ASSESSEMENT IN PERFORMANCE OF LI-RADS ALGORITHM IN DETECTING TREATMENT RESPONSE OF HEPATOCELLULAR CARCINOMA AFTER TRANS-ARTERIAL CHEMOEMBOLIZATION

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ABSTRACT

Background: Trans-arterial hemoembolization (TACE) usually indicated for unresectable hepatocellular carcinoma (HCC) on purpose as a bridging, downstaging or palliative treatment. Liver Imaging Reporting and Data Systems Treatment Response (LR-TR) was created to evaluate each lesion post-TACE, which has localized and is suitable for determining whether the tumor is still viable or Non-viable. ***Purpose:*** To assess the completion of LI-RADS version 2018 on computer tomography in the evaluation of HCC after TACE. ***Materials and Methods:*** A retrospective cross-sectional study involved 58 patients with hepatocellular carcinoma (HCC) who underwent treatment base TACE from June 2021 – September 2022. The clinical situation, AFP levels, and computer tomography (CT) of the patient after treatment were analyzed. The Radiologist evaluated pre- and post-treatment CT findings using LR-TR category, appropriately. The pooled sensitivity, specificity, and accuracy correclated between LR-TR with standard reference. ***Results:*** A total 58 patients with HCC (M/F: 13:1, mean age 56.9±11.0 years). For demonstrating the treatment response after first TACE on CT, Non-viable resulted in 32.8%(19/58), and LR-TR Viable was 67.2%(39/58), sensitivity value of 90% (36/40), specificity value of 83.3% (15/18), positive predictor value of 16.7% (3/18), a negative predictor value of 10% (4/40), accuracy value of 87.9% (51/58). The performance status response- AFP response- imaging response correlation was not statistically different, p= 0.552 and p=0.647. ***Conclusion:*** Using LR-TR on CT detects treatment response of HCC post-TACE was useful, and high sensitivity, specificity, and accuracy.

Keywords: *hepatocellular carcinoma, transarterial chemoembolization, Imaging Reporting and Data System treatment response (LR-TR), computer tomography.*

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I. INTRODUCTION:

Hepatocellular carcinoma (HCC) is a high mortality and progressive incidence; it is the third leading cause of cancer–related death worldwide.[1] Transarterial hemoembolization-TACE is indicated for patients with intermediated-stage, unresectable tumors, in patients with well-preserved liver function PS 0-2, to control tumor growth, downstaging, and improving overall survival.[2] Evaluation of the treatment response of HCC following TACE on CT is essential in determining the following treatment plan for the patient. The LI-RADS Version 2018 for treatment response of HCC by CT scans or MRI, which is an update with clinical practice guidelines of the American Association for the Study of Liver Diseases - AASLD), evaluates each lesion post-TACE,

which has localized and suitable for determining whether the tumor is still viable or non-viable.[3] Up to now, Vietnam has not had a research topic on this issue, so we do research with the aim "**Assessement in performance of LI-RADS Algorithm in detecting treatment response of HCC after TACE".**

II. MATERIALS AND METHODS

1. Materials: A total of 58 patients were diagnosed with HCC and underwent chemoembolization at K Tan Trieu Hospital Radiology and Huu Nghi Hospital Radiology during the period from June 2021 to September 2022.

Patient inclusion criteria: Patients with the definitive diagnosis of HCC who underwent treatment based on drug-eluting beads transarterial chemoembolization, had CT scans before and after the first embolization 1-3 months. Follow–up to 6 months after TACE with imaging of DSA 2nd or CT/MRI 2nd.

Patient exclusion criteria:

- Patients are receiving or have previous systemic treatment.
- Patients did not have CT scans or unsatisfactory CT images before and after the intervention.
- Patients were diagnosed with Infiltrative Hepatocellular Carcinoma.
- Patients had severe coagulopathy: platelets <50 G/l, prothrombin <60 %.
- Patients presented with Hepatic encephalopathy, rapidly relapsing ascites, and bleeding due to esophageal varices.
- Patients have an allergy to contrast materials and hepatic embolization agents.
- Patients unfollowed routine follow-ups.
- Patients did not agree to participate in the study.

2. Methods: Retrospective cross-sectional study

3. Research procedures:

Step 1 (Prepare the patient): clinical examination and AFP test.

Step 2 (Multi-slide computed tomography before embolization); Supported by the American College of Radiology (ACR) 2018 [3]: Non-enhanced CT, arterial phase 30-45 seconds post-injection, portal venous phase 70 - 90 seconds post-injection, delayed phase 2 - 5 minutes post-injection.

Step 3: Transarterial chemoembolization technique by Drug- eluting bead or Lipiodol

Step 4: The process of evaluating the effectiveness after the first embolization is 1-3 months:

- Clinical examination to evaluate the patient's overall condition according to the PTS scale or rank good - same - poor.
- AFP test
- Liver CT scans evaluate tumor changes, recurrence, and extrahepatic metastases.
- Evaluation of treatment response of TACE for HCC by LR-TR scale on CT scans

Table 1.6. ***LR-TR classification for HCC treatment response.***

* **Source**: Chernyak (2018)[3]

LR-TR non-evaluable	After treatment, the response could not be assessed due to noisy or damaged images
LR-TR nonviable	After treatment, it is unlikely or completely nonviable
LR-TR equivocal	After treatment, equivocal viable
LR-TR viable	High possibility or sure viable

4.Reference standard:

Correlation between LR-TR and Reference Standard to carry - out the sensitivity, specificity, and accuracy. We used the reference standard by Kim SW (2020) study to detect the valuation of LR-TR.[4]

+ LR-TR Viable was compared to imaging of DSA 2nd to determine whether or not hypervascularity.

+ LR-TR Non-Viable was followed, and a CT/MRI was taken 2nd after six months, determining whether or not enhancement in the arterial phase, washout in the portal vein phase.

+ We assessed the accounting sensitivity, specificity, and accuracy of LR-TR

5. Image analysis: Two radiologists with five years of experience in detecting post-TACE imaging were caught independently and discussed together to get a consensus on each lesion.

6. Statistics: Variables were collected and analyzed with SPSS 20 software. Compare the ratio characteristics of the study group based on the Chi-squared or Fisher's Exact Test.

III. RESULTS

Table 1. ***Patient characteristics:***

Characteristics	**Value (%)**
Patients (n=58)	
Age (years)	59.1 ± 11.2
Male	93.1 (54/58)
Female	6.9 (4/58)
Etiology of hepatitis	
Hepatitis B	75.9 (44/58)
Hepatitis C	18.9 (11/58)
Co-Hepatitis B and C	8.7 (5/58)
Alcoholic liver disease	36.2 (21/58)
Known cirrhosis	63.8 (37/58)
AFP Test	
Normal	37.9 (22/58)
20-400 ng/ml	34.5 (20/58)
>400 ng/ml	27.6 (16/58)
Child- Pugh classification	
A	98.3 (57/58)
B	1.7 (1/58)
C	0
PS score	
0	31.0 (18/58)
1	67.2 (39/58)
2	1.7 (1/58)
BCLC Classification	
A	67.2 (39/58)
B	32.8 (19/58)
Reference standard (n=58)	
Non - Viable	31.1 (18/58)
Viable	68.9 (40/58)

Comment: A total of 58 patients were diagnosed with HCC and underwent transarterial chemoembolization as general characteristics in Table 1. The majority of patients in our study were middle-aged males with hepatitis B; all patients had increased AFP values. Most disease-stage patients are in Child–pugh A and BCLC A. On reference standard, 18 non–viable lesions (31.1%) and 0 viable lesions (68.9%).

Table 2. ***Pre-treatment CT findings of the tumor:***

Tumor characteristics on CT scans		**n**	**%**
Location	Subsegment	33	56.9
	Segment	13	22.4
	2 segments	12	20.7
	>2 segments	0	0
Morphology	Mass nodule	36	62.1
	Mass with peripheral nodule	14	24.1
	Mass multiple nodules	8	13.8
Diameter range (cm)	≤ 5	33	56.9
	> 5	25	43.1
Diameter median(mm)	56.9±31.5		

Computer tomography (CT)

Comment: CT findings of the pre-treatment lesion are related in Table 2. The mean treated lesion size was 5.6 cm in diameter, and most tumor size was less than 5 cm (56.9%). The location of mass was commonly in one subsegment (56.9%). The morphology type of lesion was most of mass nodules type (62.1%).

Table 3. ***Correlation between LR-TR and Reference Standard:***

Reference Standard **Classified**		**Viable**	**Non-Viable**	**Total**	**p**
LR-TR	**LR-TR Viable**	36	3	39	**< 0.001**
	LR-TR Nonviable	4	15	19	
Total		**40**	**18**	**58**	

Value Classified	**Sn**	**Sp**	**FPR**	**FNR**	**Acc**
LR-TR	90% (36/40)	83.3% (15/18)	**16.7% (3/18)**	**10% (4/40)**	87.9% (51/58)

Sensitivity (Sn), specificity(Sp), false positive rate (FPR), False negative rate (FNR), and accuracy (Acc), LR-TRA: LI-RADS treatment response algorithm.

Comment: Detecting the outcome of LR-TR for tumor treatment response is described in Table 3 and Table 4. Based on the reference standard, the rate of tumors with non-viable was 31.1% (18/58), and Viable was 68.9 % (40/58). The sensitivity of LR-TR for detecting viable and non-viable and, when compared with the reference standard, was 90%, specificity 83.3%, false positive rate (FPR) 16.7 %, False negative rate (FNR) 10%, and accuracy (Acc) 87.9%.

Table 4. ***Correlation between LR-TR with clinical response and AFP test response:***

Characteristic		LR-TR		Total	P (Fisher's exact test)
		Non-viable	Viable		
Clinical response	Good response	19	38	57	0.672
	No	0	1	1	
Total		19	39	58	
AFP	Response	9	12	21	0.07
	No	2	15	17	
Total		11	27	38	

AFP: *anpha fetoprotein.*

Comment: Most of the patients had clinical improvement with 98.3%. AFP test response was 55.3%. On the other hand, there was no significant difference in clinical response and AFP response between LI-RADS non-viable and LI-RADS viable (p = 0.672 and p = 0.07, respectively).

Case report:

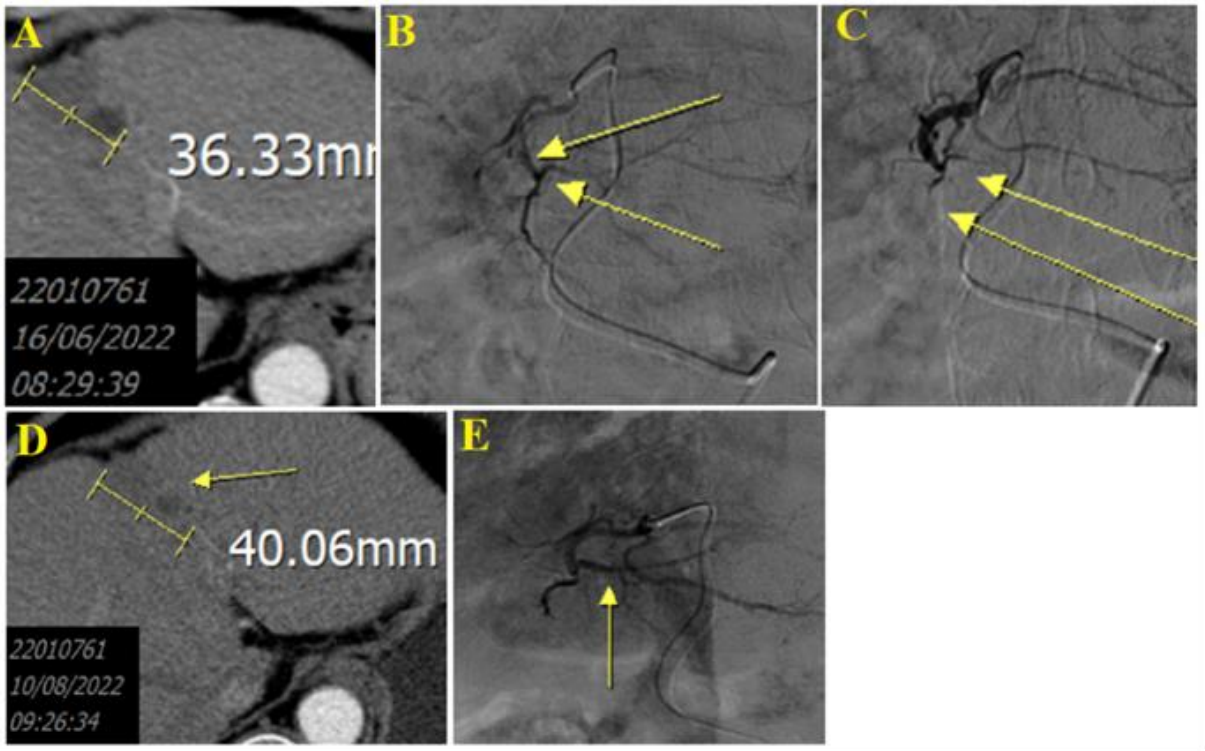

Fig. 1*A 44-year-old male with hepatocellular carcinoma in IV segment (A). Hypervascular on DSA (B). Ultimately feeding vessels (C). CT imaging post TACE in two months showed a lesion similar to the pre-treatment lesion, categorized as LR-TR Viable and considered continuous treatment by TACE, which demonstrated that the mass had increased vascularity and re-established feeding artery branches.*

IV. DISCUSSION

According to the BCLC system, TACE treats patients with intermediate-stage tumors, unresectable lesions, and well-preserved liver function (PS 0-2) to control tumor growth, increasing the survival time.[2] In patients with resectable HCC, TACE is also used to reduce HCC recurrence and combined with Portal Vein Embolization (PEV) to ensure the volume of the remaining liver.[5]

The LR-TR is used to assess response after local-regional therapy, which includes ethanol and radiofrequency or microwave ablation, transarterial chemoembolization or radioembolization, and external beam radiation therapy. The algorithm also applies to observations at the surgical margin after resection of HCC and is evaluated similarly to pre-treatment.[3] Our study demonstrated a great quantity of sensitivity, specificity, and accuracy of LR-TR on CT (83-90%). In the retrospective study, the Shropshire study assessed the performance of the LR-TR in 45 patients with 63 lesions from 2006 to 2016. The results showed that the positive predictive value of the LR-TR viable was 86%-96%, and accuracy was 60%-65% in predicting incomplete tumor necrosis; the negative predictive value of the LR-TR nonviable was 81%-87%, and accuracy was 67%-71% to predicting complete tumor necrosis.[6] In the retrospective study by Huh et al (2021), they used the LR-TR algorithm attempt to assess the imaging responses after the first time for transarterial embolization compared with the histopathology in 151 HCC base two readers, the sensitivity and specificity of CT LR-TR viable were 53.7-56.7% and 96.4-98.8%, the sensitivity and specificity of CT LR-TR Non-viable were 31.3-34,3% and 95-96%.[7] The advantage of LR-TR over previous classifications lies in the use of multi-phase post-treatment tumor response assessment, assessing not only the arterial phase as mRECIST or EASL but also detecting the phase of the portal vein, compared to pre-treatment imaging; this is consistent with the pathological HCC because the blood supply for HCC not only the arterial but also the portal vein which increases the sensitivity for the evaluated treatment.[8] The LR-TR reduces false negatives, increases sensitivity, raises specificity, and speeds up patient treatment.

Of 58 patients who underwent TACE in our study, the mean age was 59.1 years, and 93.1% were male patients; our result is similar to other studies in Vietnam due to the limited screening for early diagnosis of HCC in Vietnam.

Serum AFP is the tumor biomarker to diagnose HCC early and elevates the treatment response. Serum alpha-fetoprotein (AFP) is overexpressed in most human HCCs in approximately 70% of HCC patients. Previous studies have correlated that AFP levels are predicted response after loco-regional treatment of HCC, even after TACE. A treatment-response tumor is when AFP levels fall by 50% or more or AFP values fall below the average value (<20ng/ml).[9] Changes in AFP levels are often correlated with tumor size necrosis changing. Our study results are different from those of author Bartnik (2022), who studied 99 liver tumors undergoing TACE, with 28/99 (28.28%) cases with AFP > 200 ng/ml before treatment, after embolization, evaluating tumor response by LR-TR criteria between 2 groups, the rate of LR-TR tumor-free group < 200 ng/ml was 43.66% (31/71), and in the group > 200 ng/ml was 28.6% (8/28), the rate of LR-TR and tumor in the group < 200

ng/ml was 50.7% (36/71), and the group > 200 ng/ml is 64.3%, the difference between the two groups is statistically significant with p<0.05. The reason for this difference is that in our study group, the AFP group was divided into three groups (less than 20 ng/ml, from 20-400 ng/ml, and > 400 ng/ml) in which the majority were found. Group 2 and Group 3 patients differ from the author's study subjects.[10]

In the author Riaz's study in 2009, there was a correlation between the liver tumor response with WHO and EASL criteria and the post-embolization AFP response; specifically, the cases of no tumor had a high AFP response (9/12) in viable tumors, the AFP response rate drops to 50%. Besides, the patients responding to AFP usually have a longer average survival time than those in the no-response group (15 months with 5.3 months). The author believes that AFP is a quick, simple test that does not depend on the reader, like radiographic imaging assessing treatment response and long-term prognosis.[9,11,12]

Pre-treatment liver tumor characteristics (location, size, and morphology) affected treatment options and post-treatment outcomes, which involved the patient's survival time. The choice of intervention type and intervention level depends on tumor morphology; according to author Thai Doan Ky (2015), for confluent or diffuse liver tumors, the author often chooses non-selective intervention methods, such as embolizing from the right or left hepatic artery. Using LR-TR correlated with the tumor size. If the tumor was less than 5cm, the higher the tumor size, the higher the tumor-free response rate (p<0.05). According to the study of Thai Doan Ky (2015), the response rate of liver tumors in the group of patients with liver tumors ≥8cm in size (58.5%) is statistically significantly lower than in the group of patients with liver tumors less than 8cm in length (81.2%, p=0.011).[13] The evaluation of the treatment response algorithm after TACE is based on the size, the lesional enhancement, the recurrence lesion, and the presence of vascular invasion. In unresectable HCC, TACE has been shown to prolong survival and improve clinical symptoms. This result is achieved by controlled tumor growth and reduction in tumor size, leading to a decrease in intrahepatic mass effect and improved liver function.

Our study has several limitations. The retrospective study can not avoid selection bias. We used a reference standard modified by Kim SC's research. We followed up in six months; however, we did not have pathology as several studies as before, which may have biased the diagnostic performance, given that imaging does not detect microscopic disease. When performing angiography on DSA or CT scan, much depends on the structure of the blood vessels supplying each patient's tumor and also depends on the subjective assessment of interventionalists, so it is inevitable to be presumptuous, to limit this needs to be discussed and double-blind studies should be introduced. Lastly, diagnostic performance was not assessed on a per-patient basis.

In conclusion, many studies have proven that LR-TR has excellent value in assessing response to local treatment, compared to other standards such as post-treatment pathology, angiography, or continuous post-treatment outcome. We propose that LR-TR establish standards for selection and screening for the risk of tumors becoming

HCC, in addition to considering criteria to assess treatment response by CT/MRI.

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