LI-RADS Classification and Outcomes of Hepatocellular Carcinoma Treated with Transcatheter Arterial Chemoembolization Combined with Radiofrequency Ablation

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Abstract

Purpose

The aim of this study was to clarify the usefulness of the Liver Imaging Reporting and Data System (LI-RADS) to predict the patients' prognosis after transcatheter arterial chemoembolization (TACE) combined with radiofrequency ablation (TACE-RFA) for hepatocellular carcinoma (HCC) of Barcelona-Clinic Liver Cancer Stage (BCLC) 0 or A.

Materials and Methods

We retrospectively analyzed cases of HCC patients who underwent TACE-RFA (Jan 2005 to Dec 2015). Patients' nodules were categorized based on their LI-RADS v2018 core. The LI-RADS category was assigned to each nodule using dynamic contrast-enhanced CT. LR-3, LR-4 and LR-5 nodules were extracted. We assessed the overall survival (OS) and recurrence-free survival (RFS) among BCLC 0 and BCLC A patients.

Results

Of the 64 nodules extracted, 22 were LR-3 or -4 (14.8±6.7 mm) and 42 were LR-5 (17.1±6.9 mm). Regarding OS, there was no significant difference between LR-3 or -4 and LR-5 (p=0.278). In terms of RFS, there was a significant difference between LR-3 or -4 and LR-5 (p=0.03). In particular, patients with BCLC A with LR-5 nodules showed significantly poorer RFS than those with LR-3 or -4 (p=0.016) nodules.

Conclusions

For patients with BCLC A, LR-3 or -4 are associated with a better prognosis than LR-5 nodules.

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide, accounting for 85–90% of primary liver tumors [1–3]. HCC treatment depends on the progression, and prognosis can also vary significantly [4, 5]. Therefore, early detection of HCC is very important. Currently, HCC can be diagnosed non-invasively by image analysis.

The American Association of Radiologists has developed a standardized diagnostic algorithm termed the Liver Reporting and Data System (LI-RADS) to classify HCC using images such as dynamic multidetector computed tomography (CT), dynamic magnetic resonance imaging (MRI), and ultrasonography (US), together with other findings [6]. LI-RADS can be used to make a detailed diagnosis by understanding the patient's tumor condition, which may be useful for predicting prognosis and selecting treatment methods [7].

Prognosis remains poor for patients with advanced HCC. Patients diagnosed early, however, are eligible for curative treatment such as surgical resection, liver transplantation, and radiofrequency ablation (RFA) [8]. In addition, treatment with transcatheter arterial chemoembolization (TACE) may be performed for HCC, and there are many reports that TACE combined with RFA (TACE-RFA) has even better treatment results than TACE treatment alone [9–11]. While there are many reports on the treatment results of TACE-RFA, few studies have considered the relation between the prognosis of patients who underwent TACE-RFA and the LI-RADS of the target tumor, and the details remain to be clarified.

The purpose of this study was to assess the relation between LI-RADS grading and the treatment effect of TACE-RFA, and to clarify the prognosis of TACE-RFA treatment in patients with early-stage HCC of Barcelona-Clinic Liver Cancer Stage (BCLC) 0 and A.

Materials And Methods

Study design and patients

This was a retrospective study approved by the review board at our institution. The requirement for informed consent was waived. We retrospectively analyzed cases of HCC patients who underwent TACE-RFA between January 2005 and December 2015. A total of 562 patients were diagnosed with liver tumor by diagnostic imaging modalities such as CT, MRI and US during this period, and subsequently underwent TACE. Of these, 276 patients had no history of treatment—including TACE, RFA, or resection—and thus were receiving their first treatment for HCC. In this subgroup, 73 patients had TACE on the all tumors and RFA on the same tumors within a week. In addition, 69 of these patients had had three-phase dynamic CT images taken before TACE, and 66 of these patients had BCLC 0 and A; the latter group comprised the subjects of this study. The extracted patients were divided by BCLC stage according to the Bolondi classification [12, 13]. For all nodules, images obtained by postoperative CT confirmed the deposition of Lipiodol.

Nodules were classified according to the LI-RADS category using CT imaging. Among patients with BCLC 0 and A stage cancer, those with nodules classified as LR-3 (intermediate probability of being HCC), LR-4 (probably HCC) or LR-5 (definitely HCC) were extracted. In this assessment, patients with nodules classified as LR-M, i.e., probably or definitely malignant but not HCC specific, were excluded. Our final subject pool included 64 patients with LR-3, -4 and -5 tumors (Fig. 1).

If one patient was being treated for multiple tumors, we considered the largest one. Patient age ranged from 35–91 years (mean 71.9). The male-female ratio was 37 males (58%) to 27 females (42%). Other characteristics of patients are listed in Table 1.

Table 1
Patient Baseline Characteristics

Characteristic		
Age (y), mean±SD		71.9±9.8
Sex	Male	37
	Female	27
AFP (ng/mL), mean (range)		44.7 (1.6 - 982.7)
PIVKA-II (mAU/mL), mean (range)		579.4 (10 - 20836)
Child-Pugh	A	50
	B	14
BCLC	0	31
	A	33
LI-RADS	3	3
	4	19
	5	42
Anti-cancer drug	Epirubicin	56
	Miriplatin	8
Tumor size (mm), mean±SD		16.1±7.0

Note: Except where indicated, data are numbers of patients. AFP: alfa-fetoprotein; PIVKA-II: protein induced by vitamin K absence or antagonist-II; BCLC: Barcelona Clinic Liver Cancer Stage; LI-RADS: Liver Imaging Reporting and Data System.

We then assessed the overall survival (OS) and recurrence-free survival (RFS) between the LR-3 or -4 and LR-5 cases, and between BCLC 0 and BCLC A patients.

CT protocol

CT scans were performed at our hospital and related hospitals using a 64-section multidetector CT (MDCT) scanner (Aquilion CX TSX-101A/NA; Canon Medical Systems, Tochigi, Japan) or a 320-section MDCT scanner (Aquilion ONE TSX-301A/2A; Canon Medical Systems, Tochigi, Japan). The scanning parameters used for MDCT were as follows: 120 kVp, 200–400 mAs, rotation time 0.5 s, pitch of 0.98 (64 detectors) and 0.6 (320 detectors), and section thickness of 1 mm with a 1 mm reconstruction interval. CT images were acquired via image archives and communication systems.

For three-phase CT imaging, a total of 100 mL of contrast medium (Iopamiron 370; Bayer Schering Pharma, Leverkusen, Germany) was injected using a power injector at a rate of 3 mL/s. Each scan delay

was determined using automatic bolus tracking. Images of three phases (arterial phase, portal vein phase, and equilibrium phase) were acquired.

Transcatheter arterial chemoembolization

TACE was performed by at least one of two board certificated interventional radiologists (R.T and M.M with 12 and 10 years). In interventional radiology, we used digital subtraction angiography, CT during hepatic arteriogram (CTHA), and CT during arterial portography (CTAP) to assess the number and size of tumors and identify tumor-feeding vessels. Once the trophic arteries of the target tumor nodule were identified by this method, TACE was performed using anticancer drugs, poppy seed oil (Lipiodol; Guerbet Japan, Tokyo), and gelatin particles. As an anticancer drug, 10–60 mg epirubicin (Farmorubicin, Kyowa Hakko Kogyo, Tokyo) or 60–120 mg miriplatin (Miripla, Sumitomo Dainippon Pharma Co., Osaka, Japan) was used with iodine. The amounts of the drugs were determined by a consensus between radiologists and gastroenterologists. Anticancer drugs were mixed with 2–10 ml poppy oil and injected via a microcatheter. Gelatin particles (Gelpart; Nippon Kayaku, Tokyo) were then injected until the feeding arteries were completely embolized.

Radiofrequency ablation

All patients were treated with monopolar RFA by at least one of two board certificated gastroenterologists (K.H and M.E with 13 and 6 years of experience). RFA was performed under US guidance within three days to one week of TACE treatment. In RFA, we used a 17-gauge internally cooled electrode with a 2 or 3 cm exposed tip (Cool-tip; Radionics, Burlington, MA). When using a 2 cm needle, the output was started at 40 W and increased by 10 W every min for incineration. For a 3 cm needle, the output was started at 60 W and increased by 10 W every min for incineration. In both cases, incineration continued until the output rolled off.

LI-RADS category

We categorized the nodules for analysis according to the LI-RADS v2018 core [7]. The LI-RADS category was assigned to each nodule using dynamic contrast-enhanced CT. If two or more nodules were evaluated, we selected the largest. Major imaging features used in the classification included arterial phase hyperenhancement, observation size, washout, and capsule appearance. Patients were also categorized with hepatic observation threshold growth added to the extent possible. In addition, sub-findings were used to fine-tune the categorization (upgrade the category if there were findings supporting malignancy; downgrade it if there were findings supporting benignity). If we were uncertain about the categorization, we used tie-breaking rules that would bring us one step closer to LR-3. Images were evaluated by board certificated radiographer (Y.T with 14 years of experience) and board certificated radiologist (Y.A with 19 years of experience) according to these rules.

Statistical analysis

We evaluated OS and RFS for all patients. BCLC 0 and A were extracted according to the Bolondi classification, and OS and RFS were compared by LI-RADS category. OS was defined as the time from the

day of TACE treatment to the day of death. RFS was defined as the time from the date of TACE treatment to the date of tumor recurrence or death. Patients who remained alive at the date of the last follow up were censored in the statistical analysis. For assessment of recurrence, three-phase CT and dynamic MRI were used. Recurrence was defined when tumors that showed arterial phase enhancement and washout appeared locally or elsewhere in the liver. The observation period was 1–116 months.

Regarding OS and RFS, the whole was divided into two groups, and each item was compared. Fisher's exact test was used for comparison between the two groups. The boundaries were 70 years old, alfa-fetoprotein (AFP) 10 ng/mL, and protein induced by vitamin K absence or antagonist-II (PIVKA-II) 40 mAU/mL. Comparisons were made between the two groups A and B for Child-Pugh score, and between the two groups A and 0 for BCLC. Regarding LI-RADS, we again compared two groups, LR-3 or 4 and LR-5. These items were compared using Cox regression analysis. Also, survival was assessed by the Kaplan-Meier method and log-rank test. Variables with $p<0.2$ at univariate analysis were applied multivariate analysis to identify the most reliable prognostic marker. The evaluation was done using R (version 4.0.3; The R Foundation).

Results

Univariate analysis and multivariate analysis of OS was performed on the extracted 64 patients (Table 2). We also performed univariate analysis and multivariate analysis of RFS (Table 3). There was a significant difference only in the comparison of LI-RADS regarding RFS. For other items, no significant difference was found in both univariate and multivariate analysis.

Table 2
Univariate Analyses and Multivariate Analyses of Factors Affecting Overall Survival

		Univariate Analyses			Multivariate Analyses		
Variable	Cases	HR	95%CI	*p*	HR	95%CI	*p*
Age (>70 vs ≤70)	40 vs 24	1.81	0.76 - 4.31	0.184	1.27	0.42 - 3.80	0.675
Sex (Male vs Female)	37 vs 27	1.75	0.77 - 3.98	0.181	0.85	0.30 - 2.47	0.771
AFP (>10 vs ≤10)	25 vs 34	2.11	0.89 - 5.003	0.091	2.49	0.78 - 7.99	0.124
PIVKA (>40 vs ≤40)	18 vs 39	1.89	0.74 - 4.82	0.183	2.55	0.89 - 7.37	0.083
Child-Pugh score (A vs B)	50 vs 14	0.50	0.21 - 1.20	0.121	0.79	0.22 - 2.84	0.720
BCLC (0 vs A)	31 vs 33	2.02	0.82 - 4.97	0.128	1.68	0.56 - 5.08	0.357
Anti-cancer drug (Epirubicin vs Milliplatin)	56 vs 8	1.07	0.36 - 3.18	0.907			
LI-RADS (LR-3 or 4 vs LR-5)	22 vs 42	1.66	0.66 - 4.16	0.278	0.93	0.33 - 2.63	0.894

Abbreviations: HR: hazard ratio; AFP: alfa-fetoprotein; PIVKA-II: protein induced by vitamin K absence or antagonist-II; BCLC: Barcelona Clinic Liver Cancer Stage; LI-RADS: Liver Imaging Reporting and Data System.

[]Data were available in 59 cases.

[]Data were available in 57 cases.

Table 3
Univariate Analyses and Multivariate Analyses of Factors Affecting Recurrence-free Survival

		Univariate Analyses			Multivariate Analyses		
Variable	Cases	HR	95%CI	*p*	HR	95%CI	*p*
Age (>70 vs ≤70)	40 vs 24	1.00	0.55 - 1.82	0.993			
Sex (Male vs Female)	37 vs 27	1.58	0.87 - 2.87	0.134	1.44	0.72 - 2.87	0.297
AFP (>10 vs ≤10)	25 vs 34	1.44	0.76 - 2.72	0.259	1.53	0.78 - 3.00	0.217
PIVKA (>40 vs ≤40)	18 vs 39	1.23	0.62 - 2.44	0.559			
Child-Pugh score (A vs B)	50 vs 14	0.97	0.47 - 1.97	0.923			
BCLC (0 vs A)	31 vs 33	1.43	0.79 - 2.59	0.241	1.37	0.73 - 2.58	0.324
Anti-cancer drug (Epirubicin vs Milliplatin)	56 vs 8	0.57	0.22 - 1.46	0.241	0.44	0.15 - 1.31	0.140
LI-RADS (LR-3 or 4 vs LR-5)	22 vs 42	2.05	1.07 - 3.93	0.030	1.69	0.85 - 3.36	0.132

Abbreviations: HR: hazard ratio; AFP: alfa-fetoprotein; PIVKA-II: protein induced by vitamin K absence or antagonist-II; BCLC: Barcelona Clinic Liver Cancer Stage; LI-RADS: Liver Imaging Reporting and Data System.

[1]Data were available in 59 cases.

[2]Data were available in 57 cases.

Of the 64 patients, BCLC classification resulted in 31 patients in the BCLC 0 group, and 33 in the BCLC A group. Patients with BCLC 0 and BCLC A were then extracted and classified by LI-RADS classification. In BCLC 0 patients, 1 tumor was LR-3, 12 were LR-4, and 18 were LR-5. For BCLC A patients, 2 tumors were LR-3, 7 were LR-4, and 24 were LR-5. Table 4 shows the baselines characteristics of BCLC 0 / A with LR-3 or 4, and LR-5 patients, which were the targets of this comparison. Example clinical images are presented in Fig. 2. Fig. 2a, 2b, and 2c are images of a patient with a tumor corresponding to LR-4 at BCLC 0; Fig. 2d, 2e, 2f, and 2g are images of a patient with a tumor corresponding to LR-5 in BCLC A.

Table 4
Baseline Characteristics of LR-3 or -4 and LR-5 Patients

Characteristic	LR-3 or -4	LR-5	*p*
Age (y), mean±SD	70.0±9.1	73.2±10.0	0.159
Sex			0.495
Male	14	23	
Female	8	19	
AFP (ng/mL)			0.955
>10	9	16	
≤10	12	22	
no data	1	4	
Mean (range)	36.0 (1.6 - 179.8)	48.7 (2.1 - 982.7)	0.731
PIVKA-II (mAU/mL)			0.048
>40	3	15	
≤40	17	22	
no data	2	5	
Mean (range)	28.2 (10 - 117)	877.2 (14 - 20836)	0.288
Child-Pugh class			0.605
A	18	32	
B	4	10	
BCLC			0.217
0	13	18	
A	9	24	
Anti-cancer drug			0.073
Epirubicin	17	39	
Miriplatin	5	3	
Tumor size (mm), mean±SD (range)	14.8±6.7 (8.0 - 28.1)	18.0±6.2 (10.0 - 33.4)	0.199
Number of lesions			

Abbreviations: HR: hazard ratio; AFP: alfa-fetoprotein; PIVKA-II: protein induced by vitamin K absence or antagonist-II; BCLC: Barcelona Clinic Liver Cancer Stage.

Characteristic	LR-3 or -4	LR-5	*p*
1	18	36	
2	4	4	
3	0	2	

Abbreviations: HR: hazard ratio; AFP: alfa-fetoprotein; PIVKA-II: protein induced by vitamin K absence or antagonist-II; BCLC: Barcelona Clinic Liver Cancer Stage.

Baseline characteristics of LR-3 or -4 and LR-5 patients were shown in Table 4. Comparison of groups showed a significant difference regarding PIVKA-II. There were no significant differences in age, sex, AFP, Child-Pugh class, BCLC, anticancer drug, or tumor size.

Overall survival

In a comparison of the 64 cases, there was no significant difference in OS between LR-3 or -4 and LR-5 in univariate analysis (p=0.278) (Table 2). Fig. 3a shows the results of the Kaplan-Meier estimate. Further, for BCLC 0 and A, LR-3 or -4 and LR-5 were extracted and compared (Fig. 3b and 3c). There were no significant differences between LR-3 or 4 and LR-5 regarding the OS of the BCLC 0 or BCLC A cases (p=0.952, 0.194, respectively).

Recurrence-free survival

The next comparison of 64 cases revealed a significant difference between LR-3 or -4 and LR-5 in terms of RFS in univariate analysis (p=0.03) (Table 3). Multivariable analysis with the cox proportional hazards regression model revealed that LR-5 was independent prognostic factor (p=0.03). The Kaplan-Meier estimate is shown in Fig. 4a. As with the OS comparison, for BCLC 0 and A, LR-3 or -4 and -5 were extracted and compared. The results of the Kaplan-Meier curve for each result are shown in Fig. 4b and 4c. For the BCLC 0 cases, there were no significant differences between LR-3 or -4 and LR-5 (p=0.533). For the BCLC A cases, however, the log-rank test results showed significant differences between LR-3 or -4 and LR-5 (p=0.016). The 1-, 3-, and 5-year survival rates of LR-4 patients were 89%, 56%, and 33%, while those for LR-5 patients were 58%, 8%, and 4%, respectively.

Discussion

In this study, we examined the prognosis between patients with nodules classified as LR-3 or -4 and those with LR-5 tumors. There was a significant difference in RFS in the comparison of all 64 cases. In particular, for BCLC A, we found that LR-5 had a worse RFS than LR-3 or -4. In contrast, there was no significant difference in OS between LR-3 or -4 and LR-5 stage tumors.

The influence of tumor size might be considered. When determining the LI-RADS classification, if conditions such as arterial enhancement and washout are the same, we will divide by tumor size [7].

Larger tumors may have more vascular invasion of the tumor, and a higher probability of recurrence [14–16]. In addition, with a large tumor, some portions of the tumor that are not visible in the image may not be treatable, which may be related to the treatment results [17, 18]. It is possible that the drug did not reach the interior of the tumor with TACE, or that even if a sufficient safety margin were assumed, RFA did not sufficiently incinerate the tumor. Also, when the tumor has a capsule, the larger the size, the easier it is to infiltrate outside beyond the capsule, and thus the greater likelihood of metastasis [19, 20].

As indicated in Table 4, there were no significant differences in age, gender, or AFP values between patients with LR-3 or -4 and those with LR-5 stage tumors. However, there was a significant difference in PIVKA-II values. There is an association between PIVKA-II values and tumor vascular invasion [21]. LR-5 tumors have high PIVKA-II values, and there might be microvascular invasion that is not visible on the pretreatment image. As a result, we considered that the risk of recurrence was high in our patients with high PIVKA-II values with LR-5 stage tumors.

Regarding the washout, previous reports revealed that washout of hypervascular HCC occurred earlier as the histological grade advanced, the histological architecture got closer to pure trabecular HCC, and hypervascular HCCs with thicker tumor plates showed worse histological grade and earlier washout pattern [22, 23]. Thus, clear washout may indicate an aggressive tumor, such as a moderately to poorly differentiated HCC with thicker tumor plates.

In contrast, there was no significant difference in OS. One of the possible reasons for this is that HCC can show multicentric development [24, 25]. Even if a tumor was treated completely, new HCC, not intrahepatic metastasis, can develop elsewhere in the liver, which significantly influences survival. Unfortunately, in many cases it is difficult to tell the difference between intrahepatic metastasis from the original tumor and a newly developed tumor. Other possible factors that affected patients' prognosis included worsening liver function and cirrhosis, and these effects may have been greater than the tumor aggressiveness itself [26].

In this study, there was no significant difference between LR-3 or -4 and LR-5 in the BCLC 0 group. In the very early stage of HCC, if a tumor is well treated, the subsequent prognosis may depend on the likelihood of developing another HCC in the liver, or on the deterioration of underlying liver function [27]. There may have been cases in which recurrence unrelated to the primarily treated tumor occurred.

This study had several limitations: (1) It was a retrospective study and selection bias which could have affected the results might therefore exist. (2) Data were collected from a single center, and samples from multiple regions were required for further validation. If we could have collected more cases, we would have been able to investigate in more detail. (3) Two anticancer drugs were used during TACE. There was no significant difference observed due to the difference in anticancer drugs, but the accuracy of the study might have been improved if comparisons could have been made under the same drug conditions [28]. (4) Patients with BCLC 0 or A might be good surgical candidates; however, our hospital traditionally favored less invasive therapy such as TACE-RFA. Thus, patients who were eligible for surgery may have been included [29].

The LI-RADS classification is a classification of certainly, which is a tool for classifying images according to their major characteristics. Detailed tumor characteristics such as degree of differentiation are not included, and may be classified using other algorithms. Examining the LI-RADS classification by adding more detailed features of the tumor can provide a more detailed prognosis. It has also been reported that the combination of MRI diffusion-weighted image analysis and LI-RADS can improve confidence [30]. In the future, by combining LIRADS with various factors, we will find it easier to predict the prognosis.

In conclusion, tumors categorized as LR-5 have a worse RFS than those classified as LR-3 or -4, especially in BCLC A. LI-RADS, originally created for use at the radiologist's discretion in diagnosis, can predict patient prognosis. Tumors classified as LR-5 by LI-RADS require more attention to the patient's course than tumors of other classifications.

Declarations

Compliance with ethical standards

Funding: No funding was received for this study.

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

All methods were carried out in accordance with relevant guidelines and regulations.

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Figures

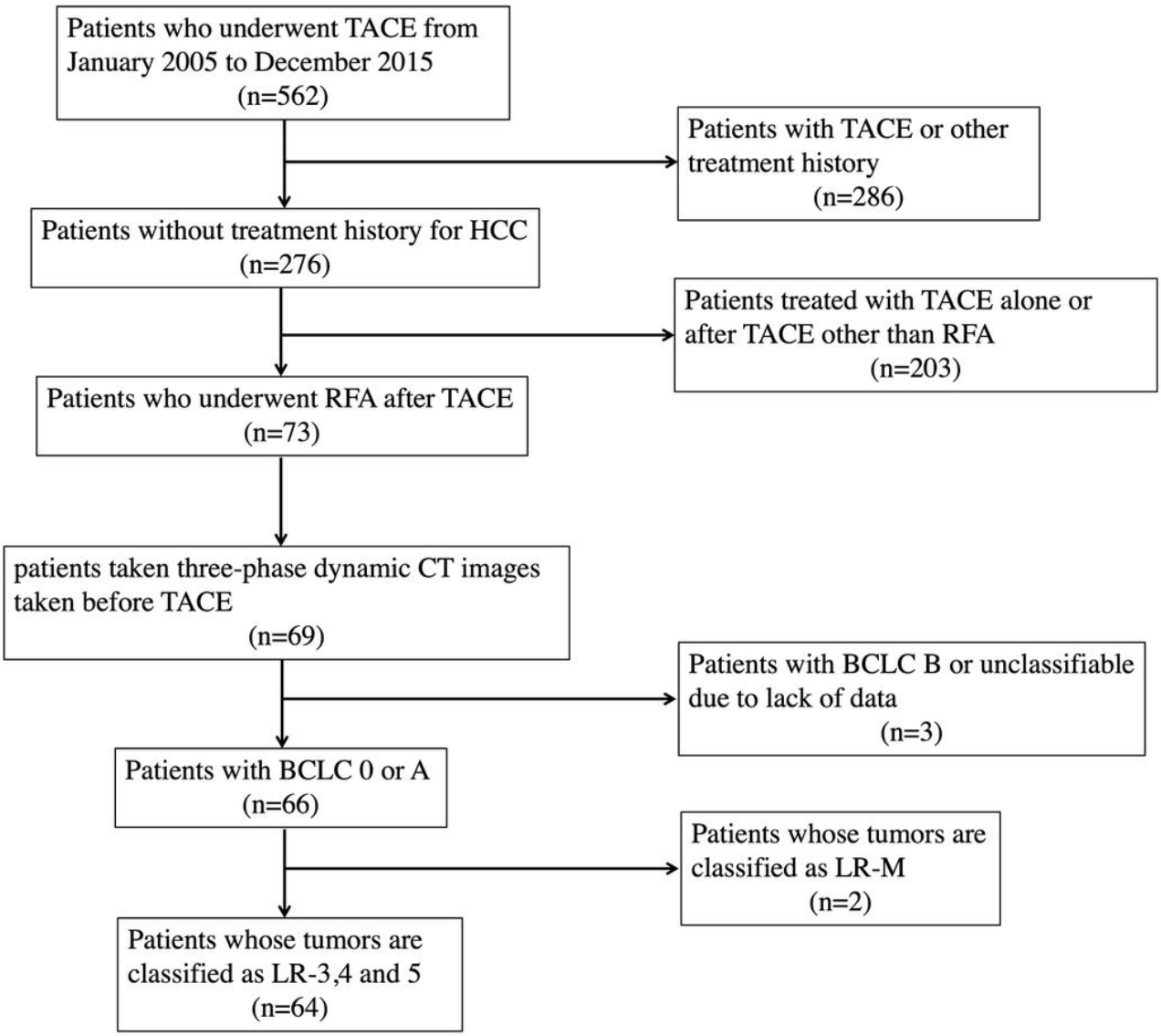


Figure 1

Survey population flow chart of patients with hepatocellular carcinoma (HCC). TACE: transcatheter arterial chemoembolization; RFA: radiofrequency ablation; CT: computed tomography; BCLC: Barcelona-Clinic Liver Cancer Stage.

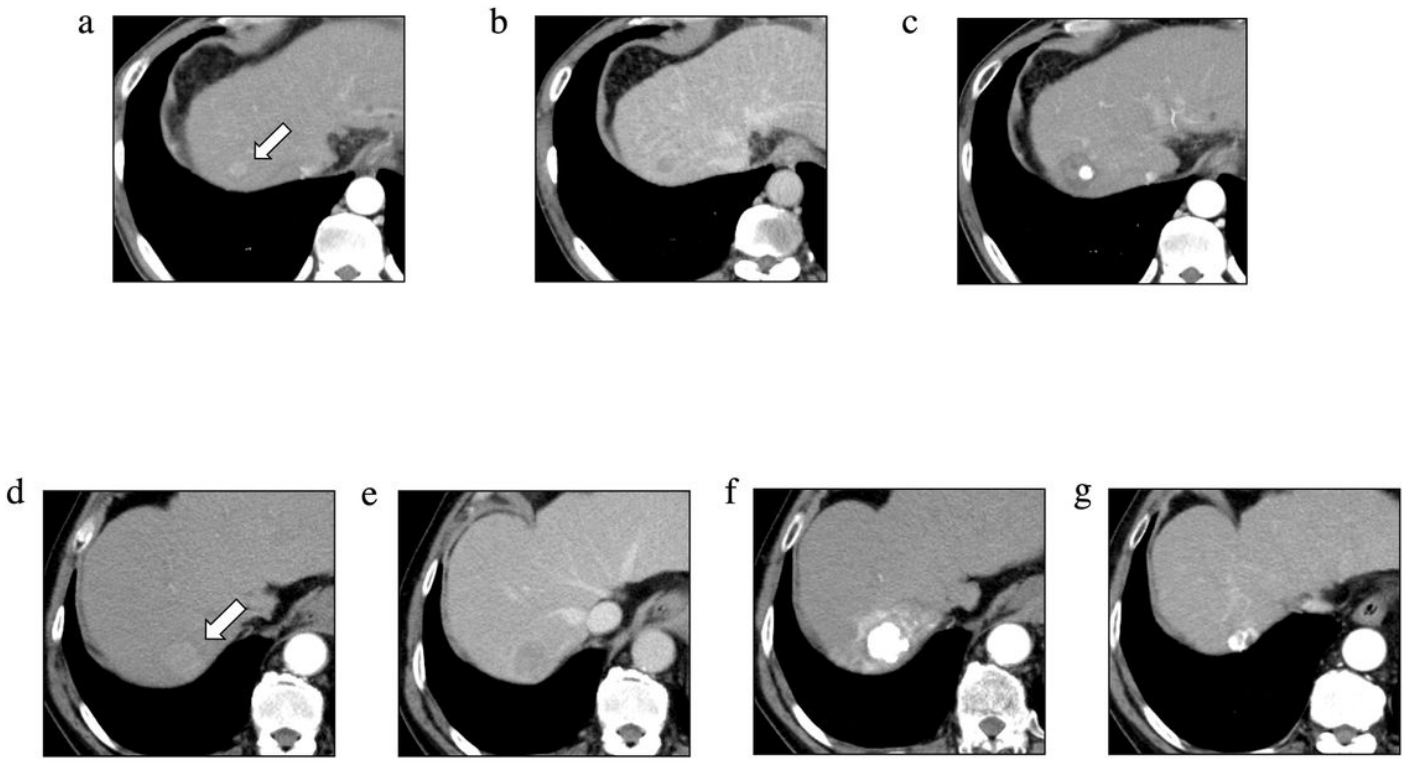


Figure 2

Clinical cases of HCC in patients with LR-4 and -5.

a) LR-4 tumor in a 68-year-old man with HCC in the right lobe of the liver. Arterial phase of the contrast-enhanced CT image before TACE. Arterial phase hyperenhancement measuring 9 mm was confirmed in liver dome.

b) Delayed phase of the contrast-enhanced CT image showed washout of the contrast.

c) Arterial phase of the contrast-enhanced CT 4 months after TACE-RFA showed good lipiodol accumulation surrounded by RFA-related hypoattenuation area. No viable lesions were seen. No recurrence was observed after 5 years.

d) LR-5 tumor in a 70-year-old man with HCC in the right lobe of the liver. Arterial phase of the contrast-enhanced CT image before TACE. Arterial phase hyperenhancement measuring 23 mm was seen in the liver dome.

e) Delayed phase of the contrast-enhanced CT image before TACE showed washout of the lipiodol.

f) Arterial phase of the contrast-enhanced CT image 3 days after TACE-RFA showed good lipiodol accumulation surrounded by RFA-related hypoattenuation area.

g) Arterial phase of the contrast-enhanced CT image taken 8 months after TACE-RFA. Arterial enhancement was confirmed adjacent to the treated site, indicating tumor recurrence.

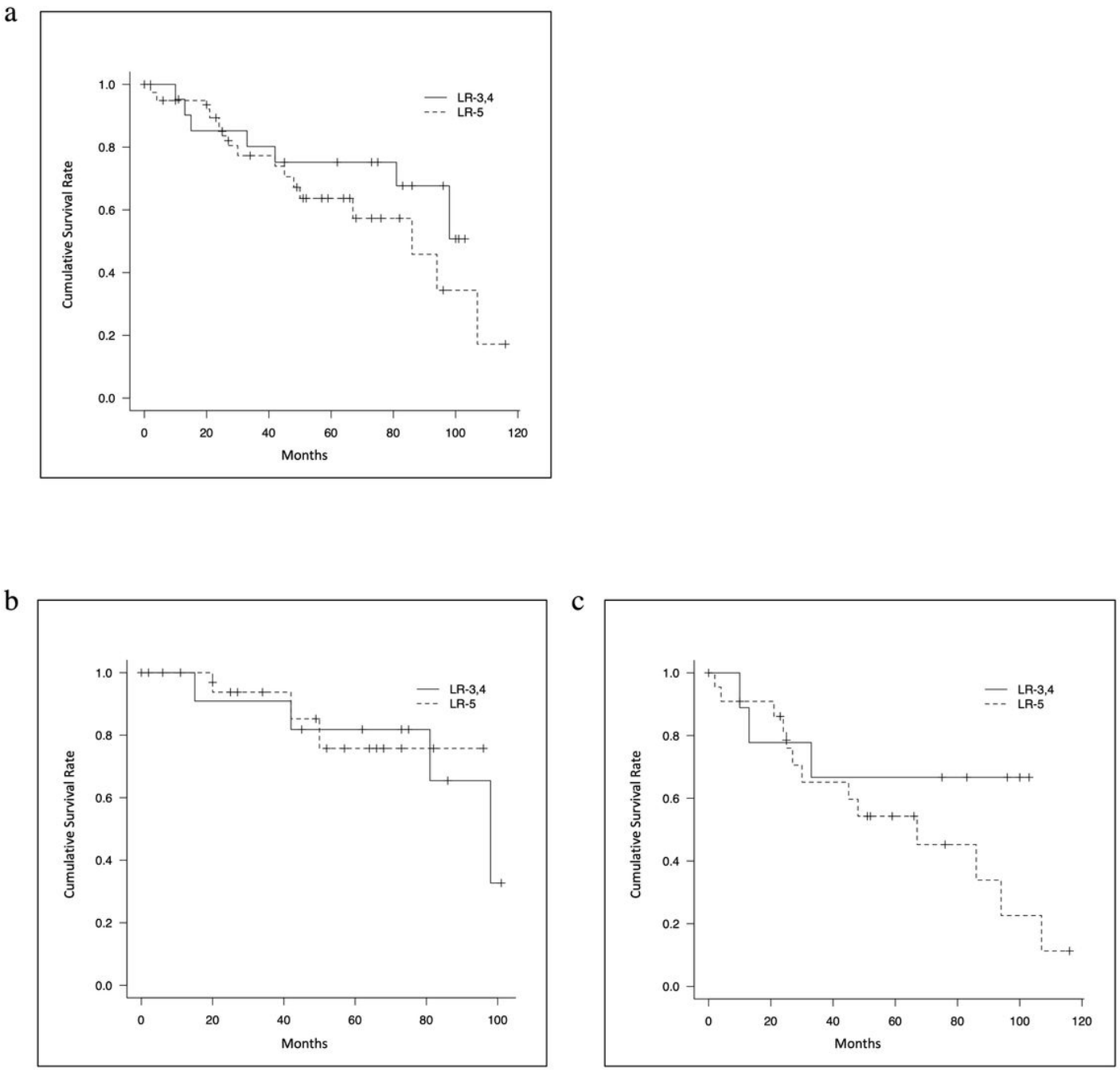


Figure 3

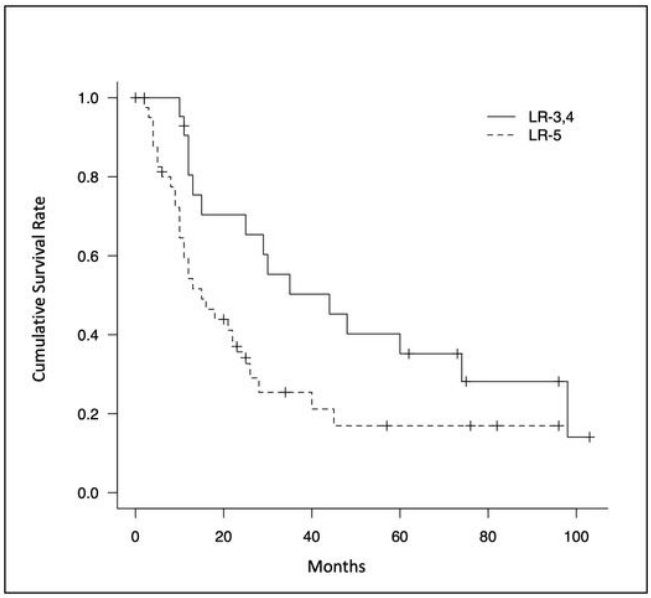
Kaplan-Meier curve comparing overall survival of LR-3 or -4 and LR-5.

a) Comparison of LR-3 or -4 and LR-5 in all cases. There was no significant difference in this comparison (p = 0.278).

b) Comparison of LR-3 or -4 and LR-5 in BCLC 0. There was no significant difference in this comparison (p = 0.952).

c) Comparison of LR-3 or -4 and LR-5 in BCLC A. There was no significant difference in this comparison (p = 0.194).

a



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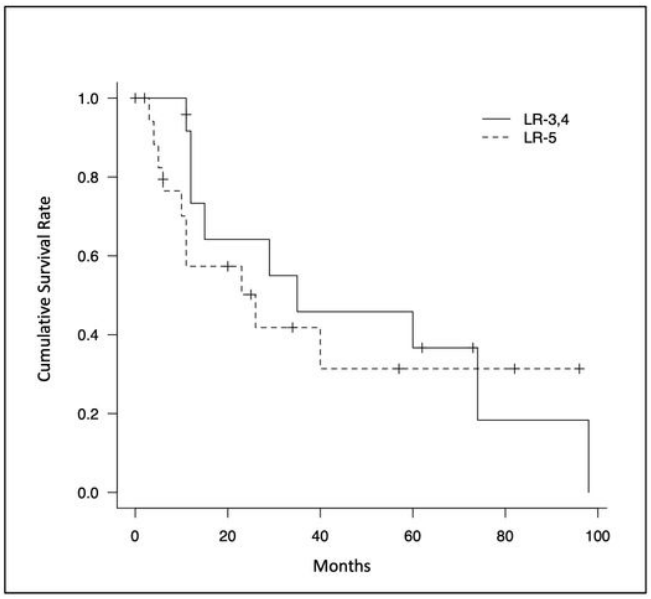

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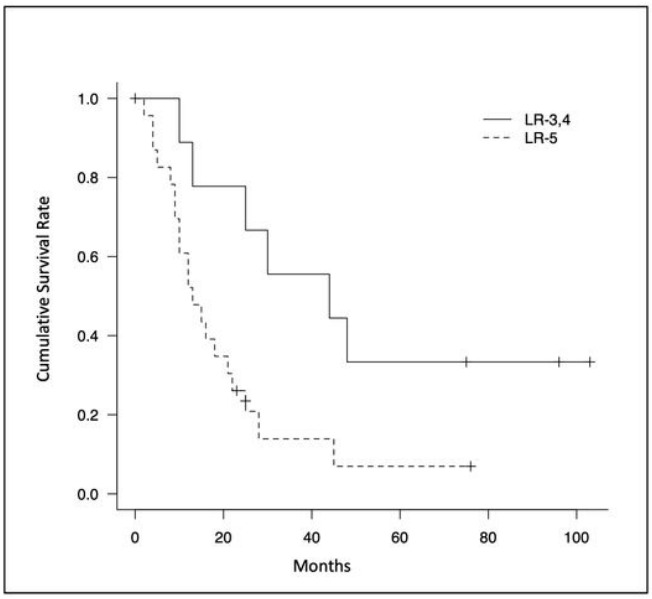

Figure 4

Kaplan-Meier curve comparing RFS of LR-3 or -4 and LR-5.

a) Comparison of LR-3 or -4 and LR-5 in all cases. There was a significant difference in this comparison (p = 0.030).

b) Comparison of LR-3 or -4 and LR-5 in BCLC 0. There was no significant difference in this comparison (p = 0.533).

c) Comparison of LR-3 or -4 and LR-5 in BCLC A. There was a significant difference in this comparison (p = 0.016).