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REVIEW

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Endoscopic ampullectomy: a technical review

Jesús Espinel[1], Eugenia Pinedo[2], Vanesa Ojeda[3] and María Guerra-del-Río[4]

[1]Department of Digestive Diseases and [2]Department of Radiodiagnosis. Hospital Universtario de León. León, Spain. [3]Department of Digestive Diseases. Hospital Universitario de Gran Canaria Doctor Negrín. Las Palmas de Gran Canaria, Spain. [4]Burton Hospitals NHS Foundation Trust. Burton on Trent, United Kingdom

ABSTRACT

Background and aim: This article provides a practical review to undertaking safe endoscopic ampullectomy and highlights some of the common difficulties with this technique as well as offering strategies to deal with these challenges.

Methods: We conducted a review of studies regarding endoscopic ampullectomy for ampullary neoplasms with special focus on techniques.

Results: Accurate preoperative diagnosis and staging of ampullary tumors is imperative for predicting prognosis and determining the most appropriate therapeutic approach. The optimal technique for endoscopic ampullectomy is dependent on the lesions size. En bloc resection is recommended for lesions confined to the papilla. There is no significant evidence to support the submucosal injection before ampullectomy. There is no consensus regarding the optimal current and power output for endoscopic ampulectomy. The benefits of a thermal adjunctive therapy remain controversial. A prophylactic pancreatic stent reduces the incidence and severity of pancreatitis post-ampullectomy.

Conclusions: Endoscopic ampullectomy is a safe and efficacious therapeutic procedure for papillary adenomas in experienced endoscopist and it can avoid the need for surgical intervention.

Key words: Papillary tumors. Ampullary adenoma. Endoscopic ampullectomy. Endoscopic ultrasound.

INTRODUCTION

Lesions of the ampulla of Vater are unusual. Benign neoplasms of the ampulla of Vater represent < 10% of periampullary neoplasms, most of which are malignant tumors arising from the duodenum, ampulla or pancreas (1-3). Ampullary adenomas have the potential for malignant transformation to ampullary carcinomas by an adenoma-to-carcinoma sequence as seen elsewhere in the gastrointestinal tract. The widespread use of esophago-gastroduodenoscopy (EGD) and ultrasonography (US) has contributed to the detection of ampullary neoplasms. Papillary adenomas can develop sporadically or in patients with familial adenomatous polyposis (FAP). Patients diagnosed with an ampullary adenoma have three therapeutic options: pancreaticoduodenectomy, surgical local excision or endoscopic ampullectomy (EA). 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). Limited data support particular techniques for endoscopic resection of ampullary tumors (e.g.: type of snare, electrocautery settings, use of pancreatobiliary sphincterotomy). The endoscopist should be familiar with the indications, advantages, and limitations of endoscopic ampullectomy in the management of these lesions. Precise preoperative evaluation of tumor staging is mandatory for marking therapeutic decisions. This paper provides a practical review to undertaking safe endoscopic ampullectomy and highlights some of the common difficulties with this technique as well as offering strategies to deal with these challenges. The PubMed and MEDLINE databases were used to search for publications through 2014 related to endoscopic resection of ampullary neoplasms with the following key words: ampulla of Vater, major duodenal papilla, endoscopic papillectomy, and endoscopic retrograde cholangiopancreatography.

LESION ASSESSMENT AND STAGING

Accurate preoperative diagnosis and staging of ampullary tumors is imperative for predicting prognosis and determining the most appropriate therapeutic approach.

Endoscopic evaluation

Endoscopic inspection with a forward-viewing endoscope is inadequate for endoscopic evaluation. The best endoscopic inspection of the ampulla 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 (21). 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 forceps biopsies have high sensitivity (> 90%) for confirming the presence of adenoma but lower sensitivity for confirming adenocarcinoma, missing the diagnosis in up to 30% of cases (11,22-24). Thus, as a general rule, the absence of carcinoma on endoscopic biopsy specimens in the setting of an ampullary adenoma does not exclude the presence of a focus of adenocarcinoma (24-29). The accuracy of endoscopic biopsies can be enhanced when additional techniques are employed. Thus, taking biopsies several days after sphincterotomy (30), and taking at least six biopsies, minimizes the chance of false negative results (31). Despite its gaps, endoscopic forceps biopsy is the mainstay of pre-excisional histologic evaluation of patients with an ampullary neoplasm. However, we should remember that resection of all ampullary adenomas may be the only way to truly exclude foci of malignancy.

Endoscopic retrograde cholangiopancreatography (ERCP) is an important part of the pretreatment staging of ampullary adenomas since tumor involvement of the pancreatic or bile duct significantly reduces the likelihood of complete resection by endoscopic resection (Fig. 1). ERCP at the time of endoscopic papillectomy permits:

a) evaluating the intraductal extension; b) deploying a prophylactic pancreatic duct stent to minimize the risk of post-ERCP pancreatitis after ampullectomy, and c) deploying, if required, a biliary duct stent for the palliation of obstructive jaundice.

Endoscopic ultrasound (EUS)

EUS is a useful adjunct to ERCP to assess for infiltration of the periampullary wall layers and pancreatobiliary ducts but it does not have to be universally incorporated into the diagnostic evaluation of an ampullary adenoma (27,32-39). The precise role of EUS in the management of ampullary adenomas is unclear. There is no agreement about whether all patients with ampullary adenomas should undergo EUS before therapy. Some experts propose that lesions less than 1 cm in diameter or those that do not have suspicious signs of malignancy (ulceration, induration, bleeding) do not require ultrasonographic evaluation before endoscopic removal (49). Others conversely claim that, if available, EUS examination should be considered before endoscopic or surgical resection is performed (41) (Fig. 2). EUS is reportedly helpful in identifying non-invasive lesions suitable for local resection, but no preoperative test has been proven to be accurate enough to substitute for clinical judgment and intraoperative pathological confirmation (27,42). A recent retrospective review of patients who underwent preoperative EUS to determine the accuracy of this technique concluded that EUS can accurately predict depth of mucosal invasion in the preoperative evaluation of
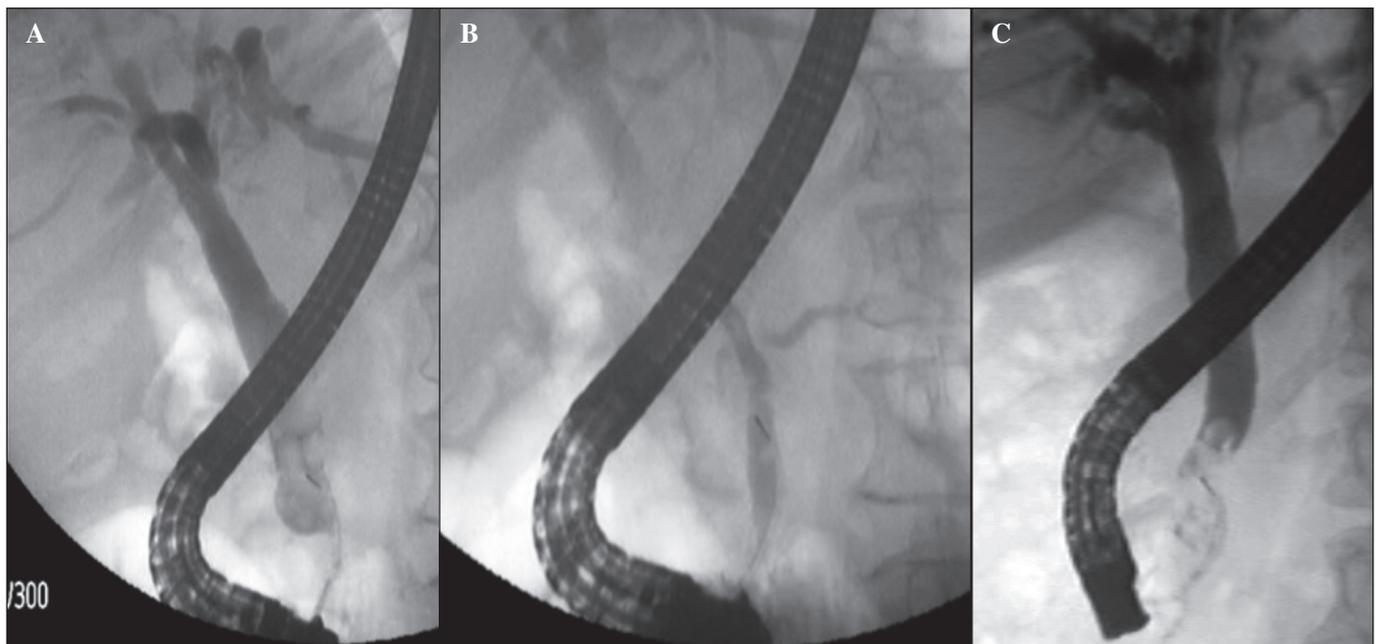

Fig. 1. ERCP evaluation of the biliary and pancreatic ducts. A and B. No evidence of tumor involvement in biliary and pancreatic ducts, respectively. C. Adenoma ingrowth into the biliary duct.

Fig. 2. Endoscopic ultrasonography (mass in the ampulla). Hypoechoic mass with invasion of the duodenal muscularis propria layer and the pancreatic parenchyma (T3) (courtesy of A. Repiso, M.D.).

suspected peri-ampullary and duodenal adenomas (specificity of 88% and negative predictive value of 90%) (35). However, EUS is an invasive technique, operator dependent, with different rates of over-diagnosis and under-diagnosis (43,44). A recent meta-analysis and a systematic review concluded that EUS has a moderate strength of agreement with histopathology in: preoperative staging of ampullary neoplasm, predicting tumor invasion and lymph node involvement (45). The modest sensitivity (77%) and specificity (78%) in predicting T1 lesions suggest that EUS is suboptimal in selecting patients suitable for endoscopic papillectomy. The pooled sensitivity and specificity for detecting nodal invasion was 70% and 74%, respectively. We believe, as other authors do, 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.

Radiologic evaluation

Magnetic resonance cholangiopancreatogrephy (MRCP) allows for non-invasive assessment of the distal common bile duct (CBD) and pancreatic duct (PD) to detect for ductal dilatation, the degree of intraductal extension (IDE) and anatomical variants such as pancreas divisum. In this case, attempts at post-resection pancreatic duct stenting may prove unsuccessful. MRCP accuracy is about 80% (38).

ENDOSCOPIC AMPULLECTOMY

Endoscopic ampullectomy (EA) was first described in 1983 by Suzuki et al. (41) and the first large case series were described in 1993 by Binmoeller et al. (4). More recently, many other series have reported low morbidity and mortality with endoscopic therapy (7-19). However, the role of endoscopic ampullectomy remains controversial and it is generally performed only in reference centers with expertise in interventional endoscopy. Endoscopic ampullectomy may be considered in patients with smaller lesions (less than 3 cm in size) that do not contain carcinoma and in patients who are poor surgical candidates. Endoscopic features such as firmness, ulceration, nonlifting with attempted submucosal injection to create a submucosal fluid cushion, and friability suggest possible malignancy and such lesions should be considered for surgical resection even in the absence of malignancy on biopsy specimens (6).

ENDOSCOPIC AMPULLECTOMY TECHNIQUE

Endoscopic ampullectomy is an advanced therapeutic intervention which must be undertaken by an endoscopist with enough training and expertise (Fig. 3). Complete en bloc excision of the entire neoplasm should be the goal with ampullary adenomas. Initially, the endoscopist must determine whether resection of the entire lesion in one piece ("en bloc") is feasible and locate the margins of the

Fig. 3. *En bloc* ampullectomy technique. A. Ampullary adenoma is identified. B. The entire lesion is snared. C. En bloc adenoma resection. D. Biliary sphincterotomy.

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 (46). It has been postulated that this technique can reduce recurrence rates, bleeding and perforation. However, comparative trials are lacking (13).

Submucosal injection

The role of submucosal injection of saline, which may be combined with epinephrine or methylene blue before ampullectomy, is controversial (6,44,47). Epinephrine and methylene blue may help minimize bleeding and enhance endoscopic visualization of the lesions margins, respectively. Local saline injection may increase technical success and decrease complications similar to mucosectomy (13,48). However, this technique is not recommended by other authors because submucosal saline injection may involve certain disadvantages: a) the center of the ampullary lesion is tethered down by the biliary and pancreatic ducts, and it may not lift; b) injection may create a dome effect and make effective snare placement for en bloc resection more difficult (13,48-50); and c) there are reports of increased risk of postresection pancreatitis. Currently, there is no significant evidence to support the submucosal injection before ampullectomy. A possible indication may be lesions with predominant lateral extrapapillary extension (50).

Endoscopic ampullary resection

There is no consensus as to which type of snare should be used for endoscopic ampullectomy. Snare size should be closely adapted to the size of the target. Oval or hexagonal snares of approximately 15 mm x 30 mm are ideal for most conventional adenomas. Standard braided polypectomy snares are typically used. Some authors recommend the use of a thin wire snare which maximizes current density for swift transection of the papilla, limiting dispersion of the energy and risk of injury to the pancreatic orifice (50). Occasionally, the use of electrosurgical needle knife to make a circumferential incision around the lesion may facilitate the snare capture (6). To resect the lesion, the snare tip is anchored above the apex of the papilla, the snare is then carefully opened and drawn down over the papilla. Then, the snare is closed maximally and, after previously checking for papilla mobility, the lesion is sectioned by continuous application of current.

Optimal electrosurgical current

There is no consensus regarding the optimal current and power output for endoscopic ampullectomy. Some investigators advocate the use of pure-cutting current (4,15,51) to avoid edema caused by the coagulation mode, although a pure cutting current has also been reported to be associated with bleeding. Others, using a blended electrosurgical current (4,6,9) or alternating cut/coagulation modes (6,44,52). Power output ranges from 30 to 150 W (6,9,13,51,53). Most experts advocate a blended current (54). We use Erbe electrosurgical generators with the setting of Endocut, effect 2 (55).

Recovery of resected specimens

All specimens should be retrieved for histological assessment. An anti-peristaltic agent (e.g.: hyoscine butylbromide or glucagon) should be given just prior to ampullectomy to prevent distal migration. 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, a retrieval net or the snare that was used for the excision are ideal. During the exchange of accessories, the resected specimen can be held using endoscopic suction to prevent tissue migration. Nevertheless, the specimen should not be aspirated through the accessory channel of the duodenoscope into a trap because this could lead to break of the specimen. Once retrieved, the specimen can be pinned to a polystyrene block to aid orientation and facilitate margin analysis.

Thermal tissue ablation

After specimen retrieval, the duodenoscope is reintroduced to examine the resection site for: a) active bleeding or bleeding stigmata; and b) 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 around the duct orifices may be difficult to excise entirely. However, the benefits of this adjunctive therapy remain controversial, with overall success rate, in a large series, similar in patients who had adjuvant thermal ablation (81%) compared with those who did not (78%) (9). Ablation can be performed with monopolar coagulation (31,48), bipolar coagulation (48), Nd: YAG laser (11,48,56), photodynamic therapy (11), and argon plasma coagulation (APC) (13,48). We prefer to use APC (setting of 40 to 50 watts) to ablate residual tissue. We perform a biliary sphincterotomy prior to fulguration to lay open the lower end of the bile duct, and we place a pancreatic stent before thermally coagulating around the pancreatic orifice.

Sphincterotomy and stent placement

The aim with a biliar or pancreatic sphincterotomy and placement of a stent is to enhance the technical success and decrease the complications of endoscopic ampullectomy (4,13,48,57-59). However, a preresection sphincterotomy has some drawbacks. First, it may interfere with subsequent en bloc resection and will hinder complete histologic evaluation of the resected specimen as a result of thermal injury. Secondly, it may increase risks of perforation, bleeding and tumor seeding (60). Normally, a careful observation of the resection site allows identification of focal biliary and pancreatic orifices within the duodenal wall. Otherwise, secretin can be infused to induce juice flow to better identify the orifice and facilitate the cannulation. The first priority after resecting the papilla is to place a prophylactic pancreatic stent to reduce the incidence and severity of pancreatitis (6,9,50,61,62). Therefore, it is advisable to place a sort 5 French pancreatic stent after ampullectomy so that the pancreatic hole can be protected (52). If ERCP or prior MRCP have demonstrated a pancreas divisum, pancreatic duct stenting is usually not necessary. Acute cholangitis after endoscopic ampullectomy is infrequent (54), and prophylactic biliary stenting is generally not necessary. However, we often perform either a biliary sphincterotomy or a prophylactic biliary stent is placed to minimize this probability. Also biliary stenting may ensure the correct bile drainage if significant bleeding occurs. The pancreatic and biliary stents are generally removed two or three weeks later, at which time any suspicious-appearing residual adenomatous tissue can be removed to ensure complete excision.

COMPLICATIONS OF AMPULLECTOMY

Complications after endoscopic ampullectomy include pancreatitis (0%-25%), bleeding (0%-25%), perforation (0%-4%), cholangitis (0%-2%), and papillary stenosis (0%-8%) (4,6,9,11,13,44,63-65) (Table I). The most serious complications are perforation, pancreatitis and delayed bleeding (44). The overall complication rate is about 15% (4,11,31,48,58). Procedure-related mortality after ampullectomy has been reported but, is very rare, occurring in 0.3% (54).

Pancreatitis. As it was previously mentioned, placement of a prophylactic pancreatic duct stent is recommended to reduce the rate and severity of post ampullectomy pancreatitis (66). This maneuver is the accepted standard. If acute pancreatitis occurs, their management is similar to other post-ERCP pancreatitis.

Bleeding. The duodenum is highly vascular. Acute bleeding can usually be managed with endoscopic hemostatic techniques (e.g.: clipping, adrenaline injection, APC) (67). If major bleeding is anticipated, then biliary stenting is helpful to prevent obstructing hemobilia. If massive bleeding occurs, urgent arteriography with embolization is initially preferred to surgical exploration. In patients with a high risk of cardiovascular events aspirin may be continued; however, all other anti-platelet agents and anti-coagulants should be discontinued.

Table I. Complications after endoscopic ampullectomy

Published series (year)	No.	Bleeding (%)	Pancreatitis (%)	Perforation (%)	Cholangitis (%)	Stricture (%)	Mortality (%)
Binmoeller (1993) (4)	25	8	12	0	0	0	0
Martin (1997) (21)	14	7	7	0	0	0	1
Vogt (2000) (63)	18	11	11	0	0	0	0
Zadorova (2001) (12)	16	13	13	0	0	0	0
Desilets (2001) (13)	13	0	8	0	0	0	0
Norton (2002) (14)	26	0	15	4	0	8	0
Han (2006) (68)	33	18	0	3	3	9	0
Catalano (2004) (9)	103	2	5	0	0	3	0
Cheng (2004) (6)	55	7	9	2	0	4	0
Bohnacker (2005) (15)	106	13	12	0	0	0	0
Harewood (2005) (61)	19	0	16	0	0	0	0
Okano (2007) (43)	20	30	15	0	5	-	0
Irani (2009) (44)	102	5	10	2	1	3	0
Boix (2009) (17)	21	5	19	0	0	0	0
Yamao (2010) (59)	36	8	8	0	3	0	0
Espinel (2013) (55)	10	10	0	0	0	0	0
Total (%)	617	8.5	10	0.6	0.7	1.6	0.2

Perforation. Perforation is usually retroperitoneal. Therefore, if perforation is suspected (ongoing pain, endoscopic features) a computed tomography with oral contrast is more sensitive than simple radiology. Not all cases of perforation require surgical intervention, selected cases may be managed conservatively (gut rest and intravenous antibiotics) (6,14). Anyway, a multi-disciplinary management between surgical and medical teams is mandatory to reach the best clinical outcome.

ENDOSCOPIC OUTCOMES

The success rates for endoscopic removal of ampullary adenomas range from 45%-90%, with recurrence rates of 0%-30% (9,68). Intraductal adenoma growth had less favorable outcomes compared with adenomas without intraductal growth (15). Predictors of success include: 1) age greater than 48 years; 2) male sex; 3) lesion size ≤ 25 mm; and 4) absence of a genetic predisposition to adenoma formation (e.g.: familial adenomatous polyposis) (48).

ENDOSCOPIC FOLLOW UP AND SURVEILLANCE

After ampullectomy, patients should remain fasting for 4-12 hours post procedure and then commence on a clear liquid diet. If they are well, they are then discharged home on a clear fluid diet and later continue with a normal diet. To minimize the risk of pancreatic ductal injury, the pancreatic stent should be removed within two or three weeks.

Adenoma recurrence has been reported in up to 25% of cases despite presumed complete removal during the index procedure (6,9,54). In the absence of symptoms, surveillance endoscopy can be completed using a side-viewing endoscope (Fig. 4). Intervals vary based on the histology and margin status of the resected lesion, history of FAP, patient age and comorbidities. So, the recommended intervals are: a) if there was no residual polyp after the primary resection, endoscopy 3 months later; b) if the result is negative for residual adenoma, surveillance 1 year later; c) beyond this, the yield of long-term surveillance in sporadic ampullary adenomas is unknown. We usually perform surveillance every 3-5 years; and d) given the risk for metachronous duodenal lesions, patients with FAP should undergo routine surveillance every 3 years.

CONCLUSION

Endoscopic ampullectomy may replace surgical interventions for the treatment of ampullary adenomas in selected cases. Endoscopic ampullectomy has lower morbidity and mortality rates than surgical approaches. The optimal technique for endoscopic ampullectomy is dependent on

Fig. 4. Surveillance by endoscopy. Endoscopic view of ampullectomy site.

the lesions size. En bloc resection is recommended for lesions confined to the papilla. Endoscopic ampullectomy is a safe and effective therapy for papillary adenomas in experienced endoscopist but the endoscopist must be alert to potential complications. Disadvantages include limited availability of experienced operators, procedural complexity sometimes requiring adjunctive modalities such as thermal ablation, the need for multiple procedures to achieve complete excision, recurrence rates approaching 30%, and the need for postprocedure endoscopic surveillance. Long-term follow-up data are needed to clarify the appropriate surveillance intervals for patients with ampullary adenomas.

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