Endoscopic transpapillary bile duct biopsy with the combination of intraductal ultrasonography in the diagnosis of biliary strictures

K Tamada, T Tomiyama, S Wada, A Ohashi, Y Satoh, K Ido, K Sugano

Background: When endoscopic retrograde cholangiopancreatography (ERCP) guided bile duct biopsy fails to demonstrate malignancy, it remains unclear how to manage patients with presumably malignant strictures.

Aims: To evaluate the value of intraductal ultrasonography (IDUS) when bile duct biopsy is negative.

Methods: Sixty two patients with strictures of the bile duct were studied prospectively. During ERCP, IDUS was performed using an ultrasonic probe (diameter 2.0 mm; frequency 20 MHz). Following IDUS, a bile duct biopsy was performed using forceps (diameter 1.8 mm). The IDUS images of the tumour were classified as polypoid lesions, localised wall thickening, intraductal sessile tumours, sessile tumour outside of the bile duct, or absence of apparent lesion. The bile duct wall structures at the site of the tumour as well as the maximum diameter of the tumour were also analysed. The IDUS findings were compared with the histological findings or clinical course.

Results: When the IDUS images showed a polypoid lesion (n=19), localised wall thickening (n=8), intraductal sessile tumour (n=13), and sessile tumour outside of the bile duct (n = 20), the sensitivities of the biopsy were 80%, 50%, 92%, and 53%, respectively. Multiple regression analysis showed that the presence of sessile tumour (intraductal or outside of the bile duct: p<0.05), tumour size greater than 10.0 mm (p<0.001), and interrupted wall structure (p<0.05) were independent variables that predicted malignancy.

Conclusion: When biopsy fails to demonstrate evidence of malignancy, the presence of sessile tumour (intraductal or outside of the bile duct), tumour size greater than 10.0 mm, and interrupted wall structure on IDUS images are factors that can predict malignancy.
stiff Zebra guidewire (Microvasive Co., Watertown, Massachusetts, USA), a 2.0 mm diameter ultrasonic probe with a frequency of 20 MHz (MP-PN20-06L; Aloka Co., Tokyo, Japan) was inserted into the bile duct along the guidewire. Endoscopic sphincterotomy was not performed. The tip of the probe had a side slit for the guidewire. The catheter generated high resolution, real time, cross sectional images with an axial resolution of 0.1 mm and a maximum penetration of approximately 20 mm. The IDUS images were recorded on S-VHS videotapes and individual still frames. After the ultrasonic probe was removed, an endobiliary biopsy was performed under fluoroscopic guidance using a clamshell-type needleless biopsy forceps (FB-39Q; Olympus Optical) with a Teflon sheath (outer diameter 1.8 mm). While maintaining the guidewire over the stricture, the biopsy forceps were inserted into the orifice of the papilla along the upper side of the placed guidewire without endoscopic sphincterotomy (n=35). When the forceps could not be smoothly inserted into the orifice of the papilla, an Olbert 5 French balloon tipped biliary catheter (Microvasive) with a length of 180 cm and a balloon length of 3 cm (maximum diameter 8 mm) was passed over the guidewire and endoscopic papillary balloon dilation (balloon sphincteroplasty) was performed using previously reported techniques.37–39 During and after the biopsy, the guidewire remained in that position. Three or more specimens were obtained from each patient. After biopsy, an endoscopic nasobiliary drainage (ENBD) tube was introduced along the guidewire when the bile duct was obstructed. During the initial study period, the biopsy was performed following withdrawal of the guidewire as we mistakenly considered that the guidewire would interfere with insertion of the forceps into the papilla (n=14). In the last cases (n=13), a new ropeway-type 1.8 mm diameter clamshell-type needleless biopsy forceps (prototype, Olympus) were used. The tip of the ropeway-type forceps had a side slit for a guidewire and therefore the guidewire was left in place during the biopsy.

Biopsy specimens were fixed in 1% formalin, embedded in paraffin, and stained with haematoxylin and eosin. When the histological examination of the biopsy specimen showed only atypical cells, the results were judged negative for malignancy.

**Study design**

The IDUS images were prospectively reviewed by two experts without information from other imaging tests, except for abdominal ultrasonography and cholangiography. The morphology of the tumour was classified as one of the following: polypoid lesion; localised wall thickening; intraductal sessile tumour; sessile tumour outside of the bile duct; or no apparent lesion. Typical cases are presented in figs 1–4. The bile duct wall structures at the site of the tumour as well as the maximum diameter of the tumour were analysed also. Analysis was
performed using the Stat View software package. The data were analysed using Fisher’s exact test. Relative significance was analysed by multivariate analysis (multiple regression). A p value <0.05 was considered significant.

RESULTS

Success rate for insertion of biopsy forceps

During the initial study period, when the forceps were inserted without the guidewire in place, endoscopic papillary balloon dilation was required in six of 14 patients. During the latter period of the study, when the ropeway-type forceps (prototype) were used, endoscopic papillary balloon dilation was not required in any case. In other patients in whom standard forceps were inserted along the upper side of the placed guidewire, endoscopic papillary balloon dilation was required in three of 35 patients to allow for insertion of the forceps. As a result, the biopsy forceps were successfully inserted into the bile duct after IDUS, and tissue materials were successfully obtained in all patients.

Relationship between IDUS and histology

The results are summarised in tables 1–3.

When IDUS showed a polypoid lesion, the biopsy was sensitive in diagnosing malignancy in 80% (8/10) of patients. It was sensitive in all patients who had polypoid lesions with cholangiocarcinoma (n=8). The two patients with false negative biopsy results had tumour thrombi from hepatocellular carcinomas (HCC). In the intrapancreatic bile duct, only two of nine patients with polypoid lesions had malignancy. On the other hand, in the extrapancreatic bile duct, eight of nine patients with polypoid lesions had malignancy.

When IDUS showed a intraductal sessile tumour, all patients had histological evidence of malignancy. All intraductal sessile tumour showed an interruption of wall structures on IDUS findings. Biopsy was sensitive in 92% (12/13) of patients.

When IDUS showed localised wall thickening, 75% (6/8) of patients had benign diseases; of the two patients with malignancy, the biopsy was sensitive in only 50% (1/2). Five of six patients with benign strictures that were described as localised wall thickening by IDUS had some clinical origin of their stenosis (two with bile duct stones, one with outmobile injury, one with chronic pancreatitis, and one with Mirizzi’s syndrome). On the other hand, two of three patients without evidence of a clinical origin of the stenosis had malignancy.

When IDUS showed sessile tumour outside of the bile duct, 95% (19/20) of patients had malignant diseases, and biopsy was sensitive in 53% (10/19) of patients. Biopsy was sensitive in 50% (6/12) of patients with pancreatic cancer.

Multiple regression analysis showed that sessile tumour (intraductal or outside of the bile duct: p<0.05), tumour size (p<0.001), and interrupted wall structure (p<0.05) were independent variables that predicted malignancy.

As shown in table 2, when the IDUS finding of interrupted wall structure was used as the criterion of malignancy, the accuracy, sensitivity, and specificity of IDUS were 81%, 75%, and 94%, respectively.

Figure 3  A 57 year old man with localised wall thickening of the bile duct. The patient initially presented with upper abdominal pain. Ultrasound showed bile duct dilatation. He underwent endoscopic lithotripsy following an endoscopic retrograde cholangiography that showed a bile duct stone. [A] Cholangiography after endoscopic lithotripsy showed a stenosis in the distal portion of the bile duct (arrow). [B] A frame from the intraductal ultrasonogram showing the probe in the bile duct (BD) within the ultrasonographic field of view. Note the localised bile duct wall thickening (arrows) with the normal structure of the bile duct. The narrow dot at the margin of the frame was 1.0 mm in width. Endoscopic transpapillary bile duct biopsy showed no evidence of malignancy. [C] Three months later, cholangiography showed persistent stenosis (arrow). [D] A frame from the intraductal ultrasonogram showed wall thickening (arrows). It showed no interval change. Endoscopic transpapillary bile duct biopsy again showed no evidence of malignancy.

Figure 4  A 64 year old woman with a sessile tumour outside of the bile duct. The patient initially presented with obstructive jaundice and underwent endoscopic retrograde cholangiography. (A) Cholangiography showed a stenosis at the intrapancreatic bile duct (arrow). [B] A frame from intraductal ultrasonography showed the probe in the bile duct within the ultrasonographic field of view. Note the tumour located outside of the bile duct (arrows). The narrow dot at the margin of the frame was 1.0 mm in width. Endoscopic transpapillary bile duct biopsy showed no evidence of malignancy. [C] The histological findings of the resected specimen revealed pancreatic cancer (arrowheads) that had invaded the bile duct (haematoxylin and eosin, ×1).
and 94%, respectively. As shown in table 3, when the IDUS finding of a tumour greater than 10 mm was used as the criterion of malignancy, the accuracy, sensitivity, and specificity of IDUS were 84%, 84%, and 83%, respectively.

Course of the patients
The clinical courses of the patients and the process of final diagnosis are summarised in table 4. Sixteen patients were judged as having no biliary tract carcinoma and were clinically observed. Two required transient replacement of their biliary endoprosthesis. Seven other patients underwent lithotripsy under endoscopic papillary balloon dilatation. One patient with Mirizzi’s syndrome was observed after laparoscopic cholecystectomy. In seven of these 16 patients, a repeat IDUS and biopsy were performed 1–6 months later (mean three months). Improvement in wall thickening or a decrease in the size of the polypoid lesion was seen in five of seven observed patients. The remaining nine of 16 patients rejected a second ERCP as they were asymptomatic. Ultrasonography and laboratory data showed no signs of biliary obstruction in these patients. No signs of malignancy were detected in any of the observed patients during the follow up period of 18–64 months.

Scoring of intraductal ultrasonographic findings
Based on the results of multiple regression analysis, (1) the presence of sessile tumour (intraductal or outside of the bile duct), (2) tumour size greater than 10.0 mm, and (3) interrupted wall structure were used as positive factors to predict malignancy on IDUS findings, and the relationship between intraductal ultrasonographic findings and final diagnosis was retrospectively analysed. As shown in table 5, in cases with no evidence of malignancy on histological findings of the biopsy specimen (n=31), if IDUS findings showed two
or three positive factors, 92% of patients showed malignancy on the final diagnosis. In contrast, if IDUS showed no positive factor, no patient showed malignancy on the final diagnosis when the biopsy specimen showed no evidence of malignancy.

**Complications**

One patient suffered from acute pancreatitis which resolved within 48 hours with intravenous fluids and analgesia. No other complications occurred as a result of ERCP, IDUS, biopsy, or ENBD.

**DISCUSSION**

Accurate characterisation of biliary strictures is particularly important in patients with benign stenoses, as most of these patients can be successfully treated by the transitory placement of biliary endoprostheses rather than surgery. However, to our knowledge, there is no previous study which clarifies the management of patients in whom the endoscopic transpapillary biopsy specimen shows no evidence of malignancy. In this study, we utilised addition of IDUS for this purpose. Of course, improving methods of tissue sampling is a better strategy for enhancing reliability than requiring an additional imaging modality. Currently, the sensitivities of fluoroscopically guided transpapillary bile duct biopsy, brush cytology, and conventional modality. Currently, the sensitivities of fluoroscopically guided transpapillary bile duct biopsy, brush cytology, and conventional bile cytology are 31–81%, 44–66%, and 30–50%, respectively. It is obvious that these results are unacceptable and that it is necessary to develop some way to compensate for these limitations. Bile duct biopsy under percutaneous transhepatic cholangioscopy (PTCS) is accurate and has a sensitivity of 93–96%, and interrupted wall structure. However, this requires an invasive procedure and is not routinely performed by endoscopists in Western countries.

Several studies have described the use of IDUS in patients with pancreatic or biliary strictures. In these studies, both benign and malignant strictures ultimately were resected. These studies provide valuable information about the accuracy of IDUS. However, the aims of the present study were not only to compensate for the false negative rate of ERCP obtained biopsies but also to prevent unnecessary surgical exploration. Previous reports have defined benign diseases as those with negative biliary duct samplings which remained cancer free during an observation period of six months, 14 months, 15 months, 18 months, or 24 months. Therefore, we followed patients for at least 18 months to confirm that the pathology was in fact benign.

According to a preliminary study, PTCS guided biopsy of polypoid-type cholangiocarcinoma is more sensitive than biopsies of other types of cancer as cancer cells are present throughout the entire bile duct mucosa in this lesion. PTCS guided biopsy of metastatic tumour was less sensitive than biopsies of primary bile duct carcinoma. According to another previous study which compared percutaneous transhepatic IDUS findings and the findings of PTCS guided biopsy, tumour size greater than 10.0 mm and interrupted wall structure on IDUS images were factors that predicted malignancy. During the period of preliminary study in these reports, we predicted that the combination of transpapillary biliary biopsy and IDUS contributes to the management of patients with biliary strictures, and performed the current prospective study.

As IDUS shows asymmetric bile duct wall thickening due to inflammatory changes as well as cancer, accurate characteristics of the demonstrated lesion are required. Menzel et al. reported that when hypoechoic masses with irregular margins and inhomogeneous echo poor areas invading surrounding tissue on IDUS were considered malignant, the accuracy, sensitivity, and specificity of these IDUS findings were 89.1%, 91.1%, and 80%, respectively. If IDUS shows tumour invasion into the hepatic artery, the portal vein, or the pancreatic parenchyma, it suggests malignant disease, as previously reported.

In our study, endoscopic biopsy of the polypoid lesions showed 100% sensitivity in patients with cholangiocarcinoma. However, the biopsy was not sensitive in polypoid lesions with tumour thrombi caused by HCC. Thomsen et al. reported a similar case of tumour thrombi caused by HCC but this patient's hepatic mass was not detected by ultrasonography prior to peroral cholangioscopy. Therefore, when biopsy of a polypoid lesion located at the hepatic hilus is negative, tumour thrombi caused by HCC should be considered. Although autoimmune deficiency syndrome related polypoid lesions of the bile duct have been reported in Western countries, we had no experience of this disease. On the other hand, the distal end of the bile duct is a common location of benign polypoid lesions including cholesterol polyps, adenomyomas, and inflammatory polyps.

Our study also showed the limitation of biopsy in patients with the tumour outside of the bile duct, including pancreatic cancer. Kubota and colleagues and Sugiyama and colleagues also reported that the sensitivity of biopsy in pancreatic cancer was inferior to the sensitivity in primary bile duct cancer. Others recommend endoscopic ultrasonography guided aspiration cytology for these patients.

Our current study indicated that (1) the presence of sessile tumour (intraductal or outside of the bile duct), (2) tumour size greater than 10.0 mm, and (3) interrupted wall structure on IDUS images were positive factors in predicting malignancy on IDUS findings. As shown in table 5, in cases with no evidence of malignancy on histological findings of biopsy specimen, if IDUS findings show none of these three factors the presence of biliary malignancy is rare. In particular, in patients with polypoid lesions located at the intrapancreatic duct and those with localised wall thickening who have some history (bile duct stones and others) may be conservatively observed. However, when IDUS shows two of these three factors, patients should be judged as having malignancy even if histological findings of biopsy specimen show no evidence of malignancy.

In our subjects, if patients with evidence of malignancy on histological findings of biopsy specimen or some positive factors on IDUS were judged to have malignant diseases, and the remaining patients were judged to have benign diseases, 95% (59/62) were appropriately treated with three false positive and no false negative results.

In conclusion, if the endoscopic biopsy of a biliary stricture shows no malignancy, the patient may be managed using IDUS in combination with other diagnostic imaging and clinical findings.

**Authors' affiliations**

K Tamada, T Tomiyama, S Wada, A Ohashi, Y Satoh, K Ido, K Sugano, Department of Gastroenterology, Jichi Medical School, Youshihi, Tochigi 329-0898, Japan
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