In Vivo Proof of Superselective Transarterial Chemoembolization with 40-mu m Drug-Eluting Beads in a Patient with Hepatocellular Carcinoma

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BRIEF COMMUNICATION

In Vivo Proof of Superselective Transarterial Chemoembolization with 40-μm Drug-Eluting Beads in a Patient with Hepatocellular Carcinoma

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Introduction

Transarterial chemoembolization (TACE) is the current standard of care in patients with hepatocellular carcinoma (HCC) when curative therapies, including hepatic resection, image-guided ablation, or liver transplantation, are precluded. In the multicenter PRECISION V study comparing conventional lipiodol-based TACE with drug-eluting bead TACE (DEB-TACE) in patients with intermediate-stage HCC, DEB-TACE was associated with lesser cardiac and hepatic toxicity although no superior survival benefit was confirmed [1]. In choosing the optimal size of DEB, the use of 100–300-μm DEB is generally recommended since this is the most commonly available size, but there is still relatively lack of comparative data on the optimal size of the beads. Recently, drug-eluting beads with a diameter of 40 ± 10 μm have been introduced. Theoretically, smaller beads penetrate deeper within a tumor allowing more effective drug delivery. We report a case of TACE with 40-μm beads in a patient with hepatocellular carcinoma with histopathological correlation.

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Case Report

Medical ethical approval is not required in our institution for anonymized case reports. Informed consent was obtained for the procedure. A 57-year-old woman with hepatitis C cirrhosis and Child-Pugh classification C underwent 3-phase contrast-enhanced computed tomography (CECT) as part of screening for liver transplantation. A solitary, 2.5-cm exophytic lesion was seen in segment 8 (Fig. 1A, B). The lesion showed marked enhancement in the arterial phase and wash-out in the delayed venous phase, and the diagnosis of HCC was made. Blood tests showed the following results: bilirubin 75 μ/L (reference range 5–21 μ/L), albumin 28 g/L (reference range 37–47 g/L), ASAT 80 U/L (reference range 12–37 U/L), alkaline phosphatase 172 U/L (reference range 30–120 U/L), thrombocytes 64×10^9/L (reference range $145–370 \times 10^9$/L), and INR 1.5 (reference range 0.8–1.2). Radio-frequency ablation (RFA) was considered as a "bridge-to-transplant", but the risk of RFA was considered to be high because of (1) the subcapsular location, (2) location in the dome of the liver, (3) Chilaiditi's sign, and (4) deranged coagulation profile. TACE with 40-μm drug-eluting beads was therefore performed as the bridging therapy (Fig. 1C, D). Catheterization was performed via a femoral artery, and superselective embolization of subsegmental arteries of segment 8 was performed using a 2.4F Progreat microcatheter (Terumo, Tokyo, Japan). Cone-beam computed tomography (CBCT) was performed to ensure that the tumor was targeted accurately and completely. One and a half milliliters of DEB 40 ± 10 μm (Tandem; CeloNova BioSciences, Newnan, GA) loaded with 50 mg of doxorubicin was injected until stasis was observed in the tumor-feeding arteries. Unenhanced CBCT

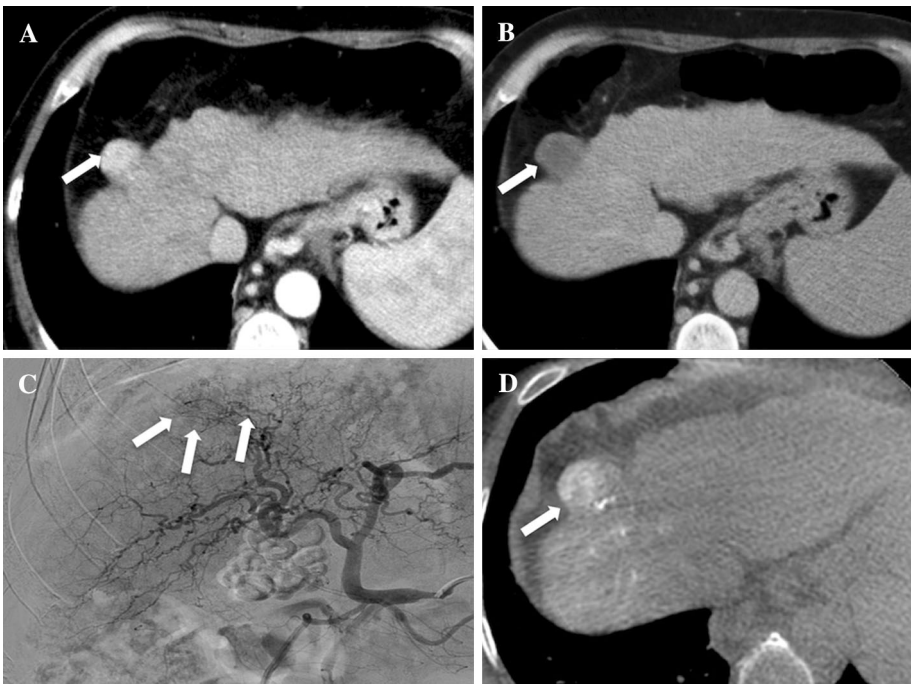

Fig. 1 **A** Axial image of arterial-phase contrast CT before treatment showed arterial-enhancing tumor within the segment 8 of the liver with Chilaiditi's sign. **B** Axial image of the delayed-phase contrast CT showed the segment 8 tumor had contrast wash-out. **C** Hepatic digital subtraction angiography before TACE showed fine tumor stains with small feeding subsegmental arteries. **D** Cone-beam CT with catheter within the subsegmental artery prior TACE demonstrated arterial enhancement within the tumor

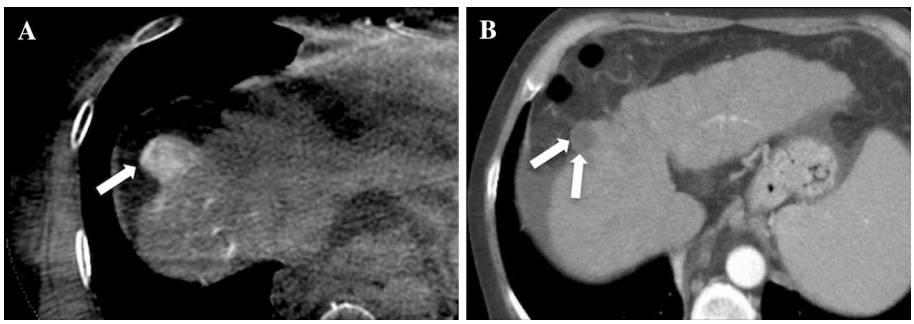

Fig. 2 **A** Superselective TACE was performed. Cone-beam CT immediately after TACE showed satisfactory staining of the tumor. **B** Follow-up CT showed devascularization and shrinkage of the tumor

was repeated immediately after the procedure and demonstrated satisfactory staining (Fig. 2A). Follow-up CECT 6 weeks later demonstrated reduction in tumor size to 1.3 cm and absence of enhancement (Fig. 2B), consistent with complete response according to modified response evaluation criteria in solid tumors (mRECIST) criteria. The patient underwent liver transplantation 5 months later. Histopathology of the liver specimen demonstrated complete necrosis of the tumor with a high number of DEB within the tumor and penetration of beads as far as into the interstitium (Fig. 3).

Discussion

Over the past decade, DEB-TACE has replaced conventional TACE in many, mostly European, centers. Most centers in Asia, where HCCs are prevalent, still use conventional TACE. The advantage of DEB-TACE is that it allows standardization of the chemotherapeutic dose with sustained, slow drug release. Yet, beads of 100–300 or 300–500 μm do not penetrate deep into the vascular bed. An animal study has demonstrated that beads of 100–300 μm size predominantly lodge in periphery of tumors with limited penetration to the central part of the lesion and that beads of 300–500 μm usually do not even reach the tumor [2]. The advantage of conventional TACE is that it allows deep, large volume penetrations of lipiodol emulsions. A previous animal study has concluded that the optimal formula of water-in-oil emulsion with a droplet diameter of 30–120 μm allows most hepatic tumor uptake with limited pulmonary uptake [3].

In a recent animal study, histological examinations showed that 40-μm Tandem microspheres do penetrate deep into the tumor [4]. Our case confirms that 40-μm Tandem beads allow deep and large volume implantation into the tumor. Histological examinations showed the

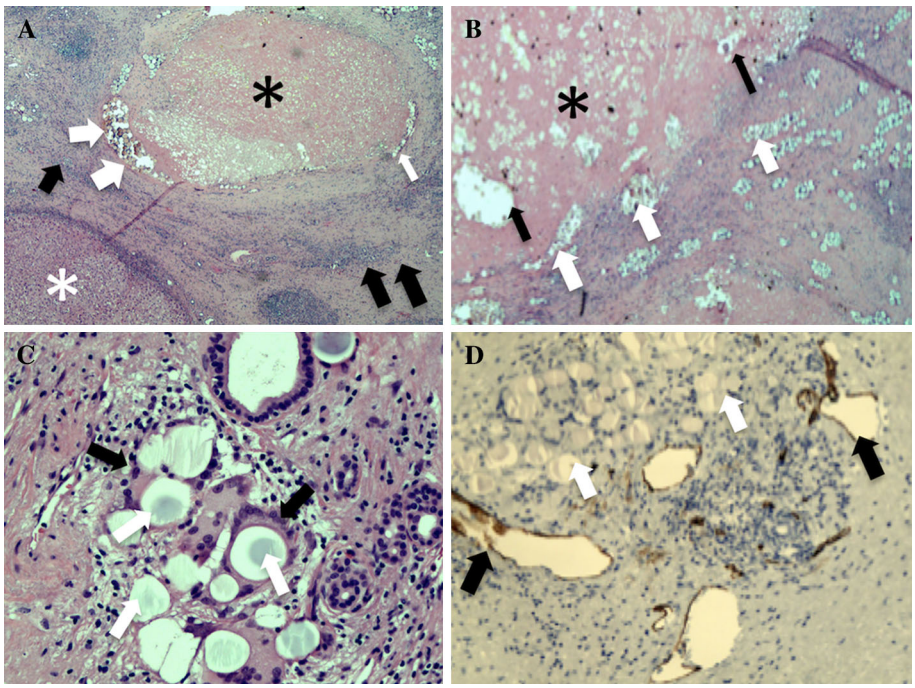

Fig. 3 Histopathology images of the explanted liver. **A** Necrotic hepatic tumor (*black asterisk*), surrounded by DEB (*white arrows*) and marked extravasation of inflammatory cells (*black arrows*). Adjacent cirrhotic nodule was present (*white asterisk*) (hematoxylin and eosin stain; original magnification, ×10). **B** Necrotic tumor (*black asterisk*) with DEB present within (*black arrows*) and surrounding the tumor (*white arrows*) (hematoxylin and eosin stain; original magnification, ×5). **C** DEB (*white arrows*) surrounded by multinucleated giant cells of foreign body type (hematoxylin and eosin stain; original magnification, ×40). **D** DEB (*white arrows*), in large numbers, within the interstitium, with adjacent capillaries observed. (CD34 immunostaining of capillaries; original magnification, ×20)

presence of doxorubicin beads within the interstitium of the tumor, the deepest level achievable. The number of beads within the tumor was remarkably high, which is probably accounted for by the fact that the 40-µm TANDEM microspheres have 21×10^8 microspheres per mL, 210 times the conventional 100–300-µm DEB.

A study by Kwan et al. demonstrated that the level of vascular occlusion and necrosis correlates with vessel size, with the odds of achieving complete necrosis for a feeding artery larger than 0.9 mm which is approximately 3–5 times higher than with a feeding artery <0.9 mm in size [5]. Nonetheless, tumors may have a large degree of variation in vessel diameter, and hence perfect matching is often not feasible. We reserved the use of 40-µm Tandem microspheres in those HCC cases where the feeding hepatic artery vessel is <1 mm in size anticipating for those cases when early stasis would be encountered with larger beads. With the smaller particle size comparable to droplet size of drug–oil emulsion, 40-µm Tandem beads may allow drug delivery deep into the tumor comparable to conventional TACE. At the same time, it offers the advantages of drug-eluting beads.

No pulmonary or biliary complications occurred in our case. Potentially, TACE with smaller-sized embolic agents can result in biliary damage and liver dysfunction [6]. It is pertinent to be aware of arteriohepatovenous shunting to avoid pulmonary damage. In cases where significant arteriovenous shunting is seen or suspected, embolization with 40-µm beads would probably be contra-indicated. Nonetheless, we should be aware of the potential pulmonary uptake through radiologically occult transtumoral arteriovenous shunts when we use smaller-sized DEB.

In conclusion, our report demonstrates that 40-µm drug-eluting beads may reach deep into a hepatocellular carcinoma and in large quantities. Careful case selection and further studies are needed to validate the use of these small-sized particles in the treatment of HCC.

Conflict of interest All authors (Hoi Lam SHE, Mark Christiaan BURGMANS, Minneke COENRAADM, and Arantza Farina SARAQUETA) have no real or perceived conflict of interest to disclose.

Statement of Informed Consent The current study is performed in accordance to the institution ethic review board, and medical ethical approval is not required in our institution for anonymized case report.

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