BILIARY DISEASE

Endoscopic transpapillary biopsies and intraductal ultrasonography in the diagnostics of bile duct strictures: a prospective study

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Background: In bile duct strictures, examination of wall layers by intraductal ultrasonography (IDUS) performed during endoscopic retrograde cholangiopancreatography (ERCP) may be diagnostically useful.

Methods: In the present study 60 patients with bile duct strictures of unknown aetiology were examined preoperatively by ERCP, including transpapillary biopsies and IDUS. Histopathological correlation was available for all patients undergoing these procedures.

Results: Postoperative diagnosis revealed 30 pancreatic carcinomas, 17 bile duct cancers, three gall bladder cancers, and 10 benign bile duct strictures. Using endoscopic transpapillary forceps biopsies (ETP), a correct preoperative diagnosis was achieved in 36 of 60 patients (60% of cases). Among the 50 malignant tumours, preoperative diagnosis by ETP revealed a sensitivity of 52% and a specificity of 100%. ERCP supplemented by IDUS allowed for correct preoperative diagnosis in 83% of cases (50 of 60 patients), which was significantly higher than the accuracy of ETP ($p=0.008$). By combining ETP with IDUS, a correct preoperative diagnosis was made in 59 of 60 patients resulting in an accuracy rate of 98%.

Conclusions: Because of its low accuracy, exclusive use of ETP is not a reliable diagnostic tool for a definitive preoperative diagnosis of bile duct strictures. By combining IDUS and ETP with ERCP however, preoperative diagnostic accuracy can be improved substantially.

Endoscopic retrograde cholangiopancreatography (ERCP) is the most valuable tool for further diagnosis as well as temporary or definitive therapy in patients with biliary strictures.¹ Although the use of endoscopic stenting techniques is very effective in patients with obstructive jaundice,² further management of patients primarily depends on the benign or malignant nature of the underlying disease.³ ERCP provides a unique opportunity to achieve biliary decompression and, simultaneously, to obtain a histological or cytological specimen of the biliary stricture. The poor results that were described in a large recently published study on biliary brush cytology³ however, have indicated the need for further studies in the analysis of tissue sampling.

Intraductal ultrasound (IDUS) of the pancreatic and bile duct system is a rapid, simple, and reliable method of providing valuable information on periductal tissue.^{4,5} High frequency ultrasound transducers adapted to the dimensions of the pancreaticobiliary system make IDUS examinations possible during ERCP in a single session. By visualising the wall layers in biliary strictures and estimating the extent of potentially cancerous infiltration, IDUS gives additional clinically important information. These data are invaluable for choosing the most appropriate treatment for the individual patient, such as placement of a stent, surgery, or chemotherapy. In the present prospective study we compared the diagnostic impact of endoscopic transpapillary forceps biopsies (ETP) with IDUS for preoperative assessment of biliary strictures, as confirmed by postoperative histopathology.

PATIENTS AND METHODS

In the present prospective study, 60 patients with bile duct strictures of unknown aetiology were enrolled from April 1994 to December 1998. The trial included all patients endoscopically examined in this period who were referred to our hospital with bile duct strictures of unknown aetiology. The study

protocol was approved by the local ethics committee of the University of Muenster and patients gave written informed consent to participate in the trial. We examined 32 men and 28 women, mean age 59.6 years (range 18–77). All 60 patients were prospectively examined by ERCP supplemented by IDUS and ETP. Because IDUS was always carried out before the assessment of ETP, physician performing IDUS did not have the histological diagnosis available until the procedures had been completed; therefore, the requirements of a blind study were satisfied.

A standard duodenoscope (Olympus JF-1T20; Olympus Optical Co, Ltd, Tokyo, Japan) was used for the transpapillary examination. Endoscopic papillotomy was performed if necessary. The 2.0 mm, 20 MHZ ultrasound probe (Aloka Co, Ltd, Tokyo, Japan) was inserted into the bile duct transpapillary. A frequency of 20 MHZ provides an axial resolution of 0.1 mm and allows for maximum penetration of approximately 20 mm. The ultrasound miniprobe system used in the present study contains a 360° radial sector scanning transducer and an ultrasound generator with a motor unit and a display (SSD-550; Aloka Co) as reported previously.⁶ A wire guided probe was not used. After transpapillary insertion, the probe tip was fluoroscopically placed. IDUS criteria included evaluation of tumour margins, invasion of surrounding tissue, and invasion of vessels. Sonographic features such as inhomogeneous echo poor lesions with irregular tumour margins were considered indicative of malignancy whereas homogeneous echo rich masses with smooth margins were

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; IDUS, intraductal ultrasonography; ETP, endoscopic transpapillary forceps biopsies; EUS, endoscopic ultrasonography.

Table 1 Final diagnosis based on histological assessment of surgical resection specimens

	No of patients
Pancreatic carcinoma	30
Bile duct cancer	17
Gall bladder cancer	3
Benign bile duct stricture	10
Chronic pancreatitis	6
Choledocholithiasis	1
Chronic cholangitis	3
Total	60

Figure 1 Topographic allocation of the bile duct strictures under study (total n=60). Modified according to the criteria of Tompkins and colleagues.⁹

considered characteristic of inflammatory lesions. Endosonographic criteria used in the present study are the generally accepted criteria for describing bile duct tumours and tumours of the pancreas.^{6,7} Penetration was defined as a continuation of the main echo poor tumour mass into adjacent structures. Tumours invading vascular structures or both hepatic ducts were classified as irresectable. No adverse events related to IDUS occurred during examination or follow up.

Transpapillary biopsies (n=4–8) were taken out of the biliary strictures by endoscopic forceps (MTW Endoscopy, Wesel, Germany). The tissue specimen was taken out of the bile duct stricture by either straight or angled endoscopic forceps. If insertion of the endoscopic forceps into the stricture was not possible, biopsies were taken from the lower margins of the bile duct stenosis. Histological analysis of the tissue specimens taken during endoscopy and surgery was performed at the Department of Pathology, and the specimens were independently assessed by two experienced pathologists. There were no complications resulting from taking tissue specimens transpapillarily. After performing IDUS and after assessment of the transpapillary biopsy, other imaging modalities (for example, computed tomography, endoscopic ultrasound, magnetic resonance imaging) were performed as required. All patients underwent laparotomy to exclude malignancy, and the final diagnosis was made by histological

assessment of the surgical resection specimens (considered the gold standard).

Statistics

For statistical analysis, sensitivity, specificity, positive and negative predictive values, and accuracy were calculated as follows⁸:

$$\text{Sensitivity} = \frac{\text{true positives}}{(\text{true positives} + \text{false negatives})}$$

$$\text{Specificity} = \frac{\text{true negatives}}{(\text{true negatives} + \text{false positives})}$$

$$\text{Positive predictive value} = \frac{\text{true positives}}{\text{all positives}}$$

$$\text{Negative predictive value} = \frac{\text{true negatives}}{\text{all negatives}}$$

$$\text{Accuracy} = \frac{(\text{true positives} + \text{true negatives})}{\text{total cases.}}$$

If the biopsy was found to be highly dysplastic—that is, cytologically highly dysplastic epithelial cells were found but invasion could not be proved because of the lack of stroma in the biopsy specimen—the case was considered positive for the purposes of statistical analysis.

Significance was calculated by McNemar's test and 95% confidence intervals were determined. Differences were considered statistically significant if $p < 0.05$.

RESULTS

Final diagnoses

In the present study series of 60 patients, the final diagnoses obtained from histopathological examination of the surgical specimen revealed 30 pancreatic carcinomas, 17 bile duct cancers, three gall bladder cancers, and 10 benign bile duct strictures (table 1). Figure 1 shows the allocation of the strictures modified according to the criteria of Tompkins and colleagues.⁹

Forceps biopsy analysis

Using ETP, a correct preoperative diagnosis was achieved in 33 of 60 patients (60%; 26 patients with malignancies, 10 patients with non-malignant lesions). Among the 50 malignant tumours, preoperative diagnosis by ETP revealed a sensitivity of 52% and a specificity of 100% (table 2). Biopsy histology was regarded as malignancy positive when invasion (n=22 patients) or highly dysplastic cells without stroma (n=4 patients) were found in tissue specimens. In this study, no further classification was made by the pathologist with regard to the origin (bile duct, pancreas, gall bladder) of the neoplastic lesion—that is, the samples were reported as adenocarcinomas with their respective histological grade (n=22) or as

Table 2 Endoscopic transpapillary biopsy (ETP) and intraductal ultrasonography (IDUS) in the diagnosis of biliary strictures (%) (n= 60)

	Final diagnosis (surgical specimen)	n	Sensitivity	Specificity	PPV	NPV	Accuracy
ETP	Benign disease	10	52	100	100	29	60
	Malignancies	50					
IDUS	Pancreatic carcinoma	30	90	83	84	89	83†
IDUS	Bile duct carcinoma	17	88	86	71	95	
IDUS	Gall bladder carcinoma	3	*	*	*	*	
ETP+IDUS							98

PPV, positive predictive value; NPV, negative predictive value.

*No separate statistical analysis because of the small number of cases.

†Relates to all three IDUS diagnoses.

Figure 2 A 67 year old male with pancreatic cancer. The patient initially presenting with obstructive jaundice was referred to our hospital for further diagnostics. (A) Endoscopic retrograde cholangiopancreatography suggested a malignant biliary obstruction. (B) Intraductal ultrasonography showed a suspected malignant mass (arrows) infiltrating the common bile duct. L, lumen of the common bile duct; HA, hepatic artery. (C) Histological analysis of a tissue specimen taken by transpapillary biopsy showed an adenocarcinoma with atypical clusters of stroma free epithelial cells (haematoxylin and eosin, $\times 200$).

cytologically positive cells with high grade dysplasia ($n=4$). All four cases with high grade dysplasia subsequently proved

to be invasive carcinomas on examination of the surgical specimen. In another 15 patients, low grade dysplastic cells ($n=2$ patients) or ulcerative/highly inflammatory cells ($n=13$ patients) were encountered in samples without definite signs of malignancy.

Figure 3 Intraductal ultrasonography. Benign stricture of the proximal common bile duct in a 46 year old female patient showing typical ultrasonographic characteristics of an inflammatory lesion: homogeneous echo rich mass with smooth margins (arrows).

Intraductal ultrasonography

IDUS allowed correct diagnosis of bile duct carcinomas with sensitivity and specificity rates of 88% and 86%, respectively (table 2). For neoplastic lesions of pancreatic origin infiltrating the bile duct, IDUS had a sensitivity of 90% and a specificity of 83% (see fig 2). For carcinomas originating in the gall bladder with infiltration of the bile duct, no separate statistical analysis was performed because of the small number of cases ($n=3$). ERCP supplemented by IDUS allowed for correct preoperative diagnosis in 83% of cases (50 of 60 patients, 48 patients with malignancies, two patients with non-malignant lesions), which is significantly superior to the accuracy of ETP (60%; $p=0.008$). By combining ETP with IDUS (table 2), a correct preoperative diagnosis was made in 59 of 60 patients (49 patients with malignancies, 10 patients with non-malignant lesions) resulting in an accuracy rate of 98%. Forty eight of 50 cases (92%) with a final diagnosis of "malignancy" (obtained from histopathological examination of the surgical specimen) had endosonographically been classified as clearly malignant according to the IDUS criteria mentioned above. IDUS did not show typical endosonographic features of malignancies in two of these 50 patients. In these two patients

Table 3 Exact 95% confidence interval and McNemar's test of endoscopic transpapillary biopsy (ETP) and intraductal ultrasonography (IDUS) with respect to localisation of biliary stenoses

Method	Stenosis (localisation)	Accuracy (No of patients)	Accuracy (%)	Lower margin (%)	Upper margin (%)
ETP	Proximal	9/12	75	42.8	94.5
	Middle	7/7	100	42.1	100
	Distal	22/41	53.7	28.5	60.3
	All	36/60	60	41.6	67.9
IDUS	Proximal	12/12	100	73.5	100
	Middle	7/7	100	42.1	100
	Distal	31/41	75.6	54.4	83.9*
	All	50/60	83.3	65.8	87.9†

Mc Nemar's test: *p=0.022 versus ETP in distal stenoses; †p=0.008 versus ETP in all stenoses.

the differential diagnosis was pancreatic carcinoma versus inflammatory lesion in the head of the pancreas by IDUS criteria (fig 3).

Comparing IDUS and ETP with regard to localisation of biliary stenoses (proximal, middle, and distal third), McNemar's test proved IDUS to be superior to ETP in the diagnostics of distal biliary stenoses (p=0.022). Because of the small number of cases, no statistically significant difference was found between IDUS and ETP in bile duct strictures of the proximal (n=12) and mid third (n=7) (table 3).

DISCUSSION

Diagnosis of strictures affecting the biliary tract using non-surgical methods is highly desirable to allow for adequate planning of surgical or non-surgical treatments.^{10 11} Although many patients are managed without histological confirmation, confirmation allows accurate decision making with reference to total patient management, including surgery, endoscopic stenting, chemotherapy, or radiotherapy.¹⁰ Brush cytology is considered an accurate technique in providing a cytopathological diagnosis of bile duct strictures. However, recently published studies on brush cytology or transpapillary forceps biopsy of bile duct strictures did not compare these techniques with histopathology of resection specimens in all patients.^{3 12 13} In the present study, all of the 60 patients underwent surgery thus allowing an accurate evaluation of the techniques.

In the past decade, several attempts have been made to examine bile duct strictures endoscopically.¹²⁻¹⁷ For brush cytology, a sensitivity of 56%, specificity of 91%, and an accuracy rate of 65% were reported (n=86, histopathologically proved n=35).³ However, results for ETP from four prospective studies have been encouraging,^{10 12 17 18} with a cancer detection rate of 65% among 275 patients.¹¹ Regarding sensitivity and specificity, our results match with those of Pugliese and colleagues, with a sensitivity of 52% (present study) compared with 53%, a specificity of 100% in both series, and an accuracy of 60% versus 68%.¹⁰

However, a diagnosis of malignancy can only be determined by the pathologist when invasion of tumour cells into the stroma is seen in the biopsy specimen. As many biopsies from bile duct strictures contain only clusters of epithelial cells without underlying stroma, it is impossible for the pathologist to prove invasive growth of the tumour which is, by definition, the criterion for malignancy. High grade dysplasia of epithelial cells suggests malignancy but does not prove invasion.

Endoscopic ultrasonography (EUS) has made an impressive impact on endoscopic imaging. Moreover, recently developed ultrasonic miniprbes can be passed through the working channel of standard endoscopes to provide high frequency ultrasonographic images. The ultrasonic miniprobe is an ideal instrument to be inserted into fluid filled tubular structures

such as the biliary and pancreatic ductal systems that are only slightly larger than the miniprobe itself.⁵

In a previous study by Menzel *et al*, conventional endosonography (EUS) was compared with IDUS in biliary strictures.¹⁹ The present study evaluated the impact of ETP and IDUS on the diagnosis of biliary strictures. EUS was not regularly performed in all patients included in this trial. The aim and techniques used in the present study differed substantially from those of Menzel *et al* as ETP were taken, and both ETP and IDUS were performed in the same session during ERCP. Therefore, more information—histology and staging of the tumour—about the bile duct strictures are obtained during a single endoscopic examination (ERCP).

In a previous study by Tamada *et al*, IDUS used for bile duct cancer diagnosis gave an accuracy of 76%.²⁰ In this study however IDUS was not compared with the histomorphology of surgical resection specimens. This fundamental limitation of many studies concerning imaging of the bile duct is due to the difficulty in comparing imaging results with histological analysis of resected specimens as most patients with benign bile duct stenoses do not undergo surgery.²⁰

Compared with standard EUS, intraductal scanning within the bile duct stricture improved diagnostic accuracy as well as estimation of local tumour extent.¹⁹ Although ultrasonography does not provide histopathological diagnosis, IDUS yields specific tissue characterisation and thus may direct the diagnostic process to the underlying disease.^{6 7 20} In the present study, the combination of IDUS and ETP allowed correct preoperative diagnosis in 98% of cases, making ERCP—supplemented by these two techniques—the most accurate and reliable procedure in preoperative evaluation of biliary strictures.

Tumour staging relies on precise delineation of the local extent and on detection of lymph nodes and distal metastases to provide a guideline for prognosis and treatment. As shown previously, endoluminal ultrasonography is generally accurate for staging the tumour category. Due to the limited ultrasonic penetration for both IDUS and EUS, understaging of biliary carcinomas in the proximal bile duct and bile duct bifurcation has been observed.¹⁹ Application of high ultrasound frequencies enhances the resolution but reduces the depth of penetration. Thus IDUS is not suitable for lymph node staging. The staging information from the present trial (preoperative histology, assessment of local tumour extension) has been used for clinical care decision in patients with bile duct strictures. Due to the lack of information regarding lymph node stage and distal metastases however, IDUS and ETP by themselves do not allow for a complete evaluation on resectability. Nevertheless, they do contribute to more accurate decision making with reference to total patient management.

In conclusion, ERCP provides a unique opportunity to obtain histological specimens from patients with biliary strictures of unknown aetiology and, additionally, allows for biliary

decompression. Preoperative assessment of tissue samples from strictures affecting the biliary tract may permit more accurate decision making in total patient management. Accuracy of ETP alone is not reliable enough to allow for a definitive preoperative diagnosis of bile duct strictures. ETP complemented by IDUS can achieve a significant improvement in preoperative diagnosis. Thus in patients with bile duct strictures, ERCP plus IDUS, ETP, and the option to drain the bile duct system can provide biliary decompression as well as a diagnosis of malignancy with a high degree of accuracy.

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REFERENCES

- 1 Choudari CP, Fogel E, Gottlieb, et al. Therapeutic biliary endoscopy. *Endoscopy* 1998;30:163-73.
- 2 Hoepffner N, Foerster EC, Hoegemann B, et al. Longterm experience in wallstent-therapy for malignant choledochal stenosis. *Endoscopy* 1994;26:597-602.
- 3 Glasbrenner B, Ardan M, Boeck W, et al. Prospective evaluation of brush cytology of biliary strictures during endoscopic retrograde cholangiopancreatography. *Endoscopy* 1999;31:712-17.
- 4 Menzel J, Domschke W. Intraductal ultrasonography (IDUS) of the pancreato-biliary duct system. Personal experience and review of literature. *Eur J Ultrasound* 1999;10:105-15.
- 5 Menzel J, Domschke W. Gastrointestinal miniprobe sonography: the current status. *Am J Gastroenterol* 2000;3:605-16.
- 6 Tamada K, Ido K, Ueno N, et al. Preoperative staging of extrahepatic bile duct cancer with intraductal ultrasonography. *Am J Gastroenterol* 1995;90:239-46.
- 7 Roesch T, Classen M. *Gastroenterologic endosonography: Textbook and atlas*. Stuttgart: Georg-Thieme-Verlag, 1992.
- 8 Armitage P, Berry G. *Statistical methods in medical research*, 2nd edn. Oxford: Blackwell Scientific Publications, 1990.
- 9 Tompkins RK, Thomas D, Wile A, et al. Prognostic factors in bile duct carcinoma. Analysis of 96 cases. *Ann Surg* 1981;194:447-55.
- 10 Pugliese V, Conio M, Nicolo G, et al. Endoscopic retrograde forceps biopsy and brush cytology of biliary stricture: a prospective study. *Gastrointest Endosc* 1995;42:520-6.
- 11 Fogel EL, Sherman S. How to improve the accuracy of diagnosis of malignant biliary strictures. *Endoscopy* 1999;31:758-60.
- 12 Sugiyama M, Atomi Y, Wada N, et al. Endoscopic transpapillary bile duct biopsy without sphincterotomy for diagnosing biliary strictures: a prospective comparative study with bile and brush cytology. *Am J Gastroenterol* 1996;91:465-7.
- 13 Vandervoort J, Soetikno RM, Montes H, et al. Accuracy and complication rate of brush cytology from bile duct versus pancreatic duct. *Gastrointest Endosc* 1999;49:322-7.
- 14 Leung JWC, Sung JY, Chung SCS, et al. Endoscopic scraping biopsy of malignant biliary strictures. *Gastrointest Endosc* 1989;35:65-6.
- 15 Foutch PG, Kerr DM, Harlan JR, et al. Endoscopic retrograde wire-guided brush cytology for diagnosis of patients with malignant obstruction of the bile duct. *Am J Gastroenterol* 1990;85:791-5.
- 16 Foutch PG. Diagnosis of cancer by cytologic methods performed during ERCP. *Gastrointest Endosc* 1994;40:249-52.
- 17 Kubota Y, Takaoka M, Tani K, et al. Endoscopic transpapillary biopsy for diagnosis of patients with pancreatobiliary ductal strictures. *Am J Gastroenterol* 1993;88:1700-4.
- 18 Ponchon T, Gagnon P, Berger F, et al. Value of endobiliary brush cytology and biopsies for the diagnosis of malignant bile duct stenosis: results of a prospective study. *Gastrointest Endosc* 1995;42:565-72.
- 19 Menzel J, Poremba C, Dietl K, et al. Preoperative diagnosis of bile duct strictures. Comparison of intraductal ultrasonography (IDUS) with conventional endosonography (EUS). *Scand J Gastroenterol* 2000;35:77-82.
- 20 Tamada K, Ueno N, Tomiyama T, et al. Characterization of biliary strictures using intraductal ultrasonography: comparison with percutaneous cholangioscopy. *Gastrointest Endosc* 1998;47:341-9.