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Article

Efficacy of Conventional Transarterial Chemoembolization for Hepatocellular Carcinoma with Glass Membrane Emulsification Device

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Simple Summary: Transarterial chemoembolization (TACE) is the standard treatment for BCLC-B hepatocellular carcinoma (HCC). The porous glass membrane pumping emulsifier (GMD) has been shown to produce a high percentage of water/oil emulsions with homogeneous and stable droplets, but there are few reports on the efficacy of GMD-conventional-TACE (GMD-c-TACE) for local recurrence. The present study indicates that the GMD-c-TACE for HCC could be prevent early local recurrence and maintain the hepatic functional reserve.

Abstract:

Background: Transarterial chemoembolization (TACE) is the standard treatment for BCLC-B hepatocellular carcinoma (HCC). The glass membrane emulsification device (GMD), a novel device, produces a high percentage of water/oil emulsions with homogeneous and stable droplets. There are few reports on the efficacy of GMD-conventional-TACE (GMD-c-TACE). We aimed to evaluate the efficacy of GMD-c-TACE.

Methods: Seventy-one patients with HCC of tumor diameter <5 cm who underwent c-TACE with and without GMD were included in this study to investigate local recurrence and hepatic functional reserve.

Results: Local recurrence rates without GMD-TACE was 3.0% at 6 months, 16.7% at 12 months, 35.0% at 18 months, and it then plateaued. Hence, the local recurrence rate in the GMD-c-TACE group was 7.7% at 14 months and 23.1% at 20 months, respectively. GMD-c-TACE had a significantly lower local recurrence. Multivariate analysis showed that GMD-c-TACE could suppress local recurrence and maintain the hepatic reserve.

Conclusions: GMD-c-TACE allows dense accumulation of lipiodol in the tumor and attainment of good local control. Additionally, the inhibition of the release of anticancer drugs may maintain the hepatic reserve. GMD-c-TACE is useful in preventing local recurrence and is expected to become the standard treatment form of c-TACE in the future.

Keywords: hepatocellular carcinoma; conventional transarterial chemoembolization; emulsion; lipiodol; glass membrane emulsification device

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Introduction

Hepatocellular carcinoma (HCC) is the leading cause of cancer-related death, accounting for more than 700,000 deaths annually [1].

Transarterial chemoembolization (TACE) developed in the early 1980s in Japan [2], and has become established as the standard treatment for hepatocellular carcinoma (HCC) that is not indicated for surgical resection or other forms of local therapy for patients with intermediate-stage hepatocellular carcinoma on the Barcelona Clinic Liver Cancer classification [**3-15].** The worldwide consensus technique of conventional transarterial chemoembolization is mixing ethiodized oil (Lipiodol; Guerbet, Villepinte, France) and doxorubicin/epirubicin solution by pumping using 2 syringes through a 3-way stopcock [16, 17]. Ethiodized oil (Lipiodol; Guerbet, Villepinte, France), is widely used in TACE; it is not only a carrier of anticancer drugs but also has a role in embolization [18-22]. By mixing it with anticancer drugs into a water/oil emulsion, it is possible to increase the gradual release of anticancer drugs and the embolization effect on target sites. The main local effects of TACE are local retention of anticancer drugs and Lipiodol and the resistive effect of the embolic substance. The better the accumulation of Lipiodol, the better the local control rate; thus, it is extremely important to improve Lipiodol accumulation in embolization therapy.

Since Lipiodol is used as a drug carrier, the ideal drug properties should be in a high-generation W/O (Water in Oil) state, but this may not be achievable in a normal three-way stopcock because the O/W and W/O areas are mixed.

The porous glass membrane emulsification device (GMD) (MicroMagic; Piolax Medical Devices, Yokohama, Japan), which is a connector for adjusting water-in-oil emulsion drug solutions, can produce stable and highly pure W/O emulsions that are used when mixing drug solutions and oil-based contrast media during TACE and injecting drugs evenly [23]. However, the clinical results are not yet clear.

Improved accumulation of lipiodol is not only expected to maintain good local control of HCC but also reduce the concentration of anticancer drugs leaking into the systemic circulation, thereby minimizing the impact of the treatment on liver function.

In this study, we investigated the outcomes and local recurrence factors in conventional-TACE (c-TACE) with the use of GMD in c-TACE for HCC less than 5 cm in size.

Subjects and Methods

1. Subjects

The study included 71 patients with HCC (71 nodules) who had c-TACE at Saiseikai Niigata Hospital between January 2018 and November 2021. The diagnosis of HCC was made by dynamic contrast-enhanced computed tomography (CT) or dynamic contrast-enhanced magnetic resonance imaging (MRI).

The exclusion criteria were as follows: 1) tumor diameter greater than 5 cm, 2) intentionally incomplete TACE performed for massive or infiltrative type tumor, 3) interval between TACE and the first follow-up CT more than 4 months, 4) no CT done during follow-up observation; and 5) nodules with locoregional therapy such as percutaneous ethanol injection (PEI), microwave coagulation therapy, laser ablation, and radiofrequency (RF) ablation as additional treatment.

We analyzed local recurrence and hepatic functional reserve in the 71 patients who underwent c-TACE due to intolerance to surgery, with or without GMD.

2. Methods

Treatment procedure

In all patients, the femoral artery was punctured by the Seldinger technique. After a 5 F introducer was inserted, a 5 F catheter was inserted, and a 3 Fr microcatheter (At-

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tendant, Terumo, Tokyo, Japan) was advanced to the sub-area or further peripheral nutritional vessels by the coaxial technique. Conventional TACE with three-way stopcock or GMD was then performed.

TACE was performed according to the standard protocol for all patients. Epirubicin hydrochloride" 50 mg (Epirubicin; Nippon Kayaku, Tokyo, Japan) was dissolved in a nonionic contrast medium; the mixing ratio of aqueous Epirubicin solution to Lipiodol was 1:2. Emulsions were generated by pumping 20 times with a conventional three-way stopcock or GMD before intra-arterial administration. The emulsion was injected into the artery nourishing the tumor and this was followed by subsequent embolization with 1-mm-diameter gelatin particles (Gelpart; Nippon Kayaku, Tokyo, Japan).

After embolization, multidirectional angiography confirmed the absence of tumor staining and the accumulation of Lipiodol in the tumor. The amount of the suspension used in both groups was determined according to the size of the nodule.

Immediately after the procedure, non-contrast CT examinations were performed using a 16-detector row scanner (Aquilion, Toshiba Medical Systems), and for lesion density measurement, a circular region of interest (ROI) lesion was set for each nodule, and the CT values of the Lipiodol that accumulated in the HCC nodule were measured. Patients were followed up after treatment to evaluate local recurrence and accumulation of Lipiodol, and CT was subsequently performed to determine whether there was local recurrence.

Contrast-enhanced CT was performed 1 to 3 months after TACE and every 2 to 3 months thereafter to determine the response to treatment.

Local recurrence was defined as either 1) a non-lipiodol-accumulated area in the post-treatment tumor that was contrasted in the early contrast phase and showed low absorption in the delayed phase or 2) a low-absorption area in the delayed phase that was contrasted in the early contrast phase and was adjacent to the lipiodol-accumulated area.

Liver function including ALBI-score was evaluated pre TACE and post TACE procedure [24-27].

Ethical statements

This study was approved by the Institutional Review Board of Saiseikai Niigata Hospital and was conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent before participating in the study.

Statistical analysis

The comparison between the two groups was determined by Chi-square test; normally distributed continuous data were presented as mean ± standard deviation, and the comparison between the two groups was determined by t-test. The differences in parameters were analyzed using a one-way measures ANOVA. Recurrence rates were estimated using the Kaplan–Meier method and differences between groups were compared using the log-rank test. The Cox proportional hazard model was used to analyze the predisposing factors for recurrence.

Statistical significance was defined as $p<0.05$. All statistical analyses were performed using EZR (Saitama Medical Centre, Jichi Medical University, Shimotsuke, Japan), a graphical user interface for R version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria) [28].

Results

Patient Characteristics

Table 1 shows the clinical backgrounds of all patients. The mean age was 72.98 ± 9.67 years, the male-to-female ratio 56:15, background liver factors HBV/HCV/AIH/Alc/NASH14 /25/4/18/10, alpha-fetoprotein (AFP) 21.96 ± 73.52 ng/mL, des-gamma-carboxy prothrombin (DCP) 1083.06 ± 5212.065 mAU/mL, total bilirubin 0.84

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± 0. 42 mg/dL, albumin 3.84 ± 0.49 g/dL, prothrombin activity 93.058 ± 12.98%, and ALBI-score -2.52 ±.0.47. The median observation period was 255 days (71–1086 days).

Table 1. Clinical characteristics of patients enrolled in this study (*n* = 71).

Variables	Number or mean ±SD
Age (years)	72.986 ± 9.627
Gender (Male/Female)	56/15
Etiology (HBV/HCV/AIH/Alc/NASH)	14/25/4/18/10
Size (mm)	32.056 ± 5.997
Location (S1/2/3/4/5/6/7/8)	1/3/7/7/5/12/14/22
Total.bilirubin (mg/dL)	0.884 ± 0.423
Albumin (g/dL)	3.845 ± 0.498
DCP (mAU/mL)	1083.06 ± 5212.065
AFP (ng/mL)	21.966 ± 73.523
ALBI score	-2.520 ± 0.470

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; AIH; autoimmune hepatitis; Alc, alcoholic hepatitis; NASH, non-alcoholic steatohepatitis; DCP, des-gamma-carboxy prothrombin; AFP, alpha-fetoprotein; ALBI score, albumin bilirubin score

On assessing the background factors of the 27 patients in the three-way-stopc-TACE group and the 44 patients in GMD-c-TACE group, the mean age was 71.40 ± 8.94 and 73.95 ± 9. 97 years, respectively. The male-to-female ratios were 22:5 and 34:10, and the causes of liver disease were HBV/HCV/AIH/Alc/NASH 6/8/2/8/3 and 8/17/2/10/7, respectively. Other background factors, including total bilirubin, albumin, prothrombin activity (%), ALT, AST, platelet count, AFP, DCP, and ALBI, were not significantly different (Table 2). However, there was no significant difference between the two groups.

Table 2. Comparison between transarterial chemoembolization (TACE) therapy characteristics according to TACE devise.

Variables	Non -GMD (n=27)	GMD (n=44)	p-Value
Age (years)	71.407 ± 8.984	73.955 ± 9.977	p=0.2823
Gender (Male/Female)	22/5	34/10	p=0.673
Etiology(Viral/Non-viral)	14/13	25/19	p=0.683
Size (mm)	30.852 ± 6.532	32.795 ± 5.593	p=0.1869
Total bilirubin (mg/dL)	1.002 ± 0.494	0.814 ± 0.362	p=0.0709
Albumin (g/dL)	3.733 ± 0.524	3.914 ± 0.475	p=0.1399
DCP (mAU/mL)	170.604± 436.403	1622.23 ± 6532.97	p=0.2632
AFP (ng/mL)	11.281 ± 13.285	28.280 ± 91.988	p=0.3537
ALBI score	-2.384 ± 0.522	-2.601 ± 0.423	p=0.0616
Post CT value (HU)	527.67 ±303.91	670.16 ±329.31	p=0.074

Abbreviations: DCP, des-gamma-carboxy prothrombin; AFP, alpha-fetoprotein; ALBI score, albumin bilirubin score; HU, Hounsfield Unit.

Recurrence rate

Local recurrence was observed in 13 of the 71 nodes. The overall local recurrence rate was 3.0% at 6 months, 16.7% at 12 months, and 35.0% at 18 months, followed by a plateau (Figure 1). The local recurrence rate in each group was 3.0% at 6 months, 16.7% at 12 months, and 35.0% at 18 months in the three-way stopcock-TACE (non-GMD) group, and 7.7% at 14 months and 23.1% at 20 months in the GMD-c-TACE group, and statistically significant differences were detected (Figure 2).

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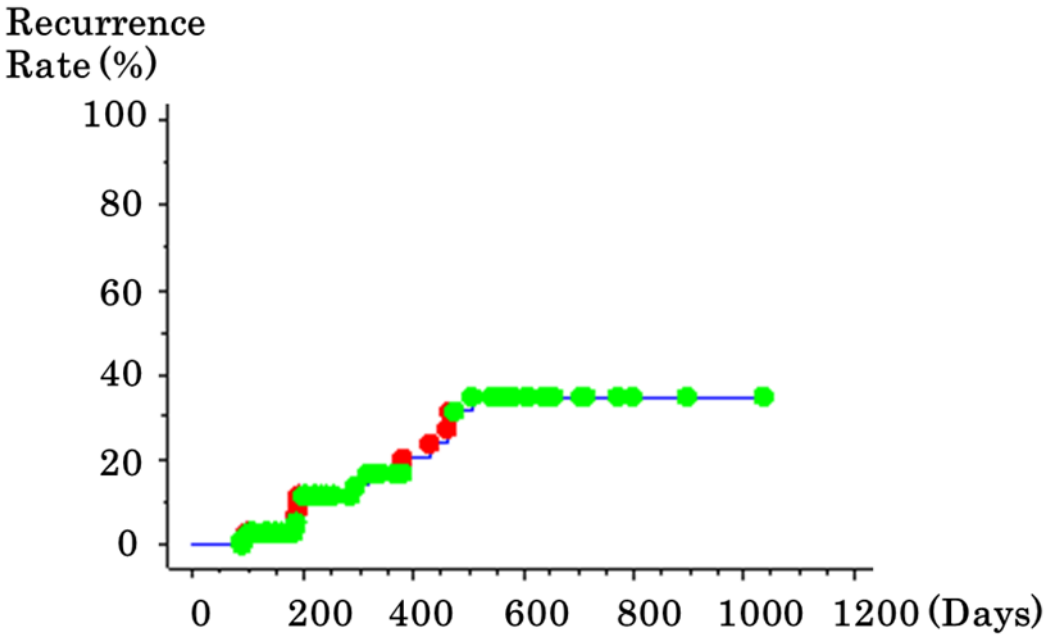

Figure 1. Local recurrence after conventional TACE.

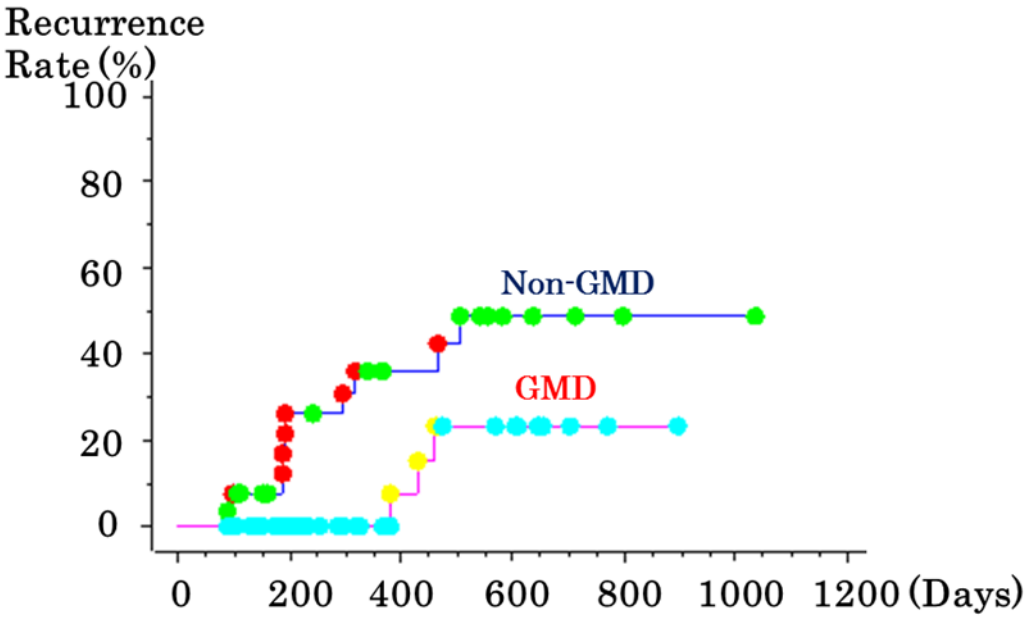

Figure 2. Local recurrence after conventional TACE according to TACE devise.

Although there were no significant differences in local recurrence rates by gender, age, background liver factors, tumor size, AFP, DCP, and Post CT values, local recurrence was significantly higher in the non-GMD group, and multivariate analysis showed significant differences in recurrence by GMD use, which was related to the recurrence factor of c-TACE without GMD. The hazard ratio was 4.655 (Table 3).

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Table 3. Prognostic factors related to local recurrence determined by multivariate analysis using Cox proportional hazard model.

Variable	Categories	HR	95% CI	p-Value
Gender	Male	1	0.135-4.431	P=0.7748
	Female	0.773		
Age	≧70 y.o	2.694	0.740-9.808	P=0.1328
	<70y.o	1		
Etiology	Viral	1	0.458-7.347	P=0.3914
	Non-viral	1.834		
Size(mm)	≧30mm	1	0.081-2.112	P=0.2886
	<30mm	0.414		
AFP (ng/mL)	≧10	1.689	0.343-8.325	P=0.5198
	<10	1		
DCP (mAU/mL)	≧100	1	0.099-3.760	P=0.5938
	<100	0.610		
Post CT (HU)	Low	1.337	0.299-5.977	P=0.7035
	High	1		
TACE devise	Non-GMD	4.655	1.192-18.171	P=0.0269
	GMD	1		

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; GMD, Glass Membrane Devise; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; HU, Hounsfield Unit.

Changes in hepatic functional reserve

Although the overall hepatic reserve did not change after 3 months, the ALBI scores worsened to 2.25±0.95 after 6 months and showed a significant difference (Figure 3).

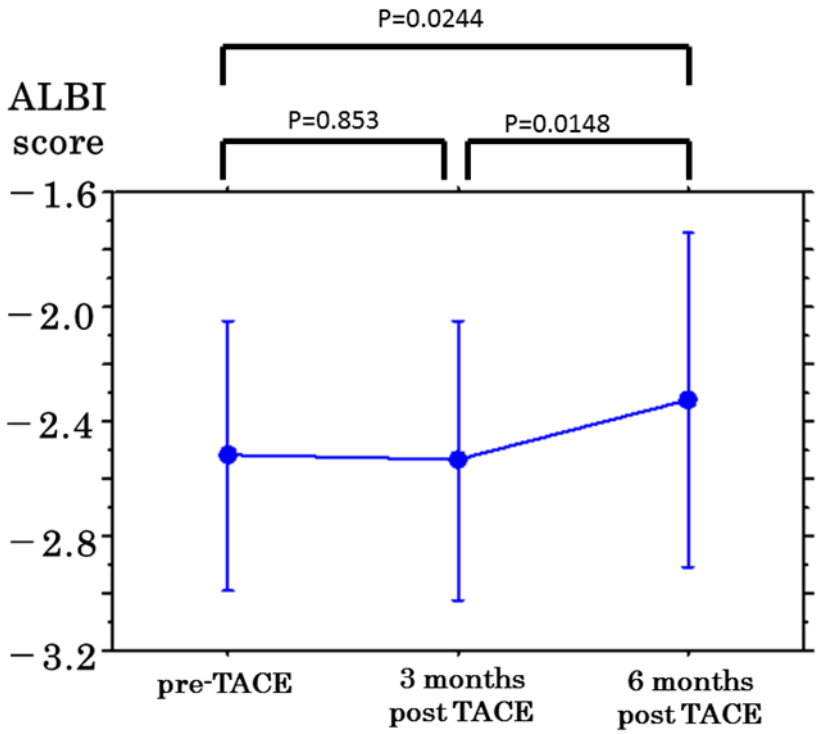

Figure 3. Dynamics of ALBI score in pre-TACE, 3months post TACE and 6 months post TACE.

Comparison of the groups showed that c-TACE with three-way stopcock resulted in deterioration after 6 months, whereas c-TACE with GMD significantly preserved hepatic reserve during the course of the study (Figure 4).

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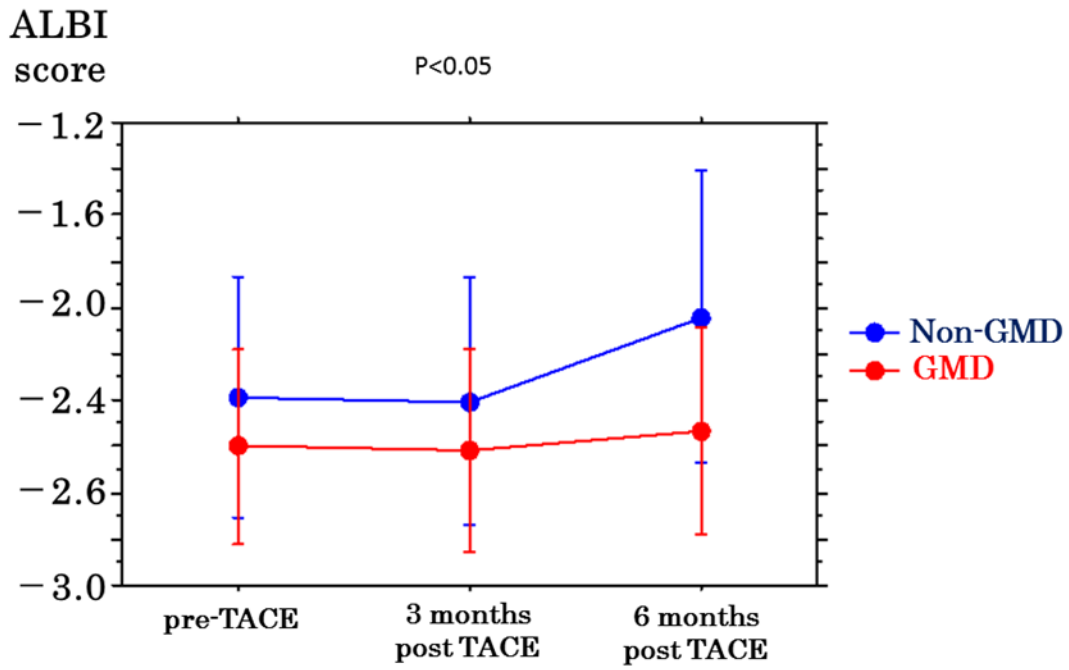

Figure 4. Dynamics of ALBI score in pre-TACE, 3months post TACE and 6 months post TACE according to TACE devise.

Adverse events

Treatment-related adverse events were assessed according to the National Cancer Institute Common Terminology Criteria, version 4.0. Adverse events were evaluated as the maximum change in the grade within 3 months after therapy. In the three way stopcock group (non-GMD), these events included an elevated aspartate aminotransferase (AST) level in 12 patients (44.4%), elevated alanine aminotransferase (ALT) level in 13 (48.18%), and hyperbilirubinemia in 1 patient (3.7%). In the GMD group, these events included an elevated AST level in 4 patients (9.1%), elevated ALT level in 7 (15.9%) and thrombocytopenia in 1 patient (2.2%). All patients spontaneously healed without requiring additional treatment for elevated liver enzymes.

Discussion

According to the Barcelona Clinic Liver Cancer (BCLC) algorithm, transarterial chemoembolization (TACE) is the standard-of-care treatment in patients with intermediate-stage HCC [6, 12, 29, 30].

However, TACE is by definition a palliative and iterative treatment, considering the low rates of complete response and the high risk of disease recurrence [10, 16, 17].

Conventional transarterial chemoembolization using ethiodized oil (Lipiodol; Guerbet, Villepinte, France) has been performed worldwide for inoperable hepatocellular carcinoma since the 1980s [2, 18, 31, 32].

Forming Lipiodol–cytotoxic drug emulsions using three-way stopcock is the standard technique of conventional transarterial chemoembolization. The standard technique of conventional TACE is the pumping emulsification of Lipiodol and doxorubicin/epirubicin solution using three-way-stopcock. A published technical recommendation mentioned that the volume of doxorubicin/epirubicin solution should be lower than that of Lipiodol to create W/O emulsion [16]. It is widely known that the physicochemical characteristics of the emulsion can differ depending on the technical parameters. Previous research studies focused on the type of emulsion (water-in-oil [W/O] or oil-in-water [O/W]) and demonstrated the advantages of W/O in conventional transarterial chemoembolization for hepatocellular carcinoma. W/O emulsion has been associated with a high embolic

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effect. It is known that the viscosity of W/O is higher than O/W [16, 19] ; a high viscosity, which can increase its tumor retention [33]; a high drug carriage capacity; and a longer drug release time [34, 35].

In conventional TACE, it is known that the property of emulsion is important to control the drug release speed. Namely, water-in-oil (W/O) can release drugs slower when compared with oil-in-water (O/W) [36-38].

However, the pumping emulsification using a 3-way-stopcock has a critical limitation. The formed emulsion includes only around 70% of W/O even when the mixture ratio of solution to Lipiodol was 1:2 [39]. Recently, a pumping emulsification device with a microporous glass membrane was developed, which can create nearly 100% W/O emulsion [23].

Theoretically, the pure W/O emulsion could achieve a slow drug release.

Furthermore, recent advances in systemic therapy for HCC have changed the indications for TACE, and conventional-TACE (c-TACE) is now required to achieve more selective and better local control [40]. Therefore, how efficiently Lipiodol can be retained in tumor tissues is an important issue [37, 41, 42]. Lipiodol is an ethyl ester of iodized fatty acids of poppy-seed oil. It accumulates in HCC by improving permeability and retention in solid tumors, and in combination with the embolization material, blocks blood flow not only to the nutrient supply vessels of the HCC but also to the surrounding sinuses through intratumoral sinuses, resulting in ischemia and necrosis [43, 44]. The conventional pumping method using a three-way stopcock is widely used for the emulsification of water-soluble anticancer drugs and ethyl ester of iodinated poppy-seed oil fatty acid (Lipiodol), but this method can only achieve a w/o production rate of about 70% and the droplet size and viscosity are unstable [39, 45].

A porous glass membrane emulsification device (GMD) has been developed to enhance the therapeutic effect of conventional TACE. The 'MicroMagic' porous glass membrane emulsifier (GMD) (Piolax Medical Devices) consists of a disk-shaped glass membrane made from volcanic ash with numerous 50 μm pores [23].

The use of GMD is expected to increase the therapeutic efficacy of TACE, as compared with the conventional 3-way stopcock pumping, as it enables the production of a higher proportion of a W/O emulsion with more homogenous and stable droplets. It has been shown to be more effective in retaining anticancer drugs in tumors in the VX2 Rabbit liver cancer model [46].

Since Lipiodol is used as a drug carrier, the ideal drug properties are to be in a state of W/O (Water in Oil) with a high generation rate, but until now, the problem has been the mixture of O/W, as W/O areas are also present in a three-way stopcock.

GMD has the following advantages:

(1) Improved intravascular distribution with stable emulsion (even, smaller vessels, peripheral drug distribution)

(2) Improved intra-tumor stagnation rate due to viscosity.

(3) Sustained release effect of the drug

(4) Reduction of side effects (decrease in blood concentration of anticancer drugs [suppression of rapid increase] is expected.

Although better TACE outcomes are expected with GMD, its efficacy in clinical practice is still unclear.

In this study, local recurrence was observed in 13 of the total 71 nodes, and the overall local recurrence rate was 3.0% at 6 months, 16.7% at 12 months, and 35.0% at 18 months, after which it plateaued. In the GMD-c-TACE group, it was 7.7% at 14 months and 23.1% at 20 months, showing that local recurrence could be suppressed significantly. In addition, when multivariate analysis was performed on the factors that suppressed local recurrence, GMD was used to perform c-TACE. Multivariate analysis also showed that non-GMD-c-TACE was the only factor related to local recurrence and showed a hazard ratio of 4.655.

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Furthermore, the hepatic functional reserve was significantly preserved in the c-TACE group that used GMD. The reason for this is that the epirubicin penetration rate in the GMD W/O emulsion was significantly higher than that with the three-way stopcock, and the drug elution rate was significantly longer, resulting in fewer systemic effects [47].

The present study also showed that there were no Grade 4 or higher adverse events, no adverse events of clinical concern, and the hepatic reserve was maintained with GMD-c-TACE.

This study has several limitations. First, the number of patients was limited. Second, investigations in numerous patients in various stages of diseases are required. Thirdly, the retrospective design of this study may introduce bias in the selection of patients for HCC treatment. Finally, the data were from a single center, and selection bias cannot be ruled out. Confirmation of these findings will require a larger prospective clinical trial.

In conclusion, although further studies with a large number of patients at various disease stages are needed, GMD-c-TACE therapy was considered to be a useful treatment strategy because of its ability to maintain the hepatic functional reserve.

Abbreviations: TACE: transarterial chemoembolization; GMD, glass membrane emulsification device; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; AIH; autoimmune hepatitis; Alc, alcoholic hepatitis; NASH, non-alcoholic steatohepatitis; DCP, des-gamma-carboxy prothrombin; AFP, alpha-fetoprotein; ALBI score, albumin bilirubin score

Author Contributions: Conceptualization, T.I. ; methodology, T.I. and T.K; investigation, T.I. and T.K.; resources, T.I.; data curation, T.I., M.K., T.K., M.A., Y.N., A.I., T.S. and T.H.; writing—original draft preparation, T.I.; writing—review and editing, T.K. and T.H.;visualization, T.I.; formal analysis, T.I.; supervision, T.I.; project administration, T.I. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study protocol was approved by the institutional ethics committee of Saiseikai Niigata Hospital. After receiving official approval, this study was conducted as a retrospective analysis of database records based on the Guidelines for Clinical Research issued by the Ministry of Health and Welfare of Japan. All procedures were completed in accordance with the declaration of Helsinki. The data were made anonymous before analysis to protect patient privacy.

Informed Consent Statement: Written informed consent was obtained from all patients before treatment and this study received ethical approval for use of an opt-out methodology based on low risk to the participants.

Data availability statement: All data generated or analyzed during this study are included in this published article.

Conflicts of Interest: None of the other authors have potential conflicts of interest to declare.

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