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Taking the *Indeterminant* Out of Biliary Strictures

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Background

- Safe, accurate, and expedient diagnosis should be prioritized
- Definitive diagnosis of cancer will have important implications
  - Surgical and oncological decision making
  - Endoscopic biliary stent selection
- Malignancy typically cannot be confirmed/excluded w/ noninvasive testing
  - CT, MRI, and EUS (without FNA) diagnostic accuracies ~ 60%–80%
  - Biomarkers, such as CA 19-9 and CEA proven even less accurate
  - ERCP has been the mainstay of tissue acquisition

Not all strictures are created the same!

- Estimated $16.9 billion annually in the United States
- 60% of panc CA w/ obstructive jaundice → 34,000 cases/yr
- ~8,000 cases of cholangiocarcinoma (3,000 cases of malignant hilar)
- 55-80% of biliary strictures are malignant

Fibroinflammatory • Chronic pancreatitis • Primary sclerosing cholangitis • Autoimmune (immunoglobulin G [IgG] 4–mediated) pancreatitis • IgG4-mediated cholangitis • Sarcoidosis • Recurrent pyogenic cholangitis • Extrinsic compression by a pancreatic fluid collection
Iatrogenic • Cholecystectomy • Liver transplantation • Local cancer treatment (chemoembolization, radiation therapy, microwave ablation, and radiofrequency ablation)
Vascular • Portal hypertensive biliopathy • Ischemic biliary injury
AIDS cholangiopathy
Mirizzi syndrome

Malignant, primary • Pancreatic cancer • Cholangiocarcinoma • Gallbladder cancer • Hepatocellular carcinoma • Ampullary cancer • Lymphoma • Rare: cystadenocarcinomas, mixed hepatocellular-cholangiocellular cancer
Malignant, metastatic • Colon cancer • Breast cancer • Renal cell cancer • Rare: squamous cell carcinoma

Key concept

1. Biliary strictures in adults are more likely to be malignant than benign except in certain well-defined scenarios.

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Elmunzer, B. Joseph MD, MSc,et al. ACG Clinical Guideline: Diagnosis and Management of Biliary Strictures. The American Journal of Gastroenterology 118(3):p 405-426, March 2023.

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What is an indeterminate stricture?

- Biliary strictures of *persistent unknown etiology*
  - cross-sectional imaging **AND** evaluation by ERCP w/ brush or biopsy
- Approx 20% of all biliary strictures are indeterminate
  - 20% of pts w/ suspected cholangiocarcinoma have benign disease

- Correctly define the problem!
  - Jaundice merits evaluation
  - CA 19-9 and CEA concerning but less accurate

- Definitive tissue diagnosis needed to guide care!
- Endoscopic therapy > percutaneous therapy
- EUS-guided sampling
  - significantly improved our diagnostic capabilities with less risk

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Fujii-Lau, Larissa L. et al., American Society for Gastrointestinal Endoscopy guideline on the role of endoscopy in the diagnosis of malignancy in biliary strictures of undetermined etiology: summary and recommendations. Gastrointestinal Endoscopy, Volume 98, Issue 5, 685 – 693
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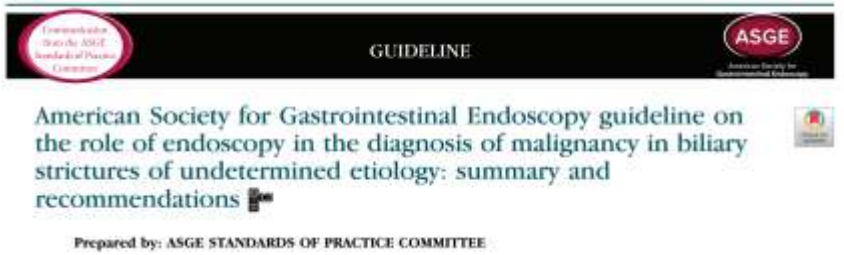
Indeterminate vs Undetermined


GUIDELINE

American Society for Gastrointestinal Endoscopy guideline on the role of endoscopy in the diagnosis of malignancy in biliary strictures of undetermined etiology: summary and recommendations

Prepared by: ASGE STANDARDS OF PRACTICE COMMITTEE

- Biliary strictures of *undetermined* etiology:
  - Potential use of multiple forms of tissue acquisition during the initial endoscopic evaluation to enhance the diagnostic approach to these strictures

    - Brush cytology: 35-52%
    - Forceps biopsy: 45-65%
    - Stent cytology: 7-35%
    - EUS: 25-45%, w/ FNB 80%

All are highly specific!

Question	Recommendation	Quality of evidence	General concepts
1	In patients with biliary strictures of undetermined etiology undergoing ERCP, the ASGE suggests the addition of fluoroscopic-guided biopsy sampling with brush cytology versus brush cytology alone to diagnose malignancy.	Conditional recommendation, very low quality of evidence	• Review all cross-sectional imaging. • Discuss patient in a multidisciplinary board or committee.

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Navaneethan, U. et al., Comparative effectiveness of biliary brush cytology and intraductal biopsy for detection of malignant biliary strictures: a systematic review and meta-analysis
Gastrointest Endosc. 2015; 81:168-176

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Extrahepatic stricture w/ apparent mass

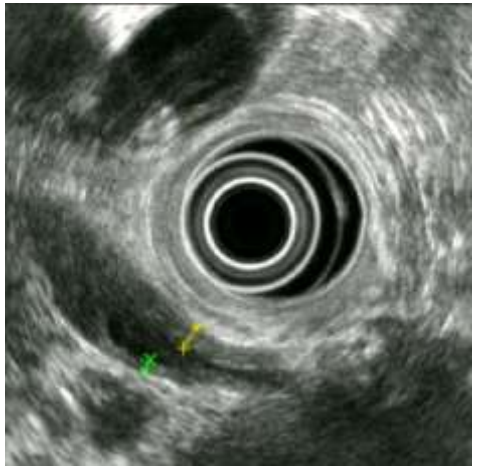
ACG Clinical Guideline: Diagnosis and Management of Biliary Strictures

1. In patients with an extrahepatic biliary stricture due to an apparent or suspected pancreatic mass, we recommend EUS with fine-needle sampling (aspiration or biopsy; FNA/B) over ERCP as the preferred method of evaluating for malignancy (strong recommendation, moderate-quality evidence).

2. In asymptomatic or minimally symptomatic patients with an extrahepatic biliary stricture due to an apparent or suspected pancreatic mass, we suggest single-session EUS and ERCP over ERCP alone for concurrent diagnosis and drainage.

Elmunzer, B. Joseph MD, MSc,et al. ACG Clinical Guideline: Diagnosis and Management of Biliary Strictures. The American Journal of Gastroenterology 118(3):p 405-426, March 2023.

EUS w/ FNB is powerful BUT…



- deMoura, et al Endosc Ultrasound 2018;7(1):10–9
  - Systematic review and meta-analysis of eight studies
    - 300 patients with suspected malignant biliary stricture
    - EUS-FNA had a pooled sensitivity of 75% compared to 49% for ERCP-based sampling
- de Moura DTH, et al. Clin Endosc 2020;53(4):417–28.
  - Meta-analysis of six studies
    - 500 patients who underwent same-session EUS-FNA and ERCP
    - confirmed that EUS-FNA had a higher sensitivity (75%) compared to ERCP (47%)

Diagnosis: perihilar stricture

In patients with biliary strictures of undetermined etiology undergoing ERCP, the ASGE suggests EUS in addition to ERCP for the diagnosis of malignancy in the presence of A, Prior ERCP with nondiagnostic ERCP results, B, Distal biliary stricture, or C, Presence of lymphadenopathy or metastatic disease on cross-sectional imaging,	Conditional recommendation, very low quality of evidence	• Upfront EUS should be considered in centers with the ability to do EUS and ERCP in the same session. • If EUS is performed in the setting of hilar strictures, it is important for the endoscopist to avoid biopsy sampling of the biliary mass itself.

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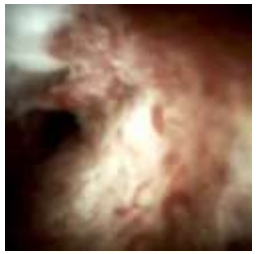
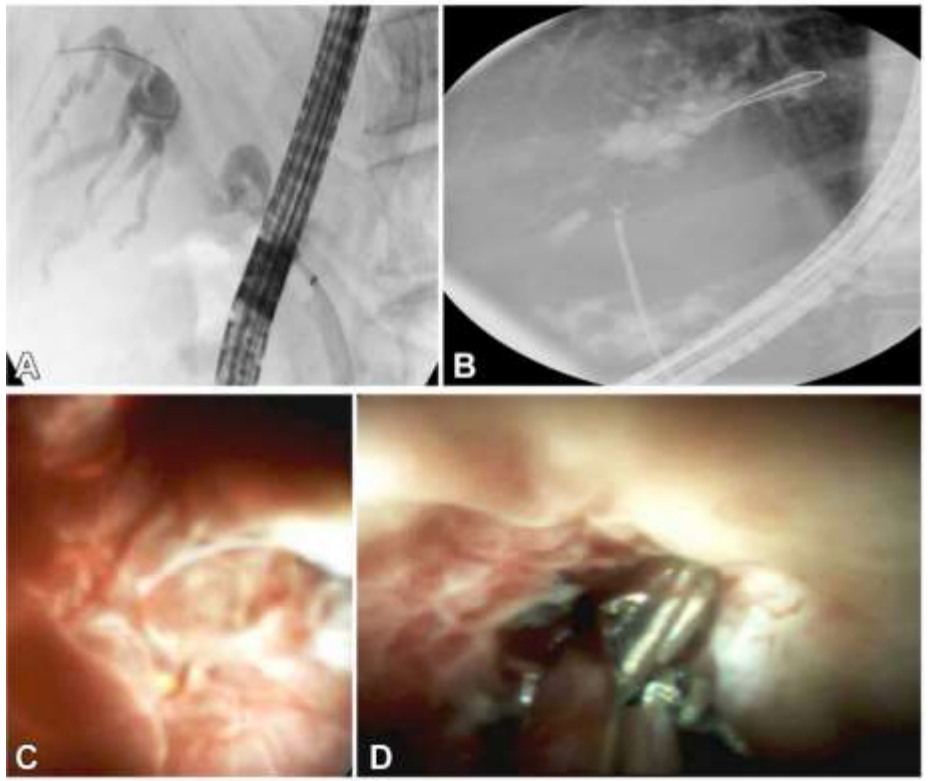
Incremental yield with multimodal sampling for perihilar strictures

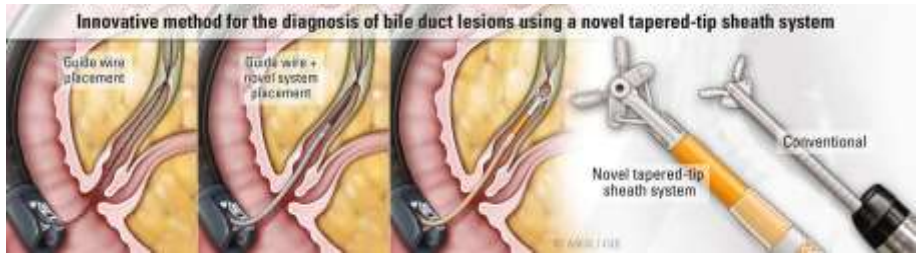
- Several techniques and devices to increase yield
- ERCP w/ biopsy, brushing and cholangioscopy

> 3. In patients with suspected malignant perihilar stricture, we recommend multimodality sampling over brush cytology alone at the time of the index ERCP (strong recommendation, low-quality evidence).

- Cholangioscopy
  - Direct visualization: 64-95% sensitivity
  - Directed biopsy: 60-75% sensitivity







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Buxbaum, James, Gastrointestinal Endoscopy, Volume 100, Issue 2, 296 - 299

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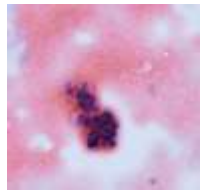
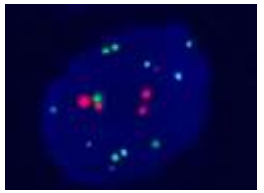
Other options to increase yield in ERCP





- Fluorescence In Situ Hybridization (FISH)
  - Increase sensitivity from 20.1% with cytology alone to 42.9%
  - Abnormal FISH 77x more likely to have carcinoma
  - Favorable performance characteristics of FISH in PSC
  - Some surgeons may use FISH to aid in decision for surgery
    - highly uncommon for oncologists to offer chemotherapy on abnormal FISH alone

- Molecular mutation profiling
  - KRAS, GNAS and tumor suppressor gene mutations
  - Molecular panels and profiling can help increase yield

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Pu, X., Zheng, H., Yang, X. et al. An assessment of chromosomal alterations detected by fluorescence in situ hybridisation in pancreatobiliary tract malignancy. BMC Gastroenterol 20, 367 (2020).
Barr Fritcher EG, Kipp BR, Halling KC, et al. A multivariable model using advanced cytologic methods for the evaluation of indeterminate pancreatobiliary strictures. Gastroenterology 2009;136(7):2180–6
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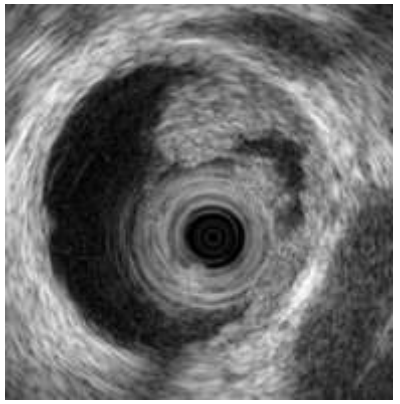
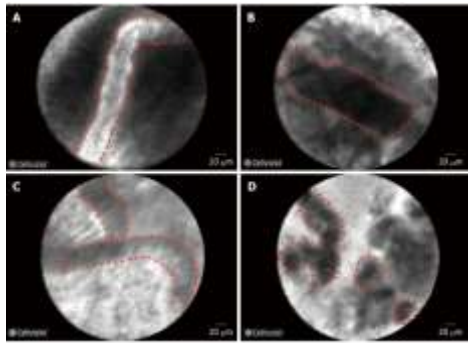
ERCP+



- Intraductal U/S
  - High frequency (12–30 MHz) US probe
  - Heinzow, Hauke S., et al. : WJG 20.30 (2014)
    - ERCP/intraductal ultrasound (IDUS) (91%) superior to EUS (74%) and CT (73%) in providing an accurate diagnosis of bile duct strictures of uncertain etiology
    - unable to provide a tissue diagnosis or assess lymphadenopathy



- Probe-based confocal laser endomicroscopy (pCLE)
  - Real-time optical biopsy of the target tissue
  - Distinguish inflammatory from malignant strictures
  - Slivka, Jamidar, et al. Gastrointest Endosc 2015;81(2):282–90
    - prospective multicenter study
      - combination of cholangiographic impression, pCLE interpretation, and histopathology
    - sensitivity and accuracy in the range of 90%

- Do not meet the threshold necessary to drive oncological decision making
  - currently remains as adjunct diagnostic modality at select referral centers

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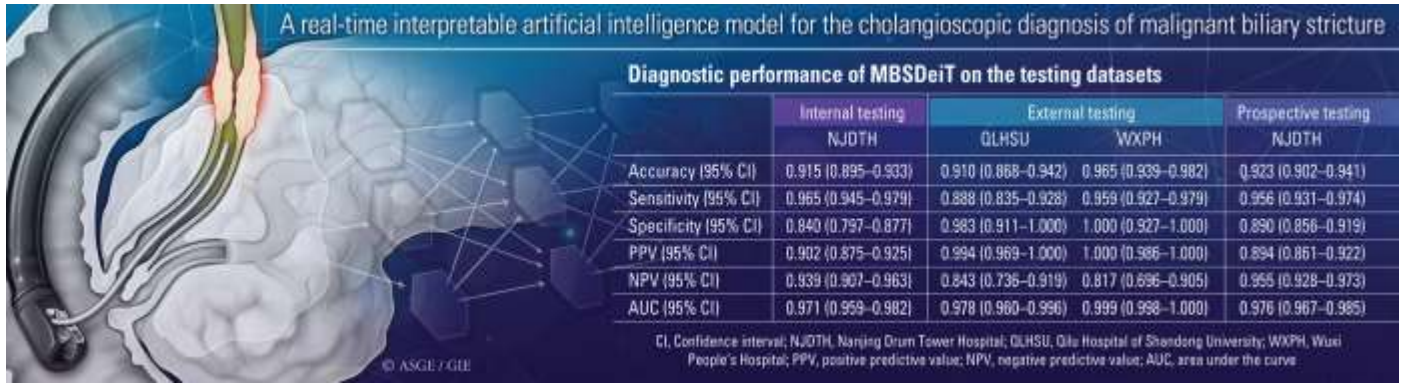
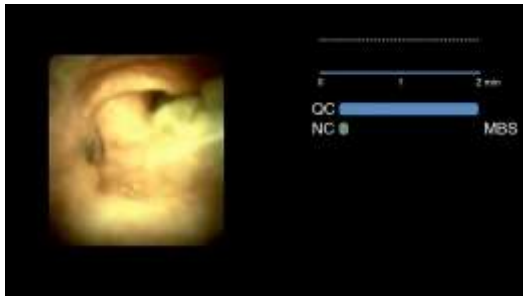
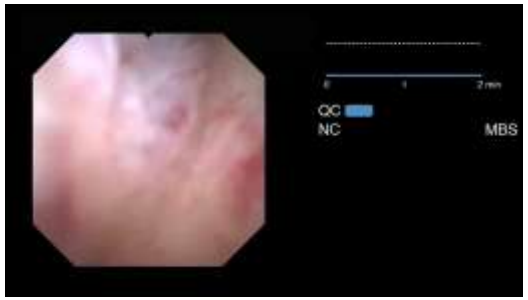
AI advancing biliary strictures to a new horizon?

- MBSDeiT model promising results in improving diagnostic accuracy under digital single-operator cholangioscopy
  - 2 models to identify qualified images
    - predict malignant biliary strictures in real time
  - significantly outperforming expert endoscopists







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Zhang X, Tang D, Zhou JD, et al. A real-time interpretable artificial intelligence model for the cholangioscopic diagnosis of malignant biliary stricture (with videos). *Gastrointest Endosc*. 2023;98(2):199-210.e10.

Next steps to achieving a better diagnosis!

- Evaluate developments to improve tissue sampling, visualization
  - cholangioscopy/ultrasound/confocal laser microscopy
- Understand the role of adjunctive pathologic analyses
  - next-generation sequencing, flow cytometry, fluorescence in situ hybridization analysis, and digital image analysis
- Focus on PSC
  - FISH analysis probably plays a higher role
- Utility of AI–guided visual interpretation and sampling during cholangioscopy and AI-guided visualization in EUS

Don’t bet against cancer!

- The majority of biliary strictures are malignant
- If asymptomatic and resectable extrahepatic mass →EUS FNA/B
  - Perioperative biliary drainage is not always necessary
- Accomplish as much as possible in one setting (when appropriate):
  - EUS/FNA
  - ERCP
  - Multimodal sampling to increase yield
    - Consider newer brushes/steerable forceps, etc..
    - FISH, molecular analysis and profiling
    - Cholangioscopy (understand visual patterns of malignancy)
- Malignancy dx **must** be obtained before deploying an uSEMS
- Think outside the box if truly indeterminate
  - IgG4, etc
  - Do not delay interval ERCP
- Surgery remains an option if remains indeterminate
  - Do not delay as an early lesion may become unresectable

Thank you!

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