EUS-FNA is superior to ERCP-based tissue sampling in suspected malignant biliary obstruction: results of a prospective, single-blind, comparative study 📹 CME

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Background: Both EUS and ERCP sampling techniques may provide tissue diagnoses in suspected malignant biliary obstruction. However, there are scant data comparing these 2 methods.

Objective: To compare EUS-guided FNA (EUS-FNA) and ERCP tissue sampling for the diagnosis of malignant biliary obstruction.

Design: Prospective, comparative, single-blind study.

Setting: Tertiary center.

Patients: Fifty-one patients undergoing same-session EUS and ERCP for the evaluation of malignant biliary obstruction over a 1-year period.

Interventions: EUS-FNA and ERCP tissue sampling with biliary brush cytology and intraductal forceps biopsies.

Main Outcome Measurements: Diagnostic sensitivity and accuracy of each sampling method compared with final diagnoses.

Results: EUS-FNA was more sensitive and accurate than ERCP tissue sampling ($P < .0001$) in 51 patients with pancreatic cancers (n = 34), bile duct cancers (n = 14), and benign biliary strictures (n = 3). The overall sensitivity and accuracy were 94% and 94% for EUS-FNA, and 50% and 53% for ERCP sampling, respectively. EUS-FNA was superior to ERCP tissue sampling for pancreatic masses (sensitivity, 100% vs 38%; $P < .0001$) and seemed comparable for biliary masses (79% sensitivity for both) and indeterminate strictures (sensitivity, 80% vs 67%).

Limitations: Single-center study.

Conclusion: EUS-FNA is superior to ERCP tissue sampling in evaluating suspected malignant biliary obstruction, particularly for pancreatic masses. EUS-FNA appears similar to ERCP sampling for biliary tumors and indeterminate strictures. Given the superior performance characteristics of EUS-FNA and the higher incidence of pancreatic cancer compared with cholangiocarcinoma, EUS-FNA should be performed before ERCP in all patients with suspected malignant biliary obstruction. (Clinical trial registration number: NCT01356030.) (Gastrointest Endosc 2014;80:97-104.)

Abbreviation: EUS-FNA, EUS-guided FNA.

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Establishing a tissue diagnosis of malignancy before surgical or oncologic therapy is an important step in evaluating patients with suspected malignant biliary obstruction. The 2 most commonly used methods for tissue sampling are ERCP-based techniques and EUS-guided FNA (EUS-FNA). ERCP-based methods, most commonly performed using cytology brushes and/or intraductal forceps, predate the availability of EUS. In numerous studies, the diagnostic yield of ERCP-based tissue sampling has ranged from 35% to 70%, with higher yields usually found when both brushing and biopsies were performed.[1-6]

EUS-FNA, although a relatively newer modality compared with ERCP-based tissue sampling, now has a well-established sensitivity, ranging from 85% to 93% in recent studies.[7-11] This high yield is even achievable in the absence of an identifiable mass on previous imaging[12] and in the setting of suspected cholangiocarcinoma (sensitivity, 73%-89%).[19-22] EUS-FNA is also preferred over percutaneous tissue biopsy because of a better yield and lower risk of tumor seeding.[13,14]

Despite the widespread pervasiveness of ERCP and increasing availability of EUS at many centers, there are scant data that directly compare the 2 modalities in terms of tissue sampling. The aim of this study was to directly compare the diagnostic yield of same-session EUS-FNA and ERCP-based tissue sampling in a prospective series of consecutive patients with suspected malignant biliary obstruction.

METHODS

At our center, same-session EUS and ERCP are routinely offered for all patients with suspected pancreaticobiliary pathology. All patients with suspected malignant biliary obstruction based on clinical presentation of painless jaundice with elevated levels on liver tests in a cholestatic pattern and evidence of biliary obstruction, stricture, or pancreatic/biliary mass on preprocedure imaging (contrast CT or magnetic resonance imaging) were invited to participate in the study. Patients with pancreaticobiliary disease without clinical concern for underlying malignancy (eg, postoperative biliary stricture, chronic pancreatitis without suspected neoplasm) were not recruited to participate.

Participants underwent EUS first using a curvilinear echoendoscope (GF-UC140 or GF-UCT140; Olympus America, Center Valley, Pa). Any pancreatic masses, focal bile duct masses, or strictures (Fig. 1), lymph nodes, and/or liver lesions were targeted for EUS-FNA with a 22- or 25-gauge needle (Echotip; Cook Medical, Bloomington, Ind). Lesions that would confer a higher stage were targeted before the primary mass. All FNA procedures were performed with the presence of on-site, cytopathologic assessment. The specimen was expressed onto 1 to 2 slides for rapid evaluation by air-dried and/or alcohol-fixed review. Air-dried smears were prepared with Diff-Quik stain (Siemens, Newark, Del); alcohol-fixed smears were

> ### Take-home Message
> - EUS-guided FNA is superior to ERCP tissue sampling in evaluating suspected malignant biliary obstruction, particularly for pancreatic masses, but also appears to be comparable for biliary masses/strictures.
> - Single-session EUS-FNA and ERCP may maximize diagnostic and therapeutic benefits.

prepared with toluidine blue followed by Papanicolaou staining. Additional material was placed in a 30-mL 10% formalin container for subsequent cell-block analysis. Additional FNA passes were made based on the cytopathologist's assessment of specimen adequacy. EUS-FNA confirmation of metastasis to regional lymph nodes or the liver was considered acceptable for the primary tumor diagnosis without necessary FNA targeting of the primary tumor site.

ERCP was then performed, if clinically indicated, by a second endoscopist blinded to EUS and FNA results. Patients who provided study consent but did not require an ERCP were not enrolled in the study. During ERCP, initial cannulation and cholangiography was performed to determine the level of the bile duct obstruction. ERCP-based tissue sampling was then performed by using the following 2 devices in sequential order (Fig. 2): a conventional, over-the-guidewire cytology brush (Fusion Cytology Brush; Cook Medical) and intrabiliary forceps (FB-40Q-1; Olympus America or Radial Jaw 4 Pediatric Forceps; Boston Scientific, Natick, Mass). Strictures were not dilated before tissue sampling. Cytology brushings were obtained using 10 to-and-fro brushing strokes across the biliary stricture. The brush was then smeared on 2 glass slides that were air-dried and placed in a 95% ethyl alcohol fixative container. The tip of the brush was cut and submitted in a 10% formalin container for analysis. The intraductal biliary forceps were then introduced to the level of the stricture under fluoroscopy; 2 to 3 intraductal biopsy specimens were obtained. These were placed in a separate 10% formalin container and submitted for histopathologic analysis.

All EUS and ERCP procedures were performed at a single session under monitored anesthesia sedation. Two separate endoscopists of 3 experienced interventionalists (J.S., Y.B., K.B.; each performing >500 EUS and >400 ERCP procedures annually) performed the EUS and ERCP procedures.

Pathologists evaluating EUS-FNA and ERCP samples were not blinded to the clinical findings or the results of the alternative sampling technique. Tissue samples obtained at EUS-FNA and ERCP were routinely classified into 1 of the following categories: (1) malignant; (2) atypical, suspect malignant; (3) atypical, favor reactive/benign; (4) benign; and (5) nondiagnostic, insufficient material. Any sample labeled by the pathologist as "malignant" or
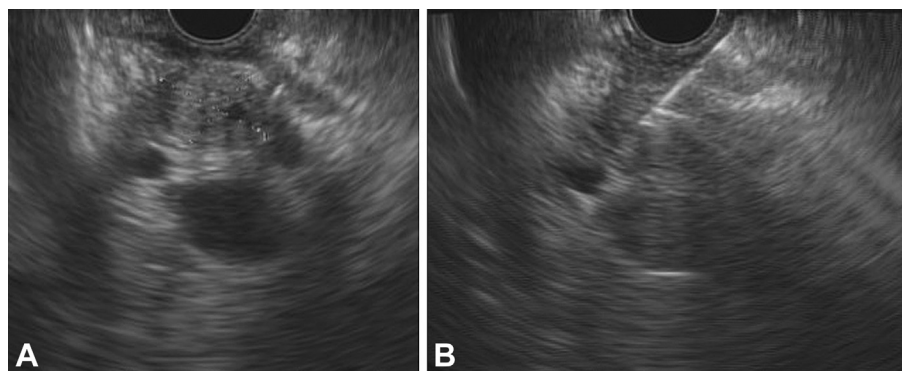
Figure 1. A, EUS reveals a focal area of bile duct wall thickening representing a biliary stricture/mass at the hilum. **B,** FNA of this area was performed.
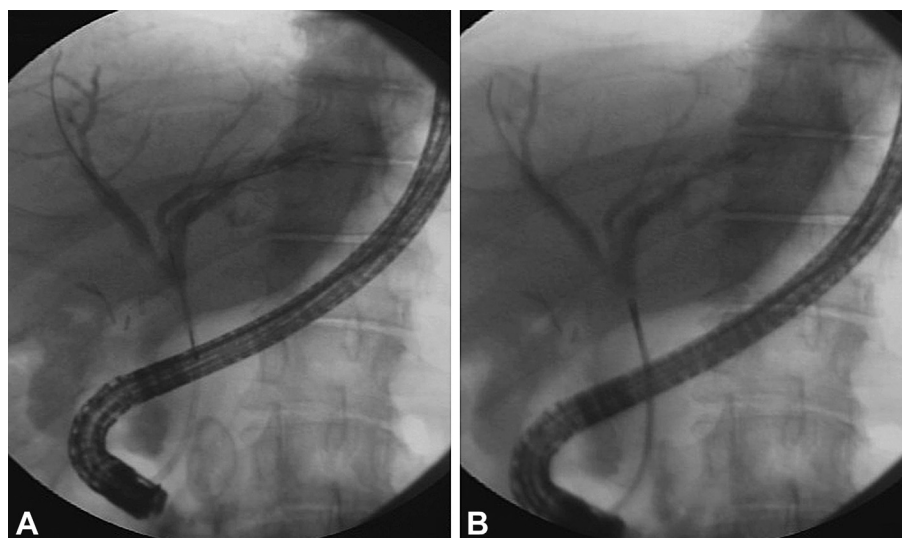

Figure 2. Fluoroscopic images from same patient as in Figure 1 show brushings (**A**) and intraductal biopsy specimens (**B**) obtained from the bile duct stricture during ERCP.

"suspicious for malignancy" was considered malignant. All "atypical" findings for either sampling method were re-evaluated by a second board-certified cytopathologist to confirm cytologic classification. Any technical failure in obtaining a tissue sample by EUS-FNA or ERCP was considered "nondiagnostic" by intention-to-treat analysis. The final diagnosis for each study patient was based on the following in decreasing priority: (1) surgical findings/pathology, (2) EUS or ERCP sampling with definite evidence for malignancy, and (3) long-term clinical follow-up (>6 months).

The Institutional Review Board at California Pacific Medical Center approved this study. All patients provided both informed consent for the procedures as well as study consent.

Statistical analysis

The primary outcome analyzed was the overall sensitivity and accuracy of EUS-FNA and ERCP tissue sampling to establish a diagnosis in patients with suspected malignant biliary obstruction. Secondary outcomes included comparative analyses of EUS-FNA and ERCP-based tissue sampling for subsets of patients with pancreatic masses, bile duct masses/strictures, and indeterminate strictures (defined as obstructive jaundice without visible mass on preprocedure CT or MRI). The Fisher exact test was used to check for statistically significant differences between EUS-FNA and ERCP sampling. Based on an anticipated yield of 90% for EUS-FNA and 65% for ERCP-based tissue sampling, we calculated that 51 patients would be needed to detect significant differences ($P < .05$) with 80% power.

RESULTS

Between May 2011 and June 2012, a total of 77 patients with clinical suspicion for malignant biliary obstruction

provided informed consent to participate in this prospective study. After the initial EUS, 26 patients patients were excluded from the study for the following reasons: (1) EUS-FNA provided on-site diagnosis of a resectable neoplasm, patient referred for expedited surgery without ERCP drainage (n = 14); (2) biliary stricture not present on ERCP (stones or other cause of biliary obstruction or jaundice) (n = 8); (3) EUS-FNA provided on-site diagnosis in patient with a patent biliary stent (n = 1); or (4) ERCP not performed after EUS revealed no evidence of biliary obstruction (suspected hepatic etiology) (n = 3).

Patient characteristics, clinical indications for EUS and ERCP, and final diagnoses in the remaining 51 patients who underwent attempts at both tissue-sampling procedures per study protocol are listed in Table 1. Nine patients had undergone ERCP (1 failed) before referral to our center with the following ERCP sampling results: benign (n = 5), and nondiagnostic (n = 3). No patients underwent previous EUS. The results of EUS-FNA and ERCP sampling from our center are listed in Table 2. EUS-FNA was technically successful in all patients and was performed without stent removal in all patients with indwelling plastic biliary stents (n = 8). ERCP-based sampling failed in 7 (14%) because of outlet obstruction and duodenal deformity. All of these patients had pancreatic cancer as final diagnoses and underwent subsequent successful EUS-guided biliary drainage (n = 5) or surgical bypass (n = 2). They were considered to have "nondiagnostic" ERCP tissue sampling by intention-to-treat analysis.

Final diagnoses were based on surgery (n = 13), findings of definite malignancy on EUS-FNA and/or ERCP sampling at the index procedure (n = 36) or a second EUS-FNA (n = 1), and long-term follow-up (n = 1). The 1 patient with a final diagnosis based on clinical follow-up alone was deemed to have cholangiocarcinoma based on evidence of tumor progression on interval imaging and death within 6 months of presentation.

Performance characteristics of EUS-FNA and ERCP-based tissue sampling are summarized in Tables 3 and 4. The sensitivity and accuracy of EUS-FNA were superior to ERCP-based tissue sampling for all study patients as a group and particularly for patients with pancreatic masses ($P < .0001$). There were no differences in the sensitivity and accuracy of EUS-FNA and ERCP-based sampling for patients with biliary masses/strictures or for those with indeterminate strictures (defined as jaundice and evidence of biliary obstruction without visible mass on preprocedure imaging). Final diagnoses among the patients with indeterminate biliary strictures included pancreatic cancer (n = 3), cholangiocarcinoma (n = 11), and gallbladder carcinoma (n = 1). Among this subset, small pancreatic neoplasms in 2 patients were found on EUS-FNA but missed on ERCP sampling and cholangiocarcinomas in 3 patients were missed on both EUS-FNA and ERCP tissue sampling.

TABLE 1. Demographic and clinical characteristics and final diagnoses of study patients	
51 patients with suspected malignant biliary obstruction	
Age, y, mean (range)	67 (42-88)
Male sex, no. (%)	29 (57)
Previous negative or nondiagnostic tissue sampling, no. (%)	
With EUS-FNA	0
With ERCP brushings	8 (16)
Clinical indication(s) for EUS, no. (%)	
Cholestatic liver tests and painless jaundice	51 (100)
Abnormal CT or MRI with pancreatic mass	32 (63)
Abnormal CT or MRI with bile duct mass	4 (8)
Abnormal CT or MRI with indeterminate stricture*	15 (29)
Technical success for EUS-FNA	51 (100)
Clinical indication(s) for ERCP, no. (%)	
Biliary stent placement	38 (75)
Tissue sampling after inconclusive on-site EUS-FNA results	13 (25)
Technical success for ERCP sampling	44 (86)
Procedure time for EUS and ERCP, min (range)	70 (40-126)
Final diagnoses	
Malignant (n = 48)	
Pancreatic cancer	34
Cholangiocarcinoma	13
Gallbladder carcinoma	1
Benign (n = 3)	
Autoimmune pancreatitis	1
Chronic pancreatitis	1
Autoimmune cholangiopathy	1

EUS-FNA, EUS-guided FNA; *MRI*, magnetic resonance imaging.
*Indeterminate stricture defined as jaundice and evidence of biliary obstruction without visible mass on preprocedure contrast CT or MRI.

Of the 15 patients with biliary strictures seen on EUS, 7 were proximal (located at or above the hilum) and 8 were distal (located below the hilum). Final diagnoses were malignant in all but 1 of the distal biliary strictures. EUS-FNA correctly identified malignancy in 71% of distal

TABLE 2. Results of EUS-FNA and ERCP-based tissue sampling in 51 patients with malignant (n = 48) and benign (n = 3) disease

	EUS-FNA, no. (%)	ERCP sampling, no. (%)
Malignant*	41 (80)	15 (29)
Atypical, suspect malignant	4 (8)	9 (18)
Atypical, favor benign	3 (6)	8 (16)
Benign	3 (6)	12 (23)
Nondiagnostic, insufficient	0 (0)	7 (14)

EUS-FNA, EUS-guided FNA.
*EUS-FNA provided a significantly higher proportion of definite malignant samples compared with ERCP-based methods (P < .0001).

TABLE 3. Overall performance characteristics of EUS-FNA and ERCP-based tissue sampling in 51 patients with final diagnoses of malignant (n = 48) and benign (n = 3) disease

	EUS-FNA, %	ERCP brush and biopsy, %	P value
Sensitivity	94	50	<.0001
Specificity	100	100	NS
Positive predictive value	100	100	NS
Negative predictive value	50	11	<.0001
Accuracy	94	53	<.0001

EUS-FNA, EUS-guided FNA; NS, not significant.

cholangiocarcinomas and in 86% of proximal cholangiocarcinomas, although 2 were from FNA of nonprimary sites (lymph node, liver lesion). No patients experienced adverse events related to EUS-FNA of bile duct strictures. All patients with a diagnosis of cholangiocarcinoma on ERCP sampling also had positive tissue diagnoses based on EUS-FNA, and there was no added diagnostic benefit from performing 1 procedure in addition to the other.

DISCUSSION

We directly compared EUS-FNA with ERCP-based tissue sampling in a large series of unselected patients with sus-

pected malignant biliary obstruction. Surprisingly, there is a paucity of studies that compare these sampling techniques. Oppong et al[15] performed a retrospective analysis of EUS-FNA compared with ERCP brushings in a series of 37 patients with suspected malignant obstruction. In their study, ERCP was performed before EUS-FNA, procedures were performed in a single session in only 56% of cases, on-site cytopathology was not available, and only 1 patient had cholangiocarcinoma in their cohort. They found that EUS-FNA had a higher sensitivity compared with ERCP brushings for diagnosing malignancy (53% vs 29%), when using strict cytologic criteria for malignancy.

Rösch et al[16] reported the only other direct prospective comparative study in 2004. In their study, 50 consecutive patients with indeterminate biliary strictures or masses in the head of the pancreas underwent single- (n = 12) or separate- (n = 35) session EUS and ERCP procedures. Although the endoscopist performing EUS or ERCP was blinded to the tissue sampling results found on the alternate examination, the endoscopist was not blinded to imaging features of the previous EUS or ERCP. Also, the sequence of tests was not standardized, on-site cytology analysis was not performed, and final diagnoses were based on surgery or procedural biopsies in only 38%. They found an overall similar sensitivity for EUS-FNA and ERCP sampling (43% and 54%, respectively). The low sensitivity for EUS-FNA was attributed to including 22 patients (44%) in the analysis who underwent EUS without undergoing FNA because of imaging findings that appeared "benign" or the inability to visualize the target because of postoperative anatomy. The sensitivity was higher for EUS in the subgroup with pancreatic tumors and was higher for ERCP in the subgroup with biliary tumors.

Our interest in conducting the current study relates to the background of scarce comparative data and our own anecdotal experience suggesting a very high yield for EUS-FNA, even in the setting of cholangiocarcinoma. Strengths of our study include that all procedures were performed in a single session (reducing any potential time confounders), blinding of the second endoscopist performing ERCP tissue sampling, and the presence of on-site cytopathologic assessment, which has been shown to improve yield.[17] Additionally, final diagnoses were based on operative findings or a definite diagnosis of malignancy on either EUS-FNA or ERCP sampling in the majority (98%) of our cohort.

Our study revealed a significantly higher overall sensitivity and accuracy for EUS-FNA (94% and 94%), compared with a dual-sampling ERCP technique (50% and 53%, respectively). Our results are in keeping with findings from noncomparative series focusing on EUS-FNA of pancreaticobiliary masses and other separate studies on ERCP tissue sampling of biliary stricture.[1-11] The negative predictive value of EUS-FNA was also significantly higher than of ERCP sampling because of the high proportion of falsely "benign" ERCP tissue sampling results. One

TABLE 4. Sensitivity and accuracy of EUS-FNA and ERCP-based tissue sampling for patients with a pancreatic mass, a biliary mass or stricture, and indeterminate biliary strictures*

	Sensitivity, %			Accuracy, %		
	EUS-FNA	ERCP	P value	EUS-FNA	ERCP	P value
Overall (N = 51)	94	50	<.0001	94	53	<.0001
Pancreatic mass (n = 36)	100	38	<.0001	100	42	<.0001
Biliary mass or stricture (n = 15)	79	79	NS	80	80	NS
Indeterminate stricture (n = 15)	80	67	NS	80	67	NS

EUS-FNA, EUS-guided FNA; *NS*, not significant.
*Indeterminate biliary stricture defined as jaundice and evidence of biliary obstruction without visible mass on preprocedure CT or magnetic resonance imaging. Final diagnoses in this group of patients included pancreatic cancer (n = 3), cholangiocarcinoma (n = 11), and gallbladder carcinoma (n = 1).

possible critique of our study is that pathologists were not blinded to both tissue samples. However, the availability of both samples for pathologic review should be a bias in favor of more similar results for EUS-FNA and ERCP sampling. We believe that pathologist blinding would have led to an even wider discrepancy between these techniques.

Previous studies have reported differential outcomes based on including only strict versus both strict and suspicious cytologic criteria as evidence for malignancy.[3,15] Our pathologists graded tissue samples into 5 categories (Table 2). We chose to categorize both "malignant" and "atypia, suspect malignant" as positive results because we believe these findings also warrant enough clinical concern for cancer. Reanalysis of the data and counting only "malignant" samples as positive leads to even more marked differences because of the significantly higher proportion of definite "malignant" samples in the EUS-FNA group. In such circumstances, the overall sensitivity of EUS-FNA and ERCP tissue sampling would be 85% and 31%, respectively.

We acknowledge that 7 patients in our cohort had "nondiagnostic" ERCP samples because of failed bile duct cannulation. All of these patients had large pancreatic tumors, and cannulation failed due to outlet obstruction and duodenal deformity. Outlet obstruction is present in approximately 20% of patients with pancreatic cancer and is a recognized issue that can limit successful ERCP.[18] Although critics may suggest that this is a study limitation in terms of comparing these 2 sampling techniques, we believe this to be a clinical reality and an accurate reflection of expected outcomes when performing ERCP for pancreatic head malignancies.

The sensitivity and accuracy for EUS-FNA were significantly superior to ERCP sampling among the 36 patients with malignant (n = 34) and benign (n = 2) pancreatic masses. These findings make intuitive sense given that EUS-FNA directly samples a pancreatic mass, whereas ERCP samples are usually obtained from the area where a mass is causing compression on the bile duct. Rösch et al[16] found similar results for patients with pancreatic masses, but their findings lacked statistical significance.

Interestingly, the sensitivity (79%) and accuracy (80%) for EUS-FNA seemed comparable to those of ERCP tissue sampling among the 15 patients with biliary masses and strictures (all but 1 malignant). Our high yield with EUS-FNA is consistent with results from several published series that revealed high sensitivity (73%-89%) for EUS-FNA in suspected cholangiocarcinoma.[19-22] Although none of these studies directly compared EUS-FNA results with ERCP sampling as ours has, most patients in these studies had previous negative ERCP brushings. One previous study reported a significantly lower sensitivity for diagnosing proximal versus distal cholangiocarcinoma (59% vs 81%).[19] Other large series have suggested high sensitivities (77%-89%) for diagnosis of proximal (hilar) tumors,[20,22] and our results are similar to these. We diagnosed both distal and proximal cholangiocarcinomas with fairly high sensitivity (71% and 86%, respectively), but our numbers are too small to directly compare these groups. We admit that 2 of the hilar cancers in our cohort were detected by FNA of a nonprimary site (portal lymph node and liver lesion), and this may have increased the sensitivity for proximal lesions. However, we believe that this ability to confirm a more advanced stage is a relative strength of EUS. There were no patients in whom ERCP sampling detected a malignancy that was missed by EUS-FNA.

Similar to other published series,[19-22] we had no adverse events related to EUS-FNA of bile duct strictures and masses. However, we acknowledge that some centers may decline to offer liver transplantation after FNA, so the benefits of establishing a preoperative diagnosis by using EUS-FNA should be considered in this context. Additionally, there may be risk of peritoneal tumor seeding from EUS-FNA of cholangiocarcinoma.[23] Although there is now 1 published study suggesting no adverse effect on

overall or progression-free survival from preoperative EUS-FNA of cholangiocarcinoma,[24] the theoretical risk of tumor seeding should be considered.

As one might expect, the yield of ERCP sampling was higher for patients with primary biliary pathology compared with pancreatic masses. Some studies suggested higher yields for ERCP sampling with cholangioscopy-directed intraductal biopsies compared with standard ERCP sampling techniques.[25,26] We did not perform cholangioscopy in our cohort and only used standard brushing and biopsy techniques. There has been some concern for a greater ERCP adverse event rate when performed with cholangioscopy,[27] and we usually consider this during a second procedure after previous negative EUS-FNA and standard ERCP tissue sampling. Regardless, the results that we achieved using ERCP brushings and intraductal forceps in this subset of patients with biliary masses/strictures are on par with the yield reported for cholangioscopy-directed biopsies.[25,26]

A few other ancillary findings from our study are noteworthy. Patients successfully underwent same-session EUS-FNA and ERCP with a mean procedure time of 70 minutes (range 40-126 minutes). No patients had cardiopulmonary adverse events related to prolonged sedation. Others have reported similar success and safety with same-session EUS-FNA and ERCP.[15,28] We believe that performing these procedures in a single session provides obvious benefits from clinical care, cost, and patient preference standpoints. We acknowledge that all procedures were performed under monitored anesthesia care and believe that this helped us perform both procedures together successfully and safely.

Another benefit of same-session EUS-ERCP that our study highlights is how EUS findings may influence the need for subsequent ERCP. A small, but important proportion of our patients who provided study consent (14 of 77; 18%) had a diagnosis of a resectable neoplasm based on EUS. These patients were good surgical candidates and were referred for expedited surgical resection without ERCP and biliary stenting. The benefits of expedited surgery without preoperative biliary decompression were proved in a recent randomized trial.[29]

We conclude that EUS-FNA has excellent sensitivity and accuracy for the investigation of malignant biliary obstruction. Overall, EUS-FNA is superior to ERCP tissue sampling, and this is especially true for pancreatic masses. Although EUS has not traditionally been considered as useful as ERCP in assessing primary biliary strictures, our study suggests that EUS-FNA may be comparable to ERCP tissue sampling in suspected cholangiocarcinoma. Given our findings, and a fourfold higher incidence of pancreatic cancer compared with extrahepatic bile duct cancers,[30] we believe that EUS should be performed before ERCP in all patients with suspected malignant biliary obstruction, regardless of the suspected underlying tumor type.

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