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Computed tomographic perfusion imaging for the prediction of response transarterial radioembolization with Yttrium-90 glass microspheres of hepatocellular carcinoma

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Abstract. – OBJECTIVE: The present study aimed to estimate the clinical value of quantitative computed tomography perfusion imaging (CTPI) parameters in predicting early treatment response, as determined by the modified response evaluation criteria in solid tumours (mRECIST), in patients with HCC who underwent transarterial radioembolization (TARE).

PATIENTS AND METHODS: This retrospective cohort study included 54 patients with HCC who had TARE treatment between July 2018 and August 2019. Each patient was evaluated using CTPI before the procedure and in the first and third months after the procedure. In the third month, treatment response was determined based on mRECIST and used as a reference. ROC analysis was performed to determine the relationship between the CTPI parameters before treatment and one month after treatment and the treatment response.

RESULTS: Significant cut-off values for three of the CTPI parameters – hepatic blood flow (BF), time to start (TTS) and hepatic perfusion index (HPI) – which were among the pre-treatment CTPI parameters, were found to predict progressive disease (PD). The TTS cut-off value was 1.29 (sensitivity: 86.7%; specificity: 6.7%), the BF cut-off value was 81.58 (sensitivity: 53.3%; specificity: 90%) and the HPI cut-off value was 88.26 (sensitivity: 33%; specificity: 96.7%).

CONCLUSIONS: BV, TTS and HPI may be predictive for PD in HCC lesions in the third month after TARE treatment. In contrast, the CTPI parameters in the first month after TARE played no significant role in predicting the treatment response and determining the effects of TARE on the microvascular level.

Key Words:
Hepatocellular carcinoma, Treatment outcome, Yttrium radioisotopes, Perfusion imaging, Tomography.

Abbreviations

ALP: Arterial liver perfusion; ANOVA: Analysis of Variance; BF: Blood flow; BV: Blood volüme; CTPI: Computed Tomography Perfusion Imaging; D-CT: Dynamic Computed Tomography; ECOG: Eastern Cooperative Oncology Group; HCC: Hepatocellular Carcinoma; HPI: Hepatic Perfusion Index; HU: Hounsfield Unit; MAA: Macro Aggregate Albumin; mRECIST: modified Response Evaluation Criteria in Solid Tumors; PD: Progressive Disease; PR: Partial Response; PVP: Portal venous perfusion; ROC: Reciever Operator Characteristics Curve; ROI: Region of Interest; SD: Stable Disease; TACE: Transarterial Chemoembolization; TARE: Transarterial Radioembolization; TTS: Time to Start; ^{90}Y: Yttrium-90.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy in the world, the fifth most common cancer in men and the seventh most common cancer in women[1]. Transarterial radioembolization (TARE) using microspheres loaded with yttrium-90 (90Y) is used in intermediate and advanced HCC treatment; although it is not suitable as a curative treatment, it considered a locoregional treatment method[2,3]. While TARE is currently a frequently used treatment method, the best criteria for evaluating TARE treatment response have not yet been determined.

It has reported that tumour size increases without enhancement in the early period after TARE[4]. Therefore, the modified response evaluation criteria in solid tumours (mRECIST) were established to evaluate tumour response after TARE[5]. In recent studies, it was named the gold

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standard method for evaluating TARE treatment response[6,7]. After TARE, tumours regress was relatively slowly compared to other treatment methods, and it takes a long time until a decrease in arterial enhancement can be observed[8].

Computed tomography perfusion imaging (CTPI) can be used in oncological evaluation because it reflects microvascular changes in angiogenesis and tumour vascularization *in vivo*[9]. It is a recently developed and remarkable technique that can obtain quantitative information about the hemodynamic properties of liver parenchyma[10]. Furthermore, it has recently been reported that CTPI parameters may play a predictive role in early evaluation in patients undergoing interventional procedures, such as transarterial chemoembolization (TACE)[11,12]. Predictive CTPI parameter values have been specified in patients with metastatic liver disease and patients with HCC lesions to evaluate the TARE treatment response[13,14]; however, no significant results were obtained for HCC[15].

The purpose of this retrospective cohort study was to estimate the clinical value of quantitative CTPI parameters in predicting early TARE treatment response, as determined by mRECIST, in patients with HCC.

Patients and Methods

This study was approved by the local Ethics Committee, and informed consent was waived given the retrospective nature of the study.

Study Population

The records of the 98 patients who received the ^{90}Y TARE treatment between July 2018 and August 2019 in our hospital were evaluated. Being 18 years of age and older and having TARE treatment due to intermediate-stage HCC were the inclusion criteria. The TARE treatment decision was made based on consensus among the radiology, medical oncology, nuclear medicine and organ transplant surgery departments. The eligibility criteria for TARE treatment in our centre were as follows: patients with HCC that could not be resected surgically; patients with measurable single or multifocal HCC lesions without extra hepatic liver metastasis; patients with an Eastern Cooperative Oncology Group (ECOG) performance of 0, 1 or 2; patients with sufficient haematological parameters for processing (white blood cell count: 2000/μL, haemoglobin level: 10 g/dL and platelet count: 105/μL); patients with a bilirubin level below 2.0 mg/dL; and patients with normal renal function (serum creatinine threshold value: 1.5 mg/dL). Two patients with a bilirubin threshold level between 2.0 and 2.5 mg/dL were included in treatment group because tumor, which was planning treatment well localized, and normal parenchymal damage were decreased. Two patients with bilirubin threshold levels between 2.0 and 2.5 mg/dL were included in the treatment group given the proper localization of their tumours and effectiveness treatment.

Eight patients who were treated for TARE due to metastatic liver disease (five patients with colorectal carcinoma metastasis, one patient with neuroendocrine tumour metastasis and two patients with breast cancer metastasis) were excluded from the study. In addition, six patients whose measurements could not be obtained according to mRECIST due to diffuse HCC, four patients whose CTPI parameters could not be clearly evaluated due to previous TACE treatment and eight patients without third month control CTPI or dynamic computed tomography (D-CT) images were excluded from the study. Eight patients whose CTPI parameters could not be calculated due to portal or splenic vein invasion were also excluded from the study (Figure 1).

After applying the inclusion and exclusion criteria, the study population consisted of 54 patients, 47 (87%) of whom were male and 7 (13%) of whom were female. Their ages ranged from 32 to 84 years old, and the mean age was 59 ± 11.53 years old. Patient characteristics are described in Table I.

TARE with ^{90}Y

All patients underwent diagnostic angiography to evaluate the suitability of the treatment and the dose calculation. Using Simplicit90Y software (Mirada Medical Ltd, Oxford Centre for Innovation, United Kingdom), viable tumour tissue, necrotic tumour tissue, areas with macro aggregate albumin (MAA) involvement, lung and gastrointestinal shunt ratios and appropriate treatment doses based on these values were calculated. A glass-based ^{90}Y microsphere device (Therasphere®, BTG, London, UK) was used for all injections. The total treatment doses given to the patients were between 90 and 150 Gy, and their mean values were 131.01 ± 18.64.

TARE procedure involves the main hepatic artery in 10 patients (18.5%), the right hepatic ar-

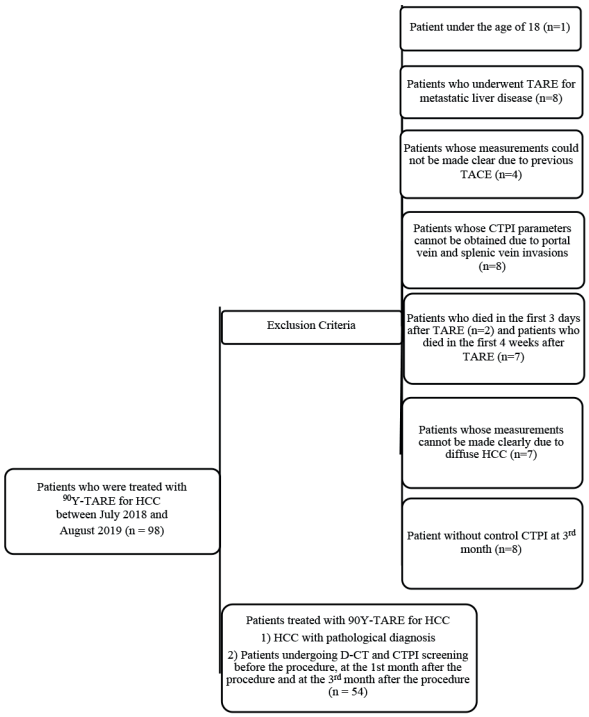

Figure 1. Diagram showing the inclusion and exclusion criteria for the current study. ^{90}Y = Yttrium-90 TARE: Transarterial Radioembolization; HCC: Hepatocellular Carcinoma; TACE: Transarterial Chemoembolization; CTPI: Dynamic Perfusion Computed Tomography; D-CT: Dynamic Computed Tomography.

tery in 26 patients (48.1%), the left hepatic artery in seven patients (13%), segment 8 artery in four patients (7.4%), and three patients (5.6%). Segment was performed separately from 6-7 arteries and from right and left hepatic artery in four patients (7.4%) (Table I). The ^{90}Y microspheres were administered on a patient-by-patient basis in a single session to either the right lobe (n = 26), the left lobe (n = 7), segment 8 (n = 4), segment 6-7 (n = 3) or the whole liver (n = 10). The procedure was performed in two sessions from both the right and left hepatic arteries in four patients with an interval of two weeks (Table I).

CT Imaging Protocol

Four-phase D-CT images with a 256-dual source multidetector were obtained before the procedure, one month after the procedure and three months after the procedure. A pre-contrast CT scan was performed after the intravenous administration of 1.5-2.0 ml/kg of iodinated contrast media (300 mg I/ml) for a fixed injection duration of 30 seconds (rate, 2-4 ml/s) followed by a 20-ml saline chaser bolus injection. Using a bolus tracking technique, the late arterial phase was performed 18 seconds after the attenuation value reached 100 Hounsfield Unit (HU) at the abdominal aorta. The portal venous phase and the delayed phase were obtained with a scan delay of 30 seconds and 150 seconds, respectively, after the end of the previous phase.

CTPI Protocol

CTPI was performed using a 256-slice dual source CT (Siemens Medical Systems®, Erlan-

Table I. Patient Demographics.

Gender	
Female	7 (13%)
Male	47 (87%)
Age (Mean ± SD)	59.51 ± 11.53 (32-84)
Underlying Liver Disease	
Liver Cirrhosis	45 (83.3%)
Hepatitis B	31 (57.4%)
Hepatitis B-D Co infection	7 (12.3%)
Hepatitis C	1 (1.8%)
Biliary cirrhosis	6 (11.1%)
Unknown Etiology	9 (16.6%)
Tumor count	
1	15 (27.8%)
2	16 (29.6%)
≥ 3	23 (42.6%)
Location of HCC lesions	
Right Lobe	17 (31.5%)
Left Lobe	6 (11.1%)
Right and Left Lobe	31 (57.4%)
Presence of portal vein thrombus	
Main Portal Vein	5 (9.3%)
Left Portal Vein	6 (11.1%)
Right Portal Vein	10 (18.5%)
Right Portal Vein Anterior Branch	4 (7.4%)
Right Portal Vein Posterior Branch	5 (9.3%)
None	24 (44.4%)
Child Score	
Child A	29 (53.7%)
Child B	27 (46.3%)
BCLC Score	
BCLC B	31 (57.4%)
BCLC C	23 (42.6%)
Previous Treatment	
Sorafenib use	4 (7.4%)
TACE	11 (20.4%)
None	39 (72.2%)
Treatment Application Places	
Truncal	10 (18.5%)
Right Hepatic Artery	26 (48.1%)
Left Hepatic Artery	26 (48.1%)
Segmentectomy (Segment 8)	7 (13%)
Segmentectomy (Segment 6)	3 (5.6%)
Right Hepatic & Left Hepatic Artery	4 (7.4%)

SD: Standart Deviation; HCC: Hepatocelluler Carcinoma; BCLC: Barcelona Clinic Liver Cancer staging system; TACE: Transarterial chemoembolization.

gen, Germany). The scan region of the tumour was based on a CT scan of the abdomen (120 kV, 180 mA) obtained without contrast medium during a breath hold at the end of expiration. The region scanned with CTPI consisted of four adjacent 6 mm-thick sections. A dynamic study of the selected area was performed in a single breath hold at the end of expiration with the administration of 50 ml non-ionic contrast agent (Omnipaque®, Nycomed Imaging AS, Oslo, Norway) at a rate of 6 ml/s *via* a power injector using a bolus tracking algorithm through an 18-gauge intravenous cubital cannula. CTPI scanning (100 mA, 80 kV, section thickness of 6 mm, rotation time of 1 second, matrix of 512 × 512 mm) was initiated 6 seconds after the injection start, and 4 contiguous sections of tissue were scanned every second for 55 seconds. The contrast agent administration was followed by a power injection of 20 ml of saline (at the same injection rate).

CTPI was performed within 72 hours before the TARE treatment decision was made. Control CTPI was performed in the first month (4-6 weeks) and third month (12-15 weeks) after the procedure.

CTPI Analysis

Quantitative analysis of the CTPI data was performed using commercially available software (Syngo Volume Perfusion CT Body, Siemens Healthcare). An integrated motion correction algorithm for anatomic alignment was applied. Volumes of interest were manually drawn around the target lesion, the spleen, the portal vein and the aorta. For better determination of the target lesions, images of those lesions from the baseline CT were used. The software then created quantitative perfusion maps and calculated the CTPI parameters and standard deviations. In HCC patients with two or more lesions, the largest targeted lesion in TARE treatment was included in a free hand-drawn region of interest (ROI) on the CTPI maps.

The following values were calculated for the tumoural area in the perfusion maps: hepatic blood flow (BF, ml/100 ml/min), representing the flow rate through the vasculature; hepatic blood volume (BV, ml/100 ml), representing the volume of flowing blood; time to start (TTS, s); arterial liver perfusion (ALP, ml/100 ml/min), representing the flow rate through the arterial vasculature; portal venous perfusion (PVP, ml/100 ml/min), representing the flow rate through the venous vasculature; and hepatic perfusion index (HPI, %), defined as the ratio between arterial liver perfusion and total liver perfusion.

Assessment of the Treatment Response

According to mRECIST, the longest viable diameter of the tumour was measured in the target lesion[5] in the liver lobe where the procedure was performed. The evaluation results from the third month were used as a reference for the treatment response.

In the perfusion examinations conducted one and three months after the procedure, the entire lesion was included in the free hand-drawn ROI, and this area was automatically defined in other maps. The perfusion parameters were calculated, and hepatic drawing and treatment response was determined by a radiologist with 4 years of experience under the supervision of an abdominal radiologist with 20 years of experience (Figure 2).

Statistical Analysis

Statistical analysis was performed using IBM® SPSS® Statistics 22 for Windows software (International Business Machines Corp., Armonk, NY, USA). The Kolmogrow Smirnov test was used as a normal distribution test. The Wilcoxon test was used for binary dependent groups that did not conform to the normal distribution, the paired *t*-test was used for binary dependent groups fitting the normal distribution, the one-way analysis of variance (ANOVA) test was used for triple groups fitting the normal distribution, and the t-test was used for independent binary groups fitting the normal distribution. The Mann-Whitney U test was used for independent binary groups that did not fit the normal distribution, the Kruskal Wallis test was used for triple independent groups that did not fit the normal distribution, and the Friedman test was used for dependent triple groups that did not fit the normal distribution. A $p < 0.05$ value was considered significant.

We used Reciever Operator Characteristics Curve (ROC) analysis to determine the effectiveness of the CTPI parameters and predict differentiation between stable disease (SD), partial response to treatment (PR) and progressive disease (PD). Although the BF, TTS and HPI values were statistically significant in areas under the curve in the separation of disease progression, their specificities were low. The positive likelihood ratio (Lr +) value was low in high sensitivity and specificity values.

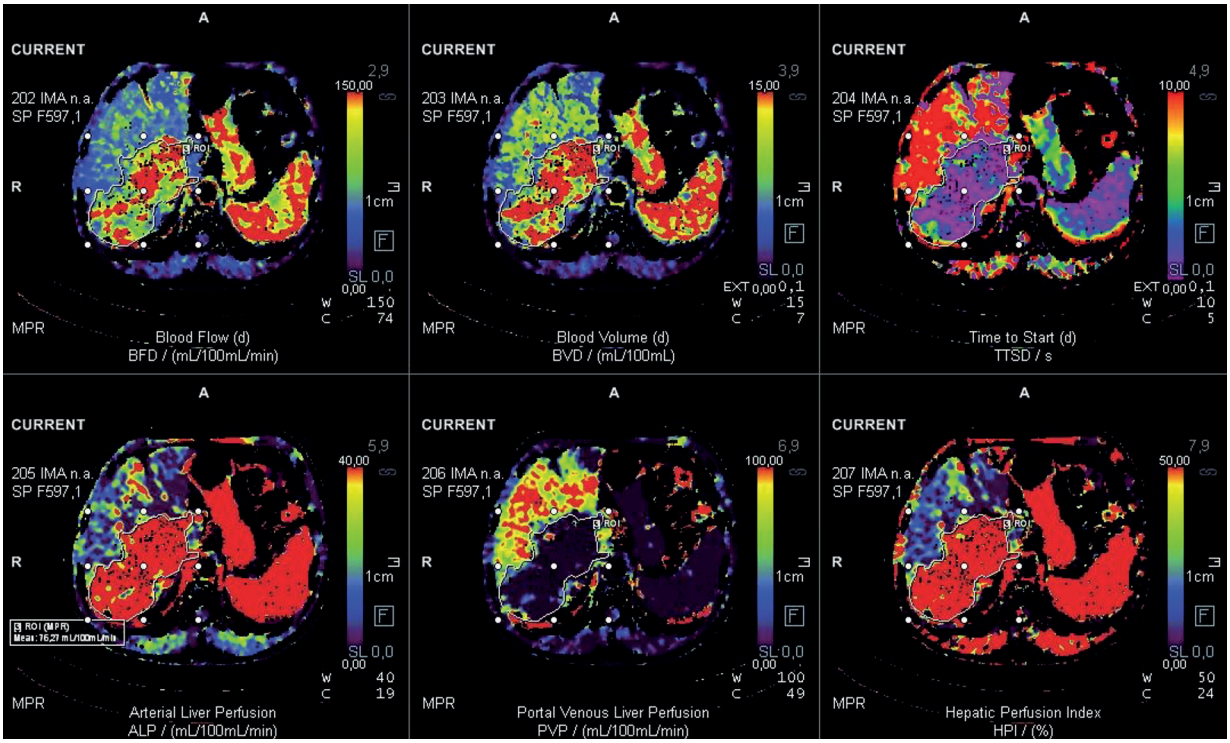

Figure 2. The appearance of a 63-year-old patient diagnosed with hepatocellular carcinoma (HCC) on the perfusion map of the tumor included within the boundaries of region of interest (ROI). Note the vascularization in the arterial liver perfusion (ALP) and hepatic perfusion index (HPI) maps and the color change due to the lack of portal nutrition in the portal venous perfusion (PVP) map.

Results

Treatment Response

According to the mRECIST-based evaluations of the targeted HCC lesions at the end of the third month, 30 patients had SD (55.6%), 9 patients had PR(%16.7) and 15 patients had PD (27.8%).

CTPI Parameter Changes After Treatment

The patients' CTPI parameters before treatment and one and three month after treatment were analysed regardless of the treatment response (Figure 3). Accordingly, the BV (p = 0.006), BF (p = 0.016), ALP (p < 0.032) and HPI (p < 0.001) values were lower in the third month after treatment than during the pre-treatment period. TTS was lower in the third month after treatment (p < 0.016), and PVP was higher in the first and third months after treatment (p = 0.006, p = 0.001) (Table II).

The perfusion parameter values for the pre-treatment period, the first and third months after treatment and the treatment response in the third month were analysed (Table III). In the first month after treatment, BF was lower in patients with PR than in patients compared with SD and higher in patients with PD compared with SD (p < 0.025) (Table III). The pre-treatment PVP was

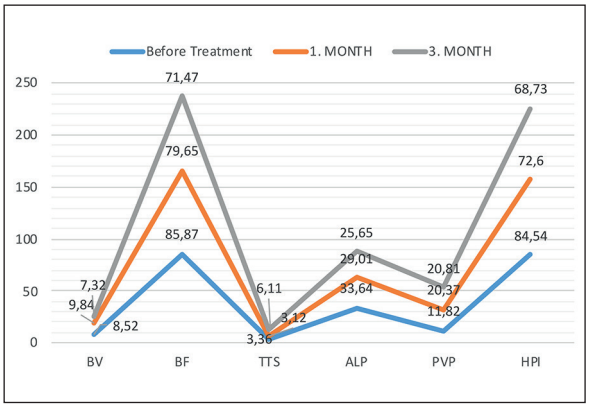

Figure 3. Perfusion values of the patients pre-treatment, after treatment first month and after treatment third month. BV: Blood Volume; BF: Blood Flow; TTS: Time to Start; ALP: Arterial Liver Perfusion; PVP: Portal Venous Perfusion; HPI: Hepatic Perfusion Index.

Table II. Perfusion values of patients before and after the procedure, 1st and 3rd months after the procedure.

	Minimum	Maximum	Mean	S.D.	p
BV Pre-treatment	2.27	43.26	8.52	5.69	
BV 1st month after the transection	0.00	95.70	9.84	13.39	**0.001**
BV 3rd month after the transection	0.98	57.74	7.32	7.81	
BF Pre-treatment	3.65	180.93	85.87	36.65	
BF 1st month after the transection	3.41	154.17	79.65	34.75	**0.001**
BF 3rd month after the transection	5.60	235.28	71.47	40.35	
TTS Pre-treatment	0.60	11.69	3.36	2.35	
TTS 1st month after the transection	0.62	7.88	3.12	1.60	**0.001**
TTS 3rd month after the transection	0.00	38.00	6.11	5.62	
ALP Pre-treatment	4.23	66.32	33.64	16.03	
ALP 1st month after the transection	6.25	65.62	29.01	15.31	**0.037**
ALP 3rd month after the transection	1.68	62.53	25.65	12.37	
PVP Pre-treatment	0.00	37.09	11.82	10.09	
PVP 1st month after the transection	1.06	74.36	20.37	16.06	**< 0.001**
PVP 3rd month after the transection	4.45	74.36	20.81	13.44	
HPI Pre-treatment	53.48	100.00	84.54	11.79	
HPI 1st month after the transection	29.58	97.05	72.60	15.23	**< 0.001**
HPI 3rd month after the transection	25.01	97.21	68.73	15.79	

SD: Standart Deviation; BV: Blood Volume; BF: Blood Flow; TTS: Time to Start; ALP: Arterial Liver Perfusion; PVP: Portal Venous Perfusion; HPI: Hepatic Perfusion Index

higher in patients with PR than in patients with SD and lower in patients with PD compared with SD ($p < 0.03$) (Table III). In the third month after treatment, HPI was lowest in patients with PR and highest in patients with PD ($p < 0.012$), and TTS was highest in patients with PR and lowest in patients with PD ($p < 0.015$) (Table III).

Prediction of Morphologic Response to TARE

ROC analysis was performed to determine the relationship between the CTPI parameters before treatment and one month after treatment and the treatment response in the third month after the procedure. When the perfusion values were

Table III. Perfusion values according to the treatment response of the patients.

	SD	PR	PD	p
BV Pre-treatment	9.12 ± 7.25	6.84 ± 3.11	8.34 ± 2.40	0.468
BV 1st month after the transection	11.50 ± 17.62	5.88 ± 2.66	8.89 ± 3.83	0.148
BV 3rd month after the transection	7.43 ± 10.10	5.90 ± 3.04	7.95 ± 3.52	0.169
BF Pre-treatment	81.92 ± 41.69	84.18 ± 33.64	94.78 ± 26.82	0.490
BF 1st month after the transection	74.61 ± 33.52	65.10 ± 30.92	98.46 ± 33.58	**0.025**
BF 3rd month after the transection	64.88 ± 39.19	61.10 ± 34.72	90.87 ± 41.57	0.094
TTS Pre-treatment	3.36 ± 2.41	4.19 ± 2.35	2.86 ± 2.25	0.215
TTS 1st month after the transection	3.23 ± 1.47	3.98 ± 2.29	2.37 ± 1.10	0.125
TTS 3rd month after the transection	6.64 ± 3.31	8.78 ± 11.35	3.44 ± 3.22	**0.019**
ALP Pre-treatment	32.43 ± 16.36	33.46 ± 17.24	36.18 ± 15.42	0.800
ALP 1st month after the transection	27.18 ± 13.58	27.88 ± 13.81	33.37 ± 19.17	0.436
ALP 3rd month after the transection 3	24.35 ± 8.18	20.73 ± 13.75	31.20 ± 16.76	0.161
PVP Pre-treatment	10.73 ± 8.30	19.72 ± 13.51	9.26 ± 9.43	**0.030**
PVP 1st month after the transection	20.88 ± 14.84	25.32 ± 13.56	16.38 ± 19.55	0.072
PVP 3rd month after the transection	20.19 ± 9.30	28.45 ± 16.35	17.46 ± 17.38	0.096
HPI Pre-treatment	83.98 ± 12.25	80.37 ± 13.12	88.18 ± 9.53	0.359
HPI 1st month after the transection	72.17 ± 13.90	65.57 ± 17.65	77.70 ± 15.48	0.165
HPI 3rd month after the transection	66.27 ± 12.84	60.62 ± 19.96	78.52 ± 14.73	**0.012**

SD: Stable Disease; PD: Progresive Disease; PR: Partial Response BV: Blood Volume; BF: Blood Flow; TTS: Time to Start; ALP: Arterial Liver Perfusion; PVP: Portal Venous Perfusion; HPI: Hepatic Perfusion Index.

Table IV. ROC analysis for pre-treatment perfusion parameters of patients with stable and progressive treatment response.

	AUC	p	95% C.I.	
			Lower	Upper
BV	0.667	0.071	0.494	0.839
BF	0.689	0.041	0.508	0.869
TTS	0.762	0.004	0.592	0.932
ALP	0.622	0.185	0.417	0.828
PVP	0.378	0.185	0.174	0.582
HPI	0.762	0.004	0.596	0.929

BV: Blood Volume; BF: Blood Flow; TTS: Time to Start; ALP: Arterial Liver Perfusion; PVP: Portal Venous Perfusion; HPI: Hepatic Perfusion Index; AUC: Area Under Curve; C.I: Confidence Interval.

evaluated according to the third-month treatment response with the ROC analysis, no statistically significant values were found in patients with SD or PR. However, the BF ($p = 0.041$), TTS and HPI ($p = 0.004$) values of the patients with SD in the third month after the procedure were associated with PD (Table IV, Figure 4). The cut-off values for these parameters were identified.

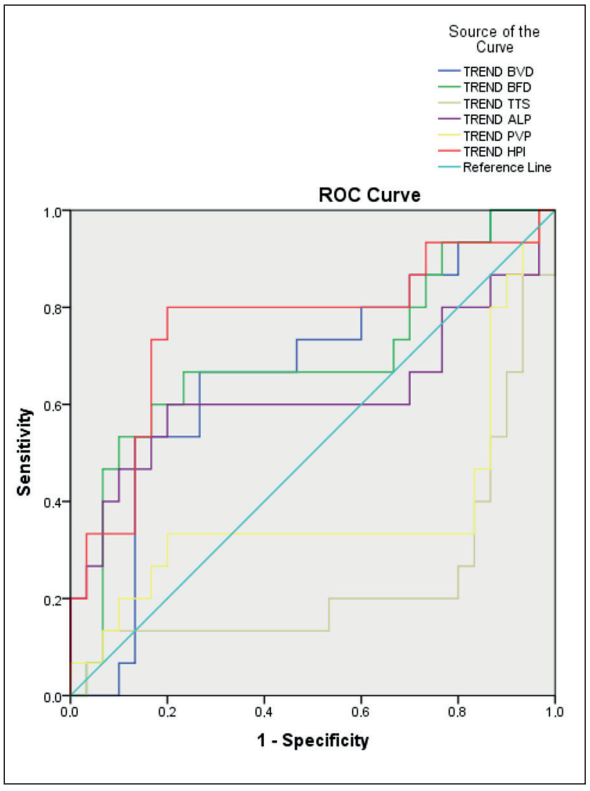

Figure 4. ROC curve and areas under the curve of the pre-treatment transarterial radioembolization (TARE) perfusion parameters of patients with stable and progressive treatment response. BV: Blood Volume; BF: Blood Flow; TTS: Time to Start; ALP: Arterial Liver Perfusion; PVP: Portal Venous Perfusion; HPI: Hepatic Perfusion Index.

For a prediction of PD in the third month after treatment, the TTS cut-off value was 1.29 (sensitivity: 86.7%, specificity: 6.7%), the BF cut-off value was 81.58 (sensitivity: 53.3%, specificity: 90%) and the HPI cut-off value was 88.26 (sensitivity: 33%, specificity: 96.7%). PD was can be predicted at values above these cut-off values (Table V).

No statistically significant values were found in the ROC analysis for the relationship between CTPI parameters in the first month after treatment and response to treatment according to mRECIST.

Discussion

BV, TTS and HPI may be predictive for PD in HCC lesions in the third month after TARE treatment. In contrast, the CTPI parameters in the first month after treatment played no significant role in predicting the treatment response or determining the effects of TARE on the microvascular level. However, as far as we know, the present study is one of the most recent studies on this topic, has the largest number of patients and provides new information about the microvascular effects and tumour efficacy of TARE treatment.

TARE treatment with glass spheres is a local, effective and targeted intravascular radiotherapy method for liver tumours. There are difficulties in evaluating the treatment response due to radiotherapeutic efficacy and changes in the vascular bed after the treatment[16]. In our study, the earliest CTPI parameter change after treatment was in the PVP value, which increased after one month. The first changes after treatment in the microvascular bed occurred during the portal phase. The PVP increase can be explained by an increase in arterial pressure secondary to the failure of

Table V. Cut off values for BF. TTS and HPI perfusion parameters under the curve in ROC analysis at the pre-treatment CTPI parameters.

	Sensitivite	1-Specifity	LR (+)	Cut-off value
BF	0.667	0.30	2.22	64.32
	0.667	0.233	2.85	70.25
	0.533	0.100	5.33	81.58
TTS	0.867	0.933	0.92	1.29
	0.867	0.967	0.89	1.04
HPI	0.800	0.367	2.18	66.96
	0.733	0.200	3.66	71.66
	0.333	0.033	10	88.26

BF: Blood Flow; TTS: Time to Start; HPI: Hepatic Perfusion Index.

the tumour in sinusoidal arterial feeding due to increased flow in preserved portal venous drainage[17]. In the present study, CTPI performed in the third month after treatment showed decreases in the BV, BF, ALP and HPI values and an increase in the TTS value. In other words, the embolizing and radiotherapeutic effects of the TARE treatment in the vascular bed largely appeared in the third month after the procedure. This indicates that evaluating CTPI parameters in the third month after the TARE procedure can determine the effects of the treatment on the vascular bed in HCC lesions. This also indicates that evaluating CTPI parameters in the first month is insufficient to determine the effects of the treatment on the vascular bed.

The effectiveness of CTPI parameters in monitoring liver lesions after antiangiogenic treatments, such as TARE and TACE, has been investigated in many studies[18-21]. Morsbach et al[17] stated that ALP values predicted one-year survival in CTPI performed in the fourth month in metastatic liver patients undergoing TARE treatment. Reiner et al[13] reported that ALP values had a predictive role in the evaluation of one-year survival in metastatic liver patients; however, CTPI parameters were not effective in the early evaluation of HCC lesions.

It has been shown that survival is less likely in patients with high hepatic arterial perfusion values and low portal venous nutrition after TACE and is associated with poor differentiation[18]. Moreover, in another study, when CTPI was performed in the first 48 hours after TACE, the ALP and HPI values were higher in patients who PD to the treatment in the first month[19]. Meanwhile, the present findings indicate that pre-treatment BV, TTS and HPI values may be predictive of the treatment response in the third month after TARE treatment. Similar results were not found for ALP. HPI is a valuable parameter because it provides information about the perfusion of the total tissue amount in order to detect the treatment response[22]. In the present study, the BV and HPI cut-off values had high specificity but low sensitivity; for the TTS cut-off value, sensitivity was high but specificity was low. However, as far as we know, the present study is the only one that has shown that CTPI parameters in a large patient population may have predictive value for the treatment response of post-TARE HCC lesions.

Our study has some limitations. First, it only includes evaluations of the first and third months after TARE treatment; long-term evaluations could lead to more meaningful results. However, important data have been obtained that may elucidate the difficulties reported in evaluating early treatment response. The data may also affect patient survival by playing a role in decisions on treatment, repetition or the use of other treatment methods. Second, mRECIST was used to evaluate treatment response even though it has been characterised as insufficient in evaluating treatment response in hypovascular liver tumours[23]. However, other studies[7,8] have indicated that it is the most appropriate method for evaluating locoregional response. Third, like many other studies on this subject, the present study is based on retrospective data; prospective studies of large patient groups are needed. Fourth, the necrotic areas that developed within the tumoural tissue were measured by evaluating them together with the lesion in the parameter measurements. However, it was thought that heterogeneous tumoral structure parameters could be evaluated. All these limitations should be considered before generalizing our data to society.

Conclusions

All together these results domonstrate that CTPI enables the evaluation of the hemodynamic response of HCC lesions after TARE treatment. BV, TTS and HPI values are useful measures for evaluating early TARE treatment response. Perfusion parameters may be effective in treating HCC lesions by helping to predict the TARE treatment response in the early stages.

Conflict of Interest

The Authors declare that they have no conflict of interests. Ela Kaplan and Selçuk Kaplan have no financial or proprietary interest in any instrument or product used in this study.

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Authors' Contribution

Ela Kaplan; Data collection, analysis and evaluation, main layout of the manuscript; Selçuk Kaplan; Statistical analysis, manuscript organization and language support.

References

1) El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012; 142: 1264-1273.e1.
2) Kennedy A, Coldwell D, Sangro B, Wasan H, Salem R. Integrating radioembolization ((90)Y microspheres) into current treatment options for liver tumors: introduction to the international working group report. Am J Clin Oncol 2012; 35: 81-90.
3) Sangro B, Iñarrairaegui M, Bilbao JI. Radioembolization for hepatocellular carcinoma. J Hepatol 2012; 56: 464-473.
4) Spina JC, Hume I, Pelaez A, Peralta O, Quadrelli M, Monaco RG. Expected and unexpected ımaging findings after 90 Y transarterial radioembolization for liver tumors. Radiographics 2019; 39: 578-595.
5) Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010; 30: 52-60.
6) Patella F, Pesapane F, Fumarola E, Zannoni S, Brambillasca P, Emili I, Costa G, Anderson V, Levy EB, Carrafiello G, Wood BJ. Assessment of the response of hepatocellular carcinoma to interventional radiology treatments. Future Oncol 2019; 15: 1791-1804.
7) Lee JS, Choi HJ, Kim BK, Park JY, Kim DY, Ahn SH, Han KH, Baek SE, Chung YE, Park MS, Kim MJ, Rhee H, Kim SU. The modified response evaluation criteria in solid tumors (RECIST) yield a more accurate prognoses than the RECIST 1.1 in Hepatocellular Carcinoma Treated with Transarterial Radioembolization. Gut Liver 2020; 14: 765-774.
8) Amorim J, França M, Perez-Girbes A, Torregrosa A, Martí-Bonmatí L. Critical review of HCC imaging in the multidisciplinary setting: treatment allocation and evaluation of response. Abdom Radiol (NY) 2020; 45: 3119-3128.
9) García-Figueiras R, Goh VJ, Padhani AR, Baleato-González S, Garrido M, León L, Gómez-Caamaño A. CT perfusion in oncologic imaging: a useful tool? AJR Am J Roentgenol 2013; 200: 8-19.
10) Kim SH, Kamaya A, Willmann JK. CT perfusion of the liver: principles and applications in oncology. Radiology 2014; 272: 322-344.
11) Su TH, He W, Jin L, Chen G, Xiao GW. Early response of hepatocellular carcinoma to chemoembolization: volume computed tomography liver perfusion ımaging as a short-term response predictor. J Comput Assist Tomogr 2017; 41: 315-320.
12) Marquez HP, Karalli A, Haubenreisser H, Mathew RP, Alkadhi H, Brismar TB, Henzler T, Fischer MA. Computed tomography perfusion imaging for monitoring transarterial chemoembolization of hepatocellular carcinoma. Eur J Radiol 2017; 91: 160-167.
13) Reiner CS, Morsbach F, Sah BR, Puippe G, Schaefer N, Pfammatter T, Alkadhi H. Early treatment response evaluation after yttrium-90 radioembolization of liver malignancy with CT perfusion. J Vasc Interv Radiol 2014; 25: 747-759.
14) Morsbach F, Sah BR, Spring L, Puippe G, Gordic S, Seifert B, Schaefer N, Pfammatter T, Alkadhi H, Reiner CS. Perfusion CT best predicts outcome after radioembolization of liver metastases: a comparison of radionuclide and CT imaging techniques. Eur Radiol 2014; 24: 1455-1465.
15) Reiner CS, Gordic S, Puippe G, Morsbach F, Wurnig M, Schaefer N, Veit-Haibach P, Pfammatter T, Alkadhi H. Histogram analysis of CT perfusion of hepatocellular carcinoma for predicting response to transarterial radioembolization: value of tumor heterogeneity assessment. Cardiovasc Intervent Radiol 2016; 39: 400-408.
16) Spina JC, Hume I, Pelaez A, Peralta O, Quadrelli M, Garcia Monaco R. Expected and unexpected ımaging findings after 90Y transarterial radioembolization for liver tumors. Radiographics 2019; 39: 578-595. doi: 10.1148/rg.2019180095.
17) Miyayama S, Matsui O, Zen Y, Yamashiro M, Hattori Y, Orito N, Matsui K, Tsuji K, Yoshida M, Sudo Y. Portal blood supply to locally progressed hepatocellular carcinoma after transcatheter arterial chemoembolization: Observation on CT during arterial portography. Hepatol Res 2011; 41: 853-866.

18) Ippolito D, Querques G, Okolicsanyi S, Franzesi CT, Strazzabosco M, Sironi S. Diagnostic value of dynamic contrast-enhanced CT with perfusion imaging in the quantitative assessment of tumor response to sorafenib in patients with advanced hepatocellular carcinoma: a feasibility study. Eur J Radiol 2017; 90: 34-41.

19) Morsbach F, Pfammatter T, Reiner CS, Fischer MA, Sah BR, Winklhofer S, Klotz E, Frauenfelder T, Knuth A, Seifert B, Schaefer N, Alkadhi H. Computed tomographic perfusion imaging for the prediction of response and survival to transarterial radioembolization of liver metastases. Invest Radiol 2013; 48: 787-794.

20) Borgheresi A, Gonzalez-Aguirre A, Brown KT, Getrajdman GI, Erinjeri JP, Covey A, Yarmohammadi H, Ziv E, Sofocleous CT, Boas FE. Does enhancement or perfusion on preprocedure CT predict outcomes after embolization of hepatocellular carcinoma? Acad Radiol 2018; 25: 1588-1594.

21) Marquez HP, Karalli A, Haubenreisser H, Mathew RP, Alkadhi H, Brismar TB, Henzler T, Fischer MA. Computed tomography perfusion imaging for monitoring transarterial chemoembolization of hepatocellular carcinoma. Eur J Radiol 2017; 91: 160-167.

22) Ippolito D, Fior D, Bonaffini PA, Capraro C, Leni D, Corso R, Sironi S. Quantitative evaluation of CT-perfusion map as indicator of tumor response to transarterial chemoembolization and radiofrequency ablation in HCC patients. Eur J Radiol 2014; 83: 1665-1671.

23) Adcock CS, Florez E, Zand KA, Patel A, Howard CM, Fatemi A. Assessment of treatment response following Yttrium-90 transarterial radioembolization of liver malignancies. Cureus 2018; 10: e2895.