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

D Domagk, C Poremba, K-H Dietl, N Senninger, A Heinecke, W Domschke, J Menzel

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. Although the use of endoscopic stenting techniques is very effective in patients with obstructive jaundice, further management of patients primarily depends on the benign or malignant nature of the underlying disease. 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 cytology 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. High frequency ultrasound transducers adapted to the dimensions of the pancreatobiliary 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 transpapillarily. 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. 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.
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. 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 transpapillarily. After performing IDUS and after formation of the main echo poor tumour mass into adjacent structures, further classification was made by the pathologist with regard to the origin (bile duct, pancreas, gall bladder) of the neoplasia. 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 follows:

- **Sensitivity** = true positives/(true positives + false negatives)
- **Specificity** = true negatives/(true negatives + false positives)
- **Positive predictive value** = true positives/all positives
- **Negative predictive value** = true negatives/all negatives
- **Accuracy** = (true positives + true negatives)/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.

**Forcips 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>
<thead>
<tr>
<th>Table 1</th>
<th>Final diagnosis based on histological assessment of surgical resection specimens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of patients</td>
</tr>
<tr>
<td>Pancreatic carcinoma</td>
<td>30</td>
</tr>
<tr>
<td>Bile duct cancer</td>
<td>17</td>
</tr>
<tr>
<td>Gall bladder cancer</td>
<td>3</td>
</tr>
<tr>
<td>Benign bile duct stricture</td>
<td>10</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>6</td>
</tr>
<tr>
<td>Choledocholithiasis</td>
<td>1</td>
</tr>
<tr>
<td>Chronic cholangitis</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Endoscopic transpapillary biopsy (ETP) and intraductal ultrasonography (IDUS) in the diagnosis of biliary strictures (%) (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Final diagnosis (surgical specimen)</td>
</tr>
<tr>
<td>ETP</td>
<td>Benign disease</td>
</tr>
<tr>
<td>ETP</td>
<td>Malignancies</td>
</tr>
<tr>
<td>IDUS</td>
<td>Pancreatic carcinoma</td>
</tr>
<tr>
<td>IDUS</td>
<td>Bile duct carcinoma</td>
</tr>
<tr>
<td>IDUS</td>
<td>Gall bladder carcinoma</td>
</tr>
<tr>
<td>ETP+IDUS</td>
<td></td>
</tr>
</tbody>
</table>

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.
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.

**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 analy-
sis 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.

**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, ×200).

**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).
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. 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. Brush cytology is considered an accurate technique in providing a cytological 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. 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. For brush cytology, a sensitivity of 56%, specificity of 91%, and an accuracy rate of 65% were reported (n=86, histopathologically proved n=35). However, results for ETP from four prospective studies have been encouraging, with a cancer detection rate of 65% among 275 patients. 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%.

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 miniprobe can be passed through the working channel of standard endoscopes to provide high frequency ultrasonicographic 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.

In a previous study by Menzel et al, conventional endosonography (EUS) was compared with IDUS in biliary strictures. 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%. 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.

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

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**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

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

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