DIAGNOSTIC ACCURACY OF QUANTITATIVE WASHOUT CALCULATED ON TRIPHASIC CT SCAN FOR DIAGNOSIS OF HEPATOCELLULAR CARCINOMA KEEPING HISTOPATHOLOGY AS GOLD STANDARD

Huma Hameed, Muhammad Nafees, Syed Sameeuddin

Combined Military Hospital Peshawar/National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To determine the diagnostic accuracy of quantitative washout calculated on Triphasic CT scan for diagnosis of hepatocellular carcinoma keeping histopathology as gold standard.
Study Design: Descriptive, cross-sectional validation study.
Place and Duration of Study: Armed Forces Institute of Radiology and Imaging Rawalpindi, from Feb 2016 to Aug 2016.
Material and Methods: A total of 132 patients of either sex with age in range 15-75 years diagnosed to have focal liver lesion on ultrasonography were included. Patients in whom focal lesion was cyst or abscess, patients with renal failure, pregnancy or known sensitivity to contrast agents were excluded. All the patients then underwent Triphasic CT scan to calculate quantitative washout on delayed phase. The lesion was diagnosed as HCC if percent attenuation ratio was >107. The results were later correlated with histopathology findings.
Results: Mean age was 49.75 ± 15.18 years. Out of 132 patients, 86 (65.15%) were males and 46 (34.85%) were females with ratio of 2:1. In Triphasic CT scan positive patients, 78 were True Positive and 09 were False Positive. Among 45, Triphasic CT scan negative patients, 07 were False Negative where as 38 were True Negative. Overall sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of quantitative washout calculated on Triphasic CT scan for diagnosis of hepatocellular carcinoma was 91.76%, 80.85%, 89.66%, 84.44% and 87.88% respectively.
Conclusion: This study concluded that quantitative washout calculated on Triphasic CT scan is a highly sensitive and accurate non-invasive modality for diagnosis of hepatocellular carcinoma.

Keywords: Hepatocellular carcinoma, Quantitative washout, Triphasic computed tomography.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and one of the most frequent causes of death in patients with liver cirrhosis[1]. Approximately three fourth of the cases of HCC worldwide occur in Asia because of a high incidence of chronic Hepatitis B and C infection with a prevalence reaching up to 39%[2]. HCC is the fourth most common hepatic disorder in Pakistan[3]. Although histopathology is the gold standard, biopsy may have inter observer variability and may always not be possible as it is an invasive technique and sometimes contraindicated in patients with severe ascites and impaired coagulation[4,5].

Computed tomography (CT) is the imaging modality most often used to evaluate focal liver lesions. Due to the complex blood supply of the liver (30% from Hepatic artery and 70% from Portal vein) a triphasic spiral CT technique is developed to image the entire liver in arterial, portal, and delayed phases[6]. HCC receives blood primarily from the hepatic arteries and therefore tends to enhance more avidly in arterial phase than background which receive 25% blood supply from hepatic artery and 75% from portal vein. Lack of portal venous supply to HCC results in characteristic washout in portovenous and delayed phases. This washout can be calculated by percent attenuation ratio of the lesion on delayed phase (100 x ratio of attenuation of adjacent liver to the lesion).

Correspondence: Dr Huma Hameed, House # 38/4 BMH Area Family Wing CMH Peshawar Pakistan
Email: humasamee@hotmail.com
Received: 22 Nov 2017; revised received: 19 Jan 2018; accepted: 23 Jan 2018

HCC shows a washout >107. Calculation of Quantitative washout is more sensitive in HCC detection than radiologist subjective evaluation with sensitivity of 100% and specificity of 75.8%[7].

Triphasic CT scan of liver is imaging modality of choice for detection of HCC in cirrhosis of liver, to select candidates for curative surgery, embolotherapy, percutaneous ethanol injection, trans-arterial chemoembolization, radiofrequency ablation and for exclusion of multifocal disease[8,9].

The rationale of this study is to determine whether the diagnostic accuracy of quantitative washout calculated on Triphasic CT scan for diagnosing HCC in our local population is comparable with internationally conducted studies and can it successfully replace biopsies as gold standard. If proven to be as accurate as in previous studies, it could be method of choice for diagnosis of HCC in our setup.

MATERIAL AND METHODS

It was a descriptive cross sectional validation study conducted from February 2016 to August 2016, carried out at Armed forces Institute of Radiology and Imaging. Sample size of 132 was calculated using sensitivity and specificity calculator by keeping prevalence of HCC 39%[2], sensitivity of quantitative washout 95%, specificity 75.6%[6], level of significance (α) for sensitivity 5%, specificity 10% and confidence interval 95%. 132 patients of either sex with age ranging from 15 to 75 years, diagnosed to have focal liver lesion (showing different echogenicity than normal liver parenchyma) on Ultrasonography (USG) were selected using Non-probability, consecutive sampling technique. Patients with deranged renal functions, extra hepatic malignancy, pregnancy, known history or showed hypersensitivity to contrast agent and patients whose focal lesions was cyst or abscess were excluded from study.

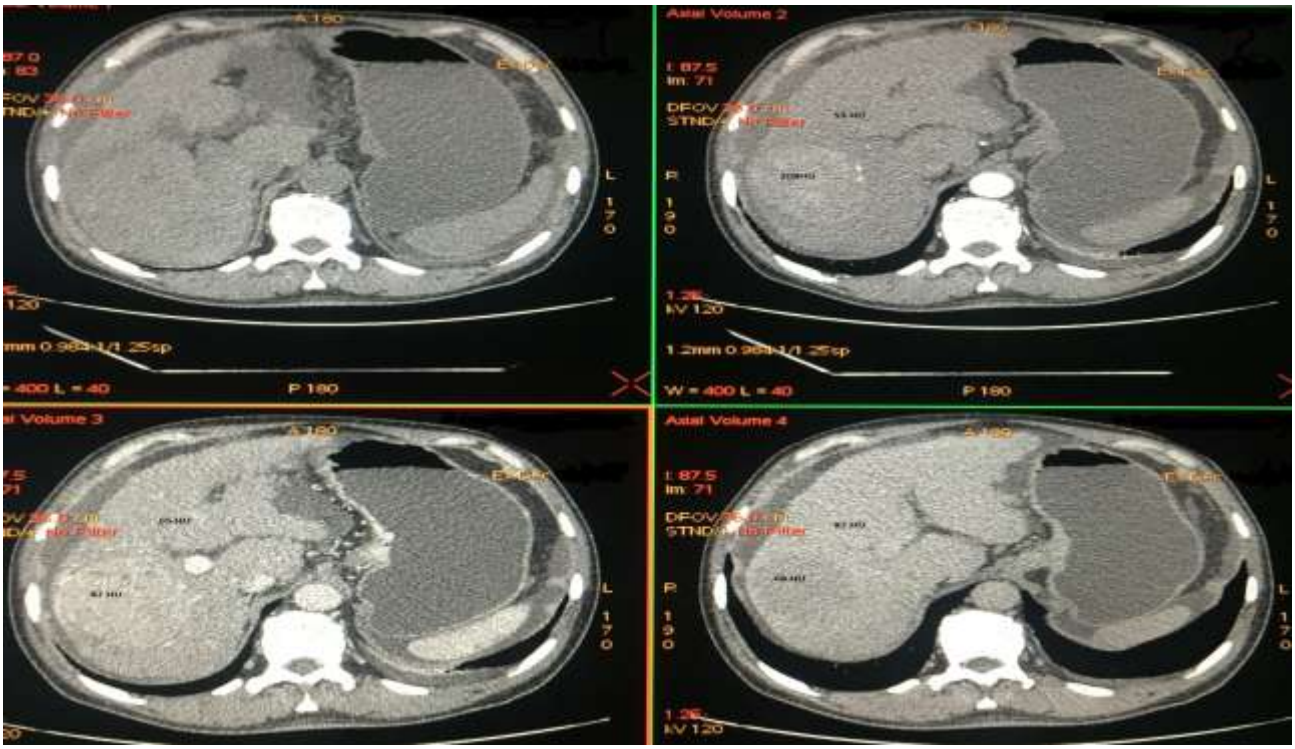

Figure-1: HCC on Triphasic CT scan showing enhancement on arterial phase and washout on portovenous phase. Lesion has become hypodense on delayed phase
Quantitative washout=100 x liver attenuation on delayed phase/lesion attenuation on delayed phase =100 x 87/68 = 127.

Data Collection Procedure

After approval by the institutional ethical Committee, informed consent was taken from all the patients prior to inclusion in the study. All patients coming for Triphasic CT meeting our inclusion criteria were enrolled for calculating quantitative washout on delayed phase. All confounding variables were excluded by keeping them in exclusion criteria.

All scans were obtained with a helical CT scanner (64 slice Toshiba Aquillion). An initial non enhanced scan was acquired with 10-mm section thickness at 20-mm intervals through the liver. Then a 20-gauge intravenous cannula was inserted, a total of 1-1.5ml/kg of nonionic contrast medium with 300 mg of iodine per milliliter (Omnipaque/Ultravist) was administered at 4-5 ml/sec. Beginning 25 seconds after initiation of the contrast material injection, a 30 second breath hold early arterial phase helical CT scan was acquired with section thickness of 5 mm and pitch (usually 1.0–1.6) sufficient to cover the entire liver within the breath hold period. Similarly portovenous and delayed phase images were acquired at 65-70 sec and 5-6 minutes respectively after the initiation of contrast injection. Images were reconstructed at 5 mm intervals with use of standard soft-tissue (window width, 400 HU; level, 40 HU) and liver (window width, 150 HU; level, 50–80 HU) display settings.

The liver and soft-tissue images for each patient were reviewed by single radiologist. Quantitative washout of lesion was calculated by percent attenuation ratio of the liver to the lesion on delayed phase.

Quantitative washout = 100 x AA_D / LA_D

Where AA_D = liver attenuation on delayed phase

LA_D= lesion attenuation on delayed phase

Lesion was diagnosed as HCC if percent attenuation ratio >107, as shown in fig-1.

The results were compared with final diagnosis obtained by histopathology. Data was analyzed using SPSS version 21. Quantitative variables like age and size of lesion and mean ± standard deviation were calculated. Qualitative variables like gender, number of lesions and pattern of lesions were measured as frequency and percentages. Effect modifiers like age, gender, size of lesion were controlled by stratification. Chi-square test was applied. A *p*-value of <0.05 was considered significant. Diagnostic accuracy, sensitivity, specificity, positive and negative predictive value, true positive, true negative, false positive and false negative were calculated.

RESULTS

Age range in this study was from 15-75 years with mean age of 49.75 ± 15.18 years. Majority of the patients 46 (34.85%) were between 46 to 65 years of age. Out of these 132 patients, 86 (65.15%) were males and 46 (34.85%) were females with ratio of 2:1. The mean size of lesion was 3.23 ± 2.16 cm with a range of 1cm to 10 cm. Triphasic CT supported the diagnosis of HCC in 87 (65.91%) patients and no HCC in 45 (34.09%) patients. Histopathology findings confirmed HCC in 85 (64.39%) cases where as 47 (35.61%) patients revealed no HCC. In Triphasic CT scan positive patients, 78 (True Positive) had HCC and 09 (False Positive) had no HCC on histopathology. Among 45, Triphasic CT scan negative patients, 07 (False Negative) had HCC on histopathology where as 38 (True Negative) had no HCC on histopathology (*p*=0.001) as shown in table-I. Overall sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of quantitative washout calculated on Triphasic CT scan for diagnosis of HCC keeping histopathology as gold standard were 91.76%, 80.85%, 89.66%, 84.44% and 87.88% respectively (fig-2). Gender stratification is shown in table-II. Stratification of diagnostic accuracy with respect to size of lesion is shown in table-III.

DISCUSSION

Triphasic CT liver can characterize different benign and malignant liver lesions[10]. The

recommended times for imaging the liver for lesion characterization are

A: Arterial phase (25 sec after IV contrast) when hypervascular liver lesions show greatest enhancement relative to background liver.

Table I: Triphasic CT and Histopathology findings.

Nature of Lesion	Positive on Triphasic CT	Negative on Triphasic CT	*p*-value
Positive on Histopathology	78 (TP)	07(FN)	0.001
Negative on Histopathology	09 (FP)	38(TN)	
Total (n=132)	87	45	

Table II: Stratification of gender (n=132).

Gender	Nature of Lesion	Positive on Triphasic CT	Negative on Triphasic CT	*p*-value
Female n=46	Positive on Histopathology	22(TP)	03(FN)	0.001
	Negative on Histopathology	03(FP)	18(TN)	
	Total (n=46)	25	21	
Male n=86	Positive on Histopathology	56(TP)	04 (FN)	0.001
	Negative on Histopathology	06(FP)	20 (TN)	
	Total (n=86)	62	24	

Table-III: Stratification of size of lesion (n=132).

Size of lesion	Nature of Lesion	Positive on Triphasic CT	Negative on Triphasic CT	*p*-value
Size 0-3 cm n=72	Positive on Histopathology	42(TP)	03 (FN)	0.001
	Negative on Histopathology	05FP)	22 (TN)	
	Total (n=72)	47	25	
Size >3 cm n=60	Positive on Histopathology	36(TP)	04 (FN)	0.001
	Negative on Histopathology	04(FP)	16 (TN)	
	Total (n=60)	40	20	

B: Portal venous phase (60–70 sec) when hypovascular liver metastases and the portal veins are best visualized and hypervascular lesions show washout of contrast.

C: Delayed phase (5-6 minutes) when washout or contrast retention relative to liver parenchyma can be best characterized.

On triphasic CT, HCC shows characteristic enhancement compared to the surrounding liver in the arterial phase, washout of contrast in the porto-venous phase, and hypodense compared to the liver in the delayed phase[11,12]. Arterial phase enhancement with porto-venous or delayed phase washout of contrast is considered diagnostic of HCC in cirrhotic livers[13], according to guidelines of European Association for the Study of the Liver (EASL)[14] and American Association for the Study of Liver Diseases (AASLD)[15].

However, some HCCs do not follow this characteristic enhancement pattern. Not all lesions with arterial phase enhancement and portovenous/delayed phase washout are HCCs. Few well-differentiated HCCs are hypodense to the liver on all phases[16]. Some hypervascular HCCs do not demonstrate washout[17]. Other liver lesions, both benign and malignant, can show washout including adenomas, focal nodular hyperplasia (FNH), regenerative nodules and

hypervascular metastases such as pancreatic Islet cell tumors[18]. We have conducted this study to determine the diagnostic accuracy of quantitative washout calculated on Triphasic CT scan for diagnosis of hepatocellular carcinoma keeping histopathology as gold standard.

Study conducted by Colli A and colleagues showed Tri-phasic CT scan (arterial phase, porto-venous and delayed phase) to be highly accurate in the diagnosis and characterization of HCC but, like ultrasound, may miss smaller lesions. Pooled estimates reveal a sensitivity of 68% and a specificity of 93%[19].

In another study conducted by Jang HJ and colleagues on 1-2 cm HCC detected on surveillance USG, arterial and delayed phases were proved to be the two essential phases providing highest specificity (99%) and sensitivity (57%) than the combination of arterial and porto-venous phases. It showed equal performance when compared with triphasic and quadriphasic combinations (specificity 98 % and sensitivity 57%) recommended by ASSLD[20].

In a study on hypervascular liver lesions conducted by Liu Yl and colleagues, a statistically significant difference was noticed on delayed phase in percentage attenuation ratio (PAR) calculated as 100 × ratio of attenuation of adjacent liver to that of the lesion between lesions that were HCC (median PAR = 121) and those that were not (median PAR = 101). PAR ≥107 on delayed phase imaging achieved maximal sensitivity (100%) with high specificity (75.8%), PPV (63.6%), and NPV (100%) in HCC diagnosis[7].

In study by Hafeez S et al on 45 patients, 136 liver lesions (125 malignant and 11 benign) were detected with the help of various enhancement patterns. Histopathological correlation of these lesions proved that Triphasic CT showed a sensitivity of 100%, specificity of 80%, negative predictive value of 100%, positive predictive value of 94.5% and diagnostic accuracy of 95.5% in differentiating malignant from benign liver lesions[3].

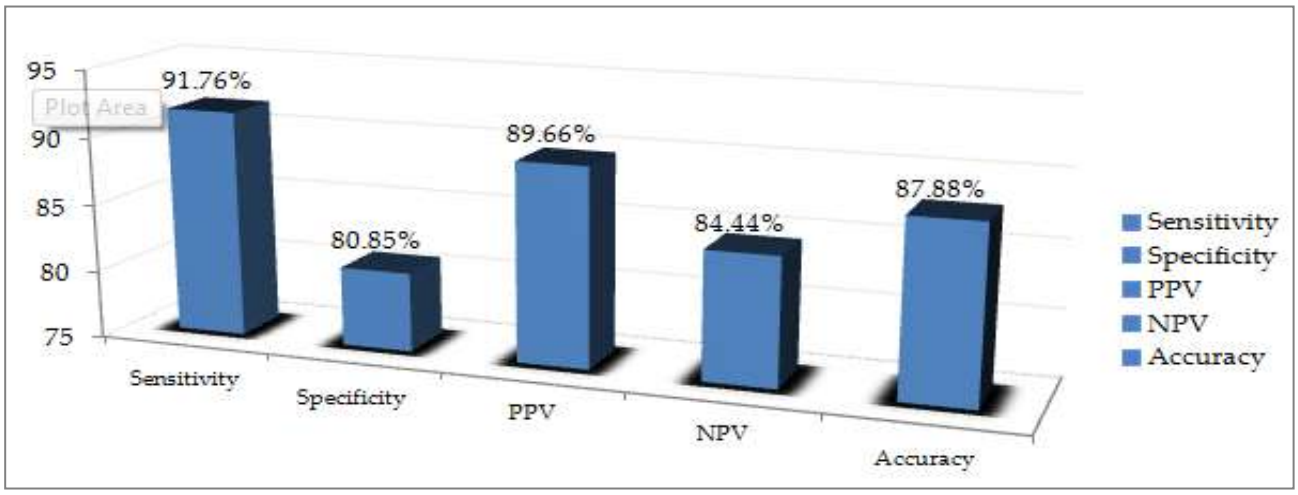

Figure-2: Diagnostic accuracy of triphasic CT for diagnosing hepatocellular carcinoma.

Our study calculates the exact quantitative washout of contrast from hepatic lesions instead of relying only on subjective observation of washout minimizing inter-observer bias. So it is concluded that quantitative washout calculated on Triphasic CT scan is a highly sensitive and accurate non-invasive modality for diagnosis of HCC keeping histopathology as gold standard.

CONCLUSION

This study concludes that quantitative washout calculated on Triphasic CT scan is a highly sensitive and accurate non-invasive modality for diagnosing HCC. We recommend that quantitative washout calculated on Triphasic

CT scan should be used routinely as a prime modality for diagnosing HCC instead of liver biopsy.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

REFERENCES

1. Forner A, Reig M, Varela M, Burrel M, Feliu J, Briceño J, et al. Diagnosis and treatment of hepatocellular carcinoma. Update consensus document from the AEEH, SEOM, SERAM, SERVEI and SETH. Medicina Clínica (English Edition) 2016; 146(11): 511-e1.
2. Memon WA, Haider Z, Beg MA, Idris M, Haq T, Akhtar W, et al. Diagnosis of hepatoma using grayscale and Doppler ultrasound in patients with chronic liver disease. Int J Gen Med 2011; 4: 751–4.
3. Hafeez S, Alam MS, Sajjad Z, Khan ZA, Akhter W, Mubarak F. Triphasic computed tomography (CT) scan in focal tumoral liver lesions. J Pak Med Assoc 2011; 61: 571-5.
4. Luca A, Caruso S, Milazzo M, Mamone G, Marrone G, Miraglia R et al. Multidetector row computed tomography (MDCT) for the diagnosis of hepatocellular carcinoma in cirrhotic candidates for liver transplantation: Prevalence of radiological vascular patterns and histological correlation with liver explants. Eur Radiol 2010; 20: 898-907.
5. Cogley JR, Miller FH. MR Imaging of benign focal liver lesions. Radiol Clin North Am 2014; 52: 657-82.
6. Li CS, Chen RC, Tu HY, Shih LS, Zhang TA, Lii JM, et al. Imaging well-differentiated hepatocellular carcinoma with dynamic triple-phase helical computed tomography. Br J Radiol 2006; 79(944): 659-65.
7. Liu YI, Shin LK, Jeffrey RB, Kamaya A. Quantitatively defining washout in hepatocellular carcinoma. Am J Roentgenol 2013; 200: 84-9.
8. Rehan N, Farooqui R, Niazi M, Ijaz M, Khan MA. Triphasic Helical CT Scan :Value of arterial phase acquisition in detection of focal lesion in cirrhotic liver. J Rawal Med Coll 2011; 15: 3-5.
9. Peijie Lv, Lin XZ, Li J, Li W, Chen K. Differentiation of small hepatic hemangioma from small hepatocellular carcinoma: Recently introduced spectral ct method. RSNA 2011; 259: 722-9.
10. Yusuf S, Kashmir SB, Mehmood RA. Frequencies of different benign and malignant focal hepatic lesions on Triphasic CT scanning in patients referred with suspicion of hepatocellular carcinoma. Rawal Med J 2016; 41(1): 39-42.
11. Iannaccone R. Hepatocellular carcinoma: Role of unenhanced and delayed phase multi-detector row helical CT in patients with cirrhosis. Radiology 2005; 234: 460-67.
12. Doyle DJ, O'Malley ME, Jang HJ, Jhaveri K. Value of the unenhanced phase for detection of hepatocellular carcinomas 3 cm or less when performing multiphase computed tomography in patients with cirrhosis. J Comput Assist Tomogr 2007; 31: 86–92.
13. Lee KH, O'Malley ME, Haider MA, Hanbidge A. Triple-phase MDCT of hepatocellular carcinoma. AJR Am J Roentgenol 2004; 182: 643-49.
14. Lovet JM, Ducreux M. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012; 56: 908-43.
15. Bruix J, Sherman M. Management of hepatocellular carcinoma: An update. Hepatology 2011; 53: 1020-22.
16. Bolondi L. Characterization of small nodules in cirrhosis by assessment of vascularity: the problem of hypovascular hepatocellular carcinoma. Hepatology 2005; 42: 27–34.
17. Kim SH. Gadoxetic acid-enhanced MRI versus triple-phase MDCT for the preoperative detection of hepatocellular carcinoma. AJR Am J Roentgenol 2009; 192: 1675–81.
18. Ronot M, Vilgrain V. Imaging of benign hepatocellular lesions: current concepts and recent updates. Clinics and research in hepatology and gastroenterology 2014; 38(6): 681-8.
19. Colli A, Fraquelli M, Casazza G. Accuracy of ultrasonography, spiral CT, magnetic resonance, and alpha-fetoprotein in diagnosing hepatocellular carcinoma: A systematic review. Am J Gastroenterol 2006; 101(3): 513-23.
20. Jang HJ, Kim TK, Khalili K, Yazdi L, Menezes R, Park SH, et al. Characterization of 1-to 2-cm liver nodules detected on hcc surveillance ultrasound according to the criteria of the american association for the study of liver disease: Is Quadriphasic CT Necessary? AJR Am J Roentgenol 2013; 201(2): 314-21.