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Original Article

# CT perfusion in hepatocellular carcinoma: Is it reliable?

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ABSTRACT

*Background:* Ninety percent of hepatic cancers are hepatocellular carcinomas (HCC) which have an unfavorable prognosis. HCC is a hypervascular tumor supplied mainly by the hepatic artery. It has a higher blood supply than the surrounding hepatic tissue due to neovascularization. Computed tomography with perfusion imaging (CTP) is a non invasive tool which quantifies the blood flow parameters of HCC and compares it to the surrounding tissue.
*Purpose:* To prove that CTP is a valuable diagnostic tool in diagnosis of HCC and posttherapeutic assessment.
*Patients and methods:* One hundred and twenty-six HCC patients with 150 focal lesions are enrolled this study. Perfusion parameters are quantified and results are compared to those of triphasic CT.
*Results:* CTP detected 141 lesions with 94% sensitivity and 40% specificity with elevated arterial perfusion (AP) and perfusion index (PI) with low portal flow (PF). It missed 5 lesions because of their hypovascularity and 4 lesions following radiofrequency ablation (RFA) and trans arterial chemo embolization (TACE).
*Conclusion:* CTP is a safe and specific imaging tool for diagnosis and assessment of therapeutic interventional procedures in HCC.


## 1. Introduction

HCC is recognized as one of the most common malignancies worldwide. At initial diagnosis, 80% of lesions are irresectable. HCCs are hypervascular tumors with the extent of neovascularization directly proportionate to the disease progress and prognosis. Thus, the evaluation of the tumor angiogenesis is of paramount importance in disease management [1].

The different imaging modalities like classic CT, magnetic resonance imaging (MRI) and ultrasonography (US) are not sufficient for assessment of pathologic angiogenesis [2]. CTP is a safe method that assesses the tumor angiogenesis quantitatively using different aspects [1].

The available literature supports the assumption that maximum tumoral contrast enhancement and blood volume on CTP is directly proportionate to the presence of vascular endothelial growth factor and microvascular network in different tumors [3].

Dynamic assessment is useful in liver cirrhosis, liver neoplasms, and infective diseases of the liver. Perfusion aspects are markedly changed when normal hepatic tissue is compared to pathologic tissue. Parameters such as blood flow, volume and permeability values are increased due to the associated neovascularization [4].

CTP is also valuable in assessment of the tumor response to anti cancer treatment where it fully demonstrates changes in hepatic perfusion, HPI, AP, PP, tissue blood volume (BV) and time to peak (TTP) [5].

### Purpose of this study

The objective of this study is to demonstrate the value of 320 MDCT perfusion methods as a reliable tool in diagnosis of HCC and related therapeutic effects and recurrence.

## 2. Patients and methods

### 2.1. Patients

This is a retrospective study conducted on 126 patients who are known to have HCC. The patients' age ranged from 40 to 79 years (median 60 years); 80 patients were males and 46 were females.

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The study was conducted during the period from November 2015 till December 2016 and approved by the local research ethical committee at the Faculty of Medicine, Ain Shams University.

**Inclusion criteria:**

- Any patient above 40 years.
- Known patients with HCC.
- HCC patients coming for post therapy (RFA and TACE) assessment.

**Exclusion criteria:**

- Children.
- Lactating and pregnant women.
- Any patient having a contraindication to contrast medium.

**All cases were subjected to the following:**

- Written consent was taken from all patients.
- Full clinical assessment including; recording of age, sex and clinical presentation.
- Laboratory investigations (liver biochemical profile, renal function tests, Alpha Feto Protein (AFP)).
- Revision of the previous histopathological results **(The gold standard in our study)** and radiological investigations (US, triphasic CT, ± MR perfusion) done for the patients.
- CTP as a retrospective study and the results were compared to laboratory, histopathology and findings of triphasic CT done 4–6 weeks before CTP for all patients.

### *2.2. Methods*

#### *2.2.1. Triphasic CT protocol of the liver*

The study was conducted using a CT scanner TOSHIBA Aquilion ONE 320-DE MDCT. The patient was instructed to fast for 4 h before the scan. An 18G or 16G IV cannula was introduced in the right antecubital vein. The patient was positioned as in a regular abdominal CT scan (supine and feet first). Scanning is performed at 120 kvp and 200–250 mAs. The maximum dose of IV contrast is 80–100 (1.5 ml/kg body weight). Image acquisition started after IV contrast injection, arterial phase scanning started after a delay of 20–40 ss, portovenous phase scanning started after a delay of 60–90 ss, and delayed phase scanning started after a delay of 2–5 mins. The enhancement pattern of each lesion was assessed in each phase and the lesions were classified according to its degree and pattern of enhancement.

#### *2.2.2. CTP protocol*

The study was conducted using the same CT scanner as the triphasic CT with the same patient preparation.

A. **Liver perfusion test bolus:**

Lateral and AP scouts were obtained. The test bolus slice was set at the hepatic hilum or at the center of D12. The contrast injection protocol was set (CTP necessitates the use of iodinated concentration of at least 350 mg/dl). Scanning began with injection at the same time. The test bolus scans were analyzed and the contrast medium entry time in the aorta was established, as needed for the perfusion protocol.

B. **Liver perfusion scan protocol:**

The scanning parameters are: 100 kv, 60 mA, rotation time: 0.5 s, sample time: 2–30 and acquisition interval: 2. AP and lateral scouts were obtained. The dynamic volume sequence was set to include the liver (16 cm in 320-detector row CT). The beginning of the first image element was determined to start 4 s before the contrast entry time in the aorta as adapted from the test bolus. It was obtained by sharply moving the site of the first image to the accurate beginning time in the time sequence display screen. Rapid injection rate of the contrast was vital with a saline flush to ensure that the contrast reaches the heart quickly. Table 1 lists the dose and contrast injection rate in relation to the body weight.

**Table 1**
Dose and contrast injection rate in relation to the body weight.

| Body weight (kg) | Injection rate (mL/s) | Contrast volume (mL) | Saline flush (mL) |
|---|---|---|---|
| <50 | 6.0 | 30 | 30 |
| 50–69 | 7.0 | 35 | 30 |
| 70–89 | 8.0 | 40 | 30 |
| 90+ | 10 | 50–80 | 40 |

After injection and imaging were synchronized, 23 volumes were obtained and reconstructed. This protocol is used to determine both the hepatic arterial and portal venous blood supply of the hepatic parenchyma.

C. **Image Post-Processing:**

The acquired data and perfusion scans were moved to **Vitrea workstation™**.

**Body registration for the liver:**

Registration was vital so that the volumes were aligned properly and to minimize the drawbacks of breathing motion between volumes.

**Liver perfusion analysis:**

- **Analysis algorithm:** Dual Input Maximum Slope.
- **Analysis Range:** Soft tissue.

The liver has a double blood supply, so the Dual Input Maximum Slope algorithm was utilized for perfusion analysis. Region of interests (ROIs) were positioned in the aorta, portal veins, normal hepatic tissue and spleen. The color coded parametric maps are plotted and simultaneously a set of **AF**, **PF** and **PI** volumes corresponding to the **TAC's** (tissue attenuation curves).

Serial rapid CT scans were obtained at the same site to determine **TAC** and measurement of **HPI.**

In case of several tumors, ROIs were plotted for all lesions, and a mean value from all of them was taken for analysis. Background ROIs are plotted in liver tissue and spleen. They are plotted far from the tumor. Perfusion parameters of tumor(s), background liver, and spleen are then measured.

**Statistical analysis:**

Data were analyzed using Statistical Program for Social Science (SPSS) version 18.0. Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

*The following tests were done:*

- Sensitivity, Specificity, PPV (positive predictive value), NPV (negative predictive value)
- Probability (P-value)
  - P-value < 0.05 was considered significant.

## 3. Results

One hundred twenty-six patients were included in this study. The patients' age ranged from 40 to 79 years and mean of 46.33 ± 5.75 years, 80 patients were males and 46 patients were females.

HCC was proven histopathologically and it was used as the gold standard in this study.

The histopathological diagnosis was unavailable in 3 cases (4 focal lesions), but the diagnosis was established through typical findings noted on serial imaging in addition to the clinical and laboratory findings that were in line with HCC (Fig. 1).

Fifteen patients (11.9%) had multicenteric HCC. Thirty-seven (29.3%) patients had well differentiated HCC, 75 (59.5%) patients had moderately differentiated HCC, while 14 (11.1%) patients had poorly differentiated HCC.

According to Child's classification, patients were classified into 3 groups as listed in Table 2.

The results of AFP for all patients are listed in Table 3.

The results of the triphasic CT and CT perfusion are listed in Tables 4 and 5.

CTP was able to detect 94% of the lesions in comparison to triphasic CT which only detected 80% of the lesions denoting its inferiority to CTP.

**Table 2**
Liver function distribution of the study group.

| Liver function | Number | Percentage |
|---|---|---|
| Child (A) | 93 | 73.81 |
| Child (B) | 30 | 23.81 |
| Child (C) | 3 | 2.38 |
| Total | 126 | 100.00 |

**Table 3**
AFP results of the study group.

| AFP | Number | Percentage |
|---|---|---|
| Less than 200 ngm/ml | 39 | 30.95 |
| More than 200 ngm/ml | 87 | 69.05 |
| Total | 126 | 100.00 |

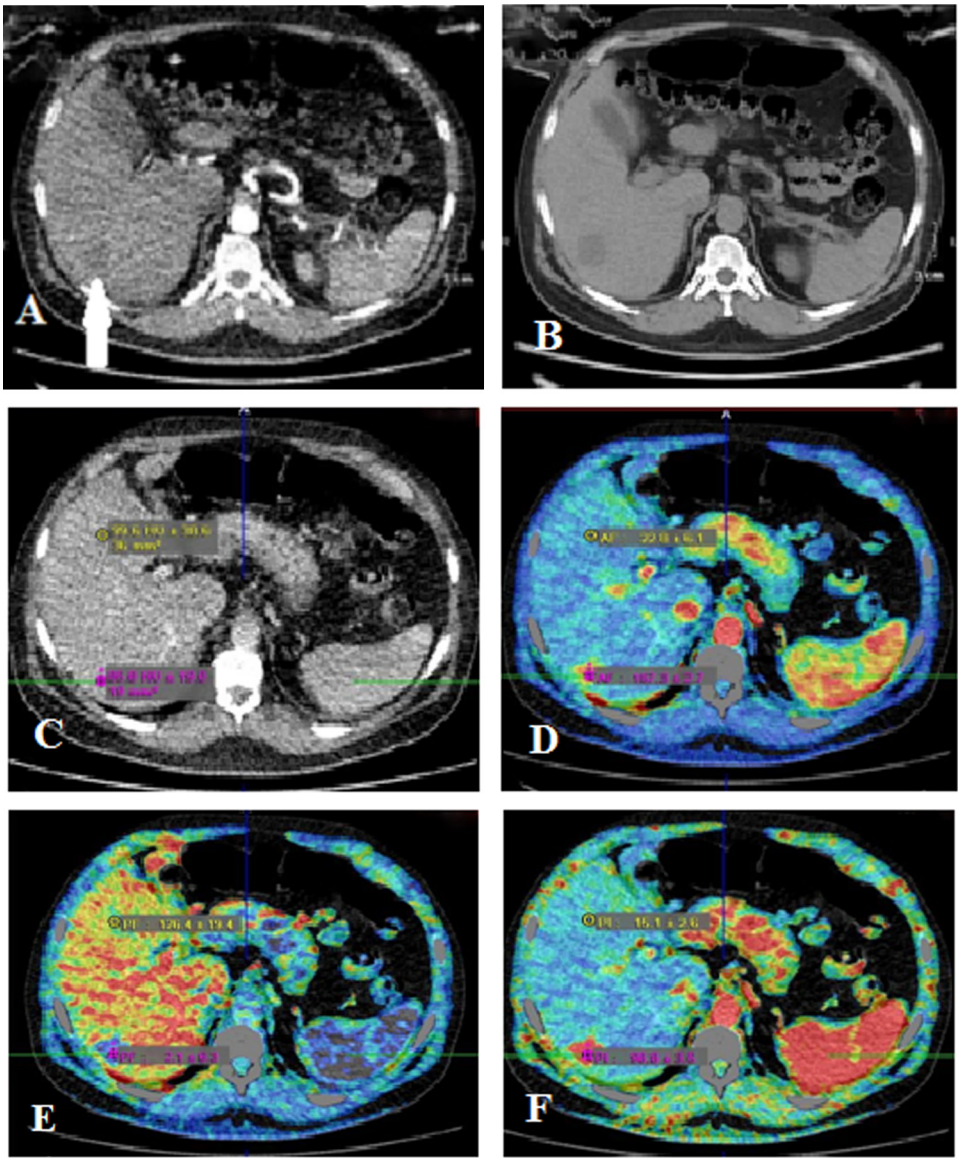


**Fig. 1.** Triphasic CT examination shows segment VII focal lesion (white arrow) with faint arterial enhancement in **A** and delayed contrast washout in delayed phase in **B. C-F**: **CTP shows** CT attenuation value of the focal lesion in first pass perfusion of contrast displays nearly the same attenuation value of the normal hepatic parenchyma (focal lesion = 85.6 HU, surrounding parenchyma = 99.6 HU), with high **(AF) in D**, low **(PF) in E** with high **(PI) in F** in relation to the surrounding hepatic parenchyma evident by the color mapping. **Diagnosis:** Right hepatic lobe HCC.

**Table 4**
Triphasic results distribution of the study group.

| Triphasic CT results | Number of lesions | Percentage |
|---|---|---|
| Indeterminate lesions | 30 | 20.00 |
| Visible lesions | 120 | 80.00 |
| Total | 150 | 100.00 |

**Table 5**
Perfusion parameters distribution of the study group.

| CTP parameters | Number of lesions | Percentage |
|---|---|---|
| Positive | 141 | 94.00 |
| Negative | 9 | 6.00 |
| Total | 150 | 100.00 |

Twenty patients (15.8%) had regional interventional procedures (13 patients had RFA and 7 patients had TACE) and were coming for post therapy assessment (Figs. 2–4). They had 26 focal lesions, conventional triphasic CT missed the true diagnosis in 19 lesions while CTP missed 4 lesions. Sensitivity and specificity of triphasic CT are 41.6% and 36.8% respectively while those of CTP are 90% and 50% respectively.

If these 20 cases (26 focal lesions) are excluded from the whole study group, triphasic CT only missed 11 cases from the remaining 124 focal lesions with 91% true positive lesions which are shown in Table 6.

This means that CTP has similar results to triphasic CT in HCC lesions which weren't submitted to RFA and TACE.

Perfusion parameters didn't markedly change according to the degree of differentiation of HCC. We didn't thoroughly investigate this entity as it was beyond the scope of our study. CTP parameters are listed in Table 7.

The overall diagnostic performance of both Triphasic CT and CTP is listed in Table 8 showing the superiority of CTP to triphasic CT.

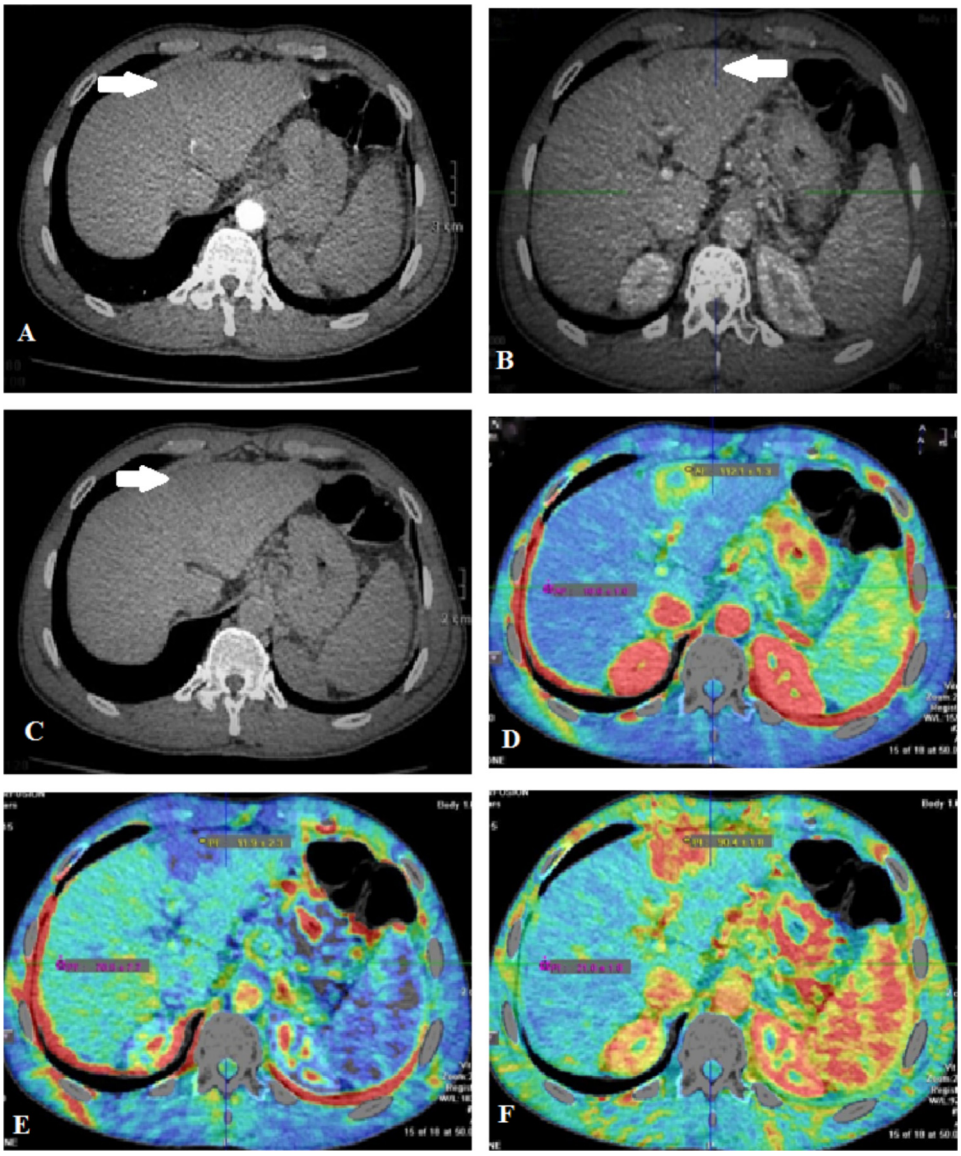


**Fig. 2.** Triphasic CT examination shows **(A)** arterial, **(B)** venous and **(C)** delayed phases for segment II post-RFA ill defined hypodense lesion with no significant contrast uptake in arterial phase, faint peripheral uptake in venous phase and washout of contrast in delayed phase (inconclusive). **CTP** in axial planes shows a fairly defined left lobe segment **(II)** focal area with high **(AF) in (D),** low **(PF) in (E)** with high **(PI) in (F)** in relation to the surrounding hepatic parenchyma. **Diagnosis**: peripheral active neovascularization with suspected tumoral activity (recurrence/residual) in left hepatic lobe HCC after RFA.

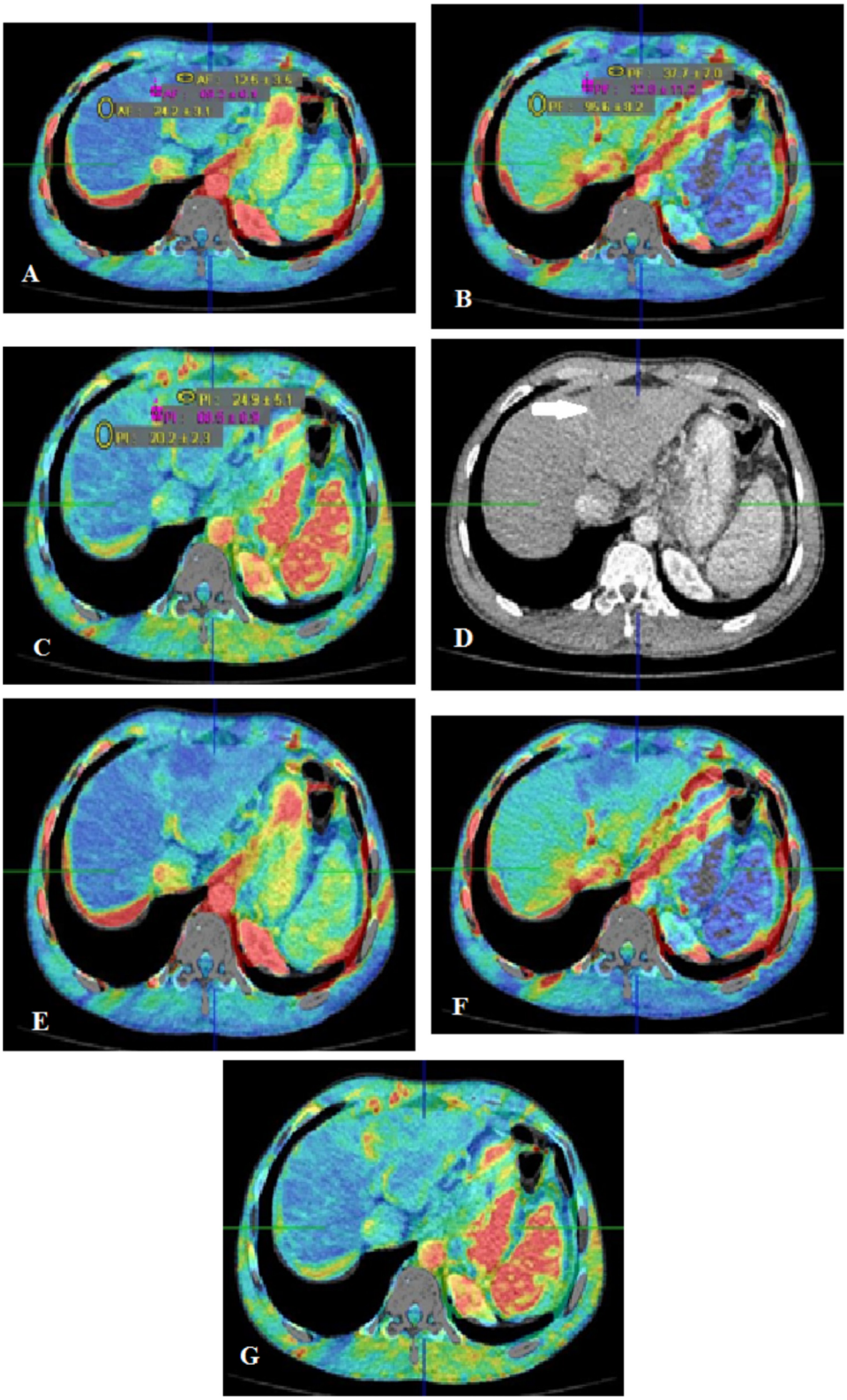


**Fig. 3.** CTP is done 6 months after the RFA. It shows the ablated left hepatic lobe (segment II) area with reduced **AF** in **(A)** as well as **PF in (B)** with low **PI in (C)** in relation to the surrounding hepatic parenchyma; **(D-F)**: same images without the perfusion parameters showing the poorly perfused left hepatic lobe area after the RFA; **(D)** the hepatic CT density (white arrow), **(E) AF**, **(F) PF** and **(G) PI** in color mapped images. **Diagnosis:** post RFA for left hepatic lobe HCC with no active tumoral tissues or recurrent lesions.

The overall CTP parameters of tumoral tissue comapared to surrounding non tumoral tissue are listed in Table 9. It is clear that **AP** and **HPI** are elevated and **PF** is lowered in tumoral tissue compared to non tumoral tissue.

## 4. Discussion

It has been almost 25 years since Miles et al. have depicted the value of liver CTP and since then, it was getting popular clinically

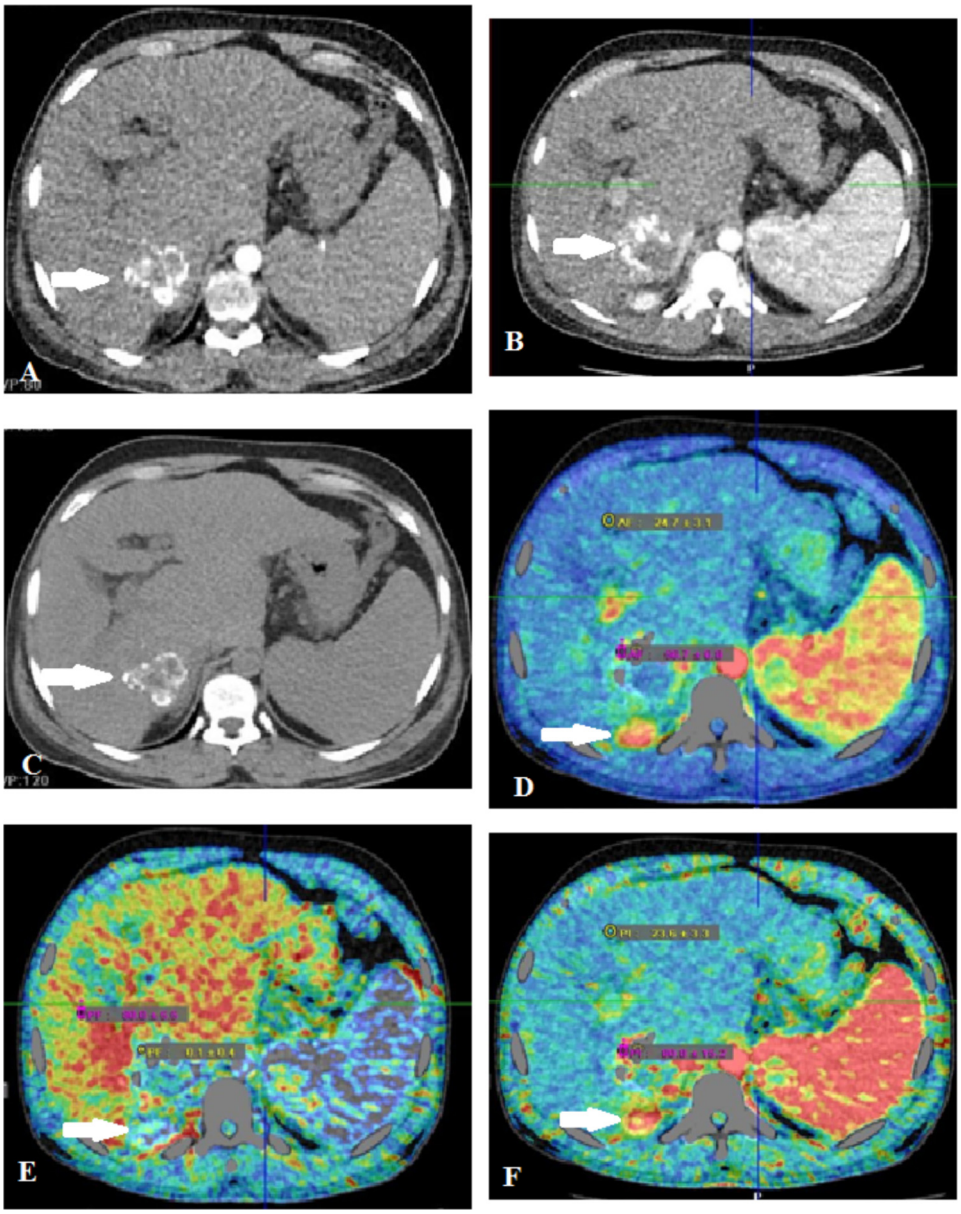


**Fig. 4.** Triphasic CT examination: **(A), (B)** and **(C)** are the arterial, venous and delayed phases respectively showing segment VII focal lesion with dense lipidiol material and no definite enhancement pattern in arterial, venous or delayed phases (white arrow). **CTP** shows peripheral active tumoral tissue (white arrow) seen with high **AF** in **(D),** low **PF (E)** and high hepatic PI in **(F)** in comparison to the surrounding hepatic tissue. **Diagnosis:** residual/recurrent right hepatic lobe segment VII HCC after TACE.

**Table 6**
Triphasic results distribution of the remaining study group after exclusion of patients coming for post therapy (RFA & TACE) assessment.

| Lesions | Triphasic CT | Percentage |
|---|---|---|
| Indeterminate | 11 | 9% |
| Visible | 113 | 91% |
| Total | 124 | 100% |

**Table 7**
Mean CTP parameters according to the degree of differentiation of HCC.

| CTP parameters | Well differentiated HCC | Moderately differentiated HCC | Poorly differentiated HCC |
|---|---|---|---|
| Mean AP | 113 ± 45.4 | 108 ± 39.6 | 111 ± 41.7 |
| Mean PF | 44.7 ± 32.4 | 43.3 ± 33.2 | 42.3 ± 36.3 |
| Mean HPI | 68.4 ± 22.2 | 69.3 ± 20.2 | 67.2 ± 22.3 |

**Table 8**
Diagnostic Performance of triphasic results and perfusion parameters in the discrimination of the patients' group.

| | Triphasic CT results | CTP parameters |
|---|---|---|
| Positive | 120 | 141 |
| Negative | 30 | 9 |
| Sensitivity | 80% | 94% |
| Specificity | 6% | 40% |
| PPV | 45.98% | 61.04% |
| NPV | 23.08% | 76.72% |
| Accuracy | 43% | 77% |
| p-value | <0.001 (HS) | <0.001 (HS) |

*HS = highly significant.

**Table 9**
Descriptive data of CTP parameters in the study group.

| CTP parameters | Range | Mean ± SD | Median (IQR) |
|---|---|---|---|
| AF | | | |
| N | 16–67 | 33.1 ± 11.1 | 31 (14) |
| T | 9–210 | 122.9 ± 46.9 | 127 (68.25) |
| PF | | | |
| N | 16–184 | 107.5 ± 44.5 | 110 (81.25) |
| T | 0–157 | 44.58 ± 38.24 | 30.5 (45.5) |
| PI | | | |
| N | 14–81 | 28.0 ± 13.2 | 22.5 (18) |
| T | 11–106 | 70.2 ± 25.1 | 75 (35) |

*N = surrounding liver tissue, T = tumoral tissue.

as an imaging tool of hepatic neoplasms. Its available clinical value includes early tumor detection, follow up of disease outcome, assessment of different treatment protocols and early detection of tumor recurrence [6].

In this study, most of HCC lesions were hypervascular and associated with early arterial enhancement with high **AF** and **PI**s and relatively low **PF** index in comparison to the surrounding non tumoral hepatic tissues. The parameters were adjusted by drawing two ROIs within the tumoral tissues and the surrounding liver.

This high **AF** and **PI** parameters in CTP is typically characteristic for hypervascular HCC lesions. Ippolito et al. demonstrated the same results with significantly increased **AF** and **PI** and significantly decreased **PF** in HCCs compared with adjacent hepatic parenchyma [1].

The available literature suggests that **AP** and **HPI** can be reliable for the assessment of neovascularization promoted by tumor proliferation as **AP** depicts the changes in vascularity with evolution of single arteries. **BV** is less reliable than **HPI** and **AP** as it depends on the presence of hepato-portal shunts which commonly occurs in cirrhotic livers [1].

Our study is consistent with both Ippolito et al. and Yang et al. who depicted that perfusion parameters didn't change significantly according to the degree of differentiation of HCC. Thus, they assumed that CT perfusion cannot be relied on to differentiate between well and poorly differentiated HCC [1,7].

But, our results were not in line with Sahani et al., 2007 who deduced that perfusion parameters of well differentiated HCC are different from other types of HCC [2].

In addition, our results were in line with the expected pathological process of the disease where **AP** is increased on the expense of **PF** which is expected to occur in neoplastic angiogenic processes of hepatic nodules [8].

CTP was able to depict 141 lesions from 150 lesions with sensitivity of 94% and specificity of 40%, while triphasic CT was able to successfully depict 120 lesions with 30 lesions being indeterminate. However, if focal lesions submitted to RFA and TACE are excluded from the results, the percentage of true positive lesions detected by both triphasic CT is increased (Table 6).

CTP also has a vital role in early detection of recurrent tumors following different imaging-guided procedures for both primary and secondary liver tumors [9].

Also, Ippolito et al., concluded that CTP is a reliable technique for assessment of post RFA and TACE where the perfusion parameters were accurate and specific and were able to differentiate between successfully and unsuccessfully treated lesions [10].

This was evident in our study as CTP was able to inspect the treatment response after RFA and/or TACE with high sensitivity 90% and specificity of 50% in some patients showing marked reduction in tumor angiogenesis followed by decreased perfusion parameters after interventional procedures (Figs. 2–4).

In such cases; the gold standard was the follow up by clinical, laboratory and imaging tools which revealed the reduced tumoral activity over time.

However, the available literature about the value of CTP in evaluating tumor recurrence after local interventional procedures is still controversial. Choi et al. analyzed that CTP wasn't able to depict future recurrence when it was done one week after TACE for lesions that showed recurrence 4 weeks after TACE [11].

Currently, Shao et al., had conducted a large study on 522 HCC patients who were submitted to locoregional procedures and were assessed by diffusion weighted MRI and CTP. They resolved that both MRI and CTP have a moderate value in assessment of treatment response [12].

We couldn't thoroughly analyze this hypothesis as only 20 patients presented in our study for assessment after interventional procedures. Larger study population is needed for further analysis of CTP in this entity.

CTP missed 9 lesions in our study, 5 of them were attributed to hypovascularity of the lesions and the remaining 4 lesions were under assessment after TACE and RFA where CTP parameters couldn't confirm recurrence or regression of the disease.

On the other hand, triphasic CT missed 30 lesions, 19 of them were in patients coming for post RFA and TACE assessment. Its sensitivity, specificity, PPV and NPV were lower than CTP, thus confirming the superiority of CTP.

Using the conventional triphasic CT, it is sometimes difficult to early depict local tumor recurrence around RFA or a nodule injected by lipidiol as tumor recurrence might be confused with the usual hyperemic changes surrounding RF- ablated region and also as HCC recurrence surrounding a lipiodolized nodule can be hidden by streaking artifacts created by high density of lipiodol [13].

CTP has the privilege that contrast enhancement is parallel to contrast accumulation in tissues which is of paramount importance in quantitative evaluation of perfusion parameters. Moreover, CTP offers a better temporal and spatial resolution which is of high value in inspection of perfusion and anatomical changes [14].

Hazards of ionizing radiation are usually limited by reduction of scanning time and improvement in detectors' quality as reported by Okada et al. [15].

Pathologic diagnosis was not available for 3 patients. However these lesions showed specific diagnostic imaging findings unchanged on serial imaging. Laboratory, clinical and radiological evaluation of these lesions did not require histopathological confirmation.

As a valuable non-invasive tool, CTP is safe, easily implemented and easily operated. Whole liver perfusion is no more a dream due to the implementation of multi-slice CT (320 MDCT which obtains nearly most of the liver in one volume).

Hepatic CTP is a valuable diagnostic tool for identifying primary or secondary neoplasms, and for inspecting tumor recurrence after local interventional procedures.

## 5. Conclusion

We conclude that hepatic CTP has introduced a new era for its clinical utility. A single CT scan can offer both anatomical and functional data, so that physicians can identify the disease before anatomical changes occurred and assess the therapeutic regimen.

CTP is superior to triphasic CT in the detection and treatment assessment in HCC. It can be easily implemented into routine imaging protocols. It definitely can replace triphasic CT.

## Conflict of interest

None.

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