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Rationale for endoscopic management of adenoma of the papilla of Vater: options and limitations

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Abstract *Background:* Several studies and our own results prove that endoscopic therapy in selected cases of benign adenomas is safe and technically feasible. In patients refusing surgery or patients with high comorbidity and poor physical health status, endoscopic resection is an excellent alternative. *Discussion:* The decision for endoscopic or surgical excision of adenomas is determined by general health status, histology, size, location, and depth of the lesion. In carcinoma of the papilla of Vater it is important to assess the tumoral ductal infiltration correctly to determine whether endoscopic resection is a viable option. Intraductal ultrasound is essential before initiating treatment and it therefore contributes to conservative therapy in patients with tumors of the papilla of Vater. Temporary placement of a short pancreatic duct stent may protect against pancreatitis and might allow more excessive ablation of adenomatous tissue, especially around the pancreatic duct orifice. After endoscopic sphincterotomy, biliary and pancreatic endoprostheses can be inserted easily in cases of obstructed pathways or cholangitis and pancreatitis due to tumor obstruction. Argon plasma coagulation can be used to treat oozing tumor hemorrhages or to vaporize tumoral residues after endoscopic snare resection. Endoscopic surveillance is essential after surgical or endoscopic resection of adenomas of the papilla of Vater.

Keywords Adenoma · Carcinoma · Papilla of Vater · Major duodenal papilla · Endoscopic snare resection · Endoscopic therapy · Endoscopic biopsy · EUS · IDUS · ERCP

Introduction

Tumors of the papilla of Vater are rare. In autopsies in the early 1930s the incidence of benign lesions of the papilla ranged between 0.04% and 0.64% [55,57]. Benign tumors of the papilla and periampullary region are detectable in 60–100% of the patients with familial adenomatous polyposis syndrome [50,60]. About 70% of neoplastic lesions occurring at the papilla and ampulla of Vater are adenomas; 25–30% of carcinomas and the rest comprise a wide range of benign and malignant disease [43]. Adenoma of the ampulla of Vater is considered to be a premalignant lesion. In adenomas of the papilla of Vater an adenoma–carcinoma sequence (ACS) is generally accepted [61]. Depending on the size of the adenoma and the presence of villous adenoma cells, carcinomatous cell aggregations inside the adenoma are found in 30% of the patients [48]. In large villous adenomas of the papilla of Vater, the histological study of surgical specimens shows carcinomatous changes in up to 60% [69,68]. Thus, management of tumors of the papilla of Vater is complicated by a high incidence of malignancy [54]. In adenomas of the papilla of Vater, the main goal is first to exclude malignancy and if neoplastic tissues must be treated, adequate tumor staging and excision are paramount. This paper focuses on spontaneous adenomas and carcinomas of the papilla of Vater. Cases associated with familial adenomatous polyposis are not discussed.

Conventional diagnostics in adenomas of the papilla Vateri

Clinical signs (duration of symptoms, weight loss, anemia, jaundice, abdominal pain), technical investigations (chest X-ray, transabdominal ultrasound, US, computed tomography, CT, and laboratory tests), and macroscopic endoscopic findings cannot predict the histological entity [43, 13, 8,52] and more than one third of carcinomas can mimic benign tumors [42]. In controlled, prospective studies, methods such as hypotonic duodenography [53], CT [9], magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP) [2], and US [21,29] were significantly inferior to endoscopic diagnosis. Macroscopic appearance, site and size of the lesion, and tumoral stenosis can be visualized selectively using endoscopy, e.g., side view duodenoscopy (SVD) [33,34]. The extent of pancreatic and common bile duct involvement can be demonstrated by endoscopic retrograde cholangiopancreatography (ERCP) and intraductal ultrasound (IDUS) [21,29]. Furthermore, the value of endoscopy lies in its being able to obtain a histological diagnosis before surgery to differentiate neoplastic tumors of the papilla from inflammatory pseudotumors of the ampulla and complications of the papilla due to lithiac disease [26].

Options and limitations of endoscopic biopsies in tumors of the papilla of Vater

Endoscopic biopsies can be obtained from the surface of the tumor using simple forceps technique. The accuracy of superficial biopsies in detecting carcinoma has been reported to range from 45 to 85% [69,68]. Superficial biopsies often result in sampling errors which are not representative for the entire lesion. Focal areas of malignancy often arise in deeper layers of adenoma and therefore often escape the surface biopsies during endoscopy. In some studies, endoscopic biopsies have produced false-negative result rates prior to surgery, ranging from 25 to 56% [69, 49, 19,11]. Biopsies taken during scheduled follow-up from intraampullary and deeper tumor parts after performing EST improved the sensitivity and specificity in predicting malignant tumors of the papilla [66, 42,13]. Using these aggressive biopsy strategies, malignancies were detected in up to 90% of the cases [52]. Nevertheless, negative prediction values (NPV) were still too low (60–75%) to exclude malignancy with certainty. If histological examination of papillary biopsies does not reveal carcinoma, EST can be recommended after endoscopic ultrasound (EUS) is performed. However, EST has some drawbacks. Firstly, it disturbs the diagnostic assessment of parietal spread by EUS. Secondly, it may lead to complications such as hemorrhage, cholangitis, and pancreatitis, which are mostly minor and easy

to treat [43]. Thirdly, over- and underestimation of histological changes (e.g., atypia-like changes early after snare resection, necrosis of tumor cells) have been reported [66, 7,17]. To avoid false-positive and false-negative results, EST should be combined with delayed biopsies of the papilla/ampulla only (up to 7–10 days later).

## Advantages and limitations of EUS and IDUS in tumors of the papilla of Vater

In adenomas of the papilla, EUS and IDUS are used to exclude malignant tumor infiltration. Most patients have small adenomas of the papilla of Vater which are easily visualized by EUS. Tumor size, depth of infiltration, the formation and echogenity of lymph nodes can be determined. Although EUS and IDUS cannot deliver a histopathologic diagnosis, they do identify features that are compatible with specific tissue diagnoses. Taking into account criteria described by Rösch et al [46], EUS and IDUS seem to differentiate localized tumor growth of adenomas and invasive growth of carcinomas of the papilla. Diagnosis must be confirmed histopathologically, either by endoscopic biopsy, fine needle biopsy or resection of the tumor.

The accuracy of EUS in assessing T1 carcinomas is reported to be 60%, whereas the accuracy is 92.3% in T2 carcinoma [63]. Overstaging is reported to occur in as many as one third of T1 lesions [31], which is often due to inflammatory edema of the submucosa or from associated pancreatitis. EUS has been used as the most accurate way of identifying superficial tumors (adenomas and intramucosal carcinomas) suitable for local resection [59, 64,31] and determining tumor stage prior to surgery [2, 53, 21, 29, 46, 63,62]. Several studies have reported an overall accuracy rate of EUS of 78–90.6% [21, 46, 62, 31,70].

The capability of IDUS in diagnosing tumors of the papilla of Vater has been reported previously [21,29]. Because IDUS has a higher ultrasound frequency than EUS (20 MHz versus 12 MHz), the exact anatomy of the papilla and of the Oddi's muscle layer can be demonstrated as a hypoechoic layer around the bile duct and the pancreatic duct 21, 27, 28, 29. Two controlled and randomized studies showed excellent results in differing T1 from T2 tumors by the use of IDUS [21,29]. The overall accuracy rate of IDUS in assessing T stage was 86.7% and 87.5%, respectively [21,29]. T1 carcinomas were correctly diagnosed in 100%, T2 in 92.3%, T3 in 100% and T4 in 75% [21].

In T3 carcinomas, accuracy of EUS and IDUS showed similar sensitivity and specificity rates (i.e., about 91.7%) [21, 63, 62,31]. Nonresectability can be assessed accurately. Underestimating the depth of invasion occurs more often in T4 carcinomas, possibly due to the limited USpenetration at large distances.

Fig. 1a–c Tubulovillous adenoma of the papilla of Vater. **a** Prior to endoscopic snare resection (ESR). **b** One week after ESR. **c** One year after ESR biopsy without adenoma
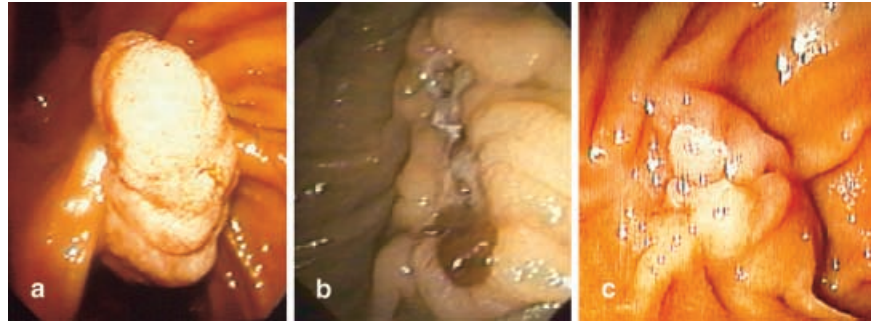
EUS is helpful in depicting lymph node metastases but is not always accurate in defining the nonmetastatic nature of lymphadenopathy. Neither IDUS nor EUS seem to be suitable for correct detection of distant lymph node metastases [68, 21, 65, 63,58]. In general, IDUS presents advantages in depicting tumor infiltration beyond the muscle layer of the sphincter of Oddi into the pancreatic parenchyma. Therefore, IDUS should be preferred for small tumors and EUS for large tumors which extend into the pancreatic parenchyma.

Staging of carcinoma of the ampulla of Vater has a reported accuracy of 80–90% in centers with special expertise in EUS and IDUS [31,58]. The value of IDUS, EUS, and CT in determining tumor staging according to the TNM classification has been assessed [29, 65, 63, 62, 47,28] and shows that IDUS is the single most accurate imaging method for diagnosing benign and malignant tumors of the papilla of Vater. In the future, minimally invasive techniques for resection of seemingly benign tumors and of small carcinomas of the papilla should preferably be based on IDUS [21,29], but EUS and IDUS may possibly give complementary information [32,27].

Intraoperative EUS

Following local surgical excision of the ampulla, some surgeons [20,16] perform intraoperative endoscopy of the dilated bile and pancreatic ducts to grossly assess the margins [15], even if the patient is not considered a candidate for partial pancreatoduodenectomy. If the duct margins are positive for tumor, local recurrence is likely and the addition of a concomitant hepatico-jejunostomy will prevent jaundice, providing more durable palliation.

Endoscopic therapy of adenomas of the papilla of Vater

Tumors of the papilla of Vater often lead to significant comorbidity. Symptoms such as abdominal pain, vomitus, anemia, jaundice, pancreatitis, and cholangitis due to bleeding and tumor obstruction of the bile and pancreatic ducts are common. The advantage of endoscopic diagnostics in tumors of the papilla of Vater is the possibility of therapeutic intervention: Treatment can be initiated during the same session of diagnostic endoscopy. In stenotic tumors, massive duodenal diverticulas, submucosal spreading of the tumor or circumferential duodenal tumor masses, the use of endoscopy for diagnosis and therapy can be limited.

Adenomas of the papilla of Vater have to be resected completely. Due to the low incidence of the disease, controlled therapy studies have not been conducted so far. Published results from surgical and endoscopic centers can hardly be compared because of significant differences in patient age, comorbidity, and general health status [57, 43, 33, 53, 42, 13, 8, 25, 12, 67, 18, 4, 6,14].

Where adenoma are pedunculated and no submucosal infiltration can be detected by EUS, a diathermy snare resection is easy to perform in one session (see Fig. 1). The papilla and parts of the ampulla are easy to resect using endoscopic diathermy snare, but a small plastic stent (5F) should be inserted into the pancreatic duct to prevent obstructive pancreatitis as a result of local edema. A protective stent might allow more liberal ablation of adenomatous tissue, especially around the pancreatic duct orifice. Complications such as mild post-interventional pancreatitis or minor oozing type bleedings are rare and easy to manage conservatively. In larger adenomas and semicircularly spreading tumors, the resection must be performed in several sessions by the snare or by large bagger forceps (piece-meal resection). Tiny tumor residues are treated by APC beamer. Additional treatment (i.e., endoscopic laser, APC beamer, photodynamic therapy) is an option, too [1,25].

The decision between endoscopic and surgical excision is determined by size, location, and depth of the lesion. A Whipple-Kausch procedure is used for radical excision and is an adequate treatment in patients with carcinoma of the papilla of Vater. A standard surgical procedure for adenomas of the papilla has so far not been established; however, Whipple's operation is often indicated, even for adenomas of the papilla, because occult carcinoma can be detected more often when the tumor is

increased in size or shows an increasing degree of dysplastic changes and in patients with pure villous adenomas [13,8]. The radical surgical approach is also recommended in some early forms of cancer because in T1 carcinomas, lymph node involvement occurs in up to 20% of cases [65].

In 1997 Cahen et al. [12] documented an acute complication rate of 64%, a late complication rate of 55%, and one surgery-related death after Whipple's resection. After local resection they reported an acute and late complication rate of 25% and 8%. The duration of hospitalization was longer after surgical treatment than after endoscopic therapy.

In adenomas of the papilla of Vater the benign disease must be weighed against the morbidity and mortality rates of local transduodenal resection and pancreatoduodenectomy. Usually, patients in good physical condition should be referred to surgical departments whereas endoscopic treatment should be preferred in patients in poor physical condition, as an alternative option with lower mortality and morbidity rates.

In a cohort of 36 patients with adenoma of the papilla of Vater, we found 16 (44%) to be unfit for surgery because of poor physical condition [67]. These patients had a median age of 80 (59–89) years and were significantly older and showed a higher rate of comorbidity than patients suitable for curative therapy (P=0.001, McNemar). In a median follow-up period of 37 (range: 13–87) months, 11 of these patients died (11 out of 16=69%), three of metastatic disease (ACS) and eight for other reasons [67]. Patient populations such as this differ significantly (age, comorbidity, treatment options) from those referred to the surgical departments [54, 33, 13, 8, 67,18].

A number of studies [57, 42,4] have demonstrated the technical feasibility and safety of endoscopic snare resection (ESR) of adenomas of the papilla of Vater. Twenty-five patients received ESR, with a low procedure-related morbidity (12%; one case of pancreatitis, two minor bleedings after papillectomy) and no deaths [4]. The recurrence rate after a median follow-up period of 37 months was 26%. All were treated by repeated ESR and only one patient developed malignancy [4].

In a separate analyses of our patients with adenoma of the papilla of Vater, we treated 12 patients who were young and fit for surgical therapy on their request by use of ESR. They had a median age of 57.5 years (range 23–69) and were followed over a median period of 91 months (range 33–123) (e.g., 83.67 patient-years). In one patient we detected malignancy during endoscopic follow-up 2 months after ESR, indicating we missed the malignancy in the biopsies and in the snare resected specimen beforehand. Because of an endoscopically and biopsy proven carcinoma, pancreatoduodenectomy was performed in which a $pT_1N_0M_0R_0$ carcinoma was excised successfully [67]. These results

and the published treatment results prove the value of ESR for adenomas of the papilla of Vater under careful follow-up [10].

The improvements in the endoscopic diagnostics and the good treatment results for tumors of the papilla of Vater justify an initial attempt of ESR, if technically feasible [4, 5, 25]. These results have also been confirmed by more recent studies [6, 14,67]. Nearly 80% of the patients were managed endoscopically; most patients received therapy with a curative intent and some with palliative intent with low morbidity and only one death. Under close endoscopic surveillance only very few patients developed adenoma recurrence or an ACS after ESR, all of which were treated by repeated ESR or by surgery successfully. As already mentioned above, retro- and prospective comparisons between endoscopic and surgical therapy of adenomas of the papilla of Vater are difficult to perform. Presently not a single prospective and randomized study has been performed in which the two treatment options have been scientifically compared.

Recently, patients were successfully selected for ESR based on IDUS. Itoh [21] and Menzel [29] proved by their studies that IDUS could correctly detect early cancer of the papilla of Vater in a stage at which other diagnostic methods failed. Even in patients with early carcinoma (T1 and T2), ESR demonstrated excellent results after selection by use of IDUS. Limited tumoral ductal infiltration was correctly assessed to determine whether endoscopic resection was possible. Therefore, IDUS is an essential examination before treatment and it contributes to conservative therapy in patients with tumors of the papilla of Vater. IDUS may help to avoid excessive surgical stress for elderly patients [21, 32,22]. In the future, the selection of patients for curative endoscopic treatment may be possible, as it is already performed in endoscopic mucosal resection of early gastric and colon cancer [27].

Relevant recurrence rates (17–26%) were detectable during short- and long- term follow-up after local surgical excision of benign adenoma of papilla of Vater [13, 8, 30,56]. Chareton et al. [13] found an ACS rate of 22% after local surgical papillectomy of benign tumors of Vater's papilla after 4 and 22 years, respectively. On account of significant recurrence rates and malignant transformation of tumors of the papilla, scheduled endoscopic follow-up is absolutely necessary after each endoscopic or surgical excision [52].

Comparisons between endoscopic and surgical therapy of carcinomas of the papilla of Vater are very difficult, too, because there are only few publications from endoscopic centers. Surprisingly, long-term results after endoscopic therapy of malignant tumors of the papilla of Vater were not inferior to those obtained after radical surgery [18, 44]. Based on Kaplan-Meier analyses, median survival in 28 surgically treated patients was 50%

after 13 months and 7% after 5 years whereas 50% of the 17 endoscopically treated patients survived 9 months and 7% 5 years. These differences were not significant (P=0.33, log-rang analyses) and may indicate the high impact of endoscopic therapy in malignant tumors of the papilla of Vater (own results, [44]). Special knowledge is mandatory for the life-long endoscopic surveillance and risk stratification of these tumors and for identifying indications for different therapeutic modalities in cases of duodenal and papillary polyps associated with familial adenomatous polyposis (SVD, enteroscopy, scheduled biopsies). Treatment options for multiple duodenal polyps in FAP are APC coagulation, laser vaporization, photodynamic therapy, endoscopic piece-meal or diathermy snare resection, surgical excision, endoscopic palliation, and the "wait and see" policy. These options are applicable depending on the following points: (1) age of the patient, (2) duration of the disease, (3) histology (dysplastic changes), (4) numbers, site and size of the polyps, (5) progression over time in size, number, and histology. However, this paper mainly deals with spontaneous adenomas of the papilla of Vater and so we refer to the literature for a further discussion of the topic [60, 10, 3, 23, 24, 35, 36, 38, 37, 39, 41, 40, 44, 45,51].

In patients with progressive malignant disease of the papilla, palliative therapy is often necessary. Palliative surgery consists of a single gastric or double (biliary and gastric) bypass operation. This procedure does not always prevent the development of local tumor complications such as bleeding, jaundice, obstructive pancreatitis, and cholangitis. To prevent these complications, several endoscopic procedures can palliate the disease and partially destroy the tumor, for example, snare resection, local or intraductal laser therapy, local or intraductal photodynamic therapy, and APC beamer therapy. Endoscopic procedures such as EST, endoscopic choledochoduodenal fistulotomy, insertion of transpapillary biliary endoprosthesis, metal stents or percutaneous transhepatic cholangiodrainages (PTCD) can be used to achieve biliary flow in case of tumor obstruction. Neither surgical nor endoscopic studies of palliative therapy in tumors of the papilla have been conducted to date. Our results may indicate the high impact of endoscopic palliative therapy of carcinoma of the papilla of Vater (see above) [44]. With increasing invasiveness of the method, complication rates may increase. Patients who receive PTCD and laser treatment might develop more complications than patients who receive simple transpapillary plastic stents or APC beamer therapy [67].

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