Current Gastroenterology Reports (2020) 22: 46
https://doi.org/10.1007/s11894-020-00784-0

PANCREAS AND BILIARY TRACT (O HALUSZKA AND H GAVINI, SECTION EDITORS)

A Comprehensive Approach to the Management of Benign and Malignant Ampullary Lesions: Management in Hereditary and Sporadic Settings

Donald R. Campbell Jr.[1] · Jeffrey H. Lee[1]

Published online: 11 July 2020

Abstract

Purpose of Review The purpose of this review was to examine the historical roots of endoscopic management of ampullary lesions and explore emerging data on improved techniques, technologies, and outcomes. Of specific interest was answering whether there exists a reasonable body of data to support one resection technique or strategy above others.

Recent Findings Review of recent literature suggests the continued use of endoscopic ampullectomy is a safe and effective means of curative treatment of ampullary adenomas. Complications are relatively infrequent and complete endoscopic resection is possible in a majority of cases, with proper patient and lesion selection.

Summary Greater than 2 decades of experience with endoscopic ampullectomy have shown this to be a viable, well-tolerated, and highly effective means of treating ampullary adenomas. While few concrete guidelines exist to advise endoscopists on the ideal technique for resection, experience, patient selection, and prior planning can greatly influence the technical and clinical success of endoscopic ampullectomy.

Keywords Ampullary lesion · Ampullary adenoma · Endoscopic ampullectomy

Introduction

While lesions of the ampulla of Vater are relatively rare, increasingly, gastroenterologists are finding, managing, and resecting ampullary and periampullary lesions. Neoplasms of the ampulla of Vater are indeed uncommon in the general population with multiple historic autopsy studies showing an overall prevalence of between 0.04 and 0.12% [1–3••, 4]. Though seemingly insignificant compared with the prevalence of colon cancer, breast cancer, and lung cancer, periampullary neoplasms hold an important but underrecognized place in the realm of gastrointestinal malignancies. Periampullary tumors now account for 5% of all newly diagnosed gastrointestinal tumors [5].

Periampullary tumors generally develop later in life and most commonly are brought to clinical attention in the sixth to eighth decades of life; they likely arise years or decades earlier and grow silently without clinical detection [6–8]. In recent years, there has been observed a significant increase in the incidence or periampullary lesions. This has been attributed to increased endoscopic screening of high-risk patients and increased use of upper endoscopy for unrelated indications [9••, 10–14]. Thankfully, this has not only resulted in an increased incidence but has also resulted in the detection of lesions at an earlier point in their development, when they are more amenable to endoscopic resection [6, 15].

While most ampullary lesions are currently discovered incidentally, a significant portion of patients will still present with a myriad of symptoms including biliary obstruction, jaundice, pancreatitis, non-specific abdominal symptoms, weight loss, abdominal pain, dyspepsia, malaise, or anorexia [3, 4, 16, 17, 18••]. No specific symptom or constellation of symptoms has been shown to be pathognomonic for ampullary lesions, and so, physicians should keep these lesions in mind when seeing a patient with atypical abdominal symptoms.

This article is part of the Topical Collection on *Pancreas and Biliary Tract*

✉ Jeffrey H. Lee
jefflee@mdanderson.org

[1] Department of Gastroenterology, Hepatology and Nutrition, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, USA

Ampullary adenomas can occur in the setting of genetic predisposition, as is the case in patients with familial adenomatous polyposis syndrome (FAP) or, more commonly, occur sporadically [3, 9, 19]. Similar to what is now widely known to occur with colon polyps, ampullary adenomas progress through an adenoma to carcinoma sequence, which allows lead time for discovery and excision of these lesions prior to malignant transformation [14, 18, 20, 21, 22••].

In this article, we will look at the latest in diagnosis, management, and surveillance of ampullary adenomas and describe our own experience at a large, tertiary referral cancer hospital.

Familial Adenomatous Polyposis Syndrome

Familial adenomatous polyposis syndrome is a well-described condition resulting from an autosomal dominant genetic mutation in the adenomatous polyposis coli (APC) gene [23, 24]. APC is a tumor suppressor gene located on long arm of chromosome 5 [24, 25]. This mutation results in the growth of adenomatous polyp in multiple locations throughout the body, but is most well-known for causing prolific growth in colonic polyps. These numerous polyps result in a nearly 100% chance of developing colon cancer, which is why prophylactic colectomy is now the standard of care [26, 27].

While the focus of the general population and most physicians has been on how FAP impacts an individual's risk of developing colon cancer, most are unaware the syndrome also conveys a significantly increased risk for cancers of the duodenal, pancreas, biliary tree, brain, and thyroid [28]. The duodenum is the second most common site of polyp formation in FAP patients with a lifetime risk of developing duodenal adenomas approaching 100% in some studies [28–38]. Duodenal adenomas typically show up approximately 15 years after the development of colon polyps and have a tendency to be found in clusters around and just distal to the ampulla of Vater [29, 31, 38–40].

Patients with FAP have a 100–330-fold increase risk of duodenal adenocarcinoma compared with the general population with an absolute lifetime risk of developing duodenal adenocarcinoma or ampullary carcinoma of 3–5% [10, 29, 30, 38, 41, 42]. Duodenal and periampullary cancers have become a leading cause of death for FAP patients since prophylactic colectomy became the standard of care [28, 42–44]. Thankfully, screening and early resection of these adenomas have become more widespread. The current European Society of Gastrointestinal Endoscopy (ESGE) recommendations suggest starting endoscopic duodenal surveillance at age 25 and continuing at intervals determined by the characteristics of previously found polyps [45]. Adequate evaluation of the duodenum can be obtained with a forward-viewing and side-viewing endoscope with or without the use of chromoendoscopy [22, 23]. Effective implementation of screening recommendations like the use of a side-viewing duodenoscope with random biopsies has resulted duodenal and ampullary adenoma detection rates as high as 70% in some studies [34, 46, 47]. However, taking a biopsy at the ampulla should be practiced with caution as it can cause pancreatitis. Thus, we recommend biopsying the ampulla only when there is a clear indication.

One 2012 study longitudinally followed 71 patients with FAP. The mean follow-up time was 4.5 years during which time 70 out of 71 had duodenal adenomas discovered; there were 13, greater than 1 cm in size. Forty-three had ampullary or periampullary adenomas and 17 patients underwent APC ablation with 100% technical success rate. No patients were found over the study period to have adenocarcinoma [42]. The management of ampullary lesions occurring in patients with hereditary syndromes is similar to those occurring sporadically. However, several key differences exist including the following: lesions in FAP patients are typically detected as part of intensive endoscopic surveillance and, due to their typically indolent nature; lesions in FAP patients are often monitored for progression in size and pathology while sporadic lesions are typically resected very shortly after discovery.

Endoscopic Management

While endoscopic management of ampullary and periampullary adenomas seems a daunting task, the 2015 American Society for Gastrointestinal Endoscopy (ASGE) guidelines for the role of endoscopy in ampullary and duodenal adenomas attempt to simplify and streamline recommendations for management. The ASGE recommends ERCP prior to resection attempts. These guidelines also recommend endoscopic ultrasound prior to resection as EUS has been shown to be superior to computed tomography in the accuracy of primary tumor staging [48–56]. We, at MD Anderson Cancer Center, first cannulate the pancreatic duct with a guidewire only without injection. Once we know where the pancreatic duct is located, we then perform, in most cases, en bloc resection.

The ASGE guidelines suggest that lesions smaller than 1 cm, in the absence of concerning features, can typically be resected without the need for EUS, but in our practice, we typically employ EUS for the evaluation of all ampullary lesions [57]. While EUS is superior for the evaluation of primary tumor staging, CT/PET and MRI should be completed prior to resection attempts as these modalities have been shown to be superior in their ability to detect seasonal small, distant metastases, and nodal metastases, respectively [55, 56].

Biopsies prior to primary resection have become standard practice for most physicians performing papillectomy; however, significant discordance rates exist between sample

biopsies and final pathology from resection specimens. Several studies have examined concordance estimates that vary between 45 and 80%. A disturbingly high false-negative rate of 16 to 60% is seen in patients with adenocarcinoma. This fact is clinically relevant as endoscopic resection should only be attempted in patients with adenocarcinoma that is staged as Tis while other stages should be referred for surgical resection. This presents a challenging clinical question as this discordance results in a relatively high number of patients undergoing ampullectomy for what is thought to be adenoma but results in a final diagnosis of adenocarcinoma, and physicians and patients are then faced agonizing decision whether endoscopic surveillance or surgery is the right next step. No clear recommendations exist for this difficult clinical scenario [1, 7, 58–64].

Advanced analysis of biopsy specimens for K-ras mutations, immunostaining, MicroRNA, and flow cytometry is available but their clinical utility has yet to be established and is not available at all institutions [20, 65–72].

The current recommendations suggest the removal of ampullary adenomas < 4–5 cm in maximal diameter is advisable. Resection of ampullary adenocarcinoma has been described and resection of Tis tumors can be curative although the most recent ASGE guidelines conclude that, "although endoscopic removal of ampullary adenocarcinoma has been described, this cannot be endorsed for routine management." [21, 73–75]. Certain endoscopic features suggestive of possible malignancy like non-lifting with injection, firmness, ulceration, and areas of depression have been proposed as indications to refer for surgical resection [21, 76].

Evidence of intraductal lesion extension is often considered to be an indication for referral to surgery, although intraductal RFA is changing this somewhat [4, 77, 78]. While injection for lifting of lesions prior to resection is commonplace in other areas of the gastrointestinal tract, injection of ampullary lesions does not enjoy such widespread acceptance. Most publications, guidelines, and expert opinion pieces leave the decision up to individual endoscopist but note that injection has the potential to be counterproductive in some lesions and may actually cause central depression due to the tethering effect of the ductal mucosa [1]. Two recent studies showed complete resection in 81% without injection vs. 50% with injection and no difference in the relative rates of bleeding or pancreatitis [22, 79]. Recent guidelines determined there was insufficient data to recommend mandatory lifting of ampullary lesions [4, 57, 78].

Techniques and Strategies to Improve Endoscopic Resection

Although the technique for optimal resection is largely a matter of personal preference, endoscopist comfort, and available equipment, some strategies have been shown to be superior in ampullary resection. There is no evidence for one type of electrocautery setting over another or one electrocautery generator over another [4, 74, 77, 78, 80, 81].

If the pancreatic duct (PD) stenting is desired, several strategies exist to aid in the PD stent placement. Some centers describe pancreatic duct cannulation and injection of a dilute solution of methylene blue prior to ampullary resection to aid in the identification of the PD for subsequent stenting [22, 82]. Other endoscopists encourage stenting of the pancreatic duct prior to resection. Still, others recommend wire-guided resection whereby the PD is first cannulated, and then, the snare is advanced over the wire and resection occurs "over the wire" [83, 84]. Following resection, the "donut" of tissue can be cut off around the wire with a needle knife, if it does not fall off on its own.

While a multitude of options and opinions exist on the "right way" to go about resection, we have found that cannulation of the pancreatic duct prior to resection without injection is helpful to obtain and fluoroscopic roadmap as to the trajectory of the PD. We then remove the guidewire, resect the ampulla, and then reattempt cannulation based on the information gained from the initial cannulation (Figs. 1 and 2). This ensures en bloc resection (Fig. 3).

To Stent or Not to Stent?

The topic of ductal stenting has been a point of the controversy of late. Several papers recommend prophylactic pancreatic duct stenting as it has been shown to decrease the rate of post-procedure pancreatitis [85–87]. Still, other sources have suggested that PD stenting may not be necessary at all [18, 88]. While the role of pancreatic duct stenting related to post-procedure pancreatitis may still be in question, its potential

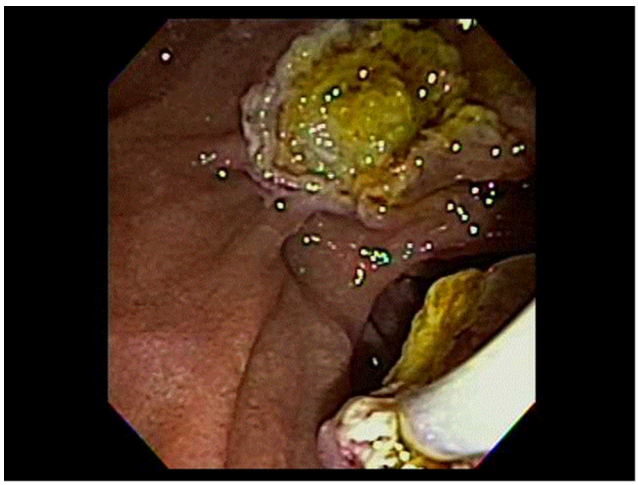

Fig. 1 En bloc resection of ampullary mass was performed. The specimen was grabbed by the snare that was used for resection

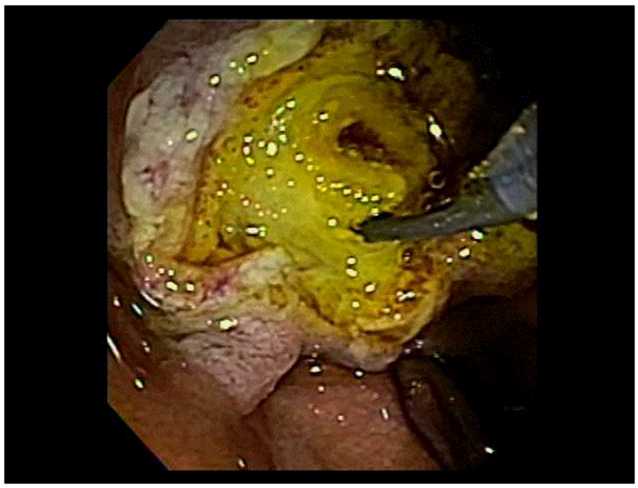

Fig. 2 Selective cannulation of the pancreatic duct was performed post-ampullectomy. Note that the orifices of the pancreatic duct and bile duct were separated post-ampullectomy

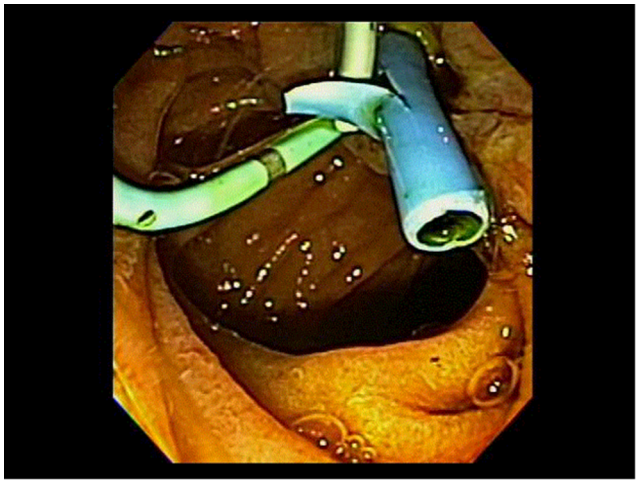

Fig. 4 The pancreatic duct was stented. Biliary sphincterotomy was performed and a plastic stent was placed

benefits of decreasing late ductal stenosis and allowing for safer use of coagulation therapies seem to justify the use of prophylactic PD stenting [4, 21, 75, 80, 89]. In our practice, we do routinely place PD stents and then remove them about 4 weeks later. This also allows for early inspection of the ampullectomy site. We have found no compelling evidence to support pancreatic sphincterotomy, but we perform biliary sphincterotomy, carefully watching the landmarks post ampullectomy [57, 76, 77, 81, 86, 89] (Figs. 4 and 5).

We recommend that retrieval of specimens should be done as quickly as possible to avoid peristalsis removing them from endoscopic reach. Once the specimen is grabbed with the snare that was used to perform ampullectomy, the specimen is brought into the stomach; the specimen can be completely brought out or be dropped in the stomach until it is removed at the end of the procedure. Adequate administration of glucagon can help decrease motility of the small bowel but, again, the degree of impact is debatable and should be determined by individual physicians.

Endoscopic Resection Success Rates

While individual endoscopist experience with ampullectomy varies, the quoted technical success for complete resection also varies quite significantly from 46 to 92% [4, 21, 74, 75, 78, 80, 89–91]. One difference to be acutely aware of is some of the studies who quote success rates toward the higher end of this range define success as complete endoscopic resection, regardless of how many sessions are required. While these

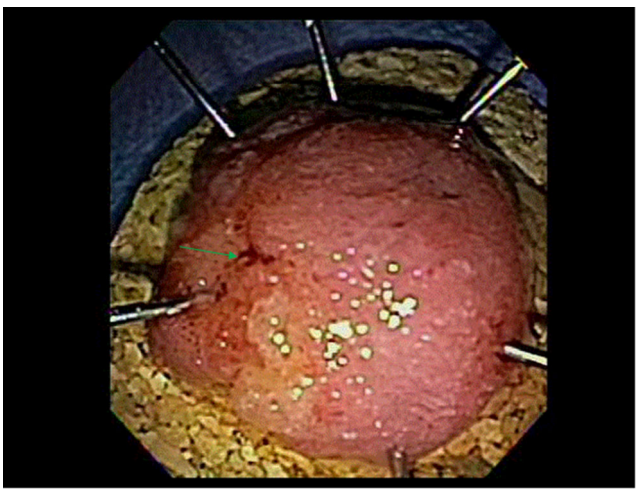

Fig. 3 Arrow, ampullary os. en bloc resection was performed. The specimen was pinned in anatomical position with 12 o'clock pointing to the proximal end

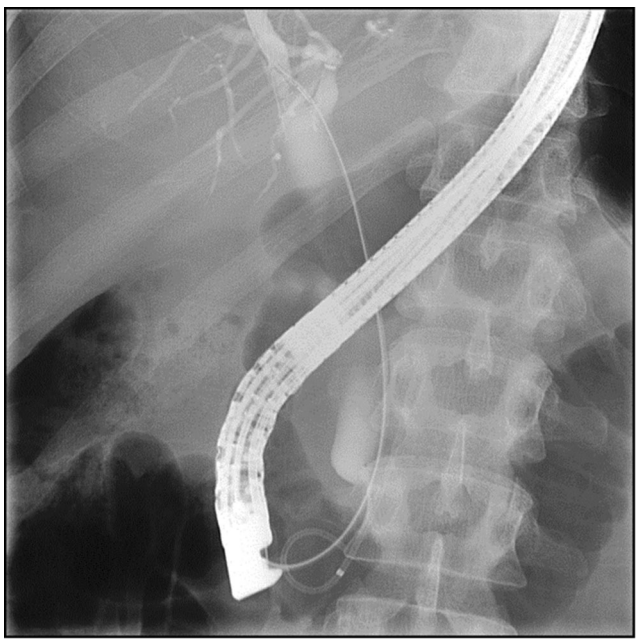

Fig. 5 Fluoroscopic image of PD stent and cannulation of the bile duct

numbers may be promising, recurrence rates are also noted to be between 2 and 33% and can occur late following resection [4, 21, 92–94]. Though this is certainly a broad range, more recent analyses with larger sample size have somewhat narrowed this range from 8 to 19%.

Patient and lesion factors play a large role in the likelihood of technical success, and so, patient selection plays a critical role in identifying cases in which success is probable. Predictors of success are male sex, age > 48, lesion size < 24 mm, and absence of FAP [1].

Potential procedural complications include perforation, pancreatitis, bleeding, ductal stenosis, and cholangitis (though few reports of this are noted). Overall complication rates are low (between 9 and 21%) and post-procedure pancreatitis is also infrequently reported (between 5 and 19%) [4, 21, 92–94]. It is worth noting when discussing this with patients that the adverse event rate for surgical resection is higher than that for endoscopic resection [95]. To minimize the adverse event rate for endoscopic resection, most endoscopists keep patients on a liquid diet 24 to 48 h and also recommend a proton pump inhibitor twice a day for at least 2 weeks.

What Really Is Proper Post Procedure Screening?

In the review of the literature and in clinical practice, it seems nearly universal that all patients are asked to follow up in 1 week to 1 month. Frequently, if this first endoscopy shows no residual lesion, routine endoscopic follow-up is scheduled at either 3-month or 6-month intervals [4, 21, 74, 75, 89, 91, 96, 97]. This typically is continued to 24 months but some institutions continue screening for much longer periods. This topic certainly requires further study to determine the optimal timing and duration of post-procedure surveillance.

As aforementioned, we routinely bring the patient back to remove the PD stent in 4 weeks, and then the 3 months from the ampullectomy to assess the ampullectomy site. If there are no residual tissues or recurrence, the next endoscopy is done in 1 year. We then annually follow the patients at least for 5 years.

Conclusions

Lesions of the ampulla, specifically ampullary adenomas, are increasingly seen in clinical practice with the proliferation of routine upper endoscopy. As such, it is of paramount importance that gastroenterologists familiarize themselves with this important topic and are well versed in both lesions occurring as part of a larger, heritable syndrome (like FAP) and also sporadically. Greater than two decades of experience with endoscopic ampullectomy have shown this procedure to be safe and effective for the management of most ampullary adenomas. Recent studies have shown complete endoscopic resection rates as high as 92% with a relatively low complication rate. Pre-resection biopsy to final pathology concordance and recurrence rates remain the areas of continued emphasis with room for improvement; however, effective and diligent use of post-resection surveillance and introduction of new modalities such as intraductal RFA are making endoscopic ampullectomy more promising than ever.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Martin JA, Haber GB. Ampullary adenoma: clinical manifestations, diagnosis, and treatment. Gastrointest Endosc Clin N Am. 2003;13(4):649–69.
2. Perzin KH, Bridge MF. Adenomas of the small intestine: a clinicopathologic review of 51 cases and a study of their relationship to carcinoma. Cancer. 1981;48(3):799–819.
3.•• Sahar N, Krishnamoorthi R, Kozarek RA, Gluck M, Larsen M, Ross AS, et al. Long-term outcomes of endoscopic papillectomy for ampullary adenomas. Dig Dis Sci. 2019; **This recent study examined > 150 patients who underwent endoscopic ampullectomy and showed a low complication rate, low rate or residual tumor, and low rat of recurrence**.
4. Catalano MF, Linder JD, Chak A, Sivak MV Jr, Raijman I, Geenen JE, et al. Endoscopic management of adenoma of the major duodenal papilla. Gastrointest Endosc. 2004;59(2):225–32.
5. Branum GD, Pappas TN, Meyers WC. The management of tumors of the ampulla of Vater by local resection. Ann Surg. 1996;224(5):621–7.
6. Jung MK, Cho CM, Park SY, Jeon SW, Tak WY, Kweon YO, et al. Endoscopic resection of ampullary neoplasms: a single-center experience. Surg Endosc. 2009;23(11):2568–74.
7. Ryan DP, Schapiro RH, Warshaw AL. Villous tumors of the duodenum. Ann Surg. 1986;203(3):301–6.
8. Gray G, Browder W. Villous tumors of the ampulla of Vater: local resection versus pancreatoduodenectomy. South Med J. 1989;82(7):917–20.
9.•• Committee ASoP, Chathadi KV, Khashab MA, Acosta RD, Chandrasekhara V, Eloubeidi MA, et al. The role of endoscopy in ampullary and duodenal adenomas. Gastrointest Endosc. 2015;82(5):773–81 **These guidelines from the ASGE provide a comprehensive review of recent and historic literature on the endoscopic management of ampullar, periampullary, and duodenal adenomas and provided tangible recommendations regarding best resection practices, patient selection, and lesion evaluation.**

10. Offerhaus GJ, Giardiello FM, Krush AJ, Booker SV, Tersmette AC, Kelley NC, et al. The risk of upper gastrointestinal cancer in familial adenomatous polyposis. Gastroenterology. 1992;102(6): 1980–2.
11. Galandiuk S, Hermann RE, Jagelman DG, Fazio VW, Sivak MV. Villous tumors of the duodenum. Ann Surg. 1988;207(3):234–9.
12. van Stolk R, Sivak MV Jr, Petrini JL, Petras R, Ferguson DR, Jagelman D. Endoscopic management of upper gastrointestinal polyps and periampullary lesions in familial adenomatous polyposis and Gardner's syndrome. Endoscopy. 1987;19(Suppl 1):19–22.
13. Lindor NM, Greene MH. The concise handbook of family cancer syndromes. Mayo Familial Cancer Program. J Natl Cancer Inst. 1998;90(14):1039–71.
14. Stolte M, Pscherer C. Adenoma-carcinoma sequence in the papilla of Vater. Scand J Gastroenterol. 1996;31(4):376–82.
15. Li S, Wang Z, Cai F, Linghu E, Sun G, Wang X, et al. New experience of endoscopic papillectomy for ampullary neoplasms. Surg Endosc. 2019;33(2):612–9.
16. Kunovsky L, Kala Z, Prochazka V, Potrusil M, Dastych M, Novotny I, et al. Surgical treatment of ampullary adenocarcinoma - single center experience and a review of literature. Klin Onkol. 31(1):46–52.
17. Pittayanon R, Imraporn B, Rerknimitr R, Kullavanijaya P. Advances in diagnostic endoscopy for duodenal, including ampullary, adenoma. Dig Endosc. 2014;26(Suppl 2):10–5.
18.•• Kang SH, Kim KH, Kim TN, Jung MK, Cho CM, Cho KB, et al. Therapeutic outcomes of endoscopic papillectomy for ampullary neoplasms: retrospective analysis of a multicenter study. BMC Gastroenterol. 2017;17(1):69 **This study examined outcomes of > 100 patients who underwent endoscopic ampullectomy at five centers in South Korea from 2007 to 2014. They showed a high rate of en bloc resection (90%), high rate of endoscopic success (89%), low rates of complications and death, and very low rate of referral for surgery following endoscopic resection.**
19. Attila T, Parlak E, Alper E, Disibeyaz S, Cicek B, Odemis B. Endoscopic papillectomy of benign ampullary lesions: outcomes from a multicenter study. Turk J Gastroenterol. 2018;29(3):325–34.
20. Chung CH, Wilentz RE, Polak MM, Ramsoekh TB, Noorduyn LA, Gouma DJ, et al. Clinical significance of K-ras oncogene activation in ampullary neoplasms. J Clin Pathol. 1996;49(6):460–4.
21. Cheng CL, Sherman S, Fogel EL, McHenry L, Watkins JL, Fukushima T, et al. Endoscopic snare papillectomy for tumors of the duodenal papillae. Gastrointest Endosc. 2004;60(5):757–64.
22.•• Kandler J, Neuhaus H. How to approach a patient with ampullary lesion. Gastroenterology. 2018;155(6):1670–6 **This article provides a comprehensive, easily navigated workflow for how to approach a patient presenting with an ampullary lesion.**
23. Campos FG, Sulbaran M, Safatle-Ribeiro AV, Martinez CA. Duodenal adenoma surveillance in patients with familial adenomatous polyposis. World J Gastrointest Endosc. 2015;7(10):950–9.
24. Kinzler KW, Nilbert MC, Su LK, Vogelstein B, Bryan TM, Levy DB, et al. Identification of FAP locus genes from chromosome 5q21. Science. 1991;253(5020):661–5.
25. Bertario L, Russo A, Sala P, Varesco L, Giarola M, Mondini P, et al. Multiple approach to the exploration of genotype-phenotype correlations in familial adenomatous polyposis. J Clin Oncol. 2003;21(9):1698–707.
26. Nieuwenhuis MH, Vasen HF. Correlations between mutation site in APC and phenotype of familial adenomatous polyposis (FAP): a review of the literature. Crit Rev Oncol Hematol. 2007;61(2):153–61.
27. Campos FG. Surgical treatment of familial adenomatous polyposis: dilemmas and current recommendations. World J Gastroenterol. 2014;20(44):16620–9.
28. Brosens LA, Keller JJ, Offerhaus GJ, Goggins M, Giardiello FM. Prevention and management of duodenal polyps in familial adenomatous polyposis. Gut. 2005;54(7):1034–43.
29. Groves CJ, Saunders BP, Spigelman AD, Phillips RK. Duodenal cancer in patients with familial adenomatous polyposis (FAP): results of a 10 year prospective study. Gut. 2002;50(5):636–41.
30. Bjork J, Akerbrant H, Iselius L, Bergman A, Engwall Y, Wahlstrom J, et al. Periampullary adenomas and adenocarcinomas in familial adenomatous polyposis: cumulative risks and APC gene mutations. Gastroenterology. 2001;121(5):1127–35.
31. Sarre RG, Frost AG, Jagelman DG, Petras RE, Sivak MV, McGannon E. Gastric and duodenal polyps in familial adenomatous polyposis: a prospective study of the nature and prevalence of upper gastrointestinal polyps. Gut. 1987;28(3):306–14.
32. Bulow S, Bulow C, Nielsen TF, Karlsen L, Moesgaard F. Centralized registration, prophylactic examination, and treatment results in improved prognosis in familial adenomatous polyposis. Results from the Danish Polyposis Register. Scand J Gastroenterol. 1995;30(10):989–93.
33. Bulow S, Bjork J, Christensen IJ, Fausa O, Jarvinen H, Moesgaard F, et al. Duodenal adenomatosis in familial adenomatous polyposis. Gut. 2004;53(3):381–6.
34. Spigelman AD, Williams CB, Talbot IC, Domizio P, Phillips RK. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. Lancet. 1989;2(8666):783–5.
35. Church JM, McGannon E, Hull-Boiner S, Sivak MV, Van Stolk R, Jagelman DG, et al. Gastroduodenal polyps in patients with familial adenomatous polyposis. Dis Colon Rectum. 1992;35(12):1170–3.
36. Saurin JC, Ligneau B, Ponchon T, Lepretre J, Chavaillon A, Napoleon B, et al. The influence of mutation site and age on the severity of duodenal polyposis in patients with familial adenomatous polyposis. Gastrointest Endosc. 2002;55(3):342–7.
37. Sourrouille I, Lefevre JH, Shields C, Colas C, Bellanger J, Desaint B, et al. Surveillance of duodenal polyposis in familial adenomatous polyposis: should the Spigelman score be modified? Dis Colon Rectum. 2017;60(11):1137–46.
38. Debinski HS, Spigelman AD, Hatfield A, Williams CB, Phillips RK. Upper intestinal surveillance in familial adenomatous polyposis. Eur J Cancer. 1995;31A(7–8):1149–53.
39. Jones TR, Nance FC. Periampullary malignancy in Gardner's syndrome. Ann Surg. 1977;185(5):565–73.
40. Wallace MH, Phillips RK. Upper gastrointestinal disease in patients with familial adenomatous polyposis. Br J Surg. 1998;85(6):742–50.
41. Latchford AR, Neale KF, Spigelman AD, Phillips RK, Clark SK. Features of duodenal cancer in patients with familial adenomatous polyposis. Clin Gastroenterol Hepatol. 2009;7(6):659–63.
42. Jaganmohan S, Lynch PM, Raju RP, Ross WA, Lee JE, Raju GS, et al. Endoscopic management of duodenal adenomas in familial adenomatous polyposis–a single-center experience. Dig Dis Sci. 2012;57(3):732–7.
43. Jagelman DG, DeCosse JJ, Bussey HJ. Upper gastrointestinal cancer in familial adenomatous polyposis. Lancet. 1988;1(8595): 1149–51.
44. de Campos FG, Perez RO, Imperiale AR, Seid VE, Nahas SC, Cecconello I. Evaluating causes of death in familial adenomatous polyposis. J Gastrointest Surg. 2010;14(12):1943–9.
45. van Leerdam ME, Roos VH, van Hooft JE, Dekker E, Jover R, Kaminski MF, et al. Endoscopic management of polyposis syndromes: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2019;51(9):877–95.
46. Bertoni G, Sassatelli R, Nigrisoli E, Pennazio M, Tansini P, Arrigoni A, et al. High prevalence of adenomas and microadenomas of the duodenal papilla and periampullary region in patients with familial adenomatous polyposis. Eur J Gastroenterol Hepatol. 1996;8(12):1201–6.

47. Iida M, Aoyagi K, Fujimura Y, Matsumoto T, Hizawa K, Nakamura S. Nonpolypoid adenomas of the duodenum in patients with familial adenomatous polyposis (Gardner's syndrome). Gastrointest Endosc. 1996;44(3):305–8.
48. Chen CH, Yang CC, Yeh YH, Chou DA, Nien CK. Reappraisal of endosonography of ampullary tumors: correlation with transabdominal sonography, CT, and MRI. J Clin Ultrasound. 2009;37(1):18–25.
49. Chen CH, Tseng LJ, Yang CC, Yeh YH. Preoperative evaluation of periampullary tumors by endoscopic sonography, transabdominal sonography, and computed tomography. J Clin Ultrasound. 2001;29(6):313–21.
50. Itoh A, Goto H, Naitoh Y, Hirooka Y, Furukawa T, Hayakawa T. Intraductal ultrasonography in diagnosing tumor extension of cancer of the papilla of Vater. Gastrointest Endosc. 1997;45(3):251–60.
51. Ridtitid W, Schmidt SE, Al-Haddad MA, LeBlanc J, DeWitt JM, McHenry L, et al. Performance characteristics of EUS for locoregional evaluation of ampullary lesions. Gastrointest Endosc. 2015;81(2):380–8.
52. Okano N, Igarashi Y, Hara S, Takuma K, Kamata I, Kishimoto Y, et al. Endosonographic preoperative evaluation for tumors of the ampulla of vater using endoscopic ultrasonography and intraductal ultrasonography. Clin Endosc. 2014;47(2):174–7.
53. Rivadeneira DE, Pochapin M, Grobmyer SR, Lieberman MD, Christos PJ, Jacobson I, et al. Comparison of linear array endoscopic ultrasound and helical computed tomography for the staging of periampullary malignancies. Ann Surg Oncol. 2003;10(8):890–7.
54. Chen CH, Tseng LJ, Yang CC, Yeh YH, Mo LR. The accuracy of endoscopic ultrasound, endoscopic retrograde cholangiopancreatography, computed tomography, and transabdominal ultrasound in the detection and staging of primary ampullary tumors. Hepatogastroenterology. 2001;48(42):1750–3.
55. Schwarz M, Pauls S, Sokiranski R, Brambs HJ, Glasbrenner B, Adler G, et al. Is a preoperative multidiagnostic approach to predict surgical resectability of periampullary tumors still effective? Am J Surg. 2001;182(3):243–9.
56. Cannon ME, Carpenter SL, Elta GH, Nostrant TT, Kochman ML, Ginsberg GG, et al. EUS compared with CT, magnetic resonance imaging, and angiography and the influence of biliary stenting on staging accuracy of ampullary neoplasms. Gastrointest Endosc. 1999;50(1):27–33.
57. Baillie J. Endoscopic ampullectomy. Am J Gastroenterol. 2005;100(11):2379–81.
58. Clary BM, Tyler DS, Dematos P, Gottfried M, Pappas TN. Local ampullary resection with careful intraoperative frozen section evaluation for presumed benign ampullary neoplasms. Surgery. 2000;127(6):628–33.
59. Elek G, Gyori S, Toth B, Pap A. Histological evaluation of preoperative biopsies from ampulla vateri. Pathol Oncol Res. 2003;9(1):32–41.
60. Lee SY, Jang KT, Lee KT, Lee JK, Choi SH, Heo JS, et al. Can endoscopic resection be applied for early stage ampulla of Vater cancer? Gastrointest Endosc. 2006;63(6):783–8.
61. Posner S, Colletti L, Knol J, Mulholland M, Eckhauser F. Safety and long-term efficacy of transduodenal excision for tumors of the ampulla of Vater. Surgery. 2000;128(4):694–701.
62. 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(3):506–15.
63. Yamaguchi K, Enjoji M. Adenoma of the ampulla of Vater: putative precancerous lesion. Gut. 1991;32(12):1558–61.
64. Yamaguchi K, Enjoji M, Kitamura K. Endoscopic biopsy has limited accuracy in diagnosis of ampullary tumors. Gastrointest Endosc. 1990;36(6):588–92.
65. Howe JR, Klimstra DS, Cordon-Cardo C, Paty PB, Park PY, Brennan MF. K-ras mutation in adenomas and carcinomas of the ampulla of vater. Clin Cancer Res. 1997;3(1):129–33.
66. Relias V, Saif MW. Biological identification of ampullary adenocarcinomas. JOP. 2014;15(4):306–7.
67. Ang DC, Shia J, Tang LH, Katabi N, Klimstra DS. The utility of immunohistochemistry in subtyping adenocarcinoma of the ampulla of vater. Am J Surg Pathol. 2014;38(10):1371–9.
68. Park SH, Kim YI, Park YH, Kim SW, Kim KW, Kim YT, et al. Clinicopathologic correlation of p53 protein overexpression in adenoma and carcinoma of the ampulla of Vater. World J Surg. 2000;24(1):54–9.
69. Sato T, Konishi K, Kimura H, Maeda K, Yabushita K, Tsuji M, et al. Adenoma and tiny carcinoma in adenoma of the papilla of Vater–p53 and PCNA. Hepatogastroenterology. 1999;46(27):1959–62.
70. Takashima M, Ueki T, Nagai E, Yao T, Yamaguchi K, Tanaka M, et al. Carcinoma of the ampulla of Vater associated with or without adenoma: a clinicopathologic analysis of 198 cases with reference to p53 and Ki-67 immunohistochemical expressions. Mod Pathol. 2000;13(12):1300–7.
71. Younes M, Riley S, Genta RM, Mosharaf M, Mody DR. p53 protein accumulation in tumors of the ampulla of Vater. Cancer. 1995;76(7):1150–4.
72. Schultz NA, Werner J, Willenbrock H, Roslind A, Giese N, Horn T, et al. MicroRNA expression profiles associated with pancreatic adenocarcinoma and ampullary adenocarcinoma. Mod Pathol. 2012;25(12):1609–22.
73. Beger HG, Staib L, Schoenberg MH. Ampullectomy for adenoma of the papilla and ampulla of Vater. Langenbeck's Arch Surg. 1998;383(2):190–3.
74. Binmoeller KF, Boaventura S, Ramsperger K, Soehendra N. Endoscopic snare excision of benign adenomas of the papilla of Vater. Gastrointest Endosc. 1993;39(2):127–31.
75. Zadorova Z, Dvofak M, Hajer J. Endoscopic therapy of benign tumors of the papilla of Vater. Endoscopy. 2001;33(4):345–7.
76. Kahaleh M, Shami VM, Brock A, Conaway MR, Yoshida C, Moskaluk CA, et al. Factors predictive of malignancy and endoscopic resectability in ampullary neoplasia. Am J Gastroenterol. 2004;99(12):2335–9.
77. Norton ID, Geller A, Petersen BT, Sorbi D, Gostout CJ. Endoscopic surveillance and ablative therapy for periampullary adenomas. Am J Gastroenterol. 2001;96(1):101–6.
78. Norton ID, Gostout CJ, Baron TH, Geller A, Petersen BT, Wiersema MJ. Safety and outcome of endoscopic snare excision of the major duodenal papilla. Gastrointest Endosc. 2002;56(2):239–43.
79. Hyun JJ, Lee TH, Park JS, Han JH, Jeong S, Park SM, et al. A prospective multicenter study of submucosal injection to improve endoscopic snare papillectomy for ampullary adenoma. Gastrointest Endosc. 2017;85(4):746–55.
80. Aiura K, Imaeda H, Kitajima M, Kumai K. Balloon-catheter-assisted endoscopic snare papillectomy for benign tumors of the major duodenal papilla. Gastrointest Endosc. 2003;57(6):743–7.
81. Saurin JC, Chavaillon A, Napoleon B, Descos F, Bory R, Berger F, et al. Long-term follow-up of patients with endoscopic treatment of sporadic adenomas of the papilla of vater. Endoscopy. 2003;35(5):402–6.
82. Poincloux L, Scanzi J, Goutte M, Pereira B, Devaud H, Joubert J, et al. Pancreatic intubation facilitated by methylene blue injection decreases the risk for postpapillectomy acute pancreatitis. Eur J Gastroenterol Hepatol. 2014;26(9):990–5.
83. Hwang JC, Kim JH, Lim SG, Yoo BM, Cho SW. Endoscopic resection of ampullary adenoma after a new insulated plastic pancreatic stent placement: a pilot study. J Gastroenterol Hepatol. 2010;25(8):1381–5.

84. Kim SH, Moon JH, Choi HJ, Kim DC, Lee TH, Cheon YK, et al. Usefulness of pancreatic duct wire-guided endoscopic papillectomy for ampullary adenoma for preventing post-procedure pancreatitis. Endoscopy. 2013;45(10):838–41.
85. Elmunzer BJ, Scheiman JM, Lehman GA, Chak A, Mosler P, Higgins PD, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. N Engl J Med. 2012;366(15): 1414–22.
86. Harewood GC, Pochron NL, Gostout CJ. Prospective, randomized, controlled trial of prophylactic pancreatic stent placement for endoscopic snare excision of the duodenal ampulla. Gastrointest Endosc. 2005;62(3):367–70.
87. Singh P, Das A, Isenberg G, Wong RC, Sivak MV Jr, Agrawal D, et al. Does prophylactic pancreatic stent placement reduce the risk of post-ERCP acute pancreatitis? A meta-analysis of controlled trials. Gastrointest Endosc. 2004;60(4):544–50.
88. Chang WI, Min YW, Yun HS, Lee KH, Lee JK, Lee KT, et al. Prophylactic pancreatic stent placement for endoscopic duodenal ampullectomy: a single-center retrospective study. Gut Liver. 2014;8(3):306–12.
89. Desilets DJ, Dy RM, Ku PM, Hanson BL, Elton E, Mattia A, et al. Endoscopic management of tumors of the major duodenal papilla: refined techniques to improve outcome and avoid complications. Gastrointest Endosc. 2001;54(2):202–8.
90. Han J, Kim MH. Endoscopic papillectomy for adenomas of the major duodenal papilla (with video). Gastrointest Endosc. 2006;63(2):292–301.
91. Vogt M, Jakobs R, Benz C, Arnold JC, Adamek HE, Riemann JF. Endoscopic therapy of adenomas of the papilla of Vater. A retrospective analysis with long-term follow-up. Dig Liver Dis. 2000;32(4):339–45.
92. Irani S, Arai A, Ayub K, Biehl T, Brandabur JJ, Dorer R, et al. Papillectomy for ampullary neoplasm: results of a single referral center over a 10-year period. Gastrointest Endosc. 2009;70(5): 923–32.
93. Bohnacker S, Seitz U, Nguyen D, Thonke F, Seewald S, de Weerth A, et al. Endoscopic resection of benign tumors of the duodenal papilla without and with intraductal growth. Gastrointest Endosc. 2005;62(4):551–60.
94. Yamao T, Isomoto H, Kohno S, Mizuta Y, Yamakawa M, Nakao K, et al. Endoscopic snare papillectomy with biliary and pancreatic stent placement for tumors of the major duodenal papilla. Surg Endosc. 2010;24(1):119–24.
95. Ceppa EP, Burbridge RA, Rialon KL, Omotosho PA, Emick D, Jowell PS, et al. Endoscopic versus surgical ampullectomy: an algorithm to treat disease of the ampulla of Vater. Ann Surg. 2013;257(2):315–22.
96. Charton JP, Deinert K, Schumacher B, Neuhaus H. Endoscopic resection for neoplastic diseases of the papilla of Vater. J Hepato-Biliary-Pancreat Surg. 2004;11(4):245–51.
97. Ponchon T, Berger F, Chavaillon A, Bory R, Lambert R. Contribution of endoscopy to diagnosis and treatment of tumors of the ampulla of Vater. Cancer. 1989;64(1):161–7.