International Journal of Gastrointestinal Intervention

journal homepage: www.ijgii.org

Review Article

Unsolved problems in endoscopic papillectomy

Nam Hee Kim and Hong Joo Kim*

A B S T R A C T

This article highlights some of the unanswered challenges in performing safe and effective endoscopic papillectomy (EP) as well as offering strategies to deal with these challenges. The authors conducted a review of studies regarding EP for ampullary tumors with specific focus on technical aspects.

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Keywords: Argon plasma coagulation; Endoscopic papillectomy; Endoscopic retrograde cholangiopancreatography; Endoscopic ultrasonography; Intraductal ultrasonography

Introduction

Papillary adenoma has potential for malignant transformation as in other benign tumors of gastrointestinal (GI) tract, such as colon adenoma by an adenoma-to-carcinoma sequence. Papillary adenoma can develop sporadically or in patients with familial adenomatous polyposis (FAP). Patients diagnosed as a papillary adenoma have three therapeutic options: pancreaticoduodenectomy, surgical local excision, or endoscopic papillectomy (EP). EP is currently recognized as a viable alternative therapy to surgery in papillary adenoma and has been reported to have high success and low recurrence rates.[1–15] In the present report, we highlight some of the unanswered challenges in performing safe and effective EP as well as offering strategies to deal with these challenges.

Definition

The term "EP" is commonly used together with the term "endoscopic ampullectomy". However, papillectomy differs from ampullectomy which consists of resection of the ampulla of Vater, via a duodenotomy, including resection of pancreas head tissue, followed by separate reinsertion of the common bile duct (CBD) and main pancreatic duct into the duodenal wall. The term "EP" refers to resection of the mucosa and submucosa of the duodenal wall, in the area of the anatomical attachments of the ampulla of Vater, including the tissue around the bile duct and the pancreatic duct orifices.

Indication

The indications of EP can be dictated by the combination of clinical parameters that can predict the complete removal of the tumor while minimizing the procedure-related complications. The accepted indications for EP include size (up to 5 cm), no evidences of intraductal growth, and no evidences of malignancy on endoscopic appearance (ulceration, friability, induration, and spontaneous bleeding).[16–20] These classic indications of EP have been gradually changing as the endoscopic technique and accompanying endoscopic accessories are rapidly evolving. Recently, the adoption of piecemeal resection for large lesion in major papilla (more than 5 cm) or laterally spreading tumor involving neighboring duodenal mucosa has been reported.[21] In this study, submucosal injection of indigocarmine dye was usually performed to elevate the extra-papillary lesions before EP. The lesions were usually resected from the anal side to the oral side. A single treatment session was possible in 104 of the 125 patients (83.2%) in the *en bloc* resection group and in 8 of the 11 (72.7%) in the piecemeal resection group. The total resection rate including additional treatments was 98.4% in the *en bloc* resection group and 100% in the piecemeal resection group.[21] Sahar et al[22] reported the

Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea
Received December 5, 2019; Revised December 17, 2019; Accepted December 17, 2019
* Corresponding author. Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 29 Saemunan-ro, Jongno-gu, Seoul 03181, Korea.
E-mail address: hongjoo3.kim@samsung.com (H.J. Kim).

pISSN 2636-0004 eISSN 2636-0012 https://doi.org/10.18528/ijgii190018
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clinical outcomes of patients who underwent piecemeal resection for laterally spreading tumor involving neighboring duodenal mucosa compared to those with tumor confined to major papilla. Thirty-five laterally spreading adenomas were treated, which were larger than adenomas confined to the papilla (mean size 38 mm vs 15 mm, $P < 0.05$) and required more piecemeal resections (77% vs 15%, $P < 0.05$). However, no difference was found in recurrence rates between the two groups (8% vs 4%, $P = 0.26$).

Intraductal extension less than 1 cm is not deemed to be contraindication to EP, because the tumor can be exposed to the luminal side after endoscopic biliary or pancreatic sphincterotomy followed by balloon sweeping, and subsequently can be resected completely.[23,24] Adenocarcinoma in the background of adenoma without invasion to the proper muscle layer of duodenal wall, pancreas, or extension to bile and pancreatic duct can be also an indication for EP.[25–29] Yamamoto et al[30] reported no tumor recurrence in patients with carcinoma *in situ* (Tis)–T1a papillary adenocarcinoma (mean follow-up 48.5 months) and T1b papillary adenocarcinoma (mean follow-up 26.5 months) who underwent EP. However, so far, good enough evidences, such as prospective randomized trial for the comparison of long-term clinical outcomes between T1 papillary adenocarcinoma and adenoma patients have not been performed.

Preprocedural Assessment

Critical issues of preprocedural assessment is achieving a reliable distinction between benign and malignant papillary tumor. Endoscopic appearance of mucosal ulceration, friability, and spontaneous bleeding are generally associated with malignant tumor. The application of magnifying endoscope or narrow band imaging can aid in differentiating malignant tumor with papillary adenoma, and assist in selecting the candidate of EP.[31,32] The preprocedural endoscopic forceps biopsy may miss the malignancy in up to 30% in tumors of major papilla.[33–35] Moreover, carcinoma in the background of adenoma cannot be excluded by preprocedural forceps biopsy. Some endoscopists advocated performing deeper forceps biopsy after endoscopic sphincterotomy for increasing the diagnostic sensitivity for malignancy.[36] However, a prospective study showed that sensitivity for malignancy was 21% before and 37% after sphincterotomy, acknowledging that endoscopic forceps biopsy could not allow for reliable preprocedural diagnosis of ampullary tumor.[37] For these reasons, in some study, EP with pathologic evaluation for an *en bloc* resected specimen may be a reliable diagnostic tool before surgical treatment for papillary tumor because of high false negative rate of forceps biopsy.[38]

Preprocedural Staging

Endoscopic retrograde cholangiopancreatography (ERCP) can be an important pretreatment staging technique of papillary tumor since tumor involvement into the CBD and main pancreatic duct can be detected (Fig. 1). Tumor involvement into the CBD and/or main pancreatic duct may hinder the complete resection of papillary tumor during the EP.

Endoscopic ultrasound (EUS) is a useful adjunct to ERCP for assessing the tumor infiltration into the duodenal wall layers and into the pancreato-biliary ducts but it does not have to be universally incorporated into the diagnostic work-up of papillary tumors.[39–46] The accurate role of EUS in the preprocedural evaluation of papillary tumor is not yet distinctive. No acceptable consensus has been made about whether all patients should have EUS examination before EP. A certain group of experts suggests that tumor less than 1 cm in diameter or tumor that do not show the suspicious signs of malignancy (ulceration, friability, induration, and spontaneous bleeding) do not require EUS evaluation before EP.[47] Others conversely argue that if available, EUS evaluation should be deemed before EP or surgical resection is performed.[48] EUS is reported to be useful in identifying the non-invasive papillary tumors which are suitable candidates for EP, but no preoperative tests have been verified to be accurate enough to replace for clinical judgement and intraoperative pathologic confirma-

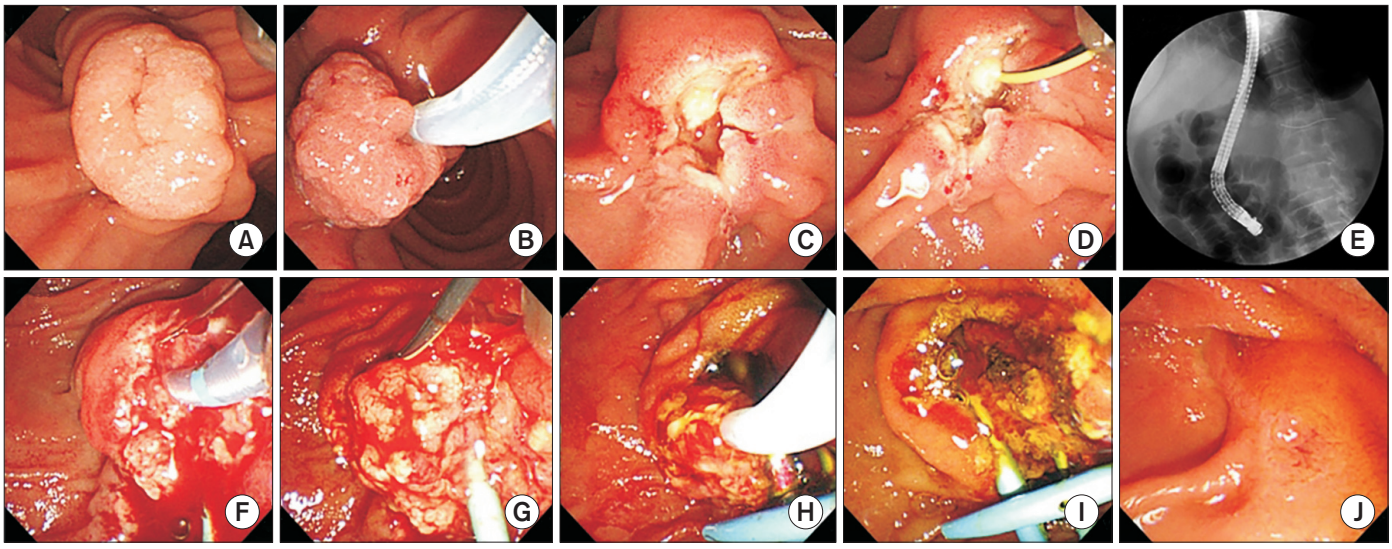

Fig. 1. Tumor extension into the distal common bile duct (CBD). (A) About 1.5 cm sized polypoid mass lesion was noted on major papilla. (B) Snare capturing for entire tumor was done. (C) After endoscopic papillectomy, the resection bed seems to be clear and no residual tumor tissue was noted. (D, E) Selective cannulation of main pancreatic duct was done and stenting with 5 cm long, 5 Fr diametered single pigtail stent was done. (F, G) Selective cannulation of CBD and endoscopic biliary sphincterotomy (EBST) was performed. After EBST, papillary mass lesion was protruded out from the distal CBD. (H) Using the snare and retrieval balloon extraction, further resection for extended tumor tissue in CBD was done. (I) After snare resection, ablative therapy using argon plasma coagulation (APC) was done. (J) After two sessions of further snare resection and APC ablative therapy, no residual tumor tissue was noted on papillectomy bed.

tion.[49,50] A recent study for patients with papillary tumors who underwent EUS as a preoperative evaluation has shown that EUS can accurately predict the depth of mucosal invasion in suspected peri-ampullary and duodenal adenomas (specificity of 88% and negative predictive value of 90%).[42] However, EUS is an invasive intervention, operator dependent, and has a variable rate of over- and underdiagnosis.[51,52] A recent meta-analysis and systemic review concluded that EUS has a moderate strength of agreement with histopathology in: preoperative staging of ampullary tumors, predicting the depth of tumor invasion, and regional lymph nodes involvement.[53] The moderate sensitivity (77%) and specificity (78%) in anticipating T1 lesions suggest that EUS is a suboptimal technique in selecting appropriate candidate for EP. The pooled sensitivity and specificity of detecting regional lymph nodes involvement was 70% and 74%, respectively. Expert's opinions are that if the clinical suspicion for invasive carcinoma is low (for example, absence of jaundice, endoscopic features of noncancerous lesion) and the papillary tumors are appeared to be amenable to endoscopic resection, then EUS may not impact the endoscopist's decision to stage the papillary tumor before EP.

Intraductal ultrasound (IDUS) using a 20 MHz frequency probe may be more accurate in visualizing mucosal layers compared to standard echoendoscope.[54,55] EUS/IDUS are able to accurately detect the CBD and main pancreatic duct involvement. Although the preprocedural evidences of the ductal systems involvement generally indicate the need for surgery, it has been reported that tumor extension of less than 1 cm into CBD and main pancreatic duct can be further resected or ablated endoscopically.[10,23,24]

Computed tomography (CT), magnetic resonance imaging, and positron emission tomography-CT scans are highly sensitive for detecting remote organ metastases, including liver.[44]

Techniques

Complete *en bloc* resection for entire tumor should be the goal of EP. Before the excision of ampullary tumor, the endoscopist should locate the margins of the ampullary tumor. The determination of the margins of the papillary tumor has several advantages: 1) increases the likelihood of complete resection, 2) provides clear margins for histopathologic evaluation, and 3) reduces the procedure time.

Whether submucosal injection should be performed before snare resection for papillary tumor during EP is still debatable. Submucosal injection of saline with or without diluted epinephrine solution to lift the tumorous lesions is frequently done in endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) in GI tract. Because ampulla of Vater is located at the confluent portion of CBD and main pancreatic duct that penetrate the muscularis propria of the duodenal wall, EP may be technically different to EMR and ESD performed at other locations of GI tract. Recently reported prospective multicenter study[56] showed that complete (*en bloc*) resection rate of papillary tumors are significantly higher in simple snare papillectomy (SSP) group compared to submucosal injection papillectomy (SIP) group (80.8% [21/26] vs 50.0% [12/24], $P = 0.02$). However, tumor persistence at 1 month (15.4% vs 8.3%, $P = 0.62$) and recurrence at 12 months (12.0% vs 9.5%, $P = 0.58$) were not different despite initial differences in the prevalence of positive resection margin. Post-papillectomy bleeding developed in 42.3% (11/26) and 45.8% (11/24) of patients, respectively ($P = 0.80$). Delayed bleeding (> 12 hours) occurred in 27.3% (3/11) and 36.4% (4/11) of patients, respectively ($P = 0.50$). Post-procedure pancreatitis occurred in 15.4% (4/26) and 25.0% (6/24) of patients, respectively ($P = 0.49$). Pancreatitis severity did not differ between the groups, and there were no procedure-related mortalities. In this study, SIP technique did not show advantages over SSP technique in terms of achieving complete tumor resection or decreasing the frequency of post-papillectomy adverse effects, such as bleeding. Because the major papilla is tethered to underlying ductal structure unlike the mucosa of the papillary mound and the surrounding duodenum, injecting fluid into the submucosa of these latter areas therefore raises them from the muscularis propria, but does not affect the region of the orifice because of ductal anchoring, which will therefore tend to sink into the elevated surrounding tissues. Because EP is visually guided, it is predictable that snare placement may be misaligned with respect to the original tumor landmarks and more likely will be too superficial in the area of the orifice, leading to an incomplete resection.

There are also no guidelines for the power output and the mode of electrosurgical current (cutting or coagulation). Some investigators[1,10,24] recommend the use of pure-cutting current to avoid the edema caused by the coagulation mode, although pure-cutting current may be associated with increased risk of bleeding. Others advocate a blended electrosurgical currents[1,4,19] or alternating cut/coagulation modes.[19,52] Power output ranges from 30 to 150 W.[4,8,19,24] The authors use electrosurgical generators with the setting of Endocut/effect 2 (ERBE™; ERBE Medical Korea, Seoul, Korea).

Post-papillectomy ablative therapy is used as an adjunctive therapy to treat residual adenomatous tissue remaining on papillectomy bed after *en bloc* or piecemeal resection. However, the benefits of this adjunctive therapy are still controversial. In a large case series, the overall success rates were similar between adjuvant thermal ablative therapy group (81%) compared to those who did not have this adjunctive therapy (78%).[4] Ablative therapy can be performed with monopolar coagulation,[57,58] bipolar coagulation,[58] Nd: YAG laser,[6,58,59] photodynamic therapy,[6] and argon plasma coagulation (APC).[6,8] The authors prefer to use APC (setting of 40 W) to ablate residual adenomatous tissue. Biliary sphincterotomy is usually performed before APC ablation for the exposure of the mucosa of far distal CBD and pancreatic duct stenting (PS; usually using the 5 cm, 5 Fr single pigtail stent) is also performed before APC to preserve the patency of pancreatic duct orifice.

The routine adoption of prophylactic PS may be an ancillary measure for the prevention of post-EP severe pancreatitis. Nonetheless, mixed results have been obtained from the published clinical studies to date addressing prophylactic PS placement during EP to avoid this critical complication.[4,7,8,60,61] Some investigators showed that the adoption of the prophylactic PS placement after EP did not correlate with the subsequent development of post-procedural pancreatitis.[9,62,63] Although prophylactic PS is moderately recommended during EP by American Society for Gastrointestinal Endoscopy, studies published to date have not reached consistent consensus regarding whether prophylactic PS should be routinely adopted for EP.[64] Recently published a systemic review and meta-analysis[65] reported that prophylactic PS decreased the odds of post-procedure pancreatitis (odds ratio [OR], 0.71; 95% confidence interval [CI], 0.36–1.40; $P = 0.325$) as well as late papillary stenosis (OR, 0.35; 95% CI, 0.07–1.75; $P = 0.200$; $I^2 = 0\%$), increased the odds of bleeding (OR, 1.32; 95% CI, 0.50–3.46; $P = 0.572$; $I^2 = 0\%$), and perforation (OR, 2.25; 95% CI, 0.33–15.50; $P = 0.412$; $I^2 = 0\%$), but not significantly. Sensitivity analysis illustrated prophylactic PS significantly decreased the risk of post-procedure pancreatitis (OR, 0.44; 95% CI, 0.24–0.80; $P = 0.007$). This meta-analysis concluded that prophylactic PS placement during EP may be an effective measure for the prevention of post-procedural complications, although not statistically

significant. Sensitivity analysis suggests the significant effect of prophylactic PS against post-EP pancreatitis.

Endoscopic Follow-up and Surveillance

PS is usually removed within two weeks to minimize the pancreatic ductal injury induced by stent. Recurrence of adenoma has been reported in up to 25% of patients despite presumed complete resection during the index procedure.[4,17,19] In the absence of symptoms, surveillance endoscopy can be completed with side-viewing duodenoscope. Follow-up interval of endoscopic examination vary according to the histology and margin status of the resected specimen, history of FAP, patient age and comorbidity. Hence, recommended intervals are: 1) if there was no residual adenoma after primary resection, endoscopy 3 months later; 2) if the results of follow-up endoscopy are negative for residual adenoma, surveillance 1 year later; 3) beyond this, the yield of long-term surveillance for the patients with sporadic papillary adenoma is unknown. The authors usually recommend surveillance endoscopy in every 2 years; and 4) given the risk for metachronous duodenal lesions, patients with FAP should undergo routine surveillance every year.

Conclusions

EP may substitute surgical intervention for the treatment of papillary tumors in selected cases. EP has lower morbidity and mortality rates than surgical treatments. Careful preprocedural assessment and staging are indispensable for complete and successful execution of EP. *En bloc* resection is recommended for the tumors confined to major papilla. EP is a safe and effective therapeutic option for papillary tumors in experienced endoscopist but the endoscopist must be alert to potential complications.

Conflicts of interest

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

ORCID

Nam Hee Kim, https://orcid.org/0000-0002-2686-9754
Hong Joo Kim, https://orcid.org/0000-0003-4121-6329

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