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The primary aim of *World Journal of Gastrointestinal Oncology* (WJGO, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc.*

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Endoscopic papillectomy for ampullary adenomatous lesions: A literature review

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Abstract

Ampullary adenomatous lesions of the gastrointestinal tract are rare and can be asymptomatic. Therefore, ampullary adenomas with malignant potential require prompt removal, regardless of whether they are adenomatous or carcinomatous lesions. Endoscopic papillectomy is a safe and effective alternative therapy to surgery to treat duodenal papillary lesions in selected patients. Accurate preoperative diagnosis and staging of ampullary adenomatous lesions are critical for predicting prognosis and determining the most appropriate therapeutic approach. Furthermore, the management and prevention of adverse events and endoscopic treatment for remnant or recurrent lesions and surveillance are essential for successful endoscopic management of ampullary adenomatous lesions. This literature review was based on PubMed and MEDLINE and focused on recent advancements in the endoscopic papillectomy technique to provide a comprehensive view of endoscopic papillectomy to treat ampullary adenomatous lesions.

Key Words: Ampullary adenomatous lesions; Endoscopic papillectomy; Endoscopic ultrasonography; Endoscopic retrograde cholangiopancreatography; Complications; Surveillance

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Core Tip: The endoscopic papillectomy for ampullary adenomatous lesions are still controversial. This review mainly focused on the recent advancements of endoscopic

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papillectomy and then introduced the indication, endoscopic evaluation, treatment and related complications and surveillance for ampullary adenomatous lesions.

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INTRODUCTION

Although rare in the gastrointestinal tract, ampullary neoplasms follow an adenoma-to-carcinoma sequence and can potentially transform into adenocarcinoma, which therefore requires prompt removal[1]. Although ampullary neoplasms may be asymptomatic, the detection of ampullary tumors has been increasing annually. It is more frequently identified at an early stage with the broader application of imaging modalities such as computed tomography, magnetic resonance imaging, magnetic resonance cholangiopancreatography, abdominal ultrasound and other advanced imaging techniques[2]. Moreover, some endoscopic examinations are helpful for the diagnosis of ampullary lesions, including esophagogastroduodenoscopy, endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP).

Pancreaticoduodenectomy and local surgical resection have been traditionally considered the treatments of choice for ampullary neoplasms because they achieve complete removal; however, they are invasive and associated with relatively high mortality and morbidity rates[3-5]. Endoscopic papillectomy (EP) was first described in 1983 by Suzuki *et al*[6], and the first large case series was reported in 1993 by Binmoeller *et al*[7]. Due to the efforts of many pancreaticobiliary endoscopists over the few years, EP has been established as an effective endoscopic therapy for the treatment of ampullary neoplasms in selected patients and has become an alternative to traditional surgical procedures[2,8]. Furthermore, the indications for EP have expanded, although they are not yet fully established. EP techniques have advanced considerably. Nevertheless, high-quality recommendations have never been established, and many challenges persist, including precise preoperative evaluation, optimal papillectomy technique and strategies to manage recurrences and adverse events.

INDICATIONS

Traditionally, the indications for EP were only benign lesions and patients who were poor surgical candidates. Following advancements in EP techniques, the indications for EP have expanded to include ampullary neoplasms such as early ampullary carcinoma, giant laterally spreading lesions and ampullary lesions with intraductal extension. Generally, ampullary adenomas with the intraductal extension of less than 10 mm are appropriate for endoscopic ampullectomy, including balloon traction technique[9]. Alternatively, surgical resection is required for lesions with more extensive intraductal involvement[10]. Recently, a study reported that ampullary tumors with ≤ 20 mm ductal extension, even in malignant forms or biliary and pancreatic involvement, could be managed by intraductal ablation[11], avoiding additional surgical treatment. The indications for ampullary carcinoma are expanding. Our study suggests that EP provides a more favorable prognosis for patients with T1a ampullary carcinoma without local lymphatic metastasis or distant metastasis; nevertheless, indications for stage T1b require further exploration, and close follow-up is necessary[2]. This conclusion was also confirmed by Yamamoto *et al*[12]. Precise preoperative evaluation of tumor staging is crucial for endoscopic therapy of ampullary lesions and is the key to determining the indications of EP.

CLINICAL EVALUATION

Most ampullary adenomas are diagnosed incidentally, and patients are asymptomatic. The most common manifestations are jaundice, chronic gastrointestinal bleeding, cholangitis, acute pancreatitis, nausea and vomiting, anorexia and weight loss. History of painless jaundice, chronic gastrointestinal bleeding and weight loss increases the index of suspicion for an underlying malignancy, and careful endoscopic examination is required.

ENDOSCOPIC EVALUATION

Manifestations alone cannot distinguish among ampullary adenomas, carcinomas and non-adenomatous polyps. Therefore, endoscopic evaluation is required. Endoscopic inspection with a side-viewing endoscope (duodenoscope) is more suitable than a forward-viewing endoscope (gastroscope) because a side-viewing endoscope can evaluate the morphological features of the lesion adequately and obtain tissue by biopsy during procedure quickly. Ulceration, friability, and spontaneous bleeding are usually associated with malignant lesions. Preoperative histological diagnosis is crucial to managing ampullary tumors. Diagnostic agreement between preampullectomy biopsy and ampullectomy ranges from 45% to 85%, with a relatively high false-negative rate[13-15]. A recent study showed that 11% of invasive carcinomas were previously undiagnosed[16]; therefore, biopsy diagnosis of adenoma does not exclude the possibility of deeper carcinoma in ampullary adenomas. Therefore, techniques that enhance the accuracy of endoscopic biopsies need to be employed. A study reported that obtaining a biopsy specimen several days after sphincterotomy and taking at least six biopsies enhanced the accuracy of endoscopic biopsies[17]. Although the false-negative rate of endoscopic biopsies is relatively high, it is an essential method for preoperative assessment of ampullary lesions, and methods and its use to improve preoperative diagnosis should be further explored.

ENDOSCOPIC STAGING

Linear and circular EUS is an essential endoscopic technique for the assessment of ampullary lesions. It is widely used in the staging and treatment of ampullary tumors. Nevertheless, there is no consensus regarding whether EUS should be used as a routine examination before EP. Some experts suggested that EUS has a limited role in small ampullary lesions (< 1 cm) without suspicion of malignancy[18,19]. However, EUS is as good as ERCP for evaluating intraductal extension and can help measure the depth of mucosal invasion in suspected benign ampullary neoplasms. The technique is also accurate in the context of regional lymph node metastasis and major vascular invasion in patients with periampullary neoplasms[20-22], especially those with a moderate strength of agreement with histopathology in preoperative staging[23]. A study showed that accurate preoperative T-staging of pancreaticobiliary malignancies was improved using contrast-enhanced harmonic imaging EUS[24]. These findings suggest that EUS should be considered for more extensive lesions or those with concern for invasive cancer[25]. Because EUS assessment is always considered for more extensive lesions or ampullary neoplasms with regional invasion, computed tomography and magnetic resonance imaging help detect distant metastases.

ERCP plays an essential role in pretreatment staging of ampullary adenomas, especially to determine intraductal extension. ERCP may deploy prophylactic pancreatic duct stents to reduce the risk of pancreatitis after EP and manage obstructive jaundice in ampullary adenomas. The performance of intraductal US during ERCP procedures also can provide helpful information for making therapeutic decisions for EP but with a shortcoming of overestimation in tumor staging[26]. Magnetic resonance cholangiopancreatography is an alternative non-invasive imaging technique that can also evaluate pancreaticobiliary conditions and intraductal invasion.

ENDOSCOPIC TECHNIQUES

The goal of EP is to achieve complete resection without severe complications.

Preoperative evaluation of indications and management of complications is crucial for performing EP successfully. EP is performed using a standard duodenoscope in a method similar to snare polypectomy of a mucosal lesion. Because it is an advanced therapeutic intervention, it must be undertaken by an experienced endoscopist. Several endoscopic resection techniques have been established for the lesions of the papilla, including snare polypectomy, argon plasma coagulation (APC) ablation, endoscopic mucosal resection and even endoscopic submucosal dissection. Nevertheless, a standardized endoscopic technique for EP has not been established, and there is no consensus regarding the power output and the mode of electrosurgical current (cutting or coagulation). A recent study showed that the efficacy and safety of autocut and endocut modes were similar to EP, and the endocut mode prevented immediate bleeding in cases with large tumor sizes but caused more frequent crush artifacts[26].

Complete resection of ampullary tumors is the ultimate goal of EP. Resection of the entire lesion in one piece (“*en bloc*”) is recommended. Doing so increases the possibility of complete removal, providing clear margins for more precise histopathologic assessment, reducing procedure time and decreasing recurrence rates[15]. Large lesions and laterally spreading lesions around the ampulla of Vater are challenging to ensure *en bloc* resection; piecemeal resection might be recommended, albeit with a higher risk of bleeding and perforation[27,28].

Submucosal injection of dilute epinephrine has been suggested to lift tumors from the wall with the effect of yielding wider resection margins and reducing the risk of perforation and bleeding. However, unlike other gastrointestinal tract segments, the complexity of the duodenal ampulla structure makes the effect of submucosal injection uncertain. A study showed that submucosal injection before EP of ampullary tumors had a recurrence rate similar to simple snare papillectomy, without the advantage of achieving complete resection or reducing post-papillectomy adverse events such as bleeding[29]. Another study demonstrated that submucosal injection was related to more frequent residual tumor and shorter recurrence-free survival[30]. These findings suggest that simple EP without submucosal epinephrine injection may be recommended for patients with ampullary adenomas.

Although prophylactic pancreatic stent placement is debated and failed to demonstrate a reduction in some studies[31], experts nevertheless recommend placement of prophylactic pancreatic stents for selected patients at high risk for post-ERCP pancreatitis (PEP)[32,33], especially those with insufficient pancreatic juice drainage after EP. A series of studies demonstrated that prophylactic pancreatic stent placement significantly decreased the risk of post-EP pancreatitis[34,35]. A meta-analysis showed that pancreatic stent placement decreased the odds of post-procedure pancreatitis and potentially reduced the risk of late post-procedure papillary stenosis [36].

In addition, the size and length of stents may also have an impact on post-procedure outcomes. Studies demonstrated that a 5-Fr pancreatic stent was preferable to a 3-Fr pancreatic stent for PEP prophylaxis[37,38]. A long (7 cm) pancreatic stent was more useful than a short (5 cm) stent for decreasing the incidence of PEP[39]. These findings suggest that longer and thicker diameter stents appear to better protect against post-procedure pancreatitis[40]. Nevertheless, the optimum lengths and diameters of prophylactic pancreatic stents require further investigation. Generally, biliary stenting after EP is helpful for cholangitis prevention. Bile juice drained far from the resection wound surface would reduce the risk of perforation and bleeding and to prevent biliary stenosis. However, preventive prophylactic plastic biliary stent placement is not uniformly recommended after EP, unless there is concern regarding inadequate biliary drainage[8,41].

EP-ASSOCIATED COMPLICATIONS

Post-ampullectomy adverse events for EP are lower than those of surgical resection; however, the overall rate of complications is 7.7% to 58.3%[42,43] and includes bleeding, pancreatitis, perforation, papillary cholangitis, papillary and duodenal luminal stenosis. EP-related mortality is very rare (approximately 0%–1.9%)[44]. Generally, most EP-associated complications could be successfully recovered through various endoscopic techniques (Table 1). However, endoscopic management for ampullary adenomatous lesions is technically challenging and has a higher risk of procedure-related complications. Therefore, the management of adverse events is indispensable for endoscopists.

Table 1 Endoscopic papillectomy associated complications and managements

Main complications related to EP	Therapeutics
Bleeding	Endoscopic hemostasis: (1) Injection; (2) Electrocoagulation; and (3) Endoclips Vascular intervention Surgical intervention
Pancreatitis	Prophylactic medical therapy: (1) NSAIDs such as indometacin, <i>etc.</i> ; (2) Hydration such as Ringer's lactate solution; and (3) Somatostatin or octreotide Endoscopic therapy: (1) ERCP; and (2) Prophylactic pancreatic duct stenting
Perforation	Endoscopic managements: (1) Closure by endoclips; (2) Bile/pancreatic duct stenting; (3) Nasobiliary/nasopancreatic drainage; and (4) Jejunal feeding tube placement Ultrasound/CT-guided interventional therapy Surgical intervention
Cholangitis	ERCP EST Bile duct stenting Medical therapy such as antibiotics
Later pancreatic or biliary stenosis	ERCP EST Balloon dilation Stenting

CT: Computed tomography; EP: Endoscopic papillectomy; ERCP: Endoscopic retrograde cholangiopancreatography; EST: Endoscopic sphincterotomy; NSAIDs: Nonsteroidal anti-inflammatory drugs.

Bleeding is a relatively common complication because of the substantial vascularization of the duodenal wall; it occurs in large laterally spreading and intraductal extension of ampullary adenomas more frequently. Bleeding includes intraoperative bleeding and postoperative bleeding. Most bleeding can be managed with conservative management and endoscopic treatment, including adrenaline injection, clips or APC ablation. For patients who have failed endoscopic hemostasis, arterial embolization or surgery may be needed. To reduce the risk of bleeding, antiplatelet and anticoagulant therapy must be discontinued before the procedure, as recommended by international guidelines.

Most episodes of post-procedural pancreatitis are mild and resolve with conservative management. Similar to PEP, the placement of prophylactic pancreatic stents reduced the incidence of post-procedural pancreatitis[45]. However, in some cases, a pancreatic stent cannot be easily placed after resection because of edema or bleeding. Various approaches have been proposed to facilitate pancreatic stent insertion, and the optimal technique has yet to be identified. Therefore, adjunctive prophylactic measures to prevent post-procedural pancreatitis must be further explored. Recently, rectal prophylactic nonsteroidal anti-inflammatory medications (100 mg diclofenac or indomethacin), administration of Ringer's lactate solution, somatostatin and octreotide were recommended for pancreatitis prophylaxis[46-49].

Complications of perforation are uncommon but severe. A careful inspection of the resection plane and the fluoroscopy images is helpful to identify perforations. For patients with exposure or injury of the muscularis propria after EP, the placement of overlength biliary and pancreatic stents helped prevent delayed perforation[50]. If perforation is suspected, computed tomography with oral contrast is recommended because perforation is usually retroperitoneal. Antibiotics should be given as quickly as possible when perforation occurs. Most perforations can be treated with clip suturing or conservative treatment. If severe, surgical treatment is required[51].

Cholangitis is rare (0%-7.3%) and is easily controlled with antibiotics and endoscopic sphincterotomy or biliary stent placement. Nevertheless, the evidence for prophylactic endoscopic sphincterotomy with biliary stenting to prevent cholangitis is weak[8].

Papillary and duodenal luminal stenosis are late complications. Papillary stenosis can be managed by sphincterotomy, stent placement and balloon dilation. Duodenal luminal stenosis occurs after resection of laterally spreading lesions of the papilla with extensive duodenal circumferential or longitudinal involvement and can be managed with stent placement.

OUTCOME

The success rates for endoscopic removal of ampullary adenomas range from 76% to 90%, and recurrences have been reported in up to 25% of cases despite presumed complete removal[52]. Jaundice, intraductal extension, occult adenocarcinoma in the resected specimen and piecemeal resection were associated with lower rates of complete resection[53]. Resected margin-positive or uncertain cases after EP may be managed with endoscopic treatment, including APC, even in adenocarcinoma cases [54]. Recurrence requires special attention after EP, and incomplete resection, final pathology diagnosis, intraductal involvement and coexisting familial adenomatous polyposis are associated with recurrence[2,10,55]. If local recurrence was observed, repeated snaring and cutting, such as snare polypectomy, APC and endoscopic mucosal resection, can be performed until all visible lesions are completely resected. A recent report showed that hybrid endoscopic submucosal dissection using a duodenoscope is technically feasible for recurrent, laterally spreading papillary adenomas < 2 cm in diameter[56]. Intraductal adenoma growth is a risk factor for recurrence[10], and intraductal radiofrequency ablation achieved significant success eradicating neoplasia in patients with residual adenomatous tissue in the bile after EP; these findings suggest this treatment is superior to surgical intervention[57].

SURVEILLANCE

Although a standardized protocol is lacking, post-EP surveillance is obligatory because of recurrence and residual lesion risks. The final pathology results may determine surveillance intervals. For patients with complete resection of ampullary adenoma, a side-viewing endoscope and multiple biopsies are recommended at 3 mo, 6 mo and 12 mo and every year after EP for a total of 5 years. Close endoscopic surveillance can be continued for patients with residual lesions or cancer every 2–3 mo until pathological clearance is achieved. Familial adenomatous polyposis can potentially be managed with surveillance alone in patients with nonadvanced ampullary lesions. Generally, surveillance intervals vary anywhere from 0.5 to 4 years, depending on the patient's Spigelman score (which considers the number and size of polyps and their histology)[58]. For patients with familial adenomatous polyposis after EP, intensive follow-up is required due to the high rates of recurrence. For patients with incomplete resection of cancer lesions, radical surgical treatment should be considered.

CONCLUSION

EP is a safe and effective alternative to surgery in selected patients. Following the substantial development of endoscopic techniques, the indications have expanded; nevertheless, exploration of the boundaries of indications continues. *En bloc* resection and prophylactic pancreatic stenting are recommended. The management of complications and the treatment of remnants or recurrent lesions has also made significant progress. Long-term post-EP surveillance is crucial.

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