ROLE OF CT PERFUSION IN MALIGNANT HEPATIC FOCAL LESIONS

Omar M Mahmoud and Doaa Mohammad Fouad

The Department of Diagnostic Radiology, South Egypt Cancer Institute, Assiut University

Abstract

Background: *The diagnosis of hepatic focal lesions is a challenging issue. Variable imaging modalities are used to reach the accurate diagnosis of hepatic focal lesions. Tumor angiogenesis represents an essential part of the pathology of hepatic focal lesions. CT perfusion provides both qualitative and quantitative evaluation regarding tumor angiogenesis and thus may help in the diagnosis of hepatic focal lesions.* ***Objective****: This study aimed to evaluate the diagnostic accuracy of the quantitative assessment of CT perfusion in malignant hepatic focal lesions.* ***Methods****: CT liver Perfusion was performed in 97 patients, 48 were hepatocellular carcinoma (HCC) and 49 were liver metastases. These focal lesions were evaluated by Triphasic multidetector CT (MDCT) before CT perfusion. These patients underwent further confirmatory methods either by biopsy, alpha-fetoprotein, or follow-up. The perfusion parameters (Blood flow (BF), blood volume (BV), Mean transit time (MTT), and Permeability surface area product (PS) were determined using CT perfusion functional maps. A quantitative analysis of each parameter of the hepatic focal lesion (HFL) and the background liver was performed to find significant changes for each one.* ***Results****: Regarding patients with HCC, there was an increase in BF and decrease in MTT in all cases compared with the background liver, while changes in BV and PS were of low validity. The metastatic cases showed an increase in the BF and decrease in MTT in 96% of cases compared with the background liver with a significant P-value ($P<0.05$). The results were not specific to differentiate between HCC and metastases.* ***Conclusion****: CT perfusion is a recent imaging technique that allows functional evaluation of tissue vascularity and gives both qualitative and quantitative information regarding tumor angiogenesis used in the diagnosis of malignant hepatic focal lesions with a marked diagnostic effectiveness.*

INTRODUCTION

Hepatic focal lesions represent a heterogeneous group of pathology ranging from benign to malignant lesions. The diagnosis of these hepatic focal lesions is still a daily challenge (1).

Hepatocellular carcinoma (HCC) is the main outstanding reason for mortality in liver cirrhosis patients. The majority of patients presented at an advanced stage with a poor prognosis. HCC is markedly increasing in incidence (2). In spite of development in various methods of HCC treatment, including liver transplantation, surgical removal, and local therapies, more than seventy percent of HCC patients presented with advanced disease and different therapeutic modalities will not be useful in these patients (3).

The vascular changes caused by tumors can be measured using CT perfusion. The current diagnostic imaging modalities provide a poor evaluation of tissue characteristics beyond morphology. Perfusion imaging of the liver has the ability to solve this problem. The power to resolve hepatic arterial and portal venous components of blood flow on a total and regional basis represents the primary objective of liver perfusion imaging. Early detection of primary and metastatic hepatic malignant tumors may be possible on the basis of relative increases in hepatic arterial blood flow associated with these tumors (4).

Tumor angiogenesis is mandatory for cancer growth and contributes a suitable target for oncologic therapies. CT perfusion is a growing imaging tool that provides both qualitative and quantitative data regarding tumor angiogenesis (5).

With the use of multidetector CT scanners, it is now possible to cover up to 16 cm in one rotation, and therefore it is available to scan entire organs such as the liver with a fixed table position. Advances in reconstruction algorithms make it possible to decrease the radiation dose for each examination to acceptable levels. Regarding liver imaging, CT perfusion is still considered a research tool, but several studies have proved it as a reliable non-invasive technique for the evaluation of vascularity. CT perfusion has also been used for tumor characterization, staging, and response evaluation of new drugs targeted against angiogenesis and as a method for early detection of recurrence after radiation and chemo-embolization treatment. There are various software solutions available based on variable perfusion methods. However, there is no agreement on the protocol and algorithm to use for specific organs (6).

Therefore, the aim of this study is to evaluate the diagnostic accuracy of the quantitative assessment of multidetector CT perfusion in malignant hepatic focal lesions.

PATIENTS AND METHODS

This study was conducted between October 2012 and October 2014, and ethical approval was taken. The study population consisted of 97 patients, 52 males, and 45 females; their mean age was 39.3 ± 11.9 (range 30-68 years). The diagnosis in hepatocellular carcinoma patients was based on Tru-cut needle biopsy and Alpha-fetoprotein. These patients did not receive any previous treatment. All of the liver metastases group had a known primary cancer. The diagnosis of liver metastases was based on biopsy or by history and follow-up (newly appeared focal lesions during follow-up of normal liver or increase in number and size of them).

The patients have been examined by CT perfusion using a 16 multidetector CT scanner (GE BrightSpeed16).

Technique of CT perfusion:

Based on the pre-contrast series for the dynamic study, a 2-cm area was selected after lesion localization (as we utilized 16 multidetector CT, which only offers 2 cm coverage for perfusion scan).

At a static table position, a dynamic study of the targeted area was done in a single breath-hold at the completion of inspiration. At a rate of 5 mL/sec, we injected a total of 50 mL of nonionic iodinated contrast medium: Iohexol (Omnipaque 350 mg of iodine/mL; GE Health Care). One second gantry rotation time, 100 kvp, 240 mA, acquisition in 4i transverse mode (four sections per gantry rotation), and 5-mm reconstructed section thickness were the CT parameters used to obtain dynamic data.

After a 5-second delay from the start of injection, we began scanning, and the images were acquired for a total of 60 seconds. Data analysis was carried out on a workstation (GE Medical Systems' Advantage Windows 4.0) using CT perfusion software (GE Perfusion 4). The following steps were used to assess functional data: images are displayed in a suitable window, such as soft tissue for the abdomen (width = 400 HU, level = 40 HU). By manually placing a region of interest (ROI) in the aorta and ensuring that the ROI did not include any mural calcification, we were able to create a reference arterial input curve. By putting a region of interest (ROI) in the main PV, portal vein branch, and superior mesenteric vein, we were able to create a reference portal input curve (SMV), as well as the splenic vein

(SV). Perfusion maps and values are then calculated. The ROI was drawn in the normal parenchyma of the liver. In the case of several tumors, ROIs were manually drawn; ROIs were drawn for all tumors in the scanning range. The perfusion values of the tumor(s) and the background liver were then calculated and shown across all four regions as follows:

Blood flow (BF): This is the volume flow rate of blood through the vasculature in a tumor. It is expressed in units of ml/min/100 g. **Blood volume (BV):** This is the volume of blood within the vasculature in a tumor that is truly 'flowing'. Any stagnant pool of blood will not be involved in the blood volume. It is expressed in units of ml/100 g. **Mean transit time (MTT):** This is the average time taken by blood elements to cross the vasculature from the arterial end to the venous end in a tumor. Mean transit time is expressed in seconds. **Permeability surface area product (PS):** it is the unidirectional flow of contrast from blood plasma to interstitial space. It is measured in units of ml/min/100 g (7).

Functional maps of BF, BV, MTT, and PS were calculated. These functional maps were shown in colors ranging from blue to red, with blue being the minimum range of display for BF, BV, and PS, and red being the maximum range of display (Figure. 1).

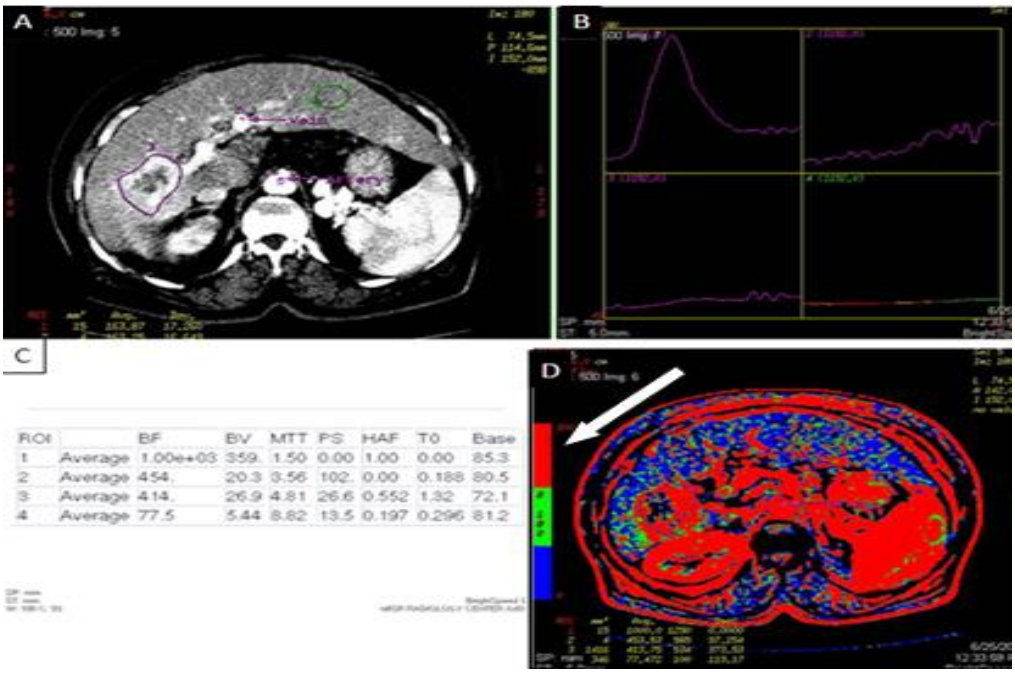

Figure.1: An example of CT perfusion data analysis in a case of HCC:

A) Transverse contrast-enhanced CT image used to draw ROIs in the aorta, left portal vein branch, tumor, and background liver parenchyma.
B) Dynamic curve of each ROI.
C) Tables of BF, BV, MTT, and PS values of each ROI.
D) Functional CT perfusion color map of BF displayed according to color scale (large arrow).

Statistical methods:

For statistical analysis, a commercially accessible program was used (SPSS release 14.0 program; SPSS Inc, Chicago, IL). The data were shown as Mean ± SD.

Mann-Whitney U test was used to compare hepatocellular carcinoma and the background liver, liver metastases, and the beachbound liver and hepatocellular carcinomas and liver metastases. We used perfusion parameters (BV, BF, MTT, and PS) as independent variables. A P-value less than 0.05 was considered statistically significant.

RESULTS

Regarding Hepatocellular carcinoma lesions:

Among the examined HCC cases, there are significant changes in certain perfusion parameters of the tumor in comparison with those measured in the background liver of the same patients (Figure 2). We found that BF was increased in all cases. Also, MTT showed a decrease in all cases. BV and PS showed an increase in 63.3% and 72.2 % of cases, respectively.

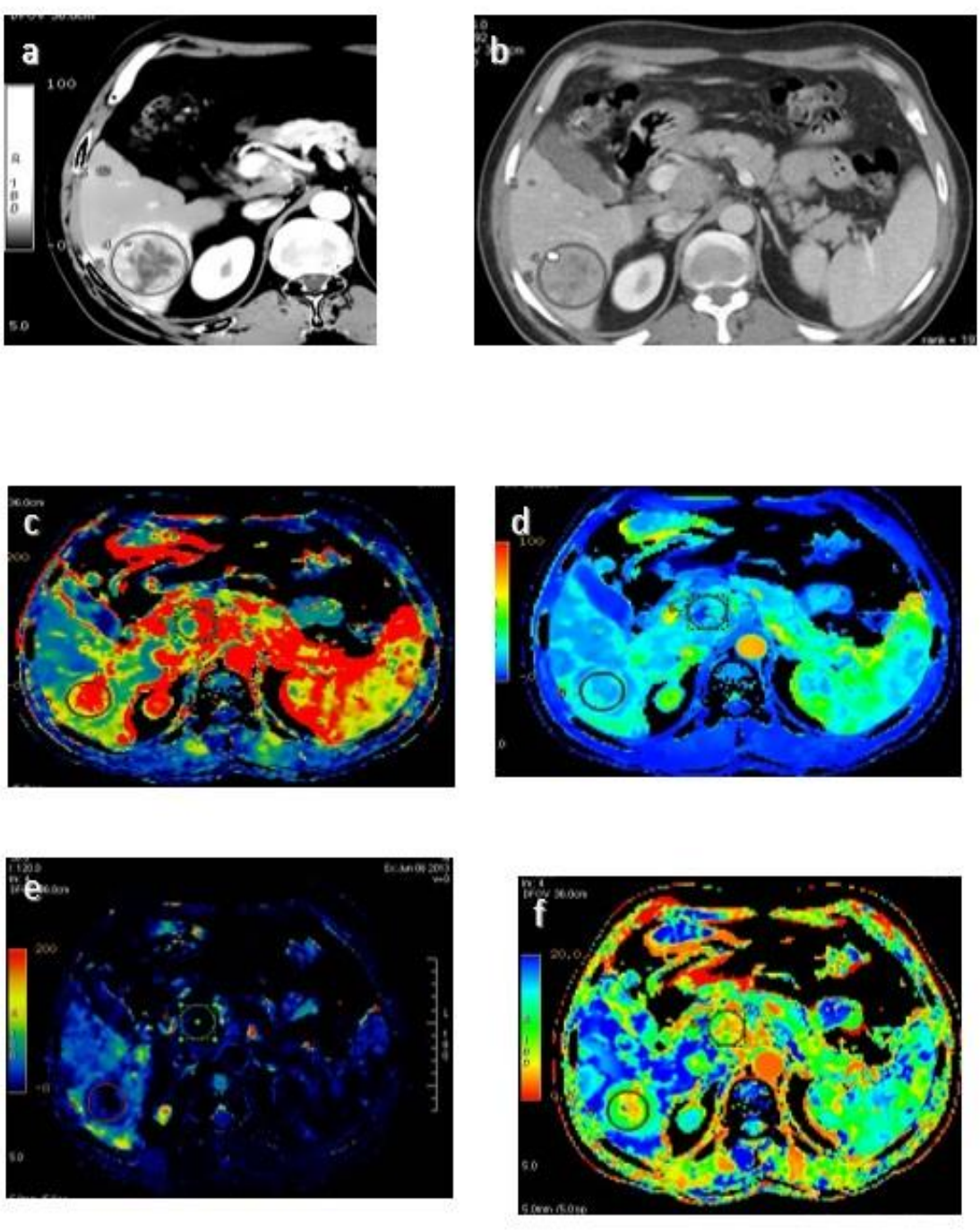

Figure. 2: Hepatic focal lesion diagnosed as hepatocellular carcinoma by biopsy. (a) The arterial phase of postcontrast CT showed early enhancement of the lesion. (b) the portal phase of postcontrast CT showed a washout of the contrast. (C) BV map. (d) BF map. (e) PS map. (f) MTT map. BV, BF, PS, and MTT of the hepatic focal lesion were 26.71, 660.9, 18.32, and 2.36, respectively. BV, BF, PS, and MTT of the background liver were 23.80, 100.7, 60.9, 4.3, and 14.9, respectively.

Table 1: Comparison between perfusion parameters of HCC and background liver:

	Background liver		HCC		
	mean	Standard deviation	mean	Standard deviation	P-value
BV	28.3	7.6	22.2	17.5	0.312
BF	71.8	13.8	280.9	222.5	0.001
MTT	22.5	2.5	8.6	4.6	0.001
PS	8.1	5.0	10.9	12.6	0.514

The perfusion parameters of HCC and the background liver are shown in table 1. We found a significant increase (near four times) in the mean BF of HCC in comparison with the background liver (P<0.01) (Figure 3). MTT showed a decrease in the HCC in comparison with the background liver (P < 0.001) (Figure 4). No significant difference was found between HCC and the background liver in BV and PS.

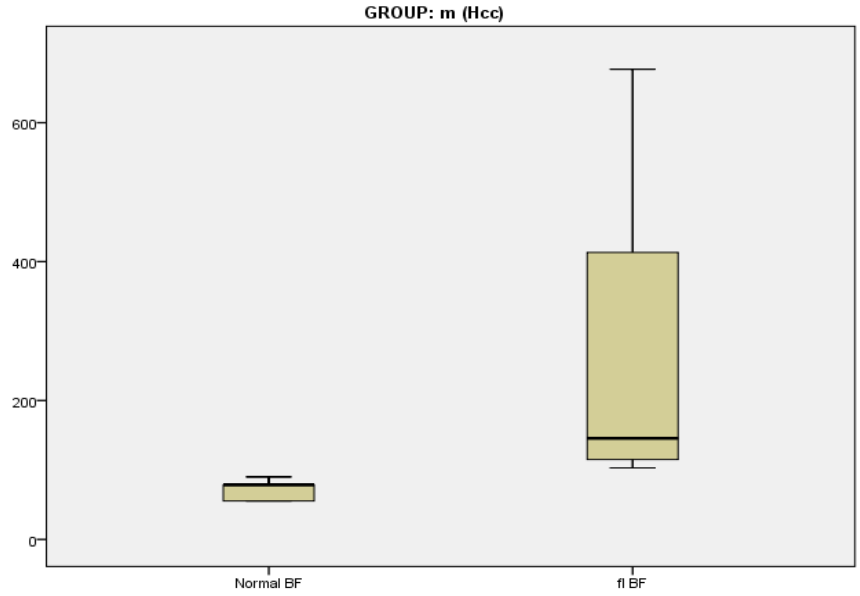

Figure 3: Box plot shows the difference in the BF between the background liver and HCC. BF of HCC is higher than that of the background liver (P<0.01).

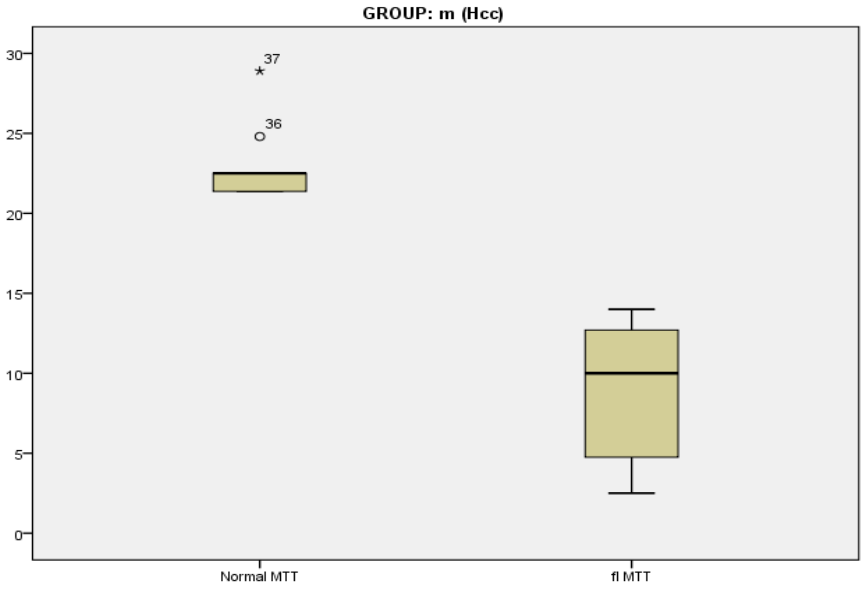

Figure 4: Box plot shows the difference in the MTT between the background liver and HCC. MTT of HCC is lower than that of the background liver (P<0.001).

Regarding the metastatic lesions:

There were significant changes in certain perfusion parameters of the metastatic focal lesions compared with those of the background normal liver in the same patients (Figure. 5). BF showed more than double increase in the metastasis (mean: 324.7 mm/min/100 g) compared with the BF of background liver (133.9 mm/min/100g) (P <0.05) (Figure 6). While MTT shows a significant decrease in these focal lesions (mean MTT was 6.4 sec.) in the metastases compared with the background liver (13.7 sec) (P <0.01) (Figure 7). PS and BV show no significant changes (Table. 2).

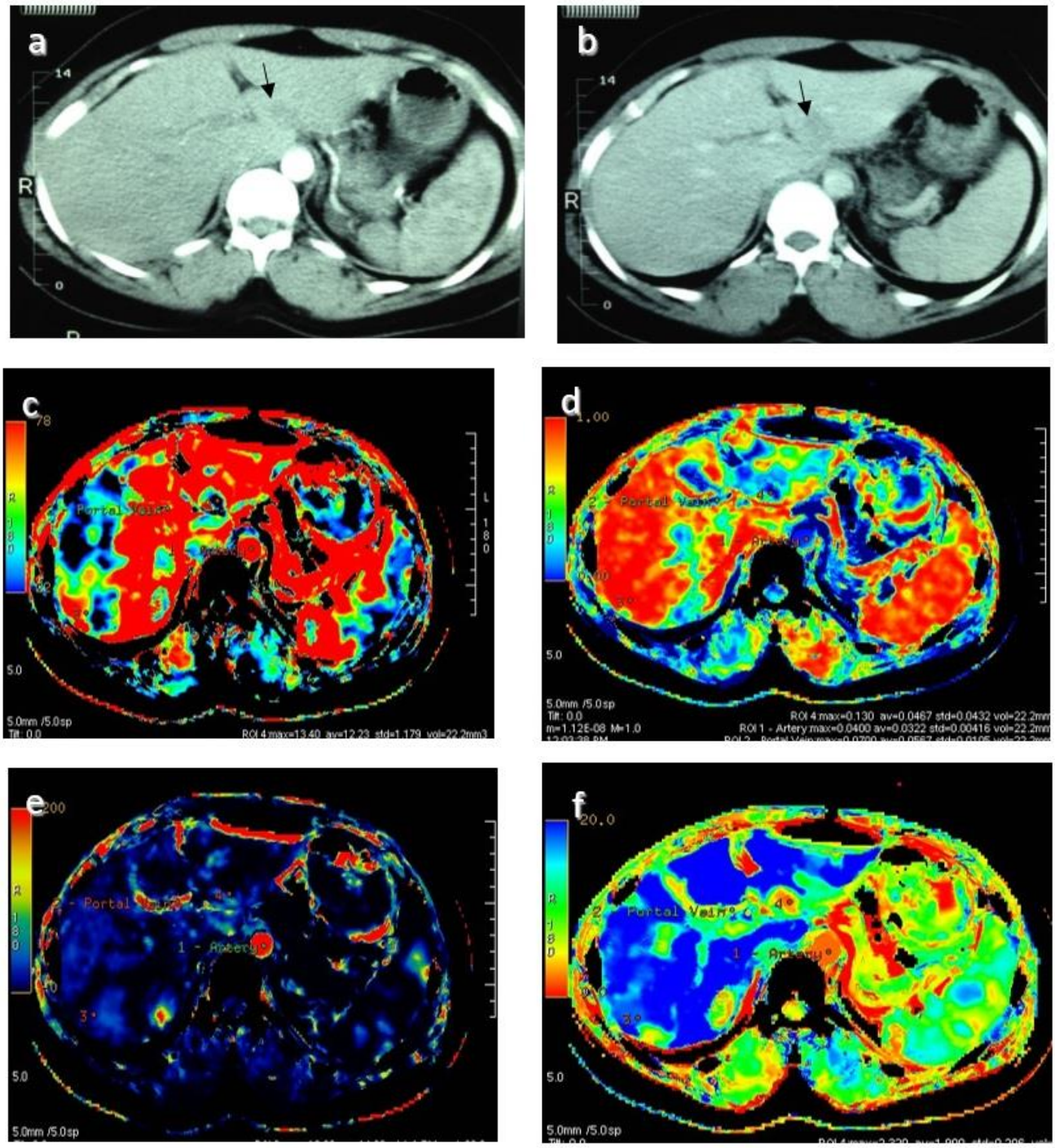

Figure 5: Hepatic focal lesion diagnosed as metastatic adenocarcinoma by biopsy. (a) Arterial (a) and portal (b) phases of postcontrast CT showed no enhancement of the lesion (arrow). (C) BV map. (d) BF map. (e) PS map. (f) MTT map. BV, BF, PS, and MTT of the hepatic focal lesion were 12.2, 240.8, 6.9, and 1.9, respectively. BV, BF, PS, and MTT of the background liver were 54.1, 180, 60.9, 14.29, and 18.2, respectively.

Table 2: Perfusion parameters in liver metastasis and background liver:

	Background liver		Metastases		
	mean	Standard deviation	mean	Standard deviation	P-value
BV	27.3	20.0	23.6	16.4	0.534
BF	133.9	175.6	324.7	279.9	0.029
MTT	13.7	5.6	6.4	8.4	0.012
PS	23.5	19.5	27.9	28.1	0.435

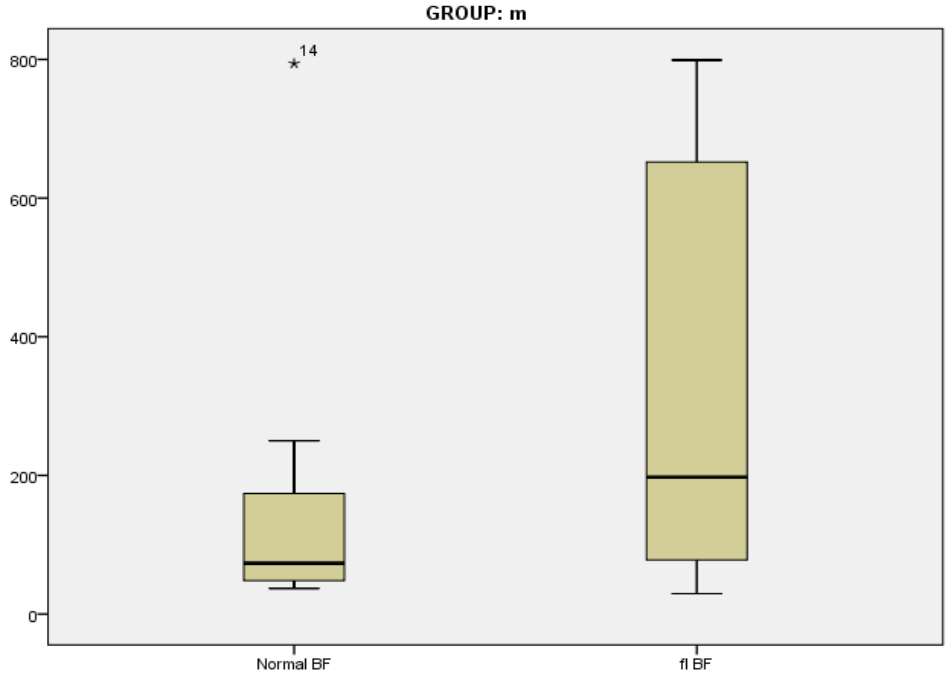

Figure 6: Box plot shows the difference in the BF between the background liver and metastases. BF of liver metastases is higher than that of the background liver (P<0.05).

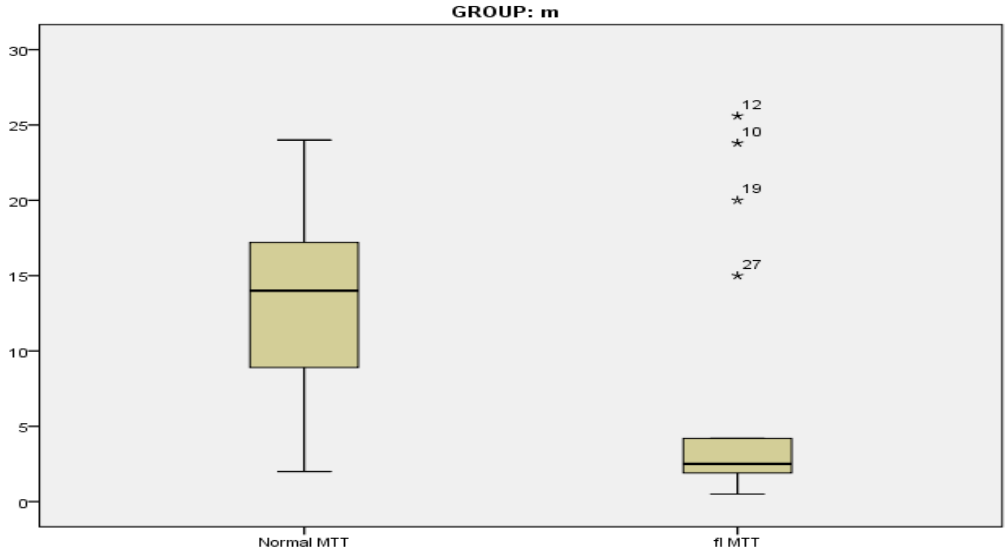

Figure 7: Box plot shows the difference in the MTT between the background liver and metastases. MTT of liver metastases is lower than that of the background liver (P<0.01).

DISCUSSION

Tumor-related angiogenesis is a multi-step process that includes the aggregation of nearby capillaries, sprouting or intussusceptive microvascular development, and endothelial precursor cell vasculogenesis. Angiogenesis is thought to be necessary for cancer growth, and strong tumor angiogenesis activity has been linked to distant metastases and a poor prognosis in human cancers, implying that tumor angiogenesis is necessary for cancer growth and a promising target for oncologic therapy (8).

CT perfusion is a new imaging technique that uses dynamic contrast-enhanced imaging techniques like CT perfusion to offer both qualitative and quantitative information on tumor angiogenesis by measuring regional blood flow (BF), blood volume (BV), and vascular permeability (9). It is currently mostly utilized as a research tool, although it is increasingly being used to monitor tumor response to anti-angiogenic medicines and to detect hidden metastatic lesions (10).

In this study, we evaluated the role of CT perfusion in the diagnosis of hepatocellular carcinoma and liver metastases. Dynamic CT examination of the selected area was performed in a single breath-hold at the end of inspiration at a static table position. Then, perfusion maps were formed and a quantitative assessment of perfusion parameters of the hepatic focal lesions was measured. We compared the perfusion parameters of the hepatic focal lesions to the background liver parameters. In this study, we used the following perfusion parameters: blood flow (BF), blood volume (BV), mean transit time (MTT), and permeability–surface area product (PS).

Regarding hepatocellular carcinoma lesions:

BF was increased in all HCC cases and this increase was nearly four times in comparison with that of the background liver ($P<0.001$). MTT was decreased in all cases in comparison with the background liver ($P<0.001$). BV and PS were increased in 63.3% and 72,2% of cases, respectively, but with no significant P-value. Our results are similar to the previous studies (11-13).

The high BF and BV in HCC lesions can be explained by the process of angiogenesis, which is based on the activation, proliferation, and migration of endothelial cells induced by secreted angiogenic factors. This process leads to the formation of a network of numerous vessels that have irregular diameters and abnormal branching patterns. On the other hand, the high PS among HCC lesions can be explained by the fact that HCC blood vessels are leaky as they lack a complete basal membrane, and are incompletely covered by pericytes (14).

MTT was decreased in the HCC comparing this with the adjacent liver. This is consistent with a previous study by Ma GL, et al. (15). This study reported that the decrease in the MTT is one of the early hemodynamic changes in HCC. This may be explained by the fact that the formation of new arterial vessels per unit mass determines a corresponding reduction in time of blood passage from arterial to venous end per second.

In our study, no significant increase in the BV which may be due to variable degree of fibrosis and cirrhosis of the background liver of the examined cases, and this may alter different liver perfusion parameters from one stage to another and so it may disturb the relative relation of BV between HCC and background liver (16). The BF relative changes were not affected by this phenomenon because it showed four times increase in HCC compared to background liver, while the increase in BV was small which can be easily affected by any changes in total liver perfusion.

These results were similar to that of Sahani et al. (17) who reported that HCC show higher BF, BV, and PS values and a lower MTT. However, our BV, BF, and PS values were higher and MTT values were lower and this may due to more fibrosis in our cases which may elevate the BV, BF, and PS values and elongate the mean transit time.

Regarding liver metastases:

BF was markedly increased in liver metastases in comparison with the background liver ($P<0.05$) and MTT was markedly decreased in the metastatic lesions ($P<0.01$). PS and BV showed no significant changes.

A previous study found that BF was significantly higher in metastasis groups than in the background liver (18). Another study reported that the blood flow of hepatic metastases from neuroendocrine tumors is higher than the background liver and the mean transit time is lower (19) which is similar to our results.

These findings may help in the early detection of metastatic focal lesions and the selection of anti-angiogenic drugs.

Study limitations:

1) Limited scan range CT perfusion (2 cm).
2) Low sample size and pathological types.
3) Exposure to an additional radiation dose when CT perfusion was done with triphasic CT examination.

CONCLUSION

CT perfusion is a recent imaging technique that allows functional evaluation of tissue vascularity and gives both qualitative and quantitative information regarding tumor angiogenesis. It may be helpful in the early detection of small lesions of hepatocellular carcinoma and liver metastases. However, differentiation between hepatocellular carcinoma and liver metastases is not possible by CT perfusion.

REFERENCES

1- Elsayes KM, Narra VR, Yin Y, Mukundan G, Lammle M, Brown JJ. Focal hepatic lesions: diagnostic value of enhancement pattern approach with contrast-enhanced 3D gradient-echo MR imaging. Radiographics. 2005 Sep;25(5):1299-320.
2- Cabrera R, Nelson DR. the management of hepatocellular carcinoma. Alimentary pharmacology & therapeutics. 2010 Feb;31(4):461-76.
3- Thomas MB, Jaffe D, Choti MM, Belghiti J, Curley S, Fong Y, Gores G, Kerlan R, Merle P, O'Neil B, Poon R. Hepatocellular carcinoma: consensus recommendations of the national cancer institute clinical trials planning meeting. Journal of clinical oncology. 2010 Sep 1;28(25):3994.
4- Pandharipande PV, Krinsky GA, Rusinek H, Lee VS. Perfusion imaging of the liver: current challenges and future goals. Radiology. 2005 Mar;234(3):661-73.
5- 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?. American Journal of Roentgenology. 2013 Jan;200(1):8-19.
6- Hansen ML, Norling R, Lauridsen C, Fallentin E, Bæksgaard L, Kofoed KF, Svendsen LB, Nielsen MB. Computed tomography (CT) perfusion in abdominal cancer: technical aspects. Diagnostics. 2013 Jun;3(2):261-70.
7- Cuenod CA, Husband J. Multidetector computed tomography in oncology: CT perfusion imaging. Miles KA, editor. London, UK: Informa Healthcare; 2007 Sep 15.

8- 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?. American Journal of Roentgenology. 2013 Jan;200(1):8-19.
9- Ebos JM, Kerbel RS. Antiangiogenic therapy: impact on invasion, disease progression, and metastasis. Nature reviews Clinical oncology. 2011 Apr;8(4):210-21.
10- Sahani DV. Perfusion CT: an overview of technique and clinical applications. InProc. Intl. Soc. Mag. Reson. Med 2010 (Vol. 18, pp. 1-12).
11- Komemushi A, Tanigawa N, Kojima H, Kariya S, Sawada S. CT perfusion of the liver during selective hepatic arteriography: pure arterial blood perfusion of liver tumor and parenchyma. Radiation Medicine. 2003 Nov 1;21(6):246-51.
12- Zhong L, Wang WJ, Xu JR. Clinical application of hepatic CT perfusion. World Journal of Gastroenterology: WJG. 2009 Feb 28;15(8):907.
13- Wang WJ, Zhong L, Hua XL, Fan Y, Li L, Xu JR. Low-dose hepatic computed tomography perfusion imaging and its preliminary study. Journal of digestive diseases. 2011 Jun;12(3):204-9.
14- Semela D, Dufour JF. Angiogenesis and hepatocellular carcinoma. Journal of hepatology. 2004 Nov 1;41(5):864-80.
15- Ma GL, Bai RJ, Jiang HJ, Hao XJ, Dong XP, Li DQ, Liu XD, Wei L. Early changes of hepatic hemodynamics measured by functional CT perfusion in a rabbit model of liver tumor. Hepatobiliary & Pancreatic Diseases International. 2012 Aug 15;11(4):407-11.
16- Ronot M, Asselah T, Paradis V, Michoux N, Dorvillius M, Baron G, Marcellin P, Van Beers BE, Vilgrain V. Liver fibrosis in chronic hepatitis C virus infection: differentiating minimal from intermediate fibrosis with perfusion CT. Radiology. 2010 Jul;256(1):135-42.
17- Sahani DV, Holalkere NS, Mueller PR, Zhu AX. Advanced hepatocellular carcinoma: CT perfusion of liver and tumor tissue—initial experience. Radiology. 2007 Jun;243(3):736-43.
18- Barnes E. CT perfusion distinguishes HCC from other liver lesions. Au ntMinnie. com staff writer. 2010 Apr 29.
19- Guyennon A, Mihaila M, Palma J, Lombard-Bohas C, Chayvialle JA, Pilleul F. Perfusion characterization of liver metastases from endocrine tumors: computed tomography perfusion. World journal of radiology. 2010 Nov 28;2(11):449.