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ORIGINAL ARTICLE

Diagnostic yield of endoscopic retrograde cholangiography and of EUS-guided fine needle aspiration sampling in gallbladder carcinomas

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Abstract
Background Obtaining histological evidence of gallbladder carcinoma (GBC) is difficult due to its extraductal nature, and pathological confirmation remains challenging. We compared the diagnostic value and safety of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) with endoscopic retrograde cholangiography (ERC) in patients with suspected GBC.
Patients Eighty-three patients with GBC were evaluated. Prior to definitive management, pathological evidence of GBC was obtained through either ERC cytopathologic sampling ($n = 33$), EUS-FNA ($n = 24$) or both ($n = 26$).
Results Among the 83 patients, 59 (71.0%) with biliary obstruction were sampled using ERC with 47.4% (28/59) sensitivity. In 19 of the remaining 31 cases, EUS-FNA sampling had 100% diagnostic sensitivity. Likewise, 50 (60.2%) of the 83 patients with suspected GBC underwent EUS-FNA of regional lymph nodes or the gallbladder (GB) mass itself with 94.8% sensitivity. The overall diagnostic sensitivity rates of ERC and EUS-FNA were 47.4 and 96%, respectively ($P < 0.001$). Post-procedural complications were seen in 6.7% of the ERC group (4/59, all were mild pancreatitis), and in none of the EUS-FNA group ($P = 0.10$).
Conclusions Gallbladder carcinoma sampling using ERC and EUS-FNA should be incorporated into the diagnostic workup of GB lesions as complementary tools, and EUS-FNA should be applied in the setting of failed or not indicated ERC.

Keywords Gallbladder carcinoma (GBC) · Endoscopic retrograde cholangiography (ERC) · Endoscopic ultrasound (EUS) · EUS-guided fine-needle aspiration (EUS-FNA)

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Introduction

Obtaining pathological evidence of gallbladder carcinoma (GBC) is medically and ethically necessary for both operable and non-operable cases, prior to resection and chemotherapy, respectively. In the pre-endoscopic ultrasound (EUS) era, endoscopic retrograde cholangiography (ERC) drainage with cytologic sampling was the initial investigation of choice to prove malignancy, especially in cases with biliary obstruction. ERC-guided sampling has a

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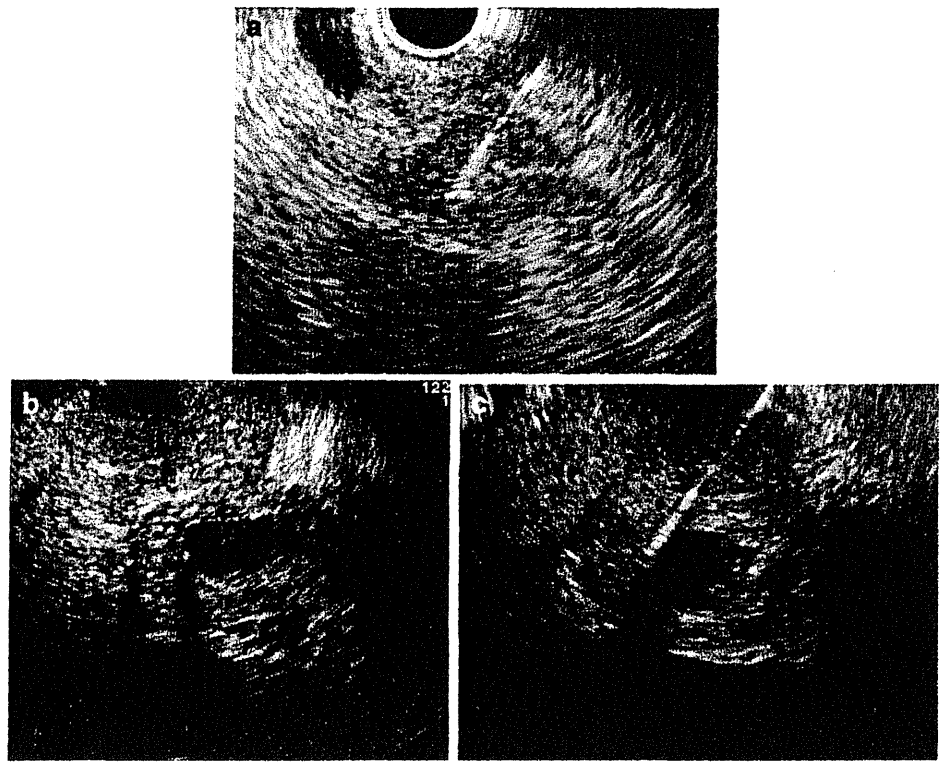

Fig. 2 EUS-FNA. **a** EUS-FNA for regional intra-abdominal lymph nodes. **b** The diffuse and irregular wall of a thickened GB. **c** EUS-FNA for a GB wall-thickened lesion. *EUS-FNA* endoscopic ultrasound-guided fine-needle aspiration, *GB* gallbladder, *LN* lymph node, *insuff* insufficient aspirate

not enlarged, inaccessible, or yielded negative sampling (Fig. 2b, c) [14].

Evaluation of complications

All patients were followed-up for 24 h after the procedure with clinical observation and measurement of serum amylase, C-reactive protein (CRP) and hematologic profiles. Post-procedural pancreatitis was diagnosed based on abdominal pain and/or a four-fold rise in baseline serum amylase. The possibility of tumor seeding, which may be associated with these procedures, was evaluated by the presence or absence of any apparent tumor involvement of the gastrointestinal wall, along the needle track, and during follow-up through imaging modalities (e.g. CT, MRI).

Statistical analysis

Samples obtained by ERC and/or EUS-FNA were categorized as positive or negative for malignancy. Any specimen interpreted as suspicious, atypical or non-diagnostic was considered negative for malignancy. Our standard references were either postoperative cytopathological findings from surgical patients, or the results of EUS-FNA coupled with the clinical, imaging and follow-up management results for non-operable patients.

Continuous variables are described as means and standard deviations, and dichotomous variables are expressed as simple proportions. The χ^2 test (with Yates correction) was used for comparative statistics. Data were statistically analyzed using SPSS software for Windows, release 11 (SPSS Inc, Chicago, IL, USA). A P value of <0.05 was considered significant.

Results

ERC sampling

Among the 83 patients, 59 (71.0%) presented with obstructive jaundice and underwent ERC cytopathological sampling. Evidence of malignancy was obtained in 28 (47.4%) of them (95% CI 34.3–60.8%).

Bile aspiration and subsequent cytological examination was performed in 30 (50.8%) of these 59 patients, and ERC add-on procedures (e.g. brushing and or biopsy forceps) were used in the remaining 29 (49.2%). Figure 3 shows details of the ERC results.

The malignancy detection rates of bile aspirate cytology and the add-on ERC cytopathology were 43.3% (13/30) and 51.7% (15/29), respectively with no statistical difference between these 2 groups ($P = 0.31$).

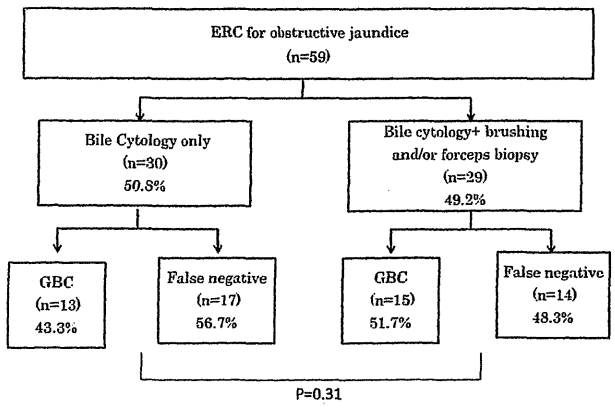

Fig. 3 Details of ERC results. The malignancy detection rates of bile aspirate cytology and the add-on ERC cytopathology were 43.3% (13/30) and 51.7% (15/29), respectively, with no statistical differences between these 2 groups ($P = 0.31$). *GBC* gallbladder carcinoma, *ERC* endoscopic retrograde cholangiography

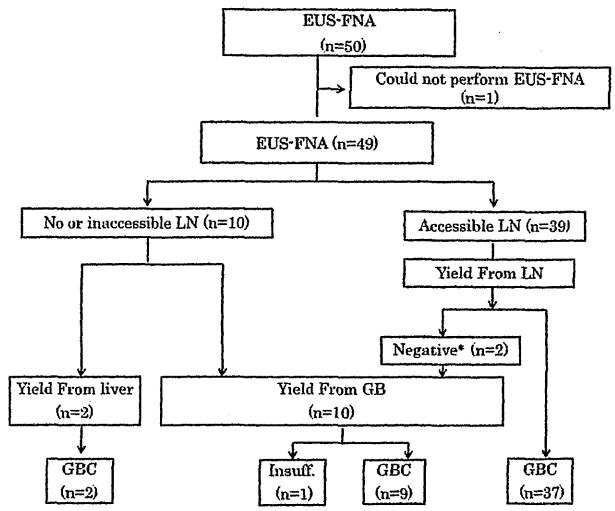

Fig. 4 Schematic diagram of gallbladder mass lesions and EUS-guided FNA yield. Our EUS-FNA sampling protocol for GB mass lesion. The overall diagnostic sensitivity rate of EUS-FNA was 96%. *EUS-FNA* endoscopic ultrasound-guided fine-needle aspiration, *GB* gallbladder, *GBC* gallbladder carcinoma, *LN* lymph node, *insuff* insufficient aspirate

Post-procedure complications were detected in 4 cases (6.7%) and all were mild pancreatitis which was managed conservatively.

EUS-FNA sampling

Fifty (60.2%) of the 83 patients with suspected GBC, according to the findings of various imaging modalities, underwent EUS-FNA. All of these patients were considered inoperable, and the aim of puncture was to obtain pathological evidence of malignancy before starting chemotherapy. Only one patient could not undergo EUS-FNA because we could not find a safe route for puncture. Enlarged intra-abdominal regional lymph nodes were detected in 79.6% ($n = 39$), and after FNA 94.8% of them ($n = 37$) were found to be positive for malignancy with immediate on site evaluation. 10 cases with absent regional LN enlargement and 2 with negative yield from LN aspirate underwent sampling of the GB mass itself ($n = 10$) or liver metastasis ($n = 2$).

Positive yield for malignancy was obtained in 90% (9/10) patients who underwent GB mass puncture, and both patients in whom the hepatic metastasis was sampled successfully. The overall diagnostic sensitivity rate of EUS-FNA was 96% (48/50, 95% CI 85.7–99.6%), with only one false-negative (FN) result because of sample insufficiency. Most of our pathological diagnoses were either adenocarcinoma or adenosquamous cell carcinoma (95.9%, 46/48) and only 2 cases were small cell carcinoma (4.1%, 2/48). The mean number of needle passes was 2.6 (range 1–4). There was no serious procedure-related complication in any case. In addition, there was no apparent tumor seeding during our follow-up periods. Figure 4 shows a detailed description of the EUS-FNA procedure results.

EUS-FNA after ERC

Endoscopic retrograde cholangiography failed to show evidence of malignancy in 52.5% of the 59 cases ($n = 31$), considered the FN yield. Of them, 19 cases were subjected to EUS-FNA with 100% positive yield for malignancy (95% CI 82.3–100%). Figure 5 shows a detailed description of these results.

EUS-FNA versus ERC (Table 1)

The overall diagnostic sensitivity rates of ERC and EUS-FNA for GBC were 47.4 and 96%, respectively ($P < 0.001$). Post-procedure complications were detected in 6.7% of the ERC-group (4/59; all were mild post-ERC pancreatitis), and none was reported in the EUS-FNA group including tumor seeding ($P = 0.10$).

Discussion

To augment any therapeutic strategy with pathologic evidence is thought to be of both ethical and medical importance. This argument is relevant to GBC when present as a mass lesion, with or without obstructive manifestations, as it si important to tailor the appropriate chemotherapy and equally to avoid using chemotherapy in a benign setting. It

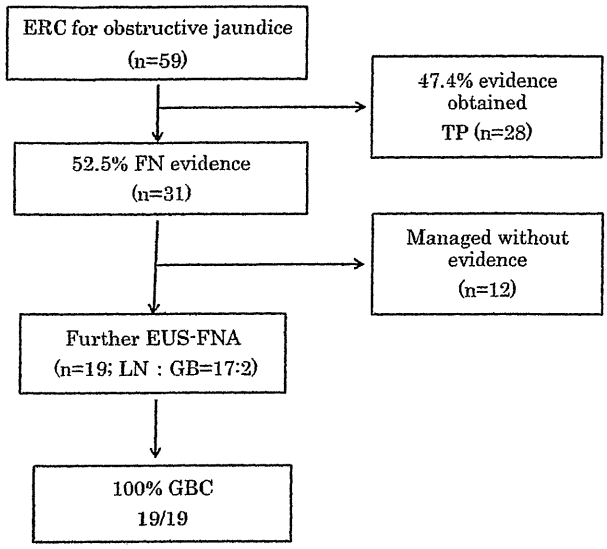

Fig. 5 Schematic diagram of EUS-FNA after ERC. ERC failed to reveal evidence of malignancy in 52.5% of the 59 cases ($n = 31$) and was considered as FN yield. Of these, 19 cases were subjected to EUS-FNA with 100% positive yield for malignancy. *ERC* endoscopic retrograde cholangiography, *EUS-FNA* endoscopic ultrasound-guided fine-needle aspiration, *GB* gallbladder, *GBC* gallbladder carcinoma, *LN* lymph node, *FN* false negative, *TP* true positive

Table 1 Comparison of EUS-FNA with ERC

	ERC-group ($n = 59$)	EUS-FNA group ($n = 50$)	*P* value*
Sensitivity	47.4% (28/59)	96% (48/50)	<0.001
Complication rate	6.7% (4/59)	0% (0/49)	0.1097

EUS-FNA Endoscopic ultrasound-guided fine-needle aspiration, *ERC* endoscopic retrograde cholangiography

* Using Fisher exact test

has been noted that a diffuse thickening of the GB wall is a common manifestation of GBC, and that this might be mimicked by benign GB lesions, such as xanthogranulomatous cholesterosis (XGC) [18–20] which further entails cytological evidence. We have previously described the nuances and yield of EUS-FNA sampling in distinguishing GBC from benign entities such as XGC [14]. Indeed, and surprisingly, two of our FNA pathological diagnoses were small cell carcinoma; this enabled us to assign the appropriate chemotherapy regimen for extra-pulmonary small cell carcinoma[21] [22]. If biliary obstruction with a suspected GB mass is the main presentation, ERC is the usual logical next step for both obtaining a pathological diagnosis and resolving the obstruction by biliary stenting. However, the reported yield of ERC-guided sampling with this technique was suboptimal, and other methods for obtaining a pathological diagnosis may be required in some cases [1, 3, 7, 9]. Among our GBC patients, biliary obstruction was evident in 59 (71.0%), and evidence of malignancy was obtained in 47.4% of them using ERC-based sampling approaches. Others have reported sensitivities of ERC-based sampling ranging from 44 to 82%, in strictures caused by cholangiocarcinoma [1–4]. The yield of ERC is believed to be lower in cases of GBC due to its extra-ductal nature; yield can be improved up to 82% by using add-on sampling methods, such as brushing and endo-biliary forceps biopsies, compared with ERCP cytology alone [3, 9]. However, these add-on manoeuvres were not accompanied by any increase in sensitivity in our GBC patients, possibly explained in some cases by its extra-ductal nature with compressive narrowing of bile duct.

One report has described endoscopic trans-papillary gallbladder drainage, in which a drainage tube is inserted into the GB using a catheter and guidewire [23]. Although an innovative technique with relatively high reported sensitivity and success rates of 81 and 83%, respectively, it needs expert operators, and might not be technically feasible for all patients with GBC. The advent of EUS and EUS-FNA has overcome the obstacles to ERC, namely, technical failure, low yield, and lack of indication such as the absence of obstruction. To date, four published reports have described EUS-FNA in patients with GBC [11–14], including sampling from the GB mass itself. As retrospectively recruited, and according to our local institutional protocols in the setting of unresectable GBC cases, the importance of initially puncturing regional LNs, when feasible, has been emphasized for many reasons. First, most advanced unresectable GBC have regional LNs; 79.6% in our study. Second, there is a potential risk of spillage and biliary peritonitis on puncturing cystic structures like GB. Third, the fear of track seeding. In the current study, we report a sensitivity rate of 94.8% when targeting a regional LN, and a diagnostic sensitivity rate of 96% when targeting the GB mass itself. On comparing the sensitivity rates of both ERC-sampling and EUS-FNA sampling, the latter was notably higher (47.4 vs 96%, $P < 0.001$). Despite the retrospective nature of the comparison and the group heterogeneity, we attempted to define the potential value of EUS-FNA especially in settings where ERC is not a valid indicator. Moreover, EUS-FNA is relatively less invasive with direct visualization of the target. We have reported 100% sensitivity of EUS-FNA for proving malignancy, and thus we recommend its application for obtaining pathological confirmation of GBC, with or without biliary obstruction. The main shortcomings of the present study include its retrospective nature, the potential for bias in selecting patients, the heterogeneity of study groups and hence the lack of standardization. We consider our findings to be preliminary,

and to the best of our knowledge, this is the only published study that has compared ERC with EUS-FNA sampling in the setting of GB masses presenting with obstructive jaundice. Nevertheless, we recommend a randomized trial to compare ERC and EUS-FNA sampling in appropriately matched groups to address the real capabilities of both modalities, in addition to testing the applicability of ultrasound-guided versus EUS-guided sampling tools. Until then, and based on the present findings, we can construct a short algorithmic approach for the diagnosis of GB mass lesions: in the presence of overt biliary obstruction, ERC should be tried first to alleviate the obstruction and to provide evidence of malignancy. If this fails, or if there is no obstruction, EUS-FNA sampling from regional LN and/or the GB mass itself should be performed as appropriate.

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THE ROLE OF EUS FOR DIAGNOSIS OF PANCREATIC MALIGNANCIES

A CONVEX EUS IS USEFUL TO DIAGNOSE VASCULAR INVASION OF CANCER, ESPECIALLY HEPATIC HILUS CANCER

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Endoscopic ultrasonography (EUS) has become an indispensable diagnostic procedure pairing endoscopy with transluminal high frequency ultrasonography. EUS provides images with a high resolution such that the depth of tumor invasion can be accurately determined. It also sees lesions outside of gastrointestinal tract, particularly those in pancreas, biliary system and periluminal lymph nodes. The most important limitation of EUS was lack of specificity, that is, the differentiation between benign and malignant lesions. In 1992, EUS-guided fine needle aspiration (EUS-FNA) was introduced with the sampling of a lesion in the pancreatic head using a convex EUS. Since then the indications of EUS-FNA have been expanded to include a variety of therapeutic uses. In addition, a convex EUS probe can also be used for detailed evaluation of the pancreatobiliary system, in lieu of a radial EUS. The vascular structures surrounding liver, biliary system and pancreas can be showed by a convex EUS system very clearly and easily compared with the more familiar radial EUS images. So we think a convex EUS is very useful for not only EUS-FNA but also screening and close examination for cancer with vascular invasion.

Key word: abdominal vessel, convex EUS, EUS, EUS-FNA, EUS procedure.

INTRODUCTION

Current endoscopic ultrasonography (EUS) systems use two types of scanning methods: radial scanning and convex scanning.[1] Radial EUS imaging is extensively used for imaging of small lesions, and diagnoses and staging of cancer.[2] In contrast, convex EUS imaging is used for EUS-guided fine needle aspiration (EUS-FNA) to obtain pathological diagnoses. Some doctors say 'A convex EUS is useful only for EUS-FNA and interventional EUS.'[3] Other doctors would say 'It is difficult to understand the ultrasound anatomy of the pancreatobiliary systems thorough a convex EUS, which is not suitable for screening for the pancreatobiliary diseases.' Are these true? We do not think so. We think a convex EUS system is very useful for screening, and has similar or even better diagnostic accuracy for pancreatobiliary diseases even without EUS-FNA, than radial EUS imaging. It has a superior accuracy for visualization of abdominal vessels.[4] So, a convex EUS is very useful for the assessment of vascular invasion with cancer.[5] In this review we will describe the procedure for visualization of upper abdominal vascular structures, and the assessment of vascular invasion with cancer using a convex EUS.[6–8]

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ULTRASOUND IMAGES OF UPPER ABDOMINAL VASCULAR STRUCTURES BY A CONVEX EUS

Scanning from the stomach

When the EUS scope has passed the esophagogastric junction, and the control knobs are free, the left lobe of the liver can usually be seen. Starting with the left liver lobe in view, we can rotate the scope clockwise to see the abdominal aorta in a longitudinal orientation. When the scope is advanced gently from this position after the abdominal aorta, the celiac artery take off will be seen. We can trace the celiac artery to its division into common hepatic artery (CHA) and splenic artery (SA) (Fig. 1). We can then follow the CHA by rotating the scope counterclockwise and slowly pulling back a little bit, and show the

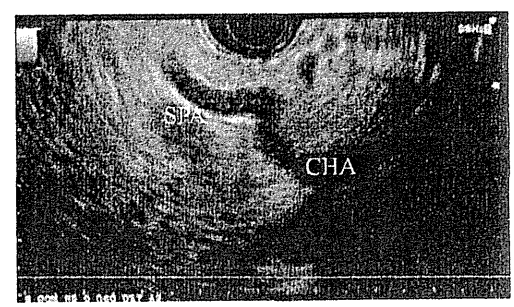

Fig. 1. The bifurcation of splenic artery (SPA) and common hepatic artery (CHA) is seen from the stomach.

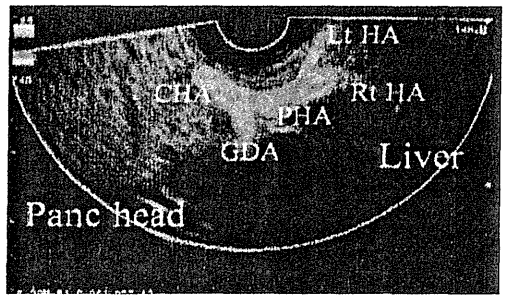

Fig. 2. Common hepatic artery (CHA), gastroduodenal artery (GDA), proper hepatic artery (PHA), right hepatic artery (Rt HA) and light hepatic artery (Lt HA) are seen clearly from the stomach using the color Doppler.

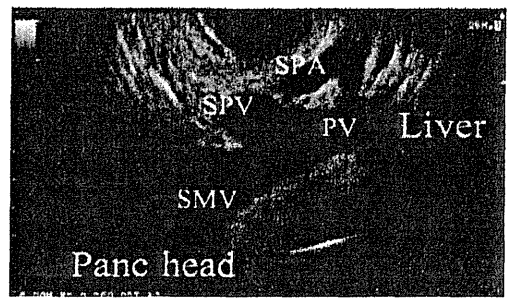

Fig. 4. Splenic artery (SPA), splenic vein (SPV), portal vein (PV) and superior mesenteric vein (SMV) are seen from the stomach.

Fig. 3. We can see the left portal vein (Lt PV), middle hepatic artery (HA) and lateral hepatic artery in the left lobe of the liver.

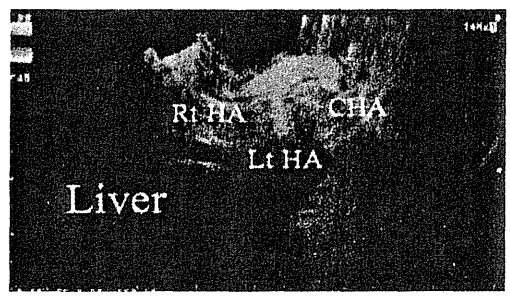

Fig. 5. The bifurcation of right hepatic arteries (Rt HA), left hepatic arteries (Lt HA) is seen from the duodenal bulb.

gastroduodenal artery and the proper hepatic artery (PHA) (Fig. 2). If we further withdraw the scope to follow the PHA toward hepatic hilum, we can see the right and left hepatic arteries (Rt and Lt HA) (Fig. 2). At the hepatic hilum, we can trace portal vein (PV) to its division into Rt and Lt PV. We can follow the Lt PV by rotating the scope counterclockwise, and recognize the middle hepatic artery (MHA) and lateral hepatic artery and left PV (Fig. 3). We can then insert the scope along the PV to show the confluence of the superior mesenteric vein and the splenic vein (Fig. 4).

Scanning from the duodenal bulb

We insert the scope into the duodenal bulb and rotate it to see the pancreatic head and CHA. If we push the scope with down angle following the PHA towards the hepatic hilum, we can see its bifurcation into Lt HA and Rt HA (Fig. 5). Following the Rt HA by pushing the scope gently, we can see its anterior and posterior branches (Fig. 6). Color Doppler mode is very useful to detect the HA and its branches. If we see the PV, we can see its Lt and Rt PV divisions at the hepatic hilum (Figs 7,8). If we rotate the scope counterclockwise following the Rt PV, we can see its further bifurcation into its anterior and posterior branches (Fig. 9).

CASE PRESENTATION

A 60-year-old woman was referred to our hospital in January 2010 for further examination of a liver tumor, which was detected by abdominal ultrasound during a health examination. The tumor was characterized as a cholangiocarcinoma by MD-CT at the referring hospital. We suspected perineural invasion surroundings the Rt HA and MHA from the CT images (Fig. 10). During the EUS study we could show the perineural invasion surroundings of the Rt HA and MHA very clearly compared with the CT images (Fig. 10). We could easily and clearly see Rt HA, Lt HA and MHA. A convex EUS was very useful to assess vascular invasion of cancer in this case.

CONCLUSION

A convex EUS is useful for not only EUS-FNA but also assessment of vascular invasion by cancer, especially at the hepatic hilum.[6,7] We recommend the increased use of a convex EUS to determine the relation of hilar cancers to the adjacent vascular structures. Because we can get the contrast tissue harmonic images by a new type convex EUS, we can get the clear images of abdominal vessel, contrast images and EUS-FNA specimen by only a convex EUS.

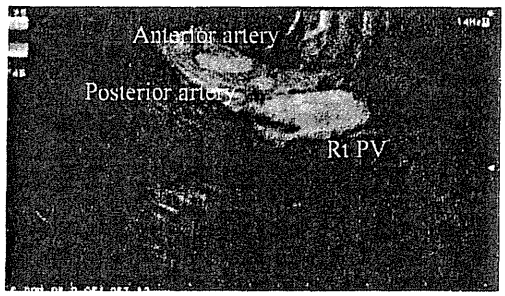

Fig. 6. We can see the anterior and posterior hepatic artery near right portal vein (Rt PV) clearly.

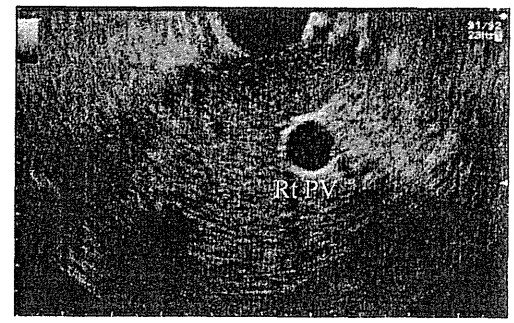

Fig. 8. Right portal vein (Rt PV) is seen at hepatic hilum.

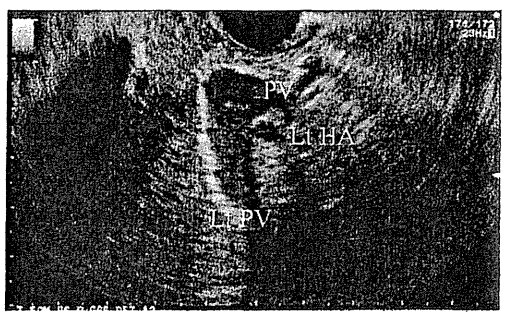

Fig. 7. Both left portal vein (Lt PV) and left hepatic arteries (Lt HA) are seen at hepatic hilum.

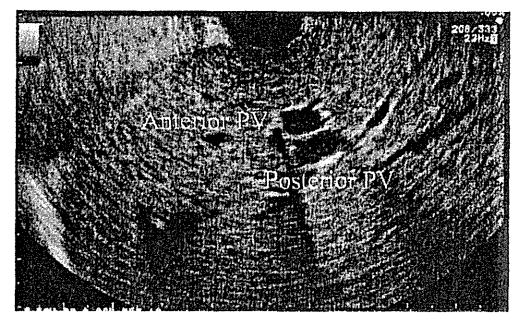

Fig. 9. We can see the bifurcation anterior and posterior portal vein (PV) in the right lobe of the liver.

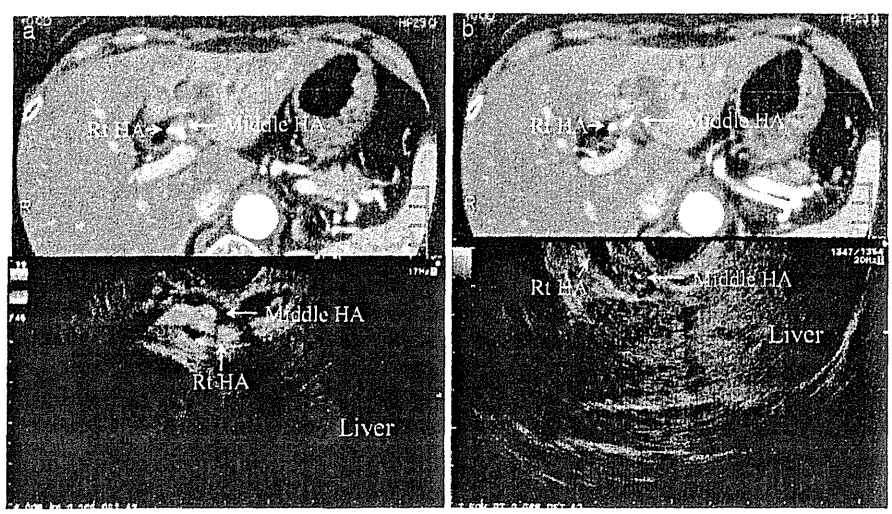

Fig. 10. Right hepatic artery (Rt HA) and middle HA are seen in the tumor at hepatic hilum. This tumor surrounding hepatic artery is perivascular invasion of cholangiocarcinoma. Rt and middle hepatic artery are seen clearly by a convex EUS.

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Prospective Clinical Study of EUS-Guided Choledochoduodenostomy for Malignant Lower Biliary Tract Obstruction

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OBJECTIVES: **Endoscopic ultrasound-guided choledochoduodenostomy (EUS-CDS) has recently been reported as an alternative to percutaneous transhepatic biliary drainage (PTBD) in cases of biliary obstruction, when endoscopic biliary drainage (EBD) is unsuccessful. However, prospective studies of EUS-CDS have not yet been performed. We conducted a prospective study to evaluate the safety, feasibility, and efficacy of EUS-CDS in patients with malignant lower biliary tract obstruction.**

METHODS: **A prospective study to confirm the safety of EUS-CDS was carried out in 6 patients, followed by a trial to evaluate the feasibility and efficacy of EUS-CDS in 12 additional patients. We placed a plastic stent from the duodenal bulb into the extrahepatic bile duct under EUS guidance using an oblique viewing echoendoscope, needle knife, guidewire, and biliary dilators.**

RESULTS: **The site of extrahepatic bile duct puncture was the common hepatic duct in 15 patients and the common bile duct in 3 patients. Mean diameter of the punctured extrahepatic bile ducts was 10 mm (range: 6–20 mm). Technical and functional success rates were 94% (17/18) and 100% (17/17), respectively. Median procedure time was 30 min (range: 10–52 min). Median duration to first oral intake after the procedure was 1 day (range: 1–3 days). Early complications were encountered in three (17%) patients, including focal peritonitis in two patients and hemobilia in one patient. During the follow-up period (median: 163 days; range: 46–484 days), 12 stent occlusion events were observed in nine patients. Re-intervention with exchange of the occluded stent was successful in 8 of 12 (66%) times. Severe early and late complications were not encountered in any patients in this study. Median duration of stent patency by Kaplan–Meier analysis was 272 days.**

CONCLUSIONS: **EUS-CDS is safe, feasible, and effective as an alternative to PTBD and EBD in cases of malignant distal biliary tract obstruction. Prospective randomized studies are needed to compare the safety and efficacy of various kinds of endoscopic devices used in EUS-CDS and to compare EUS-CDS with PTBD or EBD.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg Video content online

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INTRODUCTION

Endoscopic biliary drainage (EBD) is a well-established technique for providing biliary decompression in patients with obstructive jaundice (1,2). However, failure to achieve bile duct access still occurs in some patients because of failed biliary cannulation or inaccessible papilla because of severe duodenal stenosis caused by tumor invasion. In these cases, percutaneous transhepatic biliary drainage (PTBD) or surgical intervention is required. However, both methods have been associated with significant morbidity and mortality rates.

Endoscopic ultrasound (EUS)-guided biliary drainage (EUS-BD) is a recently described alternative to PTBD in cases of failed

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endoscopic retrograde cholangiopancreatography (ERCP). A few reports have demonstrated the feasibility and efficacy of EUS-BD in patients with failed biliary access by ERCP. However, most reports have been retrospective or included small patient numbers.

EUS-BD includes a rendezvous technique and a direct access technique. The direct access technique includes two major methodologies: EUS-guided choledochoduodenostomy (EUS-CDS) (3–5) and EUS-guided hepatogastrostomy (6). Although EUS-CDS has been reported as a useful method in cases with malignant distal biliary obstruction, prospective studies have been lacking. We, therefore, conducted a prospective study of EUS-CDS to clarify the safety, feasibility, and clinical efficacy of this procedure.

METHODS

Definition

In the present study, EUS-CDS included the placement of a plastic stent of 7- or 8.5-Fr diameter and 5-cm length into the extrahepatic bile duct through the duodenal bulb by puncturing the extrahepatic bile duct under EUS guidance.

Inclusion criteria

(i) Biliary drainage required for distal biliary obstruction caused by unresectable malignant tumor.
(ii) No tumor extension into the duodenal bulb or peri-bulbar tissues.
(iii) Maintained major organ function (marrow, heart, liver, lungs, and kidneys). Absence of heart failure, platelet counts ≥50,000/μl, prothrombin time ≥50%, and serum creatinine ≤1.5 mg/dl.
(iv) Performance status (Eastern Cooperative Oncology Group): 0, 1, 2, or 3.
(v) Predicted survival ≥1 month.
(vi) Informed consent provided by the patient.

Exclusion criteria

(i) Malignant obstruction of the gastrointestinal tract.
(ii) Block of the upstream bile duct on the hepatic side.
(iii) Pregnancy.
(iv) History of local radiotherapy or planned radiotherapy treatment of the tumor.

Study design

This was a non-randomized, prospective single-center study. First, a small-scale independent feasibility study in six patients was undertaken to confirm safety. After confirming safety in six patients, an efficacy evaluation study of EUS-CDS was done in a further 12 patients (total 18 patients). The primary end point of interest was safety (incidence and severity of adverse events). Secondary end points were assessment of the technical and clinical efficacy. This study was approved by our hospital's ethics review board (Aichi Cancer No. 6–30).

Safety assessment criteria

Treatment-related toxicities comprised the following events occurring within 30 days after EUS-CDS:

(i) fever (≥38.5 °C) lasting >7 days without stent occlusion; (ii) bleeding; (iii) alternative drainage (excluding stent occlusion); (iv) unable to resume oral intake >7 days; (v) need for laparotomy; (vi) non-hematological toxicity of at least Grade 3 (National Cancer Institute—Common Toxicity Criteria Version 3.0).

If treatment-related toxicities were seen in ≥3 of 6 patients, tolerability was to be discussed with the efficacy and safety assessment committee to re-evaluate the study plan.

Technique of EUS-CDS

(i) A convex-type ultrasound endoscope (GF-UCT240; Olympus Optical, Tokyo, Japan) was used with the tip of the endoscope placed in the duodenal bulb.
(ii) Endoscopic observation was undertaken to confirm the absence of any local mucosal lesions in the duodenal bulb.
(iii) The long axis of the extrahepatic bile duct was visualized from the duodenal bulb.

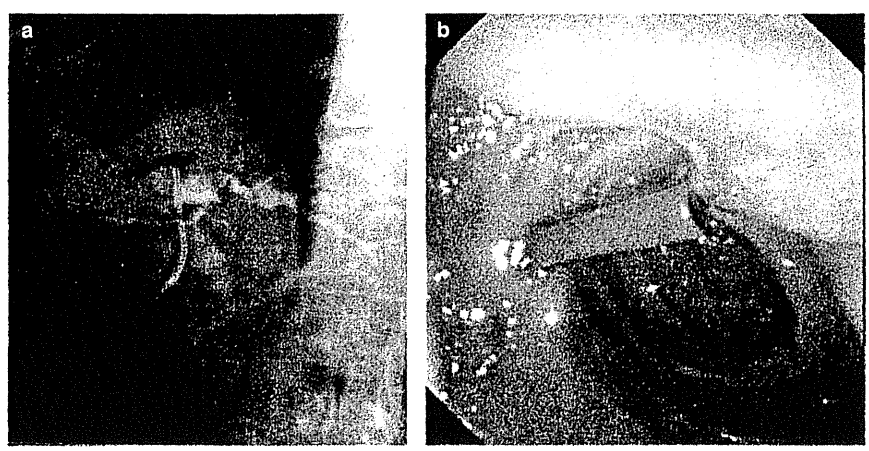

Figure 1. Technique of endoscopic ultrasound-guided choledochoduodenostomy (EUS-CDS). (**a**) Straight tube stent was placed under echoendoscopic and fluoroscopic view. (**b**) Biliary stent placed from the first portion of the duodenum to the extrahepatic biliary duct.

(iv) At this stage, the position of the scope was adjusted so that the direction of puncture was toward the hepatic hilum.
(v) The bile duct was punctured under EUS guidance using a 22-G fine needle aspiration (FNA) (NA-200H-8022; Olympus Optical) and bile was aspirated to confirm an intraductal position of the needle tip.
(vi) Contrast medium was injected through the needle to opacify the intra- and extrahepatic bile ducts.
(vii) After removal of the needle, a needle knife (Zimmon papillotomy knife; Cook Endoscopy, Winston-Salem, NC) was inserted into the bile duct, while setting the output current to the incision mode under real-time EUS guidance.
(viii) The inner needle was removed and a 0.035-inch guidewire (450 cm long, Jagwire; Microvasive Endoscopy, Boston Scientific, Natick, MA) was inserted through the outer sheath deep into the intrahepatic bile duct.
(ix) The outer sheath of the needle knife was then removed, while the intraductal position of the guidewire was maintained.
(x) The fistula (point of puncture) was dilated serially using tapered biliary dilation catheters of 6, 7, and 9 Fr size (Soehendra biliary dilation catheters; Wilson-Cook,), over the guidewire.
(xi) Finally, an 8.5-Fr straight biliary stent (Tannenbaum; Wilson-Cook; or Flexma; Microvasive Endoscopy) was inserted through the choledochoduodenal fistula into the extrahepatic bile duct (**Figure 1a, b**).
(xii) Absence of intra-abdominal leakage of contrast medium was confirmed on X-ray fluoroscopy or computed tomography (**Appendix 1** and **Supplementary video** online).

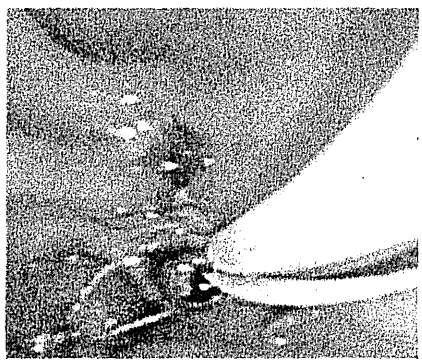

Figure 2. Guidewire-assisted stent exchange. Removal of the occluded stent using a snare with the guidewire in place.

Method for exchanging occluded stents in EUS-CDS

Two methods were used for exchanging an occluded stent in this study: the simple method and the guidewire-assisted stent exchange method.

Table 1. **Patients characteristics**

Patient no.	Age/sex	Diagnosis (carcinoma)	Reason for failed ERCP	Diameter of extrahepatic bile duct (mm)	Ascites	Duodenal stent
1	67/M	Pancreas	Papilla distortion due to tumor infiltration	10	—	—
2	73/F	Pancreas	Papilla distortion due to tumor infiltration	10	—	—
3	67/F	Pancreas	Not done	11	—	—
4	77/M	Pancreas	Not done	12	—	—
5	78/F	Uterus	Not done	10	Peri-hepatic	2nd portion
6	80/M	Pancreas	Not done	13	—	—
7	65/F	Pancreas	Not done	12	—	—
8	69/M	Pancreas	Not done	10	—	—
9	72/F	Pancreas	Not done	20	—	—
10	58/F	Pancreas	Not done	7	—	—
11	44/M	Stomach	Not done	10	—	—
12	67/F	Pancreas	Not done	11	—	—
13	58/M	Pancreas	Not done	8	—	—
14	75/F	Pancreas	Not done	10	—	2nd portion
15	64/F	Pancreas	Not done	7	Peri-hepatic	—
16	43/F	Pancreas	Not done	6	—	—
17	80/F	GB	Not done	10	—	—
18	77/M	Pancreas	Not done	11	—	—

ERCP, endoscopic retrograde cholangiopancreatography; GB, gallbladder.

Table 2. **Technical details and results of EUS-CDS**

Patient no.	Puncture site of the bile duct	Success or not	Required time for EUS-CDS (min)	Oral intake after EUS-CDS (days)	Initial stent (Fr/mm)	Early complication (within 30 days)	Late complication
1	CBD	Success	52	1	7/50	—	—
2	CHD	Success	35	3	8.5/50	—	—
3	CHD	Success	52	1	7/50	—	—
4	CBD	Success	50	3	8.5/50	—	—
5	CHD	Success	30	2	8.5/50	—	—
6	CBD	Success	45	1	8.5/50	—	—
7	CHD	Success	23	3	8.5/50	Focal peritonitis (Gr2)	—
8	CHD	Success	30	1	8.5/50	—	—
9	CHD	Success	20	1	8.5/50	—	—
10	CHD	Success	17	2	8.5/50	Focal peritonitis (Gr1)	—
11	CHD	Success	25	1	8.5/50	—	—
12	CHD	Failure	10	1	None	Hemobilia (Gr1)	—
13	CHD	Success	20	1	8.5/50	—	—
14	CHD	Success	40	2	8.5/50	—	—
15	CHD	Success	18	1	8.5/50	—	Stent slipped out
16	CHD	Success	13	1	8.5/50	—	—
17	CHD	Success	12	1	8.5/50	—	—
18	CHD	Success	35	1	7/50	—	—

CBD, common bile duct; CHD, common hepatic duct; EUS-CDS, endoscopic ultrasound-guided choledochoduodenostomy.

Simple method

The occluded stent was removed using a dormia basket through a duodenoscope.

After stent removal, an ERCP catheter was inserted through the choledochoduodenal fistula into the bile ducts, followed by placement of a guidewire. A new biliary stent was inserted over the guidewire.

Guidewire-assisted stent exchange

A 0.035-inch guidewire was inserted into the bile duct through an occluded stent using an ERCP catheter. The occluded stent was then removed using a snare with the guidewire in place, through the biopsy channel of the duodenoscope (**Figure 2**).

A new 8.5-Fr straight biliary stent was inserted into the bile ducts over the guidewire.

All study protocols were approved by the institutional review board at Aichi Cancer Center Hospital, Nagoya, Japan. All patients provided written informed consent to participate in this study.

RESULTS

Between December 2007 and July 2009, EUS-CDS was performed in 18 patients (7 men, 11 women). Mean age of the patients was 67.9±10.9 years (range: 43–80 years). The mean diameter of the extrahepatic bile ducts before needle puncture was 10 mm (range: 6–20 mm) (**Table 1**). The median procedure duration was 30 min (range: 15–38 min).

In the feasibility study to confirm safety, no treatment-related toxicities were seen in any of the patients (**Table 2**). In this study, successful extrahepatic bile duct puncture was achieved in all 18 patients (100%), with successful completion of stent insertion in 17/18 patients (94%). In the single failed case, after the common hepatic bile duct was punctured by a 22-G needle, hemobilia occurred and the subsequent procedure was cancelled without any other complications. The functional success rate was thus 100% (17/17 cases). The median procedure time was 30 min (range: 10–52 min). Early complications were seen in three patients (focal peritonitis in two and hemobilia in one patient). Severe complications were not seen in any patients. Median period until first oral intake after EUS-CDS was 1 day (range: 1–3 days). During the follow-up period (median: 163 days; range: 46–484 days), 12 stent occlusion events were encountered, with successful stent exchange in eight of these events (**Table 3**). In the remaining four patients, we could not exchange the occluded stents because of tumor infiltration of the duodenal bulb. These patients were subjected to PTBD. At stent exchange, we placed a covered metal stent (Wallflex, 10 mm diameter, 4 cm length; Boston Scientific) instead of a plastic stent in two patients. The 50% stent patency rate according to Kaplan–Meier analysis was 272 days (**Figure 3**).

DISCUSSION

Wiersema *et al.* (1) first described EUS-guided cholangiopancreatography in 1996 as a diagnostic alternative in two patients with failed ERCP. Recent reports have demonstrated the feasibility

Table 3. **Clinical follow-up and stent exchange**

Patient no.	Stent Fr/length (Fr/mm)	Status	Re-intervention	Method of stent exchange	Stent patency (days)	Follow-up periods (days)	Prognosis
1	1st 7/50	Occlusion	Exchange	Simple	97	112	Dead
	2nd 7/50	Patent	None		5		
2	1st 8.5/50	Occlusion	Exchange	Simple	88	479	Dead
	2nd 8.5/50	Occlusion	Exchange		360		
	3rd 8.5/50	Patent	None		31		
3	7/50	Patent	None	—	62	62	Dead
4	8.5/50	Patent	None	—	46	46	Dead
5	8.5/50	Occlusion	PTBD	Failure	51	88	Dead
6	8.5/50	Occlusion	PTBD	Failure	272	321	Dead
7	8.5/50	Patent	None	—	184	184	Dead
8	8.5/50	Patent	None	—	85	85	Dead
9	8.5/50	Patent	None	—	142	142	Dead
10	8.5/50	Occlusion	Exchange	Guidewire	64	138	Dead
11	8.5/50	Patent	None	—	229	229	Dead
12	Failed	Patent	PTBD	—		484	Alive
13	1st 8.5/50	Occlusion	Exchange	Guidewire	51	468	Alive
	1st 8.5/50	Occlusion	Exchange	Guidewire	126		
	3rd 10/50				118		
	4th CMS 10 mm/4 cm				173		
14	8.5/50	Patent	None	—	81	81	Dead
15	1st 8.5/50	Occlusion	Exchange	Simple	318	414	Alive
	2nd CMS 10 mm/4 cm	Patent	Patent		96		
16	8.5/50	Occlusion	PTBD	Failure	57	191	Dead
17	8.5/50	Patent	None	—	362	362	Alive
18	7/50	Occlusion	EBD	Failure	14	54	Dead

CMS, covered metal stent; EBD, endoscopic biliary drainage; PTBD, percutaneous transhepatic biliary drainage.

of EUS-guided cholangiography with biliary stent placement in patients with failed cannulation at ERCP. The present clinical trial was designed with the objective of confirming the safety and efficacy of EUS-CDS, and its inclusion criteria did not limit subjects to patients in whom ERCP had been unsuccessful. EUS-BD includes two methods (a rendezvous technique and a direct access technique) and two main approach routes (transgastric and transduodenal). EUS-BD with direct access from the stomach (the transgastric approach) is known as EUS-guided hepatogastrostomy, while that from the duodenum (the transduodenal approach) is EUS-CDS.

The present study found high technical and functional success rates for EUS-CDS in cases of mild to severe dilatation of the extrahepatic bile duct with a comparatively shorter procedure time than expected. Although the incidence of adverse events was high at 17% (3/18), there were no serious adverse events. Considering this high incidence of adverse events, the existing method of EUS-CDS that uses plastic stents can be considered as a treatment option for patients in whom ERCP was unsuccessful. However, it may be possible to prevent these adverse events by developing dedicated medical devices. Although a relatively high rate of early complications was seen, both early and late complications could be managed conservatively. Most patients could start oral intake on the day after the procedure and long-term stent patency could be obtained.

Eleven retrospective studies describing 33 cases of EUS-CDS have been reported to date (3,7–18). An overview of 51 cases of EUS-CDS, including the 33 cases in published papers and our own 18 cases in this paper, is shown in **Table 4**. No standardized method for EUS-CDS has yet been determined and individual researchers have performed the procedure in their individual ways.

For the extrahepatic bile duct puncture, a needle knife or fistulotome was used in five institutions, 19- and 22-G EUS-FNA needles in three institutions, EUS-FNA needles followed by a needle knife in two institutions, and EUS-FNA needles or a needle knife in one institution. Generally speaking, using an EUS-FNA needle to access the bile duct seems safer, though it is more difficult to sufficiently dilate the fistula for insertion of a biliary stent. Using

a needle with electrocautery seems more risky, but it is easier and quicker to dilate the fistula enough to insert a bigger stent.

Although the procedure was unsuccessful in three patients, transduodenal stents were successfully inserted in the remaining 48 patients (48/51, 94%), including a metal stent in five patients. Among the three failed cases, one case was associated with hemobilia at the time of initial puncture with a 22-G needle for obtaining a cholangiogram in this study, but the other two cases were not described in published papers minutely. The success rate of treatment was 100% (48/48) among patients with successful EUS-CDS access. Therefore, once the stent had been successfully inserted from the duodenal bulb into the bile duct, cholestasis was relieved in all patients.

The advantage of the EUS-CDS technique is that the puncture site is very close to the extrahepatic bile duct and away from the obstructing tumor (10). No large intervening blood vessels lie between the duodenal wall and extrahepatic bile duct. The echoendoscope is stable in this position and the direction of puncture is upward toward the hepatic hilum. To prevent dislocation of the guidewire and dilator, an appropriate puncture site should be selected aiming at the extrahepatic bile duct between the upper margin of the pancreas and hepatic hilum. A one-step method with direct puncture of the extrahepatic bile duct may reduce the risk of guidewire dislocation, while the instruments are exchanged.

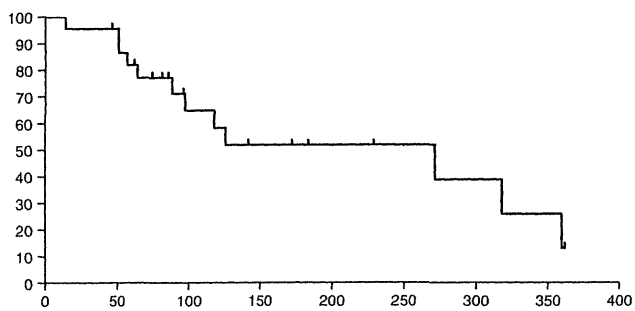

Figure 3. Stent patency by Kaplan-Meier.

Comparatively high rates of complications (15.7%) have been reported, including four cases of small focal bile peritonitis (7,12), three cases of pneumoperitoneum (8,10,14), and one case of hemobilia. However, all complications improved with conservative treatment. In this paper, severity of complications was assessed by National Cancer Institute—Common Toxicity Criteria Version 3.0. When we planned this study design, there were no systematic guidelines to assess the severity of complications by endoscopic procedures. Recently, guidelines for reporting endoscopic adverse events were published (19). Since then we have assessed the severity of complications by endoscopic procedures following the recent publication. When we reanalyzed the complications again by these new criteria, no severe complications were found. EUS-guided rendezvous technique is probably safe, but the success rate of drainage is comparatively low (20). We need to clarify the usefulness and indications of the direct choledochoduodenostomy vs. rendezvous in a future study.

We have previously reported long-term follow-up data on stent patency in patients who underwent EUS-CDS. The mean duration of stent patency was 211.8 days using Kaplan–Meier analysis (10). In our current prospective study, duration of patency was 272 days and longer than previously reported. We speculate that EUS-CDS can prevent stent clogging and tumor ingrowth and/or overgrowth by creating a fistula away from the obstructing tumor. Additionally, the stent used in EUS-CDS is significantly cheaper and can be exchanged, unlike metallic stents. Park *et al.* recently reported

Table 4. **Overview in the reported cases with EUS-guided choledochoduodenostomy**

Authors	Year	No. of cases	Device for puncture	Technical success (%)	Treatment success (%)	Initial stent (no. of cases)	Early complication (no. of cases)
Giovanini *et al.*	2001	1	NK(1)	1/1 (100)	1/1 (100)	10 Fr PS	None
Brumester *et al.*	2003	2	19G FT(2)	1/2 (50)	1/1 (100)	8.5 Fr PS	Bile peritonitis (1)
Puspok *et al.*	2005	5	NK(5)	4/5 (80)	4/4 (100)	7–10 Fr PS	None
Kahaleh *et al.*	2006	1	19G FN(1)	1/1 (100)	1/1 (100)	10mm MS	Pneumoperitoneum (1)
Yamao *et al.*	2006, 2006, 2008[a]	5	NK(5)	5/5 (100)	5/5 (100)	7–8.5 Fr PS	Pneumoperitoneum (1)
Ang *et al.*	2007	2	NK(2)	2/2 (100)	2/2 (100)	7 Fr PS	Pneumoperitoneum (1)
Fujita *et al.*	2007	1	19G FN(1)	1/1 (100)	1/1 (100)	7 Fr PS	None
Tarantino *et al.*	2008	4	19G,22G FN/NK(4)	4/4 (100)	4/4 (100)	PS[b]	None
Itoi *et al.*	2008	4	NK(2), 19G FN(2)	4/4 (100)	4/4 (100)	7 Fr PS (3), NBD (1)	Bile peritonitis (1)
Hanada *et al.*	2009	4	19G FN(4)	4/4 (100)	4/4 (100)	6–7 Fr PS	None
Park *et al.*	2009	4	19G FN/NK(4)	4/4 (100)	4/4 (100)	10mm CMS	None
Present study		18	NK(18)	17/18 (94)	17/17 (100)	7 Fr PS (2), 8.5 Fr PS (15)	*Bile peritonitis (2),* hemobilia (1)
Total		51		48/51 (94)	48/48 (100)		8/51 (15.7%)

CMS, covered metal stent; FN, fine needle; FT, fistolotome; MS, metal stent; NBD, nasobiliarydrainage; NK, needle knife; PS, plastic stent.
[a]Excluding the overlapping cases.
[b]Stent diameter is not described.

five cases of EUS-BD with one-step placement of a fully covered self-expandable metal stent (18). Although the follow-up periods were short (median: 6 months; range: 2–7 months), only one re-intervention was required because of stent migration. Longer stent patency using a fully covered metal stent can thus be expected.

In conclusion, we have reported the feasibility and efficacy of EUS-CDS among 18 patients in a prospective study design. Our results show high technical and functional success rates for the procedure. EUS-CDS is safe, feasible, and effective as an alternative to PTBD in cases with malignant lower biliary tract obstruction. Prospective randomized studies are needed in the near future to compare the efficacy and safety of EUS-CDS with EBD and EUS-rendezvous and EUS-guided hepatogastrostomy.

CONFLICT OF INTEREST

Guarantor of the article: Kazuo Hara, MD.

Specific author contributions: Revising the patient selection criteria and their clinical data, performing endoscopic procedures, assisting endoscopic procedures, and drafting the manuscript: Kazuo Hara, Kenji Yamao, Yasumasa Niwa, Akira Sawaki, Nobumasa Mizuno, Susumu Hijioka, Masahiro Tajika, Hiroki Kawai, Shinya Kondo, Yuji Kobayashi, and Kazuya Matumoto; planning of the work, revising conduction of the work, drafting the manuscript, and revising it critically for intellectual content: Vikram Bhatia; drafting the manuscript, analyzing and interpreting the data, and revising it critically for intellectual content: Yasuhiro Shimizu; planning of the work, revising conduction of the work, drafting and revising it critically for intellectual content, and the final approval of the version: Akihiro Ito, Yoshiki Hirooka, and Hidemi Goto.

Financial support: None.

Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Endoscopic ultrasound-guided biliary drainage (EUS-BD) has been introduced as an alternative to percutaneous transhepatic biliary drainage when endoscopic retrograde cholangiopancreatography is unsuccessful.
- ✓ A few case reports of EUS-choledochostomy (EUS-CDS) exist, but there is no prospective study to confirm the safety, feasibility, and efficacy of EUS-CDS.

WHAT IS NEW HERE

- ✓ We conducted a prospective study to evaluate the safety, feasibility, and efficacy of EUS-CDS in patients with malignant lower biliary tract obstruction.
- ✓ In a single-center prospective study, the technical success rate of EUS-CDS was 94% (17/18), and the functional success rate was 100% (17/17).
- ✓ Early complications were encountered in three (17%) patients, including focal peritonitis in two patients and hemobilia in one patient. No severe complications were seen.
- ✓ The stent patency was maintained for a comparatively long time, with median patency duration of 272 days by Kaplan–Meier analysis.

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CASE STUDY

Can EUS-guided FNA distinguish between gallbladder cancer and xanthogranulomatous cholecystitis?

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Background: EUS-guided FNA (EUS-FNA) is a useful modality for sampling various targets, but its applicability to gallbladder (GB) mass lesions is limited.

Objective: To determine the usefulness of EUS-FNA for diagnosing GB mass lesions.

Design: Single-center, retrospective, case-series study.

Setting: Tertiary-care referral center.

Patients: This study involved 15 consecutive patients who underwent EUS-FNA of GB mass lesions. We punctured GB masses in patients with suspected xanthogranulomatous cholecystitis to distinguish them from malignancy, and in patients with unresectable GB carcinoma for pathological confirmation. The final diagnosis was based on surgical histopathological results or follow-up outcome.

Interventions: EUS-FNA.

Main Outcome Measurements: Evaluation of EUS-FNA sampling adequacy rate and diagnostic yield.

Results: Xanthogranulomatous cholecystitis was suspected in 6 of the 15 patients. EUS-FNA revealed foam cells (n = 3), inflammatory cells (n = 1, proven by cholecystectomy), and GB carcinoma (n = 1), and the amount of the aspirate was insufficient in one case (xanthogranulomatous cholecystitis was later proven by extended hepatectomy). The mean follow-up period of the patients with xanthogranulomatous cholecystitis was 1177 days. Adenocarcinoma was confirmed by EUS-FNA in 8 of the 9 patients with suspected unresectable GB carcinoma, and the FNA was inconclusive in one. All 10 patients with GB carcinoma underwent chemotherapy. The overall sampling adequacy was 86.6%. The accuracy of EUS-FNA for detecting malignancy and for the final diagnosis was 93.3% (95% CI, 62.4%-99.9%) and 80% (95% CI, 54%-93.7%), respectively.

Limitations: A small patient cohort and a retrospective design with potential selection bias.

Conclusions: Malignant GB mass lesions can be safely and accurately differentiated by EUS-FNA. Thus, patients with xanthogranulomatous cholecystitis can avoid undue extensive surgery. (Gastrointest Endosc 2010;xx:xxx.)

Tissue samples from gallbladder (GB) mass lesions can be obtained through percutaneous image-guided (eg, transabdominal US and CT scanning) FNA and occasionally by open surgery.[1-5] The reported sensitivity and specificity of these modalities are >88% and nearly 100%, respectively. However, the performance characteristics of

Abbreviations: EUS-FNA, EUS-guided FNA; GB, gallbladder; LN, lymph node; XGC, xanthogranulomatous cholecystitis.

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TABLE 1. Detailed summary of 15 GB mass lesions

No.	Sex/age	Symptom	Clinical diagnosis	TNM	FNA aim	Location/EUS findings	Target‡	FNA passes	FNA result	Final	Confirmation	Clinical course
1	F/54	RUQ pain	XGC		Discrimination*	Fundus/homogeneous	GB	3	Ins	XCG	Operation	Alive at 1426 days
2	M/85	RUQ pain	XGC		Discrimination	Body-fundus/homogeneous high echo	GB	2	XCG	XCG	Observation	Alive at 562 days
3	F/77	Appetite loss	XGC		Discrimination	Neck/homogeneous	GB	2	XCG	XCG	Observation	Alive at 1465 days
4	F/57	Appetite loss	XGC		Discrimination	Neck-body/heterogeneous	GB	2	XCG	XCG	Observation	Alive at 951 days
5	M/57	RUQ pain	XGC		Discrimination	Body-fundus/homogeneous	GB	3	IC	XCG	Operation	Alive at 1481 days
6	F/73	Appetite loss	XGC		Discrimination	Body-fundus/heterogeneous	GB	1	GBC	GBC	Chemotherapy	Died at 177 days
7	F/59	Jaundice	GBC	T4N1M0	Evidence†	Neck-body/homogeneous	LN GB	3	GBC	GBC	Chemotherapy	Died at 1109 days
8	M/82	Jaundice	GBC	T4N1M1	Evidence	Neck-body/heterogeneous	LN GB	2	GBC	GBC	Chemotherapy	Died at 602 days
9	M/68	Appetite loss	GBC	T3N0M1	Evidence	Body/homogeneous	GB	3	Ins	GBC	Chemotherapy	Died at 706 days
10	M/51	RUQ pain	GBC	T4N2M0	Evidence	Fundus/heterogeneous	LN GB	3	GBC	GBC	Chemotherapy	Died at 60 days
11	F/81	RUQ pain	GBC	T4N2M1	Evidence	Body-fundus/heterogeneous	GB	1	GBC	GBC	Chemotherapy	Died at 82 days
12	F/67	RUQ pain	GBC	T4N2M1	Evidence	Body/heterogeneous	GB	1	GBC	GBC	Chemotherapy	Died at 1239 days
13	F/55	RUQ pain	GBC	T4N1M0	Evidence	Neck-body/homogeneous	GB	1	GBC	GBC	Chemotherapy	Alive at 126 days
14	M/82	Appetite loss	GBC	T3N0M1	Evidence	Neck/homogeneous	GB	1	GBC	GBC	Chemotherapy	Alive at 92 days
15	M/49	Jaundice	GBC	T4N1M0	Evidence	Neck-body/homogeneous	LN GB	2	GBC	GBC	Chemotherapy	Alive at 67 days

GB, Gallbladder; *TNM*, tumor/node/metastasis tumor staging; *F*, female; *RUQ*, right upper quadrant; *XGC*, xanthogranulomatous cholecystitis; *Ins*, insufficient; *M*, male; *IC*, inflammatory cells; *GBC*, gallbladder carcinoma; *LN*, lymph node.
*Discrimination between benign and malignant lesions.
†Evidence of malignancy before chemotherapy.
‡LN initially targeted; if failed, insufficient, or negative for carcinoma, GB mass lesion was then punctured.

percutaneous aspiration might be suboptimal for smaller GB lesions.[3,5,6-8] Moreover, percutaneous aspiration is associated with risks of abdominal pain (4.5%), bile peritonitis (1%-6%), and needle tract seeding.[7,8] Despite the established role of EUS-guided FNA (EUS-FNA) as a highly accurate tissue sampling modality for various lesions, with a very low complication rate,[9-12] its role in the context of suspected GB malignancies has not been elucidated.[1,2] EUS-FNA could potentially avoid these shortcomings of percutaneous aspiration of GB lesions. Therefore, we studied whether EUS-FNA could be used to differentiate GB mass lesions and diagnose clinically suspected GB malignancies.

PATIENTS AND METHODS

Between March 1997 and October 2009, 1850 EUS-FNA procedures were carried out at Aichi Cancer Center Hospital, Nagoya, Japan. Among these procedures, 51 (2.7%) were done for patients with GB mass lesions either by puncturing the GB mass itself or by targeting regional lymph nodes (LNs). The present study retrospectively included a subset of 15 consecutive patients (mean age 66.4 ± 12.7 years, 8 female) in whom EUS-FNA targeted the GB mass (Table 1).

Our rationale for using EUS-FNA in these patients was to obtain histological evidence of malignancy in clinically suspected, unresectable GB carcinoma and to distinguish between benign and malignant masses when xanthogranulomatous cholecystitis (XGC) was suspected. This clinical diagnosis was suspected after investigation by CT scanning and abdominal US. However, to definitively reach a diagnosis based on imaging features alone was difficult. When a GB mass with an enlarged, regional, intra-abdominal LN was found, we punctured the LN first. If enlarged LNs were not evident, were difficult to puncture (eg, para-aortic location), or the FNA yield from the LN was negative, we punctured the GB mass lesion itself (Fig. 1).

Study procedure

All patients underwent EUS-FNA with a convex array echoendoscope (GF−UCT240; Olympus Optical Corp Ltd, Tokyo, Japan) connected to an US scanning system (SSD 5500; Aloka, Tokyo, Japan). All FNA procedures were performed by using 22-gauge needles (NA-10J-1, NA-10J-KB, NA-11J-KB, or NA-200H-8022; Olympus Medical System Corp Ltd, Tokyo, Japan). Patients were followed-up for 48 hours after the procedure for any procedure-related complications. Cytological samples were processed and analyzed according to established methods of EUS-FNA aspirate processing.[10,13,14] All samples were interpreted through on-site cytological evaluation and by the same experienced cytopathologists (W.H., Y.Y.). Our institu-

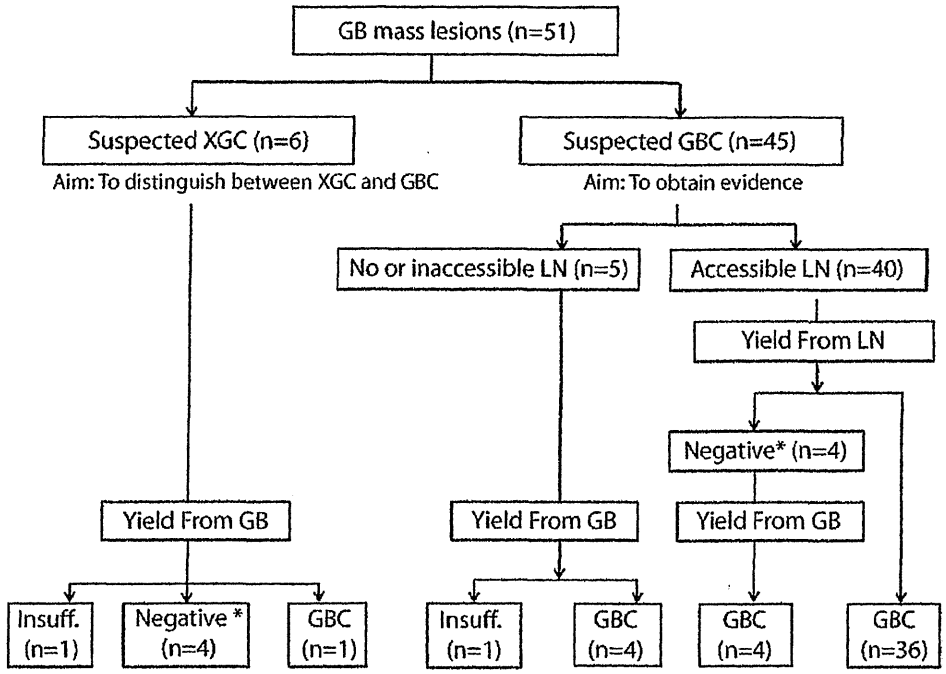

Figure 1. Schematic diagram of a gallbladder mass lesion and EUS-guided FNA yield. *GB*, gallbladder; *XGC*, xanthogranulomatous cholecystitis; *GBC*, gallbladder carcinoma; *LN*, lymph node; *insuff*, insufficient aspirate.

tional review board approved this study. Our main outcome measures were (1) the sampling adequacy rate and (2) the diagnostic yield of EUS-FNA.

Statistical analysis

We used frequencies, proportions (%), and means for descriptive analyses where appropriate. The χ^2 test (with Yates correction) was used as a univariate analysis for comparative statistics. The results of EUS-FNA were compared with the clinical follow-up or with histopathological results obtained after surgical resection. Lesions defined as malignant by EUS-FNA and finally diagnosed as malignant were considered true positive, and lesions defined as malignant by EUS-FNA and finally diagnosed as benign were considered false positive. Likewise, lesions initially categorized and finally diagnosed by EUS-FNA as benign were considered true negative, and lesions initially categorized as benign by EUS-FNA and finally diagnosed as malignant were considered false negative.

RESULTS

The main cause of referral was right upper quadrant pain in 7 patients (46.7%), loss of appetite in 5 patients (33.3%), and obstructive jaundice in 3 patients (20%). Detailed clinical features of these 15 patients are listed in Table 1.

Evaluation of the EUS findings from 51 GB masses (XGC, n = 5; GB carcinoma, n = 46) revealed that only the presence of regional LNs and a disrupted mucosal lining favored a diagnosis of GB carcinoma (Table 2).

TABLE 2. EUS features of XGC and GBC

EUS findings	XGC (n = 5) no. patients (%)	GBC (n = 46) no. patients (%)	*P* value*
Gallbladder			
Focal thickening	1 (20)	7 (15.2)	.7 (NS)
Diffuse thickening	4 (80)	39 (84.8)	
Mucosal line			
Continuous	3 (60)	5 (10.8)	.02
Disrupted	2 (40)	41 (89.1)	
Intramural hypoechoic nodule	3 (60)	12 (26.1)	.2 (NS)
Gallstone	4 (80)	16 (34.8)	.1 (NS)
Lymph node swelling	0 (0)	40 (87)	.0001

XGC, Xanthogranulomatous cholecystitis; *GBC*, gallbladder carcinoma; *NS*, not significant.
*χ^2 test with Yates correction.

A total of 19 punctures (GB masses, n = 15; regional lymphadenopathy, n = 4) were performed in 15 patients with GB masses. The sample adequacy rate for cytological evaluation was 13 of 15 (86.6%; 95% CI, 60.8%-97.5%).

Clinically suspected XGC could not be differentiated from malignancy, and regional lymphadenopathy was un-

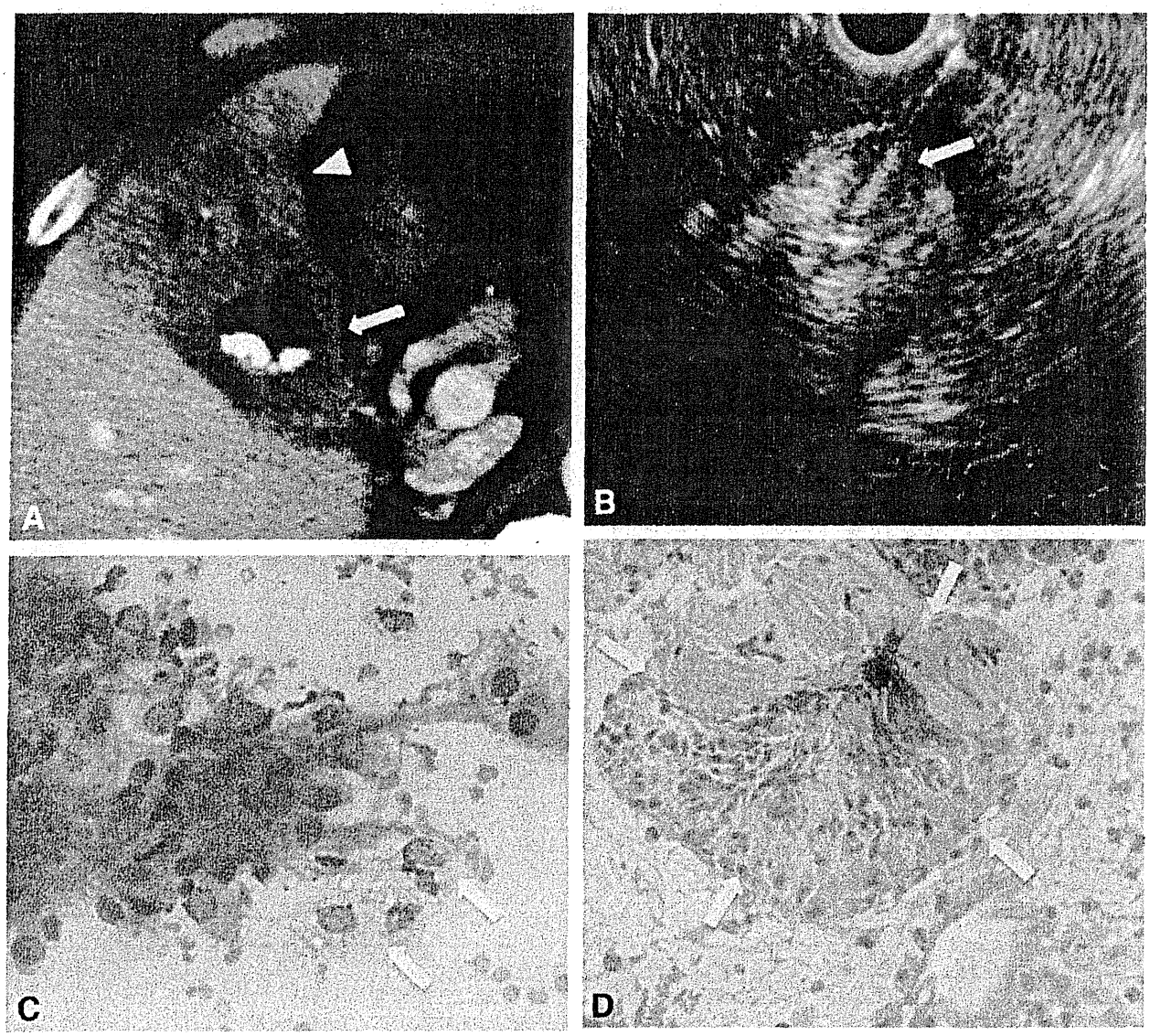

Figure 2. Findings of CT scans and EUS-guided FNA of xanthogranulomatous cholecystitis from patient 5. **A,** Abdominal CT scan shows the diffuse, irregular wall of a thickened gallbladder (*arrow*) with gall stones and irregular, low-density areas in the liver (*arrowhead*). **B,** EUS-guided FNA for a gallbladder mass lesion. The arrow shows the FNA needle inside the lesion. **C,** Foam cells in an FNA-cytology specimen (*arrow*) (Diff-Quik, orig. mag. ×400). **D,** Aggregates of foamy macrophages in cell block sections (*arrow*) (H&E, orig. mag. ×400). These were diagnosed as xanthogranulomatous cholecystitis.

detectable in 6 lesions. Among these, EUS-FNA sampling was inconclusive in 1 patient who underwent surgery (extended right lobe hepatectomy with bile duct resection, transverse colectomy, and partial duodenal resection) because of concerns about GB carcinoma, but XGC was confirmed in the resected specimen. The presence of typical foam cells in 3 patients and inflammatory cells in 1 led to a presumptive EUS-FNA diagnosis of XGC. The presumptive diagnosis was confirmed at follow-up in the 3 patients with foam cells and by simple cholecystectomy for coexistent GB stones in the other with inflammatory cells (Fig. 2). Although XGC with a liver abscess was clinically suspected in the remaining patient, EUS-FNA revealed GB carcinoma. Unresectable GB carcinoma was suspected in another 9 patients, and the aim of puncture was to obtain pathological evidence of malignancy before chemotherapy. Intra-abdominal regional lymphadenopathy was detected in 7 of these patients (4 LNs were punctured, and 3 were too small for puncture). These 4 LN punctures were negative for malignancy, and, hence, the GB mass itself was punctured (Fig. 3). Sampling was sufficient in 8 patients in whom GB carcinoma was diagnosed and yielded only atypical cells from 1 patient that were insufficient to establish a conclusive diagnosis (considered as false negative). This patient was further treated, based on the overall clinical and imaging profile, as having GB carcinoma. All patients with GB carcinoma (n = 10) received chemotherapy. No serious procedure-related com-

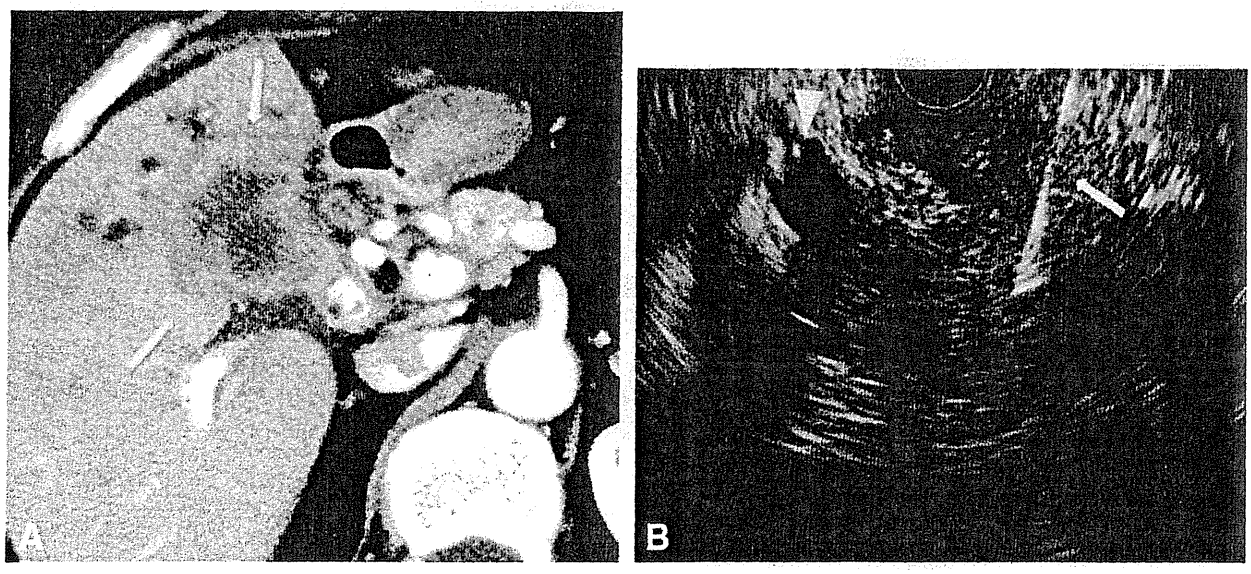

Figure 3. Findings of CT and EUS-guided FNA of gallbladder carcinoma from Patient 13. **A,** A CT image shows diffuse, irregular wall thickening and the disrupted mucosal line of the gallbladder (*arrow*). **B,** EUS-guided FNA for a gallbladder mass lesion (*arrow*, FNA needle inside the lesion; *arrowhead*, the gallbladder lumen).

plications developed in any of the 15 patients within the initial 48 hours. With regard to delayed complications, patients with XGC were followed-up as outpatients at regular intervals, and all those with GB carcinoma were followed-up as outpatients every 1 to 2 weeks for chemotherapy. No serious procedure-related delayed complications developed. The diagnostic accuracy of EUS-FNA to correctly distinguish between benign and malignant masses was 93.3% (14/15; 95% CI, 62.4%-99.9%), with a sensitivity and specificity of 90% (95% CI, 57.4%-99.9%) and 100% (95% CI, 51.9%-100%), respectively. Only one EUS-FNA result was a false negative because of insufficient sampling from unresectable GB carcinoma, and none of the results were false positive (Table 3).

The overall EUS-FNA diagnosis was concordant with the final diagnoses in 12 lesions (accuracy 80%; 95% CI, 54%-93.7%). Among the 3 discordant false-negative results, the EUS-FNA yield was insufficient, and only atypical cells or only inflammatory cells were found in one sample each.

TABLE 3. Diagnostic yield of EUS-guided FNA: benign versus malignant

	Final diagnosis	
	Benign	**Malignant**
EUS-guided FNA diagnosis		
Benign	5 (TN)	1* (FN)
Malignant	0 (FP)	9 (TP)
Total	5	10

TN, True negative; *FN*, false negative; *FP*, false positive; *TP*, true positive; *XGC*, xanthogranulomatous cholecystitis.
Five TNs comprised XGC (n = 4) and insufficient aspirate (n = 1).
*Atypical EUS-guided FNA diagnosis of one FN.

DISCUSSION

EUS-FNA is an established diagnostic tool for obtaining tissue samples from diverse types of lesions. Although EUS has the potential for staging GB masses, it has not been adequately evaluated in the context of GB mass lesions. Only 3 reports have been published. Jacobson et al[1] reviewed 6 patients (GB carcinoma, n = 5; XGC, n = 1) with an 83% accuracy rate. Varadarajulu and Eloubeidi[2] also studied 6 patients (GB carcinoma, n = 5) and achieved 100% sampling adequacy. Meara et al[15] punctured 7 GB mass lesions and obtained 100% specificity and 80% sensitivity. Our sampling adequacy was 86.6% with only 2 insufficient samples. Our approach was to distinguish between benign and malignant masses, especially those that were XGC, because the malignant potential of this lesion cannot be conclusively ruled out based on imaging alone.[16,17,18-20] One of 6 XGC punctures yielded an insufficient aspirate, and the patient underwent extended right hepatectomy, transverse colectomy, and partial duodenal resection. The other 5 patients avoided surgery or at least major resections after EUS-FNA, which justifies the use of EUS-FNA when XGC is suspected. Another point is that coexisting carcinomas cannot be ruled out, because they have been identified in 2% to 15% of patients with XGC.[21-23] Notably, most GB carcinoma associated with XGC occurs in the GB neck region,[20-22] which is thought to be due to increased pressure within the GB. Therefore, we