

ORIGINAL ARTICLE

Durable complete response is achieved by balloon-occluded transcatheter arterial chemoembolization for hepatocellular carcinoma

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Abstract

In 2013 and 2014, the development of microcatheters with balloons for the 4-Fr system and new embolization materials provided various options for transarterial chemoembolization (TACE), expanding the range of treatment strategies. At our hospital, balloon-occluded TACE (B-TACE), conventional TACE (C-TACE), and drug-eluting bead TACE (DEB-TACE) have been actively performed for hepatocellular carcinoma (HCC). This study compared the local recurrence-free (LRF) periods of nodules with complete necrosis (TE4) obtained using each treatment method by extracting the nodules evaluated as complete response by the modified Response Evaluation Criteria in Solid Tumors. We performed 580 TACE procedures between June 2013 and April 2019. Among them, 58 HCC nodules in 43 patients, 33 nodules in 30 patients, and 45 nodules in 25 patients were evaluated as having complete necrosis after C-TACE, DEB-TACE, and B-TACE, respectively. The time to local recurrence for each nodule was defined as the LRF period, and the quality of TE4 for each TACE was examined. Factors related to overall survival and the LRF period were determined by univariate and multivariate analyses, and overall survival and the LRF period were analyzed using the Kaplan–Meier method. Multivariate analysis of the LRF period showed that B-TACE was an independent factor. The median LRF periods were 39.3, 13, and 9.1 months for B-TACE, C-TACE, and DEB-TACE, respectively. Moreover, B-TACE had a significantly longer LRF period than C-TACE and DEB-TACE. **Conclusion:** There was no significant difference between C-TACE and DEB-TACE. The LRF period of nodules with TE4 was the longest with B-TACE, suggesting that B-TACE should be used to achieve a radical cure in patients with HCC.

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INTRODUCTORY STATEMENT

Hepatocellular carcinoma (HCC) was the sixth most commonly diagnosed cancer and the third leading cause of cancer-related deaths worldwide in 2020.^[1] Because many patients with HCC are often diagnosed at an advanced stage, their prognosis remains poor.^[1] Therefore, it is important to develop and refine therapeutic modalities to improve the prognosis of patients with HCC.

The Barcelona Clinic Liver Cancer (BCLC) staging system, which incorporates patient performance status (PS), number and size of nodules, presence of macrovascular invasion (MVI), and extrahepatic spread (EHS) and liver function, has been proposed as a standard method to determine prognosis and guide treatment selection among patients with HCC by the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver clinical practice guidelines.^[2–5]

Multinodular HCC without MVI or EHS is diagnosed at an intermediate stage of BCLC (BCLC B). Transcatheter arterial chemoembolization (TACE) is a standard therapy for intermediate HCC, except in some circumstances, and was first reported in the 1970s by Yamada et al.^[6]

TACE has the following categories: conventional TACE (C-TACE), drug-eluting bead TACE (DEB-TACE), and balloon-occluded TACE (B-TACE).^[7,8] Lipiodol suspended in an anticancer agent and gelatin sponge particles used as embolic agents are generally used in C-TACE. Recently, several spherical embolic agents for TACE, named DEBs, have been developed to reduce hepatic disorders and improve the sustained release of anticancer drugs.^[9] DEBs can carry high concentrations of chemotherapeutic drugs and release them continuously into tumor tissues.^[10]

Achievement of complete or partial response in TACE treatment is a favorable prognostic factor for patients with HCC. However, in some cases, TACE cannot effectively demonstrate its performance, such as in the case of hypovascular tumors. In such cases, the drugs injected during TACE cannot be distributed into the tumor because of the weak blood flow into the tumor or a narrow tumor-feeding artery. To solve this problem, a micro-balloon catheter has been developed.^[11] TACE with a micro-balloon catheter, known as B-TACE, has attracted attention as a new procedure. Recently, we and Lucatelli et al., in independent studies, reported the therapeutic effects and safety of B-TACE and identified the optimal anticancer drug for B-TACE.^[12,13] Several reports have shown that B-TACE can enhance the accumulation of lipiodol emulsion within the tumor better than C-TACE, which contributes to the improvement of local control in HCC.^[14,15] Lucatelli et al. also reported the benefit of micro-balloon interventions in treating DEB-TACE, and selective internal radiotherapy in vivo.^[16]

Kim et al. revealed that achievement of complete response (CR) is the most important factor in prolonging overall survival (OS) in patients with intermediate HCC.^[17] The Response Evaluation Criteria in Cancer of the Liver (RECICL) is recommended to assess the local therapeutic effects of TACE.^[18] TE4 indicates 100% tumor necrosis or a 100% reduction in tumor size. The achievement of TE4 indicates the success of the TACE procedure. However, even if TE4 is obtained once, the treated lesions can recur with washout of lipiodol and regrowth. Therefore, it is necessary to assess the quality of TE4 in terms of the therapeutic outcomes of TACE. Thus, a durable TE4 is essential for high-quality TACE. This study aimed to examine the quality of TE4 achieved by each TACE procedure. We compared the local recurrence-free (LRF) period after complete necrosis was achieved by C-TACE, DEB-TACE, and B-TACE with lipiodol.

EXPERIMENTAL PROCEDURES

Study design

This retrospective cohort study aimed to identify the LRF period of TE4 nodules achieved by each TACE (i.e., C-TACE, DEB-TACE, and B-TACE). The treated lesions after each TACE were assessed using RECICL^[18] and modified RECIST.^[19] We examined the period from the achievement of TE4 by each TACE to the recurrence of the treated lesions and calculated the LRF period. This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected by the prior approval of the Institutional Review Board of Kurume University (No. 19212). All examinations and treatments were performed in accordance with the relevant guidelines and regulations. An opt-out approach was used to obtain informed consent from patients, and personal information was protected during data collection.

Subjects

We performed 580 TACE procedures between June 2013 and April 2019. Among these, 58 HCC nodules in 43 patients, 33 nodules in 30 patients, and 45 nodules in 25 patients were evaluated as having complete necrosis after C-TACE, DEB-TACE, and B-TACE, respectively (Figure 1).

Diagnosis of HCC

HCC was diagnosed using a combination of serum tumor markers, such as alpha-fetoprotein (AFP) and des-gamma carboxyprothrombin (DCP), and imaging modalities, such as ultrasonography, computed

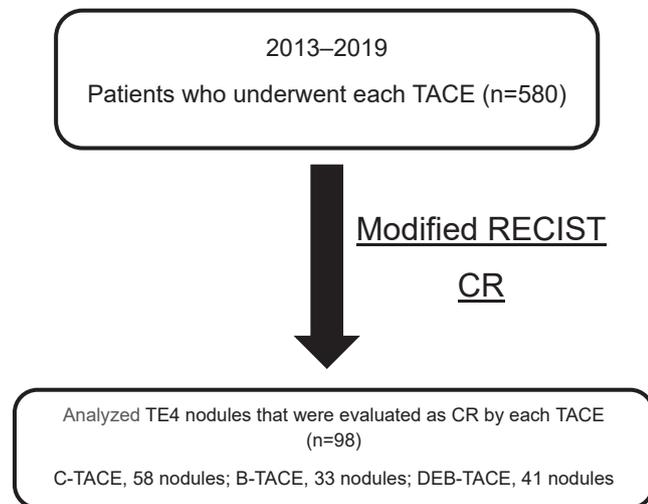


FIGURE 1 Flowchart of the study. B-TACE, balloon-occluded transcatheter arterial chemoembolization; CR, complete response; C-TACE, conventional transcatheter arterial chemoembolization; DEB-TACE, drug-eluting bead transcatheter arterial chemoembolization; RECIST, Response Evaluation Criteria in Cancer of the Liver; TACE, transcatheter arterial chemoembolization; TE, treatment effect.

tomography (CT), magnetic resonance imaging, and/or angiography, according to the Guidelines for the Diagnosis and Management of HCC.^[20]

Inclusion and exclusion criteria

The following patient inclusion criteria were used: (1) HCC, (2) age > 18 years, and (3) complete follow-up from the initial treatment for HCC until death or the study censor time (November 2019). The exclusion criteria were as follows: (1) best supportive care, (2) history of a malignant tumor other than HCC within the 5 years preceding the study, (3) participation in any other clinical trials, (4) vascular invasion, (5) Child–Pugh class C, and (6) inability to follow the TACE procedure.

Data collection

Variables related to the host, tumor, and treatment factors were retrospectively reviewed using clinical records. The following data were collected at the time of HCC diagnosis before treatment: host factors, including age, sex, Eastern Cooperative Oncology Group–PS, etiology, white blood cell count, hemoglobin level, platelet count, prothrombin activity, and serum levels of total bilirubin, direct bilirubin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, gamma-glutamyl transpeptidase, alkaline phosphatase, albumin, blood urea nitrogen, creatinine, C-reactive protein, sodium, potassium, and chlorine; tumor factors, including size and number of

HCC, number of localized segments, previous TACE history, serum levels of AFP and DCP, gross classification of HCC, and BCLC staging system (stage 0, $n = 11$; stage A, $n = 59$; stage B, $n = 21$; stage C, $n = 7$); and treatment factors, such as the selected treatment modality (B-TACE, C-TACE, and DEB-TACE) (Table 1).

Treatment for HCC

According to the Clinical Practice Guidelines for Hepatocellular Carcinoma: The Japan Society of Hepatology 2017 (4th JSH-HCC Guidelines) 2019 Update^[20] and BCLC classification, TACE was selected as the first-line therapy for patients with intermediate-stage HCC.

Balloon-occluded TACE procedure

B-TACE procedures were performed in accordance with our previous report^[12] and the report by Irie et al.^[21] Digital subtraction angiography (DSA) was performed using a contrast agent (Iopamidol 370; Teva Takeda Pharma Ltd.) from the common hepatic artery to detect tumors. After the evaluation of tumor location, a 1.8-Fr micro-balloon catheter (Logos; Piolax Inc.) was inserted into the target artery to perfuse the tumor located in the sub-hepatic or sub-subhepatic segment. Thereafter, we performed DSA to evaluate the tumor location and changes in tumor hemodynamics with and without balloon infiltration with a 0.2-ml mixture of contrast medium and heparin-added physiological saline. We selected anticancer drugs to suspend the lipiodol on demand. The maximum amount of lipiodol in the suspension was 10 ml. All drug preparations were performed in accordance with the manufacturer's instructions. After balloon infiltration, each lipiodol-suspended drug was slowly injected until the catheter was pushed back because of increased pressure. After injection of lipiodol, 1 mm of gelatin sponge agent (Gelpart; Nippon Kayaku) was injected to embolize the target artery.

C-TACE and DEB-TACE

The celiac and common hepatic arteries were catheterized with a 3-Fr or 4-Fr catheter, and DSA was performed using a nonionic contrast agent. After evaluating the segment containing the tumor, a 1.7-Fr or 1.9-Fr microcatheter (Piolax Inc.) was inserted into the subhepatic or sub-subhepatic segment containing the tumor using an adapted microwire (Piolax Inc.). For DEB-TACE, 30 mg of epirubicin was dissolved in 2 ml saline and loaded into 100–300 μm DC beads (Eisai Co. Ltd.). Epirubicin-loaded DC beads were suspended in 18 ml of dilution solution (1:1 saline/contrast agent). All of the loading procedures were performed according to the manufacturer's instructions.

TABLE 1 Baseline clinical and tumor characteristics of the patients

Factor	All patients, N or median (range)	B-TACE, N or median (range)	C-TACE, N or median (range)	DEB-TACE, N or median (range)	p-value (Kruskal–Wallis)
Age (years)	74 (51–90)	74 (62–88)	75 (51–87)	72 (63–90)	0.9776
PS 0/1	92/6	24/6	43/0	25/0	0.0007
Sex					
Male/female	67/31	21/9	29/14	17/8	0.9726
Etiology					
HBV/HCV/nonBnonC	7/62/29	1/19/10	2/28/13	4/15/6	0.1734/0.9152/0.8023
Child–Pugh class A/B	71/27	21/9	35/8	15/10	0.1751
ALBI grade 1/2/3	26/69/3	9/21/0	12/31/0	5/17/3	0.2843
PT (%)	80.5 (30–122)	80.5 (30–109)	83 (51–122)	73 (56–106)	0.0151 (between C and DEB)
T-Bil (mg/dl)	0.88 (0.28–3.14)	0.83 (0.28–1.88)	0.91 (0.4–2.12)	0.83 (0.5–3.14)	0.6588
ALB (g/dl)	3.55 (2.59–4.58)	3.61 (2.63–4.53)	3.69 (2.81–4.33)	3.42 (2.59–4.52)	0.2863
Tumor size (mm)	19 (8.8–65)	21.0 (11.3–65)	19.35 (10.7–54.3)	18.07 (8.8–42.8)	0.0604
AFP (ng/ml)	7.6 (1.3–9851)	7.75 (1.1–9851)	7.6 (1.3–8014)	12.1 (1.3–4128)	0.3192
DCP (mAU/ml)	65 (10–8245)	50 (10–8245)	76 (12–4441)	68 (11–8748)	0.5350
BCLC stage 0/A/B/C	11/59/21/7	1/15/7/7	6/29/8/0	4/15/6/0	0.0069
Number of tumor localized segment (>2/≤2)	17/81	11/19	6/37	7/18	0.0716
Number of tumor nodules (≥4/<3)	24/74	6/24	6/37	5/20	0.7316
Previous TACE history (with/without)	67/31	13/17	9/34	9/16	0.1069

Abbreviations: AFP, alpha-fetoprotein; ALB, albumin; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; DCP, des-gamma carboxyprothrombin; HBV, hepatitis B virus; HCV, hepatitis C virus; PS, performance status; PT, prothrombin time; T-Bil, total bilirubin.

After catheterization into the artery that flowed to the tumor-containing area, suspended DEBs were administered slowly; the contrast agent cleared within 2–5 heartbeats. After 5 min, DSA was performed to confirm the stasis of blood flow in the treated artery. If revascularization was observed, the DEBs were re-administered. In the event of intratumoral bleeding during DEB administration, a gelatin sponge agent was administered until the pooling of the contrast agent ceased. The maximum epirubicin dose was 30 mg in one session; if the treatment was not completed in the session, the remnant nodules were treated in an additional session. C-TACE received a mixture of 30 mg epirubicin manually emulsified with lipiodol (Guerbet), depending on the size and number of tumors, followed by embolization with absorbable gelatin sponge particles (Nihon Kayaku).

Main outcomes

LRF period

The LRF period is the period until local recurrence after TE4 is achieved with each TACE procedure. The cutoff date for this analysis was August 31, 2020.

OS period

The OS period was defined as the period from the initial HCC treatment to the study censorship date.

Follow-up process and assessment of response

At the first follow-up, enhanced CT was performed 1 month after initial treatment. The imaging examination for each patient was performed according to the same protocol. For the CT examination, three contrast phases were obtained after the precontrast scans. All CT scans were performed using more than 64 raw systems (GE Healthcare Japan). After the first follow-up, regular imaging follow-up was performed every 2–3 months. The scanned images were read and diagnosed by two independent radiologists and one hepatologist. LFR periods of the target nodules were observed. If each TACE or systemic chemotherapy (e.g., methylthioadenosines [MTAs]) was administered to the same area during the observation period, that date was considered a local recurrence day.

Statistical analyses

All data are expressed as numbers or medians (range). All statistical analyses were performed using JMP Pro statistical analysis software version 15 (SAS Institute Inc.). The LRF and OS periods were calculated using the Kaplan–Meier method and analyzed using the log-rank (Wilcoxon test) test or the Bonferroni method. Between-group comparisons were performed using the chi-squared test or Wilcoxon rank-sum test. Factors associated with the achievement of LRF survival were evaluated via univariate and multivariate analyses using the Cox proportional hazards model. Variables associated with LRF achievement in univariate analysis ($p < 0.10$) were subjected to the multivariate regression model. A two-tailed p -value < 0.05 was considered statistically significant. Comparative analysis of LRF periods, both unadjusted and adjusted with propensity score, were performed between C-TACE and B-TACE, B-TACE and C-TACE, and C-TACE and DEB-TACE, respectively. Propensity score was estimated using six factors as follows: maximum tumor diameter, AFP, number of tumors, first TACE or not, three or more segments, and ECOG PS. Adjusting by propensity score was conducted using inverse probability treatment weighting (IPTW).

RESULTS

Characteristics of patients and HCCs

The characteristics of the 98 patients with HCC who achieved CR after each TACE are given in Table 1. The median age of the patients was 74 years, and 68% of the patients were men. The median tumor size, AFP level, and DCP level were 19 (8.8–65) mm, 7.6 (1.3–9851) ng/ml, and 65 (10–8245) mAU/ml, respectively. In the BCLC classification, 60.2% of patients had BCLC A. The median albumin level, total bilirubin level, and prothrombin time (PT) were 3.55 g/dl (2.59–4.58), 0.88 mg/dl (0.28–3.14), and 80.5% (30–122), respectively. Liver function was evaluated using the albumin-bilirubin (ALBI) and Child–Pugh scores.^[22] The ALBI score was calculated as previously described^[23] based on serum albumin and total bilirubin levels, $ALBI\ score = (\log_{10}\ bilirubin\ [\mu\text{mol/L}] \times 0.66) + (\text{albumin}\ [g/L] \times -0.085)$, and was graded as follows: grade 1, ≤ -2.60 ; grade 2, > -2.60 to ≤ -1.39 ; grade 3, > -1.39). The etiology of HCC was unrelated to hepatitis B or C virus in 29.5% (29 of 98) of patients, and 72.4% of patients were classified as having Child–Pugh A. ALBI grade 2 was observed in 70.4% (69 of 98) of the patients. The B-TACE group had a worse PS than the other TACE groups. The PT% was worse in the DEB-TACE group than in the

C-TACE group, but there was no significant difference between them.

Anticancer drugs used in TACE

In this study, epirubicin was used in all patients treated with DEB-TACE. In patients treated with B-TACE, 21 (70%) used epirubicin, 7 used miriplatin, and 2 used cisplatin. In those treated with C-TACE, 40 (93%) used epirubicin and 3 used cisplatin. In addition, the average dose of epirubicin was 20.5 mg, 20.8 mg, and 31.2 mg in the B-TACE, C-TACE, and DEB-TACE groups, respectively.

OS and LRF period in all CR cases

The mean survival time of all patients was 41.4 months (Figure 2A). Moreover, the 1-year and 2-year survival rates were 92.8% and 77.9%, respectively. The LRF period for all nodules was 12.1 months (Figure 2B).

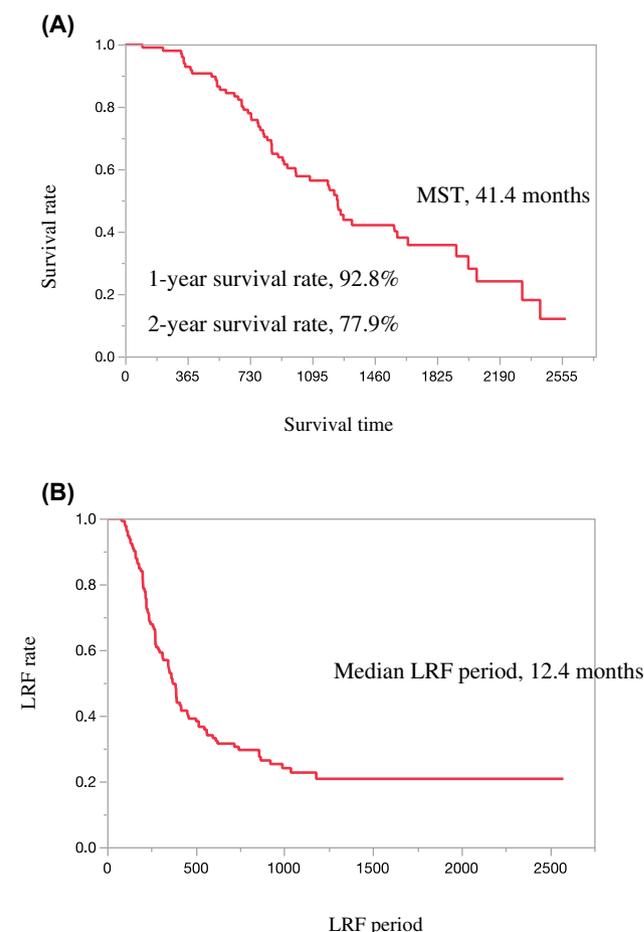


FIGURE 2 Overall survival and local recurrence-free (LRF) period in all patients. (A) Overall survival of all patients. The median survival time (MST) of all patients was 41.4 months. The 1-year and 2-year survival rates were 92.8% and 77.9%, respectively. (B) Local LRF for all nodules. The LRF period for all nodules was 12.1 months.

LRF period in CR cases of each TACE

The LRF periods obtained with B-TACE, C-TACE, and DEB-TACE were 1180, 386, and 272 days, respectively (Figure 3). There was a significant difference in the comparison of LRF periods between B-TACE and C-TACE ($p = 0.0002$) and between B-TACE and DEB-TACE ($p < 0.0001$). However, there was no significant difference in the comparison of the LRF periods between C-TACE and DEB-TACE ($p = 0.0173$, Bonferroni analysis). The representative images in each TACE are shown in Figure 4.

Univariate and multivariate analyses of factors associated with OS

The univariate and multivariate analyses for OS are found in Table 2. In the univariate analysis related to OS, age ($p = 0.0348$), PS ($p = 0.0028$), ALBI score ($p = 0.0689$), BCLC stage ($p = 0.0308$), number of tumor localized segments ($p = 0.0361$), and number of tumor nodules ($p = 0.0592$) were identified as significant factors. Multivariate analysis showed that PS (0 or 1; $p = 0.0144$; hazard ratio [HR], 0.25 [0.09–0.68]) was an independent factor associated with OS.

Univariate and multivariate analyses of factors associated with the LRF period

Univariate and multivariate analyses for the LRF periods are given in Table 3. In the univariate analysis related to LRF periods, age ($p = 0.0650$), PS ($p = 0.0524$), tumor diameter = 29mm ($p = 0.0019$), BCLC stage

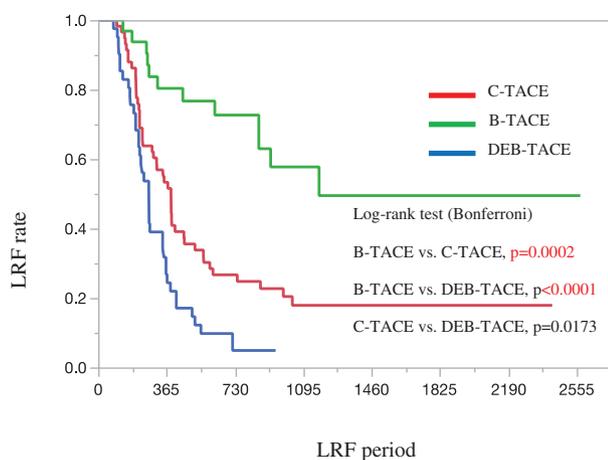


FIGURE 3 LRF period in each TACE. Blue line, DEB-TACE; red line, C-TACE; green line, B-TACE. There were significant differences among TACE procedures (green/red p -value = 0.0002, green/blue p -value < 0.0001 , red/blue p -value = 0.0173). The median LRF period obtained with B-TACE was 1180 days. The median LRF period after C-TACE was 389 days. The median LRF period after DEB-TACE was 272 days.

($p = 0.0804$), and TACE type ($p < 0.0001$) were identified as significant factors. Subsequently, multivariate analysis showed that tumor diameter = 29mm ($p = 0.0236$; HR, 0.44 [0.20–0.95]) and TACE type (B-TACE; $p = 0.0003$; HR, 0.32 [0.16–0.64]) were identified as independent factors associated with longer LRF period.

Comparison of LRF periods across the TACE groups (unadjusted and adjusted using IPTW)

Adjustment of tumors and patient background was conducted using propensity score IPTW (Table 4). In the unadjusted group, the HR of C-TACE compared with that of B-TACE was 3.092; DEB-TACE compared with that of B-TACE was 6.352; and C-TACE compared with that of DEB-TACE was 1.859. In the adjusted group using IPTW, the LRF period was 2.624 for B-TACE and C-TACE, 6.729 for B-TACE and DEB-TACE, and 2.091 for C-TACE and DEB-TACE (Table 4). For the IPTW method, p -values were = 0.0036 for B-TACE and C-TACE, < 0.0001 for B-TACE and DEB-TACE, and = 0.0018 for C-TACE and DEB-TACE (Table 4). Even after adjustment of tumors and patient background, B-TACE was the most effective in prolongation of LRF period.

Incidence rate of severe adverse events in each TACE

We assessed the development rate of severe adverse events (AEs) ($>$ grade 3 as assessed by CTCAE version 5.0) for each TACE procedure. Thirty patients experienced severe AEs (%). Among them, 15 of 43, 11 of 30, and 4 of 25 patients undergoing C-TACE, B-TACE, and DEB-TACE experienced AEs, respectively. There were no significant differences in the incidence rates of severe AEs among the groups. In all patients who experienced severe AEs, symptoms improved with conservative treatment.

DISCUSSION

This study aimed to clarify the clinical question of whether there are differences in the quality of complete necrosis after TACE. The results showed that B-TACE had a significantly longer LRF period than other TACEs. In addition, the factors associated with a longer LRF period were larger tumor size (> 29 mm) and choice of the B-TACE procedure.

TACE is a standard therapy for intermediate-stage HCC according to the BCLC B classification.^[5] The most important factor, which is associated with

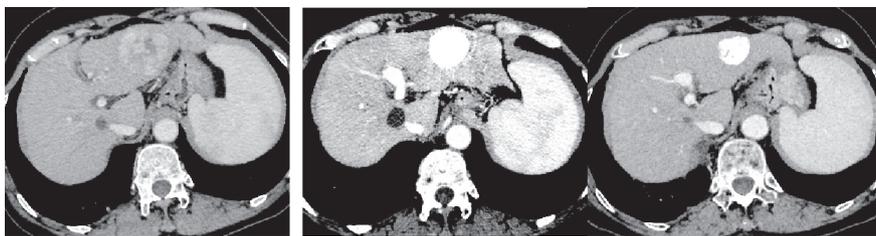
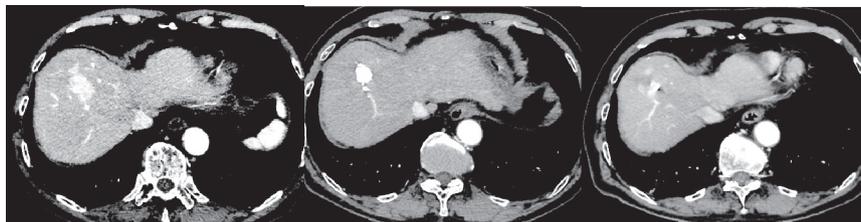
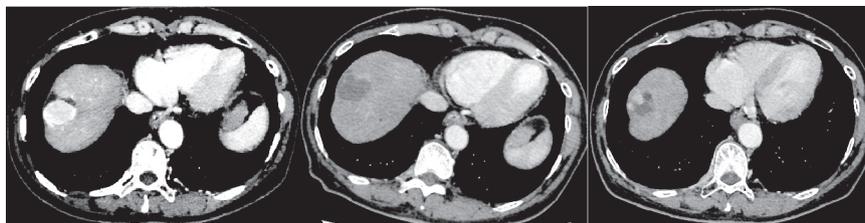
(A) B-TACE**(B) C-TACE****(C) DEB-TACE**

FIGURE 4 Representative computed tomography (CT) images treated with each TACE. (A) Representative CT images treated with B-TACE. Left panel shows arterial phase of contrast-enhanced CT before treatment. Middle panel shows the treated hepatocellular carcinoma (HCC) just after B-TACE. Right panel shows the treated HCC after 6 years from B-TACE. (B) Representative CT images treated with C-TACE. Left panel shows arterial phase of contrast-enhanced CT before treatment. Middle panel shows the treated HCC just after C-TACE. Right panel shows the recurred HCC after 6 months. (C) Representative CT images treated with DEB-TACE. Left panel shows arterial phase of contrast-enhanced CT before treatment. Middle panel shows the treated HCC just after DEB-TACE. Right panel shows the recurred HCC after 4 months.

better prognosis, in TACE for intermediate HCC is to obtain CR.^[17] However, there are some cases in which local recurrence occurs despite CR achievement. In this study, we assessed the quality of complete necrosis (TE4) in nodules treated with TACE for the first time. Several studies have reported on the quality of TACE. Miyayama et al. and Iwamoto et al. reported that the quality of TACE can be improved by refinement of the TACE.^[24,25] B-TACE has been developed to increase the quality of TACE procedure. In this study, B-TACE showed the best LRF duration. Irie et al. reported that CR obtained with B-TACE had a high concentration of lipiodol,^[14] suggesting that high-density drug storage contributed to the prolongation of the LRF period. In contrast, the LRF periods for C-TACE and DEB-TACE were shorter than that for B-TACE, even when TE4 was achieved. For C-TACE, there are many subjective factors, such as the operator's thought and the dose of the injection chemotherapeutics. Moreover, once TE4 is achieved by C-TACE, its quality may not be

sustained. In addition, DEB-TACE is an excellent treatment with results similar to those of C-TACE.^[26] This has never been validated for the LRF period. In the present study, there was no significant difference in the LRF period between C-TACE and DEB-TACE; however, DEB-TACE tended to have the shortest LRF period. Due to the nature of DEB-TACE, the embolic material remains in the tumor-feeding artery, not in the drainage vein, and the embolizing power is considered to be weaker than that of other TACE procedures. Iwamoto et al.^[25] and Miyayama et al.^[24] reported that embolization in the peripheral portal branches, which are drainage veins for tumors, can cause high-quality complete necrosis and that DEB-TACE may be inferior at this point. A loading dose of epirubicin used for DEB-TACE is generally recommended to be 50 mg. The average dose of epirubicin used for DEB-TACE was 30 mg in this study, which might have caused less therapeutic effects in the study. Lucatelli et al. reported on the importance of not only the loading dose, but also particle size

TABLE 2 Univariate and multivariate analyses for the factors for overall survival

Factor	Univariate analysis p-value	Multivariate analysis p-value	Hazard ratio (95% CI)
Age (65< or ≥65 years)	0.0348	0.7452	
PS 0 or 1	0.0028	0.0144	0.25 (0.09–0.68)
Sex			
Male/female	0.3294		
Etiology			
HBV/HCV/nonBnonC	0.1035/0.4348/0.7905		
ALBI score (≤−2.159/>−2.159)	0.0689	0.8742	
PT	0.6023		
Tumor size (mm)	0.3351		
AFP (≤200 or >200 ng/ml)	0.9969		
DCP (≤258 or >258 mAU/ml)	0.4615		
BCLC stage (0+A or B+C)	0.0308	0.5336	
Number of tumors localized segment (>2/≤2)	0.0361	0.2998	
Number of tumor nodules (≥4/<3)	0.0592	0.1694	
Previous TACE history (with/without)	0.6860		
B-TACE, C-TACE, DEB-TACE	0.2095		

Abbreviation: CI, confidence interval.

TABLE 3 Univariate and multivariate analyses for the factors for LRF periods

Factor	Univariate analysis p-value	Multivariate analysis p-value	Hazard ratio (95% CI)
Age (65< or ≥65 years)	0.0650	0.1251	
PS 0 or 1	0.0524	0.8310	
Sex			
Male/female	0.7438		
Etiology			
HBV/HCV/nonBnonC	0.5326/0.5056/ 0.5909		
Child–Pugh class A or B	0.9626		
ALBI score (≤−2.159 or >−2.159)	0.3206		
Tumor size ≥29 mm			
≥29	0.0019	0.0236	0.44 (0.20–0.95)
<29			2.27 (1.04–4.91)
AFP (≤200 or >200 ng/ml)	0.1380		
DCP (≤258 or >258 mAU/ml)	0.9006		
BCLC stage 0+A/ B+C	0.0804	0.9261	
Number of tumors localized segment (>2/≤2)	0.1151		
Number of tumor nodules (≥4/<3)	0.9682		
Previous TACE history (with/without)	0.9850		
B-TACE vs. C-TACE, DEB-TACE			
B-TACE+	<0.0001	0.0003	0.32 (0.16–0.64)
B-TACE−			3.10 (1.56–6.16)

in DEB-TACE.^[27] Refinement of the procedures in DEB-TACE might contribute to improvement of the local control rate.

Systemic treatment for unresectable HCC is entering a multi-MTA era (e.g., atezolizumab plus bevacizumab combination therapy, lenvatinib, sorafenib).^[28–30]

TABLE 4 Comparison of LRF periods for each TACE by unadjusted and inverse probability treatment weighting

Method	N	Category	HR	95% CI		p-Value
HRs of LRF periods between B-TACE and C-TACE						
Unadjusted	91	B-TACE	1			
		C-TACE	3.092	1.632	5.857	0.0005
IPTW	91	B-TACE	1			
		C-TACE	2.624	1.37	5.025	0.0036
HRs of LRF periods between B-TACE and DEB-TACE						
Unadjusted	74	B-TACE	1			
		DEB-TACE	6.352	3.101	13.012	<0.0001
IPTW	74	B-TACE	1			
		DEB-TACE	6.792	3.253	14.18	<0.0001
HRs of LRF periods between C-TACE and DEB-TACE						
Unadjusted	99	C-TACE	1			
		DEB-TACE	1.859	1.194	2.893	0.006
IPTW	91	C-TACE	1			
		DEB-TACE	2.091	1.315	3.324	0.0018

Abbreviation: IPTW, inverse probability treatment weighting.

Therefore, the role of TACE has changed. The treatment algorithm for AASLD has been revised to partly recommend atezolizumab plus bevacizumab therapy as first-line therapy in BCLC B.^[4,5] In addition, the concept of TACE refractoriness/unsuitability has been established.^[31] Prospective and retrospective studies of TACE combined with MTAs have been conducted and demonstrated their usefulness.^[32–34] Currently, there are many alternative therapeutic modalities for intermediate HCC, although TACE was the only modality used several decades previously. In the multi-MTA era, the high quality of TACE, especially that of TE4, is required.

The results of the analysis showed that B-TACE had a significantly longer LRF period than other TACEs. There are two reasons for the inadequate efficacy of TACE procedures: technical problems and tumor factors. One reason for this study is that B-TACE using a new device may provide a solution to some of the previously mentioned problems with common TACE techniques.

In this study, we performed an analysis of factors related to the quality of TE4. B-TACE was one of the factors involved in the long LRF period; however, the large tumor diameter (≥ 29 mm) was also a factor. This finding in our study supports previous reported findings. Lucatelli et al. and Golfieri et al. reported that B-TACE achieved the best clinical performance for 3–5 cm of nodular size in treatment.^[35,36] It is still unclear why B-TACE is more effective in cases with a bigger tumor size. However, a report showed the relationship between an increase in microvascular invasion or microsatellite lesions and bigger tumor size.^[37,38] Expanding the treatment area around the tumor to the drainage area, and treating the drainage area of the tumor using B-TACE, may have led to good local control.

A certain tumor diameter may be necessary because the tumor-feeding arteries become thinner or undetectable on DSA, which can be a negative factor for embolization by embolic agents during TACE.

LIMITATION

Although the current study indicated an important finding regarding TACE for HCC, it has some limitations. First, this was a single-center retrospective study. Second, the sample size was relatively small. In addition, the selection of which TACE was performed was dependent on the operator's thoughts, which can be a selection bias. Comparing the backgrounds of the three groups in this study, there were no significant differences in tumor factors, such as tumor size, number of tumors, and tumor localization, but the other factors were not clear. Therefore, a future prospective study should be conducted to assess the quality of TE4 in each TACE procedure.

CONCLUSION

In this study, we evaluated the quality of TE4 achieved using each TACE procedure. Once TE4 was achieved by TACE, the longest LRF period was obtained by B-TACE. In the era of multi-MTAs, the high quality of TACE procedure is required. Moreover, B-TACE is considered useful in clinical practice.

AUTHOR CONTRIBUTIONS

Study concept and design: Tomotake Shirono and Hideki Iwamoto. *Data acquisition and interpretation:*

Tomotake Shirono, Hideki Iwamoto, Shigeo Shimose, Takashi Niizeki, Akira Kajiwara, Hiroyuki Suzuki, Naoki Kamachi, Yu Noda, Shusuke Okamura, and Ryoko Kuromatsu. *Manuscript draft*: Tomotake Shirono and Hideki Iwamoto. *Statistical analysis*: Kenta Murotani. *Analysis, data interpretation, and critical revision*: Hironori Koga and Takuji Torimura.

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CONFLICT OF INTEREST

Nothing to report.

DATA AVAILABILITY STATEMENTS

The data sets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki, as reflected by the prior approval of the Institutional Review Board of Kurume University (approval #19212). An opt-out approach was used to obtain informed consent from patients, and personal information was protected during data collection. None of the patients were institutionalized.

PATIENT CONSENT FOR PUBLICATION

Not applicable.

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