Indications and Outcome of Endoscopic Papillectomy of the Major and Minor Papilla—a Prospective 5-year Study

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Abstract: Endoscopic papillectomy is a promising and challenging endoscopic intervention. The aim of this study was i) to classify the differential indication, and ii) to study the outcome in papillectomy of suspicious tumor lesions of the papilla of Vater (papilla).

Methods: Thirty nine patients were enrolled (22 males/17 females; range of age, 21–88 years) who underwent endoscopic papillectomy because of a polypoid tumor at the papilla revealed by previous endoscopic ultrasonography (EUS) over a time period of 5 years. Follow-up EUS and histologic investigation were performed within 28 days(d).

Results: I) All tumors were detectable using EUS (range of tumor size, 1–4.5 cm). II) Indications, histologic diagnoses and their distribution were as follows: Group(Gr.)1 ($n = 21$): Adenoma ($n = 18$), uT1 carcinoma(Ca) of high risk patients ($n = 3$) with R0 resection ($n = 17$) vs. R1 ($n = 4$; all reapproached using argon beamer). On the 28th postinterventional d, all subjects were free of tumor. Recurrent tumor growth was found in 3 cases after 6, 18 and 26 months respectively (range of endoscopic follow up [$n = 14$], 3–60 months). Three patients (free of tumor) died from other causes after 3, 8 and 18 months, respectively. Gr. 2 ($n = 8$): Contradiction between EUS (infiltrating tumor growth) and histologic finding (adenoma or unspecific inflammation); histological findings were: Adenomyomatosis of the papilla ($n = 5$), infiltrating Ca of the papilla or peripapillary region ($n = 3$). Gr. 3 ($n = 4$): Neuroendocrine tumors of the major ($n = 2$) or minor papilla (n = 2): 2 benign, 1 Ca and 1 carcinoid tumor. Gr. 4 ($n = 6$): Non-introducible catheter through the minor papilla in case of suspected pancreas divisum ($n = 2$) or through the major papilla ($n = 1$) after previous gastric resection (Billroth II) or because of Ca of the papilla with no successful attempts to drain the bile duct ($n = 3$): Catheter insertion was achieved after papillectomy ($n = 3$) or partial tumor resection ($n = 3$). III) Complications: 8 of 39 patients (20.5%) developed postinterventional pancreatitis (severe course, $n = 1$); in 7 cases, bleeding occurred, no perforation was seen. The rate of recurrent tumor growth after R0 resection was 17.6% (3 of 17 subjects).

In **summary**, papillectomy is feasible in the case of i) polypoid tumor of the papilla, ii) infiltrating tumor growth revealed by EUS and negative histologic investigation (optional: plus deep biopsy), and iii) tumor lesion, through which catheter can not be placed to get access to the pancreatobiliary system.

In **conclusion**, endoscopic papillectomy fulfills diagnostic as well as therapeutic requirements and can be recommended as minimally invasive but appropriate method for well-defined indications of papillary tumor lesions.

Keywords: papillectomy, endoscopic, ultrasonography(EUS), adenoma, carcinoma(Ca), carcinoid-like tumor, adenomyomatosis

Introduction

Tumors of the papilla of Vater (papilla) are rare. In autopsy studies, incidence of benign lesions of the papilla has been reported to be 0.04%–0.64% (Stolte and Pscherer, 1996). Neoplastic lesions of the papilla are divided into adenomas (70%) and carcinomas(Ca) (20%–25%). Adenomas possess a potential for malignant transformation according to the adenoma-carcinoma sequence (Bohnacker et al. 2006; Catalano et al. 2004; Stolte and Pscherer, 1996; Treitschke et al. 2000). Interestingly, there are malignantly transformed cells in about 30% of cases; whereas in villous adenomas, the detection rate of malignant cells is 60% (Stolte and Pscherer, 1996). For decision-making with regard to the appropriate therapeutic approach (endoscopic/surgical papillectomy *vs*. duodenopancreatectomy), differentiation between the invasive malignant and the locally growing benign tumor lesion is essential.

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The differentiation between benign and malignant cells with a biopsy obtained from the surface of the papilla has been reported to be 45%–85%, but this seems to be not suitable (Yamaguchi and Enjoi, 1987; Yamaguchi et al. 1990). In 25%–56% of cases, false-negative findings in biopsies can occur (Stolte and Pscherer, 1996; Treitschke et al. 2000; Witzigmann et al. 2000). Using more aggressive techniques for taking biopsies (deep biopsy after papillotomy or diagnostic papillectomy), detection rate can be increased up to 90% (Sauvanet et al. 1997). EUS allows to differentiate between the invasively growing malignant and the only locally growing benign tumor lesions in 80%–95% of cases (Cannon et al. 1999; Palazzo, 1998; Tio et al. 1996). Therefore, EUS appears required to be included in the diagnostic spectrum (Zadorova et al. 2001).

Endoscopic papillectomy is a promising and challenging endoscopic intervention with diagnostic and therapeutic potential (Aiura et al. 2003; Jung et al. 2001; Lee et al. 2002; Mc Cutcheon, 1997; Rollhauser and al-Kawas, 1997; Silvis, 1993; Sriram et al. 2000), which is increasingly used (Bohnacker et al. 2005; Bohnacker et al. 2006).

The aim of this study was i) to classify the differential indication for endoscopic papillectomy, ii) to characterize the spectrum of histologic diagnoses, including the percentage of malignant lesions, iii) to determine the complication rate of endoscopic papillectomy, and iv) to study outcomes in endoscopic papillectomies of suspicious tumor lesions of the papilla in a representative number of patients, in which extensive experiences are lacking because of their low incidence and the fact that optimal management of such tumor lesions has not yet been established (Silvis, 1993).

Patients and Methods

All consecutive patients, who underwent endoscopic papillectomy using high frequency diathermia loop (Olympus Optical Co. [GmbH], Hamburg, Germany) mainly of polypoid lesions of the papilla and other reasons as listed below revealed by previous EUS (Hitachi Medical Systems, Lübbecke, Germany) (Fig. 1) were enrolled in the study and prospectively evaluated. Papillectomy was executed under mild sedation of the patient using Propofol (Recofol®, curaMED Pharma GmbH, Karlsruhe, Germany).

Individuals enrolled in the study were subdivided into 4 groups according to their diagnosis. Indications for papillectomy were as follows:

Group 1: –Adenoma and uT1 tumor lesion (n = 21; Patients with more advanced tumor growth than uT1uN0 were excluded),
Group 2: –Contrary EUS and histologic findings (n = 8),
Group 3: –Neuroendocrine tumors (n = 4),
Group 4: –Papilla with no possible catheter insertion (n = 6).

After papillectomy, each patient underwent sphincterotomy and in a few patients, in particular, in those of group 4, a 5-French prosthesis (GIP Medizintechnik [GmbH], Achenmühle, Germany) was inserted into the pancreatic duct temporariely (for 4 days) (Fig. 2).

Follow-up EUS investigation and histologic investigation were performed within 28 days, every three months for one year and then every six months.

A written consent was obtained from each patient enrolled in the study.

Results

We report on 39 consecutive patients (sex ratio, 17 females, 22 males; age range, 21–88 years) out of 311 subjects with EUS-detectable suspicious tumor-like lesions at the papilla of Vater or minor papilla and 75 individuals with papillary and peripapillary tumors, respectively (in total, 4,832 EUS investigations), over a time period of 5 years.

The spectrum of indications for EUS was comprised of suspicious findings at the papilla in upper endoscopy, jaundice, unclear cholestasis indicated by laboratory parameters, discomfort in the upper abdomen, and unclear tumor growth at the papilla or in the peripapillary region, which had been revealed in previous imaging procedures such as ERCP, CT or MRI.

All tumors were detectable, imaged, and characterized with regard to the locoregional tumor growth using EUS (detection rate, 100%). Tumor size ranged between 1 and 4.5 cm. Histopathologic diagnosis was definitively found in each case (100%).

The four main differential indications for papillectomy, histologic diagnoses and their distribution are listed as follows (Fig. 3):

Group 1: Twenty one patients (53.8%) underwent papillectomy with curative intention in diagnosed adenoma (n = 18) or uT1 carcinoma in high risk patients (n = 3); EUS revealed a tumor growth limited to the two inner layer(s) of the wall with no infiltration of the "lamina muscularis propria" or the distal segment (near the duodenum) of the common bile duct, or suspicious locoregional lymph nodes.

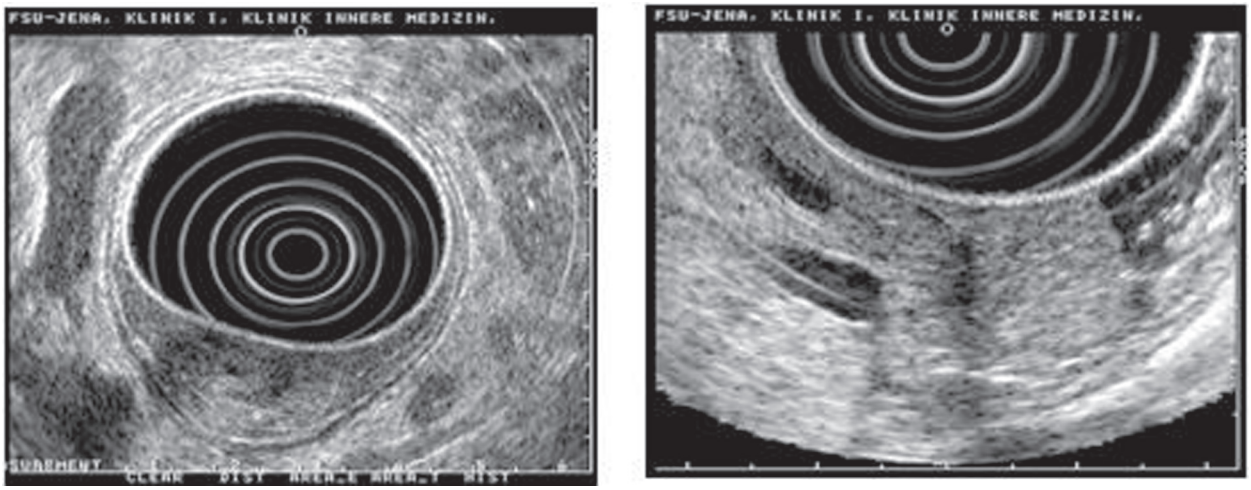

Figure 1. Tumor mass within the first layer at the papilla of Vater (uT1), which is detected by EUS (Hitachi Medical Systems, Luebbecke, Germany) of different size: A) 2.5 × 1.5 cm. B) 1.5 × 1.0 cm.

uT1 tumor stage was confirmed by histologic investigation (pT1) including no lymph node invasion in all 3 cases. While 17 R0 resections (81%) were achieved, only 4 R1 resections were elucidated, after which tumor residuals were reapproached and encrusted by electrocoagulation (Zadorova et al. 2001) using Argon beamer ICC200 (Erbe Elektromedizin GmbH, Leipzig, Germany) within one week after the first intervention. Histologic investigation revealed tumor-free status by day 28, the 1st follow up. Three times, recurrent tumor growth (initially: 2 × R1, 1 × R0) after 6, 18 and 26 months, respectively, was found (range of endoscopic follow up, 3–60 months). This resulted in a rate of recurrent tumor growth of 14.3% (3 of 21 cases). Two patients with adenomas were reapproached endoscopically, and one patient with a carcinoma underwent surgical resection. Three patients died from other disorders after 3, 8 and 18 months, respectively, but no recurrent tumor growth was detected.

Group 2: Eight patients (20.5%) with contradiction between EUS finding (deeply infiltrating tumor growth) and histologic finding (adenoma or unspecific inflammation) underwent preferentially diagnostic papillectomy. While 5 times, adenomyomatosis of the papilla was diagnosed (in these cases, papillectomy was curative), 3 infiltrating carcinomas of the papilla or the peripapillary region were found according to the histologic investigation of the specimen. The latter underwent surgical intervention.

Group 3: Four patients (10.3%) with neuroendocrine tumors of the major ($n = 3$) or minor papilla ($n = 1$). Histologic investigation revealed two benign neuroendocrine tumors, one neuroendocrine carcinoma, and one carcinoid-like tumor. The patient with neuroendocrine carcinoma was transferrred to surgical resection. The remaining 3 patients were controlled by follow-up EUS with no detectable recurrent tumor growth yet. Interestingly, the primary EUS findings indicated a tumor lesion limited to the first layer according to the inclusion criteria of the study.

Group 4: In 6 patients (15.4%), catheter could not be inserted into the minor papilla ($n = 2$) (in initially suspected and confirmed "pancreas divisum"), nor into the major papilla after previous gastric resection according to the procedure II by Billroth ($n = 1$; no suspicious tumor lesion of the papilla) and more advanced carcinoma of the papilla than uT1 with cholestasis ($n = 3$). Endoscopic papillectomy was performed according to a decision of the interdisciplinary tumor board to achieve a drainage of the bile duct because of the severe cholestasis and the associated bad physical condition prior to possible surgery. Endoscopic papillectomy was also performed at the minor papilla. Histologic investigation revealed an adenoma in both cases. Catheter insertion into the pancreatic duct and the common bile duct after papillectomy ($n = 3$) or partial tumor resection ($n = 3$) was possible in each case. However, the latter three patients underwent surgical intervention after an appropriate time period of drainage. Histologic investigation of the surgical specimen confirmed the former EUS finding.

The greatest percentage of the patients with papillectomy was observed in group 1, the EUS-detectable adenomas and uT1 tumor mass; the lowest

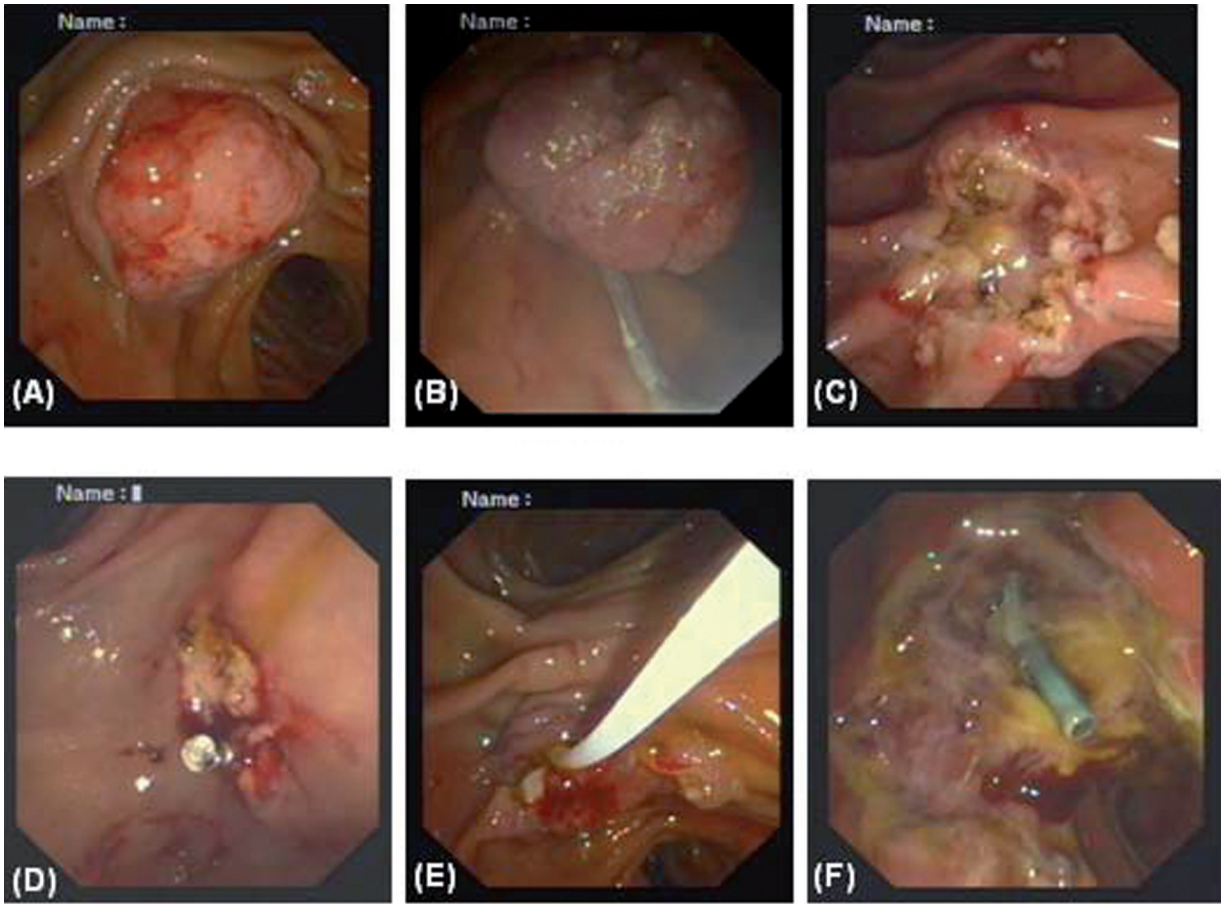

Figure 2. Steps of endoscopic papillectomy using a high frequency diathermia loop (Olympus Optical Co. [GmbH], Hamburg, Germany) of an adenoma of the papilla of Vater (size, 1.5 cm in diameter) and management of possible complications: A) Optical identification of the adenoma at the papilla. B) Papillectomy. C) Resection area after papillectomy (no bleeding). D) Endoscopic clipping because of bleeding (different case). E) Inserted catheter into the pancreatic duct. F) Inserted stent out of the mouth of the pancreatic duct.

was found in group 3, patients with neuroendocrine tumors.

In 8 of 39 patients, an acute pancreatitis was diagnosed after papillectomy (20.5%) showing a severe course in only one case and was considered a major complication. Postinterventionally, mostly slight bleeding occurred in 7 of 39 subjects (18%; no major complication), but no perforation and no postinterventional stenosis of the orifice at the papilla of Vater were seen. Endoscopic control of bleeding was possible in each case. Despite a considerable periinterventional morbidity of 30.8%, consisting exclusively of acute pancreatitis and bleeding (major complication rate, 2.6% [1/39]), in 12 of 39 patients (3 patients with both acute pancreatitis and bleeding), there was no intervention-related death (mortality, 0%).

In total, 10 carcinomas were found: $n = 3$ in group 1, 2 and 4, $n = 1$ in group 3, respectively. While all patients from group 2, 3, and 4 underwent surgical intervention, only one patient of group 1 showing recurrent tumor growth revealed in follow-up EUS after initial papillectomy was finally transferred to the surgical department despite high-risk potential for anesthesia and surgical intervention as initially assessed.

The rate of recurrent tumor growth after R0 resection was 17.6% (3 of 17 subjects, group 1).

Discussion

The spectrum of indications for endoscopic papillectomy has been increased (Aiura et al. 2003; Jung et al. 2001; Lee et al. 2002; Mc Cutcheon, 1997; Rollhauser and al-Kawas, 1997; Silvis, 1993; Sriram et al. 2000). The purpose of this study was to demonstrate i) the differential indications for a papillectomy in the broad spectrum of suspicious findings at the papilla of Vater or even at the minor papilla (Nakamura et al. 2007) in our institution and ii) the

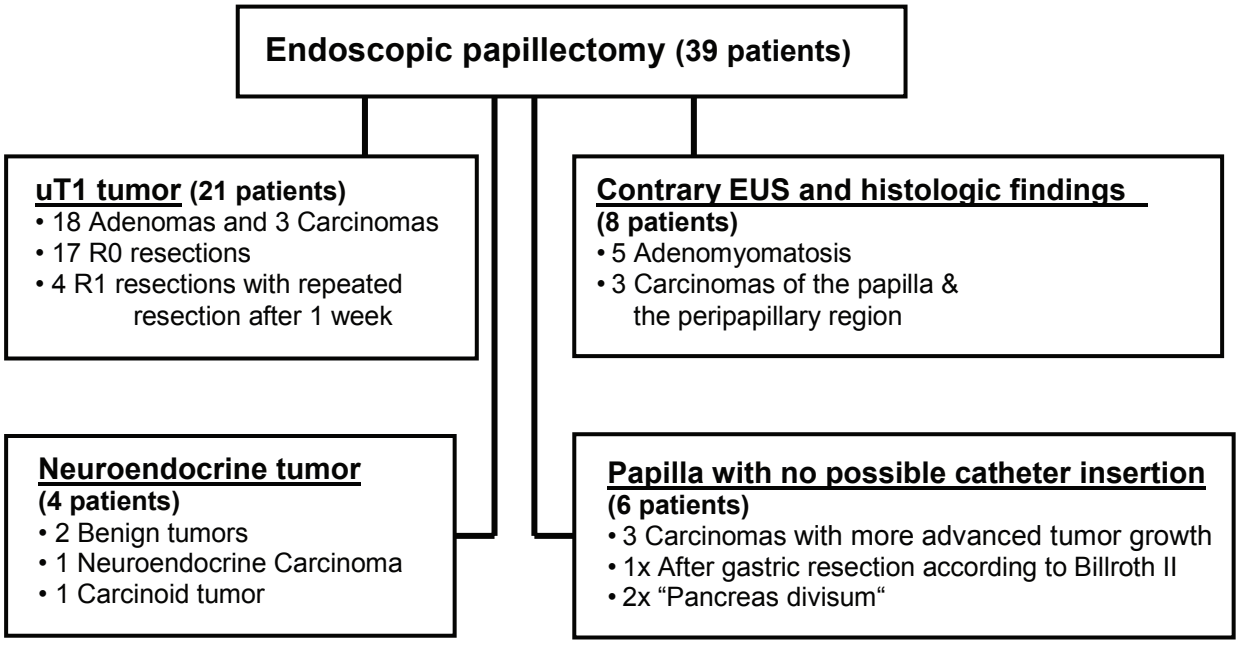

Figure 3. Scheme of basic results grouped according to the histologic diagnosis in the cohort of patients undergoing endoscopic papillectomy because of a polypoid tumor lesion at the papilla of Vater ($n = 39$; Ca, carcinoma).

results to assess feasibility and justification of this interventional endoscopic approach. In addition to exclusively diagnostic aspects of EUS-guided fine needle aspiration biopsy at other tumor sites, endoscopic papillectomy after previous EUS aims for diagnostic as well as therapeutic purposes (Jung et al. 2001; Lee et al. 2002; Mc Cutcheon, 1997; Rollhauser and al-Kawas, 1997; Sriram et al. 2000). In particular, while it allows to (re)investigate histopathology of a representative specimen (Bertonie et al. 1997) (group 1–3) and, thus, to clarify diagnosis (group 2,3), it can, simultaneously, (fully [group 1–3]) resect a (suspicious [group 2,3]) tumor(-like [group 4]) lesion controlled by EUS follow-up investigation (group 1–3). But prior to the papillectomy, EUS is also required to confirm the correct indication as listed (group 1–4).

Due to the low incidence of adenomas of the papilla, there are no controlled studies comparing a surgical with an endoscopic approach (Farrell et al. 1996a). The surgical approach (conventional duodenopancreatectomy) is associated with a considerable morbidity (10%–30%) and mortality (1%–20%) (Farrell et al. 1996a; Michalski et al. 2007). If there is a diagnostic tool such as EUS that excludes definitively a submucosal infiltration of a polypoid adenoma (group 1 and differential diagnosis for group 2 and 3), endoscopic papillectomy even with curative intention is justified (Ito et al. 2007). However, though the handling has been established and the technical difficulties have been solved sufficiently, expertise in the use of EUS and the appropriate execution of papillotomy/papillectomy including EUS-based follow-up to provide a low risk for the patient and a low rate of recurrent tumor growth is urgently required. Again, although there was a considerable periinterventional morbidity of 30.8% (acute pancreatitis, bleeding, but no perforation as previously reported [Bertoni et al. 1997; Moon et al. 2005; Norton et al. 2002; Zadorova et al. 2001], no postinterventional stenosis of the orifice (Catalano et al. 2004; Khandekar and Disario, 2000; Norton et al. 2002) occurred, mortality was 0% (as also reported by several authors (Binmoeller et al. 1993; Bohnacker et al. 2006; Cheng et al. 2004; Catalano et al. 2004; Zadorova et al. 2001)) and the major complication rate was only 2.6% underlining the feasibility of the procedure. The complications were manageable with conservative measures. A surgical intervention as an emerging consequence was not required emphasizing the safety of the papillectomy in experienced hands (Bertoni et al. 1997). Taken together, papillectomy is justified for R0-resectable adenomas (Bohnacker et al. 2006) and uT1 carcinomas in older high-risk patients (e.g.) 9.1 severe cardiopulmonary disorders) (group 1–3), which has to be controlled by histologic investigation of the resection margins and periodic EUS follow-up

investigations. A further purpose of papillectomy is in that it is part of a therapeutic concept such as drainage of the bile or pancreatic duct (group 4) in cholestasis or in case of an increased intraluminal pressure, respectively (Farrell et al. 1996a; Farrell et al. 1996b; Rollhauser and al-Kawas, 1997).

Many authors do not regard EUS as a prerequisite for endoscopic papillectomy. However, the authors favor mainly this tool because of its diagnostic (description of a preinterventional finding according to the indication for an endoscopic intervention such as papillectomy) and therapeutic options (image guidance) for the reasons mentioned above, namely, in particular,

- the diagnostic role of EUS (Ito et al. 2007) in describing size, shape, echogenicity of a tumor lesion including exclusion/confirmation of an infiltrating tumor growth;
- the guidance in endoscopic papillectomy for diagnostic as well as therapeutic purposes (Jung et al. 2001; Lee et al. 2002; Mc Cutcheon, 1997; Rollhauser and al-Kawas, 1997; Sriram et al. 2000);
- it allows to (re)investigate histopathology of a representative specimen (Bertonie et al. 1997); and
- the role in follow-up investigation.

After papillectomy, it is recommended i) to check the orifices of both the major and minor papilla and, in addition, ii) to perform a sphincterotomy at the orifice of the bile duct for prevention of a postinterventional stenosis. In selected cases, the temporary insertion of a 5-French prosthesis into the pancreatic duct (Fig. 2F) is necessary (for 4 days) to drain the pancreas sufficiently because of possible postinterventional swelling of the papilla (Bertonie et al. 1997) or stenosis (Catalano et al. 2004) and to prevent pancreatitis (Moon et al. 2005).

A diagnostic papillectomy or papillotomy including a deep biopsy is indicated in cases of EUS-based suspicion of infiltrating tumor growth and an initially negative histologic finding (group 2). Adenomyomatosis as found in three cases in group 2 is a diagnosis with considerable diagnostic difficulties (Kayahara et al. 2001) if there is no adequate specimen for histologic investigation. Interestingly, three carcinomas of the papilla and the peripapillary region have been diagnosed only by the additional papillectomy, which, otherwise, would have been overlooked.

Adenoma was the most common tumor of the papilla as reported (Binmoeller et al. 1993; Elek et al. 2003; Norton et al. 2002; Treitschke et al. 2000). If there are hints for a malignant and/or infiltrating tumor growth revealed by the histologic investigation, which could not be resected achieving an R0 resection status, residual tumor has to be reapproached with a surgical intervention such as local resection or duodenopancreatectomy (Bohnacker et al. 2005; Bohnacker et al. 2006). We favor this approach in each case of operability since there is a probability of about 20% of occuring lymph node metastases in the case of submucosal infiltration (group 1).

Curative resection using endoscopic papillectomy in uT1 carcinoma can only be recommended in high-risk patients related to their general health status. Following this rule, an R0 resection rate of 81% was achieved. The four patients with R1 resection status were re-approached using Argon beamer with a good long-term result. Interestingly, there were 2 adenomas of the three cases in whom recurrent tumor growth occured (group 1). Both cases were re-treated (since adenomas are premalignant lesions (Aiura et al. 2003)) endoscopically as reported by Zadorova (Zadorova et al. 2001), because they were high-risk patients for anesthesia and surgical intervention. In contrast, Matsumoto et al. (Matsumoto et al. 1997; Stolte and Pscherer, 1996) confirmed that at least in familial adenomatous polyposis, aggressive endoscopic or surgical removal is unnecessary for adenomas. The third patient required surgery, despite his high-risk status, to provide the best prognosis.

The data suggest that endoscopic papillectomy appears to be feasible and a reasonable alternative treatment option (Bohnacker et al. 2005; Farrell et al. 1996b; Zadorova et al. 2001) in cases where i) there is an unclear but resectable tumor growth even after histologic investigation of a biopsy, and ii) catheter cannot be easily inserted into the papilla because of tumor growth at the papilla or inflammatorily deformed papilla to achieve a drainage of the biliary tree by endoscopic insertion of a drain through the resected papilla (Farrell et al. 1996a; Farrell et al. 1996b; Rollhauser and al-Kawas, 1997). Diagnostic papillectomy (or papillotomy in selected cases) including deep biopsy is recommended if there are an infiltrating tumor growth revealed by EUS and negative findings in the initial histologic investigation. Unlike laser or thermal ablation, papillectomy allows complete histologic

investigation of the pathologic tissue (Bertoni et al. 1997). However, decision-making for a minimally invasive endoscopic approach is influenced by the spectrum and risk of possible complications such as perforation or bleeding. In this context, EUS has turned out to be a valuable tool not only because of its higher sensitivity and specificity in detecting and assessing tumor-like lesions (in particular, at the [peri-] papillary region), but also in preparation, execution, and follow-up of papillectomies.

The role of endoscopic papillectomy in the treatment of early papillary carcinoma is currently under discussion (Yoon et al. 2007). However, it appears to be still unclear what the "gold standard" might be for decision-making considering the substantial number of 8 cases (approximately 20% [!]) in this study indicating a "contradiction between EUS finding (deeply infiltrating tumor growth) and histologic finding (adenoma or unspecific inflammation)" in several patients who could undergo diagnostic papillectomy according to the definition of patient group 2. A possible solution might be that the decision should usually based on the diagnosis after histologic investigation (Bohnacker et al. 2006) of a (deep) biopsy (after former papillotomy) or even of a representative specimen obtained by endoscopic papillectomy including the preinterventional EUS (Ito et al. 2007).

In conclusion, endoscopic papillectomy fulfills diagnostic as well as therapeutic requirements and can be recommended as a minimally invasive but appropriate and safe method (Bohnacker et al. 2005; Bohnacker et al. 2006) and a reasonable alternative to open surgery (Bohnacker et al. 2006; Cheng et al. 2004; Yoon et al. 2007) for well-defined indications of tumor lesions at the papilla including an adequate surveillance (Bohnacker et al. 2005; Bohnacker et al. 2006; Cheng et al. 2004).

Disclosure

The authors report no conflicts of interest.

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