Tumor Vessel: a Valuable Cholangioscopic Clue of Malignant Biliary Stricture

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INTRODUCTION

It is essential to define whether biliary stricture is benign or malignant because of the varied available treatment options. Since percutaneous cholangioscopy was introduced for the complementary evaluation of the biliary tree, several endoscopic findings predicting malignancy have been described in the literature. These include irregularly dilated and tortuous vessels, known as tumor vessels. This study aimed to evaluate the usefulness of tumor vessels as a cholangioscopic clue in differentiating malignant from benign biliary strictures.

The irregularly dilated and tortuous vessel, so called tumor vessel, is considered to be one of the reliable...
cholangioscopic findings of biliary malignancy. It is frequently noted on the mucosa over cholangiocarcinoma and provides a valuable diagnostic clue. To our knowledge, however, the utility of this tumor vessel for the differentiation of malignant stricture from benign one has not been studied in detail. The aim of this study was to evaluate the value of tumor vessel in discrimination between benign and malignant biliary stricture.

**PATIENTS AND METHODS**

From August 1997 to August 1998, the patients who underwent percutaneous transhepatic cholangioscopic (PTCS) examination for the evaluation of biliary stricture were included in this study. Biliary stricture was diagnosed at endoscopic retrograde cholangiograms (ERC) or cholangiograms obtained by percutaneous transhepatic biliary drainage (PTBD) tubes. In all the patients, radiological feature of dilated bile duct proximal to stricture and biochemical features of biliary obstruction, i.e., elevated serum aminotransferase, alkaline phosphatase, or conjugated bilirubin, were observed. On the basis of imaging study, patients with lesions delineated as an intraluminal mass in or around biliary stricture, the finding of which has been known as a distinct clue of biliary malignancy, were excluded. The patients who did not undergo PTCS examination or showed uncertainty of final diagnosis were also excluded. Sixty-three patients were finally enrolled.

Tumor vessel was defined by the abnormally proliferating and tortuous vascular structure revealed on the bile duct mucosa adjacent to stricture (Fig. 1). By the observation of tumor vessel, strictures were preoperatively characterized to be benign or malignant and the results were compared to those by PTCS-guided biopsy and final diagnosis. Malignant strictures were finally confirmed when malignant cells were observed on the specimens obtained by cholangioscopic biopsy or surgery. Strictures were considered benign when malignant cells were not found in resected specimen from the patients who underwent surgery or when there was no clinical and radiologic evidence of disease progression during more than one year follow-up in patients with negative endoscopic biopsy finding and no surgery.

As the first step of PTCS examination, PTBD was performed through the anterior abdominal or chest wall in accordance with Takada's method. As the next step, the sinus track of PTBD was dilated to 16 or 18 Fr at one sitting and PTCS examination was done 7 to 10 days later. PTCS examination was made with instillation of normal saline using cholangioscope, Olympus CHF-P200 or Pentax FCN-15X. The lesions of strictures were carefully examined to check the presence of abnormal dilated vessel and targeted biopsy was performed with 1.8-mm diameter biopsy forceps (FB-19SX-1, Olympus) under the direct control of cholangioscope. More than three pieces of
biopsy specimen per patient were obtained. Biopsy was performed once more if malignant cells were not documented at initial examination. In all the patients, PTCS examinations were performed successfully without complications.

The presence of tumor vessel was independently decided by two expert cholangioscopists who had no clinical or other imaging information. They were blinded to each other and the tumor vessel was regarded to be present only when their opinions were identical. Informed consent was obtained from the patients prior to cholangioscopic procedures and the study was approved by the Institutional Review Board at the Hospital.

Sensitivity, specificity and positive- and negative predictive values for each modality were calculated and were compared using chi-square test. Values for \( p < 0.05 \) were considered statistically significant.

RESULTS

Forty-one patients were confirmed to have malignant biliary strictures and twenty-two patients to have benign ones. The mean age of the patients with malignancy was 60 years (43–81). Malignant strictures were detected by surgical resection (n=31) or PTCS-guided biopsy (n=10). The causes of malignant strictures were 23 of hilar cholangiocarcinoma, 11 of common bile duct cancer, 3 of anastomosis site cancer (previous lobectomy and hepaticojejunostomy due to the hepatolithiasis), 2 of pancreatic cancer, and 2 of intrahepatic cholangiocarcinoma. Benign strictures were confirmed by surgical resection (n=13), cholangioscopic biopsy and clinical follow-up (n=9). The mean age of twenty-two patients with benign strictures was 47 years (24–72). Underlying causes of benign strictures were as follows: 11 of recurrent cholangitis due to hepatolithiasis, 5 of stricture after biliary surgery (lobectomy and hepaticojejunostomy due to hepatolithiasis 3, laparoscopic cholecystectomy 2), 3 of recurrent cholangitis due to choledocholithiasis, and 3 of secondary biliary change due to chronic pancreatitis. The locations of malignant and benign strictures are summarized in Table 1.

One hundred fifty six pieces of biopsy specimens were taken from the 41 malignant tumors and 72 pieces were taken from 22 benign diseases during PTCS examination. Biopsy was positive in 80.4% (33/41) of patients with the final diagnosis of malignancy. The overall agreement rate on the presence of tumor vessel by two endoscopists was 100%. Tumor vessels

<table>
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<tr>
<th>Table 1. The location of benign and malignant strictures</th>
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<tr>
<td><strong>Benign stricture</strong> (n=22)</td>
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<tr>
<td>Intrahepatic bile duct</td>
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<tr>
<td>Hilar area</td>
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<td>Extrahepatic bile duct</td>
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<td>Choledochoenteric anastomosis site</td>
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<th>Table 2. Diagnostic accuracy for PTCS-guided biopsy, tumor vessel observation and combination of PTCS-guided biopsy and tumor vessel observation.</th>
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<td><strong>Biopsy</strong></td>
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<tr>
<td>Sensitivity</td>
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<td>Specificity</td>
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<td>Positive predictive value</td>
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<td>Negative predictive value</td>
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*Sensitivity and negative predictive value by the combination of PTCS-guided biopsy and tumor vessel observation were significantly increased compared to that by PTCS-guided biopsy or tumor vessel observation alone (\( p < 0.05 \)).
were revealed on 61% (25/41) of patients with malignant strictures. No one with benign strictures demonstrated tumor vessels. Among eight patients who had a negative PTCS-guided biopsy result with a final diagnosis of malignancy, six demonstrated tumor vessels.

By tumor vessel observation combined with PTCS-guided biopsy, the accurate diagnosis of malignant biliary stricture was achieved in 96% (39/41) of patients, and the diagnostic rate was significantly increased compared to that by biopsy or tumor vessel observation alone (p<0.05). These results are summarized in Table 2.

**DISCUSSION**

By the cholangiographic findings, cholangiocarcinoma has been classified into three types: stenotic, diffuse sclerosing and polypoid type.9,10 The stenotic type is the most frequent and characteristically presents itself as focal biliary stricture, sometimes mimicking benign lesion. In Far East, benign biliary stricture is common because of the high incidence of hepatolithiasis and/or recurrent pyogenic cholangitis.11-13 Moreover, cholangiocarcinoma associated with hepatolithiasis is frequently encountered. In those cases, most of cholangiocarcinoma mainly manifested in strictures.14 Differentiation of malignant strictures from benign ones is, therefore, often perplexing.

Accurate characterization of biliary stricture is fairly essential as the choice of appropriate treatment modality depends on whether the stricture is benign or malignant. PTCS-guided biopsy has been applied for the histological diagnosis of biliary stricture. However, obtaining adequate PTCS-guided biopsy specimen is sometimes difficult in certain types of cholangiocarcinomas because of striking fibroplastic and inflammatory stromal responses around cancer.5,15,16

As an adjunct to PTCS-guided biopsy, we studied the use of tumor vessel. Tumor vessel, which was synonymous with vascular dilatation or capillary sign, was first mentioned by Yamase.6 It is defined as an abnormal tortuous and serpentine vascular structure on the bile duct mucosa and is localized on surrounding mucosa of cancer, not on mucosa of benign lesion. This may reflects that it is a neosynthesized nutritional vessel for the tumor.

According to our results, combination of tumor vessel observation and PTCS-guided biopsy significantly improved the preoperative diagnostic accuracy of biliary strictures. In addition, our result that tumor vessel was present in 6 out of 8 patients with false negative biopsy finding suggests that tumor vessel may play a role as an additional tool for the detection of bile duct cancer.

In our study, we restricted study population to the patients with biliary lesions manifesting in strictures without definitive intraluminal mass. On histology, the majority of cancer cases demonstrated infiltrative growth pattern. In this infiltrative-type cholangiocarcinoma, intramural spread beneath the bile duct epithelium and abundant fibrosis interfering with adequate biopsy lead to higher rates of false negative biopsy result than in polypoid type cholangiocarcinoma.17 Meanwhile, larger tumor burden in infiltrative-type cholangiocarcinoma may result in the evolvement of plentiful neovascularization and more frequent observation of tumor vessel. In particular, since hilar cholangiocarcinoma, so called klatskin tumor, is popular in Asia and most of hilar cholangiocarcinoma is of infiltrative type, the value of tumor vessel observation may be enhanced in our study population, and feasibility of present study may be guaranteed.17

This technique of PTCS is more commonly used in Japan, Taiwan, Korea and perhaps European countries than USA. Our results, however, may impact the
practices of endoscopist in the USA. For example, in case of primary sclerosing cholangitis more common in USA, cholangiocarcinoma arising in primary sclerosing cholangitis often manifests in stricture indistinguishable from that of primary sclerosing cholangitis itself. PTCS examination and concomitant observation of tumor vessel can also be usefully applied to discriminate between malignant and benign stricture in primary sclerosing cholangitis.

To apply this tumor vessel as a universal pathognomonic marker of biliary malignancy, reliability of tumor vessel detection should be considered. By our experiences, tumor vessel distinctively differs from normal vascular structure of biliary mucosa and its detection is reproducible without difficulty by expert cholangioscopist experts. Actually, we asked two individual endoscopists blinded to each other about the presence of tumor vessel and their opinions were identical for all the patients under study. We suggest, therefore, tumor vessel may be a reliable sign and could be used with validity as a potential clue of malignancy.

Recently, usefulness of magnetic resonance cholangiography (MRC) or intraductal ultrasonography (IDUS) on the characterization of biliary stricture has been sporadically reported. The consensus about the imaging findings of malignancy by MRC or IDUS or both, however, are not established. Up to now, observation of tumor vessel in tandem with biopsy during PTCS is suggested as a more applicable and informational tool for the differentiation of biliary stricture.

In summary, the irregularly dilated and tortuous vessel, so called tumor vessel, is one of the reliable cholangioscopic findings of biliary malignancy. Combination with PTCS-guided biopsy with tumor vessel observation may significantly improve the correct preoperative diagnosis of biliary malignancy manifesting strictures.

REFERENCES