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Liver parenchyma access and lesion marker via the endovascular route

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ABSTRACT

Background: Neoadjuvant chemotherapeutic regimens for metastatic colorectal cancer are now so effective that they can cause "vanishing" lesions. With new advances such as local ablation, intra-arterial treatments in bolus with pumps or with beads, and isolation of hepatic perfusion, the need for a working channel to the liver may be warranted, ideally reducing the risk of spreading neoplastic cells.

Materials and methods: The endovascular trans-vessel wall Extroducer device makes it possible to gain direct access to the liver parenchyma. The distal tip is then detached, to act as both a marker and a securing plug in the vessel defect. We used *ex vivo* and *in vivo* tests to evaluate the device as a working channel for local administration of substances to the parenchyma and as a marker for detection with both transabdominal and intraoperative ultrasonography.

Results: We could deploy the Extroducer device without any hemorrhagic or thromboembolic complications *in vivo*, and we were able to detect all markers *ex vivo* and *in vivo* using both transabdominal and intraoperative ultrasonography. Furthermore, we found that it is possible to administer substances to the liver parenchyma using the catheter.

Conclusions: The trans-vessel wall technique can be used to establish a working channel to the liver parenchyma for administration of any substance, such as chemotherapeutic agents or cells. The detached device can also be used as a marker for ultrasound-guided partial liver resection in "vanishing lesions." The technique should have a low risk of seeding of neoplastic cells. This study in large animals forms a strong basis for translation to clinical studies.

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1. Introduction

From the first liver resection for metastatic colorectal cancer [1], significant progress has been made. Several large studies have further confirmed that liver resection is effective and has a curative aim [2–4]. With the introduction of the oxaliplatin-based chemotherapy regimens, it was suggested that such regimens could be used to downstage or convert patients from the unresectable category to resectable, with long-term outcome approaching the post-neoadjuvant staging [5].

An emerging and paradoxal difficulty in the treatment of liver metastases of colorectal cancer is the improving responses to neoadjuvant chemotherapy. Disappearing or vanishing metastases on imaging are often clinically challenging to handle because their exact location may be difficult to determine during surgery. Several studies have shown that most vanishing liver metastases still contain viable tumor cells and will indeed recur [6,7]. They should therefore be removed during surgery if possible. However, because they are not macroscopically visible, it can be very challenging to achieve a curative resection. In these situations, it would be advantageous to be able to locate these vanishing metastases.

Intraoperative ultrasonography (IOUS) has been developed to facilitate radical resection of lesions. Despite the advancements with IOUS, some vanishing lesions are still difficult to find, which would warrant use of a marker of some kind. Placement of markers using the transabdominal approach would mean a risk of needle-tract deposits. Data from animal experiments [8–10] and clinical studies [11,12] suggest spread of neoplastic cells by way of puncture canals. Human-based data have been reviewed by Cresswell *et al.* [13]. The possibility of needle-tract deposits makes the trans-vessel wall approach interesting to explore. Furthermore, avoidance of the percutaneous approach for local administration of substances or cells by the endovascular route, thereby avoiding possible needle-tract metastasis, might possibly add another method to the toolbox of neoadjuvant therapies.

Modern imaging-based interventional techniques now provide alternatives to open surgical access, and arteries and veins can be regarded as "internal routes" to essentially anywhere in the body. Here we propose trans-vessel wall access to the liver parenchyma based on the use of a prototype catheter system [14–16]. A standard endovascular clinical catheter system, including an introducer, a guide catheter, and a microcatheter, is used to navigate within the vasculature to the hepatic artery. Once the microcatheter is in the desired location within the microvasculature, the prototype system is advanced through the microcatheter. The prototype catheter (distal outer diameter 0.193 mm ± 0.0127 mm, inner diameter 0.104 ± 0.0127 mm, and total length 1700 mm) then safely penetrates the arterial wall, as a "nano"catheter, to reach the extravascular space, for example, the parenchyma of the liver, using the same principle as the introducer (see schematic Fig. 1) [15,17]. A working channel is then established, and one has the possibility to either administer substances or perform sampling. At the end of the procedure, the most distal part is detached and left in place as a securing plug in the vessel wall to prevent bleeding. This is well tolerated, and it has been followed for over 1 y in swine pancreas with no adverse effects [14].

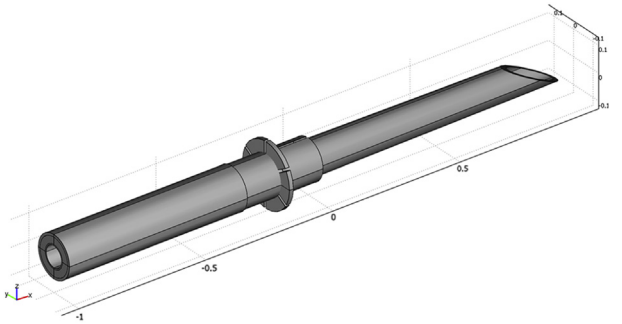

Fig. 1 – A principal drawing of the most distal part of the design is depicted with an intrusion depth-limiting collar. The catheter itself has the following properties: outer diameter 0.193 mm ± 0.0127 mm, inner diameter 0.104 ± 0.0127 mm, and total length 1700 mm. (Color version of figure is available online.) The figure is reprinted from *Lundberg J, Jonsson S, Holmin S (2010) New Endovascular Method for Transvascular Exit of Arteries and Veins: Developed in Simulator, in Rat and in Rabbit with Full Clinical Integration. PLoS ONE 5(5): e10449. doi:10.1371/journal.pone.0010449* under the Creative Commons Attribution License.

The main aim of this study was to test the feasibility of establishing a trans-vessel wall working channel to the liver parenchyma. Secondary objectives were to use the distal tip as a marker for IOUS and possibly transabdominal ultrasound (US), to be used for surgical planning and to administer different local injections to the liver parenchyma as a simulation of administration of therapeutic substances.

2. Materials and methods

All animal studies were conducted according to the Karolinska Institutet guidelines for animal experiments. The studies were approved by the regional ethics committee for animal research in Stockholm, Sweden, and they followed the ARRIVE guidelines.

2.1. *Ex vivo*

Initial *ex vivo* US tests were used to determine the visibility of the Extroducer device with US. Thus, the device was placed in US gel of increasing thickness (Aquaflex US gel pad and Aquasonic 100 US transmission gel; Parker Laboratories, Fairfield, NJ) and examined. Thereafter, two calf livers were obtained from a carcass. Detached distal tips were introduced from a syringe to the interior of the liver and then visualized in different projections by placement of the US probe on the surface of the liver.

2.2. *In vivo*

Three Swedish female rural swine were included for acute testing of the trans-vessel wall working channel with four