



Effect of drug-eluting bead transarterial chemoembolization loaded with cisplatin on normal dogs

Ko NAKASUMI¹⁾, Naoki YAMAMOTO²⁾, Taro TAKAMI²⁾, Harumichi ITOH³⁾, Kazuhito ITAMOTO³⁾, Hiro HORIKIRIZONO⁴⁾, Toshie ISERI⁴⁾, Munekazu NAKAICHI⁴⁾, Yuki NEMOTO¹⁾, Hiroshi SUNAHARA¹⁾ and Kenji TANI¹⁾*

¹⁾Department of Veterinary Surgery, Joint Faculty of Veterinary Medicine, Yamaguchi University, 1677-1 Yoshida, Yamaguchi, Yamaguchi 753-8515, Japan

²⁾Department of Gastroenterology & Hepatology, Yamaguchi University Graduate School of Medicine, Yamaguchi University, 1-1-1 Minami Kogushi, Ube, Yamaguchi 755-8505, Japan

³⁾Small Animal Clinical Science, Joint Faculty of Veterinary Medicine, Yamaguchi University, 1677-1 Yoshida, Yamaguchi, Yamaguchi 753-8515, Japan

⁴⁾Department of Veterinary Radiology, Joint Faculty of Veterinary Medicine, Yamaguchi University, 1677-1 Yoshida, Yamaguchi, Yamaguchi 753-8515, Japan

ABSTRACT. Transcatheter arterial embolization (TAE) and transcatheter arterial chemoembolization (TACE) are standard treatments for advanced hepatocellular carcinoma (HCC) and particularly for unresectable tumors or liver metastases in humans. However, reports on TACE used in veterinary medicine are few. This study aimed to evaluate the feasibility and safety of drug-eluting bead transarterial chemoembolization (DEB-TACE). We performed DEB-TACE in four clinically normal dogs and pharmacokinetically compared the results against hepatic arterial infusion (HAI) of cisplatin in two dogs. Drug-eluting beads (DEB) loaded with cisplatin were injected through a microcatheter for selective embolization of the left hepatic artery. After embolization, computed tomography (CT) images and histological examination findings were obtained during a 4-week observation period. Serum platinum concentrations were measured to evaluate cisplatin after each procedure. Biochemical analysis was performed during a 12-week observation period. Embolization was successful in all dogs, and there were no clinically apparent abnormalities. Embolization was confirmed up to 4 weeks after DEB-TACE in two of the four dogs and up to 1 week in the other two dogs using postoperative CT images. Cisplatin was not detected in peripheral veins in all dogs after DEB-TACE, but it was detected in trace amounts after HAI. DEB-TACE using cisplatin was safe and well tolerated by normal dogs. DEB-TACE may be useful in terms of determining systemic toxicity and drug concentration within tumors.

KEY WORDS: cisplatin, drug-eluting bead transarterial chemoembolization, hepatocellular carcinoma

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Unresectable advanced hepatocellular carcinoma (HCC) has a poor prognosis with limited treatment options in veterinary medicine. Transcatheter arterial embolization (TAE) and transcatheter arterial chemoembolization (TACE) are widely used standard treatments for unresectable advanced HCC and liver metastases in humans [5, 10, 24, 25]. Improved survival rates, reduced pain, and local control have been reported after arterial embolization of unresectable HCC. The general concept of TACE is to combine the local infusion of chemotherapeutic agents with selective embolization of the feeding arteries of the tumor. No consensus exists on the most effective embolizing agent. Drug-eluting beads (DEB) is a novel drug delivery system that is specifically designed to deliver a drug directly into the tumor tissue at a slow rate [15]. Drug-eluting bead transarterial chemoembolization (DEB-TACE) is expected to function both as a drug delivery system and an embolic agent for feeding artery occlusion. Bland TAE in healthy beagles was reported to be safe [21, 23] and possibly effective in veterinary practice [22]. Reports of TACE performed in dogs are rare [2, 32], and to the best of our knowledge, no reports have been published on DEB-TACE performed in dogs. This study sought to determine the feasibility and safety of DEB-TACE in dogs in terms of clinical signs, biochemical data, computed tomography (CT) findings, histological findings, and pharmacokinetics.

*Correspondence to: Tani, K.: ktani@yamaguchi-u.ac.jp

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MATERIALS AND METHODS

Animals

Eight healthy adult beagles were enrolled in this study. Physical examination, hematology, and routine biochemistry were within normal limits in each of these dogs. This study was approved by our institutional ethics committee (Approval number 455). Dogs were housed in cages with free access to water, and food was withheld for 12 hr before anesthesia.

Transarterial chemoembolization

We performed DEB-TACE on four dogs. Anesthesia was induced via slow intravenous administration of propofol (1% intravenous propofol, 7 mg/kg; Maruishi Pharmaceutical Co., Ltd., Osaka, Japan) and maintained with isoflurane (Isoflur, 1.4–2.5%; Daiinippon Sumitomo Pharma Co., Ltd., Tokyo, Japan) and oxygen. All dogs were administered an antibiotic (cefazolin sodium; 25 mg/kg intravenously) and analgesic (buprenorphine; 20 µg/kg intramuscularly) after induction.

The right femoral artery was punctured with a 20-G needle and cannulated with a 4-French (Fr) introducer sheath (Vaivt A; Medikit Co., Ltd., Tokyo, Japan) [26]. A guidewire (Radifocus guidewire M, diameter: 0.89 mm, angled, 80 cm; Terumo Co., Ltd., Tokyo, Japan) and catheter (PA catheter, 4 Fr, 40 cm; Terumo Clinical Supply Co., Ltd., Gifu, Japan) were inserted into the aorta and celiac artery under fluoroscopic guidance (ARCADIS Varic; Siemens Healthcare Japan, Tokyo, Japan). A microguidewire (Radifocus guidewire, diameter: 0.41 mm, angled, 150 cm; Terumo Clinical Supply Co., Ltd.) was advanced into the common hepatic artery through the catheter. A 1.7-Fr microcatheter (Derniere, 105 cm; Create Medic Co., Ltd., Yokohama, Japan) was placed in the left hepatic artery toward the left lateral lobe prior to the injection of a contrast agent (Optiray 350; Covidien Co., Ltd., Tokyo, Japan) under digital subtraction angiography (DSA). Chemoembolization was achieved with DEB (Hepasphere, 50–100 µm; Nippon Kayaku Co., Ltd., Tokyo, Japan). DEB swelled with contrast medium and cisplatin (IA-call; Nippon Kayaku Co., Ltd.) following the manufacturer's instructions. In all dogs, DEB before overflow was observed (approximately 0.3–0.4 ml of DEB was injected, and cisplatin was contained in 0.21–0.28 mg). After embolization, arteriograms were obtained to confirm complete occlusion of the left hepatic artery. After removing the sheath, the puncture site was manually compressed. All dogs were monitored for 12 weeks after DEB-TACE.

Hepatic arterial infusion (HAI) and intravenous cisplatin

Anesthesia administration and catheter insertion were performed similar to those of DEB-TACE. Cisplatin was injected into the left hepatic artery toward the left lateral lobe in the same dose as that for DEB-TACE for two dogs. To compare pharmacokinetics, we injected cisplatin (50 mg/m²) into the cephalic vein for two dogs.

Evaluations

After chemoembolization, physical examination was performed once a day for 2 weeks and then twice a week for the remaining 10 weeks. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GGT), total bilirubin (T.Bil), lipase (LIP), C-reactive protein (CRP), blood urea nitrogen (BUN), and creatinine (CRE) levels were measured before the procedures were performed and at 1 and 3 days after DEB-TACE. These tests were repeated at 1, 2, 4, 8, and 12 weeks after DEB-TACE. To evaluate serum platinum (Pt) concentration, blood sampling was immediately performed after each procedure and was repeated at 5, 15, 30, and 60 min and at 2, 6, 12, 24, 48, and 72 hr after the procedures. Serum Pt was measured by atomic absorption spectrometry (Z5700; Hitachi High-Tech Co., Ltd., Tokyo, Japan).

Computed tomography (CT; ECLOS 8; Hitachi Medical Co., Ltd., Tokyo, Japan) was performed before and immediately after embolization and was repeated at 1, 2, and 4 weeks. Each study included four phases: abdominal survey, arterial phase, portal phase, and equilibrium. Iopamidol (Oiparomin 370; Fuzi Pharmaceutical Co., Ltd., Toyama, Japan) was intravenously injected to provide contrast during vascular imaging. Three-dimensional reconstructions of the hepatic vessels were generated using Ziostation2 software (Ziosoft, Inc., Tokyo, Japan).

Liver biopsies were obtained via laparoscopy after DEB-TACE at 1 and 2 weeks. All samples were taken from the left lateral lobe of the liver, fixed in 4% paraformaldehyde, and embedded in paraffin. Tissue sections were stained with hematoxylin–eosin (HE), periodic acid–Schiff, and Azan stains.

Data analysis

Body weight and duration of DEB-TACE were reported as mean ± standard deviation. Statistical analysis was not conducted in this study because of the small sample size.

RESULTS

The mean body weight of the dogs in our study was 9.57 ± 1.32 kg. Postembolization hepatic arteriograms (Fig. 1) and CTs of all dogs confirmed complete occlusion of the left hepatic artery toward the left lateral lobe. The mean duration of DEB-TACE was 39.25 ± 7.36 min and that of HAI was 21.5 ± 0.5 min. Postoperative CT confirmed recanalization at week 1 in two of the four dogs (dogs 3 and 4); however, the remaining two dogs successfully maintained embolization during the 4-week observation period (Fig. 2).

LIP was increased in one dog, CRP in four dogs, and ALP in two dogs after DEB-TACE, but these were generally within the

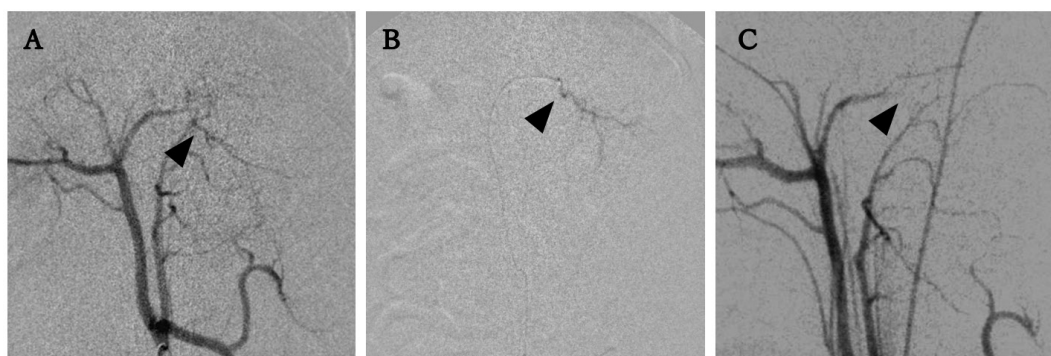


Fig. 1. Ventral–dorsal digital subtraction images of a dog. **A.** Pre-embolization hepatic arteriogram. **B.** During embolization, injecting Hepasphere into the left hepatic artery toward the left lateral lobe. **C.** Postembolization hepatic arteriogram showing complete occlusion of the left hepatic artery toward the left lateral lobe. The black arrowhead indicates the left hepatic artery toward the left lateral lobe.

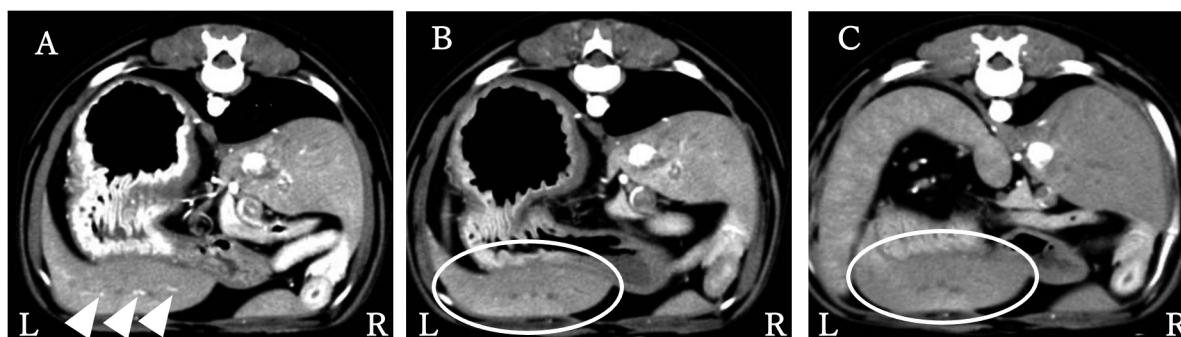


Fig. 2. Transverse computed tomography (CT) images. **A.** An arterial phase CT of pre-embolization (white arrowheads indicate the left hepatic artery toward the left lateral lobe). **B.** An arterial phase CT 1 week after DEB-TACE. The left hepatic artery toward the left lateral lobe (surrounded by a white circle) was embolized. **C.** An arterial phase CT 4 weeks after DEB-TACE. The left hepatic artery toward the left lateral lobe (surrounded by a white circle) remained embolized.

normal range throughout the study period (Fig. 3). ALP was also increased in all dogs after HAI, but the increase was quite less (around 300 IU/l).

The serum concentrations of Pt were below detection limit in all dogs after DEB-TACE and were found in trace amounts in dogs after HAI (only 6 hr after administration). In dogs intravenously administered cisplatin, Pt was reduced biphasically as previously reported (Fig. 4) [9].

There were no obvious abnormalities in the left lateral lobes further distal to the embolization site and no perivascular hemorrhage or inflammation in the vessel wall or surrounding tissues after DEB-TACE (Fig. 5). Moreover, clinical readings remained within normal limits throughout the study.

DISCUSSION

In healthy beagle dogs, DEB-TACE with cisplatin may reduce the side effects of cisplatin because the drug's sustained release keeps the blood concentration of the anticancer drug lower than that with intravenous or intrahepatic arterial administration. In this study, Pt was found in HAI and DEB-TACE below or close to the detection limit, suggesting that the side effects could be greatly reduced compared with intravenous cisplatin. However, only ~42% of cisplatin (approximately 0.12 mg) was contained within DEB, and the remaining 58% was outside DEB. There was more cisplatin outside DEB, and the pharmacokinetics may not be much different between HAI and DEB-TACE. The tumor intravascular volume may be larger in clinical cases with HCC, resulting in a higher dose, which could indicate a significant difference between HAI and DEB-TACE.

The DEB (Hepasphere) gradually released cisplatin into the liver and embolized the hepatic artery so that the time of exposure of the liver to cisplatin was increased, and cisplatin accumulated in the liver with a low discharge into the systemic circulation [4, 31]. In humans, cisplatin was administered through the hepatic artery and through an intravenous line, and serum Pt concentration was lower in the intra-arterial group than that in the intravenous group [28]. Furthermore, in previous reports [1, 6, 28], the anticancer drug concentration in the tumor was higher with HAI than with systemic administration. In addition, in a study on intrahepatic administration of cisplatin in rabbits [7], the cirrhotic group tended to have a higher anticancer drug concentration in the liver, and

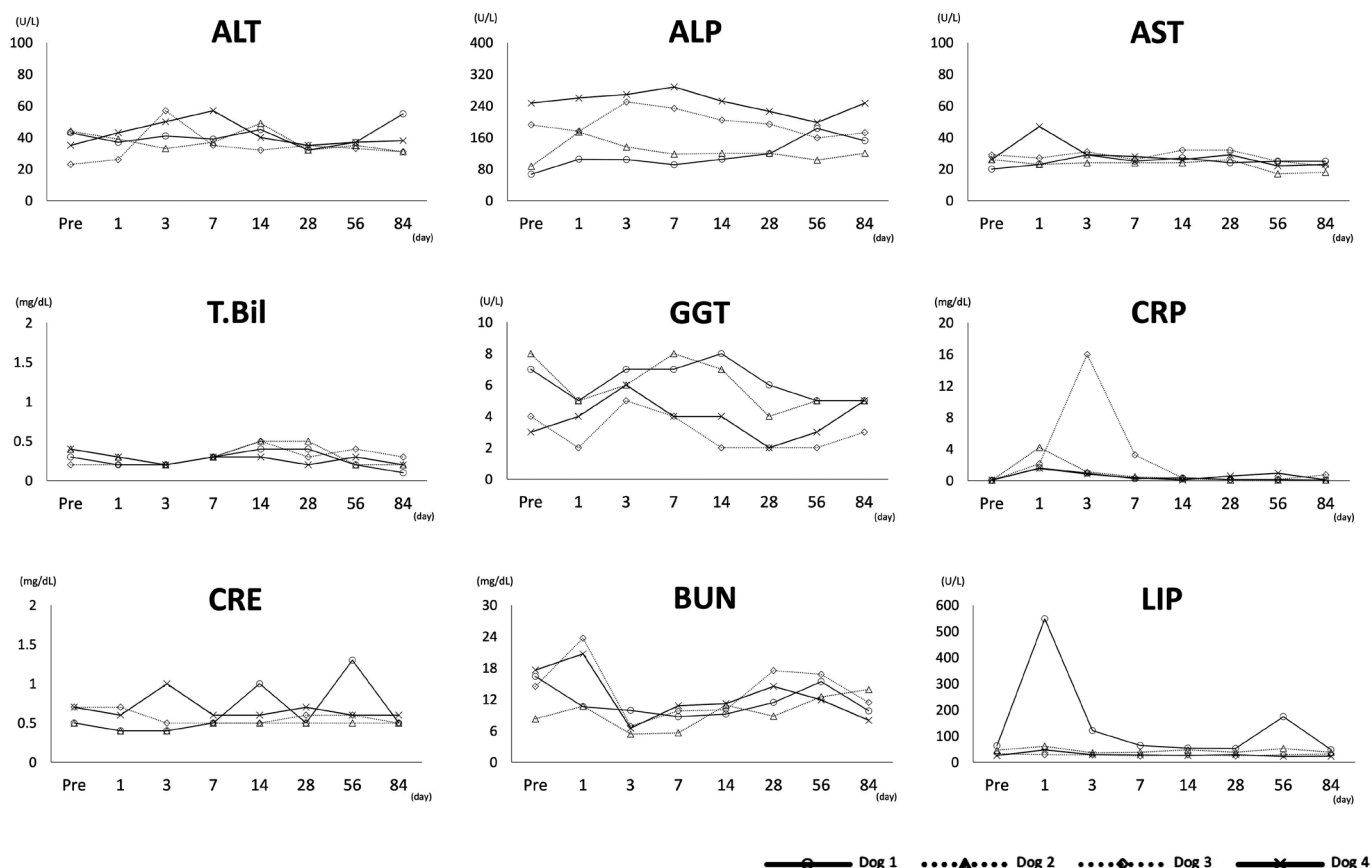


Fig. 3. Changes in alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), total bilirubin (T.Bil), γ -glutamyl-transpeptidase (GGT), C-reactive protein (CRP), creatinine (CRE), blood urea nitrogen (BUN), and lipase (LIP) levels during the clinical period.

the serum Pt concentration was initially lower in the cirrhotic group than that in the normal liver group. Pharmacokinetics may be altered in patients with hepatic tissue damage and impaired liver function. For these reasons, DEB-TACE can possibly keep serum concentrations low through the intra-arterial administration of anticancer drugs, prolonging the accumulation of anticancer drugs in the liver by blocking blood flow.

In our study, embolization of the hepatic artery persisted for 4 weeks in two of four dogs, but the remaining two dogs were recanalized 1 week later. Hepasphere is considered a permanent embolic agent, but the beads move distally by redistribution [3, 29]. The permanent occlusion of the hepatic artery imaged by DSA is not achieved with beads as small as 700 μm [30]. A previous report [14] described that beads redistributed to deeper regions could be phagocytosed or ejected out of the vessel. We used Hepasphere with a size of 50–100 μm before expanding and a diameter of about 540 μm after expanding, so the beads may have moved to more peripheral vessels because of redistribution and recanalization. Furthermore, Hepasphere released the drug gradually, which may have reduced its size and caused recanalization. According to Kocyigit *et al.* [12], occlusion of the feeding artery for a short period of time was found sufficient for achieving satisfactory ischemia. In addition, TACE was performed multiple times and was scheduled to be repeated every 2–6 months [13] or on demand [8], during which TACE was added as the tumor remained or relapsed. For these reasons, permanent embolization of the vessel in a single treatment may not be necessary.

In this study, no obvious abnormalities in the liver tissue distal to the embolization site were observed. The liver blood supply is provided by two vessels, the hepatic artery (approximately 20%) and portal vein (approximately 80%) [19]; however, HCC is mainly perfused by the hepatic artery [17, 20]. Therefore, TACE is believed to be able to embolize the tumor's feeding artery while sparing the surrounding liver parenchyma [16, 33, 34]. Although this study was conducted in normal dogs, selective embolization of the tumor's feeding artery is expected to have little effect on the normal liver tissue in HCC.

Embolization with smaller particles has been found to increase tumor ischemia, but it is also more likely to cause complications such as bile duct injury or liver necrosis [5, 23, 27]. We used a small-sized particle for DEB-TACE, but no such pathological abnormalities were observed in this study. The use of small particles for DEB-TACE may not be associated with those complications, although a smaller volume of embolization was carried out in this study than that used in a case with tumor.

In veterinary medicine, liver lobectomy is considered the gold standard for dogs with HCC even with incomplete resection [11, 18], and interventional radiology (IVR) is still not widely used. The less number of dogs in each group, lack of a control group,

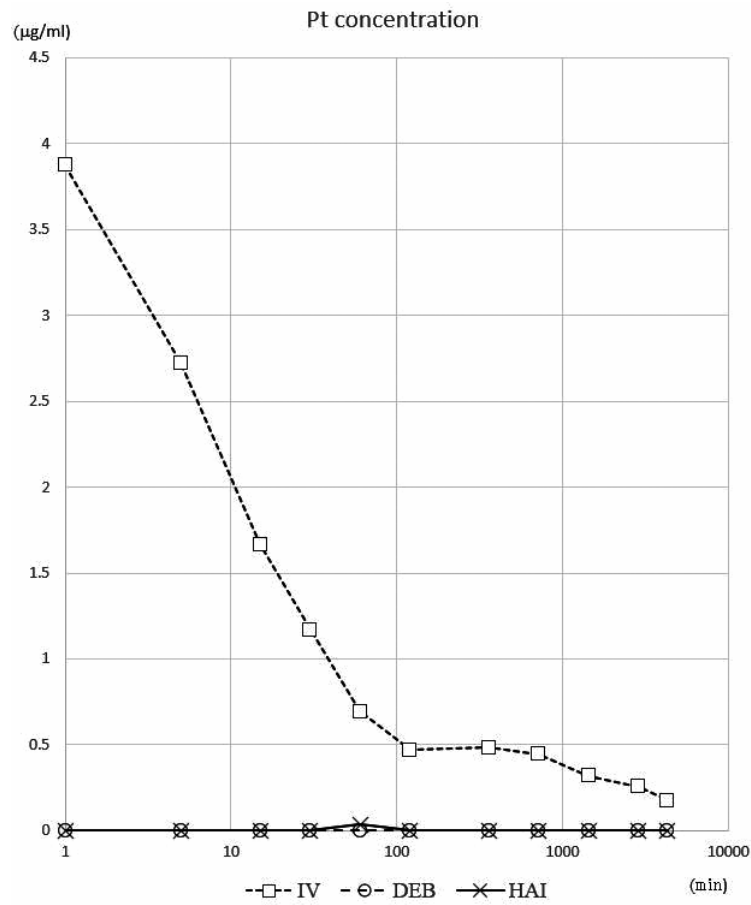


Fig. 4. Blood levels of serum platinum (Pt) in dogs after treatments with hepatic arterial infusion (HAI), drug-eluting bead transarterial chemoembolization (DEB-TACE), or intravenous infusion (IV) of the cephalic vein. A trace amount of Pt was detected in two dogs only 6 hr after administration, although it was close to the detection limit.

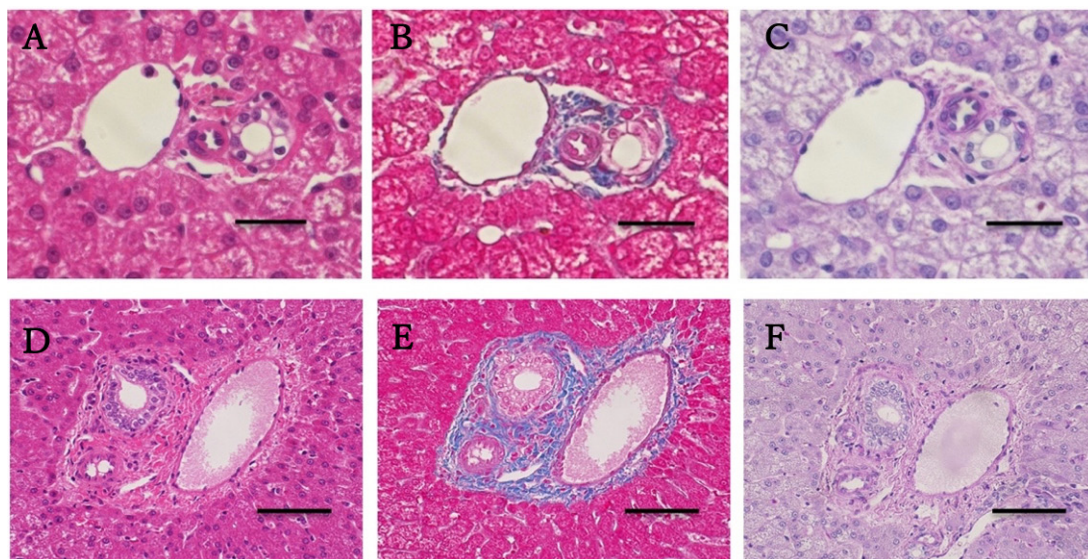


Fig. 5. Histological appearance of the left lateral liver lobes 1 week after treatment. Staining with **A.** hematoxylin–eosin, **B.** Azan, and **C.** periodic acid-Schiff. At 2 weeks after treatment, after staining with **D.** hematoxylin–eosin, **E.** Azan, and **F.** periodic acid-Schiff. No obvious abnormalities were observed in these liver tissues. Scale bar=100 µm.

and use of DEB doses different from those used in clinical practice were the limitations of this study. These may have affected the accuracy of the investigation. Despite these limitations, DEB-TACE has been demonstrated to be safe in normal dogs. It was noted that DEB-TACE embolized the hepatic artery while reducing systemic exposure to the anticancer drug through sustained release in normal dogs. Further studies are needed to assess whether the application of DEB-TACE is more clinically relevant in dogs with unresectable hepatocellular carcinoma.

CONFLICT OF INTEREST. The authors declare no conflicts of interest.

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