Endoscopic suction can also prevent the tissue migration. However, the specimen should not be aspirated through the accessory channel of the duodenoscope into a trap because this could lead to fragmentation of the specimen. Once retrieved, the specimen can be pinned to a polystyrene block to aid orientation and facilitate margin analysis.

Residual tissue ablation

After specimen retrieval, the duodenoscope is reintroduced to examine the resection site for: (1) active bleeding or bleeding stigmata; and (2) residual tissue ablation. Usually, ablation therapy is used as adjunctive therapy to treat residual adenomatous tissue remaining after, en bloc or piecemeal, snare resection. With piecemeal excision, the tissue near the duct holes may be hard to excise completely. However, the benefits of this adjunctive therapy remain controversial. The overall success rate was comparable in patients with and without adjuvant thermal ablation (81% *vs* 78%, respectively)[9]. Ablation can be performed with monopolar or bipolar coagulation[49,70], and others devices[11,13,70,78]. We often use argon plasma coagulation (APC) (setting of 40 to 50 watts) to ablate residual tissue. We carry out a biliary sphincterotomy prior to fulguration, and we place a pancreatic stent before thermally coagulating around the pancreatic orifice.

Sphincterotomy and stent placement

The aim with a pancreatic or biliar sphincterotomy and stent placement is to enhance the technical success and decrease the complications of endoscopic ampullectomy[4,13,70,79-81]. However, a preresection sphincterotomy has some drawbacks. First, en bloc resection can be more difficult and will hinder total

histologic evaluation of the resected specimen as result of thermal injury. Secondly, it may increase risks of bleeding, perforation and tumor seeding[82].

Usually, a meticulous inspection of the ampullectomy site allows identification of focal biliary and pancreatic orifices within the duodenal wall. Otherwise, secretin administration can produce juice flow to identify the pancreatic orifice. A 5 French pancreatic stent placement is advised to decrease the incidence and severity of pancreatitis[6,9,81,83,84]. Therefore, pancreatic duct stenting after endoscopic ampullectomy appears recomendable[74]. If ERCP or prior MRCP have demonstrated a pancreas divisum, pancreatic duct stenting is usually not necessary. Acute cholangitis after papillectomy is uncommon[76], and prophylactic biliary stent placement is generally unnecessary. However, we often perform either a biliary sphincterotomy or a prophylactic biliary stent is placed to minimize this probability. Biliary stenting may ensure the correct bile drainage if major bleeding occurs. The pancreatic and biliary stents are generally removed two or three weeks later, at which time any suspicious-appearing residual polypoid tissue can be removed to ensure complete excision.

COMPLICATIONS OF AMPULLECTOMY

Complications after endoscopic ampullectomy include bleeding (0%-25%), pancreatitis (0%-25%), perforation (0%-4%), papillary stenosis (0%-8%) and cholangitis (0%-2%)[4,6,9,11,13,62,85-87]. Pancreatitis, perforation and delayed bleeding are the most severe complications[62]. The overall complication rate is around 15%[4,11,49,70,80]. Ampullectomy-related mortality is exceptional, occurring in 0.3%[76].

Bleeding

The duodenal wall has a high vascularization. Bleeding can habitually stopped by hemostatic procedures (*e.g.*, adrenaline injection, APC, clipping)[88]. If substantial bleeding is expected then, biliary stent placement is useful to avoid cholagitis. If massive bleeding occurs, urgent arteriography is probably the best diagnostic and treatment option. In patients with a high risk of cardiovascular incidents aspirin may be continued; however, anti-coagulants agents should be discontinued.

Perforation

Perforation is usually retroperitoneal. Therefore, if perforation is suspected (endoscopic features, ongoing pain) a computed tomography is more sensitive than simple radiology. Not all cases of perforation need surgical treatment, selected patients can be treated conservatively (intravenous antibiotics, gut rest)[6,14]. In anycase, a multi-disciplinary management is imperative to reach the best result.

ENDOSCOPIC OUTCOMES

The success rates for endoscopic resection of ampullary adenomas is high (range: 45%-92%), with recurrence rates of 0%-33%[9,89]. Intraductal adenoma growth had less favorable outcomes compared with adenomas without intraductal growth[15]. Predictors of success include: (1) lack of a genetic predisposition to adenoma formation (*e.g.*, FAP); (2) age > 48 years; (3) male sex; and (4) lesion size < 2.4 cm[70].

ENDOSCOPIC FOLLOW UP AND SURVEILLANCE

After ampullectomy patients should remain fasting for 4-12 h. Then, they are discharged home on a liquid diet and later continue with a normal diet. To reduce the risk of ductal lesion, the pancreatic stent should be removed in 2 wk.

Adenoma recurrence can occur in up to 25% of cases despite of complete removal during the index procedure[6,9,76]. In the absence of symptoms, surveillance endoscopy can be accomplished using a side-viewing duodendoscope without ERCP. Intervals change based on the histology and margin status of the resected lesion, history of FAP, patient age and comorbidities.

Recommended intervals (Table 1): (1) If there was no residual polyp after the primary resection: endoscopy 3 mo later; (2) If the result is negative for residual adenoma: surveillance 1 year later; (3) Beyond this, the yield of long-term surveillance in sporadic ampullary adenomas is unknown. We usually perform surveillance every 3-5 years; and (4) Given the risk for metachronous duodenal lesions, patients with FAP should undergo routine surveillance every 3 years.

CONCLUSION

Advances in endoscopy, EUS and ERCP have influenced the management to patients with ampullary lesions. Endoscopic ampullectomy has replaced surgical interventions for the treatment of ampullary adenomas without ductal extension. Endoscopic ampullectomy has lower morbidity and mortality rates than surgical approaches. Disadvantages include: difficult technique, few experienced endoscopists, several procedures to achieve total resection, moderate recurrence rates (30%), and, as with surgical ampullectomy, the need for postprocedure endoscopic surveillance. The best technique for endoscopic ampullectomy is subject to the adenoma size. En bloc resection is recomended for lesions confined to the papilla. Endoscopic ampullectomy is an effective and safe treatment for ampullary adenomas in experienced endoscopist but, the endoscopist must be alert to potential complications. Long-term follow-up information is required to clarify the appropiate surveillance interval for patients with sporadic ampullary adenomas.

ACKNOWLEDGEMENTS

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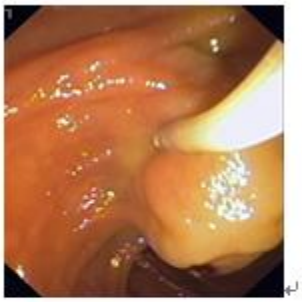
Footnotes

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Figure Legends

A

B



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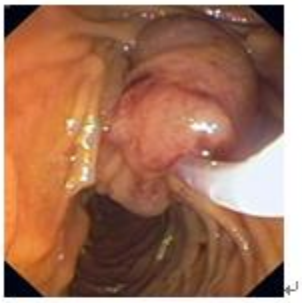

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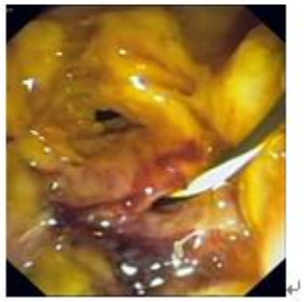

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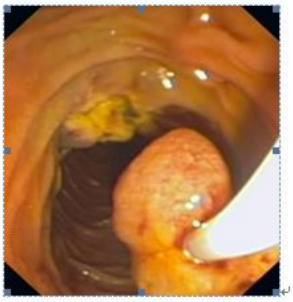

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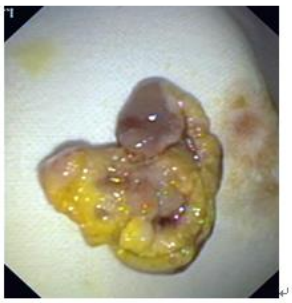

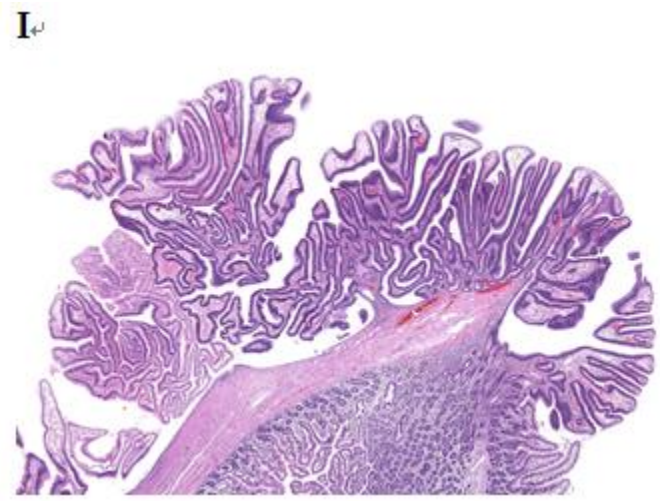

Figure 1 Technique of en-bloc ampullectomy. A: Lesion is identified; B: Submucosal (saline + epinephrine) injection; C: With the snare tip anchored above the papillary mound the entire papilla is snared; D: Check mobility and ensure the snare is firmly closed; E: En-bloc ampullary resection. Biliary and pancreatic (guidewire) orifice is identified; F: Biliary and pancreatic stents are placed. Adjuvant APC therapy is applied; G: Tissue retrieval with the snare; H: Ampullectomy specimen; I: Ampullary adenoma: tubulovillous architecture that shows neoplastic epithelial cells with pseudostratified and enlarged hyperchromatic nuclei. Adjacent there is normal duodenal mucosa. (HE, 20 ×). (Courtesy of Mercedes Hernando, MD). APC: Argon plasma coagulation.

Table 1 Recommended intervals for endoscopic surveillance after ampullectomy

	Surveillance
No residual polyp after the primary resection	3 mo later
If negative result for residual adenoma	1 yr later
Beyond this	every 3-5 yr
Patients with FAP	every 3 yr

FAP: Familial adenomatous polyposis.