Ampulla of Vater tumors : Impact of intraductal ultrasound and transpapillary endoscopic biopsies on diagnostic accuracy and therapy

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Abstract

Background and study aims : **To evaluate the diagnostic impact of intraductal ultrasound (IDUS) and endoscopic transpapillary forceps biopsies (ETP) in ampullary tumors.**

Patients and Methods : **Seventy-two patients with suspected ampullary tumor were examined by ERCP, including IDUS and ETP. Histopathological correlation or long-term follow-up was available for all patients undergoing these procedures. Final diagnosis revealed ampullary adenoma in 40 patients and ampullary carcinoma in 32 cases. Sensitivity, specificity, accuracy rates as well as positive and negative predictive values (PPV, NPV) for each of the diagnostic measures were calculated including T and N stage accuracy.**

Results : **Four carcinomas were misclassified by IDUS giving sensitivity, specificity and accuracy rates of 87.5%, 92.5% and 90.2%, respectively. Using ETP a correct pre-interventional diagnosis of ampullary carcinoma was achieved in 22 out of 32 patients resulting in a sensitivity, specificity and accuracy data of 68.7%, 100% and 86%, respectively. Improvement of sensitivity and accuracy to 97% and 94.5%, respectively, could be achieved by IDUS in combination with ETP. IDUS accuracy for T1, T2 and T3 stages was 86%, 71% and 86%, respectively. For N0 and N1 stages accuracy of 75% each was calculated.**

Conclusions : **IDUS+ETP substantiate the diagnosis and further management of ampullary tumors. ETP alone is not useful in detecting malignancy (false-negative rate of 31.3%). IDUS accurately predicts T and N stages in patients and is able to accurately predict cases which potentially are treatable endoscopically.** (Acta gastroenterol. belg., **2011**, 74, **509-515**).

Key words : biliary tract diseases, ampullary tumors, intraductal ultrasound, transpapillary biopsies, T staging, N staging.

Introduction

Benign lesions of the ampulla of Vater are rare with a prevalence of 0.04 to 0.12 percent in autopsy series (1-3) and only account for about 10 percent of periampullary tumors. Malignant tumors arising from the duodenum, ampulla, or pancreas represent the majority of lesions of the ampulla of Vater (4,5). Malignant transformation of benign ampullary adenomas to ampullary carcinomas is possible and follows the adenoma-carcinoma progression sequence that also occurs elsewhere in the gastrointestinal tract (2). Common benign lesions are villous and tubulovillous adenomas ; others include hemangiomas, leiomyomas, leiomyofibromas, lipomas, lymphangiomas, and neurogenic tumors (6,7).

It may be difficult to distinguish adenoma from carcinoma without complete resection since carcinoma cells may be found within an adenoma (8). Patients with suspected bile duct or pancreatic duct obstruction should undergo cholangiography via endoscopic retrograde cholangiopancreatography (ERCP) which allows performing endoscopic interventions and further diagnostics with IDUS and biopsy in the same session and, therefore, potentially provides useful information for tumor staging.

However, biopsies obtained during ERCP cannot reliably exclude the presence of a malignant focus within an adenoma of the papilla. In previous studies, false-negative results from endoscopic biopsies have been described in 16 to 60% and diagnostic accuracy rates of 45 to 80% in patients with carcinoma (9-16). In several studies, sensitivity, specificity and accuracy rates of 84-91%, 80-94%, and 84-90%, respectively, were found for biliary IDUS indicating the tremendous diagnostic impact of IDUS in the bile duct system (17-19). Adequate preoperative staging of ampullary tumors is still a matter of debate and various imaging modalities compete with each other. Endoscopic ultrasonography (EUS) has been proven to be as sensitive as ERCP and superior to CT and transabdominal US in detecting small ampullary tumors (20,21). However, in a comparative prospective study of 40 patients with ampullary carcinoma, Ito and colleagues (22) were able to demonstrate IDUS to be more accurate than EUS with respect to T-staging.

Our retrospective study aimed to evaluate the diagnostic and therapeutic impact of IDUS and ETP in papilla of Vater tumors.

Patients/materials and methods

At the tertiary referral center of Muenster University Hospital, we retrospectively analyzed the data of our patient cohort undergoing diagnostics and treatment for ampullary tumors between December 2000 and December 2009. A total of 96 patients were referred to

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Table 1. — **Baseline characteristics and clinicopathological details of two patient groups (adenoma group A and carcinoma group B)**

	Group A Adenoma	Group B Carcinoma	p-Value
Total (n)	40	32	
Age (years) ± SEM	69.7 ± 15.0	75.2 ± 7.5	0.18
Sex (m/f)	19/21	20/12	0.27
Long-term follow-up (months) ± SEM (Range)	50.9 ± 30.9	(12-107)	
Diagnostics :			
IDUS (n)	40	32	n.c.
ERCP + ETP (n)	40	32	n.c.
Therapy :			
Papillectomy	22	3	n.a.
Sphincterotomy and stent implantation	13	0	n.a.
Surgery	5	32	n.a.

SEM = standard error of the mean ; n.a. = not analyzed ; n.c. = not calculated.

our Department of Medicine B (Gastroenterology) at Muenster University Hospital. All patients included into the study could be identified by looking for Code D13.5 according to the International Classification of Diseases (ICD). Thus, it could be ensured that all patients with suspected ampullary tumor were included. Clinical records of patients were collected and carefully analyzed. Baseline characteristics (e.g. age, sex) were retrieved as shown in table 1.

Exclusions

Twenty-four out of 96 patients with ampullary tumors were excluded from this study. In 23 patients IDUS was not performed and in one patient histopathological correlation or long-term follow-up was not available.

Procedures

All remaining 72 patients enrolled in the present study underwent endoscopic retrograde cholangiography (ERCP), endoscopic transpapillary forceps biopsies (ETP) and intraductal ultrasound (IDUS). Additionally, all patients were histopathologically controlled or long-term follow-up for those patients who have not undergone surgery was available. The mean follow-up for a benign ampullary tumor was 50.9 months (range 12-107 months). No patient had developed malignancy during follow-up. The histopathological reports were viewed by the Department of Pathology at our institution. The individual procedure was performed after written informed consent had been obtained from the patients or related persons. All endoscopic manoeuvres were executed by four highly experienced investigators according to the generally accepted guidelines with an ERCP case volume above 200/year. The procedures were performed under fluoroscopic guidance using a side-viewing duodenoscope (Olympus VR 160, Olympus, Ltd, Tokyo, Japan) (Figs. 1a and 2a). Patients were monitored by continuous recording of oxygen saturation and pulse rate as well as intermittent measurement of blood pressure.

For IDUS a 2 mm ultrasound miniprobe was used with a radial scanner of 20 MHz frequency at the tip of the probe (Aloka Co., Ltd, Tokyo, Japan) and transpapillarily inserted into the common bile duct. Thus a radial real-time image of 360° view was possible for optimal investigation of the area surrounding the probe (Figs. 1b and 2b). The visible depth was about 20 mm with an axial resolution of 0.1 mm. All IDUS procedures were performed prior to stenting of the distal bile duct and prior to sphincterotomy to avoid inflammatory thickening of the biliary wall leading to limitation of IDUS accuracy (23). Accepted criteria for benign appearance on endoscopic ultrasonography were the presence of homogeneous echo of the tumor with smooth margins and no signs of infiltrative processes. Signs of malignancy were inhomogeneous echo of the tumor with infiltration into the sphincter of Oddi or the duodenal wall.

Transpapillary biopsies (n = 4-8) were taken out of the ampullary tumor by endoscopic forceps (MTW Endoscopy, Wesel, Germany). All biopsy specimens were taken after endoscopic sphincterotomy. Additionally all patients underwent prophylactic plastic stent insertion to avoid complications due to post-interventional oedema.

After completion of diagnostics by ERCP, IDUS and ETP all patients enrolled in the present study underwent either endoscopic therapy (sphincterotomy with stent implantation or papillectomy) or surgical therapy (exploration or modified Whipple's procedure). All tissue retrieved was sent for histopathologic evaluation. Patients with proven malignancy by ETP or suspected malignancy by IDUS in spite of adenoma finding by ETP were transferred for surgical exploration with or without modified Whipple's operation to the Department of General Surgery, Muenster University Hospital.

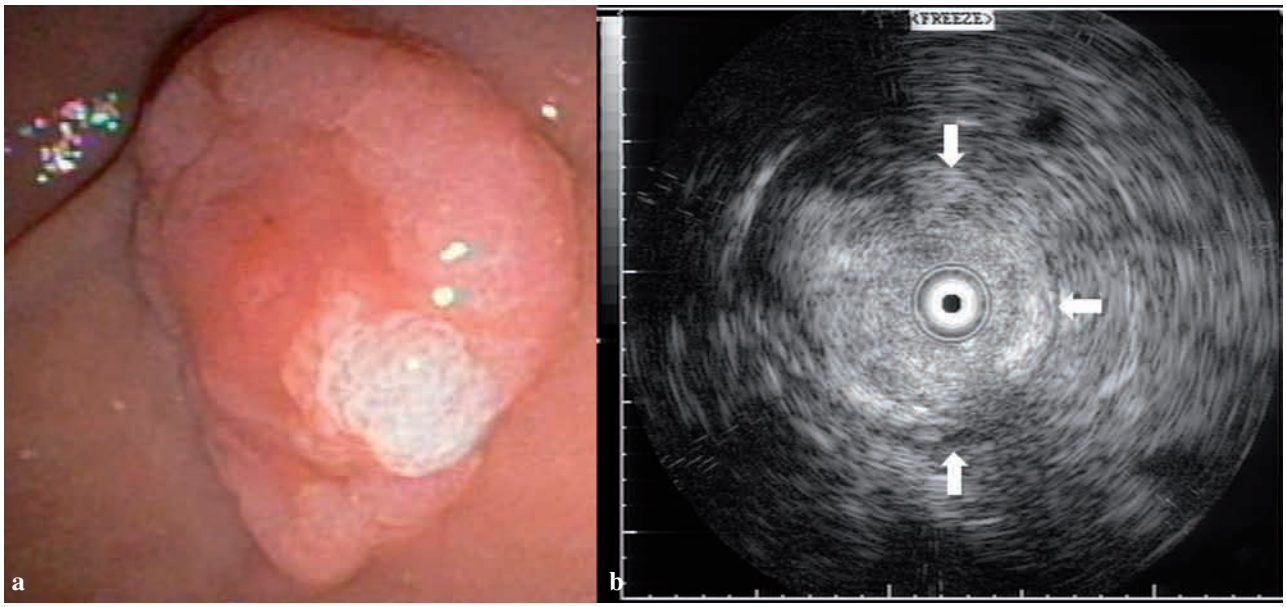

Fig. 1. — a) Macroscopic aspect upon ERCP, adenoma of the ampulla of Vater ; b) intraductal ultrasound. Benign lesions of the ampulla of Vater showing typical ultrasonographic characteristics : homogeneous echo of the adenomatous mass with smooth margins (arrows) and no signs of infiltrative processes.

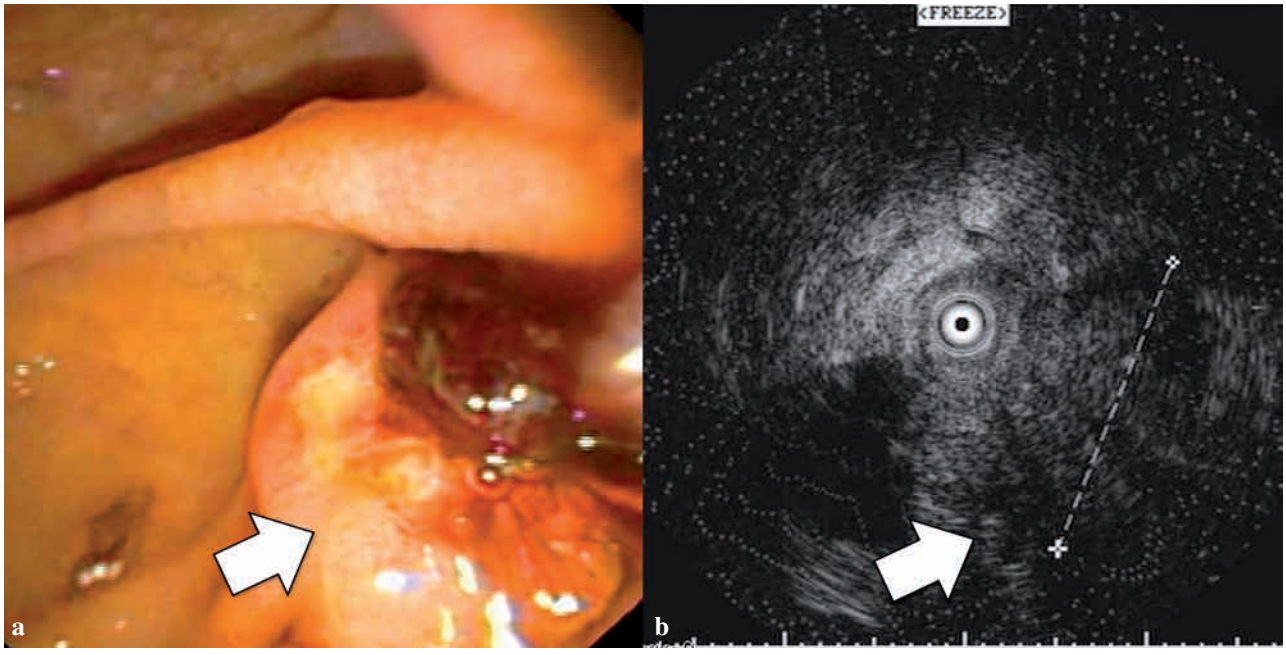

Fig. 2. — a) Duodenoscopic aspect of ampullary carcinoma with malignant ulcer (indicated by arrow). b) Application of IDUS in the same patient. Malignant lesion of the ampulla of Vater showing typical ultrasonographic characteristics in terms of inhomogeneous echo of the tumor with infiltration into the sphincter of Oddi and the duodenal wall (indicated by arrow).

IDUS T and N staging

In 28 out of 32 patients with histologically proven ampullary carcinoma IDUS T staging was available. In four patients T stages were not documented after IDUS procedure because of initial classification as benign and were therefore not available. IDUS staging was based on the TNM classification system (22,24). T1 : tumor limited to the ampulla of Vater or sphincter of Oddi ; T2 : tumor infiltrates the duodenal wall ; T3 : tumor infiltrates the pancreas ; T4 : tumor infiltrates the peripancreatic soft tissues or adjacent organs. In all 28 patients N

staging was additionally possible. IDUS classification of N stage was as follows. N0 : no regional lymph node metastasis ; N1 : regional lymph node metastasis.

Lymph nodes were considered positive, if at least one of the following criteria could be assessed : lymph node larger than 10 mm, delineated borders, hypoechoic structure resembling the primary tumor, roundish shape. Due to a penetration depth of only 20 mm, IDUS merely allows a vague evaluation of N stages.

IDUS staging was compared to the postoperative pathohistological staging, allowing the calculation of sensitivity, specificity, accuracy, overstaging, and understaging for T and N stages. M staging by IDUS was not performed as due to the limited penetration depth of IDUS.

Statistical analysis

Data were analyzed using SPSS 17.0 (Chicago, IL, USA). Results are expressed as medians and ranges. Sensitivity, specificity and accuracy rates for each of the diagnostic measures were calculated for each individual T and N stage. In all cases the gold standard was the histopathologic staging of specimens. Comparison between groups was performed by using the Mann-Whitney U-test and the χ-squared test as appropriate. P-value < 0.05 was considered statistically significant. For statistical analysis, sensitivity, specificity and accuracy rates were calculated as follows : sensitivity = true positives/ (true positives + false negatives) ; specificity = true negatives/ (true negatives + false positives) ; accuracy = (true positives + true negatives)/total cases (17) ; positive predictive value (PPV) = true positives / (true positives + false positives) ; negative predictive value (NPV) = true negatives / (true negatives + false negatives).

Results

The study cohort included 72 patients (39 men and 33 women ; median age 71.5 ± 13.1 years). Patients were classified into two groups : group A with histologically proven adenoma (n = 40) and group B (n = 32) with histologically proven ampullary carcinoma (Table 1).

Intraductal ultrasound (IDUS)

Thirty-seven histologically adenomatous lesions were correctly diagnosed (Fig. 1b) as such while in three patients the IDUS procedure misclassified ampullary adenoma as malignant (Fig. 2b). These patients had surgical exploration. Twenty-eight ampullary carcinomas diagnosed by IDUS were truly malignant in final histopathology after surgery whereas four ampullary carcinomas were misclassified by IDUS as benign (in three patients carcinoma was detected by ETP, one patient had high grade dysplasia in ETP with carcinoma in subsequent endoscopic papillectomy). Thus, for IDUS sensitivity is 87.5% while specificity is 92.5% resulting in an overall accuracy of 90.2% (Table 2).

Table 2. — **IDUS and accuracy rate in differentiation of adenoma from carcinoma (n = 72)**

Final diagnosis according to histopathology or long-term follow-up		
Method, Classification	Adenoma (n)	Carcinoma (n)
IDUS, benign	37	4
IDUS, malignant	3	28
ETP, benign	40	10
ETP, malignant	0	22
IDUS + ETP, benign	37	1
IDUS + ETP, malignant	3	31

IDUS : sensitivity 87.5% ; specificity 92.5% ; accuracy 90.2% ; PPV 90.3% ; NPV 90.2%

ETP : sensitivity 68.7% ; specificity 100% ; accuracy 86% ; PPV 100% ; NPV 80%

IDUS+ETP : sensitivity 97% ; specificity 92.5% ; accuracy 94.4% ; PPV 91.2% ; NPV 92.5%.

Endoscopic transpapillary forceps biopsy (ETP)

In ten patients with ampullary carcinoma the initial diagnosis by ETP was adenoma or normal ampullary tissue. Postoperative histopathology assessed carcinoma in these patients. There were no false-positive results in forceps biopsy histopathology leading to sensitivity, specificity and accuracy rates of 68.7%, 100% and 86%, respectively (Table 2).

In our patient cohort, 3 additional ampullary carcinomas could be detected by ETP which were misdiagnosed by IDUS alone as benign (Table 2) resulting in sensitivity, specificity and accuracy rates of 97%, 92.5% and 94.4%, respectively when combining IDUS with ETP.

Accuracy of IDUS in T and N staging

With regard to intraductal ultrasound miniprobe use overall results for T and N stages are given in Tables 4 and 5. The accuracy in assessing early T stage (T1) was 85.7% while that for T2 tumors was 71.4% (Table 3). For N0 and N1 stages accuracy rates of 75% each were calculated (Table 4).

All patients with histologically proven adenocarcinoma in this study underwent surgical exploration and modified Whipple's procedure as standard therapy. When using the IDUS results as possible basis for therapeutic decision-making (endoscopic papillectomy if uT1N0 versus Whipple's procedure if uT2Nx or T1N1), 23 out of 28 patients (82%) would have been correctly assigned to endoscopic or surgical therapy. Three out of 20 pT2/3Nx patients (15%) would not have received the appropriate Whipple's therapy (undertreatment), while 2 of 8 pT1N0 patients (25%) would have been overtreated with Whipple's procedure (Table 5).

Discussion

In various ampullary tumor studies, endoscopy and biopsies as the most important pre-therapeutic diagnostic

Table 3. — **Histopathology versus IDUS T staging of histologically proven ampullary carcinoma (n = 28)**

Histopathology						
IDUS	pT1	pT2	pT3/4	Σ	OS	US
uT1	7	3	0	10	0	3
uT2	1	6	4	11	1	4
uT3	0	0	7	7	0	0
Σ	8	9	11	28	1	7
Sensitivity (n) %	(7/8) 87.5	(6/9) 66.7	(7/11) 63.6			
Specificity (n) %	(17/20) 85	(14/19) 73.7	(17/17) 100			
Accuracy (n) %	(24/28) 85.7	(20/28) 71.4	(24/28) 85.7			

OS = overstaged, US = understaged.

Table 4. — **Histopathology versus IDUS N staging of histologically proven ampullary carcinoma (n = 28)**

Histopathology			
IDUS	pN0	pN1	Σ
uN0	15	5	20
uN1	2	6	8
Σ	17	11	28
Sensitivity (n) %	(15/17) 88	(6/11) 54.5	
Specificity (n) %	(6/11) 54.5	(15/17) 88	
Accuracy (n) %	(21/28) 75	(21/28) 75	

Table 5. — **Accuracy of IDUS regarding the correct therapeutic approach : endoscopic papillectomy (T1N0) vs. surgical exploration**

Final Histopathology after surgery		
IDUS	pT1N0	pT2/3Nx
uT1N0 (n)	6	3
uT1N1 (n)	1	0
uT2/T3Nx (n)	1	17

Accuracy regarding correct therapeutic approach : (23/28) 82%
pT1N0 : endoscopic papillectomy possible
pT2/3Nx : Surgical exploration needed.

tools regarding local findings showed accuracy rates of only 40% to 89%, even when biopsy specimens were taken after endoscopic sphincterotomy (25-27). In our patient cohort, ETP assessment revealed sensitivity, specificity and accuracy rates of 68.7%, 100% and 86%, respectively. The false-negative rate of 31.3% is similar to that of other previously published studies (27) reporting false-negative rates from 40 to 85%. When applying IDUS, improvement of sensitivity, specificity and accuracy up to 88%, 92.5% and 90.4%, respectively, was achieved. Sensitivity and accuracy could be further improved by applying both IDUS and EPT to 97% and 94.4%, respectively because three additional ampullary carcinomas were detected by ETP (in IDUS alone classified as adenoma). This means that 24 patients had to be examined with ETP in order to diagnose one additional ampullary carcinoma (number to diagnose).

In the era of endoscopic ultrasound (EUS/IDUS), however, sensitivity, specificity and accuracy rates of endoscopic diagnosis could substantially be increased possibly leading to fewer unnecessary surgical interventions in patients with benign ampullary adenomas.

As mentioned before, in our patient cohort we observed sensitivity, specificity and accuracy rates of 97%, 92.5% and 94.4%, respectively, when combining ERCP, IDUS and ETP. This is in accordance with findings by Ito et al. in a preoperative evaluation of ampullary neoplasms with EUS and IDUS demonstrating tumor depiction in 95% by EUS and 100% by IDUS (22). Clearly, further prospective multicenter studies need to be conducted for comparison of imaging modalities in ampullary tumor diagnostics.

It is consistently accepted that tumor depiction by means of US and CT is difficult, but that tumors can appropriately be diagnosed through EUS or IDUS (28,29). Although IDUS is superior regarding diagnostics of tumor extension to the pancreatic or biliary duct as well as pancreatic and duodenal invasion, the use of IDUS generally has not been incorporated into clinical routine yet.

The prognosis of ampullary carcinoma depends primarily upon the degree of local tumor extent, as reflected by the T stage, and the presence of lymphatic spread, as reflected by the N stage. The limited depth of IDUS ultrasound penetration impairs its use in assessing tumor M stage as well as extended tumor-stages > T3 (30) and restricts the evaluation of preoperative N stages. In our study, with respect to N0 and N1 stages, IDUS accuracy rates of only 75% each were calculated. Possibly, an improvement of preoperative uN staging can be achieved by combining EUS and IDUS. To our knowledge, however, only one study with a limited number of patients exists so far comparing IDUS and EUS with respect to N

staging of ampullary tumors (31). That study was neither able to clearly identify the superiority of one method over the other, nor could it confirm the clinical value of IDUS and EUS for preoperative N staging with an accuracy rate of only 62.5%.

At our institution we follow a work-up strategy of combining endoscopic imaging modalities (EUS, IDUS) with radiological imaging options such as magnetic resonance imaging or high-resolution computed tomography. Clearly, prospective studies need to be conducted to evaluate the most adequate combination of imaging modalities assuring the most accurate preoperative staging.

So far, minimally invasive nonsurgical therapies have been adapted to the treatment of ampullary adenomas and include endoscopic snare resection, Neodym :YAG laser ablation, and photodynamic therapy (28,32-34). The literature on these techniques in the setting of ampullary carcinoma is limited to only small series (35-37). Our findings indicate that IDUS is capable of assessing early T stage (T1) with an accuracy of 82% for correct endoscopic or surgical therapy. In accordance with previous findings by Woo and colleagues (38) no ampullary carcinoma of T1 stage had metastasized to lymph nodes, thus leaving endoscopic therapy as an option. Further large prospective studies clearly need to be conducted to definitely establish endoscopic treatment as a viable alternative to surgery in patients with early stage ampullary carcinoma.

To summarize, IDUS seems to be capable of differentiating between malignant and benign ampullary tumors and, therefore, of substantiating diagnostic and therapeutic processes. Moreover, our study shows appropriate diagnostic accuracy of IDUS T and N staging in ampullary carcinoma. Most importantly, our study implies the ability of IDUS to distinguish between limited (pT1N0) and advanced disease (pT2/3Nx), thus accurately guiding the use of less invasive endoscopic treatment options.

Admittedly, this study has several limitations. Firstly, the number of patients still was relatively small. Secondly, the possibility of selection bias may have been present because this study was conducted retrospectively. Clearly, further large-scale prospective studies are needed to overcome these limitations.

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