



EUS-guided portal vein interventions

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The American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee provides reviews of existing, new, or emerging endoscopic technologies that have an impact on the practice of GI endoscopy. Evidence-based methods are used, with a MEDLINE literature search to identify pertinent clinical studies on the topic and a MAUDE (Food and Drug Administration Center for Devices and Radiological Health) database search to identify the reported adverse events of a given technology. Both are supplemented by accessing the “related articles” feature of PubMed and by scrutinizing pertinent references cited by the identified studies. Controlled clinical trials are emphasized, but in many cases data from randomized controlled trials are lacking. In such cases, large case series, preliminary clinical studies, and expert opinions are used. Technical data are gathered from traditional and Web-based publications, proprietary publications, and informal communications with pertinent vendors. Reports on emerging technology are drafted by 1 or 2 members of the ASGE Technology Committee, reviewed and edited by the committee as a whole, and approved by the Governing Board of the ASGE. When financial guidance is indicated, the most recent coding data and list prices at the time of publication are provided. For this review, the MEDLINE database was searched through September 2016 for relevant articles by using the key words “portal vein,” “endoscopic ultrasound,” “vascular intervention,” and “portal hypertension.” Reports on emerging technologies are scientific reviews provided solely for educational and informational purposes. Reports on emerging technologies are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment or payment for such treatment.

EUS combines real-time imaging and minimally invasive therapeutic capabilities. Vascular access and therapy are an emerging application for EUS-based interventions.¹ The proximity of vessels to the GI tract enables detailed visualization and an alternative port of entry to conventional femoral, jugular, or subclavian approaches.^{1,2} EUS, with its unique view and access to the portal vein (PV), has the potential to expand our diagnostic and therapeutic armamentarium in both benign and malignant conditions. Previous studies have confirmed the feasibility of EUS-guided PV imaging and access.³⁻⁸

This document reviews the various potential applications for EUS-guided PV interventions including staging of hepatocellular carcinoma, sampling PV blood for circulating tumor cells in pancreaticobiliary malignancies, targeted drug delivery to the liver, PV angiography and pressure measurement, creation of portosystemic shunts, and selective PV embolization in patients with liver metastases, as shown in [Table 1](#).

POTENTIAL APPLICATIONS

EUS-guided FNA of PV thrombosis for staging of hepatocellular carcinoma

Tumor invasion into the PV by direct extension or metastasis portends poor prognosis in hepatocellular carcinoma and precludes curative resection or liver transplantation.^{9,10} Sonography may be useful in distinguishing a bland thrombus from a tumor thrombus by detecting abnormal vascular flow patterns within the lesion by using various duplex Doppler modes.^{11,12} However, cytopathologic confirmation by FNA is desirable, given its implications for further management. Sampling of a PV thrombus with transabdominal US guidance may lead to erroneous results because of inadvertent inclusion of normal hepatocytes or associated liver masses.¹² Further, potential adverse events of transabdominal PV sampling include serious biliary or vascular injury. EUS-guided FNA (EUS-FNA) of PV thrombi represents an alternative approach that may overcome these limitations. EUS may be particularly suited for access to the extrahepatic PV, thus avoiding the need for a

TABLE 1. EUS-guided PV interventions

Hepatic and pancreaticobiliary malignancies	
EUS-FNA of PV tumor thrombus (human studies)	
Sampling of circulating tumor cells in PV (human studies)	
EUS-guided PV injection of chemotherapy (animal studies)	
Selective PV embolization (animal studies)	
Portal hypertension	
PV pressure measurement (human studies)	
EUS-guided intrahepatic portosystemic shunt (animal studies)	

PV, Portal vein; EUS-FNA, EUS-guided FNA.



Figure 1. Portal vein thrombus detected by EUS.

transhepatic approach and resultant hepatocellular carcinoma sampling that may lead to a false-positive cytology interpretation. Successful transduodenal EUS-FNA of malignant PV thrombi by using 25G needles has been reported without adverse events (Fig. 1).¹¹⁻¹⁴ Case reports have described the diagnosis of hepatocellular carcinoma by EUS-FNA of malignant PV thrombi in patients with no hepatic mass visualized on cross-sectional imaging.^{11,12}

EUS-guided PV sampling of circulating tumor cells in pancreaticobiliary cancers

Circulating tumor cells (CTCs) disseminate from the primary tumor through the vasculature to distant sites while maintaining traits similar to those of the tumor of origin.¹⁵ CTCs have been reported to facilitate the metastasis of many solid tumors, including pancreatic cancer, and are potentially detectable even before the appearance of the primary tumor.^{15,16} Although CTCs are detected frequently in peripheral blood in the setting of some malignancies (eg, advanced prostate or breast cancer), they are inconsistently detected in the peripheral blood in patients with pancreaticobiliary cancers, possibly because of sequestration in the portal circulation and subsequent hepatic filtration.¹⁷ Indeed, PV CTCs were detected in the majority of 60 patients undergoing pancreaticoduodenectomy for resectable pancreatic or periampullary cancer, and the PV CTC burden was found to predict the future development of liver metastases.¹⁸ Further, PV CTCs may be used for molecular

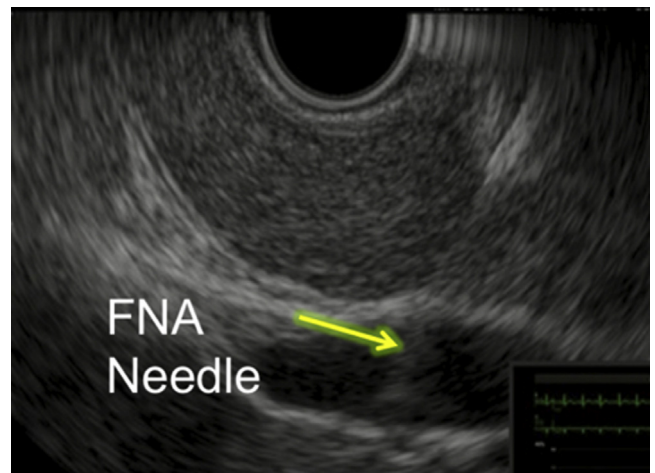


Figure 2. Transhepatic access of the portal vein with a 19G needle to aspirate blood for circulating tumor cell analysis. This image was originally published with a Creative Commons Attribution-NonCommercial-No Derivatives License.²⁸

characterization of pancreaticobiliary cancers and metastases; as such, enumerating CTCs and performing mutational analyses may inform prognostic stratification and therapeutic decision making.¹⁶ Because CTCs are considered to be reflective of the tumor signature, they may serve as source material for tumor cell lines, human tumor xenografts, and organoids to test therapeutic regimens and evaluate drug resistance mechanisms.¹⁹

A single-center prospective study reported the safety and feasibility of EUS-guided sampling of PV blood in 18 patients with metastatic and nonmetastatic pancreatic and biliary cancers to evaluate for CTCs.¹⁶ Under EUS guidance, a 19G needle was advanced transhepatically into the PV, and 2 to 4 aliquots of 7.5 mL of blood were aspirated, with no adverse events observed (Fig. 2). CTCs were detected in the PV in all 18 patients (100%) whereas CTCs were detected in peripheral blood samples in 4 of 18 patients (22%). The mean (\pm standard deviation) number of PV CTCs was 118.4 (\pm 36.8) per 7.5 mL, compared with a mean of 0.8 \pm 0.4 CTCs per 7.5 mL in peripheral blood ($P < .01$). Thus, EUS-guided sampling of PV blood for CTC analysis appears feasible and safe.

EUS-guided portal injection chemotherapy by using drug-eluting microbeads

Management options for patients with diffuse liver metastases usually are limited to palliative systemic chemotherapy. Systemic toxicities limit maximum tolerated drug doses and may result in suboptimal hepatic tissue levels, underscoring the need for strategies that target hepatic delivery and limit adverse events. Transarterial microbead injection into the hepatic artery results in high hepatic drug levels and low systemic levels, but there is a risk for ischemic biliary strictures, because the bile duct receives its blood supply from the hepatic artery. EUS-guided PV injection of chemotherapy (EPIC) by using drug-eluting

microbeads or nanoparticles was successfully demonstrated in 24 anesthetized pigs.²⁰ In this study, EPIC was performed with irinotecan-loaded microbeads, doxorubicin-loaded microbeads, and albumin-bound paclitaxel nanoparticles. With all 3 agents, significantly higher hepatic drug levels and significantly lower systemic drug levels were observed.²⁰ Although further evaluation of this technique is warranted, this study demonstrated that EPIC is feasible in a nonsurvival animal model. It also may be possible to use this technique for primary liver malignancies, such as hepatocellular carcinoma.

Selective PV embolization

Selective embolization of the right or left branch of the PV to produce a compensatory hypertrophy of the contralateral hepatic lobe before resection for hepatic malignancy has been described.²¹ Preliminary results from an animal model suggest EUS-guided microcoil embolization of the right PV can produce intended hypertrophy of the left hepatic lobe.²¹ In a related proof of concept study, Matthes et al²² injected an ethylene-vinyl alcohol copolymer into the main PV of a Yorkshire pig, resulting in an immediate increase in PV pressure from a baseline of 3 mm Hg to 15 mm Hg, and a solid thrombus in the main PV with extension into the left PV was noted at necropsy on day 7.

PV pressure measurement

PV pressure measurement provides vital information that assists in the diagnosis and management of portal hypertension. Direct percutaneous transhepatic portal pressure measurement is fraught with technical challenges and risk for adverse events and is thus not routinely performed. Instead, indirect pressure measurements derived from a wedged hepatic portal vein pressure gradient serve as a surrogate for portal pressure. The wedged hepatic portal vein pressure gradient may not reliably reflect the actual portal pressure, particularly for the pre-hepatic and post-hepatic etiologies of portal hypertension.

EUS has been used to study hemodynamic changes in portal hypertension, including PV flow, vessel dilation, and the development of collaterals.²³ EUS also may facilitate the direct monitoring of PV pressure and has been evaluated extensively in animals and in a preliminary human study. Direct EUS-guided PV pressure measurement by using a 22G needle advanced into the extrahepatic PV was initially reported by Lai et al.⁶ The investigators successfully obtained PV pressure measurements in 18 of 21 (86%) anesthetized farm swine by using a fluid-filled manometer and pressure recorder attached to the proximal end of the needle. Reported challenges included the small caliber of the FNA needle and difficulty in maintaining a stable needle position within the PV.⁶ In another study, transhepatic PV catheterization by using a modified ERCP catheter was used to obtain continuous portal pressure readings



Figure 3. A compact manometer for portal pressure measurement used in the study by Huang et al.²⁴

in a porcine model (n = 3).³ Consistent results and minimal variability were noted within each animal; animal respiration and endoscope movement did not affect catheter position. Successful and reproducible EUS-guided portal pressure measurements by using a digital pressure wire (Pressure Wire Aeris; St. Jude Medical, St. Paul, Minn) advanced through a 22G needle were reported in 5 Yorkshire pigs.⁸ EUS-guided measurement of the portal pressure gradient (the pressure difference between PV and hepatic vein [HV]) was reported by using a 25G needle and a small battery-operated manometer; the left PV, right HV, and intrahepatic inferior vena cava were accessed in 3 Yorkshire pigs to obtain these measurements.⁵

In the first human pilot study, 28 participants with a history of liver disease or suspected cirrhosis underwent EUS-guided portal pressure gradient measurement by using a 25G FNA needle and a new compact manometer (Cook Medical, Bloomington, Ind) (Fig. 3).²⁴ The EUS examinations were coupled with a routine EGD examination and were variably performed with moderate sedation or general anesthesia with patients in a supine position. Measurements were recorded in the intrahepatic PV near its bifurcation and in the HV approximately 2 cm from its takeoff from the intrahepatic inferior vena cava (or directly from the intrahepatic inferior vena cava when HV access was not

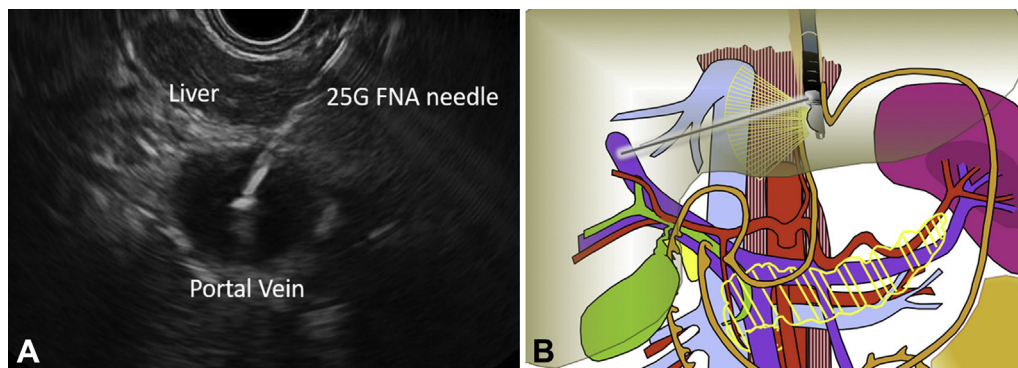


Figure 4. A, Linear EUS view of left portal vein. B, Illustrated view of left portal vein accessed with a 25G needle for pressure measurement.²⁴

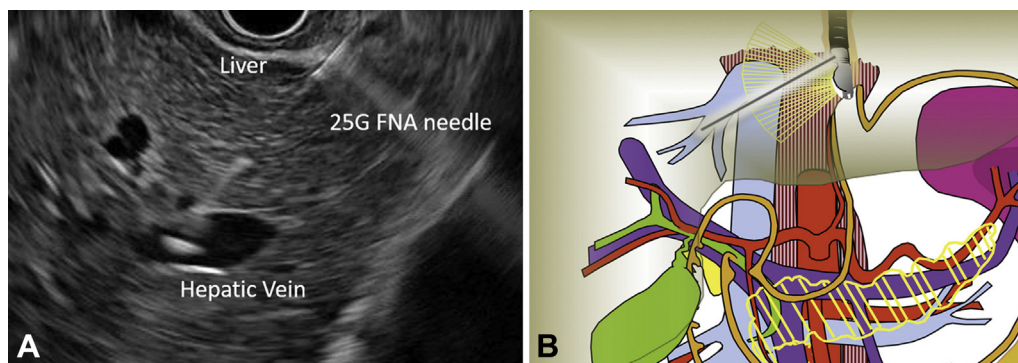


Figure 5. A, Linear EUS view of left hepatic vein. B, Illustrated view of left hepatic vein accessed with a 25G needle for pressure measurement.²⁴

possible) (Figs. 4 and 5). Measured portal pressure gradients correlated well with clinical parameters of portal hypertension (eg, varices, portal hypertensive gastropathy), and no adverse events were noted.²⁴

Intrahepatic portosystemic shunt

Transjugular intrahepatic portosystemic shunting, which involves creation of a low-resistance channel between the PV and HV, is typically performed under angiography and is a common procedure to decompress the portal system. Transjugular intrahepatic portosystemic shunting has been associated with adverse events including cardiac arrhythmias as well as inadvertent biliary or arterial injury.²⁵ EUS-guided creation of an intrahepatic portosystemic shunt may offer an alternative approach.^{25,26} In a study of 10 anesthetized pigs, the left HV and the left PV were visualized with a linear echoendoscope positioned in the stomach and were sequentially punctured with a 19G FNA needle.²⁶ A 0.035-inch guidewire was advanced through the needle into the left PV, and a 6 to 10 mm × 40 to 80 mm uncovered metal biliary stent (Zilver; Cook Endoscopy, Winston-Salem, NC) was advanced over the guidewire and deployed with its distal end inside the left PV and

proximal end in the left HV under sonographic and fluoroscopic guidance (Fig. 6).²⁶ In 4 of 10 pigs, a second stent was required to fully bridge the distance between the PV and HV. Eight animals immediately euthanized after intrahepatic portosystemic shunt creation showed no evidence of bleeding or hematoma at necropsy. Two animals kept alive for 2 weeks after the procedure appeared healthy and without distress and at necropsy had no evidence of bleeding, peritonitis, or stent migration. Two groups have reported use of a fully covered lumen-apposing metal stent to create an intrahepatic portosystemic shunt in a live swine model by using a similar technique.^{25,27} In 1 of these studies, 3 of 5 animals were noted to have partial in-stent thrombosis at necropsy 2 weeks after the procedure.²⁵ These early investigations suggest that intrahepatic portosystemic shunt creation is feasible, but further refinement of devices and techniques is needed.

AREAS FOR FUTURE RESEARCH

The ability of EUS to access the PV potentially enables a broad spectrum of diagnostic, staging, and therapeutic

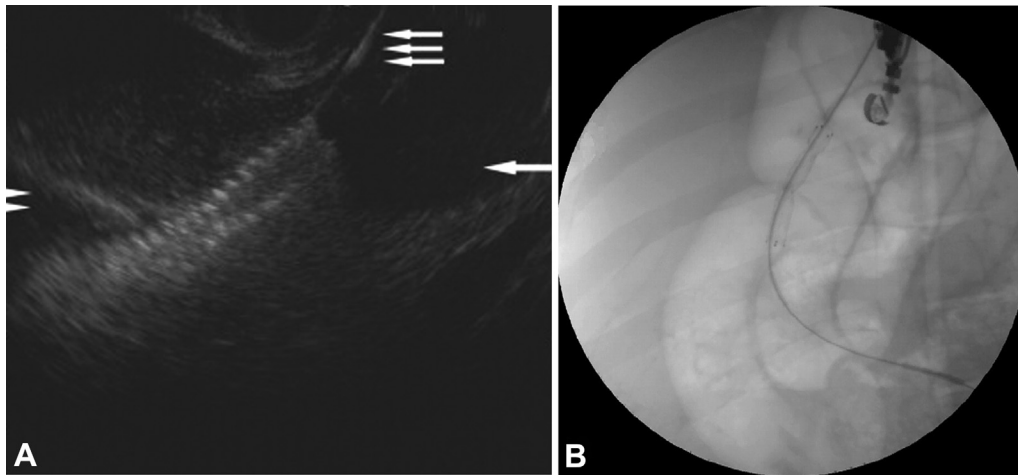


Figure 6. **A**, Linear EUS view of a metal stent creating an intrahepatic portosystemic shunt. Note the proximal end of the stent in the left hepatic vein (1 arrow), the distal end of the stent in the left portal vein (2 arrows), and the guidewire (3 arrows). **B**, Fluoroscopic view of fully deployed stent.²⁶

interventions. Further evaluation of the safety profile of EUS-guided PV interventions will be crucial in determining the eventual clinical adoption of these techniques. Future studies should better define the incidence and clinical outcomes of PV thrombosis and other adverse events related to these interventions and evaluate possible prophylactic measures (eg, antibiotics to prevent infection) and variations in techniques to minimize adverse outcomes. In addition, the development of new devices specifically designed to facilitate EUS-guided vascular interventions is needed. For those EUS-guided PV interventions that are sufficiently mature to currently warrant ongoing evaluation in humans, additional data are needed to refine techniques and establish indications and efficacy.

PV sampling to detect CTCs appears to be a potentially useful advance in the evaluation and management of patients with pancreatic and biliary cancers. However, a more robust experience with the diagnostic and prognostic utility of CTCs in these patients is needed to determine whether this technique will fulfill its promise.¹⁵ Additionally, mechanisms of detecting peripheral blood CTCs are evolving rapidly, and if these technologies improve, the incremental value of PV sampling will need to be re-evaluated.

EUS-guided PV injection of chemotherapeutic agents is a promising therapeutic technique. However, there are several aspects that require further study. Drug delivery mechanisms (microbeads) that are specifically designed for this approach and are preferably biodegradable need to be developed. In addition, the biocompatibility of these delivery mechanisms should be broad enough to enable the delivery of various medications depending on the malignancy. Phase I human clinical trials should be conducted in patients with liver metastases once these logistic challenges are overcome. The human clinical trials should address the relative toxicity

and efficacy of PV injection compared with systemic therapy.

Direct measurement of PV pressure with EUS guidance represents a novel approach. Well-designed, comparative trials to determine the accuracy and safety of this technique compared with transjugular pressure measurements are essential. The creation of an EUS-guided portosystemic shunt is a new frontier in therapeutic EUS that has recently been described. Future studies should be focused on refining and standardizing the technique in animal models and performing feasibility studies in humans.

SUMMARY

EUS-guided PV access and therapeutic interventions represent an exciting new technical advance in interventional EUS. Several technical applications have been shown to be feasible in animal models and in small, preliminary human studies. For this field to continue to advance, well-designed studies will be needed to establish the efficacy and safety profile of these interventions, particularly in comparison to any current competing techniques. The development of devices specifically designed and approved for these applications is critical. Although EUS-guided PV interventions remain largely investigational at present, they represent a promising new frontier with the potential to enhance diagnostic and therapeutic capabilities in patients with pancreaticobiliary malignancies and portal hypertension.

DISCLOSURES

M. Bhutani is on the global advisory board of Medi-Globe, Inc. N. Thosani is a consultant for Boston Scientific and Mederi Inc. U. Navaneethan is a consultant for AbbVie and Janssen and is on the speaker bureau for

Takeda. M. Parsi is a consultant for Boston Scientific. All other authors disclosed no financial relationships relevant to this publication.

Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; CTC, circulating tumor cells; EPIC, EUS-guided PV injection of chemotherapy; EUS-FNA, EUS-guided FNA; HV, hepatic vein; PV, portal vein.

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