ROLE OF DUAL ENERGY CT LIVER PERFUSION IN DIFFERETIATION OF HEPATOCELLULLARCARCINOMA

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ABSTRACT:

Background*: Purpose of This retrospective study for assessment of hepatic tumor response to the anti-angiogenic drugs via perfusion CT.*

Aim of the work: *To elucidate the role of CT perfusion in characterization and differentiation of hepatic focal lesion and give a true assessment of the hemodynamic status of the liver parenchyma.*

Patients and Methods: This study will be done on patients presenting with proven hepatic focal lesion after abdominal CT with IV contrast media injection, Perfusion parameters collected.

Results: *Our study suggests that perfusion parameters obtained in liver effectively discriminate between ROIs that contain malignant or metastatic lesions from sites containing healthy liver tissues.*

Moreover, the resulting characteristics are potentially useful for prognostication and staging, since it has been demonstrated that tumors exhibiting high vascularity tend to be more aggressive and respond poorly to chemotherapy and radiation therapy.

Conclusion: *CT perfusion imaging of the liver provides functional information about the microcirculation of normal parenchyma and focal liver lesions and is a promising technique for assessing the efficacy of various anticancer treatments.*

Keywords: *CT perfusion. Hepatocellular carcinoma (HCC). anticancer treatments. primary tumors. metastatic tumors. anti-angiogenic drugs. neo-vasculature angiogenesis.*

INTRODUCTION:

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide and it most often occurs in patients with pre-existing cirrhosis or chronic hepatitis. HCCs are highly vascular and derive neo-vasculature through the process of angiogenesis[(1)].

Early detection of HCC and pre-malignant dysplastic nodules has implication on the management options of tumor ablation, liver resection and trans-plantation[(2)].

Imaging plays a Crucial role in the management of hepatic malignancies, including screening populations at risk, confirming the diagnosis, planning treat-ment, guiding therapy, and follow up after treatment. The inherent distortion of the appearance of liver parenchyma by the underlying pathologic changes of cirrhosis can obscure and may simulate malignancy at imaging[(3)].

Patients with chronic liver disease such as hepatitis C are at risk for developing HCC hence they undergo periodic liver screening for focal liver detection. Screening with α-

fetoprotein and US is a useful tool for early diagnosis of HCC.

However, US-based screening for HCC has a suboptimal sensitivity and specificity, especially when liver cirrhosis is present. Hence patients with an abnormal liver US showing cirrhosis or focal mass often undergo a contrast enhanced CT or MRI examination.

Currently, tissue sampling for the evaluation of tumor micro vessel density is considered the most accurate direct marker of angiogenesis. However, tissue sampling is invasive and therefore impractical for longitudinal patient monitoring[(4)].

The liver has a dual blood supply, and changes of blood supply are always caused by liver diseases, so it is important to evaluate the hemodynamic changes to discover the diseases early and assess the therapeutic response. At present, the perfusion imaging techniques of multi-slice CT allow quantification of the perfusion parameters of tissues[(5)].

Regenerative nodules receive most of their blood supply from the portal vein, and the evolution from a low-grade dysplastic nodules to HCC is associated with increased arterial blood supply, mainly due to tumor related arterial neovascularization[(6)].

These hemodynamic and physiological properties can be measured serially using the functional computed tomography perfusion (CTp) technique and multi-parameter imaging maps.

Mathematical methods are used to calculate perfusion parameters.

Perfusion CT is an evolving CT technology which allows functional evaluation of tissue vascularity. Though primarily still used as a research tool, perfusion CT is emerging as a preferred technique for assessment of tumor response to the anti-angiogenic drugs[(1)].

Computer tomographic CTp allows quantitative assessment of various parameters, such as tumor blood flow (BF), blood volume (BV), mean transit time (MTT), and permeability–surface area product (PS)[(5)]Given that functional changes precede morphologic changes after treatment, perfusion CT allows earlier assessment of treatment effect than conventional methods which rely on tumor size[(2)].

AIM OF THE WORK:

To elucidate the role of CT perfusion in characterization and differentiation of hepatic focal lesion and give a true assessment of the hemodynamic status of the liver parenchyma.

PATIENTS AND METHODS:

This study will be done on patients presenting with proven hepatic focal lesion who will be referred by the Hepatology departments of different Hospitals. During dual energy Multi-detector abdominal CT with IV contrast media injection , Perfusion parameters of blood flow (BF), blood volume (BV), arterial perfusion (AP), portal perfusion (PP), and hepatic perfusion index (HPI) will be calculated in the normal liver parenchyma and hepatic focal lesions samples. **All the studied patients were subjected to the following:**

1. Full history taking, thorough clinical examination and laboratory investigations.
2. **CT of the abdomen and pelvis:** using multi-slice CT Toshiba 320 dual processor.
3. **The medical ethics were considered**:

- The patients agreements were obtained and had to get benefit from the examination.
- The feedback of the medical, surgical and histo-pathological data was obtained whenever available.

Inclusion Criteria:

1. Patients over 40years old.

2. Both sexes are included.
3. known patient with hepatic focal lesion.
4. -Average kidney function tests.

Exclusion Criteria:

1. Children.
2. lactating and pregnant females.
3. Allergy to contrast media .

CT perfusion study results

1. AGE

Thirty patients were included in this study. The patient's age was ranging from 40-79 years and mean age of 60-63 years.

Table (1): Age distribution of the study group.

Age (years)	No.	%
≤46 years	8	26.6
>46 years	22	73.3
Range [Mean±SD]	60-63 [46.33±5.75]	

This table shows that patients ≤ 46 years were (57.5%) and >46 years were (42.5%) of the study group.

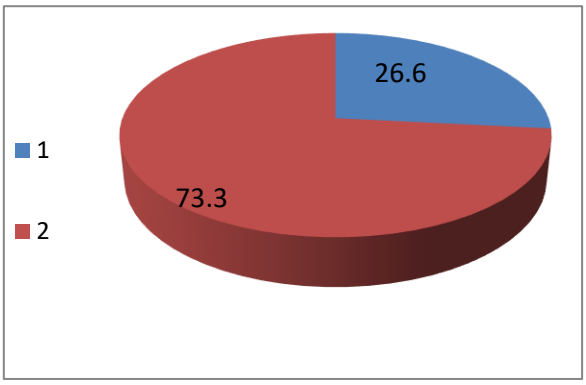


Diagram (1): Piechart of age distribution of the study group.

2.***SEX***

Among the patients; 25 were males and 5 were females.

Table (2): Sex distribution of the study group.

Sex	**No.**	**%**
Female	5	16.6
Male	25	83.3
Total	30	100.00

This table shows that male patients were (83.3%) and female were (16.6%) of the study group.

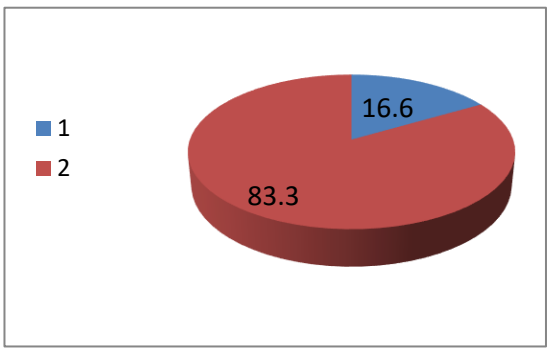


Diagram (2): Piechart of Sex distribution of the study group.

Patient Condition:

1. Child classification:

Table (3): Liver function distribution of the study group.

Liver function	No.	%
Child (A)	19	63.3
Child (B)	9	30
Child (C)	2	6.7
Total	30	100.00

This table shows that Child A patients were (63.3%), Child B were (30%) and Child C were (6.7%) of the study group.

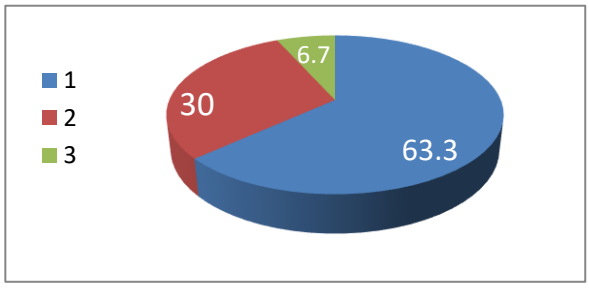


Diagram (3): Piechart of Liver function distribution of the study group.

2. Alpha feto protein:

Table (4): Alpha feto protein distribution of the study group.

Alpha feto protein	No.	%
Less than 200ngm/ml	10	33.3
More than 200ngm/ml	20	66.6
Total	30	100.00

This table shows that patients with α-feto protein level less than 200 were (33.3%) and more than 200 were (66.6%) of the study group.

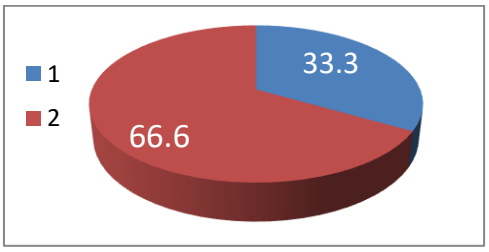


Diagram (4): Pie chart of Alpha feto protein distribution of the study group.

<u>Comparison between of triphasic results and CT perfusion results</u>:

Table (5): Triphasic results distribution of the study group.

Triphasic results	No.	%
Non visible lesion	8	20.00
Visible lesion	32	80.00
Total 83.3	40	100.00

This table shows that triphasic results in non visiblelesions (20%) and visible lesion (80%) of triphasic results.

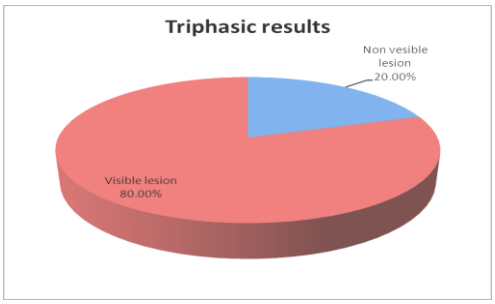


Diagram (5): Pie chart triphasic results distribution of the study group.

Table (6): Perfusion parameters distribution of the study group.

Perfusion parameters	No.	%
Positive	37	92.5
Negative	3	7.5
Total	40	100.00

This table shows that patients were negative (7.5%) and positive (92.5%) in perfusion parameters.

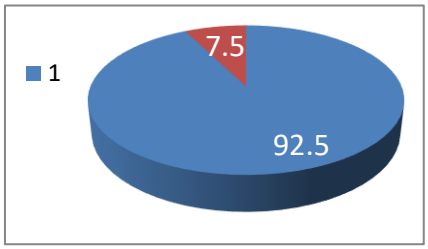


Diagram (6): Pie chart perfusion parameters distribution of the study group.

Table (7): Descriptive data perfusion parameters of the study group. Where the N refers to the normal liver tissue while T refers to the diseased one.

Perfusion 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)
N	14-81	28.0± 13.2	22.5 (18)
T	11-106	70.2± 25.1	75 (35)

Table (8): Diagnostic Performance of triphasic results and perfusion parameters in discrimination of the patients group.

	Triphasic results	Perfusion parameters
Positive	32	37
Negative	8	3
Sensitivity	80%	94%
Specificity	6%	40%
+PV	45.98%	61.04%
-PV	23.08%	76.72%
Accuracy	43%	77%
p-value	<0.001 (HS)	<0.001 (HS)

Case I

Clinical history:55-year-oldmale patient presented with right hypochondrial pain, weight loss and yellowish discoloration of the sclera.

Laboratory investigations: AFP = 76 ng/ml; (normal: up to 5.8 ng/ml).

(*Figure *1).

Triphasic CT examination: cirrhotic liver with right lobe (segment VII) focal lesion with atypical enhancement pattern (showing faint arterial enhancement and delayed washout of contrast in delayed phase)

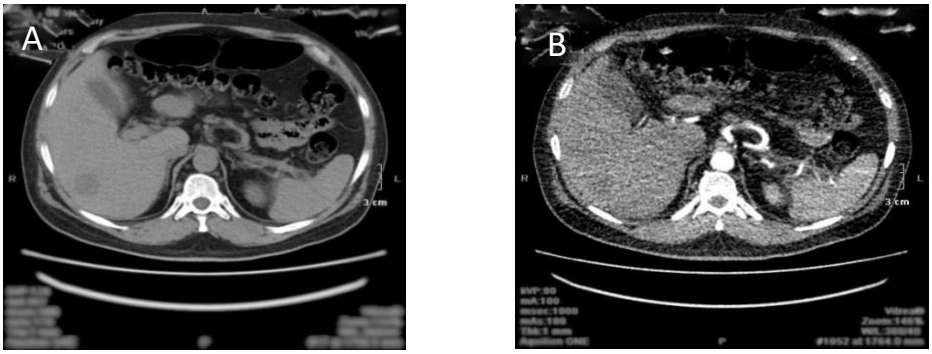


Figure 1*: Explains the arterial and delayed phases in a triphasic CT study for hepatic focal lesion. It shows faint arterial phase f the segment VII right hepatic lobe focal lesion (A), with washout of contrast in the delayed phase (B).*

CT perfusion pattern: a fairly defined right lobe segment (VII) focal lesion with high arterial flow (AF) = 157.3±2.7 ml/min/100ml, low portal flow (PF) = 2.1±6.3ml/min/100ml indices with high hepatic perfusion index (PI) = 98.8±3.5% in relation to the normal hepatic parenchyma; (AF = 22.8±6.1 ml/min/100ml, PF = 126.4±19.4ml/min/100ml and PI = 15.1±2.6%) evident by the color mapping **(Figure *2).***

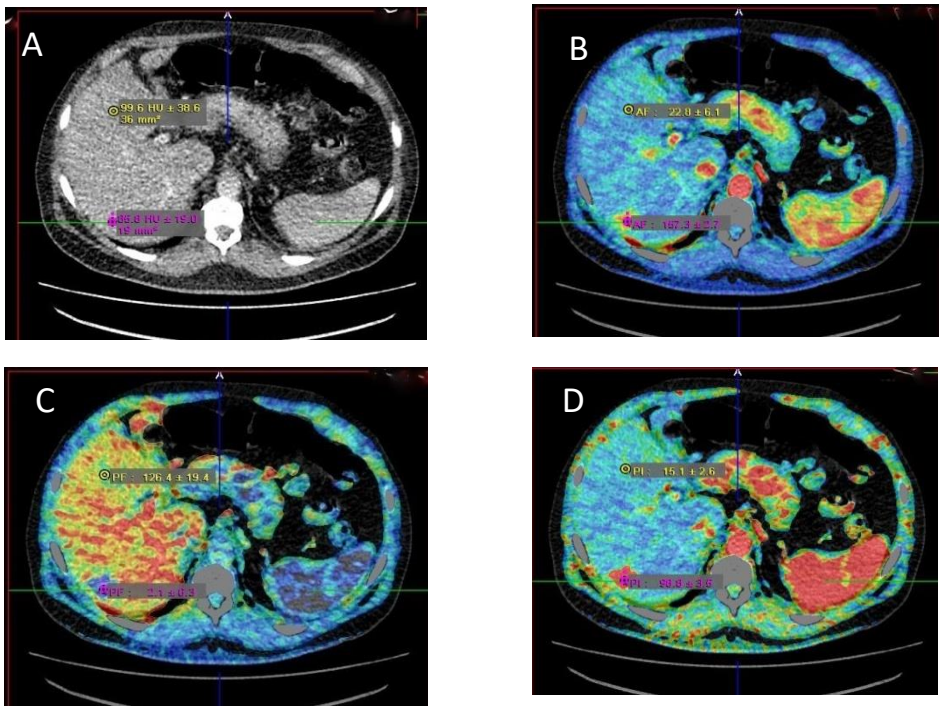


Figure 2*: CT perfusion of the right hepatic lobe focal lesion shows: (A) CT attenuation value of the focal lesion in first pass perfusion of contrast displays nearly the same attenuation value of the normal hepatic parenchyma (focal lesion = 85.6 HU, normal parenchyma = 99.6 HU). (B) High arterial flow (AF) of the focal lesion (157.3 ml/min/100ml). (C) Low portal flow (PF) of the lesion (2.1 ml/min/100ml). (D) Perfusion index of the lesion higher than the normal liver (PI=98.8).*

Diagnosis: Right hepatic lobe HCC.

Case II

Clinical history:59-years-old male patient with liver cirrhosis, weight loss, jaundice and abdominal distension.

Laboratory investigations: AFP: 26 ng/ml.

Triphasic CT examination: cirrhotic liver with multiple right hepatic lobe variable sized subcapsular and lower segment focal lesions with early contrast uptake in arterial phase and rapid washout of contrast in portal and delayed phases ***(*Figure*3).***

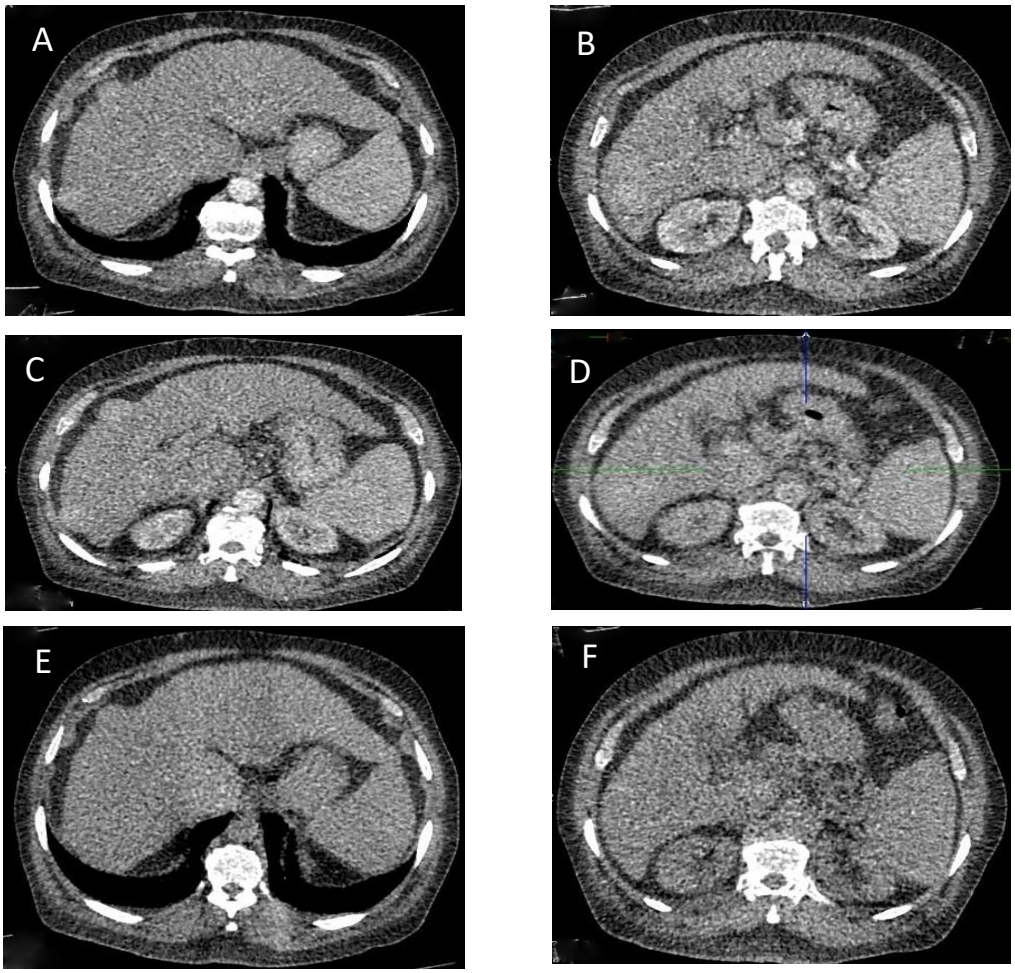


Figure *3:* *Triphasic CT shows: (A & B) two different levels of the liver in arterial phase showing two, right hepatic lobe, early enhancing focal lesions being subcapsular and segment V ill defined area of heterogenous enhancement, (C & D) the same levels in porto-venous phase showing rather same enhancement of the subcapsular lesions with washout of contrast at the segment V one, (E & F) the delayed phase with washout of contrast in all lesions.*

CT perfusion pattern: the perfusion parameters of the multifocal right hepatic lobe lesions show high arterial flow (AF), low portal flow (PF) and high perfusion index

(PI). For example; the right hepatic lobe anterior segment/subcapsular lesion (segment VIII) shows high arterial flow (AF) = 158.1 ± 7.7 ml/min/100ml, low portal flow (PF) = 0.1 ± 0.6ml/min/100ml indices with high hepatic perfusion index (PI) = 100.1 ± 0.3 % in comparison to the normal hepatic parenchyma; (AF = 48.1 ± 4.5 ml/min/100ml, PF = 161.5 ± 15.6 ml/min/100ml and PI = 23.1 ± 3.3 %) as in the color mapped images ***(*Figure*4 and 5).***

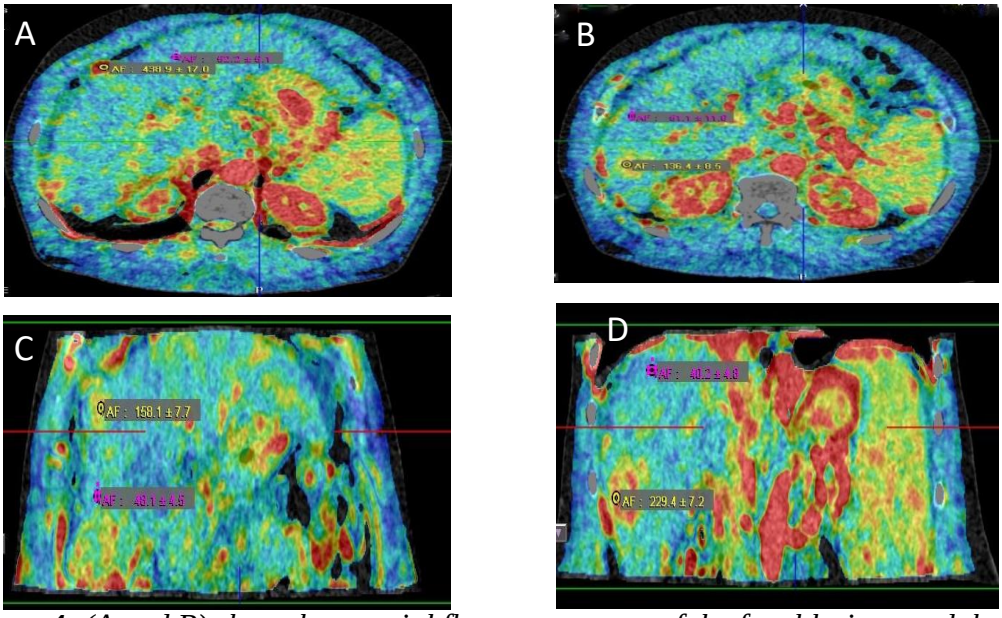


Figure *4 :**(A and B) show the arterial flow parameters of the focal lesions and the hepatic tissue in axial plane (C and D) show the AF in the same areas in coronal images.*

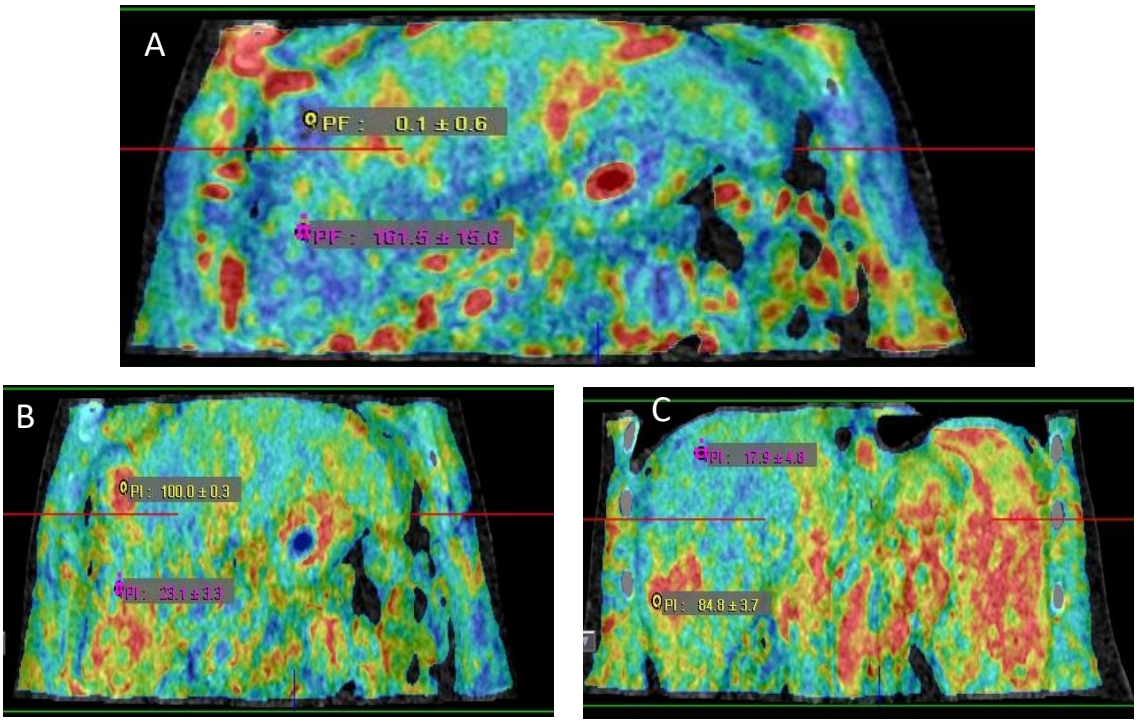


Figure *5 :(A) portal flow (PF) parameter of the right lobe segment VIII subcapsular lesion in comparison with the normal tissue (B and C) show the perfusion index (PI) for the multiple hepatic lesions in coronal reconstructed images.*

Diagnosis:

Right hepatic lobe multifocal HCC

Case III

Clinical history:48-years-old female known patient with right lobe HCC (segment VII) followed by RF ablation.

Laboratory investigations:AFP: 220ng/ml

Triphasic CT examination:early arterial peripheral enhancement seen with sustained enhancement in porto-venous phase and washout of contrast in delayed phase ***(*Figure *6).***

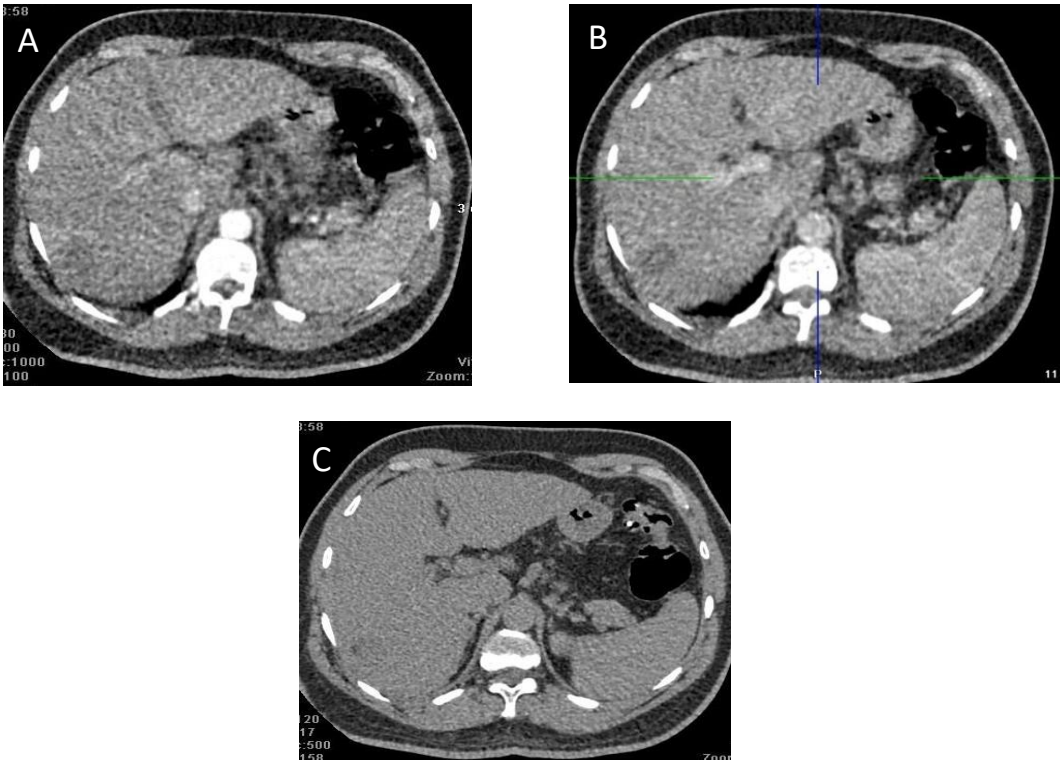
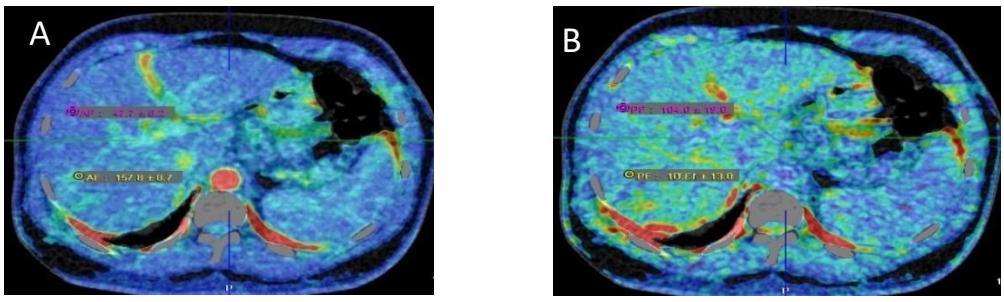


Figure *6:* *Triphasic study for the right lobe (segment VII) post RF ablation showing (A) arterial faint peripheral enhancement with (B) sustained peripheral enhancement in portal phase and (C) washout of contrast in delayed phase.*

CT perfusion pattern: shows the active peripheral tumoral tissue with the characteristic high arterial flow and perfusion index with low portal flow in comparison with the normal (non-tumoral) hepatic tissue. (The diseased tissue AF = 157 ± 8.7 ml/min/100ml, PF = 103.3 ± 13.0 ml/min/100ml with PI = 60.5 ± 2.9 % in relation to the normal hepatic parenchyma; (AF = 47.7 ± 8.2 ml/min/100ml, PF = 104.0 ± 19.0 ml/min/100ml and PI = 31.6 ± 4.5 %) ***(*Figure *7).***



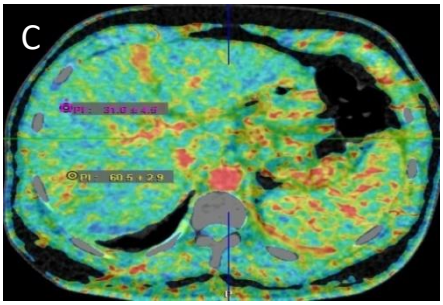


Figure *7:* *showing the CT perfusion parameters in comparison to the hepatic tissue with high AF (A), low PF (B) and high perfusion index PI (C).*

Diagnosis: Post RF ablation for right hepatic lobe; segment VII HCC with active peripheral tumoral tissues (recurrent/residual HCC).

Case IV

Clinical history:44-years-old male known patient with right lobe HCC underwent trans-arterial chemoembolization (TACE).

Laboratory investigations:AFP: 40 ng/ml

Triphasic CT examination:shows right hepatic lobe (segment VII) focal lesion with dense lipidol material and no definite enhancement pattern in arterial, venous or delayed phases ***(*Figure *8).***

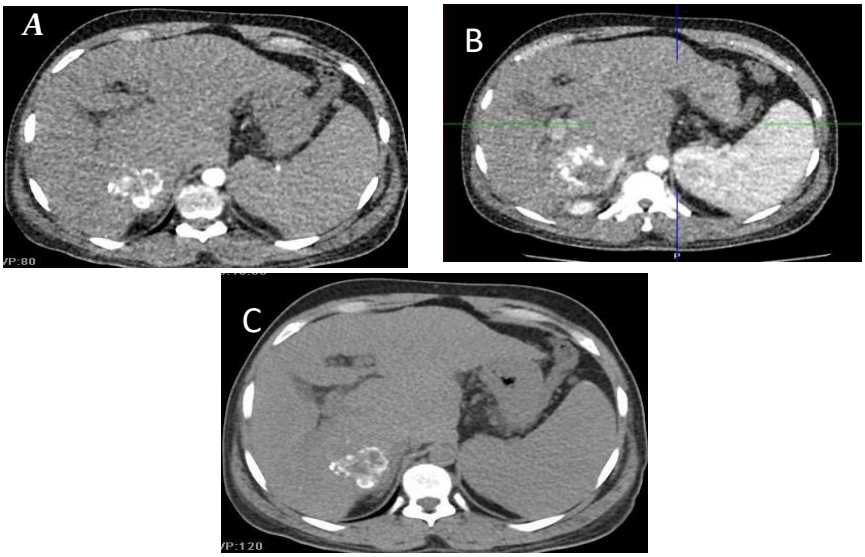
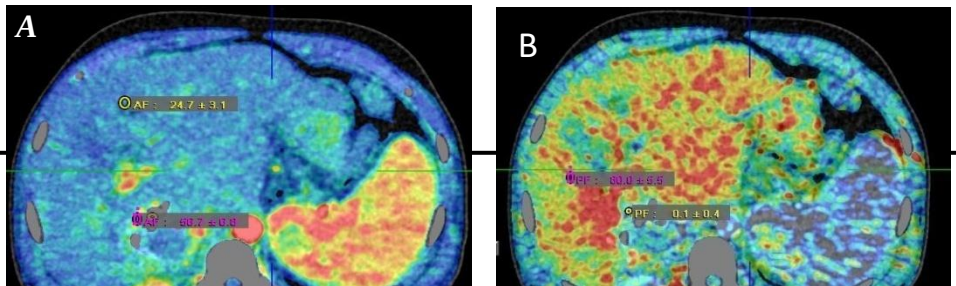


Figure *8:(A), (B) and (C) are the arterial, venous and delayed phases; respectively for triphasic CT study upon post TACE of right lobe HCC with no definite enhancement in the three phases.*

CT perfusion pattern: peripheral active tumoral tissue is seen with high AF, hepatic PI in comparison to the hepatic tissue and low PF parameters (AF = 56.7 ± 6.8 ml/min/100ml, PF = 0.1 ± 0.4 ml/min/100ml with PI = 80.8 ± 15.2 % in relation to the normal hepatic parenchyma; (AF = 29.7 ± 3.1 ml/min/100ml, PF = 80.6 ± 5.5 ml/min/100ml and PI = 23.6 ± 3.3 %) ***(*Figure *9 and 10).***



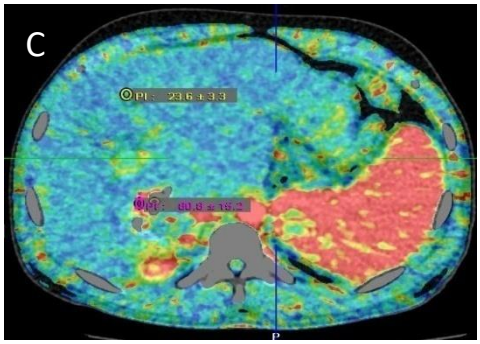


Figure *9 : (A) high AF, (B) with low PF and (C) relatively high PI at a peripheral area of high perfusion parameters in comparison to the normal non-tumoral hepatic tissues.*

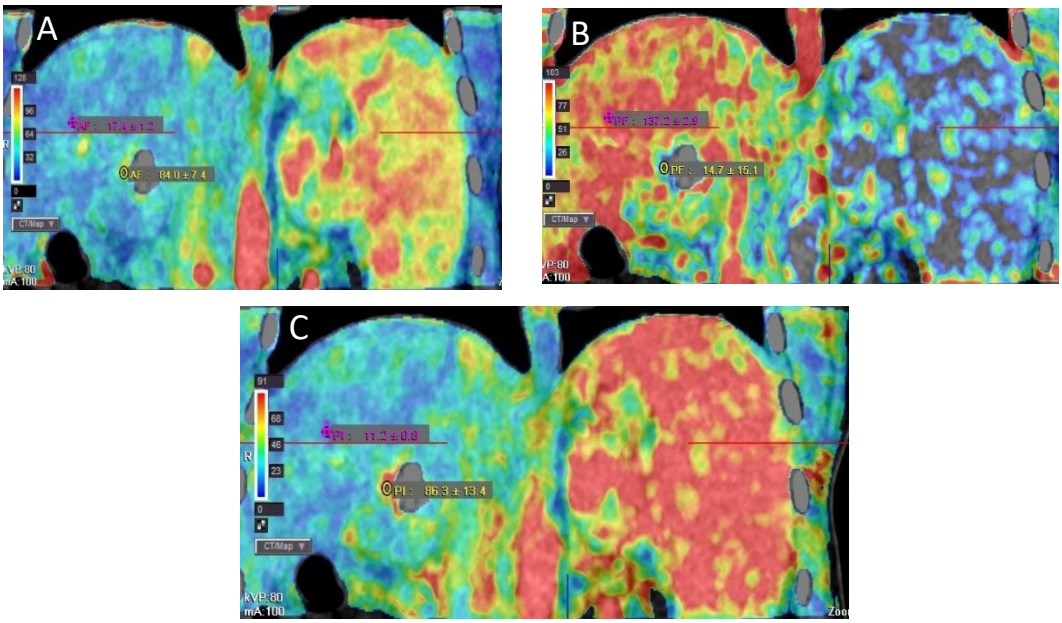


Figure *10: The same lesion displaying high perfusion parameters in coronal reconstructed images.*

Diagnosis: residual/recurrent right hepatic lobe segment VII HCC after TACE.

DISCUSSION

The liver is an organ in which various benign or malignant primary or secondary masses can be detected.

clinical applications of liver CT perfusion include early detection of tumors, assessing disease prognosis based on tumor vascularity, monitoring therapeutic effects of various treatment regimens including antiangiogenic drugs and early identification of tumor recurrence after treatment.(1)

We noticed that the majority of HCC lesions were hyper vascular with high arterial flow and perfusion indices, and few cases were hypo vascular despite being HCC on pathology. This high AF and PI parameters in CT perfusion is typically characteristic for well differentiated HCC lesions. Ippolito et al demonstrated the same results with significantly increased AF and PI with significantly decreased PF in HCCs compared with adjacent normal parenchyma. (4)

In this study we concluded that CT perfusion has multiple advantages and applications in liver HCC imaging:

- *Early detection of liver tumors*
- *Assessment Of Prognosis Based On Tumor Perfusion*
- *Monitoring therapeutic effects*
- *Diagnosis of Tumor Recurrence*

Conclusion

CT perfusion imaging of the liver provides functional information about the microcirculation of normal parenchyma and focal liver lesions and is a promising technique for assessing the efficacy of various anticancer treatments.

CT perfusion also shows promising results for diagnosing primary or metastatic tumors, for predicting early response to anticancer treatments, and for monitoring tumor recurrence after therapy.

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دور الأشعة المقطعية بإستخدام خاصية تدفق الدم في تفرقة سرطان الخلايا الكبدية

اشرف عبد الحليم راضي و احمد مصطفي محمد و حسام موسي صقر و شيرين محمد شرارة

خلفية عن البحث : الهدف من هذه الدراسة قياس استجابة الاورام الكبدية للادوية **المثبطة لتكوين اوعية دموية** جديدة عن طريق قياس نسبة التشبع بالاشعة المقطعية .

الهدف من البحث :

لاظهار دور قياس نسبة التشبع بالاشعة المقطعية فى تحديد و توضيح البؤر الكبديه و اعطاء تقييم حقيقى لحالة التشبع فى نسيج الكبد.

المرضى و الوسائل :

هذه الدراسة ستجرى على مرضى ثبت وجود بؤر كبدية لديهم و بعد عمل اشعة مقطعية بالصبغة تم حقنها عن طريق الوريد يتم جمع عوامل التشبع .

النتائج:

دراستنا تقترح ان عوامل نسبة التشبع التى تم الحصول عليها من الكبد تفرق بوضوح بين المناطق التى تحتوى خلايا سرطانيه او ثانويات و بين خلايا الكبد السليمة

واكثر من هذا ان نتائج التفرقة توضح بشدة التشخيص و المرحلة التى بها البؤرة السرطانيه و ذلك منذ ان ثبت ان البؤر التى لديها نسبة تشبع عالية تكون اكثر شراسة و لديها استجابة ضعيفة للعلاج الكيماوى و الاشعاعى .

الاستنتاج :

التصوير بالاشعة المقطعية بخاصية التشبع يمدنا بمعلومات وظيفية عن الدورة الدموية على مستوى الشعيرات الدموية لانسجة الكبد السليمة و البؤر المصابة بخلايا سرطانيه و هى تقنيه واعدة لقياس تاثير مختلف العلاجات للبؤر السرطانيه .