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# Endoscopic Ultrasonography in the Evaluation of Indeterminate Biliary Strictures

Mark Topazian

Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, Rochester, MN, USA

Biliary strictures may be due to a variety of benign and malignant processes. Imaging with endoscopic ultrasonography (EUS) often suggests the diagnosis, but is usually not definitive. EUS-guided fine needle aspiration (FNA) facilitates the diagnosis of extrahepatic biliary strictures, although peritoneal metastases due to needle tract seeding may occur after EUS-FNA of cholangiocarcinoma. In addition to diagnosis of strictures, EUS may play an important role in staging of cholangiocarcinoma.

**Key Words:** Endoscopic ultrasound; Pathologic constriction; Fine-needle biopsy; Bile ducts

## INTRODUCTION

Biliary strictures may be due to a variety of benign and malignant disease processes. "Indeterminate" biliary strictures lack a definite diagnosis and are puzzles that often require multiple diagnostic modalities to solve, including cross-sectional imaging, endoscopic retrograde cholangiopancreatography (ERCP), cholangioscopy, intraductal ultrasound, endoscopic ultrasonography (EUS), and sometimes surgical resection. EUS and EUS-guided fine needle aspiration (FNA) play an important role in the evaluation of some patients with indeterminate biliary strictures.

## DIAGNOSIS OF BILIARY STRICTURES

Indeterminate biliary strictures include those without a definite diagnosis after cross-sectional imaging and ERCP with intraductal tissue sampling. The differential diagnosis of indeterminate biliary strictures includes chronic pancreatitis,

pancreatic cancer, autoimmune pancreatitis, cholangiocarcinoma, gallbladder cancer, metastatic malignancy, benign or malignant disease in porta hepatis or hilar nodes, Mirizzi's syndrome, cystic duct neuromas, sclerosing cholangitis, IgG4-related cholangiopathy, ischemic cholangiopathy, radiation stricture, and inflammatory strictures due to stones, trauma, infection, or surgery. The differential diagnosis can often be narrowed based on the patient's history and the location, radiologic appearance, and number of strictures, but for "indeterminate" strictures the presence or absence of malignancy has not been conclusively determined.

EUS typically images extrahepatic bile duct strictures well, although some common hepatic duct and hilar strictures cannot be visualized.<sup>1</sup> EUS imaging may be diagnostic (as in bile duct varices) or suggestive of a diagnosis (such as chronic pancreatitis or Mirizzi's syndrome). The presence of a pancreatic head mass, an irregular outer edge of the bile duct wall, or a bile duct wall thickness of >3 mm on EUS have all been associated with malignancy in indeterminate biliary strictures,<sup>2</sup> but these findings do not firmly establish the presence or absence of cancer. Diffuse thickening of the bile duct wall over a long segment is suggestive of a benign process, but may be seen in primary sclerosing cholangitis, IgG4-related cholangiopathy, or cholangiocarcinoma.

EUS-FNA may establish the diagnosis of indeterminate biliary strictures (Fig. 1). In a recent review of six published series,<sup>3</sup> sensitivity for diagnosis of malignancy ranged from 27% to 83%, with a mean of 59%. In the two series that reported

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Correspondence: Mark Topazian

Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, 200 1st Street Southwest, Rochester, MN 55905, USA

Tel: +1-507-266-6931, Fax: +1-507-266-3939

E-mail: [topazian.mark@mayo.edu](mailto:topazian.mark@mayo.edu)

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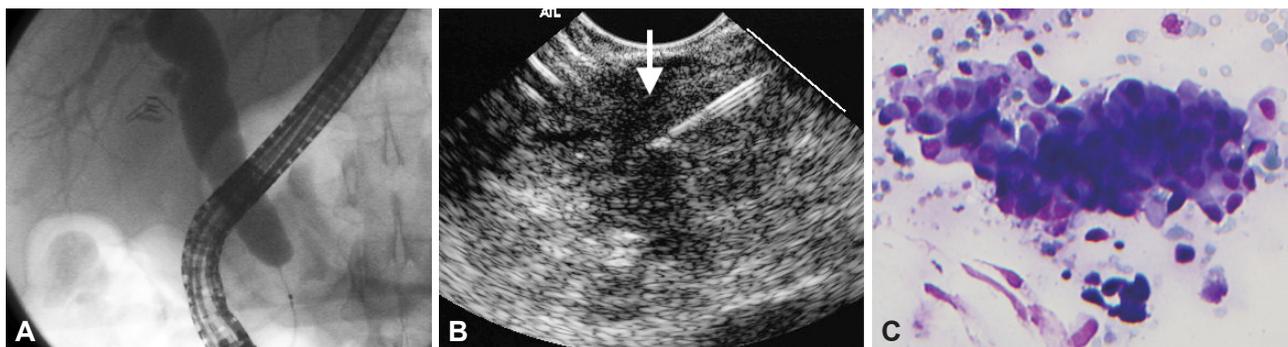
patients with prior negative ERCP-guided intraductal tissue sampling, sensitivity of EUS was 77% and 89%, highlighting the ability of EUS-FNA to diagnose malignancy when ERCP-guided tissue sampling is negative. A major concern with EUS-FNA of bile duct strictures is the potential for needle track tumor seeding, or the implantation of cancer cells along the pathway of a biopsy needle. This is less important for pancreatic head lesions, since the needle track of trans-duodenal EUS-FNA will be fully resected during pancreaticoduodenectomy, but is a concern following EUS-FNA of bile duct lesions in the porta hepatis, since the EUS needle traverses peritoneum and omental fat that will not be resected. In most clinical settings the true incidence and significance of needle track seeding following EUS-FNA is difficult to determine, but relevant data are available for cholangiocarcinoma. A large group of cholangiocarcinoma patients enrolled in the Mayo Clinic liver transplantation protocol has undergone a staging laparotomy prior to transplantation. During staging laparotomy, peritoneal tumor implants were found in 83% (5/6) of those who had undergone a previous diagnostic trans-peritoneal bile duct FNA or biopsy, vs. 8% (14/175) of those who did not undergo trans-peritoneal biopsy ( $p < 0.01$ ).<sup>4</sup> Although this is retrospective data, it suggests that needle track tumor seeding is a common occurrence after trans-peritoneal FNA of bile

duct malignancies. Liver transplantation is among the most successful therapies for patients with unresectable cholangiocarcinoma confined to the liver and bile ducts with a 5-year survival of approximately 75%.<sup>5</sup> Post-transplantation immunosuppression may enhance the possibility of tumor recurrence in patients with peritoneal tumor seeding. For this reason, performance of EUS-FNA of a primary bile duct tumor is usually considered a contraindication to subsequent liver transplantation. Instead of FNA, intraductal tissue sampling should be used to diagnose cholangiocarcinoma in liver transplant candidates. Both cholangioscopy-directed intraductal biopsies and fluorescent *in situ* hybridization of biliary brush cytology samples may increase the diagnostic yield.<sup>6</sup>

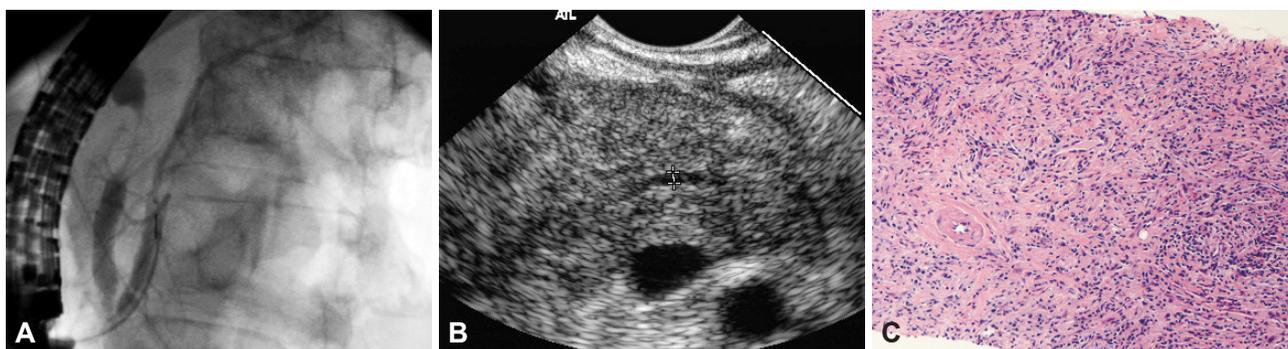
EUS-guided core biopsy may also be useful in some patients with indeterminate biliary strictures, particularly if there is associated nodal or pancreatic disease that has not been adequately diagnosed with FNA (Fig. 2).

## CHOLANGIOCARCINOMA STAGING

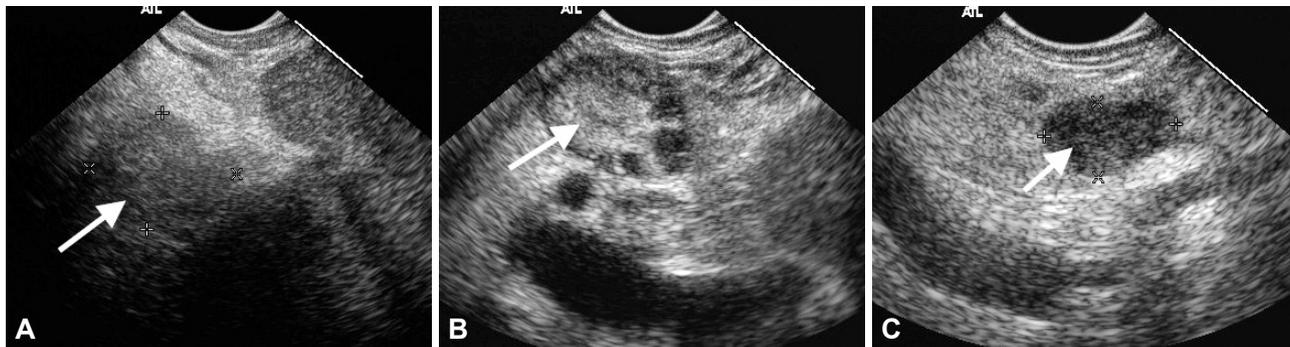
EUS may play an important role in staging of cholangiocarcinoma, depending on the management strategy of the treating institution. Intraductal ultrasound may be the most accurate overall test for determining the T stage and longitu-



**Fig. 1.** Distal bile duct stricture caused by pancreatic head adenocarcinoma. (A) Endoscopic retrograde cholangiopancreatography shows a bile duct stricture. (B) Endoscopic ultrasonography-guided fine needle aspiration (EUS-FNA) of the pancreatic head mass (arrow indicates FNA needle). (C) Cytology of the EUS-FNA specimen (papanicolaou stain,  $\times 400$ ). Part C courtesy of Dr. Michael Henry, M.D.



**Fig. 2.** Autoimmune pancreatitis type 1. (A) Endoscopic retrograde cholangiopancreatography shows a bile duct stricture and a long pancreatic duct stricture. (B) Endoscopic ultrasonography (EUS) of the pancreas body. (C) Histology of EUS-guided Trucut biopsy of the pancreas (H&E stain,  $\times 200$ ). Part C courtesy of Dr. Thomas Smyrk, M.D.



**Fig. 3.** Hilar cholangiocarcinoma. (A) Endoscopic ultrasonography (EUS) of hilar bile duct mass (arrow). (B) EUS of malignant peri-duodenal node (arrow). (C) EUS of malignant peri-gastric node (arrow).

dinal extent of cholangiocarcinoma. EUS-FNA plays a central role in determining nodal staging of cholangiocarcinoma. The presence of regional or distant lymph node metastases may up-stage the malignancy<sup>7</sup> and affect choice of treatment. In this regard regional nodal disease is often considered a contraindication to subsequent liver transplantation for cholangiocarcinoma. Nodal malignancy cannot be determined by lymph node appearance in patients with cholangiocarcinoma (Fig. 3). Unlike esophageal cancer, nodal malignancy in cholangiocarcinoma is not associated with a specific morphologic appearance or set of echo features. Most malignant nodes in cholangiocarcinoma are oval or geographic in appearance, with a hypoechoic rim-features often associated with benign porta hepatis nodes.<sup>8</sup> FNA thus plays an important role in nodal staging, especially if liver transplantation is being considered.

## INDETERMINATE PANCREATIC DUCT STRICTURES

Few published data are available regarding EUS diagnosis of indeterminate pancreatic duct strictures, with or without FNA, in the absence of a mass. The presence of a pancreatic duct stricture with associated duct wall thickening or mass is concerning for malignancy, but can also be due to non-malignant diseases. Thickening of long segments of the pancreatic duct wall, or the presence of a hypoechoic halo around the duct, may be suggestive of autoimmune pancreatitis.

The overall utility of EUS-FNA for diagnosis of pancreatic masses is high, with a pooled sensitivity of 85% and specificity of 98% in a recent meta-analysis.<sup>9</sup> The performance characteristics of EUS-FNA for evaluation of pancreatic duct strictures

without a mass have not been determined.

## CONCLUSIONS

Indeterminate biliary strictures may pose a diagnostic challenge. EUS and EUS-FNA facilitate diagnosis in some patients, and play an important role in cholangiocarcinoma staging.

## Conflicts of Interest

The author has no financial conflicts of interest.

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