

[CASE REPORT]

Huge Hepatocellular Carcinoma Treated with Radical Hepatectomy after Drug-eluting Bead Transarterial Chemoembolization

Masashi Fujita¹, Ken Okai¹, Manabu Hayashi¹, Kazumichi Abe¹, Atsushi Takahashi¹, Takashi Kimura², Akira Kenjo², Shigeru Marubashi², Yuko Hashimoto³ and Hiromasa Ohira¹

Abstract:

We performed split drug-eluting bead transarterial chemoembolization (DEB-TACE) in a patient with huge unresectable hepatocellular carcinoma and multiple intrahepatic metastases. However, TACE was discontinued at the fourth application because the tumor was fed by the cholecystic artery. As most intrahepatic metastases disappeared following DEB-TACE, the patient was able to undergo radical hepatectomy, and has maintained a complete response. DEB-TACE enables cancer treatment without reducing the liver or renal function. However, it is associated with a risk of ischemia in other organs in patients whose arteries feed both tumors and other organs; thus appropriate selection is required.

Key words: huge hepatocellular carcinoma, hepatectomy, drug-eluting beads, transarterial chemoembolization

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Introduction

Transarterial chemoembolization (TACE) is effective for huge unresectable hepatocellular carcinoma (HCC). In Japan, conventional TACE (cTACE) has typically been performed using various chemotherapies with different embolic agents and lipiodol (1). TACE using drug-eluting beads (DEB) was introduced in Japan in 2014, and the treatment response and overall survival of patients treated with DEB-TACE have been reported to be better than those of patients treated with cTACE (2-4). However, no standard treatment for huge unresectable HCC has been established-especially with DEB-TACE.

We herein report the systematic performance of split DEB-TACE in a case involving a patient with huge unresectable HCC. Following split DEB-TACE, the patient was able to undergo radical hepatectomy and has maintained a complete response (CR). We discuss the effectiveness and limitations of DEB-TACE for huge unresectable HCC.

Case Report

In May 2014, a 60-year-old man, who had been diagnosed with diabetes 10 years previously and who had undergone total cystectomy for bladder cancer six years previously was found to have a 12 cm liver tumor by computed tomography (CT) in a local hospital. He had no family history of liver disease. He had not previously received any blood transfusions, nor did he regularly consume alcohol. Multidetector CT showed a huge focally enhanced lesion in segment 4, and multiple small enhanced lesions in the liver in the arterial phase, which were washed out in the delayed phase (Fig. 1). Dilatation of the left intrahepatic bile duct was observed, and in June 2014, the patient was referred to our hospital.

In the hepatobiliary phase of gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (Gd-EOB-DTPA-MRI: EOB-MRI), the huge tumor and multiple small tumors in the liver showed hy-

¹Department of Gastroenterology, Fukushima Medical University School of Medicine, Japan, ²Department of Hepato-Biliary-Pancreatic and Transplant Surgery, Fukushima Medical University School of Medicine, Japan and ³Department of Diagnostic Pathology, Fukushima Medical University School of Medicine, Japan

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Correspondence to Dr. Ken Okai, okaken@fmu.ac.jp

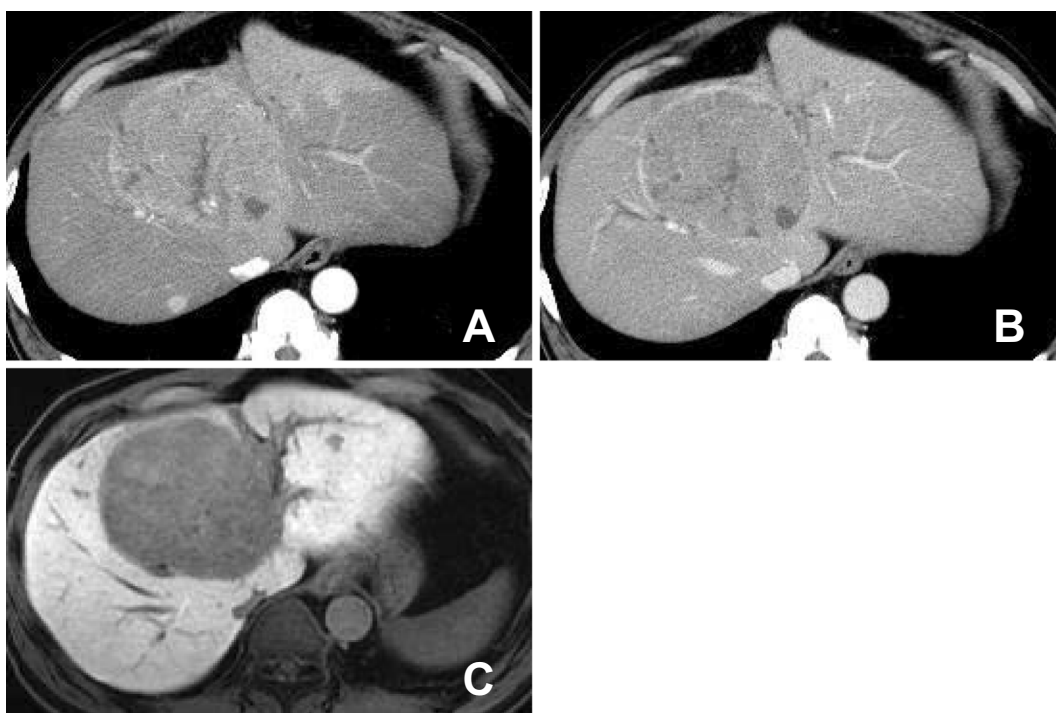


Figure 1. Multidetector CT and EOB-MRI on admission. **A:** Multidetector CT showed a huge focally enhanced lesion in segment 4, and multiple small enhanced lesions in the whole liver in the arterial phase. **B:** CT also showed that the lesions were washed out in the delayed phase. **C:** EOB-MRI in the hepatobiliary phase revealed hypointensity. The primary tumor size was 12 cm in size.

pointintensity. There was no distant metastasis, and the patient was diagnosed with HCC [clinical stage: T4N0M0, stage IV A, Barcelona clinic liver cancer (BCLC) stage B] and non-alcoholic steatohepatitis (NASH). He was ineligible for hepatectomy, and was admitted to our hospital to undergo TACE in July. We planned to perform DEB-TACE without administering the maximum doses of epirubicin (100 mg) or cisplatin (50 mg) and to repeat the DEB-TACE procedures (split DEB-TACE) if DSA after DEB-TACE did not show complete tumor blush extinction. In each procedure, we stopped administering beads when they began to stagnate in the feeding vessels.

On admission, there were no abnormal physical findings with the exception of the presence of an ileal conduit in the right lateral region of the abdomen. The laboratory findings revealed that the levels of alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA-II) were significantly increased (Table 1). His Child-Pugh score was 5 (class A).

We performed interventional radiology (IVR), and observed a huge hypervascular tumor in segment 4, as well as four small tumors, which we considered to be metastases, in the liver (Fig. 2). The tumors showed enhancement on CT during hepatic arteriography (CTHA) and showed no enhancement on CT during arterial portography (CTAP). The primary tumor was 12 cm in size, while the secondary tumors were each approximately 3 cm in size. On CTAP, because the primary tumor was pressing on the left portal vein, the left lobe was not enhanced. Digital subtraction an-

giography (DSA) performed from the proper hepatic artery (PHA) showed that the middle hepatic artery (MHA) and right hepatic artery (RHA) fed the tumors. We mixed 50 mg of epirubicin with 300-500- μ m microspheres (DC bead[®], Eisai, Tokyo, Japan), and added the compound to a mixture of 12 mL of contrast media and 6 mL of physiological saline. We made 40 mL of a 10-times diluted solution (2 vials) and injected 18 mL each into the MHA and RHA. DSA of the PHA after DEB-TACE showed that tumor blushes were significantly reduced.

A month after the first DEB-TACE treatment, the patient was admitted to our hospital and received a diagnosis of liver abscess [Common Terminology Criteria for Adverse Events (CTCAE) version 4.0: grade 3] and septic shock (CTCAE, version 4.0: grade 4). He recovered with antibiotics and percutaneous transhepatic drainage. We considered that the abscess occurred in the normal part of the liver due to reflux of the DEBs. A CT scan performed three months after the first DEB-TACE treatment showed that over 50% of the areas of all tumors was necrotic (Fig. 3A), intrahepatic metastasis in the left lobe of the liver had disappeared, and the metastatic tumors in the right lobe of the liver were reduced in size. The treatment effect (TE) evaluated using the Response Evaluation Criteria in Cancer of the Liver was a partial response (PR) (5). Additionally, the AFP and PIVKA-II levels were significantly decreased (Fig. 3).

We performed IVR in December, 5 months after the first DEB-TACE treatment. CTAP revealed that the tumor in segment 4 had decreased in size to 9 cm. Considering that there

Table 1. Laboratory Findings on the First Admission.

Hematologic test		Glucose	158 mg/dL
White blood cells	8,800 / μ L	HbA1c	7.4 %
Red blood cells	473 \times 10 ⁴ / μ L		
Hemoglobin	14.5 g/dL	TSH	3.620 μ U/mL
Platelet count	24.2 \times 10 ⁴ μ L	Free T4	1.06 ng/dL
		Free T3	2.60 pg/mL
Coagulation			
PT	90.7 %	Immunoglobulin G	1,563 mg/dL
APTT	26.5 s	Immunoglobulin A	201 mg/dL
		Immunoglobulin M	84 mg/dL
Chemistry		ANA	<80 (-)
AST	98 U/L	AMA-M2	2.1 (-)
ALT	91 U/L	LKM-1	<5 (-)
LD	312 U/L		
ALP	435 U/L	Hyaluronic acid	60.7 ng/mL
γ -GTP	164 U/L	Type IV collagen	4.8 ng/mL
Total bilirubin	0.7 mg/dL	CRP	0.81 mg/dL
Direct bilirubin	0.1 mg/dL		
Total protein	8.5 g/dL	Alpha fetoprotein	123.5 ng/mL
Albumin	4.3 g/dL	PIVKA-II	122,100 mAU/mL
Ammonia	58 mmol/L		
		HBs-Ag	(-)
BUN	18 mg/dL	HBc-Ab	(-)
Creatinine	0.92 mg/dL	HCV-AB	(-)
Sodium	137 mmol/L		
Potassium	4.9 mmol/L		
Chloride	104 mEq/L		

PT: prothrombin time activity, APTT: activated partial thromboplastin time, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γ -GTP: γ -glutamyl transpeptidase, BUN: blood urea nitrogen, TSH: thyroid stimulating hormone, ANA: anti-nuclear antibody, AMA-M2: anti-mitochondrial M2 antibody, LKM-1: liver/kidney microsome antibody type 1, CRP: C-reactive protein, PIVKA-II: protein induced by Vitamin K absence or antagonists-II

was a possibility that the DEBs had caused the liver abscess and that the TE of small HCC was not a CR, we decided to perform cTACE with miriplatin and lipiodol. We mixed 75 mg of miriplatin with lipiodol (total 4 mL) and 1-mm gelatin sponge particles (Gelpart[®], Asteras, Tokyo, Japan) with 3 mL of contrast media, and injected them into the MHA and RHA.

CT performed in January 2015 showed the pooling of lipiodol in the primary tumor and secondary tumors in the right lobe of the liver, and the TE was a PR. However, the viability of primary tumor cells was observed. On the other hand, the TE of the small HCC was a CR. The primary tumor was still large, and we performed the second DEB-TACE treatment in April of the same year. We mixed 25 mg of cisplatin with 50-100 μ m microspheres (HepaSphere[®], Nippon Kayaku, Tokyo, Japan), made 10 mL of a 5-times diluted solution, and injected it into the branches of the MHA and RHA.

Next, in August 2015, we performed the third DEB-TACE treatment with a solution of 50 mg of epirubicin mixed with microspheres and added the compound to a mixture of 12 mL of contrast media and 6 mL of physiological saline. We

made 20 mL of a 10-times diluted solution (1 vial) and injected 6 mL of the solution into the branches of MHA and 4 mL into the branches of RHA. DSA of the PHA after DEB-TACE revealed that the tumor blushes at the border of the tumor remained; these were fed by the cholecystic artery (Fig. 3C). Thus, we could not continue the TACE procedure because of the risk of cholecystitis due to embolization of this artery.

The liver function was maintained during all four TACE cycles, and EOB-MRI performed in October only showed tumor cell viability in the primary tumor and one secondary tumor that was located nearby. Thus, after consultation with liver surgeons, we considered that the patient was eligible for hepatectomy, to which he consented. The patient underwent extended left hepatectomy in December 2015. The pathological findings were as follows: well-to-moderately differentiated HCC; liver (S4) H1; simple nodular type with extranodular growth of up to 10 \times 12 mm; eg; fc(+); fc-inf(+); sf(-); s0; vp0; vv0; va0; b0; sm(-); and stage III. Most of the primary tumor was necrotic, and a significant number of beads were present in the tumor vessels. On the other hand, tumor cell viability was observed on the border

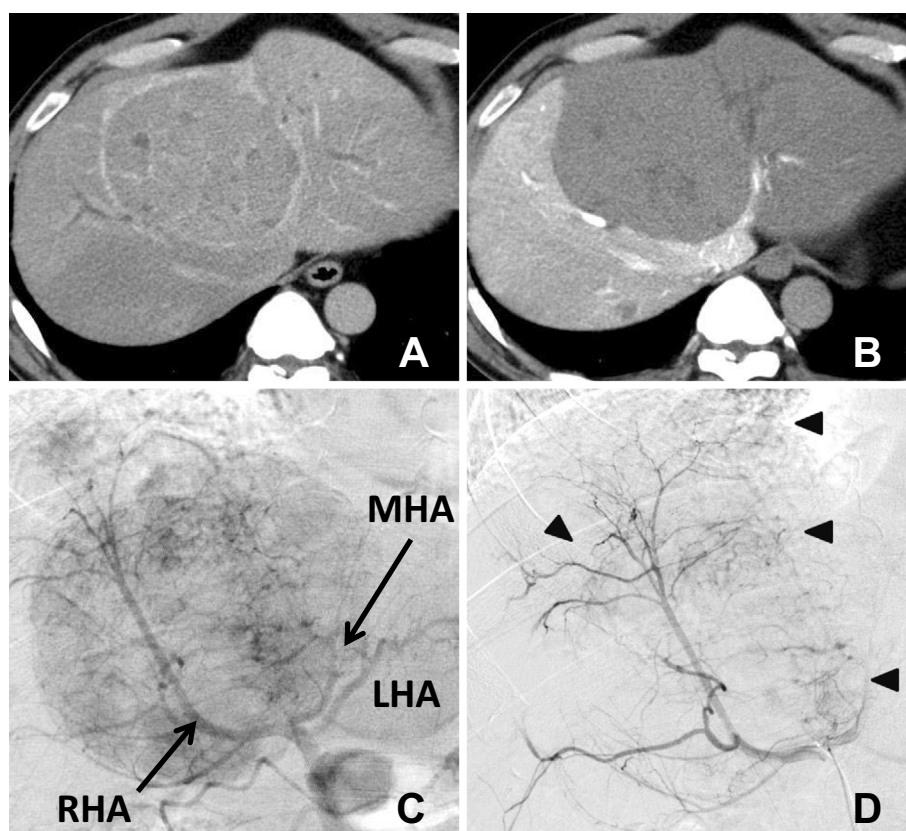


Figure 2. CTHA, CTAP, and DSA before and after the DEB-TACE procedure on first angiography. **A:** The tumors showed enhancement on CTHA. **B:** The tumors showed no enhancement on CTAP. **C:** DSA of the PHA demonstrated two hypervascular tumors. **D:** DSA after DEB-TACE showed tumor blush (arrowheads). CTHA: CT during hepatic arteriography, CTAP: CT during arterial portography, DSA: digital subtraction angiography, DEB-TACE: drug-eluting bead transarterial chemoembolization, PHA: proper hepatic artery, MHA: middle hepatic artery, RHA: right hepatic artery, LHA: left hepatic artery

of the primary tumor and intrahepatic metastases nearby, and there were few beads in their vessels (Fig. 4A-C). There was a marked fatty change, ballooning and Mallory-Denk body formation (Fig. 4D) and fibrosis in the non-cancerous sections of the surgical specimen as a result of NASH. The non-alcoholic fatty liver disease activity score (6) was 5, and the histological subgroup, according to the histological classification proposed by Matteoni (7), was type 4.

The patient was discharged on postoperative day 14. His AFP and PIVKA-II scores have remained within normal limits since surgery, and CT at one year showed no recurrence in the remaining liver (Fig. 3D).

Discussion

According to the clinical practice guidelines for HCC of the Japan Society of Hepatology, TACE is regarded as the first choice of treatment for HCC patients with grade A or B liver damage and multiple tumors of 3 cm or larger (8). On the other hand, in patients with huge HCC, hepatectomy is more effective than TACE (9, 10). Yasuda et al. reported the case of a patient with a huge HCC and multiple intrahepatic metastases who had undergone TACE after hepatectomy for

the primary tumor and who had a good prognosis (11). Furthermore, according to Huang et al., the five-year survival rate of patients who did not undergo hepatectomy was 7% (12), and their prognosis was poor.

In 2014, DEB-TACE was approved for the treatment of HCC in Japan; it has since been used to treat many patients. In a prospective randomized study of DEB-TACE vs. cTACE (PRECISION V), the DEB-TACE group showed higher CR, objective response, and disease control rates in comparison to the cTACE group (2). The same study reported that DEB-TACE was more effective in the treatment of patients with advanced disease (Child-Pugh B, performance status 1, bilobar disease, and recurrent disease) than cTACE (13). DEB-TACE is said to be more effective for HCC patients whose tumor is more enhanced in the arterial phase of multidetector CT (14) or patients with tumors of less than 5 cm in size (15).

DEB-TACE uses beads made of synthetic resins such as polyvinyl alcohol; the beads are smaller than 1 mm in diameter, which is same as the of the gelatin sponge used for cTACE. Thus, DEB-TACE has a stronger ischemic effect than cTACE due to the embolization of the peripheral tumor vessels. Furthermore, DEB-TACE the controlled release of

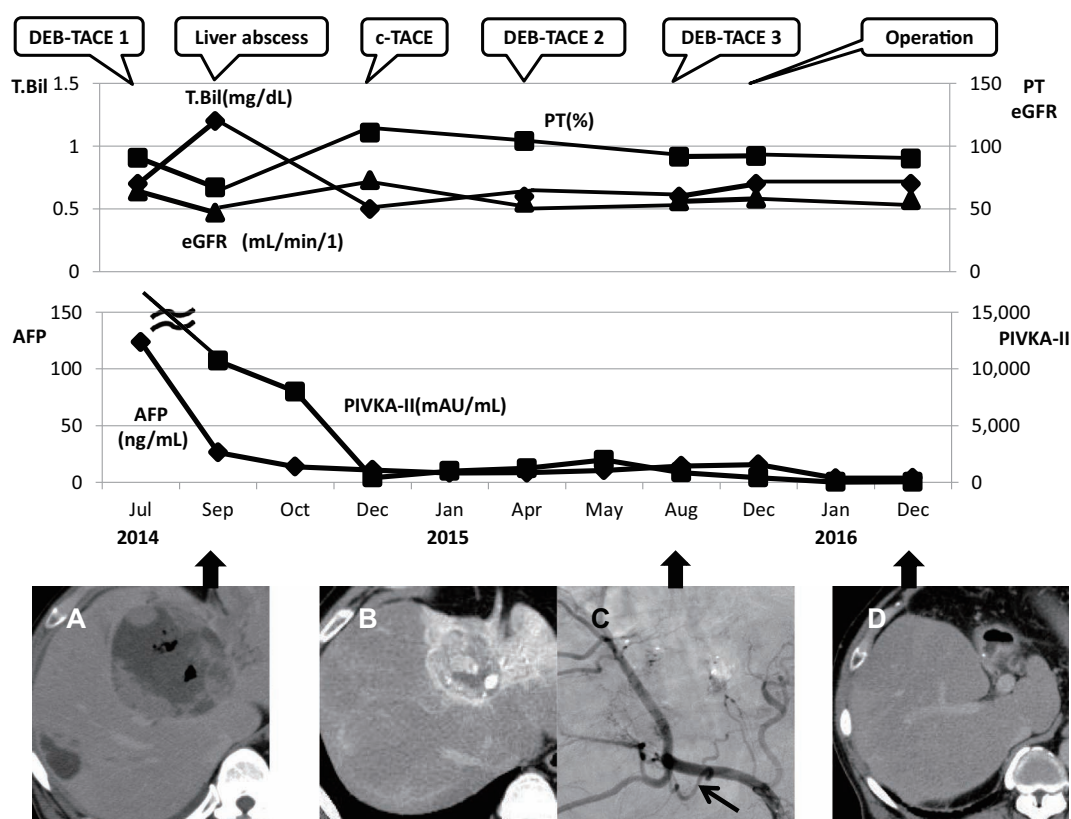


Figure 3. The clinical course with all treatments. The levels of AFP and PIVKA-II were significantly decreased as a result of the first DEB-TACE procedure. After surgery, they remained within the normal limits. The liver and renal function remained good throughout the treatments. A: CT on admission showed a huge HCC (12 cm). B: The tumor size was reduced after four cycles of TACE, but viability was observed on the border. C: On the third DEB-TACE procedure, DSA of the PHA revealed that the cholecystic artery fed the tumor. D: One year later, CT revealed no recurrence in the remaining liver. AFP: alpha-fetoprotein, PIVKA-II: protein induced by vitamin K absence or antagonist-II, DEB-TACE: drug-eluting bead transarterial chemoembolization, HCC: hepatocellular carcinoma, DSA: digital subtraction angiography, PHA: proper hepatic artery

anticancer drugs provides a strong effect. Taken together, this result indicates that the blood concentration of anticancer drugs can be maintained at a low level (16); thus, DEB-TACE is a safer option than cTACE for the treatment of HCC. Moreover, the patient of the current report was able to undergo hepatectomy without hypofunction of the liver and kidneys despite receiving multiple treatments and suffering septic shock as a result of a liver abscess (Fig. 3).

On the other hand, DEB-TACE is associated with a risk of severe complications, including acute cholecystitis (3.3%), acute pancreatitis (5%), and gastric ulcers (3.3%) due to strong embolization (17). There have also been reports of fatal pulmonary embolus (18), liver abscess, and bile leakage (19) caused by small beads (40-120 μm) that passed through a blood flow shunt or of overdose in association with beads. Thus, we should perform superselective catheterization of the tumor feeders and inject beads while being careful to avoid reflux of the beads. Our patient developed liver abscess as a complication of DEB-TACE, and we retrospectively considered that this occurred due to the excessive embolization or reflux of DEB from the tumor ves-

sels. We therefore performed superselective catheterization and reduced the injection volume of DEB (1 vial) in the second and third DEB-TACE cycles and were able to successfully perform the treatment without causing further abscess. Although we considered that DEB-TACE is indicated for most patients with huge HCC in BCLC-B, we should exercise caution in relation to the selection of the injection site and the amount of solution that is injected in order to avoid adverse events, especially when treating elderly people or patients with Child-Pugh class B.

Padia et al. compared patients who underwent DEB-TACE with small-size (100-300 μm) and medium-size (300-500 μm) beads and observed that the small-size-bead group showed a significantly lower incidence of postembolization syndrome and fatigue after TACE than in the medium-size-bead group (20). In our case, we used medium-size particles in the first DEB-TACE procedure with the expectation of strong embolization effects. However, cell viability was observed at the border of the primary tumor on CT after the first DEB-TACE procedure. Thus, we used small-size particles in the second and third DEB-TACE procedures.

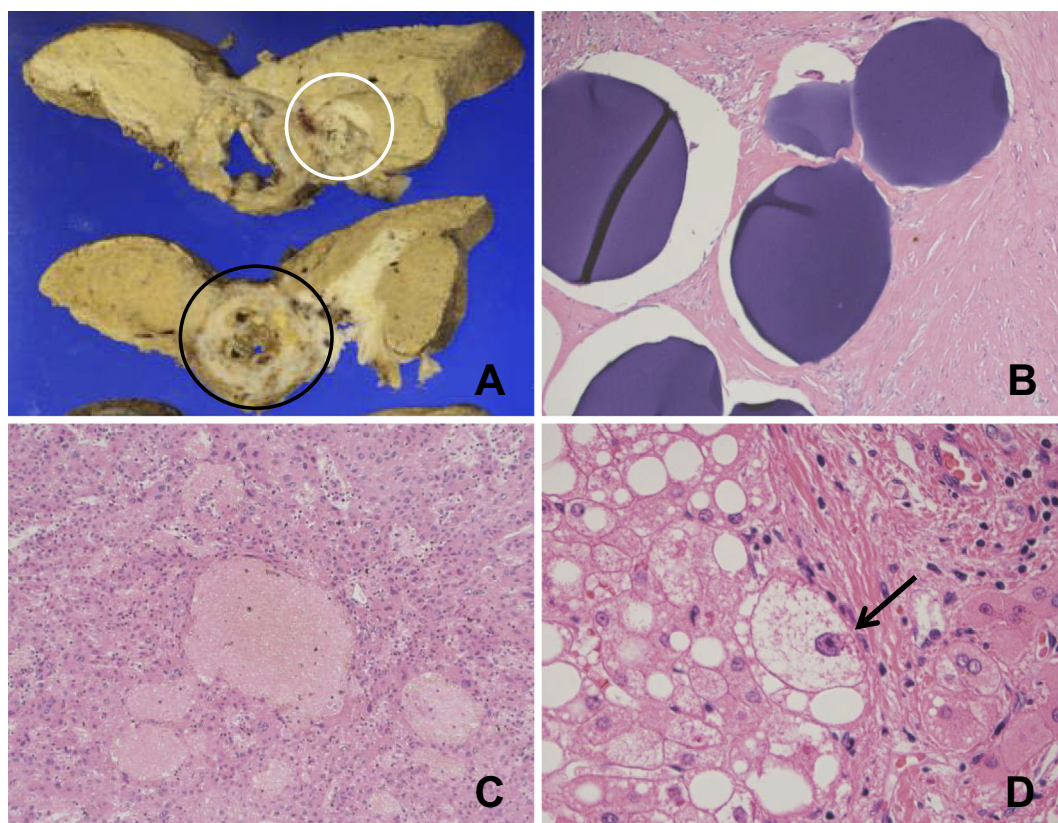


Figure 4. Surgical specimens and the pathologic findings. A: Cut specimen, B is a magnified image of the black circle and C is a magnified image of the white circle. B: The central part of the tumor had become necrotic, and the small blood vessels were full of beads. Hematoxylin and Eosin (H&E) staining, magnification $\times 100$. C: Viability was observed on the border of the tumor. H&E staining, magnification $\times 200$. D: Ballooning with Mallory-Denk body formation (arrow) was observed in the non-cancerous sections of the surgical specimen. H&E staining, magnification $\times 400$.

Vesselle et al. reported that complete tumor blush extinction on DSA after DEB-TACE was one of the useful parameters linked to a CR (15). Thus, it is desirable to adapt the administered dose to reach complete tumor blush extinction in each DEB-TACE procedure. However, we considered that complete blush extinction of some types of tumors (e.g., huge and aggressive tumors) in a single treatment would be associated with a high risk of tumor lysis syndrome (TLS) (21), which is a potentially fatal complication of cancer therapy. TLS is caused by the accumulation of components and metabolites of tumor tissue due to sudden oncolysis. TLS patients can have increased levels of serum uric acid, phosphorus, and potassium, and can develop hypocalcemia, lactic acidosis, and acute renal failure with oliguria (22). Tosi et al. reported the following risk factors for TLS. Host-related factors, including dehydration, hyponatremia, pre-existing renal impairment, obstructive uropathy, and hyperuricemia. Disease-related factors, including massive tumor as well as cancer with a high and rapid response to anticancer therapy (23). In the current case, we performed split DEB-TACE and were able to reduce the dose of contrast media in each treatment as well as the risk of renal failure. Thus, we believe that split DEB-TACE can also reduce the risk of TLS in patients undergoing treatment

for huge HCC.

In the current case, DSA of the PHA and CTHA in the third DEB-TACE procedure showed cell viability on the border of the primary tumor, which was fed by the cholecystic artery; thus, the patient could not continue TACE because of the risk of cholecystitis due to embolization of the cholecystic artery. However, the primary tumor's size was significantly reduced, and tumor cell viability was observed only on the border of the primary tumor and at the site of intrahepatic metastasis, which was nearby. The other secondary tumors had disappeared after the first DEB-TACE and cTACE procedures. His liver and renal function remained good, and we were able to perform radical hepatectomy. This was due to the two previously described effects.

At the time of writing, in the present case, no recurrence of HCC has been observed for two years. To date, there are two case reports of patients who underwent radical hepatectomy after multiple DEB-TACE procedures (Table 2) (24, 25). Ikeda et al. reported that a patient who could not undergo surgery because of his drinking habit received DEB-TACE (24). He underwent surgery after achieving abstinence from alcohol. Kurniawan et al. reported that the condition of a patient who was diagnosed with BCLC stage B improved to BCLC stage A as a result of DEB-

Table 2. Two Cases with Huge HCC are Reported in which Patients were Able to Undergo Surgery after DEB-TACE.

Reference	Gender	Year	Stage	Tumor size	TACE	Child-Pugh score
24	male	60s	T4N0M0 stage IV A	9 cm	3 times	5, Class A
25	male	40s	T3N0M0 Stage III	7 cm	2 times	5, Class A
Our case	male	60s	T4N0M0 stage IV A	12 cm	4 times	5, Class A

HCC: hepatocellular carcinoma, DEB-TACE: drug-eluting bead transarterial chemoembolization

TACE, enabling the patient to undergo surgery (25). On the other hand, the present case indicates not only the usefulness of DEB-TACE for huge HCC but also the limitations of DEB-TACE alone in attempting to achieve a radical cure for HCC with an extrahepatic collateral blood supply (e.g., cholecystic artery, gastric artery and/or adrenal artery). Treatment plans should be flexible to meet changes in the clinical situation.

Currently, DEB-TACE is not an established treatment for huge unresectable HCC. In fact, Vesselle et al. reported that a CR can be achieved after DEB-TACE in cases involving tumors of less than 5 cm in size (15). Kudo proposed the Kinki criteria, wherein BCLC-B classified HCCs into three sub-stages: B1 (Child-Pugh score 5-7 and within up-to-seven criteria), B2 (Child-Pugh score 5-7 and beyond up-to-seven criteria) and B3 (Child-Pugh 8-9 and any up-to-seven criteria) and suggested a heterogeneous treatment strategy for BCLC-B HCC (26). In this strategy, DEB-TACE was found to be a good treatment option for multiple huge HCC in sub-groups B1 and B2, whereas hepatic arterial infusion chemotherapy (HAIC) or sorafenib were selected over DEB-TACE for cases involving more than six tumors. Furthermore, for sub-group B3, selective DEB-TACE, HAIC and BSC were selected in patients with multiple huge HCC. We hope that treatment for huge unresectable HCC, including DEB-TACE, will be established.

The authors state that they have no Conflict of Interest (COI).

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