의학박사 학위논문

Feasibility and safety of endoscopic ultrasonography-guided selective portal vein embolization with coil and cyanoacrylate in a live porcine model

돼지모델에서 coil 과 cyanoacrylate 를 이용한
내시경초음파 유도하 선택적 간내문맥혈관 색전술의
기술적 실현 가능성과 초기 안전성 평가

울산대학교대학원
의 학 과
박 태 영

Feasibility and safety of endoscopic ultrasonography-guided selective portal vein embolization with coil and cyanoacrylate in a live porcine model

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이 논문을 의학박사 학위 논문으로 제출함

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Abstract

Introduction: Preoperative portal vein (PV) embolization using the percutaneous transhepatic approach has been performed in patients with hepatobiliary malignancy prior to extensive liver resection. The procedure increases remnant future liver volume and prevents post-operative hepatic failure. The aim of this study is to evaluate the technical feasibility and initial safety of endoscopic ultrasonography (EUS)-guided selective PV embolization using a coil and cyanoacrylate in a live porcine model.

Materials and methods: EUS-guided selective intrahepatic PV embolization with a coil and cyanoacrylate was performed in 9 pigs under general anesthesia using a linear array echoendoscope. The selected PV was punctured with a 19-gauge fine needle aspiration (FNA) needle, and the coil was inserted under EUS guidance. The cyanoacrylate was then immediately injected through the same FNA needle. The blood flow change in the embolized PV was evaluated using color Doppler EUS. A necropsy was performed following the 1-week observation period.

Results: The identification and puncture of the selected PV was successfully performed without difficulty in all 9 animals. The success rates for the coil and cyanoacrylate delivery were 88.9% (8/9) and 87.5% (7/8), respectively. In 1 case, the coil migrated into the hepatic parenchyma. In another case, the cyanoacrylate injection failed due to early clogging in the FNA needle. There was complete blockage of blood flow confirmed by color Doppler EUS

in the embolized PV after coil and cayanoacrylate treatment. There was coil migration into the hepatic parenchyma in 1 case. There was no animal distress observed during the 1-week observation period prior to necropsy. The necropsy showed no evidence of damage to the embolized PV or intra-abdominal organs, and the selected PV was totally occluded with embolus.

Conclusions: Our findings indicate EUS-guided selective PV embolization is both technically feasible and initially safe in an animal model. Further animal studies are needed to demonstrate the long-term safety and efficacy of this challenging intervention.

Keywords: endoscopic ultrasonography, portal vein, embolization, feasibility, safety

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Abbreviations

PV, portal vein; EUS, endoscopic ultrasonography; FNA, fine needle aspiration; TIPS, transjugular intrahepatic portosystemic shunt.

Introduction

Preoperative percutaneous trasnsheaptic portal vein (PV) embolization was first introduced in 1986 in hepatocellular carcinoma patients prior to hepatic resection.[1] Preoperative PV embolization using the percutaneous transhepatic approach is now performed in patients with hepatocellular carcinoma, intrahepatic cholangiocarcinoma, and hilar cholangiocarinoma receiving extensive liver resection including right hepatectomy or extended right hepatectomy.[1,2] The embolization of the portal venous branch of the hepatic segments to be resected can redirect portal blood flow to non-embolized hepatic segments. The treatment induces atrophy of the embolized lobe to be resected and causes compensatory hypertrophy of non-embolized remnant hepatic segments. As a result, this preoperative management increases remnant future liver volume and prevents postoperative hepatic failure.[3] Preoperative PV embolization is safe and effective prior to major liver resection.[4]

Linear echoendoscopy has been used to image the portal venous system and endoscopic ultrasonography (EUS)-guided vascular intervention has expanded to include PV intervention.[5-7] EUS-guided PV intervention has several advantages over the conventional percutaneous approach. EUS provides detailed images of the portal venous system and both color Doppler and pulse-wave Doppler can give real-time blood flow characteristics and delineate vascular structures.[5,8,9] Furthermore, the use of color Doppler EUS reduces the risk of nephrotoxicity from contrast and exposure to radiation.

Our group previously reported two studies[8,10] on EUS-guided vascular interventions. We reported the usefulness of the combination of color Doppler and contrast-enhanced harmonic EUS for the evaluation of visceral vascular diseases, including dissection or stenosis of the celiac artery and superior mesenteric artery in humans.[8] In our recent animal study, we performed EUS-guided transhepatic main PV stenting, which is used to treat malignant PV obstruction by interventional radiologists through the percutaneous transhepatic access route in clinical practice.[10,11]

Preoperative PV embolization is currently performed by interventional radiologists through the percutaneous transhepatic approach. The aim of this study is to evaluate the technical feasibility and initial safety of EUS-guided selective PV embolization using a coil and cyanoacrylate in a live porcine model.

Materials and methods

Preparation of animals

Nine male mini pigs (*Sus scrofus domesticus*) (12 months old; 30 kg) were used for the experiments. Food was withheld for 48 hours prior to the procedure. The pigs received only clear sugar-sweetened water for gastric preparation. All procedures were performed under general anesthesia provided by a qualified veterinarian. The pre-anesthesia medication included intramuscular injection of atropine sulfate (0.05 mg/kg), tiletamine hydrochloric

acid (HCl) plus zolazepam (7.5 mg/kg; Zoletil®; Virbac animal health, Fort Worth, Texas, United States), and xylazine HCl (1–2 mg/kg; Rompun®; Bayer Health care, Lerverkusen, Germany). The animals were intubated with a 6.5 mm endotracheal tube (Well Lead Medical Co., Guangdong, China). General anesthesia was maintained with 1.5% isoflurane (Forane®; JW Pharmaceutical, Korea). The animal blood pressure, heart rate, respiration rate, and arterial oxygen saturation were monitored continuously during anesthesia. This animal study was approved by the Research Animal Care Committee of Asan Medical Center.

Endoscopic procedure

This study used an anterior oblique-viewing linear array echoendoscope (GF-UCT240; Olympus Medical Systems, Tokyo, Japan) with an EUS processor (EU-ME1; Olympus Medical Systems, Tokyo, Japan). The echoendoscope was advanced into the stomach, and the left intrahepatic PV branch was identified by EUS and color Doppler at a frequency of 7.5 MHz. The PV was distinguished from the hepatic vein by its thickened hyperechoic wall on EUS view. The blood flow in the intrahepatic PV was confirmed by color Doppler EUS. The embolization coil used in this study was a pushable helical coil (Nester®; MWCE-35-14-12-NESTER; diameter inch 0.035 inch, extended embolus length 14 cm, coiled embolus diameter 12 mm; Cook Medical, Limerick, Ireland). The adhesive liquid embolic agent used in this study was cyanoacrylate (Histoacryl®; N-butyl-2-cyanoacrylate; BRAUN Aesculap, Tuttlingen, Germany). Before beginning the procedure the helical coil was preloaded into the distal end of a 19-gauge fine needle aspiration (FNA) needle (Expect™ 19ga Flex Needle;

Boston Scientific Co., Natick, MA, United States). The selected intrahepatic PV was punctured with the FNA needle under EUS guidance, and then the embolization coil was inserted into the selected intrahepatic PV using a stylet pushing device. We then immediately injected 0.5 cc cyanoacrylate through the same FNA needle, which was followed by 0.8 cc ethiodized oil (Lipiodol®; Guerbet, Princeton, NJ, United States) and 1 cc saline to prevent early clogging and leakage of cyanoacrylate in the FNA needle. After completing the coil and cyanoacrylate delivery, we monitored the change of blood flow in the embolized intrahepatic PV branch using color Doppler EUS. The echoendoscope was removed after confirming there was complete blood flow block.

Monitoring and necropsy

The animals were monitored for procedural, immediate, and delayed complications. During the endoscopic procedure the blood pressure, heart rate, respiration rate, and arterial oxygen saturation were monitored (procedural complication). After the endoscopic procedure, the animal was monitored closely for 2 hours to identify sudden or fatal complications (immediate complication). The animals were then observed for 1 week to assess delayed complications. The animals were euthanized after the 1-week observation period using intravenous potassium chloride under general anesthesia. The injection was performed by a qualified veterinarian, and the animals were necropsied to evaluate the damage to the embolized intrahepatic PV and other intra-abdominal organs.

Results

Feasibility

The branch of the intrahepatic PV was identified by EUS and color Doppler (Fig. 1). The EUS-guided puncture of the intrahepatic PV branch was successfully performed without difficulty using a 19-gauge FNA needle in all 9 animals (Fig. 2). The embolization coil was placed successfully into the selected intrahepatic PV in 8 of 9 animals (8/9, 88.9%) (Fig. 3). In 1 case, the embolization coil migrated into the hepatic parenchyma and was not located in the selected intrahepatic PV. The cyanoacrylate injection was successful in 7 animals (7/8, 87.5%) (Fig. 4). In 1 case, the cyanoacrylate injection failed due to early clogging of cyanoacrylate in FNA needle. The feasibility results of EUS-guided selective PV embolization on 9 animals is summarized in Table 1.

Efficacy

The baseline blood flow was evaluated using color Doppler EUS before conducting the intrahepatic PV puncture (Fig. 5). There was partial blockage of blood flow in the selected intrahepatic PV noted after inserting the embolization coil (Fig. 6). There was complete blockage of blood flow in the embolized intrahepatic PV after both coil insertion and cyanoacrylate injection, and the result was confirmed by color Doppler EUS (Fig. 7). The necropsy was performed one week postoperatively. The embolized intrahepatic PV was totally occluded with an embolus consisting of the helical coil, adhesive cyanoacrylate, and

thrombus (Fig. 8).

Safety

The vital signs were stable during the endoscopic procedure in all 9 animals. There were no signs or symptoms of peritonitis and bleeding in the animals during the 1-week observation period. The necropsy was performed one week later and there was no gross evidence of damage to the embolized intrahepatic PV, hepatic parenchyma, and intra-abdominal organs. The safety data for EUS-guided selective PV embolization on 9 animals are summarized in Table 2.

Discussion

Preoperative PV embolization has been widely used in clinical practice. It is an important procedure due to the beneficial effect of preventing post-operative hepatic failure in patients with hepatobiliary malignancy. Preoperative PV embolization is conventionally performed through the percutaneous approach. The EUS-guided intervention technique was recently developed, and the indications have expanded to include vascular therapy.[6,7] There have been several attempts to evaluate the feasibility of EUS-guided vascular interventions, including transjugular intrahepatic portosystemic shunt (TIPS),[12] portal venous pressure measurement[13,14] and main portal vein stenting.[10] These indications have been conventionally performed by an interventional radiologist through the percutaneous approach. A human pilot study examining EUS-guided portal pressure gradient measurements was successful in

all 28 patients with liver disease and showed no adverse events.[15]

There was an experimental report of EUS-guided PV embolization in 2005.[16] One animal was involved and the selected PV was punctured using a 22-gauge FNA needle via the transduodenal route. The authors measured PV pressure before and after PV embolization. The embolization was conducted with 4 cc of Enteryx® (ethylene-vinyl alcohol mixed with dimethyl sulfoxide). In our study, EUS-guided selective intrahepatic PV embolization was conducted in nine animals. We used permanent embolic agents including a 0.035 inch, 14 cm coil and 0.5 cc cyanoacrylate and delivered the agents with a 19-gauge FNA needle. The success rates of coil and cyanoacrylate delivery were 88.9% (8/9) and 87.5% (7/8), respectively. The complete blockage of blood flow to the embolized PV was confirmed by color Dopper EUS. There was one case of coil migration into the hepatic parenchyma. The necropsy findings indicated there was no evidence of damage to the embolized PV and intra-abdominal organs. Additionally, the selected PV was totally occluded with embolus.

Our study has several strengths compared with the previously reported study.[16] First, the 19-gauge FNA needle was selected to insert the 0.035 inch diameter helical coil and adhesive cyanoacrylate. Furthermore, to prevent early clogging and leakage of cyanoacrylate we injected Lipiodol® (ethiodized oil) after completing the cyanoacrylate injection through the same FNA needle. Therefore, sufficient embolic agents were delivered to the selected PV. The PV embolization was performed more effectively, which would be limited by a 22-gauge FNA needle. Second, two types of permanent embolic agents including a pushed

helical coil and adhesive liquid cyanoacrylate were used in this study. These agents are commonly used for therapeutic embolization in clinical practice.[17-19] The adhesive cyanoacrylate (Histoacryl®) has several advantages over non-adhesive ethylene-vinyl alcohol copolymer (Enteryx®). The cyanoacrylate works instantly and completely occludes vessels. Additionally, it is non-toxic and rarely causes vasospasm or vascular necrosis.[20] Therefore, our method is a more practically preferred and favorable strategy for EUS-guided selective PV embolization.

This study has several limitations. First, there was no assessment of liver volume change performed in this study. The primary aim of the preliminary study is to evaluate the technical feasibility and initial safety. Furthermore, 3-dimensional volumetric computed tomography or technetium-99 m-galactosyl human serum albumin scintigraphy[4] used for liver volume measurements in clinical practice are not available for animal models. The compensatory hypertrophy of the non-embolized hepatic segment can reach its maximum in 2-6 weeks after PV embolization in humans, and this was not confirmed in the current experiment. Microscopic examination of specimen to evaluate hepatic parenchymal change and portal vein wall inflammation also did not performed. Thus, the final therapeutic effect of this intervention could not be evaluated. Second, the procedure was conducted in healthy animals without portal hypertension, coagulopathy, and biliary obstruction. As a result, the risk of procedure-related complications including bleeding and bile peritonitis can be underestimated. Especially, infection is a potential drawback of EUS-guided vascular

intervention; this could result in bacteremia and affect long-term survival. There was no evidence of infection during 1 week observation period in the current study. However, infection can progress to disseminated sepsis and become life-threatening in immunocompromised cases with liver cirrhosis or malignancy. Further studies of portal hypertensive or biliary obstructive animal models are required to determine the long-term safety and efficacy of EUS-guided PV embolization.

Conclusion

This experimental study indicates that EUS-guided selective PV embolization with a coil and cyanoacrylate is technically feasible and shows initial safety in a live porcine model. Further animal studies are required to demonstrate the long-term efficacy and safety.

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Table 1. Feasibility of EUS-guided PV embolization (n=9)

Case	Portal vein identification	Portal vein puncture	Coil placement	Cyanoacrylate injection
1	Success	Success	Success	Success
2	Success	Success	Success	Success
3	Success	Success	Failure*	-
4	Success	Success	Success	Failure†
5	Success	Success	Success	Success
6	Success	Success	Success	Success
7	Success	Success	Success	Success
8	Success	Success	Success	Success
9	Success	Success	Success	Success
Success,n(%)	9/9 (100%)	9/9 (100%)	8/9 (88.9%)	7/8 (87.5%)

EUS, endoscopic ultrasonography; PV, portal vein.

* Embolization coil migrated into the hepatic parenchyma, not in the selected intrahepatic portal vein.

† Cyanoacrylate injection failed due to aspiration needle deflection and early clogging of cyanoacrylate.

Table 2. Safety of EUS-guided PV embolization (n=9)

Case	Procedural adverse event*	Immediate adverse event†	Delayed adverse event‡	Survival for 1 week	Necropsy after 1 week
1	-	-	-	Yes	-
2	-	-	-	Yes	-
3	Migration of coil	-	-	Yes	Coil in hepatic parenchyma
4	-	-	-	Yes	-
5	-	-	-	Yes	-
6	-	-	-	Yes	-
7	-	-	-	Yes	-
8	-	-	-	Yes	-
9	-	-	-	Yes	-

EUS, endoscopic ultrasonography; PV, portal vein.

* Procedural complication was defined as adverse event that occurred during endoscopic procedure.

† Immediate complication was defined as adverse event that occurred 2 hours after endoscopic procedure.

‡ Delayed complication was defined as adverse event that occurred 1 week after endoscopic procedure.

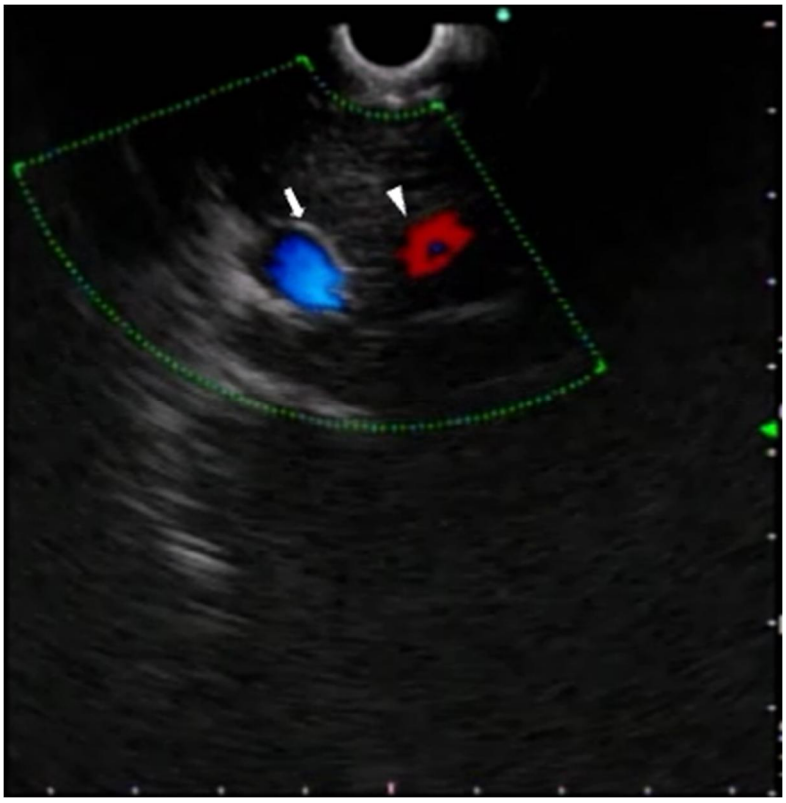

Fig. 1. Identification of the intrahepatic PV by EUS. Portal vein (arrow) was distinguished from hepatic vein (arrow head) by its thickened hyperechoic wall.

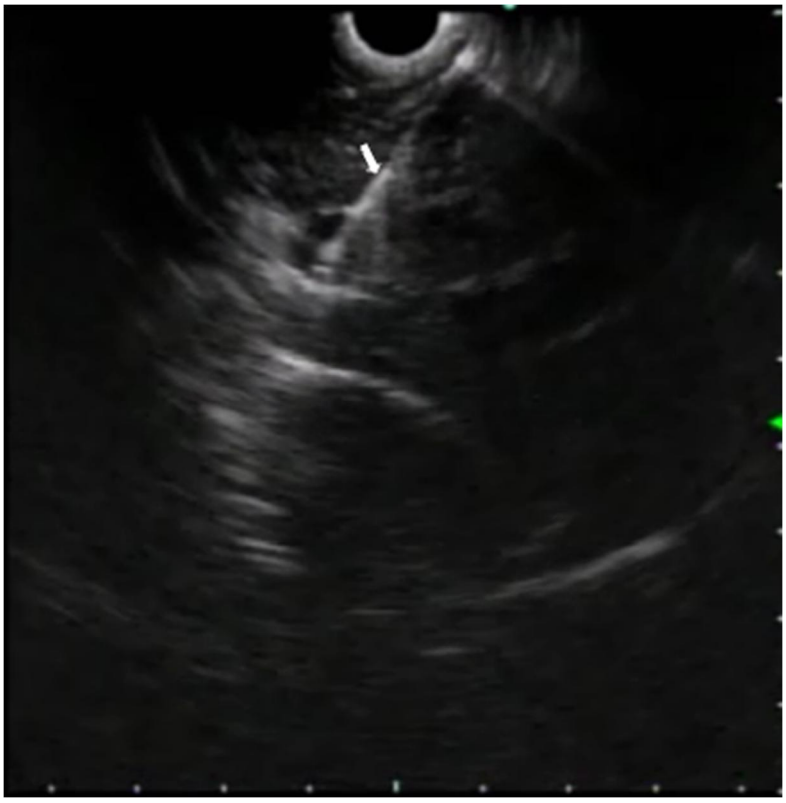

Fig. 2. Puncture of intrahepatic PV branch by FNA needle (arrow).

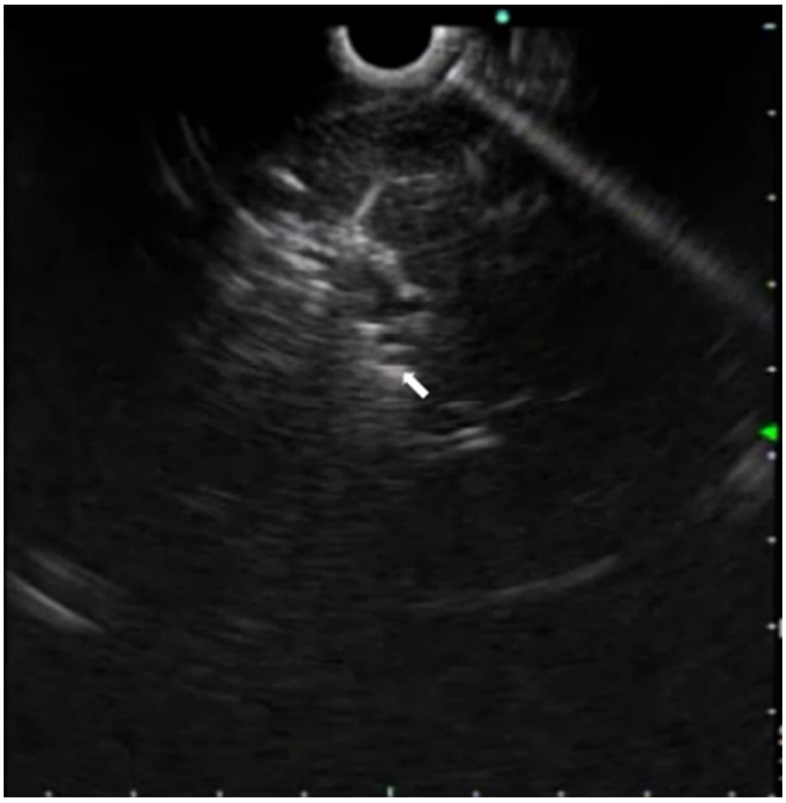

Fig. 3. Embolization coil (arrow) placement into the selected PV.

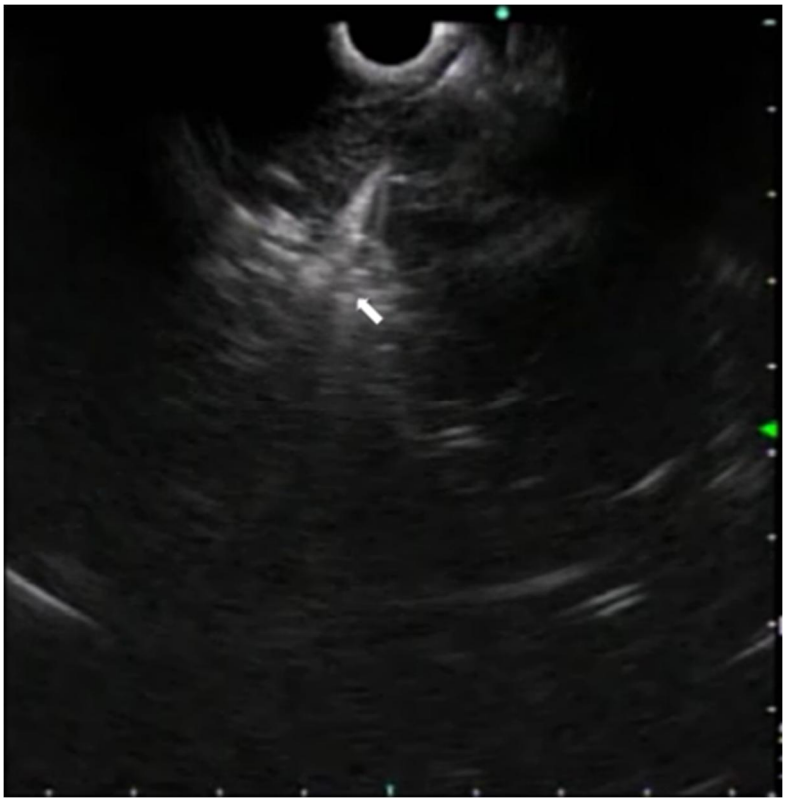

Fig. 4. Cyanoacrylate (arrow) injection into the selected PV.

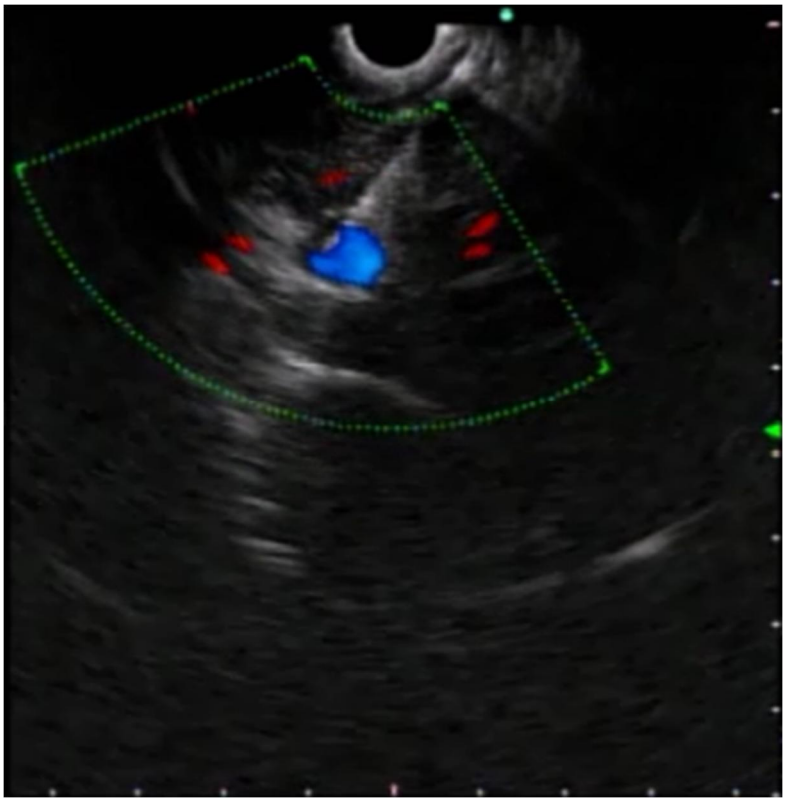

Fig. 5. Baseline blood flow in the selected PV on color Doppler EUS.

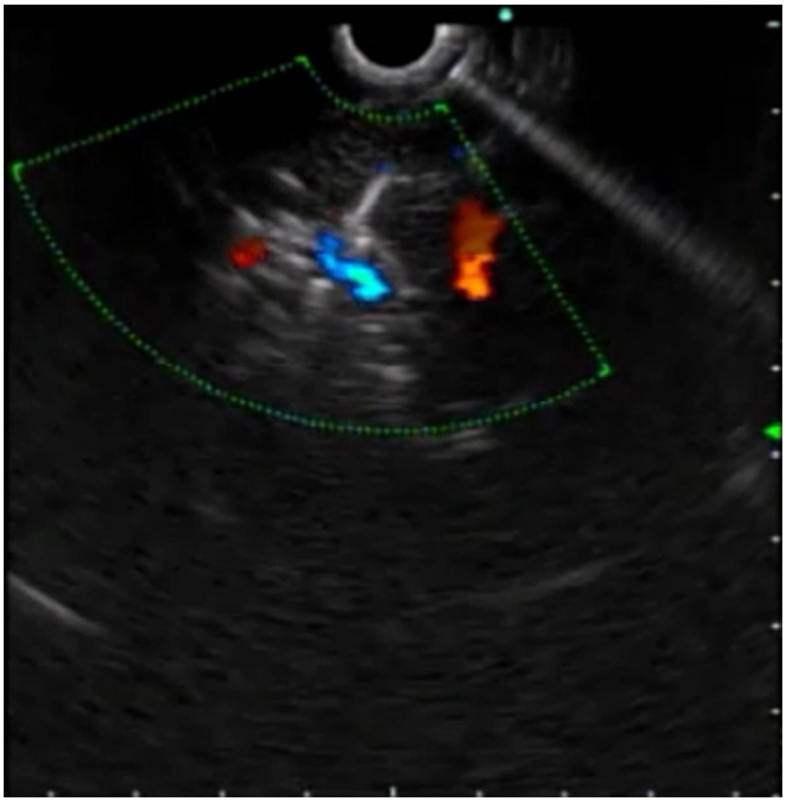

Fig. 6. Partial blockage of blood flow after coil placement.

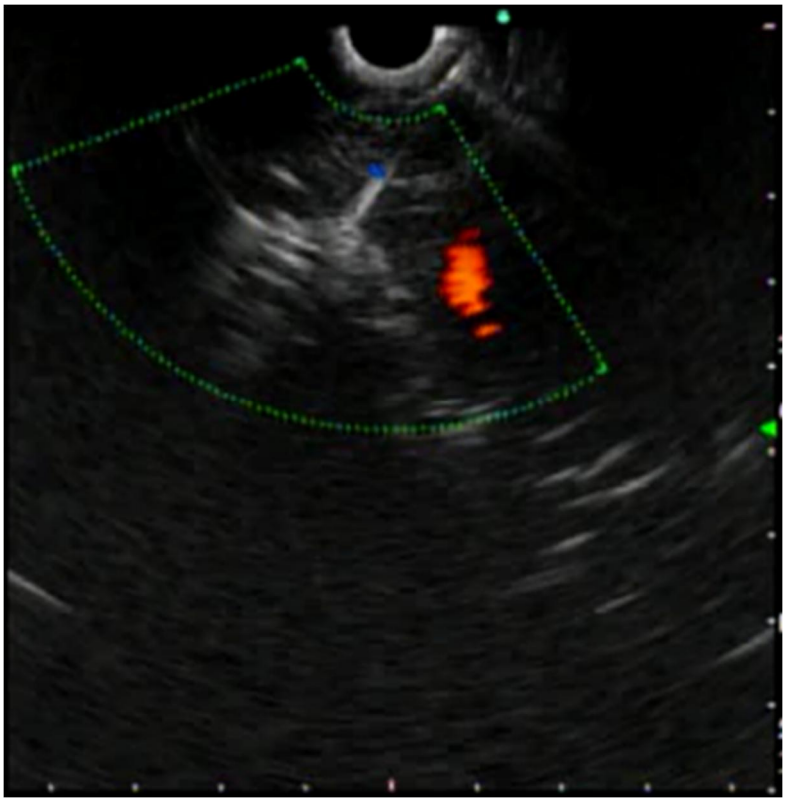

Fig. 7. Complete blockage of blood flow in the embolized PV using coil and cyanoacrylate.

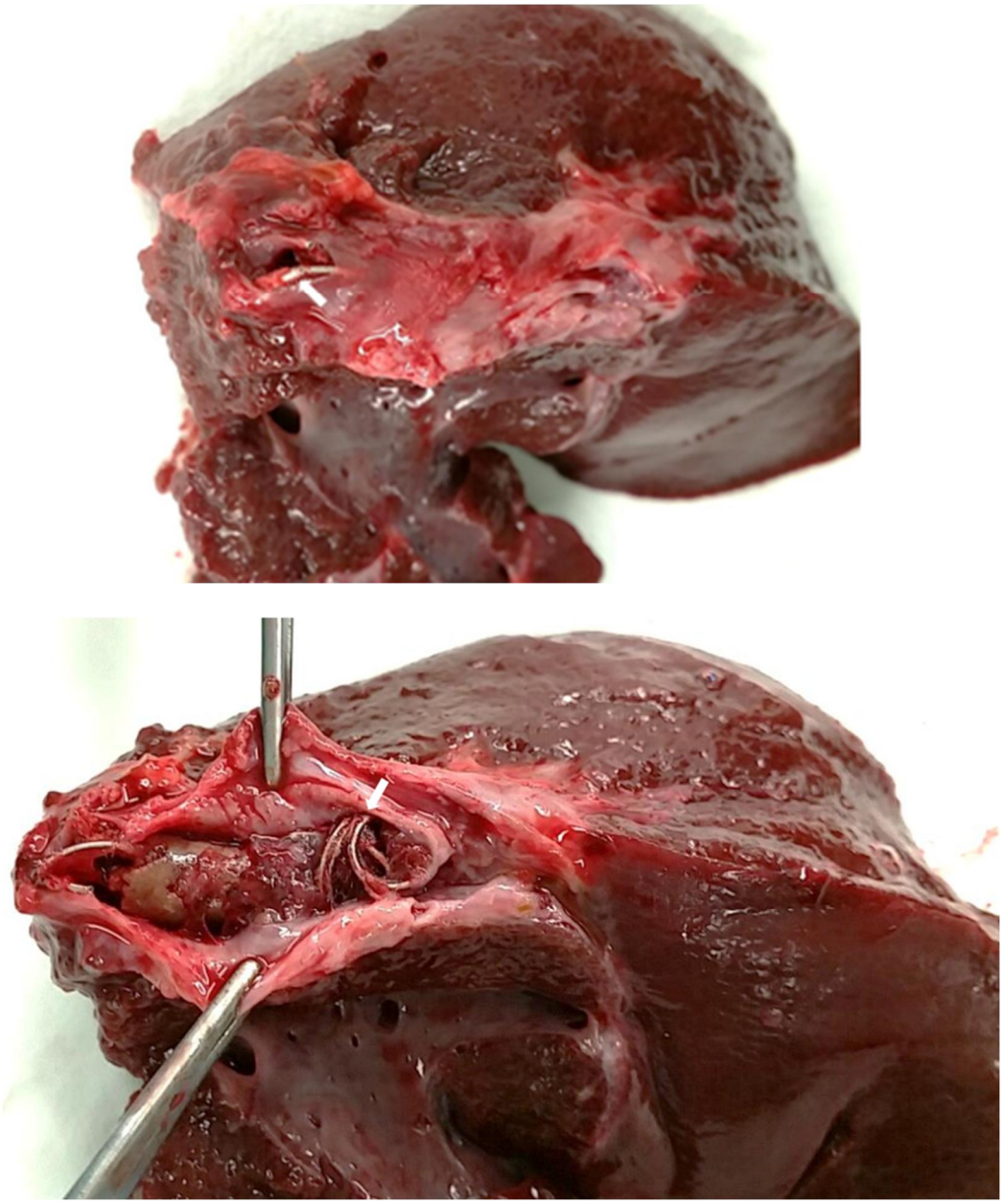

Fig. 8. Total occlusion of the embolized PV (arrow) on necropsy.

Korean abstract

서론: 수술 전 경피적 경간 간문맥 색전술은 대량 간절제술을 계획하고 있는 간담췌 악성종양 환자에서 시행되고 있다. 절제될 간 구역에 간문맥 색전술을 시행하면 잔류 간의 비대를 유발하여 수술 후 간부전을 예방할 수 있다. 본 연구에서는 돼지모델에서 coil 과 cyanoacrylate 를 이용한 내시경초음파 유도하 선택적 간내문맥혈관 색전술의 기술적 실현 가능성과 초기 안전성을 평가하고자 한다.

방법: 전신마취 상태의 9 마리 돼지에서 선형 주사 내시경초음파를 이용하여 선택적 간내문맥혈관 색전술을 시행하였다. 내시경초음파 유도하 19-gauge 세침 흡인 바늘로 간내문맥혈관을 천자한 후에 coil 과 cyanoacrylate 를 선택된 간내문맥혈관에 주입하였다. 내시경 초음파의 도플러 기능을 이용하여 색전된 간내문맥혈관의 혈류변화를 평가하였고 시술 후 1 주 동안 동물을 관찰한 후에 부검을 하였다.

결과: 간내문맥혈관의 식별과 천자는 9 마리 동물에서 어려움없이 성공하였다. coil 삽입 성공률은 88.9% (8/9), cyanoacrylate 주입 성공률은 87.5% (7/8) 였다. 간 실질로의 coil 삽입 1 례, cyanoacrylate 의 세침 흡인 바늘 내에서의 응고 1 례가 있었다. 도플러 초음파를 이용하여 색전술에 성공한 간내문맥혈관의 혈류 흐름이 완전히 차단되었음을 확인하였다. 시술과 연관된 합병증은 없었다. 부검 전 1 주 동안의 관찰기간동안 출혈이나 복막염의 증상을 보이는 동물은 없었다. 부검에서 색전된 문맥혈관과 복강내 장기에 손상은 관찰되지 않았고 선택된 간문맥혈관은 색전물로 완전히 폐쇄되었음을 확인하였다.

결론: 돼지모델에서 coil 과 cyanoacrylate 를 이용한 내시경초음파 유도하 선택적 간내문맥혈관 색전술은 기술적으로 실현이 가능하고 시술 후 단기간 안전성을 확인하였다. 이 시술의 장기간의 안전성과 간 위축효과를 확인하기 위해서는 추가 동물실험이 필요하다.