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TECHNICAL NOTE

Development of Repeatable Microcatheter Access Port for Intra-arterial Therapy of Liver Cancer

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Abstract
Purpose To develop an implantable port in which a microcatheter can be inserted for a combination therapy of repeated transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC) for advanced liver cancer.
Materials and Methods The design of a currently used implantable port was modified. A funnel part was constructed in the port. The septum was punctured by a 20-gauge indwelling needle, and 2.0-Fr non-tapered microcatheter was inserted into the port. In the in vitro studies, the advance of a microcatheter out of the funnel part was evaluated via seven different septum puncture sites. A 5-Fr indwelling catheter connected to the port was placed in a vascular model, and a microcatheter catheterization was evaluated. In an in vivo study, the port–catheter system was implanted in the hepatic artery in a pig. A microcatheter was percutaneously inserted through the port into the hepatic arterial branches, and embolization was performed.
Results In the in vitro studies, the microcatheter was smoothly advanced out of the port and catheterizations into the hepatic arteries were successful via all septum puncture sites. In the in vivo study, repeated selective embolization through the port was successfully conducted on 7, 14 and 21 days after the implantation.
Conclusion The developed implantable port can be used for repeated catheter insertion into the hepatic artery. The combination of repeated TACE and HAIC could be possible using this device.

Keywords Transarterial chemoembolization · Hepatic arterial infusion chemotherapy · Implantable port

Introduction

There are various treatment options in intra-arterial therapy for advanced liver cancer [1–3]. Transarterial chemoembolization (TACE) using drug-eluting microspheres is widely performed in liver metastases, i.e., colorectal cancer (mCRC) [4, 5]. Hepatic arterial infusion chemotherapy (HAIC) is also an effective treatment for mCRC [6–8].

In general, for advanced liver cancers, repeated TACE is required. The previous reports showed that TACE using irinotecan-eluting microspheres is performed 2–5 times in mCRC patients [9]. Longer progression-free survival by repeated TACE may improve the overall survival duration [10]. Therefore, smaller or biodegradable microspheres have been innovated to improve the repeatability of TACE [11–16].

After achieving a tumor response using TACE, effective maintenance chemotherapy is required. Alternative treatments of TACE and chemotherapies may be effective [17]. However, many patients who are receiving TACE have already been refractory to standard systemic

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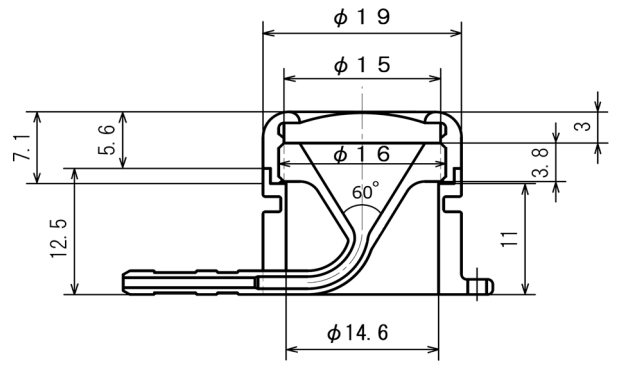
chemotherapies [18, 19]. In such a situation, HAIC might be promising to suppress tumor regrowth after TACE.

To perform combination treatments of repeated TACE and HAIC, a repeatable microcatheter access port was developed. Herein the in vitro and in vivo experimental results using this device are shown.

Materials and Methods

Concept and Development of Repeatable Microcatheter Access Port

The design of a currently used port was modified. This developed port was constructed in three parts, a body, a funnel and a cap. A silicon septum was inserted into the cap part. The diameter of the septum was set 15 mm for a needle to easily puncture the septum. The slope of the funnel was set at a 60° angle for a microcatheter to smoothly slide along the funnel wall to the bottom (Fig. 1). The surface of the inner lumen of the funnel part was carefully polished by a polish machine (SMAP, Toyo Kenmazai Kogyo Ltd., Tokyo, Japan) to achieve a smooth insertion of a microcatheter. TAMACHI INDUSTRIES Co., Ltd. (Tokyo, Japan), manufactured this prototype port.



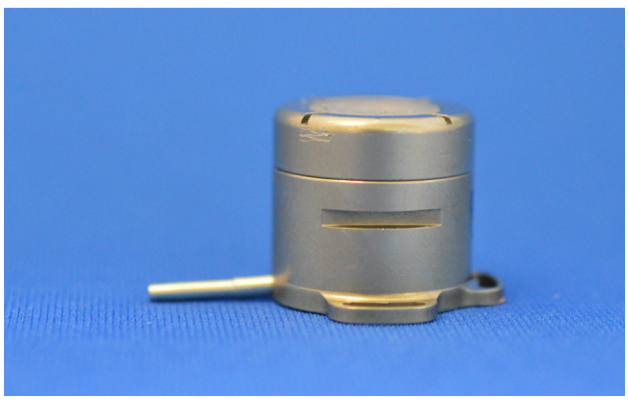


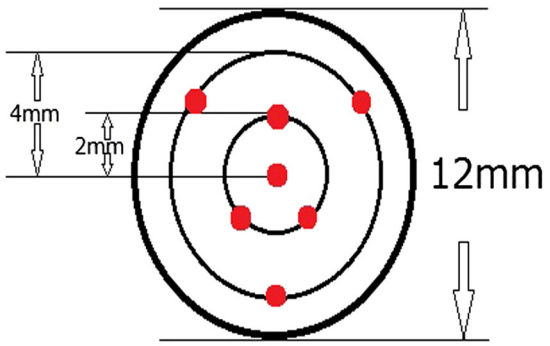
Fig. 1 Design and picture of the port. The diameter of the septum is 15 mm. The slope of the funnel is 60° angle. The height of the port is 18 mm

A 20-gauge indwelling needle consisting of an inner needle and outer cylinder needle was used for the puncture of the septum of the port allowing for a 2.0-Fr microcatheter to be inserted.

In Vitro Evaluation

Firstly, advance of a microcatheter out of the port was tested. A total of seven puncture sites were selected on the septum, center, and 2 mm and 4 mm concentrically from the center (Fig. 2). The septum was punctured vertically by a 20-gauge indwelling needle (Surflo; Terumo, Tokyo, Japan). After removal of the inner needle, a commercially available 2.0-Fr non-tapered microcatheter (Carnelian Marvel, Tokay Medical Product, Kasugai, Japan) with an 0.014-inch guidewire (GT wire, Terumo) was inserted into the port. The success rate of the microcatheter with a guide wire which was passed through the funnel part was evaluated.

Secondly, an anticoagulant-coated indwelling catheter, with a 5-Fr proximal shaft and a 2.7-Fr distal shaft (Anthron PU catheter, Toray Medical, Urawa, Japan), was



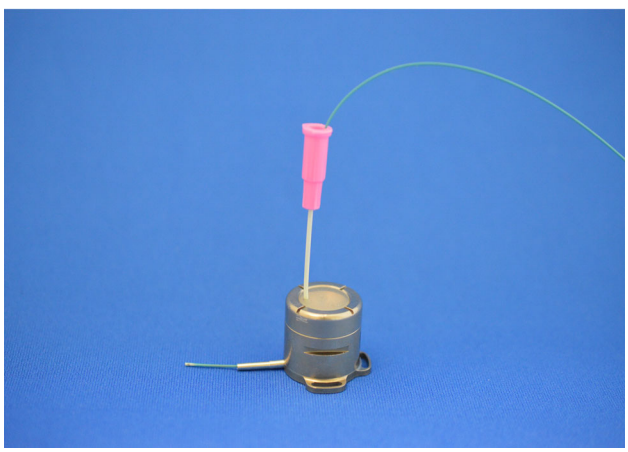


Fig. 2 First part of the in vitro study. A total of seven puncture sites were selected on the septum, center, and 2 mm and 4 mm concentrically from the center. The septum was punctured vertically by a 20-gauge indwelling needle, and a microcatheter was inserted through the needle

placed in a vascular model. A side hole approximately 3 mm in size was created with a scissor cut at the transition zone from the shaft to the tapered tip (Fig. 3). The tip of the catheter was inserted into the gastroduodenal artery, and the side hole was positioned in the common hepatic artery. The proximal end of the catheter was connected to the developed port. A microcatheter was inserted into the port at each of the seven puncture sites, and the tip of the microcatheter was ejected from the side hole. Then, the microcatheter was inserted into the right and left hepatic arteries (Fig. 4). The success rate of the selective insertion of the microcatheter into the hepatic arterial branch was evaluated.

In Vivo Evaluation

The study was performed at Veterinary Medical Center, Osaka Prefecture University, Japan. The study protocol was approved by the State Committee of Osaka Prefecture University. One pig weighing 55 kg was used. After intramuscular premedication atropine and ketamine, anesthesia was induced by intravenous injection of diluted pentobarbital. The animal was orotracheally intubated and mechanically ventilated with an oxygen–air mixture containing halothane.

The right iliac artery was exposed via a surgical cutdown, and a 4-Fr sheath (Hanako Medical, Tokyo, Japan) was introduced. A 4-Fr cobra-shaped angiographic catheter (Hanako Medical) was inserted into the celiac trunk, and a celiac angiogram was obtained. A 2.5-Fr, 105-cm-long microcatheter (Renegade, Boston Scientific, Marlborough, USA) was inserted into the gastroduodenal artery. A 0.018-inch, 205-cm stiff guide wire (Rainbow, Piolax Medical Devices, Yokohama, Japan) was inserted through the microcatheter. Then, the whole system, including the sheath, the angiographic catheter and the microcatheter,

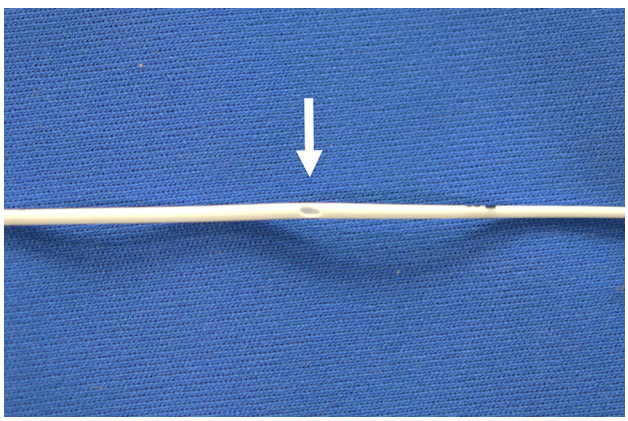


Fig. 3 Tapered indwelling catheter. A side hole approximately 3 mm in size was created at the transition zone from a 5-Fr proximal shaft to a 2.7-Fr tapered tip (arrow)

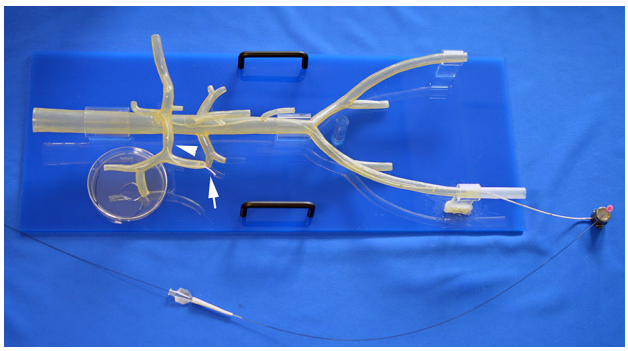


Fig. 4 Second part of the in vitro study using a vascular model. A 5-Fr indwelling catheter was placed in the vascular model. The catheter tip was inserted into the gastroduodenal artery (arrow), and the side hole was positioned at the common hepatic artery (arrowhead). A microcatheter with a guidewire was inserted into the hepatic artery through the indwelling port–catheter system

was replaced by the indwelling catheter with a handmade side hole (Anthron PU catheter) which was used in the in vitro study. The catheter tip was inserted into the distal gastroduodenal artery, and the side hole was positioned at the common hepatic artery. The side-hole position was confirmed by contrast material injection. A microcatheter was coaxially inserted into the indwelling catheter and advanced into the gastroduodenal artery through the side hole. Embolizing metallic coils (Tornado; Cook, Bloomington, USA) were placed into the gastroduodenal artery through the microcatheter to occlude the gastroduodenal artery and fix the indwelling catheter tip to the gastroduodenal artery [20]. Finally, at the right inguinal region, a U-shaped subcutaneous tunnel was created up from the iliac arterial puncture site. The proximal end of the catheter was connected to the developed port embedded under the skin.

Seven days after the implantation of the port–catheter system, the port was punctured percutaneously by a 20-gauge needle, and a 2.0-Fr non-tapered microcatheter with a 0.014-inch guidewire was introduced into the port. The microcatheter was inserted into the hepatic arterial branch in a segmental level selectively, and lipiodol emulsion was injected. Repeated embolization with an emulsion of lipiodol 4 mL and contrast material 2 mL was performed every week for 3 weeks. After each embolization procedure, the microcatheter was removed and heparin at a dose of 2.5 mL was injected in the port–catheter system. The pig was moved to a CT room, and a CT scan was obtained to confirm the embolization area.

Results

Accessibility of a Microcatheter Through the Port

In the first part of the in vitro study, the microcatheter was advanced out of the funnel part via all seven puncture sites. In the second part, in all seven puncture sites, the microcatheter was ejected via the side hole and was inserted into the left and right hepatic arteries of the vascular model.

Feasibility of Selective TACE Through the Port

The catheter–port system was successfully placed into the pig. On day 7 after the port–catheter system implantation, the pig was carried to the angio-room and a hepatic arteriography was obtained via the port (Fig. 5). Then, a microcatheter was inserted percutaneously through the port. The tip of the microcatheter was extracted through the side hole and selectively inserted into the left hepatic artery. During the catheterization procedure, no bleeding occurred beside the inserted microcatheter. Embolization with lipiodol emulsion was performed in the left lateral segment. This procedure was successfully repeated. The right anterior and middle hepatic arteries were embolized on days 14 and 21, respectively (Fig. 6).

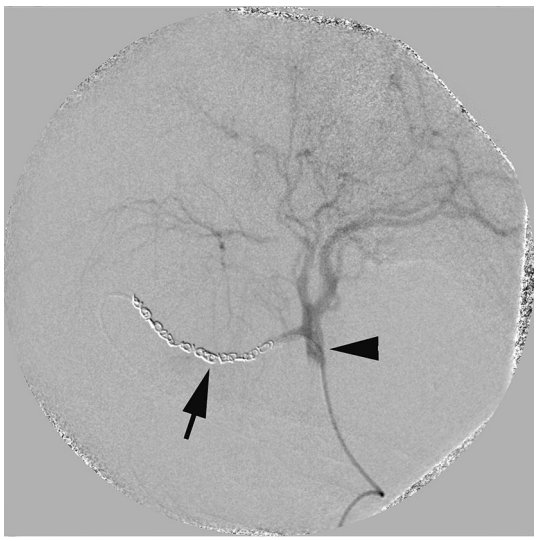


Fig. 5 Hepatic arteriography via the port. A 5-Fr indwelling catheter was placed in the vascular model. The catheter tip was inserted into the gastroduodenal artery (arrow), and the side hole was positioned at the common hepatic artery (arrowhead)

Discussion

Previously, Itano et al. [21] reported their development of a microcatheter accessible system, System-i, in which a latex rubber cap was connected to an indwelling 5-Fr catheter and subcutaneously implanted. In their system, the rubber cap had to be punctured for the microcatheter insertion, which was technically quite difficult because the puncture target was a small size and the puncture direction was parallel to the skin. To overcome the difficulty of the puncture, the shape and design of our device were modified based on currently used central venous or arterial ports. The top of the port can be easily punctured vertically to the skin. The septum with 15 mm in diameter also allowed a needle to blindly hit.

In the construction of this port, the shape of the funnel part was paramount. A microcatheter inserted through the septum must allow smooth advance out of the port. The peripheral puncture site in the septum could make it difficult. However, the advance of a microcatheter was successful via all puncture sites. The funnel with a standard angel of 60° could be optimal for a microcatheter to slide to the bottom. The 18 mm height of the port was based on the ratio of the diameter of the septum to the angle of the funnel. This height could be acceptable for subcutaneous implantation.

The in vivo study showed the feasibility of the repeated selective TACE. The microcatheter was successfully inserted via the port, and selective catheterization was performed every week for 3 weeks. No bleeding occurred through the needle puncture site. The system was not obstructed during the observation period. In this pig study, the iliac artery was exposed via a surgical cut-down to prevent kinking of the catheter due to any leg movement. In clinical practice, percutaneous catheter insertion technique was established without any difficulties in HAIC using the port–catheter system.

The concept of this device is to perform repeated TACE and also to perform HAIC. Intermittent tumor volume reduction could be achieved by repeated selective or non-selective TACE and maintenance therapy by HAIC which could suppress tumor regrowth. The efficacy of this combination must be evaluated in clinical studies.

There are several limitations in this study. Firstly, the in vivo study was performed using only one pig. Secondly, we used a normal puncture needle. Before clinical use of this system, development of a Huber needle with an outer cylinder is essential. Thirdly, the tolerability of the silicon septum by multiple punctures using a 20-gauge needle must be checked.

In conclusion, a microcatheter access port was developed and the feasibility of repeated microcatheter insertion

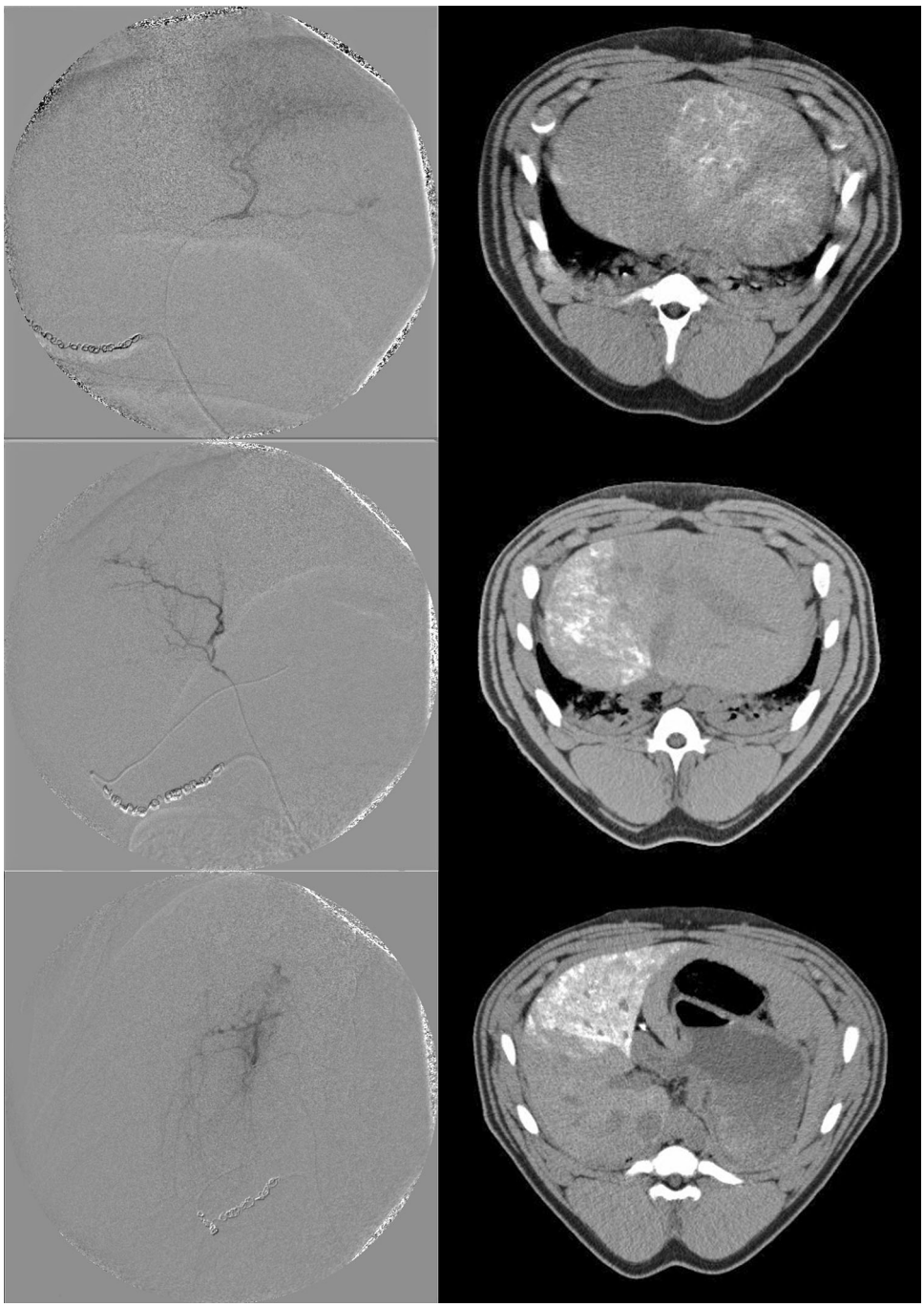


Fig. 6 Selective arteriography and CT after injection of lipiodol emulsion. A microcatheter was inserted into the left hepatic artery on day 7 (top), the right anterior hepatic artery on day 14 (middle) and the middle hepatic artery on day 21 (bottom)

was shown in an in vitro and an in vivo study. The combination of repeated TACE and HAIC for liver tumors could be possible using this device.

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Compliance with Ethical Standards

Conflict of interest All authors have no conflicts of interest and financial disclosures to declare.

Ethical Approval All applicable institutional and national guidelines for the care and use of animals were followed.

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