Review Article
Endoscopic management of ampullary neoplasm
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A B S T R A C T

Neoplastic lesions of ampulla, although infrequent, represent a significant portion of precancerous lesions arising within duodenum. Occurring either as sporadic, solitary lesion, or as a part of multiple adenomas within duodenum, due to its potential for malignant transformation, ampullary adenoma warrants a careful evaluation with the intention of curative resection when possible. The removal of ampullary lesion can be accomplished either surgically, or endoscopically if feasible. Here, we provide a brief review of endoscopic management of ampullary neoplasm.

Keywords: Cholangiopancreatography, endoscopic retrograde; Duodenal neoplasms; Endoscopic mucosal resection; Gastrointestinal endoscopy

Introduction

Neoplasms of ampulla of Vater is rare, with estimated 3,000 cases per annum in the United States, and accounting less than 0.5% of all neoplastic lesions arising from gastrointestinal tract.1 If left alone, however, some of these lesions can undergo malignant transformation, leading to ampullary cancer.2,3 Ampullary neoplasm can occur as sporadic, solitary lesion or as a part of hereditary syndrome, such as familiar adenomatous polyposis (FAP) syndrome. Up to 50% to 90% of patients with FAP will develop adenoma(s) within duodenum, with predilection for ampulla as the site of neoplasia formation. In those with FAP, the risk of developing ampullary cancer is greater than 100 fold of general population, and can reach up to 12% in their lifetime.4,5 Among the malignancy arising in choledochoduodenal junction (pancreatic, biliary or duodenal primary), ampullary cancer comprises up to 12% of all cancers.6

The overwhelming majority of patients with duodenal neoplasm remain clinically silent, contributing to incidental discovery in the majority of the patients, with the exception in the patients with FAP who require routine surveillance endoscopy. It is only when the size of lesion becomes prohibitive of adequate bile flow that the patients present with obstructive jaundice.7 Non-specific symptoms such as nausea, vomiting, malaise and weight loss are often signs of advanced stage of the disease.8 Pancreatitis, and cholangitis are a rare presentation of advanced stage of ampullary neoplasm.9

Traditional approach to ampullary neoplasm has been surgical resection until the turn of 20th century. Although first reported in 1983 by Suzuki et al,10 it was Binmoeller et al11 in 1993 who first reported a case series of successful endoscopic resection with curative intent. With proven track records of safety and efficacy, the endoscopic resection is currently considered first line of treatment in the appropriate subset of patients with ampullary neoplasm. While considered less invasive and associated with lower morbidity, endoscopic resection of ampullary neoplasm requires a careful pre-procedure evaluation and endoscopic technical proficiency beyond the ability to perform a simple mucosal resection.

Diagnostic Approach

Non-endoscopic evaluation

The diagnostic approaches can vary among the patients with ampullary lesion due to heterogeneity in its population. Among the patients with high risk of developing duodenal/ampullary lesion (such as FAP patients) that undergo routine surveillance. Ampullary lesions are often diagnosed prior to symptom development. In those with sporadic ampullary neoplasm, however, the characteristics of symptoms often dictate the flow of diagnostic approach. For example, among the patients with the symptoms indicative of biliary obstruction such as jaundice or biliary colic type abdominal pain, endoscopic and radiographic imaging and laboratory work up to exclude malignant process or gallstone-
related disease are performed during the initial stage of work up.

Although abdominal ultrasound can readily detect significant bile duct dilation and the presence of stone(s) within bile duct system, its sensitivity in detecting ampullary neoplasm is rather poor and significantly inferior to computed tomography (CT). Still, the sensitivity of CT scan in detecting ampullary neoplasm is highly variable, ranging from 20% to 70% with the accuracy no greater than 30%, and largely dependent upon the size of lesion. Magnetic resonance imaging (MRI) and/or magnetic resonance cholangiopancreatography (MRCP) can also provide refined details of bile duct as well as configuration of ampullary mound. In addition, MRCP can detect intraductal extension of ampullary neoplasm, which often confers to more advanced stage of disease and can potentially avert the patients from unnecessary endoscopic resection attempts. A small study from Korea reported MRI can distinguish benign ampullary lesion from malignant ones with the sensitivity and specificity of 84.2% and 86.4% respectively, if patients present with signs of biliary obstruction.

**Endoscopic evaluation**

When evaluating for ampullary neoplasm, the use of both forward-viewing gastroscope and side-viewing duodenoscope is helpful. The gastroscope readily allows the detection of synchronous neoplastic/adenomatous lesions within upper gastrointestinal tract, while the duodenoscope permits adequate visualization of ampulla (Fig. 1). Several studies have suggested a direct correlation between the size of lesion and the risk of the presence of frank malignancy. The morphological assessment with a duodenoscope is helpful in distinguishing benign neoplasm from potentially malignant one. The endoscopic features suggestive of benign lesion include 1) well-defined margin, 2) absence of ulceration or depression, 3) soft consistency of lesion, and 4) the absence of overt mucosal friability or spontaneous bleeding. Visual inspection however—although helpful—does not negate the need for the procurement of biopsy sample. In addition, there also remains significant limitation in regards to the accuracy of biopsy. While highly sensitive in the detecting the presence of adenoma, the ampullary biopsy can miss the presence of underlying carcinoma up to 30% of the time. There has been some studies that suggested acquiring biopsy after biliary sphincterotomy (after “filleting”), and taking at least six sample can reduce the risk of false negative results.

Endoscopic retrograde cholangiopancreatography (ERCP) remains as the quintessential endoscopic modality in the diagnosis and treatment of ampullary neoplasm. Not only it provides the most optimal endoscopic visualization of ampulla, cholangiogram and/or pancreatogram obtained during the procedure offers invaluable assessment for intraductal extension of neoplasm. Although some studies reported similar sensitivities between MRCP and ERCP, ERCP is more accurate in distinguishing choledocho-lithiasis in distal bile duct from neoplastic process than MRCP. The therapeutic role of ERCP in the resection of ampullary neoplasm is discussed detail in the section of endoscopic treatment for ampullary neoplasm.

**Utility of endoscopic ultrasound (EUS)**

The role of EUS has evolved from an optional adjunct to mainstream diagnostic modalities such as ERCP and MRI to a requisite for the staging of ampullary carcinoma (Table 1). Equally—if not more—sensitive than MRCP, EUS can provide information on pancreatobiliary ductal involvement, depth of tumor infiltration to duodenal wall layer, presence of concerning lymphadenopathy and also allows sample acquisition with fine needle aspiration. These information are critical when assessing the feasibility of endoscopic resection of ampullary neoplasm. Although dependent on the size of lesion, the reported accuracy of EUS in ampullary cancer staging ranges from 67% to 92%. Notably, the sensitivity and specificity of EUS in detecting T1 lesion, the tumor depth which the endoscopic resection is feasible, are 77% and 78%, respectively. Despite the room for improvement, many experts agree that the EUS should be a part of diagnostic work up to determine the feasibility of endoscopic resection, not to mention being a diagnostic requisite for those with concerning clinical (e.g., obstructive jaundice) and endoscopic features (e.g., lesion size greater than 2 cm, presence of high grade dysplasia, irregular margins, ulcerations or bleeding).

Intraductal ultrasound (IDUS) is an ultrasound probes that is passed through the working channel of therapeutic duodenoscope, generating sonographic image from within pancreatobiliary ductal lumen. As IDUS uses higher frequency than conventional EUS.
(20–30 MHz vs 7.5–12.5 MHz), the images generated from IDUS is sharper and more refined than EUS. IDUS is particularly useful when there is a concern for possible neoplastic process above the sphincter of Oddi into ductal lumen.  

Endoscopic Treatment

Patient selection

To date, no definitive guideline exists outlining optimal patient selection process for endoscopic removal of ampullary neoplasm. Indeed, although fairly similar from one another, some subtle differences exist regarding the size of lesion, depth of infiltration and the fitness of patients that can safely undergo endoscopic resection. Fig. 2 represents the management algorithm for ampullary lesion adopted in our institution.

In cases of benign lesion (i.e., adenomatous lesion with varying degree of cellular atypia without carcinoma), the size, degree of its extension into biliary or pancreatic duct (PD), involvement of surrounding duodenal wall, and depth of infiltration by the neoplasm determine the feasibility of endoscopic resection. In general, the lesions that are less than 3 cm in size, with no evidence of neoplastic extension into pancreaticobiliary ductal lumen, or involvement of muscularis propria can be considered for endoscopic resection. Although ductal involvement is considered a relative contraindication, if the residual lesion within bile duct is deemed accessible for further treatment, endoscopic resection could still be considered. In FAP patients with benign ampullary lesion, the degree of cellular atypia in synchronous neoplastic process adds another layer of consideration. As some studies suggest that duodenal cancers among FAP patients are often non-ampullary in its origin, endoscopic removal of adenomatous ampullary lesion does not appear to reduce the need for the definitive surgical treatment (pancreaticoduodenectomy). Consequently, endoscopic resection of ampullary lesion among FAP patients should be based on Spigelman classification of the patient.

If the lesion is cancerous, the detailed staging work up must ensue, including EUS and MRCP. The primary lesion classified as T0 or T1 and without the evidence of intraductal extension, or lymph node involvement, should be considered for endoscopic treatment.

Endoscopic resection technique

The endoscope of choice for endoscopic ampullectomy is side-viewing therapeutic duodenoscope. Although the basic concept of endoscopic ampullectomy is similar to that of snare polypectomy, given its delicate location and proximity to biliary and pancreatic ductal lumen, all endoscopic ampullectomy should be performed by an expert interventional endoscopists. Upon successful insertion and positioning of duodenoscope, inspection of the lesion to assess for the presence of features concerning malignancy as well as the feasibility of en bloc (in one piece) resection should follow (Fig. 3). En bloc resection permits the most accurate staging of neoplasm as its depth and lateral margin of involvement can be assessed. Furthermore, it reduces

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**Table 1** Staging Classification Criteria and Definition Based on American Joint Committee on Cancer TNM Classification, 7th Edition

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>T (primary tumor)</td>
<td></td>
</tr>
<tr>
<td>Tx</td>
<td>Unable to assess primary tumor</td>
</tr>
<tr>
<td>T0</td>
<td>Unable to visualize primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor limited to ampulla of Vater or sphincter of Oddi</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades duodenal wall</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades pancreas</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades peripancreatic soft tissue or other adjacent organs or structures</td>
</tr>
<tr>
<td>N (nodal assessment)</td>
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<tr>
<td>Nx</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node involvement</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node involvement</td>
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<tr>
<td>M (metastasis status)</td>
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</tr>
<tr>
<td>Mx</td>
<td>Metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
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</tbody>
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**Fig. 2.** Management algorithm of ampullary neoplasm. EUS, endoscopic ultrasound; CT, computed tomography; MRCP, magnetic resonance cholangiopancreatography.
the procedure time as well as the amount of electrocautery exposure. Although no definitive rules exist, an attempt for en bloc resection should be made for the lesion size less than 2 cm. If en bloc resection is deemed not feasible, piecemeal resection should be sought as the next step.

The purpose of submucosal injection is to provide an additional protective cushion between the area of electrocautery and muscularis propria, thus reducing the risk of full thickness injury. In addition, if the lesion does not lift with appropriate submucosal injection (indicated by adequate lifting of surrounding tissue but not the lesion itself), one must reconsider the feasibility of endoscopic removal, as “non-lifting” sign often indicates the infiltration of neoplasm deeper than what endoscopic resection can safely address. The choice of injectant varies, but often is a combination of saline mixed with diluted epinephrine (1:10,000–1:20,000) and some sort of coloring agent (such as methylene blue). The routine use of submucosal injection remains controversial, as some deleterious outcomes, including difficulty in identification of biliary and PD orifice, and increased risk of pancreatitis can result. In our institution, en bloc resection is routinely performed without the aid of submucosal injection.

After careful inspection and the decision on submucosal injection are rendered, cannulation and sphincterotomy follow. While pancreatic sphincterotomy and subsequent PD stent placement are routinely done to prevent post procedure pancreatitis, biliary sphincterotomy and bile duct stent placements are performed in selectively situation where delay or absence of bile flow is observed. Incidentally, some endoscopists proceed to snare ampullectomy prior to sphincterotomy due to the concern for increased risk of bleeding and theoretical difficulty of en bloc resection. However, we find it easier to place stent later on if sphincterotomy is done prior to resection as edema and inflammatory reaction at resection site can impede successful cannulation. To abate these difficulties, Moon and colleague reported wire guided ampullectomy where guidewire was inserted to PD prior to resection to assist the placement of PD stent.

During resection phase, complete capture of entire lesion by placing a thin wire or braided snare (oval or hexagonal shape) at the base of the lesion should be attempted. Typical direction of snare deployment is cranio-caudal, where the tip of snare is anchored above the apex of the papilla with the base of snare positioned at the bottom of ampulla. Due to the configuration of duodenum, visualization and securing distal margin of lesion with standard snare technique can be challenging. Target submucosal injection of caudal margin of lesion to bring the lesion toward the scope camera can assist in optimal capture of the lesion. Several studies also have demonstrated the benefit of balloon catheter assisted ampullectomy where an extraction or dilator balloon is pulled, further exposing and elevating the neoplastic tissue to its entirety.

To date, no consensus regarding type of electric current and power setting has been established. Many experts advocate blended cut which is comprised of cutting and coagulating currents delivered together in one waveform, while others favor endocut which delivers cutting and coagulating effect in turn in short bursts with an intermittent pause with ERBE generator (ICC 200EA; USA Incorporated Surgical Systems, Marietta, GA, USA). The key to minimize the risk of full thickness injury and post procedure pancreatitis is to reduce the total amount of energy during the resection.

During piecemeal resection, careful attention should to be given not to leave any “islands” of neoplastic tissue between each
resection site. When possible, the neoplastic area encompassing biliary and pancreatic orifice should be resected in one piece to minimize the amount of energy delivered, and the remainder of the neoplastic tissue can be addressed based on the discretion of the performing endoscopist. Repeated submucosal injection between the resection can aid in maintaining protective cushion between residual lesion and duodenal wall layer.

**Prophylactic stent placement**

Following ampullectomy, subsequent edema and inflammatory response can lead to stenosis of pancreatic orifice, resulting in pancreatitis.\(^6\) Currently, it is considered as the standard of practice to place a pancreatic stent to maintain the patency of PD. A short (less than 5 cm), 5-French diameter, single pigtail plastic stent is the stent of choice in our institution. In our institution, we routinely place a PD stent after ampullectomy as a careful inspection of ampullary site often reveals PD orifice, typically located at 5 o’clock position from the center of ampulla. The stent is left for one to two weeks with subsequent endoscopic removal.

While biliary sphincterotomy is common practice, the placement of bile duct stent appears to be more selective. However, it should be considered strongly in the patients with signs of poor biliary drainage, or in those with the complications of post ampullectomy bleeding where tamponading effect of stent could augment the endoscopic hemostasis.

**Residual tissue ablation**

If residual neoplastic tissue is noted upon re-inspection, the endoscopist can choose to continue with resection, or eradicate the rest of lesion with endoscopic ablation. In addition, hemostasis for any active bleeding, or a prophylactic measure to prevent bleeding can be accomplished with thermal ablation. Ablative fulguration can be obtained with monopolar, bipolar or argon plasma coagulation (APC).\(^6,10,20,40\) Because both monopolar and bipolar ablation rely on coaptive approach where the electrode is firmly pressed down to thinned wall of duodenum after the resection, there is a theoretical increase in the risk of full thickness injury and subsequent perforation with these methods. APC on the other hand, relies on non-contact ablation where the creation of plasma arc results in the destruction of superficial layer of the target tissue. Hence, APC is the most commonly used ablative method. The power setting and flow of argon gas should be adjusted as the resection site may not tolerate high flow rate, or power that may be acceptable prior to resection.

**Efficacy and Safety Outcomes**

The technique of endoscopic ampullectomy has evolved over last two decades, resulting in an improved efficacy and safety profile. The successful eradication of ampullary neoplasm should be defined based on two-phase assessments. In the early phase, the confirmation of the complete destruction of the neoplasm at the end of the procedure is required. In the late phase, persistent absence of neoplastic lesion confirmed during a follow up endoscopy (typically performed within 6 months of index procedure) is needed. The reported successful eradication rate ranges from 71% to 95% and are dependent upon several factors including the size of lesion, ductal involvement, expertise of endoscopists and concurrent co-morbidities of the patients.\(^11,15,30,41\) The reported rate of recurrence ranges from 2% to 33%.\(^5,11,15,30,41,42,44,45\) Some studies suggested the larger lesion size, longer follow up period, and lack of adjunctive thermal ablation are associated with increased risk of recurrence. Regarding the lack of thermal ablation being a culprit of neoplastic recurrence, it is plausible there is increase risk leaving small focus of neoplastic tissue when the “touch-up” by thermal ablation is not performed.\(^5\)

The range of overall complication rates reported in relevant literatures is 10% to 25%.\(^11,15,30,41\) These include pancreatitis, bleeding and perforation. The size of lesion, depth of infiltration, and the level of expertise of the performing endoscopist have all been reported as factors influencing the rate of adverse outcomes.\(^16,46\)

Pancreatitis is the most common complication of endoscopic ampullectomy.\(^11,15,30,31\) While prophylactic pancreatic stent placement has been accepted as the standard of practice, no large prospective study exists to date validating its benefit. Its use is justified largely based on its proven benefit of reducing post-ERCP pancreatitis in other indications such as management of ducal stenosis and sphincter of Oddi dysfunction, and a small, prospective, randomized control study by Harewood et al.\(^7,47,48\) The benefit of prophylactic rectal indomethacin in prevention of post-ERCP pancreatitis during a procedure where significant PD manipulation is anticipated has lent itself to routine use during endoscopic ampullectomy.\(^49\) The validation of its use during endoscopic ampullectomy, however, is yet to be offered.

Bleeding is also a common complication of endoscopic ampullectomy. Conventional endoscopic hemostasis methods such as hemoclip, thermal ablation are often adequate to provide a meaningful hemostasis. If conventional methods are not successful, or if there is a concern for hemobilia, placement of biliary stent(s) to create additional mechanical tamponade can be considered.

**Surveillance and Follow Up**

As the recurrence rates of ampullary neoplasm remain significant, a judicious surveillance plan is required. After the endoscopic ampullectomy, the first follow up endoscopy should be performed preferably within 3 months, certainly no later than 6 months.\(^50,51\) Biopsies at the ampullectomy site, even in the absence of obvious residual lesion, is routinely performed in our institution. If no recurrence is confirmed, the subsequent endoscopic surveillance can be performed every six months for one year, then annually or biennially. Once the patient is free of recurrence after 5 years, the surveillance can be done at the discretion of the performing physician.

**Conclusion**

Endoscopic ampullectomy has provides a less invasive, safer alternative to surgical resection for selective patients with ampullary neoplasms. Careful patient selection, pre-procedure planning, and the proficiency in complex endoscopic maneuvers are requisite for a successful long-term outcome. Future studies focusing on technical refinement to reduce the rate of complication and recurrence are necessary.

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

**References**


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