Symposium V

Endoscopic Treatments for Ampullary Neoplasm

Department of Gastroenterology, University of Ulsan College of Medicine, Asan Medical Center

Sang Soo Lee

Tumors arising from the major duodenal papilla account for 5% of GI neoplasms[1] but are being identified more frequently with increasing use of upper endoscopic examination and ERCP. Of a wide variety of benign papillary tumors, adenoma is the most common. It is clinically important because of its premalignant potential. Although complete resection of papillary adenomas is standard practice, opinions differ as to the optimal method of excision.[2-4]

Adenoma of the major duodenal papilla can be excised either surgically or endoscopically. The surgical options include transduodenal local excision (ampullectomy) and radical pancreatoduodenectomy.[3,5-9] Endoscopic treatment methods consist of endoscopic resection and thermal ablation.[4,10-13] Surgical resection has been the mainstay for resection of adenomas of the major duodenal papilla.

Accumulating evidence indicates that endoscopic papillectomy can be used as an alternative first-line therapy.[10,12] Because the ampulla of Vater is strategically located at the confluence of the pancreatic and common bile ducts, endoscopic resection of papillary neoplasms may be technically different from EMR in other parts of the GI tract. The best method of endoscopic ablation and the optimal period for surveillance have not been established.

Indication

Although careful patient selection is a prerequisite to successful endoscopic papillectomy, indications for endoscopic papillectomy are not yet fully established. Criteria for selecting patients who would benefit the most from endoscopic papillectomy vary from one study to another. According to the study by Binmoeller et al,[14] adenomas of the major duodenal papilla that met the following criteria were selected for endoscopic papillectomy: (1) size less than 4 cm, (2) no evidence for malignancy based on endoscopic appearance (regular margins, no ulceration) and soft consistency, and (3) benign histologic findings on forceps biopsy (minimum of 6 biopsies). In another study, only histologically proven adenomas in which en bloc resection was possible were included.[15] For widespread flat adenomas, huge bulky tumors >5 cm in diameter and suspected local infiltration into deeper submucosal layers, surgical resection was attempted. Desilets et al[16] considered that the following criteria indicated resectability in endoscopic papillectomy: (1) a soft tumor that was not indurated or ulcerated; (2) the ability to elevate tumor by submucosal injection; (3) the absence of extension into pancreatic or biliary ducts; and (4) a size no greater than half the circumference of the duodenum, which is about 4 cm in maximal diameter.

Predetermined selection criteria for endoscopic papillectomy in one large multicenter study[10] were that previously untreated, endoscopically accessible lesions of the major duodenal papilla with endoscopically benign features (pale lobulated, well marginated without malignant features, such as firmness to palpation, induration, ulceration, depressed areas) were included. Patients with direct biliary or pancreatic extension of the lesion demonstrated at ERCP and histologically proven carcinoma were referred for surgical resection. Cheng et al[12] used the following criteria to select patients for endoscopic papillectomy: (1) tumor diameter less than 4.5 cm; (2) no endoscopic evidence of malignancy (e.g., absence of ulceration, excessive friability, and spontaneous bleeding); (3) a soft consistency to palpation with any device; and (4) benign histopathologic features in prior forceps biopsy specimens. On

the other hand, indications for endoscopic papillectomy proposed by one Japanese group[17] are as follow: (1) exposed-type adenoma or carcinoma in situ, (2) without invasion of duodenal muscularis, and (3) no infiltration into the pancreas or the bile duct. These indications differ from criteria by other investigators that the size of adenoma is not included and carcinoma in situ is included. It should be noted that these criteria are expert opinions and are based on Grade C evidence. Patients with direct biliary or pancreatic extension of the lesion demonstrated at ERCP or at EUS are referred for surgical excision even if the lesion is confined to mucosa in one study.[10] In two other studies,[18,19] however, adenoma with less than 1 cm of intraductal extension has been successfully resected by endoscopic papillectomy. Simple intraductal extension does not seem to be an absolute contraindication for endoscopic papillectomy, because the tumor can be exposed to the luminal side with sphincterotomy and/or balloon sweeping and, thus, resected completely. Direct infiltration or invasion of the tumor into intraductal mucosa precludes endoscopic papillectomy.

Indications for endoscopic papillectomy are the collection of features that can predict complete removal of adenomas, while minimizing procedure-related morbidities. As experience with endoscopic papillectomy accumulates, endoscopic techniques improve, and novel diagnostic modalities appear, indications for endoscopic papillectomy will and must evolve. Actually, indications for endoscopic papillectomy for adenoma of the major duodenal papilla are changing. The most notable change in indication is a gradual increase in the size of the tumor resected. Application of piecemeal resection when appropriate has contributed much to this. For example, tumors up to 7 cm in diameter have been successfully resected piecemeal.11 As increased application of EUS and/or intraductal US (IDUS) has contributed to more accurate staging of early cancer of the ampulla of Vater contained within the Oddi's muscle, there have been attempts to expand indications for endoscopic papillectomy to include early cancer of the ampulla of Vater.[20,21]

Techniques of Endoscopic Snare Papillectomy

1. Submucosal injection

Injecting saline solution into the submucosal layer beneath the lesion to lift the lesion for safe resection is a very common practice in cases of EMR in other parts of the GI tract. In adenomas of the major duodenal papilla, however, some investigators do not recommend submucosal injection. Firstly, not only the surrounding mucosa at the region of the duodenal papilla but also the tumor is lifted by submucosal injection, so capturing the lesion with a snare becomes difficult.[22] Secondly, submucosal injection may blur the margin of the tumor and does not elevate the bile duct that runs through the duodenal wall.[23] Several studies have been conducted without submucosal injection, but there have been no reports of difficulty in complete resection or an increase in complication.[11,13,14,21,24-28]

2. Modes of resection

1) Snaring: Endoscopists use polypectomy snares of various diameters, ranging from 11 to 27 mm, depending on the size of the tumor.[10,12,18,29] The tumor, together with the papilla, is grasped and excised. In some cases, an incision is made with an electrosurgical needle knife circumferentially around the lesion to facilitate snare capture.[12] Two studies advocated snaring the tumor from the cephalad to the caudal side (the snare apex was placed at the superior margin of the exposed ampullary epithelium) because ensnaring the entire papilla was easier.[18,22] A standard polypectomy snare can be used to grasp the tumor either from the cephalad to the caudal side or from the caudal to the cephalad side on an individual case basis. Secure snaring of the tumor is possible with grasping from either side.

2) Electrosurgical currents: There is no established consensus regarding power output and the mode of electrosurgical current used for endoscopic papillectomy. Many studies do not mention the power and the mode of electrosurgical current used. When mentioned, all used monopolar current.[23,26,30] The power output ranges from 30 to 150W, usually with an effect of 2 or 3.[10,12,16,26] The mode of the current also varies from study to study. Some use blended electrosurgical current, whereas some use pure-cutting current.[10,13,26,30] It is difficult to compare various power outputs and modes of current used, because there is no randomized controlled trial that compares these settings.

3) En bloc or piecemeal resection: Like other issues regarding endoscopic papillectomy, whether en bloc or piecemeal resection is the best method for successful endoscopic papillectomy remains unresol-

ved. It also is not clear whether recurrence rates differ according to the method of endoscopic resection. Nevertheless, en bloc resection is fundamental to the treatment of neoplastic lesions, because it enables complete removal of the lesion with the advantage of submitting ample tissue for more precise histopathologic examination.[23,31] Even though complete removal of these tumors seems possible by piecemeal resection, it may increase the chance of tumor seeding, increase the number of ERCP sessions required for complete excision, and make precise histopathologic assessment of the resected specimens impossible. In addition, an average of 2.7 sessions of ERCP was needed for piecemeal resection, while only a single treatment session was required for en bloc resection. En bloc resection should probably be attempted first in all cases, but, if not possible, residual adenoma should be removed by piecemeal resection and/or thermal ablation during the same session.

3. Stents

1) Pancreatic-duct stents: The results of many studies suggest that placement of a pancreatic stent reduces the risk of pancreatitis after endoscopic papillectomy. Routine placement of a pancreatic stent may decrease both postpapillectomy pancreatitis and papillary stenosis.[10-12,16,17,19,22,24,25] On the other hand, others advocate pancreatic stent placement only if delayed drainage of the pancreatic duct is noted after endoscopic papillectomy.[13,14,18,26] To date, there is no randomized trial of the efficacy of pancreatic stent insertion.

In the study by Cheng et al,[12] prophylactic placement of a pancreatic stent was associated with a lower, but not statistically significant, rate of postpapillectomy pancreatitis (9.6% vs. 25%; p=0.33). Those who endorse selective placement use a pancreatic stent only in the setting of delayed pancreatic-duct drainage after pancreatic sphincterotomy or visual evidence of remnant lesion in close approximation to the ductal epithelium requiring additional intervention.[14,18]

Just like other ERCP-related procedures, the function of the minor duodenal papilla may affect the development of postpapillectomy pancreatitis.[32] A patent duct of Santorini on ERCP obviated the need for pancreatic-duct stent placement after endoscopic papillectomy in one study.[23]

2) Biliary stents: Although there is extensive discussion about pancreatic-duct stent placement, there is very little discussion regarding the need for biliary stents. There have been occasional reports of a biliary stent placement after endoscopic papillectomy.[12,14-17] The diameter of the stent used varied widely, from 7 F to 10 F.[12,14,16,18] Theoretically, cholangitis can occur after endoscopic papillectomy by the same pathogenetic mechanism as postpapillectomy pancreatitis.[10,14,26] A case of cholangitis after endoscopic papillectomy has been reported.[33] Similar to prevention of postpapillectomy pancreatitis, placement of a biliary stent after endoscopic papillectomy may prevent postpapillectomy pancreatitis. Although there is little evidence to determine the best approach, perhaps routine Cholangiography after endoscopic papillectomy could guide the need for biliary stent placement. Both biliary sphincterotomy and stent placement could be considered if the bile duct orifice is not clearly visible and there is difficulty in cannulation after resection of the tumor. This approach would be comparable with pancreatic sphincterotomy and stent placement for the prevention of postpapillectomy pancreatitis.

4. Tissue preparation after retrieval

The retrieved specimen can be flattened and pinned down at the periphery to a plate of polystyrene to aid orientation and to make identification of lateral and horizontal margins easier. It then can be fixed in buffered formalin solution and examined microscopically after H&E staining. The fixed specimen should be sectioned serially at 3-mm intervals for histologic evaluation. Size, gross appearance, histology, microscopic depth of tumor, and involvement of the lateral and horizontal margins should be reported in detail.

5. Additional adjunct therapy

If a remnant lesion is suspected immediately after excision of the tumor, additional removal with snare resection can be attempted in the same session if technically feasible. However, removal with biopsy forceps or adjunct thermal ablation can be used instead if not amenable to snare resection.[12,26] Modalities for adjunct thermal ablation include argon plasma coagulation, monopolar/multipolar electrocoagulation, and photodynamic therapy.

6. Strategy According to Histologic Findings of Resected Specimen

After receiving the final report on histopathologic findings of the resected tumor, the need for further treatment can be determined. Adenoma and carcinoma/high-grade dysplasia frequently coexist in 25% to 60% of papillary adenoma.[34-36] One study[37] on the im-

pact of the grade of dysplasia in ampullary adenomas on the prognosis observed an increased risk of postoperative recurrence and development of invasive carcinoma after the primary diagnosis of an adenoma with high-grade dysplasia, whereas no recurrence was observed in the low-grade dysplasia group after local resection and benign postoperative histology. If histopathologic evaluation of the resected specimens reveals high-grade dysplasia or carcinoma in situ, additional surgery should be recommended.[37] However, close follow-up with periodic endoscopy and biopsy may be sufficient in cases of focal high-grade dysplasia or carcinoma in situ, which was removed completely when the patient was at high risk for surgery or refuses surgery.[31] For those patients with a positive resection margin whose histopathologic evaluation reveals low-grade dysplasia, further endoscopic snare resection or adjunct thermal ablation can be applied.[10,11,14,32]

Outcomes

1. Success rate and recurrence

Reported success rates for endoscopic papillectomy range from 46% to 92%, and recurrence rates of ampullary adenoma after endoscopic papillectomy range from 0% to 33%.[10-12,14,16,19,24-26,30] Risk factors for recurrence included larger size and probably the absence of adjunct thermal ablation at initial papillectomy.[6] Most recurrences could be removed endoscopically, but some recurrent adenomas exhibited intraductal extension and had to be treated surgically. After endoscopic papillectomy, the rate of recurrence of adenoma for which surgery is required ranges from 10% to 33%.[10-12,14] Predictors of successful endoscopic papillectomy in one large multicenter study[10] included age greater than 48 years, lesion size of 24 mm or less, and male gender. In another study,[38] age, gender, lesion size, and submucosal injection were not significantly associated with endoscopic success.

2. Complications

Complications of endoscopic papillectomy can be classified as early (pancreatitis, bleeding, perforation, and cholangitis) and late (papillary stenosis) complications.[10]

The two most common complications are bleeding and postpapillectomy pancreatitis. Most bleeding can be controlled by conservative management and endoscopic hemostasis. Most postprocedural pancreatitis was mild and resolved with conservative management only. Only one patient who had not undergone pancreatic-stent placement after endoscopic papillectomy died from severe pancreatitis.[18]

Papillary stenosis is a late complication that may occur 7 days or up to 24 months after endoscopic papillectomy.[26,30] It was more frequent without short-term pancreatic- duct stent placement (15.4% vs. 1.1%).[10] This complication usually was treated with endoscopic sphincterotomy followed by stent placement, but one patient required surgical sphincteroplasty because the cannulation failed.[10,12,26] Like cholangitis, this late complication may be prevented by selective endoscopic sphincterotomy and stent placement after excision of the tumor.

Postpapillectomy Surveillance

Consensus has not been reached yet as to the interval and the method of surveillance after complete excision of adenoma of the major duodenal papilla. Therefore, these vary somewhat from one study to another and are largely dependent on the individual endoscopist's preference.

A complete endoscopic resection of ampullary adenoma generally is defined as the absence of endoscopically visible and histologically proven residual adenoma for a follow-up of 3 to 6 months.[12,24,29] According to the results of one large multicenter study,[10] the following recommendations can be made on the schedules of the postpapillectomy surveillance: (1) if removal of adenoma of the major duodenal papilla is incomplete, endoscopic treatment and ERCP should be repeated every 2 to 3 months until complete resection is achieved; and (2) if excision/ablation is complete, follow-up endoscopy with ERCP and multiple biopsies should be performed every 6 months for a minimum of 2 years. Thereafter, patients with familial adenomatous polyposis syndrome should have endoscopy at 3-year intervals.

References

1. Scarpa A, Capelli P, Zamboni G, et al. Neoplasia of the ampulla of Vater. Ki-ras and p53 mutations. Am J Pathol 993;142:1163-72.
2. Sobol S, Cooperman AM. Villous adenoma of the ampulla of Vater. An unusual cause of biliary colic and obstructive jaundice. Gastroenterology 1978;75:107-9.
3. Tarazi RY, Hermann RE, Vogt DP, et al. Results of

surgical treatment of periampullary tumors: a thirty-five year experience. Surgery 1986;100:716-23.
4. Shemesh E, Nass S, Czerniak A. Endoscopic sphincterotomy and endoscopic fulguration in the management of adenoma of the papilla of Vater. Surg Gynecol Obstet 1989;169:445-8.
5. Rattner DW, Fernandez-del Castillo C, Brugge WR, et al. Defining the criteria for local resection of ampullary neoplasms. Arch Surg 1996;131:366-71.
6. Beger HG, Treitschke F, Gansauge F, et al. Tumor of the ampulla of Vater: experience with local or radical resection in 171 consecutively treated patients. Arch Surg 1999;134:526-32.
7. Bjork KJ, Davis CJ, Nagorney DM, et al. Duodenal villous tumors. Arch Surg 1990;125:961-5.
8. Posner S, Colletti L, Knol J, et al. Safety and long-term efficacy of transduodenal excision for tumors of the ampulla of Vater. Surgery 2000;128: 694-701.
9. Gray G, Browder W. Villous tumors of the ampulla of Vater: local resection versus pancreatoduodenectomy. South Med J 1989;82:917-20.
10. Catalano MF, Linder JD, Chak A, et al. Endoscopic management of adenoma of the major duodenal papilla. Gastrointest Endosc 2004;59:225-32.
11. Zadorova Z, Dvofak M, Hajer J. Endoscopic therapy of benign tumors of the papilla of Vater: a clinicopathologic study. Am J Gastroenterol 1992;87:37-42.
12. Cheng CL, Sherman S, Fogel EL, et al. Endoscopic snare papillectomy for tumors of the duodenal papillae. Gastrointest Endosc 2004;60:757-64.
13. Norton ID, Geller A, Petersen BT, et al. Endoscopic surveillance and ablative therapy for periampullary adenomas. Am J Gastroenterol 2001;96:101-6.
14. Binmoeller KF, Boaventura S, Ramsperger K, et al. Endoscopic snare excision of benign adenomas of the papilla of Vater. Gastrointest Endosc 1993;39:127-31.
15. Beger HG, Staib L, Schoenberg MH. Ampullectomy for adenoma of the papilla and ampulla of Vater. Langenbecks Arch Surg 1998;383:190-3.
16. Desilets DJ, Dy RM, Ku PM, et al. Endoscopic management of tumors of the major duodenal papilla: refined techniques to improve outcome and avoid complications. Gastrointest Endosc 2001;54:202-8.
17. Maguchi H, Takahashi K, Katanuma A, et al. Indication of endoscopic papillectomy for tumors of the papilla of Vater and its problems [review]. Dig Endosc 2003;15(Suppl):S33-5.
18. Kahaleh M, Shami VM, Brock A, et al. Factors predictive of malignancy and endoscopic resectability in ampullary neoplasia. Am J Gastroenterol 2004;99:2235-9.
19. Bohnacker S, Seitz U, Seewald S, et al. Endoscopic snare resection of benign ampullary tumor: can intraductal growth be treated endoscopically? [abstract]. Gastrointest Endosc 2003;57:AB101.
20. Jung S, Kim MH, Seo DW, et al. Endoscopic snare papillectomy of adenocarcinoma of the major duodenal papilla. Gastrointest Endosc 2001;54:622.
21. Ito K, Fujita N, Noda Y, et al. Case of early ampullary cancer treated by endoscopic papillectomy. Dig Endosc 2004;16:157-61.
22. Hirooka Y, Itoh A, Goto H. EUS/IDUS and endoscopic papillectomy [review]. Dig Endosc 2004;16 (Suppl):S176-7.
23. Aiura K, Imaeda H, Kitajima M, et al. Balloon-catheter-assisted endoscopic snare papillectomy for benign tumors of the major duodenal papilla. Gastrointest Endosc 2003;57:743-7.
24. Vogt M, Jakobs R, Benz C, et al. Endoscopic therapy of adenomas of the papilla of Vater. A retrospective analysis with long-term follow-up. Dig Liver Dis 2000;32:339-45.
25. Fukushima T, Fogel EL, Devereaux BM, et al. Use of ERCP and papillectomy in management of ampullary tumors: seven-year review of 75 cases at Indiana University Medical Center [abstract]. Gastrointest Endosc 2001;53:AB88.
26. Norton ID, Gostout CJ, Baron TH, et al. Safety and outcome of endoscopic snare excision of the major duodenal papilla. Gastrointest Endosc 2002;56:239-43.
27. Ponchon T, Berger F, Chavaillon A, et al. Contribution of endoscopy to diagnosis and treatment of tumors of the ampulla of Vater. Cancer 1989;64:161-7.
28. Ito K, Fujita N, Noda Y, et al. Modes of spread in early ampullary cancer in terms of establishing proper indications for endoscopic papillectomy. Dig Endosc 2004;16:224-8.
29. Yasuda K, Uno K, Tanaka K, et al. Endoscopic resection of tumor of papilla Vater: our experiences. Dig Endosc 2003;15(Suppl):S31-2.
30. Saurin JC, Chavaillon A, Napoleon B, et al. Long-term follow-up of patients with endoscopic treatment of sporadic adenomas of the papilla of Vater. Endoscopy 2003;35:402-6.
31. Charton JP, Deinert K, Schumacher B, et al. Endoscopic resection for neoplastic diseases of the papilla of Vater [review]. J Hepatobiliary Pancreat Surg 2004;11:245-51.
32. Fujita N, Noda Y, Kobayashi G, et al. Endoscopic papillectomy: is there room for this procedure in clinical practice? Dig Endosc 2003;15:253-5.
33. Choi JJ, Kim MH, Kim GD, et al. Papillary stenosis and cholangitis caused by endoscopic mucosal resection of ampullary adenoma [in Korean with English abstract]. Korean J Gastrointest Endosc 2003;27: 249-53.

34. Yamaguchi K, Enjoji M. Carcinoma of the ampulla of Vater: a clinicopathologic study and pathologic staging of 109 cases of carcinoma and 5 cases of adenoma. Cancer 1987;59:506-15.
35. Seifert E, Schulte F, Stolte M. Adenoma and carcinoma of the duodenum and papilla of Vater: a clinicopathologic study. Am J Gastroenterol 1992;87:27-42.
36. Ryan DP, Schapiro RH, Warshaw AL. Villous tumors of the duodenum. Ann Surg 1986;203:301-6.
37. Heidecke CD, Rosenberg R, Bauer M, et al. Impact of grade of dysplasia in villous adenomas of Vater's papilla. World J Surg 2002;26:709-14.
38. Han J, Lee SK, Park DH, et al. Treatment outcome after endoscopic papillectomy of tumors of the major duodenal papilla [abstract in Korean]. Korean J Gastroenterol 2004;29:395.