**Efficacy of combined bland embolization and chemoembolization for huge (≥10 cm) hepatocellular carcinoma**

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**Abstract**

**Introduction**: To assess the efficacy of combined therapy involving bland transarterial embolization using gelatin sponge particles (bland GS-TAE) followed by transarterial chemoembolization using lipiodol mixed with anticancer agents and GS particles (Lip-TACE) to reduce the adverse events and increase the therapeutic effect of Lip-TACE in the treatment of huge (≥10 cm) hepatocellular carcinoma (HCC).

**Materials and methods**: Twenty-one consecutive patients with huge HCCs (≥10 cm in diameter) were enrolled in this study. First, bland GS-TAE was performed to reduce the tumor volume, and then Lip-TACE was performed to control the remaining tumor at intervals of around 3 weeks. The tumor response, survival, and adverse events of this combined therapy were assessed.

**Results**: The tumor response was assessed 3 months after combined TACE, with complete response in 38.1% and partial response in 57.1%. Severe adverse events were seen in two patients, acute cholecystitis and tumor rupture. The median survival time was 2.7 years, and the 1-, 2-, 3-, and 5-year overall survival rates were 76.2%, 66.7%, 42.9%, and 25.0%, respectively.

**Conclusion**: Combined therapy involving bland GS-TAE followed by Lip-TACE can be performed safety and may improve survival in patients with huge HCCs.

**Keywords:** huge hepatocellular carcinoma, transarterial chemoembolization, bland embolization

## Introduction

Transarterial chemoembolization (TACE) using iodized oil (Lipiodol®; Guerbet, Villepinte, France) mixed with an anticancer agent and gelatin sponge (GS) (Gelfoam; Upjohn, Kalamazoo, MI) particles (Lip-TACE) is a widely used treatment for hepatocellular carcinoma (HCC) [1-6]. Furthermore, Lip-TACE is also effective for inoperable HCC even larger than 5 cm in diameter [7]. However, Lip-TACE has not been established in the treatment of huge HCC (≥10 cm), and there is concern that the use of more than 10 mL of Lipiodol in one session may induce adverse events such as deterioration of liver function, acute tumor lysis syndrome and pulmonary embolism through shunts [8,9].

We hypothesized that Lip-TACE after bland transarterial embolization using GS particles without an anticancer agent (bland GS-TAE) would not require a high volume of Lipiodol and, as a result, would contribute to reducing the adverse events and enhancing the therapeutic effect of the Lip-TACE in the treatment of huge (≥10 cm) HCCs. Therefore, we attempted combined therapy involving bland GS-TAE and Lip-TACE and retrospectively investigated its efficacy and adverse events.

## Materials and methods

In all procedures, written, informed consent was obtained from each patient before each bland GS-TAE, Lip-TACE, and other therapeutic procedures. Indications for treatment of each patient were determined by a tumor board, which included several hepatic surgeons and hepatologists in our institution. This retrospective study was approved by the institutional review board of our institution. The data were extracted from the medical charts and diagnostic imaging records of this institution.

***Patients***

Between 1998 and 2013, TAE was performed as an initial treatment for inoperable HCC for 793 patients. Of these patients, 21 consecutive cases fulfilled the following criteria: (i) HCC with a diameter of 10 cm or larger, without infiltrative type tumor (in the gross classification of HCC that was accepted by the Liver Cancer Study Group of Japan (LCSGJ) [10]) that spread to the whole liver; (ii) no previous treatment for HCC; and (iii) no major portal vein tumor thrombus extending into the 1st portal branch (i.e.Vp3 or 4 of the general rules for the clinical and pathological study of primary liver cancer stated by the LCSGJ). The following conditions were also considered contraindications to embolization: severe thrombocytopenia (platelet count < 30,000/mL), hyperbilirubinemia (serum bilirubin >3 mg/dL), and severe hepatic dysfunction (Child-

Pugh class C). The 21 patients' characteristics and disease profiles are shown in Table 1. There were 19 men and 2 women, with an average age of 65.2 years (range, 47-89 years). All patients had underlying cirrhosis that was related to hepatitis C virus in 11 patients and hepatitis B virus in 6 patients (with both in one patient). The liver function of 20 patients (95.2%) was classified as Child-Pugh A, and one (4.8%) was Child-Pugh B.

The clinical diagnosis of HCC was based on imaging studies including contrast-enhanced computed tomography (CECT) with bolus contrast injection. A lesion that was seen as a hypervascular nodule in the arterial phase and as a relatively low density on the portal venous phase was diagnosed as HCC. Ten patients (47.6%) had a solitary tumor, and another eleven (52.4%) had multiple tumors. The mean diameter of the largest tumor was 12.3 ± 2.2 (range, 10-16) cm.

Three patients had portal venous invasion (Vp1: invasion distal to the second order branches of the portal vein, but not of the second order branches, or Vp2: invasion of second order branches of the portal vein) [10], and another three patients had invasion to the inferior vena cava (Vv3) [10]. Extrahepatic metastases were observed in three patients (thoracic spine, lumbar spine, and right adrenal gland). According to the Barcelona Clinic Liver Cancer (BCLC) staging classification [11], 8 patients had stage

A tumors, 6 had stage B, and 7 had stage C. These 7 patients with BCLC-C had been enrolled in this combined therapy, because all of them were thought to have huge intrahepatic masses as the most critical factor affecting their prognosis, and we believed that control of the huge tumor could contribute to improving their prognosis despite the presence of extrahepatic lesions or vascular invasion. Serum alpha-fetoprotein (AFP) levels exceeded the upper normal limit (20 ng/mL) in 14 patients (median: 29285 ng/mL, range: 23.8-89,273 ng/mL). The serum protein induced by vitamin K absence or antagonist-II (PIVKA-II), also known as des-gamma-carboxy prothrombin (DCP) [12], level exceeded the upper normal limit (40 mAU/mL) in 20 patients (median: 13,811 mAU/mL, range: 529-297,300 mAU/mL).

***Concept of combined therapy***

Bland GS-TAE was performed first to reduce tumor volume to decrease the volume of Lipiodol at the following Lip-TACE. Lip-TACE was then performed to the remaining viable tumor within about 3 weeks after bland GS-TAE, waiting for improvement of liver function, if residual tumor was confirmed by CECT 1-2 weeks after GS-TAE. The end point of treatment was the disappearance of tumor enhancement after bland GS-TAE or subsequent Lip-TACE.

***Methods of combined therapy***

Bland GS-TAE was performed using a catheter with a long, tapered tip (5.5-and 4.5- Fr or 5-and 4- Fr outer diameters of the shaft and tip, respectively) placed into the right and/or left hepatic artery. Then, 2-mm GS particles soaked in contrast medium were injected. The end point of bland GS-TAE was complete occlusion or stagnation of arterial flow in the feeding artery.

Inside the embolized tumor, a non-enhanced low density area suggested a necrotic area on CECT. An enhanced high-density area was defined as remaining viable tumor. Subsequent Lip-TACE to the remaining viable tumor was planned about 3 weeks after bland GS-TAE. However, when deterioration of a patient's condition and/or liver functions or markedly effective CT findings were seen, the time of subsequent Lip-TACE exceeded 3 weeks.

Subsequent Lip-TACE was performed using a microcatheter placed as selectively as possible to the tumor-supplying arterial branches. Lipiodol mixed with epirubicin (Farmorbicin; Pfizer, Tokyo, Japan) was used with the dosages determined based on the remaining viable tumor size and liver function, with up to 10 mL of Lipiodol and 60 mg of epirubicin [3,5,6]. Lipiodol emulsion was prepared by pumping the mixture 20–30 times

using a three-way stopcock, mixing Lipiodol inside one syringe with a small amount of nonionic contrast medium and saline-dissolved epirubicin inside another syringe [6]. Then, 1-mm GS particles were injected until the occlusion or stagnation of the feeding artery. Lip-TACE was repeated until complete tumor response was obtained in the whole intrahepatic tumor.

***Follow-up after combined therapy and additional treatments for recurrences and extrahepatic metastases***

All patients were sequentially followed using clinical data such as AFP and PIVKA-II and diagnostic imaging such as CECT, contrast-enhanced magnetic resonance imaging, and enhanced ultrasound at 3-month intervals. When local tumor recurrence and/or new tumors were observed, they were treated by Lip-TACE or local ablation therapy such as radiofrequency ablation (RFA) as soon as possible. Repeated Lip-TACE was performed by superselective techniques for target vessels including various collaterals as the extrahepatic blood supply. Local ablation therapy was indicated for patients when it seemed more suitable because of poor vascularity or small tumor recurrence. When intrahepatic viable tumors became disseminated and uncontrollable by Lip-TACE, arterial infusion chemotherapy was indicated. Tumor thrombus in the portal vein or

inferior vena cava and distant metastases were controlled by radiotherapy.

### *Assessments*

Early tumor response was assessed by CECT at 1-2 weeks after bland GS-TAE, and tumor response to combined therapy was assessed by CECT 3 months after combined therapy, according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [13]. Overall survival was also assessed. Univariate analysis to identify predictors of survival was performed by the Kaplan-Meier method and compared by the log-rank test. Fourteen variables were assessed, including sex, age, presence of hepatitis B (HBV), presence of hepatitis C (HCV), Child-Pugh score, tumor size, number of tumors, vascular invasion, metastases, AFP, PIVKA II, BCLC staging, extrahepatic collateral vessels, and tumor response to combined therapy. All statistical analyses were performed using SPSS statistics 21.0 (IBM Japan, Tokyo, Japan).

Adverse events of bland GS-TAE and Lip-TACE were evaluated by the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 [14].

## Results

GS-TAE was technically successful in all patients. Two patients (9.5%) achieved

complete tumor necrosis by bland GS-TAE alone as the planned procedure, and these patients therefore did not receive the subsequent Lip-TACE. They underwent Lip-TACE for local recurrence after 229 and 446 days, respectively. The remaining 19 patients underwent combined therapy involving bland GS-TAE and Lip-TACE. Of these 19 patients, 16 had one session of Lip-TACE for treatment of all intrahepatic tumors, two patients had two sessions of Lip-TACE, and one patient had three sessions of Lip-TACE. The mean amounts of drug per session in combined therapy were Lipiodol 7.5 (2-10) mL and epirubicin 45.0 (20-60) mg. The mean interval between bland GS-TAE and the first Lip-TACE was 24.8 (8-50) days.

Six of 7 patients with BCLC-C had radiation therapy for the extrahepatic lesions and/or vascular invasion after this combined therapy.

Follow-up duration after this combined therapy was from 4.8 to 84.3 months (mean: 33.8 ± 24.0, median: 32.6 months). Nineteen patients had already died (from 4.8 to 84.3 (mean: 33.8 ± 24.0, median: 32.6) months) by the year 2014 when the survey was conducted, and the remaining 2 patients were alive. The causes of death of the 19 patients were hepatic failure in 7, advanced cancer in 9, intestinal bleeding in 1, and pneumonia in 2.

A representative case is shown in Fig. 1a-c.

***Tumor response***

Early tumor response assessed by CECT after bland GS-TAE showed complete response (CR) in 2 patients and partial response (PR) in 19 patients. Tumor response assessed by CECT 3 months after combined therapy showed that 8 patients (38.1%) had achieved CR, 12 patients (57.1%) had achieved PR, and one patient (4.8%) had achieved stable disease (SD). No patients showed progressive disease (PD). The response rate was 95.2% (20/21).

***Survival and factors affecting survival***

Cumulative overall survival rates at 1, 2, 3, and 5 years were 76.2% (95% confidence interval (CI), 58.0-94.4%), 66.7% (95% CI, 46.5-86.9%), 42.9% (95% CI, 21.7-64.1%), and 25.0% (95% CI, 5.2-44.8%), respectively, and median survival time (MST) was 2.7 years (95% CI 1.8-3.6 years) (Table 2, Fig. 2). Determinants of cumulative survival rates are shown in Table 2. Child-Pugh score (Child A group vs. a single Child B case, $P < 0.001$), BCLC staging (stage A vs. stage B or C, $P = 0.039$), and tumor response to combined therapy (CR vs. not CR, $P = 0.006$) were significantly related to survival. The other factors were not significantly related to survival.

***Adverse events of combined therapy***

Severe adverse events after bland GS-TAE were seen in 2 of 21 patients. The one with acute cholecystitis (grade 3) was treated by temporary gallbladder drainage. The other one was tumor rupture (grade 4) the day after bland GS-TAE, and re-embolization was performed immediately. However, a liver abscess occurred 18 days after additional TAE, and temporary drainage was required. Lip-TACE was performed 50 days after initial bland GS-TAE.

Postembolization fever, grade 1 (38.0 - 39.0°C) or grade 2 (>39.0 - 40.0°C), occurred in 16 (85%) of 21 patients, and it continued for an average of 3.7 days (0-13 days). Other minor adverse events such as nausea and slight abdominal pain resolved with conservative therapies.

No severe adverse events occurred after the initial Lip-TACE following bland GS-TAE. Postembolization fever, grade 1 or grade 2, was seen in 14 (60%) of 21 patients, and it continued for an average of 3.0 days (0-16 days). Other minor adverse events such as nausea and slight abdominal pain resolved with conservative therapies.

**Discussion**

Recently, although advances in diagnostic imaging techniques and the widespread application of screening programs for high-risk groups have facilitated the detection of small HCC, HCCs with a diameter of 10 cm or larger are still occasionally discovered in clinical practice. In the 18th follow-up survey of primary liver cancer in Japan, huge HCC (≥10 cm) was reported to account for 5.7% of all HCCs in Japan [15]. Though surgical resection seems to be the best therapy for huge HCCs (≥10 cm) [16-20], curative resection has been performed for only limited numbers of patients because of tumor extension, multicentricity, and the presence of liver cirrhosis.

TACE has been accepted as effective treatment for inoperable advanced HCC to prolong survival [1]. In paticular, selective or superselective Lip-TACE has been promising as an effective and safe locoregional treatment for small HCC. The criteria in many Japanese institutions for the dose of Lipiodol used for selective or superselective TACE state that that the average dose (mL) of Lipiodol is roughly equal to the tumor diameter (cm) to obtain a good therapeutic effect [4-7]. However, more than such a predicted amount of Lipiodol is needed for large HCC, since a tumor with a diameter of 10cm has a volume of 500ml. On the other hand, use of a large amount of Lipiodol (>10mL) may cause the following complications. Chung [8] reported that the use of over 20 mL of Lipiodol causes pulmonary oily embolism after Lip-TACE for HCC, and

Sakamoto [9] also reported acute tumor lysis syndrome caused by Lip-TACE in a patient with a large HCC, in whom 10 mL of Lipiodol were given once, and 15 mL were given once. Poon [21] reported that patients who have inoperable HCC > 10 cm and poor liver function (serum albumin <35 g/L) may not be suitable candidates for TACE treatment using lipiodol of up to 30 mL because of a high mortality rate (20%). Although a large volume of Lipiodol is needed in Lip-TACE for large HCC, Miyayama [7] reported that stepwise Lip-TACE, which can reduce the volume of Lipiodol per one chemoembolization session to avoid the complications related to too much volume of Lipiodol, could be effective for large HCC.

However, the ordinary method of Lip-TACE for huge HCC (>10cm) , larger than the cases reported by Miyayama, has not yet been established, because the dose of lipiodol required for adequate embolization to the entire huge tumor must be much greater and must exceed 10 mL. As mentioned, administration of such a large dose of Lipiodol may cause severe complications. Therefore, the rationale of our combined therapy is that, as the first step, TAE is performed with only 2-mm gelatin sponge particles, which may not induce severe complication related to Lipiodol, and an anticancer agent, which can obtain tumor volume reduction. The 2-mm gelatin sponge particles may be distributed predominantly into the larger feeding arteries and may have less effect on the tiny

peribiliary vessels, and serious adverse events such as acute tumor lysis syndrome, abscess, and biloma may be avoided. Then, as the second step, Lip-TACE mixed with an anticancer agent could be performed for the residual viable portion without such a large volume of Lipiodol to obtain a good therapeutic result. If residual tumor remained after the first step, GS-TAE, we would perform repeated Lip-TACE as the second step in some cases.

The tumor response assessed by CECT 3 months after combined therapy was CR in 8 patients (38.1%) (including 2 patients with CR as the early tumor response to bland GS-TAE), and PR in 12 patients (57.1%). On the basis of these results, our combined therapy involving bland GS-TAE followed by Lip-TACE seems to show good results. Min [22] reported in a comparative study that the 1-, 3- and 5-year overall survival rates of surgical treatment and TACE were 73.8%, 54.8%, and 39.8% vs. 37.8%, 16.3%, and 9.7%, respectively, and after propensity score matching, the surgery group showed higher 1- and 3-year overall survival rates than the TACE group (69.7% and 51.7% vs. 40.2% and 18.5%, respectively). Despite the present series involving various types of huge HCCs, some of which were not indicated for surgical resection, the cumulative overall survival rates of 76.2%, 42.9%, and 25.0% at 1, 3, and 5 years, respectively, are considered much higher and acceptable.

According to reports of the surgical resection of huge HCCs (≥10 cm), significant prognostic factors varied and included solitary tumor [16-19], vascular invasion [17,19,20], absence of portal vein tumor thrombus [16,18], serum AFP level [17,19], absence of tumor rupture, and curative surgery [18], among others. On the other hand, according to reports of Lip-TACE for HCC, significant prognostic factors were degree of liver damage, tumor size, number of tumors, vascular invasion [6,23], and serum AFP level [23]. In the present study, although a significant difference in survival rates was seen between Child A and Child B groups, this significant difference was considered unreliable because there was only a single patient in the Child B group. BCLC staging (stage A vs. stage B or C, P = 0.039) and the tumor response (CR vs. not CR; P = 0.006) were significantly related to survival. With respect to the number of tumors, vascular invasion, serum AFP level, and serum PIVKA-II level, there were no significant differences in the present small series.

In the present study, severe adverse events after bland GS-TAE were seen in 2 patients (acute cholecystitis and tumor rupture) who were successfully treated using interventional procedures. Post-embolization syndrome, such as fever, and adverse events such as nausea and slight abdominal pain occurred and resolved with conservative therapies. No severe adverse events were seen after initial Lip-TACE

following bland TAE. Post-embolization syndrome was mild compared with ordinary Lip-TACE and resolved with conservative therapies

As the first step of this combination therapy in the present series, bland TAE was performed only with 2-mm gelatin sponge particles, but we can also use microspheres (MS), which have been promising as a newly effective and permanent embolic material for the embolization of liver tumors. It has also been reported that the effect of TAE using MS on liver function was less than that of Lip-TACE, and that MS can be used for patients with poor performance status, poor liver function, and bilobar tumors (PRECISION) [24]. MS-TAE could have fewer complications than conventional TACE. Even in huge HCC, MS might be useful to reduce complications. Unfortunately, during the period of the present study, MS including yttrium-90 resin MS was not yet available in Japan.

This study had several limitations. First, it was retrospective in nature and spanned a long period. Thus, a prospective study is needed. Second, the number of patients was small, and the results may require further confirmation with a large sample size.

In conclusion, this study demonstrated that combined therapy involving bland GS-TAE followed by Lip-TACE can be performed safely and may improve survival of patients with huge (≥10 cm) HCCs.

**Figure 1.** A 65-year-old man with HCC of 10 cm in diameter. **(a)** Contrast-enhanced CT (CECT) shows a large hypervascular tumor in the right lobe. **(b)** Common hepatic arteriogram shows a large tumor with hypervascular tumor vessels. Selective right hepatic arterial bland GS-TAE was performed, and 20 days later Lip-TACE was performed to the tiny residual tumor vessels. **(c)** CT obtained 6 months after Lip-TACE shows markedly reduced tumor size and disappearance of tumor enhancement. Tumor response was assessed as complete response.

**Figure 2.** Cumulative survival rates of all patients after initial bland GS-TACE. The 1, 2, 3, and 5-year survival rates are 76.2%, 66.7%, 42.9%, and 25.0%, respectively, and the MST is 2.7 years.

**Table 1.** Patient and disease profiles (n=21)

HBV = hepatitis B virus; HCV = hepatitis C virus; Vp1 = invasion distal to the second order branches of the portal vein; Vp2 = invasion of the second order branches of the portal vein; Vv3 = invasion of the inferior vena cava; BCLC = Barcelona Clinic Liver Cancer.

**Table 2.** Determinants of cumulative survival rates: Univariate analysis

HBV = hepatitis B virus; HCV = hepatitis C virus; AFP = alpha-fetprotein; PIVKA-II = protein induced by vitamin K absence or antagonist-II; BCLC = Barcelona Clinic Liver Cancer; CR = complete response.

**The authors declare no conflicts of interest.**

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