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Original Article

Clinical and prognostic value of CT perfusion imaging parameters in patients with primary liver cancer after therapy

Yiming Li, Yuzhou Li, Yuan Sui, Guangyao Lin, Wenqi Huang, Yinshi Zheng

Medical Imaging Center, The First People's Hospital of Shangqiu City, Shangqiu 476100, Henan Province, China

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Abstract: Objective: To explore the value of arterial enhancement fraction (AEF) of CT perfusion in evaluating the postoperative treatment efficacy on liver cancer (LC). Methods: Clinical data of 60 patients with LC who were treated with transcatheter arterial chemoembolization for LC in our hospital from Jan. 2015 to Jan. 2017 were analyzed retrospectively. They underwent CT scanning before and after surgery. The change of arterial enhancement fraction (AEF) was analyzed, and its value in efficacy evaluation was assessed. Results: After surgery, the AEF value of the effective group decreased greatly ($P<0.05$) and was significantly lower than that of the ineffective group ($P<0.05$). Alpha fetal protein (AFP) of both groups decreased after surgery, with a significantly lower AFP level in the effective group than that in the ineffective group ($P<0.05$). AEF and AFP were positively correlated. According to the follow-up results, patients with a low AEF level showed a higher survival rate than those with a high level. Cox regression analysis revealed that AEF was an independent factor for patients' prognosis. Conclusion: CT perfusion imaging parameters are of high clinical value for patients with primary LC after therapy and can be used as independent factors for their prognosis.

Keywords: CT perfusion imaging parameters, primary liver cancer, prognosis, arterial enhancement fraction

Introduction

Primary liver cancer (PLC) is a common digestive system cancer worldwide and also the most common type of liver cancer (LC) [1]. Approximate 90% of the LC patients are PLC, and PLC affects about 626,000 new patients worldwide each year, ranking the third in cancer-associated deaths in Asia-Pacific region and the second common cancer after lung cancer in China [2, 3]. PLC is dangerous due to both high incidence and mortality. According to the statistics of the WHO in 2012, its mortality in 2012 was approximate 95.4%, and more than half of them were in China [4]. The most common risk factor of hepatocellular carcinoma (HCC) worldwide is chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) [5]. Additionally, alcoholism, obesity, and type 2 diabetes mellitus are all correlated with an increased risk of HCC [6]. At the current stage, surgery is the first option for HCC therapy, but PLC is usually ignored by patients due to its occult symptoms [7]. Accordingly, patients with PLC usually miss the optimal surgery timing at the time of diagnosis, and this is probably one of the reasons for the increased mortality of PLC [8]. Therefore, it is imperative to identify specific and sensitive biomarkers for early diagnosis of LC.

At the current stage, PLC is mainly treated by surgery to control its development [9]. However, not all patients are suitable for surgical treatment. Transcatheter arterial chemoembolization (TACE) is a primary treatment for patients not suitable for hepatectomy [10]. However, if patients' lesions are not completely necrotic after TACE, there will be residual lesions or tumor blood vessel re-formation, inducing tumor recurrence again [11]. Thus, it is of profound importance to search for a quick and accurate index to evaluate residual lesions and tumor blood supply for a better treatment in the future. The curative effect after surgical treatment is mainly evaluated through imaging

examination (CT and MRI) in clinical practice [12]. However, because of the irregular diffusion of lipiodol deposition, the evaluation of curative effect after tumor therapy according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) depends on radiologists' experience and subjective judgment to a great extent [13]. The functional characteristics of tumors change earlier than morphological features. Therefore, routine CT perfusion imaging (CTPI) is adopted to obtain arterial enhancement fraction (AEF) reflecting the ratio of arterial and venous blood supply in clinical practice. With it, the survival of HCC patients treated by TACE before and after surgery can be evaluated without increasing the external radiation dose [14].

In this study, we retrospectively analyzed the evaluation and prognostic value of AEF combined with AFP in PLC treatment for the first time to provide reference for clinical treatment and prognosis observation.

Methods and materials

Clinical data

A total of 60 patients (40 males and 20 females, 60.5±7.2 years old) with PLC confirmed in our hospital from Jan. 2016 to Jan. 2018 were selected for retrospective study. All of them received TACE therapy. All patients signed the informed consent form. This study was approved by the ethics committee of our hospital, with approval number of HN2020 (review) LL014.

Inclusion and exclusion criteria

The inclusion criteria: Patients confirmed with PLC by pathological imaging examination; patients meeting TNM staging criteria (version 8) [15]; patients who had received anti-tumor therapy before this treatment, and received treatment for the first time; and patients with detailed case data and follow-up records.

The exclusion criteria: Patients with other comorbid tumors, liver diseases, kidney diseases, malignant tumors, severe cardiovascular or cerebrovascular diseases, severe inflammation or severe immunodeficiency.

Therapeutic regimen

All the patients were treated with TACE. Specifically, the patient was ordered to lie flat on a DSA bed, with the skin of bilateral groin area disinfected routinely and a sterile towel laid and given local anesthesia. Then a small incision about 5 mm was cut on the skin, followed by implementation of the improved Seldinger puncture to the right femoral artery. The patient was also given chemotherapeutic drugs including 80-100 mg oxaliplatin (Qilu Pharmaceutical Co., Ltd., China, State Food and Drug Administration (SFDA) approval no.: H20093167), 10-20 mg epirubicin (Pfizer Pharmaceuticals Limited, China, SFDA approval no.: H20000497), 0.5-1.0 g 5-fluorouracil (Hainan Changan International Pharmaceutical Co., Ltd., China, SFDA approval no.: H20050981), and 5-30 ml iodipin as embolic agent, at doses determined according to the patient' tumor size, body surface area, and tumor blood supply. After surgery, extubation and compression dressing were conducted.

CT detection and data analysis

The patient was scanned with a Siemens Definition Flash 64-slice CT (Siemen, Germany) scanner from head to foot and from diaphragm to anterior superior iliac spine. First, the patient was given conventional plain scan, and injected with 100-120 ml contrast agent ultravist (320 mgI/ml, 2 ml/kg weight) through the median cubital vein at an injection rate of 3 ml/s. After 28 h, the delayed arterial phase scanning was performed. After 30 s, the portal pulse scan was performed. The scanning parameters were as follows: tube voltage of 120 kV, tube current of 250 mAs, Caredose4D, conventional scanning layer of 5 mm, and reconstruction layer of 5 mm. The collected data were imported into CT Kinetics (Siemen, Germany) workstation. The abdominal aorta and portal vein were selected to fit the arterial input function (AIF) of dual blood supply to liver, and the region of interest (ROI) was selected by two radiologists with more than 5-year experience in abdominal imaging diagnosis. The parenchymal part of liver tumor was selected from the site without cystic degeneration and necrosis not near the vascular area, and the largest slice of lesion area was selected as ROI for calculation of the distribution of AEF in the ROI.

Outcome measures

Primary outcome measures: The clinical efficacy of patients after treatment was evaluated according to the New Response Evaluation

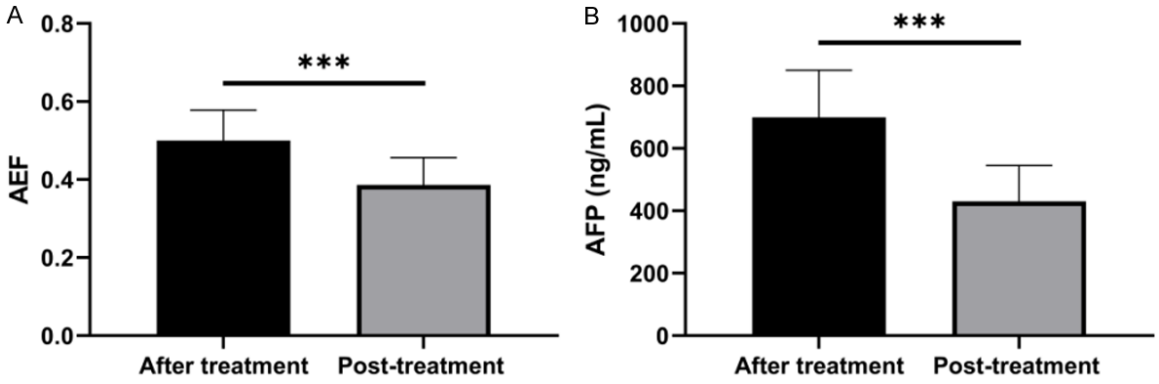

Figure 1. Changes of AEF value and AFP level in patients with PLC before and after treatment. A. Changes of AEF value in patients with PLC after treatment. B. Changes of AFP level in patients with PLC after treatment. Note: ***P<0.001. The data were compared between groups by the paired-samples t test.

Criteria in Solid Tumors (RECIST). Patients with complete remission (CR) and those with partial remission (PR) were assigned to the effective group (n=47), and patients with stable disease (SD) and those with progressive disease (PD) were assigned to the ineffective group (n=23). The two groups were compared in AEF value before and after therapy. Additionally, ROC curves were drawn to analyze the evaluation value of AFE.

Secondary outcome measures: 5 mL of peripheral blood samples from patients were collected before and after treatment and centrifuged at 1500 g for 10 min to collect serum for the detection of the changes of alpha-fetoprotein (AFP), using automatic chemiluminescence immunoassay. Pearson test was used to analyze the correlation between AEF and AFP, and Cox regression was used to analyze the prognostic factors of patients.

Statistical analyses

The collected data were statistically analyzed using SPSS20.00, and the figures were rendered using Graph Pad 8. The Kolmogorov-Smirnov (K-S) test was adopted for data distribution analysis, and those in normal distribution were analyzed via the t test and compared between groups via the independent-samples t test. Paired t test was used for comparison within groups. Additionally, the Kplan-Meier and log-rank tests were adopted to analyze patients' survival, and ROC curves were used to analyze the diagnostic value of AEF in patients with PLC. Area under the curve (AUC) >0.5 denotes a diagnostic value. Cox regression was conducted to analyze the prognostic factors of patients. Univariate analysis was conducted by the forward method, and multivariate analysis was conducted by the backward LR method. P<0.05 suggested a statistically significant difference.

Results

Clinical baseline data of patients

The enrolled patients consisted of 40 males and 20 females with a mean age of 60.5±7.2 years. There were 33 patients with tumor size ≥4 cm and 27 patients with tumor size <4 cm, 16 patients in stage II, 18 patients in stage III, and 26 patients in stage IV, 28 patients in grade A and 32 patients in grade B in ChildPugh classification.

Changes of AEF value and AFP level in patients with PLC before and after therapy

We compared the changes of serum AFP and AEF of CT in patients with PLC before and after TACE treatment, and found that AEF value and AFP concentration in patients after treatment were both lower than those before treatment (**Figure 1A** and **1B**, both P<0.05).

Changes of AEF value and AFP level before and after treatment in the effective group and the ineffective group

According to the clinical efficacy in patients after treatment, the patients were assigned to the effective group or ineffective group. We fur-

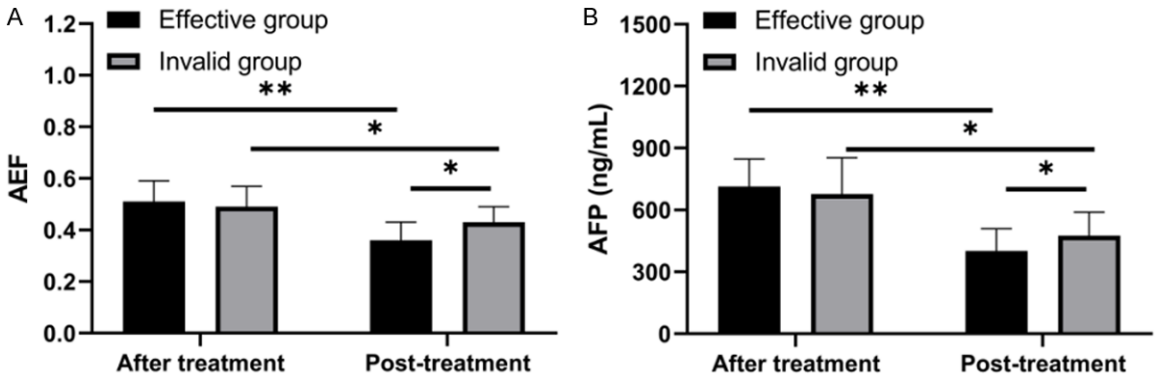

Figure 2. Changes of AEF value and AFP level in the effective and ineffective groups before and after treatment. A. Changes of AEF value in the effective group and ineffective group before and after treatment. B. Changes of AFP level in the effective group and ineffective group before and after treatment. Notes: *indicates P<0.05 and **indicates P<0.01. The data were compared between groups by the paired-samples t test, and compared without groups using the paired t test.

Table 1. ROC parameters

Index	AUC	95% CI	*P*-value	Sensitivity	Specificity	Youden index	Cut-off
AEF	0.778	0.662-0.894	0.003	78.26	67.56	45.83	>0.385
AFP	0.679	0.538-0.821	0.020	39.13	91.89	31.02	>523.13
Combination of the two	0.821	0.717-0.925	<0.001	82.60	75.67	58.28	>0.340

Note: AUC: area under curve; 95% CI: confidence interval.

ther compared the changes of AEF value and AFP level before and after treatment between the two groups, and found that there was no difference between them in AEF value and AFP level before surgery (P>0.05), and the AEF value and AFP level in the effective group were greatly lower than those in the ineffective group (**Figure 2A**, **2B**, P<0.05).

Evaluation value of AEF and AFP in the treatment efficacy

For the purpose of further determining the evaluation value of AEF and AFP in the treatment efficacy, we drew ROC curves according to each index after treatment (**Table 1**). According to the results, AEF value had an AUC of 0.778 and a cut-off value of 0.385 (**Figure 3A**), AFP level had an AUC of 0.679 and a cut-off value of 523.13 (**Figure 3B**), and combination of the two had an AUC of 0.821, and a cut-off value of 0.340 (**Figure 3C**).

Evaluation value of AEF in the overall survival (OS) rate of patients

We divided the patients into high and low expression groups according to the cut-off value of AEF in ROC curve. Analysis of the OS rate of patients revealed that the OS rate in the low expression group was notably higher than that in the other group (**Figure 4**, P=0.009).

Cox regression analysis

Lastly, we collected clinical data of patients and analyzed the prognostic factors. According to Univariate Cox regression analysis, clinical stage, ChildPugh grade, AFP level, and AEF value all impacted the prognosis of patients (**Table 2**, P<0.05). According to multivariate analysis, clinical stage, AFP level, and AEF value were all independent prognostic factors (**Table 3**, all P<0.05).

Discussion

PLC is a common malignant tumor worldwide. According to the data published by American Cancer Society, LC ranks the fifth among common cancers in incidence, and the third among malignant tumors in mortality, showing an annually growing incidence [16]. TACE is currently recognized as an effective non-surgical treatment for patients without surgical indications and those refusing to undergo surgical

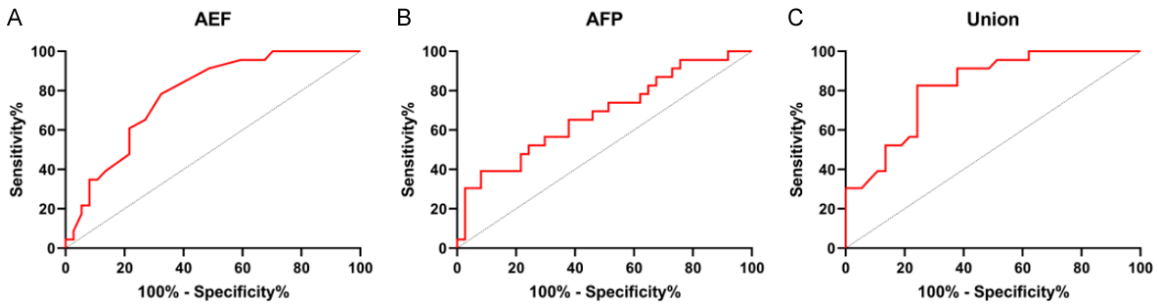

Figure 3. Evaluation value of AEF and AFP in the treatment efficacy of patients. A. ROC curve of AEF value in efficacy evaluation of patients. B. ROC curve of AFP level in efficacy evaluation of patients. C. ROC curve of AEF combined with AFP in efficacy evaluation of patients. Note: ROC-based analysis was adopted.

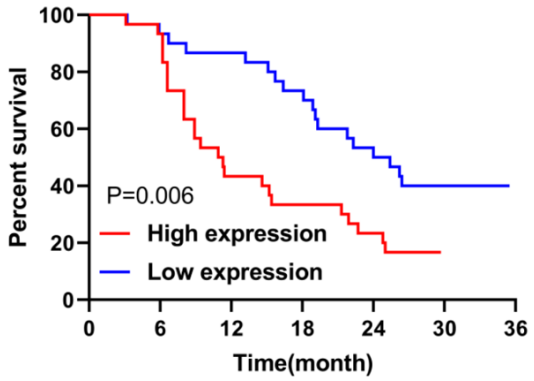

Figure 4. Evaluation value of AEF in the OS rate of patients. Note: The K-M test was adopted.

resection of LC [17], but it can hardly completely inactivate tumors. According to one study [18], only 15-55% of patients had local response after TACE. Accordingly, it is imperative to search for a timely and accurate assessment scheme. However, each inspection has both advantages and limitations.

CT perfusion is to transport blood into a unit volume of tissue per unit time, which usually means to transport blood in capillaries [19]. According to prior research, the time-density curve of ROI in a specific slice can be obtained by continuously scanning the slice with bolus intravenous injection of contrast agent. Various concerned parameters can be obtained by calculating curves with different mathematical models [20]. AEF is a quantitative parameter that reflects the ratio of blood supply to arteries and veins [21]. In this study, the AEF value of patients increased significantly after treatment. After TACE, stenosis and occlusion of the internal and peripheral arteries of the tumor trigger a decrease in the flow velocity of the proper hepatic artery. For tumors sensitive to chemotherapy that can obtain favorable embolization effect, the decrease in the flow velocity of the proper hepatic artery is consistent with the decrease or disappearance of the internal blood flow of the tumor, which can be explained by perfusion parameters [22]. In addition, according to comparison of groups with different efficacy, the effective group showed a lower AEF value than the ineffective group after treatment. It can be explained by the fact that areas with tumor blood vessels and those with abundant blood flow are often areas with strong tumor growth and metabolism [23]. After operation, patients have sparse lipiodol deposition, high hepatic artery perfusion according to AEF, and still blood flow area, which indicate incomplete embolism that may be the basis of tumor recurrence and metastasis, and also indicate the requirement for further treatment [24]. We also found a positive correlation between AEF and AFP through correlation analysis, which indicated that AEF value can be used as a reference index to evaluate TACE efficacy in patients with PLC. In order to determine the evaluation value of AEF, we drew a corresponding ROC curve of AEF after treatment. The ROC curve showed that with the help of AEF value, AFP can better help evaluate the efficacy in patients, which further supports the evaluation value of AEF.

At the end of the study, we followed up the patients and collected their clinical data for Cox regression analysis. According to Cox regression analysis, clinical stage, AFP level, and AEF value were independent risk factors affecting the patients' prognosis. Liu et al. [25] have revealed that AEF value can be used as an evaluation index for the survival of patients with

Table 2. Univariate Cox analysis

Factors	β	S.E	Wald	*P*-value	HR-value	95.0% CI	
						Lower part	Upper part
Gender (male *vs.* female)	0.254	0.321	0.629	0.428	0.289	0.688	0.417
Age (≥60 years *vs.* <65 years)	0.491	0.308	0.546	0.111	0.634	0.894	2.989
Tumor size (≥4 cm *vs.* <4 cm)	0.244	0.307	0.634	0.426	1.277	0.700	2.331
Clinical staging (II *vs.* III *vs.* IV)	0.581	0.198	8.628	0.003	1.789	1.213	2.636
ChildPugh classification (grade A *vs.* grade B)	0.828	0.322	6.623	0.010	2.289	1.218	4.301
AFP (F400 ng/mL *vs.* 400 ng/mL)	0.922	0.332	7.717	0.005	2.516	1.312	4.823
AEF (<0.385 *vs.* 0.385)	-0.800	0.313	6.547	0.011	0.449	0.243	0.829

Note: The forward method was used for multivariate Cox regression analysis.

Table 3. Multivariate Cox analysis

Factors	β	S.E	Wald	*P*-value	HR-value	95.0% CI	
						Lower part	Upper part
Clinical staging (II vs. III vs. IV)	0.691	0.226	9.352	0.002	1.997	1.282	3.110
ChildPugh classification (grade A vs. grade B)	0.450	0.339	1.762	0.184	1.568	0.807	3.047
AFP (≥400 ng/mL vs. 400 ng/mL)	1.002	0.348	8.279	0.004	2.724	1.376	5.390
AEF (<0.385 vs. 0.385)	-1.085	0.337	10.335	0.001	0.338	0.174	0.655

Note: The backward LR method was used for multivariate Cox regression analysis.

PLC. In the present study, we have confirmed this point through research. Compared with their research, our study had a much larger sample size, so it can more strongly confirm the value of AEF in evaluating TACE efficacy in patients with PLC.

We have verified the evaluation value of AEF in treatment efficacy among patients with PLC after TACE through a retrospective study. However, this study still has some limitations. First of all, in our retrospective study, patients could not be grouped like randomized controlled studies, so the data may be biased. Second, at the current stage, most of the clinical treatment schemes are combined treatment, which leads to the low guiding significance of our research results to clinical practice. Therefore, we hope to carry out a randomized controlled experiment in the follow-up study to observe the value of AEF in evaluating the postoperative efficacy in patients with PLC after different treatment schemes.

To sum up, CT perfusion imaging parameters are of high clinical value for patients with PLC after therapy and can be used as independent factors for their prognosis.

Disclosure of conflict of interest

None.

Address correspondence to: Yinshi Zheng, Medical Imaging Center, The First People's Hospital of Shangqiu City, 292 Kaixuan South Road, Shangqiu 476100, Henan Province, China. Tel: +86-1360370-9100; E-mail: doc19848899@163.com

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