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Endoscopic resection for neoplastic diseases of the papilla of Vater

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Abstract
Optimal management of neoplastic diseases of the papilla of Vater is still controversially discussed. Until a few years ago, surgical resection or transduodenal local excision were routinely performed as definitive treatments. In order to decrease mortality and morbidity, investigators systematically started in the late 1980's to evaluate alternative methods, particularly following an endoscopic strategy. In recent years, endoscopic resection procedures (e.g., snare resection, piecemeal resection, thermal ablative techniques) proved to be feasible and safe alternatives, especially for benign neoplastic diseases of the papilla. The following review summarizes criteria for the selection of patients and describes endoscopic resection techniques. In addition, outcome concerning recurrence rates and complications of surgical and endoscopic resection procedures are evaluated.

Key words Papilla of Vater · Adenoma · ERCP · Endoscopic resection

Introduction

Benign and malignant neoplastic diseases of the papilla of Vater are rare, but with growing use of endoscopy and, especially, endoscopic retrograde cholangiopancreatography (ERCP), they are detected more and more often. Until recently, treatment of neoplastic diseases of the papilla of Vater was considered a strictly surgical topic. Usually surgical resection (radical pancreaticoduodenectomy) or transduodenal local excision (ampullectomy) were routinely performed as definitive treatments. Among the benign lesions, villous and tubular-villous adenomas are most often diagnosed. Adenomas occur sporadically or in the setting of familial polyposis syndromes, e.g., familial adenomatous polyposis (FAP). As the adenoma-carcinoma sequence is established for papillary tumors, too, and as histopathologically diagnosed adenomas potentially harbor focal malignant tissue, complete removal of these lesions is of tremendous importance. Because of the significant mortality and perioperative morbidity of radical surgical resections, investigators were searching for alternative, less-invasive treatment options. In the late 1980s, the first descriptions of endoscopic resection procedures for neoplastic diseases of the papilla of Vater were published. Today, endoscopic resection constitutes an additional therapeutic option, particularly for benign neoplastic diseases of the papilla of Vater. Of course, accurate diagnosis and tumor staging are essential to select patients for adequate therapy. The following review outlines criteria to identify patients who are suitable for endoscopic treatment and describes techniques for endoscopic resection of papillary neoplastic diseases. Furthermore, outcome and complications of endoscopic procedures are summarized.

Diagnosis and selection of patients

Optimal management of neoplastic diseases of the papilla of Vater is still not established. In addition, the individual decision of the patient and general health status, comorbidity, histology, size, infiltration depth, and location of the neoplastic lesion contribute to determine the therapeutic strategy. If surgery or an interventional endoscopic procedure is generally possible, the treatment of choice is curative excision of the tumor. In cases of papillary invasive carcinoma, pancreaticoduodenectomy (Whipple operation) and pylorus-preserving pancreaticoduodenectomy (PPPD) remain the type of resection of first choice.[1–3] Patients with a malignant neoplasm of the papilla of Vater, who are not fit for surgical resection due to severe

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comorbidity or who refuse any surgical procedure, can be taken into consideration for an endoscopic resection procedure or palliative endoscopic biliary drainage.

Concerning benign neoplastic diseases of the papilla of Vater, the treatment of choice remains controversial. Radical surgical procedures, as mentioned above, and less radical operative approaches (local excision) are still recommended therapeutic options.[4,5] With technical development and growing expertise, endoscopic excision procedures have recently become a feasible and safe alternative.

Careful diagnostic staging precedes any therapy. After clinical examination and laboratory check, usually ultrasound and/or computed tomography (CT) examinations are performed. As small ampullary neoplasms often cannot be detected by these techniques, endoscopic diagnostic procedures (ERCP and endoscopic ultrasound [EUS]) are necessary. Both forward-viewing and, particularly, side-viewing endoscopes are used to visualize the papilla of Vater and the duodenal wall. Side-viewing instruments give a more precise view of the papilla and allow better biopsy precision. Macroscopic evaluation of the tumor can reveal obvious signs of malignancy such as induration, ulceration, and submucosal or intraductal tumor extension. Moreover, the granularity of the mucosa and vital dye staining (with methylene blue or indigocarmine) may help to differentiate between benign and malignant tumors.[3] On the other hand, intramurally growing papillary carcinomas covered with normal duodenal mucosa are difficult to detect. Further endoscopic criteria for a benign lesion are a regular, well-defined margin and a soft, pale tumor.[6,7]

Sphincterotomy and sampling of the intraampullary mucosa increase diagnostic accuracy. Ponchon et al.[8] reported of a series of 52 patients presenting with ampullary tumors. In 37% of these patients the tumor was detected only after sphincterotomy, while the papilla was macroscopically normal. These results have been confirmed by other study groups, but even endoscopic forceps biopsies after sphincterotomy do not really guarantee reliable histological diagnosis of neoplastic diseases, and malignancy cannot be excluded with certainty.[9] Several authors recommend further intraampullary biopsy sampling during follow-up.[8,10]

Tumor extension is further evaluated by magnetic resonance or endoscopic retrograde cholangiopancreatography (MRCP/ERCP). It depends on the ductal infiltration, too, whether the endoscopic excision of a papillary tumor is technically feasible or not. Endoscopic snare resection is generally considered to be contraindicated if the tumor extends into the biliary or pancreatic duct.[3,10] Furthermore, cholangiography and pancreatography are performed to rule out associated stones or strictures.

Additional important information is given by conventional EUS and intraductal ultrasound (IUS). EUS is essential to assess the tumoral infiltration correctly[10,11] and is considered as an accurate method for the TNM staging of ampullary tumors.[12,13] Concerning the detection of an ampullary neoplasm, EUS seems to be superior to CT, especially in early tumor stages.[11] On the other hand, EUS cannot reliably differentiate between early carcinoma and benign adenoma,[14,15] and some authors even report of "overstaging" of the tumor due to EUS.[7]

Menzel and co-workers[16] studied the diagnostic value of IUS in comparison with EUS and CT. These authors concluded that the overall accuracy rate of local tumor diagnosis with IUS was significantly superior to that with EUS,[16] and that IUS was essential before initiating treatment.[10]

Most investigators recommend that, for endoscopic resection, the size of the tumor should not exceed 4 cm in maximal diameter, otherwise this procedure appears to be hazardous and is unlikely to be successful.[6,7]

The success of our treatment, of course, depends on the characteristics of the tumor and, therefore, every diagnosis should be confirmed by histopathology. Prior to any further therapy, a minimum of six endoscopic forceps biopsy specimens should be obtained and histopathologically examined.[6] However, even multiple endoscopic forceps biopsies (including intraductal biopsies) cannot rule out the presence of small foci of carcinoma within ampullary adenomas.[8] Several studies reported the poor sensitivity of endoscopic biopsies with regard to malignancy.[17,18] Therefore, complete excision of the papillary adenoma is essential to guarantee high diagnostic accuracy.

Benign neoplasms are mainly identified as adenomas, which are subdivided into villous, tubulovillous, and tubular adenomas.[4,19] Adenomas occur sporadically or in the setting of familial polyposis syndromes (e.g., FAP). Comparable to other malignancies (e.g., colorectal carcinoma), the adenoma-carcinoma sequence also applies to the papilla of Vater, and therefore these adenomas are considered as premalignant lesions.[20–22] The risk of transformation to malignancy in ampullary adenomas appears to be even greater than elsewhere in the duodenum.[23,24] Extremely rarely, hemangiomas, leiomyomas, leiomyofibromas, lipomas, lymphangiomas, hamartomas, and neurogenic tumors can be diagnosed.[3,4,25]

Adenomas and carcinomas/high-grade dysplasias of the papilla of Vater frequently coexist within the same neoplasm. Siewert and co-workers (Heidecke et al.[26]) recently studied the impact of grade of dysplasia in villous adenomas of Vater's papilla on the patients' prognoses. They found out that many preoperatively diagnosed adenomas with low-grade and high-grade

dysplasia exhibited invasive carcinoma at the postoperative histological examination (27% and 29%, respectively). In addition, they observed an increased risk of postoperative recurrence and development of invasive carcinoma after the primary diagnosis of an adenoma with high-grade dysplasia, while no recurrence was observed in the low-grade dysplasia group following local resection and benign postoperative histology.[26] Similar results were published by Hoyuela and colleagues.[27] This study group also described divergent pre- and postoperative diagnosis of ampullary tumors. Even intraoperative frozen study was unable to detect malignancy in one patient with infiltrating carcinoma.[27] Therefore, it is of vital importance to resect and microscopically examine the entire neoplastic lesion for the reliable exclusion of any focus of carcinoma or high-grade dysplasia. Otherwise, the presence of malignancy may be missed. Recently, Desilets and coworkers[7] reported very high positive and negative predictive values shown when well-defined macroscopic and radiographic criteria were strictly applied to distinguish between benign and malignant lesions.

Duodenal and, particularly, periampullary adenomas are found in 50%–100% of FAP patients.[24,28,29] The cumulative risk of periampullary adenocarcinoma in FAP patients is 10% at the age of 60 years.[24] Due to prophylactic colectomy, today periampullary carcinoma is one of the leading causes of mortality in FAP patients.[30] Therapy for FAP patients with periampullary adenomas remains controversial, because resection of one adenoma does not eliminate the continued risk of malignant transformation of other adenomas.[24,31] Therefore, patients with FAP should have regular endoscopic periampullary surveillance, including tissue sampling, to detect the development of high-grade dysplasia and carcinoma.[31,32] While some authors recommend surveillance every 3 to 5 years,[33] others perform control endoscopy more frequently: at 3 months following ablative therapy and yearly thereafter.[34]

These remarks are meant to underline the critical importance of diagnosis before endoscopic treatment of papillary tumors. Without any endoscopic, radiographic, and bioptic sign of malignancy, according to the criteria mentioned above, curative endoscopic excision of papillary neoplasms constitutes a real therapeutic option.[7,35] En-bloc resection improves histopathological diagnosis of the tumor and is important to exclude or detect focal high-grade dysplasia or even carcinoma. In cases of carcinoma, still more radical surgical resection procedures are recommended, provided that no serious comorbid conditions exist and the patient does not generally refuse surgery. Endoscopic follow-up must be ensured to guarantee early detection of residual or recurrent neoplastic tissue after endoscopic resection.[35]

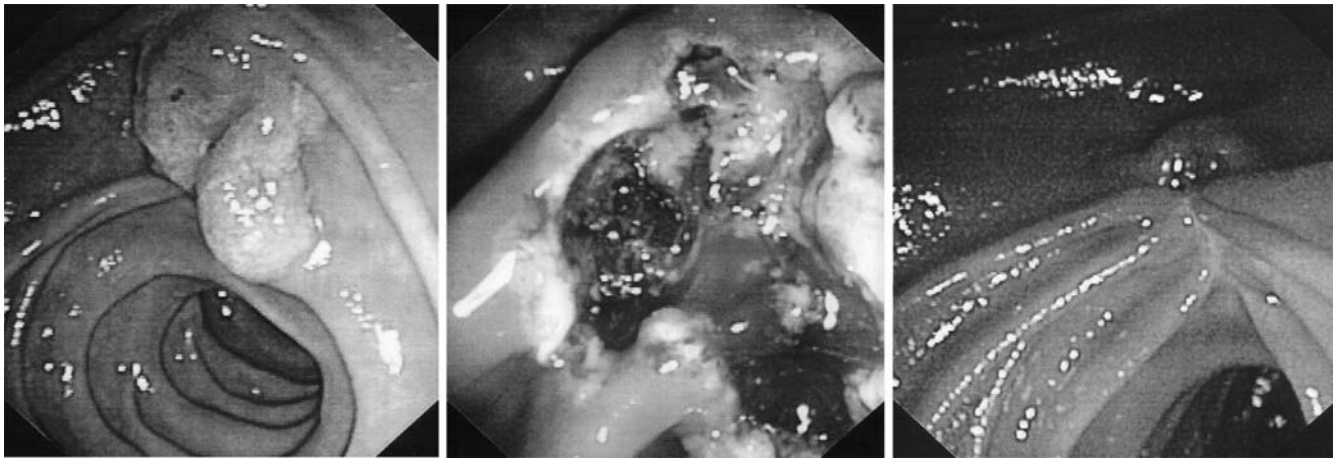
Techniques of endoscopic resection and ablative therapies

Generally, different endoscopic procedures are practiced: options include snare excision, piecemeal resection, and several endoscopic thermal ablative techniques.[6,32]

The first methodical excisions and ablative techniques were reported in 1988 and 1989.[8,36,37] Depending on the individual circumstances, very often combined treatment modalities are practiced.

At the beginning of the endoscopic excision procedure, the endoscopist identifies the extension/margins of the neoplastic lesion to determine whether en-bloc excision is feasible or not. En-bloc resection is the preferable method, as it enables complete removal of the neoplastic lesion with the advantage of submitting ample tissue for histopathological examination (Fig. 1a–c). To faciliate snare excision, some groups prefer to elevate and separate the tumor from the underlying muscle layer by submucosal injection of saline.[7] Epinephrine is optionally added to reduce bleeding.[7] Methylene blue can be added to the saline to improve the endoscopic visualization of the tumor and, particularly, its margins. The submucosal injection of a saline solution can serve as a criteria of malignancy, too, because lack of elevation may be an indication of invasive growth of the tumor. Pre-resection sphincterotomy is often performed and may faciliate excision, particularly if adenomatous tissue is located in the biliary orifice.[7] Some investigators recommend extending sphincterotomy to normal duodenal tissue to improve drainage after polypectomy.[7] Pancreatic and biliary duct stenting is optionally performed, to prevent pancreatitis and cholangitis, respectively. Moreover, prophylactic stenting may allow more radical ablation of neoplastic tissue, especially around the biliary and pancreatic duct orifices.

The aim of endoscopic snare excision is to obtain adequate resection margins. If the adenoma cannot be resected completely or if en-bloc resection is not technically feasible, additional treatment options are available. Residual adenomatous tissue is eliminated by further snare resection, piecemeal resection, or by different thermal modalities: monopolar/bipolar coagulation, Nd-YAG-Laser, photodynamic therapy, and argon plasma coagulation (APC) are most common,[7,8,32,36,37] although today some are considered inferior to others, e.g., Nd-YAG laser ablation can cause deep tissue injury. Particularly around the biliary and pancreatic orifices, thermal methods are suited to the coagulating of residual tissue. Furthermore, tumor bleeding can be stopped by coagulation.[10] Still, thermal ablative methods appear effective, but the significant disadvantage is the lack of histopathological control,



a,b c

Fig. 1a–c. Papillary adenomas. **a** Before resection; **b** immediately after snare resection, in two pieces; **c** 3 months after resection, without any residual adenomatous tissue

if patients are treated exclusively by these techniques. Neoplastic lesions may be underestimated and carcinoma overlooked. Therefore, thermal ablation is predominantly used as a complementary method. Resection is usually followed by a cholangiogram to ensure adequate biliary drainage.[15]

In most cases, endoscopic snare excision or piecemeal resection can be performed in a single session,[6,15] but if necessary, resection can be completed in a second or even further sessions.[7] If the neoplastic lesion is resected completely and there is no sign of residues in control biopsies, the patient should undergo close regular endoscopic surveillance, including biopsy taking: usually follow-up duodenoscopies are performed at 1, 6, and 12 months after resection and yearly thereafter. In cases of carcinoma in situ, detected by histopathological examination and removed completely, the patient should undergo close endoscopic and bioptic observation. If invasive carcinoma is diagnosed, the patient should be referred to surgery for pancreaticoduodenectomy.[27]

Discussion

Until a few years ago, surgery was considered the standard treatment for neoplastic diseases of the papilla of Vater. Especially in cases of proven or suspected malignancy, radical resection procedures were performed. On the other hand, pure adenomas, which are, by definition, confined to the mucosa, do not have to be resected radically. Therefore, investigators were searching for alternative, less-invasive treatment options, in order to reduce mortality and perioperative morbidity. Local surgical resection procedures have been well-established for many years. In recent years, endoscopic resection techniques have been developed and evaluated.

Information concerning outcome after radical and local surgical resections differs considerably. The mortality of pancreaticoduodenectomy performed for ampullary tumors today generally varies from 0 to 10%,[1,2,14,18,38] although not all studies distinguished between benign and malignant papillary tumors. Recurrence rates after pancreaticoduodenectomy are lower than those after local resection methods, but, in comparison, radical surgical procedures are associated with potentially increased mortality and morbidity and longer duration of hospitalization.[2,6,14,18] Today, specialized high-volume centers achieve notably low mortality rates.[2] Particularly, local surgical resection procedures can be performed very safely and effectively. Treitschke and colleagues[4] reported surgical ampullectomy in 49 patients with papillary adenoma. They observed no perioperative mortality and no recurrence after a median follow-up of 45 months (range 6–180 months).[4] Other surgical study groups have reported smaller series with higher recurrence rates after local excision, the rates being comparable to those in endoscopic resection procedures.[18,41–43] Moreover, Cahen and colleagues[18] reported a high percentage of incomplete tumor excisions after local surgical resection.

The first methodical results of endoscopic treatment (snare resection and thermal ablative therapies) of ampullary adenoma were published in the late 1980s.[8,36,37] Lambert et al.[37] reported laser-photodestruction (Nd-YAG and argon; partially associated with snare resection) in 8 patients with ampullary adenoma and observed only one recurrence after 2 years.[37] Shemesh et al.[36] treated 4 patients diagnosed with recurrent

ampullary adenoma after local surgical resection by endoscopic sphincterotomy and fulguration. During a 12- to 24-month follow-up, there were no recurrences. Ponchon and colleagues[8] were the first to treat a collective of 11 patients with ampullary tumors (adenomas and adenomas with an intramucosal carinomatous focus) by endoscopic snare resection alone, laser photodestruction alone, or a combination of both. The study group observed only one recurrence (range of follow-up 14–53 months). After these promising first results further studies followed.

In the meantime, several study groups have published data (some published as abstracts alone) concerning the safety, technical feasibility, and outcome in patients with papillary adenoma treated endoscopically, but data on long-term endoscopic follow-up are still rare.

Endoscopic resection procedures imply specific complications that have to be considered. Immediate complications are bleeding, acute pancreatitis, and perforation of the duodenum.[32]

Bleeding due to snare and piecemeal resection is usually mild and can mostly be managed endoscopically by local injection.[6,32] To reduce bleeding, many endoscopists add epinephrine to the saline solution that is used for tumor elevation.[7] Mild postprocedure pancreatitis has been described in up to 15% of procedures,[6,32,39] and individual cases of severe necrotizing pancreatitis have been reported, too.[40] Pancreatic duct stenting before resection is often practiced to protect from postprocedure pancreatitis,[10,34] but results are not consistent.[6,32] Therefore, the discussion concerning prophylactic pancreatic duct stenting is still controversial. Biliary endoprotheses are inserted in patients with obstructed ducts or to prevent cholangitis,[6,10] although cholangitis is only described in a very few cases.[39] Particularly, if piecemeal resection and/or thermal ablative methods are used, it is recommended to place stents to assure biliopancreatic drainage. Stents are usually removed after a few days or 1 week. Duodenal perforation is a rare complication. Norton et al.[32] described one patient who was treated endoscopically by use of a hemoclip. In summary, periinterventional morbidity after endoscopic resection procedures is low and most complications can be handled conservatively.

Concerning late complications, stenoses of the pancreatic and bile ducts at the papillectomy site are observed and may cause pancreatitis and/or cholestasis, respectively.[3,32] These patients, too, are usually treated by temporary stenting. Procedure-related deaths are extremely rare; most investigators reported no procedure-related death at all.[6,7,15] Very few individual cases of death due to necrotizing pancreatitis and duodenal perforation after endoscopic resection procedures are described.[39,40]

In terms of recurrence rates, the following data are available. Binmoeller and co-workers[6] were the first to report a relatively large collective of 25 patients with benign adenoma of the papilla of Vater who were treated by snare papillectomy (en bloc and piecemeal resection). At a median follow-up of 37 months (range 7–79 months), they detected 6 patients with recurrent benign adenoma (24%). Five of these patients could be retreated endoscopically by snare resection and/or diathermic fulguration and 1 was referred to surgery due to intraductal tumor spread.[6]

Another study group reported 41 patients with benign and malignant papillary tumors.[7] If there was no endoscopic or radiographic sign of malignancy, these patients were treated by biductal sphincterotomy with pancreatic duct stenting, followed by piecemeal resection and thermal ablation. The study group preferred piecemeal resection to snare excision because of the former procedure's very few complications (2 of 41 patients [4.9%]; 2 of 108 ERCPs [1.9%]) without any perforation. Thirteen patients finally had endoscopic resection; 12 of these 13 patients were lesion-free after a total of 32 ERCPs (mean no. 2.7; range 1–5). By subsequent use of defined criteria (concerning diagnosis and selection of patients) to distinguish between benign and malignant lesions, none of the endoscopically resected adenomas finally turned out to contain carcinoma, while one high-grade dysplasia and one low-grade dysplasia were detected. On the other hand, cancer was histopathologically confirmed in 13 of 15 suspicious tumors (the missing 2 were not resected at all because of comorbid conditions).[7] Except for 1 patient with FAP with a very aggressive residual tumor, all patients with adenomas had successful endoscopic resection. Over a mean follow-up of 19 months (range 2–66 months), no recurrence was detected.

Norton and co-workers[32] recently presented a retrospective study including 26 patients with papillary adenoma who were treated by endoscopic snare excision. Follow-up endoscopy (available for 21 patients; median 9 months; range 2–32 months) revealed recurrent/residual adenomatous tissue in only 2 patients (10%). Thus, despite a lack of studies with identical patient collective and inclusion criteria, outcome concerning adenoma recurrence rates after endoscopic resection is comparable to outcome following transduodenal ampullectomy.[18,32]

In addition to these reports, several smaller studies were published.[15,27] Park et al.,[15] for example, treated four patients with ampullary adenoma. They observed no mortality and no recurrence after 16–37 months of follow-up (one patient was lost to follow-up).

In conclusion, recurrent adenomas or residual adenomatous tissue are observed in about 0–26% of patients after endoscopic resection,[6,7,15,32] possibly de-

pending on patient selection and inclusion criteria. These patients can either be retreated endoscopically (by snare excision, piecemeal resection, and/or thermal ablation), undergo regular endoscopic surveillance with periodic biopsies, or undergo a surgical procedure (pancreaticoduodenectomy or local resection), depending on histopathology. Recent results indicate that, with precise diagnosis and careful patient selection according to defined criteria, a very high percentage of successful endoscopic resections of papillary adenomas can be achieved.[7,32]

These results suggest that the outcome of treatment of papillary adenomas at either surgical or gastroenterological centers has significantly improved over the past few years. Particularly, high-volume centers with great specific expertise report promising results after local resection procedures, and very low recurrence rates.

Even after careful patient selection, the risk of recurrence and the possibility of malignant transformation after local (endoscopic or surgical) resection still should not be underestimated. Therefore, regular endoscopic surveillance after local resection is strongly recommended, especially in patients with familial polyposis syndromes.

Current data and our own experience prove that endoscopic resection and/or ablative procedures in well-selected patients with benign papillary adenomas are safe and technically feasible.[15,34] In addition, patients with papillary tumors that do not fulfill the above-mentioned criteria, and even those with carcinoma (if there are serious comorbid conditions or if the patients refuse any surgical procedure), can be treated endoscopically. Because of the co-expression of benign adenoma and malignant tumors, the adenoma-carcinoma sequence of papillary tumors and the experience that endoscopic forceps biopsies still often fail to detect invasive carcinoma and high-grade dysplasia, complete resection of papillary neoplasms is strongly recommended. Endoscopic resection can also be performed as a palliative procedure. However, every patient with a papillary tumor still requires an individual therapeutic decision, and surrounding factors must be considered.

The most successful method of endoscopic resection and/or thermal ablation remains to be determined. Because of the technical equipment and personal expertise needed, interventional endoscopic procedures should be restricted to high-volume centers. The effectiveness and safety of the resection procedure depends on the experience of the endoscopist. Further studies, particularly direct comparisons between surgical and endoscopic procedures, are required to improve patient selection and define therapeutic guidelines.

References

1. Allema JH, Reinders ME, van Gulik TM, van Leeuwen DJ, Verbeel de Wit LT, Gouma DJ (1995) Results of pancreaticoduodenectomy for ampullary carcinoma and analysis of prognostic factors for survival. Surgery 117:247–253
2. Beger HG, Treitschke F, Gansauge F, Harada N, Hiki N, Mattfeldt T (1999) Tumor of the ampulla of Vater — experience with local or radical resection in 171 consecutively treated patients. Arch Surg 134:526–532
3. Kim MH, Lee SK, Seo DW, Won SY, Lee SS, Min YI (2001) Tumors of the major duodenal papilla. Gastrointest Endosc 54: 609–620
4. Treitschke F, Beger HG, Meessen D, Schoenberg MH (2000) Gutartige Tumore der Papilla Vateri. Dtsch Med Wochenschr 125:1030–1034
5. Hartenfels IM, Dukat A, Burg J, Hansen M, Jung M (2002) Adenome der Ampulla Vateri und des Duodenums. Chirurg 73:235–240
6. Binmoeller KF, Boaventura S, Ramsperger K, Soehendra N (1993) Endoscopic snare excision of benign adenomas of the papilla of Vater. Gastrointest Endosc 39:127–131
7. Desilets DJ, Dy RM, Ku PM, Hanson BL, Elton E, Mattia A, Dowell DA (2001) Endoscopic management of tumors of the major duodenal papilla: refined techniques to improve outcome and avoid complications. Gastrointest Endosc 54:202–208
8. Ponchon T, Berger F, Chavaillon A, Bory R, Lambert R (1989) Contribution of endoscopy to diagnosis and treatment of tumors of the ampulla of Vater. Cancer 64:161–167
9. Menzel J, Poremba C, Dietl KH, Böcker W, Domschke W (1999) Tumors of the papilla of Vater — inadequate diagnostic impact of endoscopic forceps biopsies taken prior to and following sphincterotomy. Ann Oncol 10:1227–1231
10. Vogt M, Jakobs R, Riemann JF (2001) Rationale for endoscopic management of adenoma of the papilla of Vater: options and limitations. Langenbeck's Arch Surg 386:176–182
11. Nattermann C, Dancygier H (1993) Endosonography in oncology of the upper gastrointestinal tract. Schweiz Med Wochewschr 123:919–931
12. Rösch T, Braig C, Gain T, Feuerbach S, Siewert JR, Schusdziarra V, Classen M (1992) Staging of pancreatic and ampullary carcinoma by endoscopic ultrasonography. Comparison with conventional sonography, computed tomography and angiography. Gastroenterology 102:188–199
13. Kubo H, Chijiiwa Y, Akahoshi K, Hamada S, Matsui N, Nawata H (1999) Pre-operative staging of ampullary tumours by endoscopic ultrasound. Br J Radiol 72:443–447
14. Rattner DW, Fernandez-del Castillo C, Brugge WR, Warshaw AL (1996) Defining the criteria for local resection of ampullary neoplasms. Arch Surg 131:366–371
15. Park SW, Song SY, Chung JB, Lee SK, Moon YM, Kang JK, Park IS (2000) Endoscopic snare resection for tumors of the ampulla of Vater. Yonsei Med J 41:213–218
16. Menzel J, Hoepffner N, Sulkowski U, Reimer P, Heinecke A, Poremba C, Domschke W (1999) Polypoid tumors of the major duodenal papilla: preoperative staging with intraductal US, EUS, and CT — a prospective, histopathologically controlled study. Gastrointest Endosc 49:349–357
17. Yamaguchi K, Enjoji M, Kitamura K (1990) Endoscopic biopsy has limited accuracy in diagnosis of ampullary tumors. Gastrointest Endosc 36:588–592
18. Cahen DL, Fockens P, de Wit LT, Offerhaus GJ, Obertop H, Gouma DJ (1997) Local resection or pancreaticoduodenectomy for villous adenoma of the ampulla of Vater diagnosed before operation. Br J Surg 84:948–951
19. Scarpa A, Capelli P, Zamboni G, Oda T, Mukai K, Bonetti F, Martignoni G, Iacono C, Serio G, Hirohashi S (1993) Neoplasia of the ampulla of Vater. Ki-ras and p53 mutations. Am J Pathol 42:1163–1172

20. Yamaguchi K, Enjoji M (1991) Adenoma of the ampulla of Vater: putative precancerous lesion. Gut 32:1558–1561
21. Stolte M, Pscherer C (1996) Adenoma-carcinoma sequence in the papilla of Vater. Scand J Gastroenterol 31:376–382
22. Wittekind C, Tannapfel A (2001) Adenoma of the papilla and ampulla — premalignant lesions? Langenbeck's Arch Surg 386: 172–175
23. Seifert E, Schulte F, Stolte M (1992) Adenoma and carcinoma of the duodenum and papilla of Vater: a clinicopathologic study. Am J Gastroenterol 87:37–42
24. Björk J, Åkerbrant H, Iselius L, Bergman A, Engwall Y, Wahlström J, Martinsson T, Nordling M, Hultcrantz R (2001) Periampullary adenomas and adenocarcinomas in familial adenomatous polyposis: cumulative risks and APC gene mutations. Gastroenterology 121:1127–1135
25. Sobol S, Cooperman AM (1978) Villous adenoma of the ampulla of Vater. An unusual cause of biliary colic and obstructive jaundice. Gastroenterology 75:107–109
26. Heidecke CD, Rosenberg R, Bauer M, Werner M, Weigert N, Ulm K, Roder JD, Siewert JR (2002) Impact of grade of dysplasia in villous adenomas of Vater's papilla. World J Surg 26:709–714
27. Hoyuela C, Cugat E, Veloso E, Marco C (2000) Treatment options for villous adenoma of the ampulla of Vater. HPB Surgery 11:325–331
28. Bulow S, Alm T, Fausa O, Hultcrantz R, Jarvinen H, Vasen H (1995) Duodenal adenomatosis in familial adenomatous polyposis. DAF Project Group. Int J Colorectal Dis 10:43–46
29. Church JM, McGannon E, Hull-Boiner S, Sivak MV, Van Stolk R, Jagelman DG, Fazio VW, Oakley JR, Lavery IC, Milsom JW (1992) Gastroduodenal polyps in patients with familial adenomatous polyposis. Dis Colon Rectum 35:1170–1173
30. Arvanitis ML, Jagelman DG, Fazio VW, Lavery IC, McGannon E (1990) Mortality in patients with familial adenomatous polyposis. Dis Colon Rectum 33:639–642
31. Bleau BL, Gostout CJ (1996) Endoscopic treatment of ampullary adenomas in familial adenomatous polyposis. J Clin Gastroenterol 22:237–241
32. Norton ID, Gostout CJ, Baron TH, Geller A, Petersen BT, Wiersema MJ (2002) Safety and outcome of endoscopic snare excision of the major duodenal papilla. Gastrointest Endosc 56:239–243
33. Sawada T, Muto T (1995) Familial adenomatous polyposis: should patients undergo surveillance of the upper gastrointestinal tract? Endoscopy 27:6–11
34. Norton ID, Gostout CJ (1998) Management of periampullary adenoma. Dig Dis 16:266–273
35. Schäffer M, Becker HD. Diagnostik und Therapie des Papillentumors. Dtsch Med Wochenschr 124:69–72
36. Shemesh E, Nass S, Czerniak A (1989) Endoscopic sphincterotomy and endoscopic fulguration in the management of adenoma of the papilla of Vater. Surg Gynecol Obstet 169:445–448
37. Lambert R, Ponchon T, Chavaillon A, Berger F (1988) Laser treatment of tumors of the papilla of Vater. Endoscopy 20:227–231
38. Chareton B, Coiffic J, Landen S, Bardaxoglou E, Campion JP, Launois B (1996) Diagnosis and therapy for ampullary tumors: 63 cases. World J Surg 20:707–712
39. Vogt M, Jakobs R, Benz C, Arnold JC, Adamek HE, Riemann JF (2000) Endoscopic therapy of adenomas of the papilla of Vater. A retrospective analysis with long-term follow-up. Digest Liver Dis 32:339–345
40. Martin JA, Haber GB, Kortan PP, Raijman I, Abedi M, DuVall JA et al. (1997) Endoscopic snare ampullectomy for resection of benign ampullary neoplasms (abstract). Gastrointest Endosc 45:AB139
41. Branum GD, Pappas TN, Meyers WC (1996) The management of tumors of the ampulla of Vater by local resection. Ann Surg 224:621–627
42. Ryan DP, Schapiro RH, Warshaw AL (1986) Villous tumors of the duodenum. Ann Surg 203:301–306
43. Alstrup N, Burcharth F, Hauge C, Horn T (1996) Transduodenal excision of tumours of the ampulla of Vater. Eur J Surg 162:961–967