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Comparison of Local Recurrence Between LEN-TACE and TACE for Hepatocellular Carcinoma According to Lipiodol Accumulation

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Abstract. *Background/Aim: Transarterial chemoembolization (TACE) is the standard treatment for patients with hepatocellular carcinoma in the intermediate stage; however, with advances in systemic therapy, the indications for TACE have gained significance. While lenvatinib (LEN)-TACE offers the potential for good outcomes, local recurrence has not yet been adequately investigated. Therefore, this study investigated local recurrence factors for each type of TACE, focusing on the lipiodol (Lip) value in LEN-TACE and conventional TACE. Patients and Methods: Fifty patients (50 nodes) with hepatocellular carcinoma and a tumor size <7 cm who underwent LEN-TACE or TACE between January 2022 and June 2023 were included in this study to investigate local recurrence and its influencing factors. Results: The local recurrence rate after LEN-TACE was 5.6% at 6 months and 11.5% at 12 months, whereas those after TACE were 6.4% at 6 months and 13.2% at 12 months (p=0.028). There were no significant differences in local recurrence rates according to background liver factors, alpha-fetoprotein (AFP), des-γ-carboxy prothrombin (DCP) values, sex, age, and albumin-bilirubin (ALBI) score. Lipiodol (Lip) values immediately after LEN-TACE were significantly higher than those after TACE alone (p=0.021). Multivariate analysis showed that LEN-TACE had a recurrence hazard ratio of 0.184. Conclusion: LEN-TACE provided good local tumor control. Local recurrence factors included LEN pretreatment, and Lip CT values were higher immediately after LEN-TACE. Thus, LEN-TACE after upfront LEN administration may increase the effectiveness of TACE.*

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Hepatocellular carcinoma (HCC) represents approximately 90% of primary liver cancers and ranks as the sixth most common carcinoma globally, with a dismal prognosis (1). Transarterial chemoembolization (TACE) is a well-established treatment for primary HCC that is not amenable to surgical resection or other local therapies (2). However, no promising pretreatment biomarkers for HCC have been recognized, although complete response (CR) is a surrogate marker for overall survival (OS).

The treatment response was a stronger predictor of prognosis compared to alpha-fetoprotein (AFP) or vascular invasion in the REFLECT trial (3). Similarly, treatment response emerged as a strong predictor of OS in the combined immunotherapy Atezo/Beva IMbrave 150 trial (4); thus, establishing the response at the time of HCC treatment is a good predictive marker of OS (5). However, regarding the association between response and prognosis with TACE, both the initial and the best response predicts OS effectively. Moreover, achievement of treatment response at an early time point is still the most robust predictor for favorable outcomes (6). In analyses of conditions up to 7 inches, both the initial and best responses during repeated transarterial chemoembolization were significantly associated with OS in patients with intermediate-stage HCC and preserved liver function (7). In other words, in TACE, it is important to ensure that CR is achieved under the appropriate conditions. The efficacy of LEN-TACE has been previously reported (8-11); however, studies on the presence or absence of local recurrence to achieve an early treatment response are limited. In a prior study, we demonstrated that obtaining a sufficient

lipiodol (Lip) level in miriplatin (MPT) B-TACE was associated with reduced local recurrence (12). Therefore, we sought to better understand the importance of obtaining an adequate Lip in LEN-TACE. In this study, we compared Lip values and incidences of local recurrence between LEN-TACE and conventional TACE.

Patients and Methods

Patients. A total of 50 patients (50 nodes) with HCC who underwent LEN-TACE or TACE at Saiseikai Niigata Hospital between January 2020 and December 2023 were included in this study. We investigated the outcomes and factors contributing to local recurrence in patients who underwent either TACE or LEN-TACE for HCC measuring <7 cm. The diagnosis of HCC was based on dynamic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI).

The exclusion criteria were as follows: 1) tumor diameter of >7 cm; 2) invasive and intentionally incomplete TACE; 3) interval between TACE and the first follow-up CT of >4 months; 4) no CT performed during follow-up observation; 5) nodules requiring locoregional therapy, such as percutaneous ethanol injection (PEI), microwave coagulation therapy, laser ablation, or radiofrequency (RF) ablation as additional treatment; 6) extrahepatic metastasis from HCC; and 7) other malignancies.

Methods. In all patients, TACE was performed by puncturing the femoral artery using the Selginger technique, inserting a 5F introducer followed by a 5F catheter, and advancing a 3Fr microcatheter by a coaxial technique to the subregion or further peripheral feeding vessel. TACE was performed in all patients following the standard protocol. Epirubicin hydrochloride 50 mg (Epirubicin; Nippon Kayaku, Tokyo, Japan) was dissolved in a nonionic contrast medium; the mixing ratio of aqueous Epirubicin solution to Lip was 1:2 (13).

The emulsion was injected through a microcatheter inserted into the tumor-feeding artery, which was subsequently embolized using 1 mm-diameter gelatin particles (Gelpart; Nippon Kayaku, Tokyo, Japan).

After embolization, multidirectional angiography confirmed the absence of tumor staining and sufficient accumulation of Lip in the tumor. The volume of the emulsion used in both groups was determined according to the nodule size.

Immediately after TACE, non-contrast CT examinations were performed using a 16-detector row scanner (Aquilion, Toshiba Medical Systems, Tokyo, Japan), and for lesion density measurement, a circular region of interest (ROI) lesion was set for each nodule. The CT values of the Lip that accumulated in the HCC nodule were measured. The lesion density was presented in Hounsfield units (HU) on the CT.

The patients were followed up after treatment to assess local recurrence and accumulation of Lip, and subsequent CT was used to investigate local recurrence. In the LEN-TACE group, lenvatinib (Eisai Co., Ltd, Tokyo, Japan) was administered orally at 8 mg once per day in patients with weight <60 kg or at 12 mg per day in patients with weight ≥60 kg based on the recommended doses published in the REFLECT trial (3), 14 days before TACE.

Local recurrence was determined in one of the following cases: 1) if an area in the tumor after treatment in which Lip did not accumulate showed contrast in the early phase and exhibited low absorption in the delayed phase, or 2) if an area in contact with the Lip-accumulated area was contrasted in the early phase and showed low absorption in the delayed phase. Lesions located some distance from the Lip accumulation area were not considered local recurrences.

Ethics statement. This study was approved by the Institutional Review Board of Saiseikai Niigata Hospital and conducted following the principles outlined in the Declaration of Helsinki. Prior to participating in this study, written informed consent was obtained from all patients.

Statistical analysis. The two groups were compared using the Chi-square test. Normally distributed continuous data were expressed as mean±standard deviation and compared using *t*-tests. The differences in parameters were analyzed using a one-way repeated measures analysis of variance. Recurrence rates were estimated using the Kaplan–Meier method and differences between groups were compared using the log-rank test. Multivariate analysis was performed to identify independent prognostic factors, and the Cox proportional hazards model was used to calculate the adjusted hazard ratio (HR) and 95% confidence interval (CI). Statistical significance was set at $p<0.05$. 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) (14).

Results

The clinical background of all patients is shown in Table I. The average patient age was 72.16±7.48 years. The male-to-female sex ratio was 42:8. The background liver factors HBV/HCV/NonHBVNonHCV were 6/11/33. The average AFP and DCP values were 20.11±46.15 ng/ml and 2,434.46±8,579.31 mAU/ml, respectively. The average tumor size was 40.01±9.72 (mm), and the average ALBI score was –2.52±0.48.

Local recurrence was observed in 13 of the 50 nodes, with 10 local recurrences in the 25 patients in the TACE group and three local recurrences in the 25 patients in the LEN-TACE group. The local recurrence rate with LEN-TACE was 5.6% at 6 months and 11.5% at 12 months, whereas the local recurrence with TACE was 6.4% at 6 months and 13.2% at 12 months ($p=0.028$). There were no significant differences in the local recurrence rates according to background liver factors, AFP and DCP levels, sex, age, or ALBI score. The Lip value immediately after LEN-TACE was 527.48±334.78, significantly higher than that after TACE alone at 341.35±195.46 ($p=0.021$) (Table II). In multivariate analysis, LEN-TACE was associated with recurrence, with an HR of 0.184 for higher CT values (Table III).

Adverse events (AEs). In this study group, no vascular complications of the hepatic artery were observed, and there were no complications during the TACE procedures.

Table I. *Demographic and clinical characteristics of 50 patients with unresectable hepatocellular carcinoma.*

Demographic variables	Mean±SD	Range
Age (years)	72.16±7.48	56-86
Sex (Male:Female)	42:8	
Etiology (HBV/HCV/NonHBVNonHCV)	6:11:33	
AFP (ng/ml)	20.11±46.15	1.4-300.8
DCP (mAU/ml)	2434.46±8579.31	12.4-42242.1
Size (mm)	40.01±9.72	22.0–67.5
ALBI score	–2.52±0.48	–3.26 - –1.49
CT value (Hounsfield Unit)	434.41±287.13	105.1-1614.0

SD: Standard deviation; HBV: hepatitis B virus; HCV: hepatitis C virus; NonHBVHCV: non-HBV non-HCV; AFP: alpha-fetoprotein; DCP: des-gamma-carboxy prothrombin; ALBI: albumin–bilirubin.

Table II. *Comparison of patient characteristics between the lenvatinib-transarterial chemoembolization (LEN-TACE) and TACE alone groups.*

Demographic variables	LEN-TACE (n=25)	TACE (n=25)	*p*-Value
Age (years)	74.12±6.53	70.20±8.01	0.065
Sex (Male:Female)	22:3	20:5	0.699
Etiology (HBV/HCV/NonHBVNonHCV)	4:6:15	2:5:18	0.865
AFP (ng/ml)	17.43±28.21	22.76±59.49	0.687
DCP (mAU/ml)	2,348.21±8,197.93	2,520.70± 8,725.24	0.943
Size (mm)	40.72±9.85	39.34±9.76	0.623
ALBI score	–2.53±0.46	–2.45±0.50	0.324
CT value (Hounsfield Unit)	527.48±334.78	341.35±195.46	0.021

HBV: Hepatitis B virus; HCV: hepatitis C virus; NonHBVNonHCV: non-HBV non-HCV; AFP: alpha-fetoprotein; DCP: des-gamma-carboxy prothrombin; ALBI: albumin–bilirubin.

Hypertension, hand-foot syndrome, and anorexia (all Grade 1) were observed as AEs associated with lenvatinib administration in three patients (12.0%) in the LEN-TACE group. During the perioperative period, within two weeks after TACE, 60% patients had post-embolization syndrome. However, they recovered, exhibiting no abnormalities within a week.

LEN-TACE-associated events, including increased AST in 10 patients (40.0%), increased ALT in 11 patients (44.0%), and hyperbilirubinemia in one patient (4.0%), were observed. In the TACE group, events such as increased AST in 8 patients (32.0%) and ALT in 10 patients (40.0%) were recorded. All patients healed spontaneously without additional treatment for elevated liver enzymes.

There were no significant differences between the two groups in any parameter.

Discussion

TACE is the standard treatment for intermediate-stage HCC (2). However, in practice, the evidence for TACE is based on a meta-analysis of six randomized controlled trials (RCTs) that compared the efficacy of TACE without treatment (15). Given that effective systemic therapies are available, there is an urgent need to establish evidence for the benefits of TACE alone *versus* TACE with some degree of tumor necrosis and shrinkage preceded by systemic therapy.

Locoregional therapy after drug administration is actively used as a treatment option for intermediate-stage HCC. Lenvatinib (16) is an orally acting multi-kinase inhibitor approved by the Food and Drug Administration that targets vascular endothelial growth factor (VEGF) receptors, fibroblast growth factor receptors (FGFR), platelet-derived growth factor receptor-alpha (PDGFRα), and RET and KIT proto-oncogenes. After the SHARP trial (17), sorafenib was the only systemic therapy with proven efficacy in the treatment of patients with advanced HCC. In the REFLECT trial (3), lenvatinib demonstrated a similar OS rate but improved progression-free survival (PFS). A representative example is LEN-TACE sequential therapy, which has a high response rate with lenvatinib.

Administering anti-VEGF inhibitors is associated with a reduction in microvessel density, tumor vasculature normalization, and tumor stromal pressure reduction. The administration of anti-VEGF inhibitors improves the efficacy

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

Variables	Categories	HR	95%CI	*p*-Value
Age (years)	≥70	1.662	0.415-6.653	0.7583
	<70	1		
AFP (ng/ml)	<40	0.894	0.186-4.289	0.6050
	≥40	1		
DCP (mAU/ml)	<2,000	0.426	0.081-2.245	0.2437
	≥2,000	1		
Size (mm)	≥40	1.318	0.305-5.689	0.7604
	<40	1		
ALBI score	≥–2.5	0.759	0.194-2.965	0.8836
	<–2.5	1		
CT value (Hounsfield Unit)	≥500.0	0.612	0.128-2.919	0.4659
	<500.0	1		
TACE	LEN-TACE	0.184	0.039-0.866	0.0418
	TACE	1		

HR: Hazard ratio; CI: confidence interval; AFP: alpha-fetoprotein; DCP: des-gamma-carboxy prothrombin; ALBI: albumin–bilirubin; TACE: transarterial chemoembolization; LEN: lenvatinib.

of TACE by reducing microvessel density, normalizing tumor vasculature, lowering tumor stromal pressure, and reducing vascular permeability, thereby improving drug delivery (18). Ischemic effects and normalization of tumor vessels have also been confirmed in studies of changes in hepatic arteries in real-life clinical practice with upfront LEN administration (19).

However, the early efficacy of LEN-TACE has not yet been established, and the Lip values and local recurrence after LEN-TACE have not been investigated. Therefore, we analyzed local recurrence using Lip values in LEN-TACE and TACE for HCC in the present study. LEN administration before TACE contributed to an increase in Lip values and a decrease in local recurrence.

The TACTICS-L study, representing LEN-TACE sequential treatment, showed good PFS, an objective response rate (ORR), and prolonged OS. LEN-TACE sequential therapy is an established treatment for TACE-unsuitable intermediate-stage HCC. Furthermore, the use of upfront systemic therapy in TACE-unsuitable patients has been endorsed by the recent ESMO guidelines (20), which recommend that TACE-unsuited patients be treated first with pharmacological therapy. The AASLD guidelines were updated in 2020 to recommend pharmacotherapy as a treatment option for intermediate-stage liver cancer with a high tumor burden in addition to TACE (21).

In particular, as an induction therapy with up to seven criteria, it has 1) a high response rate, 2) a fast effect, 3) effectiveness in multinodal fusion and poorly differentiated types, and 4) a synergistic effect with TACE. LEN-TACE sequential therapy, which synergizes with TACE, is currently used for patients with TACE-unsuitable intermediate-stage HCC. This approach is favored because it is cancer-free, drug-free, and prolongs prognosis even if CR is not achieved. TACE sequential therapy is expected to be an established treatment for TACE-unsuitable intermediate-stage HCC. Furthermore, it has been reported that upfront administration of LEN for advanced HCC can be useful in combination with proton beam therapy and conversion surgery (22, 23). LEN-TACE is also expected to be a good option for advanced stage HCC.

In the present study, no significant differences in local recurrence rates were found according to background liver factors, AFP and DCP values, sex, age, and ALBI score. However, significant differences in local recurrence rates were recorded according to whether CT values immediately after LEN-TACE were above average, and upfront LEN-TACE was found to significantly reduce local recurrence in multivariate analysis. Although LEN-TACE is useful because the Lip values are higher when LEN is administered upfront, sufficient CT values must be obtained to reduce local recurrence.

Study limitations. First, the number of patients was small. Second, it is necessary to investigate a large number of patients in various stages of the disease. Third, the retrospective design of this study may introduce bias in the selection of patients with HCC for treatment. Finally, the data are from a single center. More extensive prospective clinical trials are needed to confirm these findings with greater accuracy.

Conclusion

This study revealed that LEN-TACE can suppress local recurrence by achieving highly dense Lip deposition. Future

studies are needed to prospectively investigate this treatment strategy in a large number of patients and analyze the synergistic effects of pharmacotherapy and TACE, to better understand the generalizability of our findings.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Conceptualization: Toru Ishikawa; Data curation: Toru Ishikawa; Formal analysis: Toru Ishikawa; Investigation: Toru Ishikawa, Ryo Sato, Ryo Jimbo, Yuji Kobayashi, Toshifumi Sato, Akito Iwanaga, Tomoe Sano, Junji Yokoyama, Terasu Honma; Methodology: Toru Ishikawa; Project administration: Toru Ishikawa; Resources: Toru Ishikawa; Software: Toru Ishikawa; Visualization: Toru Ishikawa; Writing – original draft: Toru Ishikawa; Writing – Review & editing: Toru Ishikawa, Ryo Sato, Ryo Jimbo, Yuji Kobayashi, Toshifumi Sato, Akito Iwanaga, Tomoe Sano, Junji Yokoyama, Terasu Honma.

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