

Diagnosis and management of ampullary adenoma: The expanding role of endoscopy

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Abstract

Ampullary adenoma is a pre-cancerous lesion arising from the duodenal papilla that is often asymptomatic. It is important to distinguish whether the adenoma is sporadic or arises in the setting of familial adenomatous polyposis as this has important implications with respect to management and surveillance. Multiple modalities are available for staging of these lesions to help guide the most appropriate therapy. Those that are used most commonly include computed tomography, endoscopic ultrasound, and endoscopic retrograde cholangiopancreatography. In recent years, endoscopy has become the primary modality for therapeutic management of the majority of ampullary adenomas. Surgery remains the standard curative procedure for confirmed or suspected adenocarcinoma. This review will provide the framework for the diagnosis and management of ampullary adenomas from the perspective of the practicing gastroenterologist.

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Key words: Ampullary adenoma; Ampullectomy; Duodenal papilla; Familial adenomatous polyposis; Papillectomy

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INTRODUCTION

Ampullary adenomas are glandular dysplastic lesions that arise in and around the duodenal papilla. Adenomatous tissue has been found in up to 90% of resection specimens of ampullary adenocarcinoma, suggesting that these lesions have pre-malignant potential^[1-6]. Autopsy series have estimated the prevalence of ampullary adenoma to be 0.04% to 0.12%^[7,8]. They may occur sporadically or in the setting of familial adenomatous polyposis (FAP). Patients with FAP almost invariably develop duodenal adenomas and have a risk for ampullary carcinoma that is 124-fold greater than the general population^[3,9,10]. In fact, ampullary carcinoma is the most common malignancy and leading cause of death in FAP patients who have previously undergone colectomy^[11-16]. Consequently, surveillance upper endoscopy is an important aspect of management for these patients. Ampullary adenomas are more frequently being recognized because of the increased availability of endoscopy for evaluation of gastrointestinal-related symptoms as well as surveillance programs for patients with FAP. Multiple modalities are now available for diagnosing and staging these lesions. Therefore, a good understanding of the diagnostic and therapeutic options available is essential for making an informed management decision.

Historically, ampullary adenomas were removed by radical surgery. Endoscopic advances in recent years have

shifted the paradigm of treatment toward attempted endoscopic resection prior to consideration of surgery because endoscopy is less invasive and has lower morbidity. Nevertheless, the complications associated with endoscopic removal of ampullary adenomas are high compared to other endoscopic therapies, making it imperative that it be performed in experienced hands. In patients with ampullary adenocarcinoma, surgery remains the standard curative therapy, but endoscopy can provide adequate palliation in cases where the patient is deemed not to be a surgical candidate. This review will discuss the clinical manifestations, diagnosis, and management of ampullary adenomas, with particular focus on the endoscopic management of these lesions.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Clinical presentation

Ampullary adenomas are often asymptomatic and incidentally discovered on endoscopy. Patients may present with symptoms related to obstruction of the biliary or pancreatic duct. These symptoms may include jaundice from biliary obstruction, which in rare instances progresses to cholangitis^[17,18]. Acute recurrent pancreatitis may result from pancreatic duct obstruction^[19]. Other non-specific symptoms may include nausea, vomiting, abdominal pain, and weight loss. Significant weight loss in a patient with an ampullary lesion should alert the clinician to the possibility of a more invasive process.

Diagnosis

The diagnosis of ampullary adenoma is based on endoscopic appearance and histology. In order for endoscopic evaluation of the lesion to be complete, a side-viewing endoscope is necessary. Endoscopic features suggesting that these lesions are benign include regular margins, no ulceration, soft consistency, and no spontaneous bleeding^[20,21]. Confirmation of adenoma is necessary with biopsy of the suspect lesion. The accuracy of forceps biopsy has been questioned due to several factors. Intra-observer variability exists between pathologists in interpreting the histologic specimen, making it particularly important to have the specimen reviewed by an experienced pathologist prior to deciding to undergo therapeutic intervention. In addition, forceps biopsy may not take a representative sample of the lesion and may miss foci of adenocarcinoma within adenomatous tissue. Bellizzi *et al.*^[22] recently reported a diagnostic agreement of only 64% when comparing biopsy samples to the eventual resected specimen. Forceps biopsy has been associated with accuracy rates of 62% to 85% in other series^[23-27]. Therefore, final histologic assessment should be based on the resected specimen.

Staging

Once adenoma is confirmed by biopsy, further evalua-

tion is necessary to help dictate management decisions. Modalities that may be used include trans-abdominal ultrasound (US), computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), endoscopic US (EUS), and intraductal US (IDUS).

Both trans-abdominal US and CT do not adequately visualize the ampullary area for staging of adenomatous lesions. Their primary role is to identify biliary and pancreatic ductal dilation. In cases of ampullary adenocarcinoma, CT can also provide valuable information by identifying locoregional lymphadenopathy and distant metastatic lesions.

EUS can provide information regarding the depth of the ampullary lesion as well as locoregional lymph node status. Multiple studies have shown that EUS is superior to CT, MRI, and transabdominal US in local peri-ampullary tumor staging^[28-30]. IDUS is a newer imaging modality that was originally developed to visualize arterial structures in various pancreaticobiliary diseases. IDUS has higher resolution than EUS because of the use of high frequency waves (20-30 MHz) compared with EUS (7.5-10 MHz). Several studies have reported increased accuracy in staging of ampullary neoplasms with IDUS as compared to EUS^[31-34]. Nevertheless, IDUS is not routinely performed as part of the ampullary adenoma staging, mainly due its lack of availability at many centers.

MRCP is typically reserved for patients with bile duct abnormalities previously identified on CT or US that need further clarification prior to more invasive investigative studies. ERCP is performed to visualize the extent of the ampullary lesion into the biliary or pancreatic duct as well as to perform decompression if there is evidence of obstruction. Given the sensitivity of other modalities now available for initial staging, ERCP with both biliary and pancreatic duct evaluation is usually performed immediately preceding possible endoscopic therapeutic intervention in the same session^[35]. The use of cholangiopancreatography at the time of ERCP to evaluate for intraductal spread of the adenoma has also been described^[36].

ENDOSCOPIC THERAPY

An important distinction when considering the appropriate management for newly diagnosed ampullary adenoma is whether the adenoma is sporadic or arises in the setting of FAP. Patients with FAP often have multiple duodenal polyps. Spigelman *et al.*^[11] devised a classification system for duodenal polyps in the upper gastrointestinal tract in the setting of FAP (Table 1). Severity of polyposis is assessed by assigning a score (1-3) in each of four categories. Spigelman stage is then determined by the sum of the four categories (Stage 0: Score 0, Stage I: Score 1-4, Stage II: Score 5-6, Stage III: Score 7-8, Stage IV: Score 9-12). Traditionally, patients with Spigelman stage 0-III are followed with close endoscopic surveillance programs, while those with stage IV undergo more ag-

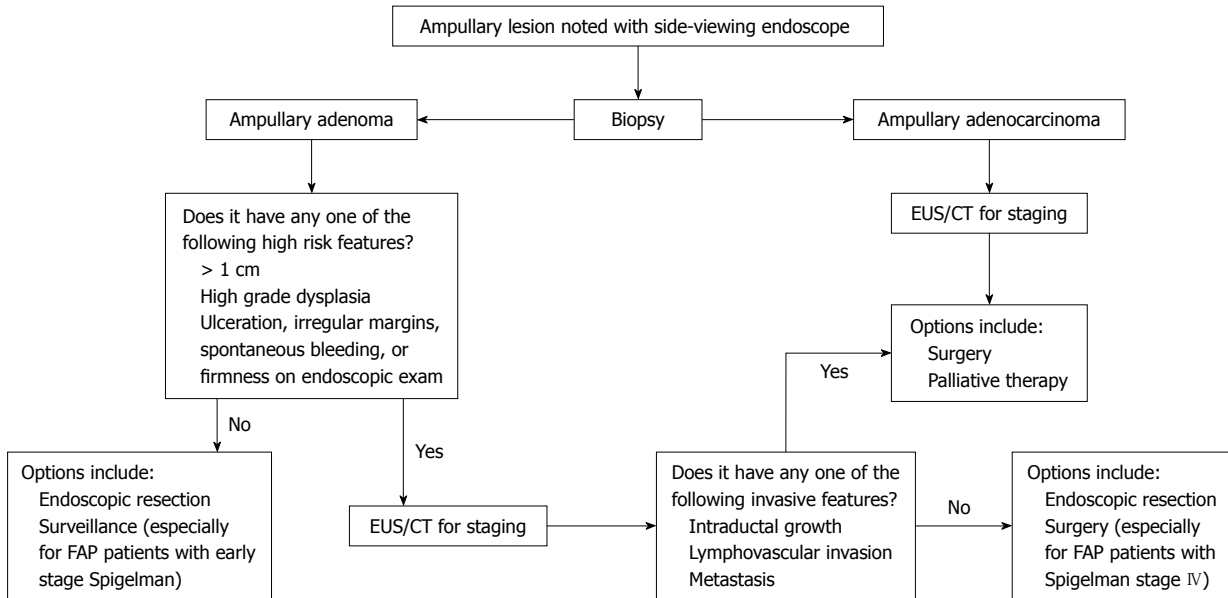


Figure 1 Suggested algorithm for management of ampullary lesion noted with side-viewing endoscope. FAP: Familial adenomatous polyposis; EUS: Endoscopic ultrasound; CT: Computed tomography.

Table 1 Spigelman classification of duodenal polyps in familial adenomatous polyposis

| | Score | | |
|---------------|----------|---------------|---------|
| | 1 | 2 | 3 |
| No. of polyps | 1-4 | 5-20 | > 20 |
| Size (mm) | 1-4 | 5-10 | >10 |
| Histology | Tubulous | Tubulovillous | Villous |
| Dysplasia | Mild | Moderate | Severe |

gressive therapy. In FAP, endoscopic resection has not been shown to decrease the need for eventual pancreaticoduodenectomy, as the malignancy risk is related to the extent of polyposis within the duodenum and not just the ampullary lesion^[20,37]. Interestingly, studies have found that the progression in Spigelman classification categories over time has more to do with the increase in size and number of polyps as opposed to changes in histology^[38].

A suggested algorithm for the management of newly diagnosed ampullary adenoma is shown in Figure 1. Given the heterogeneity of the lesions and patient population, it is difficult to set out guidelines that would encompass all possible scenarios, so each case must be taken on an individual basis. Advances in endoscopic therapy have allowed clinicians to be more aggressive in endoscopic resection of adenomas and there have even been case reports of focal ampullary adenocarcinomas removed endoscopically^[21,39-43]. Most clinicians would agree that patients with known ampullary adenocarcinoma should be offered surgery if they are deemed appropriate surgical candidates. On the other hand, management of high grade dysplasia (HGD) is a controversial topic. A retrospective review of 23 patients who had endoscopic resection for what turned out to be HGD or focal T1 ampul-

lary adenocarcinoma found that none of these patients had residual tumor on follow-up endoscopy or surgically resected specimen^[44]. Therefore, the authors concluded that endoscopic resection is appropriate management for ampullary adenomas with HGD. Other investigators have advocated endoscopic resection for HGD if the tumor is only intraductal, and in situations where intraductal growth is less than 1 cm^[45]. Proponents of radical surgery for HGD point to several studies that underlie the fact that diagnostic yield for picking up foci of adenocarcinoma and lymphovascular invasion pre-operatively is sub-optimal^[46,47].

Endoscopic resection technique

Endoscopic removal of ampullary adenomas remains non-standardized and highly variable, which reflects the relatively small number of formal investigations into this topic. Furthermore, there is no uniform agreement on the terminology used to describe various resection modalities. The terms papillectomy and ampullectomy are frequently used interchangeably but some authors restrict the use of “papillectomy” for endoscopic resection and “ampullectomy” for surgical resection^[48]. The following is a discussion of the most commonly used endoscopic resection techniques based on a review of the literature and our experience.

Submucosal injection prior to papillectomy may be performed similar to the technique used when performing endoscopic mucosal resection for colorectal polyps. The failure of a lesion to manifest a “lift sign” is associated with malignancy and is considered a contraindication to attempts at complete endoscopic removal^[49,50]. It is speculated that injection of epinephrine may also decrease the risk of bleeding during resection. Most commonly injected fluids include saline and epinephrine,

although methylene blue and viscous material such as hydroxypropyl methylcellulose and sodium hyaluronate have also been used^[3,43,49-54]. Successful endoscopic resection of adenomas has also been described without the use of submucosal injection^[40,55,56]. In fact, we generally avoid submucosal injection at our institution for two main reasons. One is the concern that injection may distort the ampullary anatomy due to the “anchoring” effect from the bile and pancreatic duct running through the lesion, creating a central depression at the site of the ampullary opening. Second, injection may create a “dome” effect and make effective snare placement for *en bloc* resection more difficult.

Endoscopic papillectomy is performed by the use of endoscopic snares and electrocautery. Standard or “braided” polypectomy snares are typically used, although fine wire snares specifically designed for ampullary resection are available^[3,50,57]. If the lesion can be completely ensnared, *en bloc* resection with electrocautery may be performed. This has the advantage of shortened procedure time, reduced use of electrocautery, and providing complete tissue specimen for pathologic examination. Some authors have described the use of an electrosurgical needle knife to make an incision circumferentially around the lesion to facilitate snare capture^[3]. Piecemeal resection is sometimes necessary for lesions larger than 2 cm or in cases where visible tissue is left in place with *en bloc* technique. The type of current and power settings used for ampullary resection are variable. Many authors describe the use of blended current, whereas others utilize pure-cutting current^[58-60]. Few have also described the use of pure coagulation current^[50].

The role of ablative therapies [argon plasma coagulation (APC), laser, bipolar electrocautery] is mainly to destroy any remaining tissue that may be left following snare resection of a specimen. APC is most frequently used for this purpose. The main disadvantage in using this technique is tissue that is ablated cannot be retrieved for pathology review. In fact, some clinicians avoid the use of APC altogether primarily for this reason^[35]. Catalano *et al.*^[58] reported their results from 103 papillary resections and found no difference in overall rate of success or recurrence in patients who did and did not have APC.

Pancreatic or biliary sphincterotomy is often performed following papillectomy, with the goal of improving pancreaticobiliary drainage. One of the known complications of papillectomy is pancreatitis. Placement of a pancreatic duct stent following ampullary adenoma resection has been found to reduce the incidence of post-ERCP pancreatitis based on a meta-analysis of five prospective series^[61]. Recently, a randomized control trial also showed a decrease in the rate of pancreatitis in patients who received a pancreatic duct stent^[62]. Some authors perform sphincterotomy and placement of pancreatic duct stent prior to resection^[21,50], although we favor post-resection stent placement in an attempt to maximize the opportunity for *en bloc* resection. Placement of a biliary stent to reduce the risk of post-procedural cholangitis

is infrequently performed, and mainly done if there is concern for incomplete biliary drainage despite biliary sphincterotomy^[3,50,63]. In our institution, we place a pancreatic duct stent in every patient undergoing endoscopic papillectomy as the data available strongly support its use. We reserve the use of a biliary stent only for patients that are believed to have slow drainage after biliary sphincterotomy.

Outcome

A systematic review by Han *et al.*^[48] reported the success rates for endoscopic removal of ampullary adenomas to range from 46% to 92%, and recurrence rates to range from 0% to 33%. Most recently, a large retrospective series which included 102 patients diagnosed with ampullary adenoma that underwent endoscopic resection showed a success rate of 84%^[64]. Factors affecting success in this study were smaller lesion size (< 2 cm) and the absence of dilated ducts.

Complications

Even in experienced hands, complications arising after endoscopic papillectomy are high compared to other endoscopic procedures. They include pancreatitis, perforation, bleeding, cholangitis, and papillary stenosis. In their review, Han *et al.*^[48] found a morbidity rate of 23% (range 10%-58%) and a mortality rate of 0.4% (range 0%-7%). Bleeding and pancreatitis were the most common complications. Each occurred in up to 25% of cases in one small study, although the remainder of the studies showed bleeding rates of 0% to 21% and pancreatitis rates of 0% to 15%^[48].

Surveillance

There is no consensus regarding the most appropriate surveillance interval following endoscopic resection of ampullary adenomas. Initial surveillance endoscopy is generally performed at 1 mo to 6 mo following resection. Following the initial surveillance endoscopy, the clinician may decide to follow with endoscopy every 3 mo to 12 mo for the next 2 years, and then less frequent intervals thereafter^[3,50,52,58,63,65-67]. A side-viewing endoscope should be used for surveillance purposes. One recent study suggests improved rates of detection of duodenal polyps with the use of chromoendoscopy in FAP patients^[68]. Patients with sporadic ampullary adenomas are at increased risk for colon polyps and should be offered screening colonoscopy.

NON-ENDOSCOPIC THERAPY

Surgery

Surgery had been the traditional approach for removal of ampullary adenoma before the advances related to endoscopic therapy in the last 10 to 20 years. Surgery remains the standard curative therapy for confirmed or suspected ampullary adenocarcinoma, although endoscopy can provide adequate palliation in patients deemed not to be surgical candidates.

Surgical approaches may include pancreaticoduodenectomy, surgical ampullectomy, and pancreas-preserving duodenectomy. The reason for the shift towards endoscopic removal of adenoma is related to the significant morbidity and mortality associated with radical surgery. Data from multiple series for pancreaticoduodenectomy demonstrated an operative mortality of 1% to 9% and operative morbidity as high as 41%^[69,70]. Less invasive surgical options such as surgical ampullectomy are available, but recurrence is a possibility when these less invasive surgical interventions are employed. Similar to endoscopy, these patients will also require follow-up endoscopy, whereas those who receive pancreaticoduodenectomy do not require further surveillance. FAP patients are unique in that they will require surveillance regardless of intervention given their propensity to develop adenomas throughout the duodenum.

Medical therapy

Non-invasive therapy is also an option in certain cases of diagnosed ampullary adenoma. While there is no data studying the effect of non-steroidal anti-inflammatory drugs (NSAIDs) specifically on ampullary adenomas, there is literature that studies the effect of NSAIDs on duodenal and colorectal polyps in the FAP population. The most commonly studied NSAIDs have been celecoxib and sulindac. In a randomized control trial involving 49 post-colectomy FAP patients, celecoxib was found to significantly reduce duodenal polypsis when compared to placebo^[71]. Another study involving 24 post-colectomy FAP patients found that sulindac reduced rectal polyp progression, but had no significant effect on duodenal polyp regression^[72]. Increased erosions at the anastomotic site in the NSAID group have also been reported in at least one study^[73].

CONCLUSION

Endoscopic advances in recent years have expanded the role of endoscopy in the therapeutic management of ampullary adenomas. Prior to considering therapy, clinicians should utilize the staging modalities available in order to make the most appropriate management decision for these patients. Radical surgery remains the treatment of choice for ampullary adenocarcinoma, adenomas with extensive intraductal growth, and should be strongly considered in a certain subset of FAP patients. Future studies and case experience will allow us to make more definitive guidelines with respect to appropriate treatment and surveillance for ampullary adenoma.

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