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Development and validation of a novel porcine bile duct dilation model for EUS training

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ABSTRACT

Background and study aims Image-guided minimally invasive techniques have transformed the management of malignant and benign bile duct obstructions. These evolving techniques are being widely adopted and applied and hands-on training using high quality models is required to improve the proficiency of practitioners. This experimental study aimed to validate an in vivo porcine model created to simulate bile duct dilation for interventional endoscopic ultrasound (EUS) hands-on training curriculums.

Materials and methods Thirty-six porcine models were involved and the procedures were performed in an experimental hybrid operating room under general anesthesia. Animals underwent endoscopic duodenal papilla clipping with several hemostatic metallic clips. After a survival period of 24 to 48 hours, the models with effective intrahepatic and extrahepatic bile duct dilatation were included in the hands-on training. Trainees and faculty were given structured evaluations of the model realism and usefulness.

Results Extrahepatic bile duct and gallbladder dilation was achieved in all 36 of the models, and in 11 of the 36 models, a treatable intrahepatic duct dilatation was achieved. During the hands-on training, EUS-guided biliary drainage, EUS-guided transgastric gallbladder drainage, and EUS through-the-needle microbiopsy forceps procedures were feasible. Overall, 75 % of the experts and trainees evaluated the training as excellent.

Conclusions We present a minimally invasive, reliable and time- effective model of extrahepatic dilation suitable for interventions. The model was less effective for intrahepatic ducts, which should be considered if intrahepatic biliary dilation is required for training.

Introduction

Hepatobiliary and pancreatic malignant and benign diseases can lead to bile duct outflow restriction that requires a diagnostic or therapeutic intervention. While these interventions can be performed with surgery or percutaneous image-guided approaches, endoscopic ultrasonography (EUS) is playing an increasingly important role in both diagnosis and treatment. EUS interventions for bile duct and gallbladder dilation, such as drainage, stenting, biopsy, and others, are now widely used and have been proven to be effective, particularly after failed endoscopic retrograde cholangiography (ERCP) [1]. For instance, malignant hepatobiliary diseases affecting the biliary tract are highly prevalent. In 2020 alone in the United States, 42,810 people were diagnosed with liver cancer and intrahepatic bile duct cancer, another 11,980 had gallbladder cancer or extrahepatic biliary tract cancers, an estimated 60,430 people were diagnosed with pancreatic cancer; in 2021, approximately 48,220 people were expected to die from the disease [2]. Benign diseases affecting the bile ducts, such as strictures, lithiasis, and non-malignant stenosis caused by postoperative injury after cholecystectomy and pancreatitis, are common as well

[3]. EUS provides excellent visualization of the organs near the duodenum and stomach, including the liver, pancreas, bile ducts (intrahepatic, extrahepatic), and the gallbladder, providing a diagnostic and therapeutic opportunity without the need for radiation exposure.

Unfortunately, interventional EUS is difficult to learn and master due to scarce training and the need for extensive manual skill and image interpretation practice. There is increasing recognition that simulation and laboratory practice is needed for acquisition and refinement of the skills [4]; however, this is technically challenging as well due to lack of appropriate training models, particularly for interventional procedures like fine-needle aspiration biopsy, drainage, and stenting [5–7]. The use of animal models while expensive, is probably the best alternative to practicing on humans, as to date, useful virtual reality simulators for EUS do not exist. The creation of bile duct models in animals for training using methods such as laparoscopic common bile duct (CBD) ligation [8, 9], endoscopic papilla clipping [10], endobiliary radiofrequency ablation [11], and peroral cholangioscopy [12] has been described, but they have several shortcomings. Some require invasive and morbid surgery, long survival times, proprietary and hard-to-access equipment or result in poor or inconsistent dilatation. The ideal training or research model would be reproducible, very minimally invasive, use commonly available equipment, require a very short survival time, and result in adequate intrahepatic and extrahepatic duct dilatation. We describe our minimally invasive solution for the creation of such a model, along with its validation during interventional endoscopic ultrasound (EUS) hands-on training curriculums (so-called ITEC).

Materials and methods

Survival porcine models

Thirty-six large white pigs (Sus scrofa domesticus), mean weight 45 to 55 kg, were used as live animal models. They were handled according to the European Directive 2010/63 and French laws concerning animal protection in laboratories. Procedures were approved by the local Ethical Committee and authorized by the French Ministry of Education, Research and Innovation under protocol notification N° 16259–2018072416083965 v1.

The pigs were housed in a group and acclimatized for 48 hours in an enriched environment, respecting circadian cycles of light-darkness, and with constant humidity and temperature conditions. They were fasted 24 hours before the intervention, with ad libitum access to water, and finally sedated (zolazepam + tiletamine 10 mg/kg intramuscularly) 30 minutes before the procedure to decrease stress; no intubation was required for the first procedure. Following the endoscopic biliary papilla clipping procedure, the pigs recovered from the anesthesia and were housed again during a survival period of 24 to 48 hours to achieve bile duct dilatation.

Before the hands-on training, the sedation protocol above was repeated and general anesthesia was induced using intravenous (IV) (18G IV catheter in-ear vein) propofol 3 mg/kg, followed by orotracheal intubation and maintained with rocuronium 0.8 mg/kg along with inhaled isoflurane 2 %. At the end of the training, the animals were euthanized with an IV injection of pentobarbital 40 mg/kg IV (Exagon ND, Axience). To maximize the use of the animals, usable organs are harvested for other teaching or research purposes.

Hybrid operating room, equipment, and tools

The study was conducted in the experimental hybrid operating rooms of the IHU-Strasbourg.

A standard adult colonoscope (Karl Storz GI, Silver Scope series) was employed to perform the endoscopic duodenal papilla clipping protocol. For bile duct dilation assessment, a computed tomography (CT) contrast-enhanced scan was performed just before the training session. (CT Scanner, Siemens Healthineers, Germany). During the hands-on training sessions, a video processor with an EG38-J10UT echoendoscope (Pentax, Medical Europe), ultrasound console Arrieta V70 (Hitachi Medical Europe), and Cios Fusion mobile C-Arm (Siemens Healthineers, Germany) were used. All animals were under general anesthesia during experiments and euthanized at the end of the hands-on training session.

Study design

The study had a first feasibility phase using eight survival pigs to develop the protocol and assess its safety and efficacy. This was then validated in 20 pigs during four interventional EUS training sessions from October 2018 to February 2020. A written survey to assess the quality of the model was administered to the faculty trainers during the hands-on training sessions.

Endoscopic duodenal papilla clipping protocol

All pigs were positioned in left lateral decubitus under general anesthesia. The endoscopic duodenal papilla clipping was performed by senior endoscopists. A standard colonoscope with a 3.8-mm working channel was used (Karl Storz GI, Silver Scope series), the scope was advanced to the duodenum, and once the major biliary papillae were reached (located at 6 o'clock just past the pylorus), four to six clips were used to occlude the papilla. Clips were placed both to close the ampullary orifice (2–3 clips) and to compress the intramural portion of the common duct (1–2 clips). The clips were positioned at 90 degrees (perpendicular) to the duodenal papilla wall, with the sequence of clipping starting with the occlusion of the papilla exit, then left and right of the first clip, and finally, the CBD wall. After the endoscopic procedures, the pigs underwent a 24– to 48-hour survival period. During postoperative and survival periods, surveillance and assessment of pain were required, buprenorphine 0.03 mg/kg IM (Buprecare ND 0.3 mg/mL, Axience) was used on demand, and in addition, ursodeoxycholic acid was given at 200 mg three times a day, omeprazole 20 mg twice a day, and a liquid diet and sucralfate orally were administered as ulcer prophylaxis.

Validation of the model

Validation was in the context of four hands-on EUS therapeutic courses (https://www.ihu-strasbourg.eu/en/faites-passer-votre-pratique-de-lechoendoscopie-therapeutique-au-niveau-su-

▶ **Table 1** Interventional procedures performed to validate the model.[1]

EUS procedures	No.	Complications
EUS-guided biliary drainage procedures (hepaticogastrostomy, hepaticoesphagostomy or choledochogastrostomy)	33	
EUS-guided trans gastric gallbladder drainage	32	
EUS through-the-needle microbiopsy forceps	32	
Total	97	7

[1] Pigs (n = 36) underwent a duodenal papilla clipping protocol.

perieur/) performed at the IHU-Strasbourg. These courses are targeted to practicing EUS clinicians and are intended to improve mastery of interventional procedures and teach new EUS therapeutic technologies. The procedures performed to validate the model were: EUS-guided biliary drainage procedures (EUS-BD), EUS-guided transgastric gallbladder drainage, and EUS-through-the-needle microforceps biopsy of the gallbladder (▶ **Table 1**).

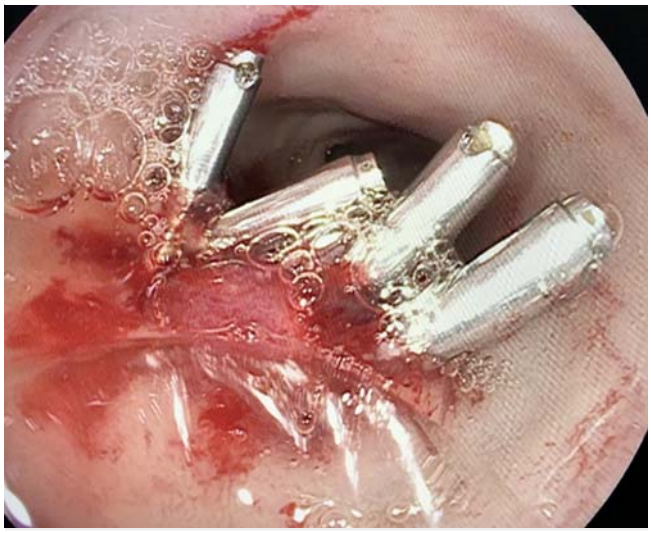
Results

Endoscopic duodenal papilla clipping protocol

A total of 36 pigs underwent the endoscopic duodenal papilla protocol, all procedures were performed in the hybrid operating room by senior endoscopists.

Several different clips were used for the permanent papilla occlusion: NOVA clip Life Partners Europe (80 % of the clips used), Instinct Cook hemostatic clip (10 % of the clips used), and Resolution clip from Boston Scientific (10 % of the clips used).

A total of 181 clips were used (range 4–6 per pig), 174 of which were correctly deployed on the papilla and seven of which were removed with the biopsy forceps due to incorrect deployment or position. During the hands-on training session, the visualization of the clips directly and under fluoroscopy guidance was noted and 98 % of the clips were in place. The mean procedure time to perform the endoscopic procedure was 20 minutes (range 15–30 min) (▶ **Fig. 1**).

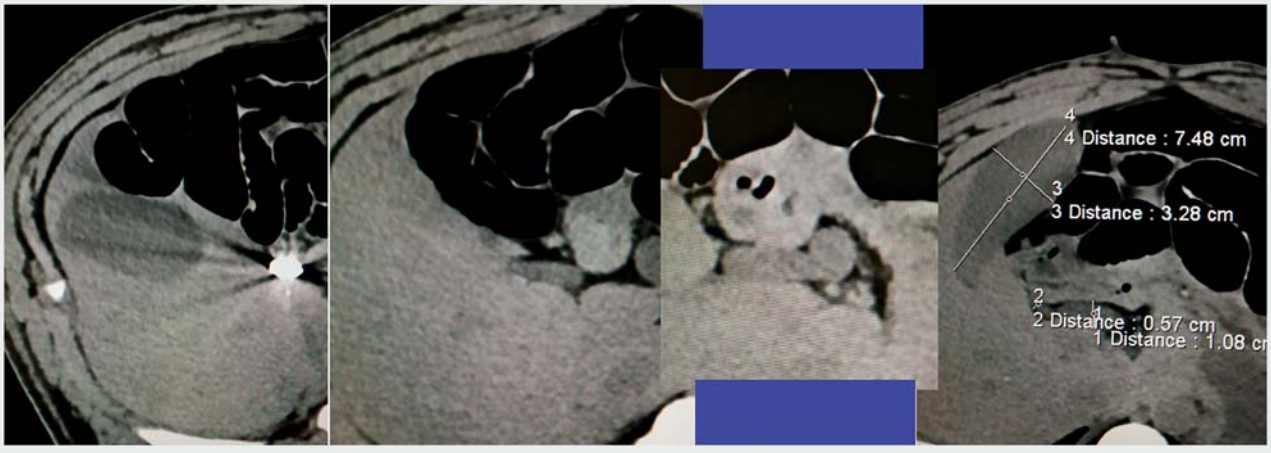


▶ **Fig. 1** Clips showing adequate adherence to the duodenal and papilla wall.

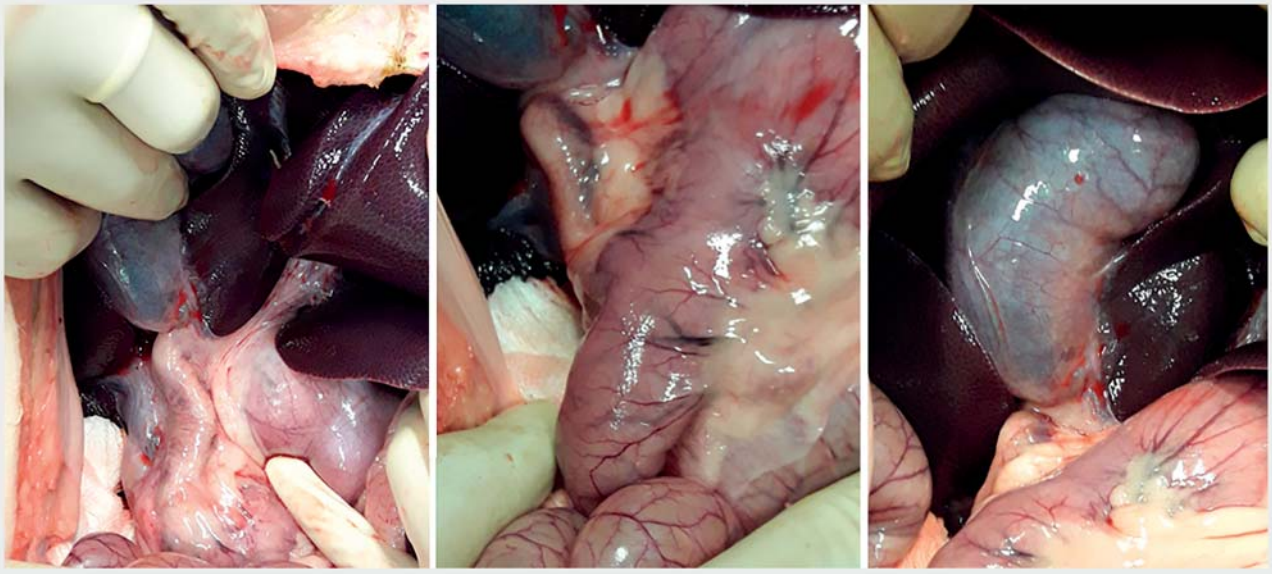
Bile duct dilation assessment

After survival for 24 to 48 hours, and before the training session, a CT contrast-enhanced abdominal scan was performed to assess the bile duct dilation (▶ **Fig. 2**).

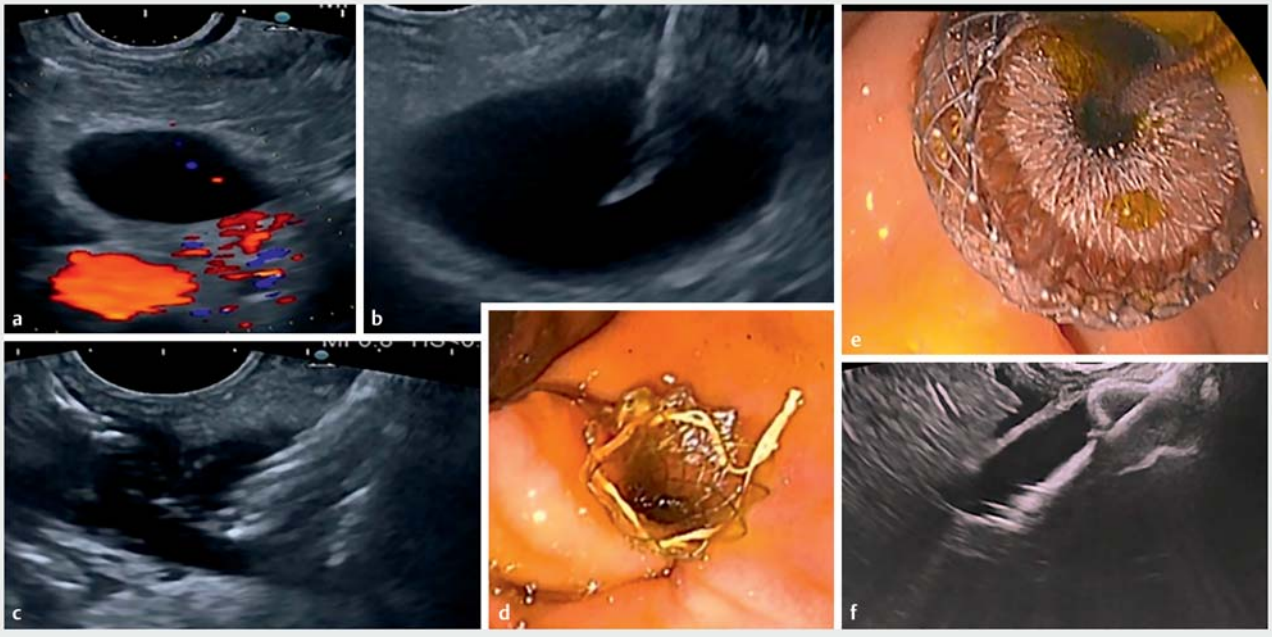
In all 36 pigs, ubstantial extrahepatic biliary dilation was achieved, especially in the CBD and gallbladder (▶ **Fig. 3**). In 11 pigs (31 %), intrahepatic bile duct dilation was achieved, with the right intrahepatic biliary ducts not achieving significant dilation, but the left biliary branches being substantially dilated adjacent to the distal esophagus or the gastric cardia. The intra-



▶ **Fig. 2** CT contrast-enhanced abdominal scan was required to assess the bile duct dilation.



▶ **Fig. 3** Extrahepatic biliary dilation was achieved, especially in the common bile duct and gallbladder.



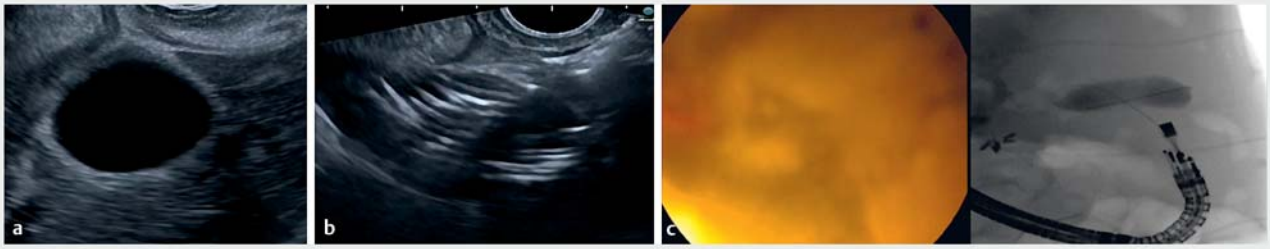
▶ **Fig. 4** EUS-guided common biliary drainage with SEMS. **a** Portal vein in the botton and dilated CBD in the top (25 mm). **b** Needle puncture in the CBD used to pass contrast and guide wire. **c** SEMS half open. **d** SEMS open in the stomach. **e** Endoscopic visualization of the proximal flange and bile in the stomach lumen. **f** Deploying the distal flange of a metallic stem in the dilated CBD.

hepatic bile duct dilation was not assessed near to the fundus or near the gastric pig's diverticula.

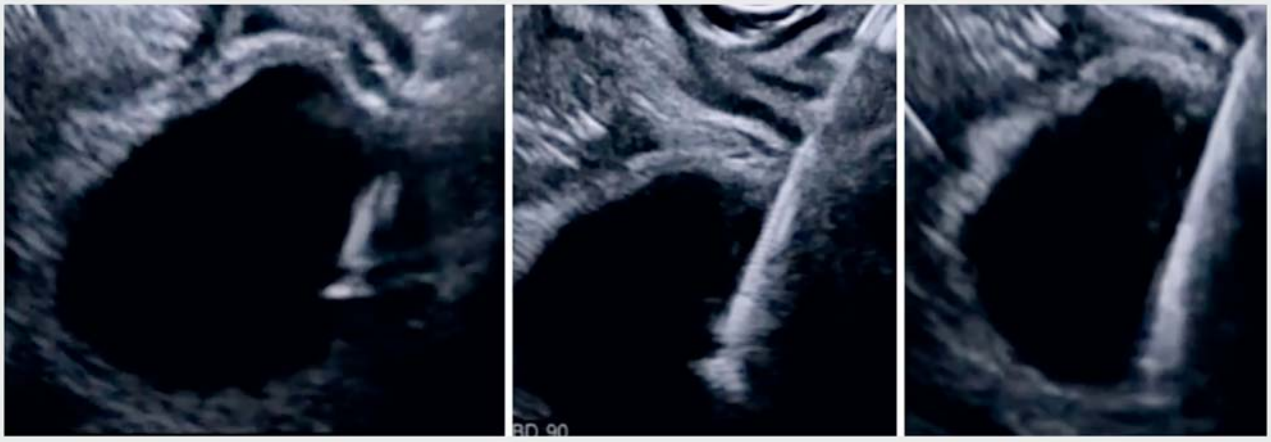
Main pancreatic duct dilation was observed in two pigs for reasons unlikely to be from the papilla clipping. It is worth mentioning that the pig anatomy has a separate main pancreatic duct papilla, which is 15 to 20 cm from the biliary papilla.

Training procedure validation

A total of seven interventional EUS procedures were performed in the 36 in vivo models with eight to 10 pigs in each training course and the courses occurring from October 2018 to February 2020.



▶ **Fig. 5** EUS-guided transgastric gallbladder drainage. **a** Gallbladder dilation. **b** Echogenic SEMS in the gallbladder. **c** Close contact with the stomach (top) and contrast media in the gallbladder before deployment of the SEMS.



▶ **Fig. 6** EUS through-the-needle microbiopsy forceps. Moray microforceps performing a gallbladder biopsy through a 19G EUS needle.

EUS-guided biliary drainage procedures

A total of 33 dilated CBDs were successfully drained by placing stents (LAMS 6– to 8-mm hot Axios Boston Scientific and cold Niti-s or Nagi Taewoong Medical) through the stomach wall. The mean diameter of the CBD was 25 mm (range 20–30 mm). In the pig model, the dilated CBD is located near the antrum lipoma and the gallbladder is located adjacent to the anterior mid gastric body on the lesser curve. No complications were reported while performing the procedure (▶ **Fig. 4**).

In 11 pigs with good intrahepatic dilation, hepatogastric or hepatoesophageal drainage was successfully performed. In 25 of the pigs, no treatable intrahepatic dilation was noted, so this procedure was not performed.

EUS-guided transgastric gallbladder drainage

A total of 32 gallbladders were drained satisfactorily with a lumen apposing metallic stent system. The mean size of the gallbladder was of 35 mm in the transverse axis and the longitudinal axis was 60 mm. In one case, the gallbladder was located intrahepatic and it was not possible to drain endoscopically. Both hot and cold systems were used;, therefore, for the hot in a one-step with no exchange technique, and a multistep process technique for the cold system, self-expanding metal stents were used in a few cases. No complications were reported while performing these procedures (▶ **Fig. 5**).

EUS through-the-needle microbiopsy forceps

In 32 pigs the gallbladder was used to simulate a biopsy of pancreatic cysts using a Moray microforceps. Several microbiopsy forceps specimens were obtained under EUS guidance from each animal (▶ **Fig. 6**) (Moray needle through a 19G EUS needle inside the gallbladder).

Evaluation form assessment

During each training course, experts and participants filled out evaluation forms regarding the model with the following results.

The model usefulness to perform and simulate each procedure was evaluated on a scale of 1–5 (1 = poor; 2 = fair; 3 = good; 4 = very good; 5 = excellent).

The mean evaluation score for the CBD and gallbladder drainage procedure, EUS through-the-needle micro biopsy forceps, for hepatic gastric drainage was 4.75; 4.50; and 4.04 respectively, with an overall usefulness evaluation of 4.43 (87%).

Other values were assessed as well: usefulness of imaging techniques: Doppler: 4.94 and elastography: 2.92. Apprecia-

tion in terms of quality of technical assistance: 4.83; facility: 4.76 and resources (equipment): 4.60. The overall model evaluation was: 71 % excellent rating (scale 8–10), 24 % good (scale 7–4), and 5 % poor (scale 1–3).

Complications

During the survival period after the first operation (papillae endoscopic clipping protocol) no complications or deaths were observed. All pigs with 48-hour survival presented with well-tolerated jaundice. Overall complications during the practice sessions occurred in seven of 36 pigs: two minor liver bleeds and five gastric perforations (19 %). Mortality happened in six pigs, four directly related to the hands-on training procedures (gastric perforation due to scope manipulations, cardiac arrest, shock, hyperthermia), and two deaths related to an anaphylactic reaction to medications (17 %).

Discussion

Interventional EUS-guided approaches are increasingly being used for diagnostic and therapeutic purposes, particularly in cases of bile duct obstruction and other biliopancreatic diseases and usually after failed ERCP. As advanced EUS skills are difficult to master, ways to enhance and improve interventional EUS skills are needed, particularly when they are not regularly performed by beginners. At our institute, we have implemented a program, to train practitioners with basic skills to advanced proficiency using high-fidelity, hands-on models before the procedures are transferred to real cases. The development of different models for training has been proposed by several groups and some are already commercially available. Models using virtual EUS simulators [13], explants [14], and 3 D printed bile ducts with dilation for EUS-guided biliary drainage [15] and rendezvous procedures [16] have been described, but most clinicians find them unrealistic or lacking haptic validity. Several more sophisticated and realistic in vivo models created by laparoscopic CBD ligation [8, 17], laparoscopic double-balloon occlusion [9], by thermal radiofrequency injury creating biliary strictures [11, 18, 19] and endoscopic clipping with band ligation [20] have been described and shown to be effective. However, these efforts have several limitations, including up to 2-week survival periods required to achieve bile duct dilation [10] and the inability to obtain realistic gallbladder dilation.

In vivo animal models are the most realistic model, with the advantages of a EUS porcine model including anatomy similar to humans, haptic feedback while inserting needles or deploying stents, perfused tissue which has the possibility of bleeding, and the possibility to assess complications in a realistic clinical scenario. The in vivo model allows students to perform procedures in the context of a real operating room allowing anesthesiology, vital sign monitoring, control of anatomical position, and use of other image-guided technologies, including imaging such as fluoroscopy.

An advantage of the model presented is the ability to achieve a large extrahepatic bile duct dilation, including both the CBD and the gallbladder. The mean size of the BD and gallbladder dilatation was 25 mm, and 35 mm × 60 mm respectively. The ability to achieve a treatable intrahepatic dilation in 11 of the pigs, at the same time allowing the performance of multiple procedures in one pig, fulfills the principles of reduce, refine, and replace for animal welfare, while still allowing the training of multiple trainees with a close-to real simulation. Due to the short time of survival required (48 hours) and 20 minutes to create a model, we believe this is a time-effective model.

In a few pigs (n = 3), a 24-hour survival was tested for a novel porcine bile duct dilation model for EUS training to assess the degree of intrahepatic bile duct dilation. However, this shorter time between clipping and assessment did not result in good intrahepatic dilation, although it was sufficient for marked gallbladder dilation.

It is worth mentioning that our model was rated as poor in 12 pigs, due to the inability to visualize the main pancreatic duct, or to perform a rendezvous procedure due to the permanent occlusion of the papilla, and non-treatable intrahepatic left biliary ductal dilation was noted in 25 of the models. Finally, the model has not been tested by beginners. Most of the trainees were experts with more than 3 years of experience.

Conclusions

We present a reliable and time-effective model of extrahepatic biliary dilation validated to be suitable for EUS or other interventions. The model was less effective for intrahepatic ducts and this should be considered if intrahepatic biliary dilation is required for training.

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Competing interests

The authors declare that they have no conflict of interest.

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