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MDCT Contrast Enhancement Patterns of HCC

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ABSTRACT

Hepatocellular Carcinoma (HCC) 'responsible for a large proportion of cancer deaths worldwide' is frequently diagnosed after the development of clinical deterioration with poor survival. Triple phase CT scan enables good characterization and diagnosis even at an early stage and could improve survival. **Objectives:** To describe the frequency of (Heterogonous Mosaic) enhancement pattern of Hepatocellular carcinoma in cirrhotic patients on triple phase MultiDetector CT. **Study Design:** Descriptive Case series. **Material & Methods:** Study was performed in Radiology Department of FPGMI / Shaikh Zayed Hospital Lahore from September 30 2008 to March 30 2009. Sixty cirrhotic patients with ultrasound and histopathological evidence of Hepatocellular cancer underwent Triple phase contrast enhanced CT. **Results:** In sixty patients, 110 lesions detected. Eighty one (73.6%) of these were heterogeneous in appearance, while 55.5% of these were hyperattenuating as well. Seventy five (61/81) percent heterogeneous lesions showed mosaic pattern of enhancement. Twenty nine lesions (26.4%) were homogenous and 89% of these were hyperattenuating. **Conclusion:** Majority of the hepatocellular carcinoma lesions appear as heterogeneous and hyperattenuating. Mosaic internal contrast distribution is the leading pattern in these nodular lesions followed by ring enhancement.

Key Words: Hepatocellular Carcinoma, Triple-Phase Multidetector CT, Enhancement Pattern.

INTRODUCTION

Hepatocellular Carcinoma (HCC) is one of the most common abdominal malignancies worldwide and occurs most often in patients with chronic liver disease and cirrhosis compounds this problem. Patients who are carriers of chronic hepatitis B or C virus infection, or those who have cirrhosis caused by alcohol or hemochromatosis are at greater risk of developing HCC.[1] HCC classically arises and grows in a silent fashion, making its discovery challenging prior to the development of later stage disease. Various clinical presentations generally relate to the extent of hepatic reserve at time of diagnosis. Life expectancy of patients with HCC is poor, with a mean survival of 6–20 months and likely reflects the mortality/incidence ratio, which is close to 1.[2] These figures have remained steady despite of substantial progress in the diagnostic and therapeutic arena of HCC. Radiological imaging plays essential role in early detection, staging and treatment of the tumor thus creating hopes for better long-term outcome.[3-6]

Various diagnostic and imaging techniques are used with merits and demerits. Alpha Feto-protein (AFP) levels have high sensitivity but they can be elevated in other pathologies as well. Ultrasound (US) is frontline investigation to see focal lesions in the liver but small hyperechoic masses seen on US require further evaluation because they can represent hemangioma, metastatic disease, or, less likely, HCC. [7, 8]

Primary goal of imaging is detection and characterization of the lesion. Additional roles of imaging include tumor staging and surveillance. A complete preoperative evaluation is critical for the appropriate selection of patients with HCC for whom surgical treatment may be attempted. Sonography, CT, and MRI may play a role in the evaluation of patients with suspected HCC. Of these imaging modalities, CT is the most commonly used in the diagnosis, staging, and surveillance of HCC. [9]

Typically, HCC shows rich arterial neovascularization with a decrease in the portal

supply and, therefore, are better detected during a phase of maximal arterial enhancement. Consequently, computed tomography (CT) protocols have been optimized for hepatic arterial phase acquisition followed by a portal venous phase *i.e.* biphasic CT.[10]

MDCT has rapidly gained acceptance as the preferred CT technique for routine liver evaluation because it provides image acquisition at peak enhancement of the liver parenchyma. [11] Using an additional delayed phase of acquisition can possibly help to confirm lesions of HCC and better characterization of these detected lesions in context of contrast enhancement patterns. [12]

The rationale of proposed work is to portray the utility of the multiphase MDCT not only in detection of hepatocellular cancer lesions of variable sizes but also characterize the patterns of enhancement of these lesions. This will aid in depiction of maximal number of tumor lesions non-invasively, which in turn will affect the staging, management decisions and long-term prognosis.

OBJECTIVES

To describe the frequency of enhancement patterns of hepatocellular carcinoma in cirrhotic patients on triple phase MultiDetector CT.

MATERIALS AND METHODS

After the approval of the ethical committee of institute this work was conducted in Radiology Department in collaboration of Gastroenterology and Histopathology Departments. Study population was selected as per inclusion criteria which includes diagnosed cirrhotic cases of hepatocellular carcinoma (HCC) on histopathology through ultrasound guided FNAC. We included all grades of tumor including Grade I (well), Grade II (moderate) and Grade III poorly differentiated lesions and 35-60 years from both genders. Patients with known contrast allergies or serum creatinine levels of >1.8 mg/ml, those in hepatic encephalopathy and patients with dual malignancy or tumors other than HCC were excluded from this work.

Study population was selected under non-probability purposive sampling and study design was described as descriptive case series.

Selected subjects of this study had an informed written consent. With the help of Gastroenterology Department, diagnosed cirrhotic patients with hepatocellular cancer were included in the study and detailed demographic features of subjects were obtained as laid out in the proforma.

Triple phase CT scan was obtained on a 64 slice Multidetector CT scanner (LightSpeed VCT, General Electric Medical Systems,) using 1.5 ml/Kg of non-ionic contrast medium injected at rate of 3.5 mL/sec into an antecubital vein. The scanning parameters included a collimation 5 mm; reconstruction interval 2.5 mm; table speed 11.25 mm per rotation; pitch 3; factors 120 kV; and 190–370 mA. After acquiring unenhanced sequence, an arterial (30 sec after injection), portal venous (60 sec after injection) and delayed (5 minutes) scans were obtained with a standard reconstruction algorithm for number and size of the lesions. Effect modifiers were size of lesion (small <2 cm, medium 2-5 cm and large >5 cm). Appearance and enhancement pattern of lesions after contrast was documented as heterogeneous mosaic while others included homogeneous (hypo, iso or hyper-attenuating) or heterogeneous (ring or peripheral nodular) in all three phases of scan.

Statistical analysis

Collected data was analyzed using statistical soft ware SPSS for windows. Qualitative variables included appearances and contrast enhancement pattern of lesion as heterogeneous mosaic lesions. Frequencies and percentages were calculated. While quantitative data included size and number of lesions. Mean and standard deviation was calculated. Data was stratified for size of lesions to explain effect modifier.

RESULTS:

Sixty patients fulfilling the inclusion criteria were registered for this study. Thirty Eight (63.3%) subjects were male, mean age of population in this study was 53.9±11.2 years.

Histopathology of tumor lesions showed as most of the patients (50%) had moderately well differentiated tumors on FNAC results. Forty

(66.7%) patients were with positive viral serology for hepatitis C followed by 30% with HBV serology. Thirty-eight (63.3%) patients in this study had high values of alpha-fetoproteins.

Table 1: Age distribution of data.

Gender	n	Mini.	Maxi.	Mean	SD
Age (Years)	60	30	88	53.88	11.22

Table 2: Size of lesions of data

Lesion Size	n	Mini.	Maxi.	Mean	SD
Size (cm)	110	1.30	11.2	4.22	2.13

Table 3: Enhancement patterns of lesions

Pattern	Frequency	Percentage
Mosaic	61	75.3
Wavy ring	10	12.3
Irregular ring	9	11.1
Peripheral nodular	1	1.3
Total	81	100

Table 4: Enhancement distribution on scan phases.

Pattern	Frequency	Percentage
Hyperattenuating	45	55.5
Hypoattenuating	26	32.1
Isoattenuating	10	12.4
Total	81	100

A total of 110 tumor lesions were detected in these 60 patients on triple phase CT scan with MDCT. These scans were interpreted by a senior radiologist with >5 years working experience of cross sectional imaging with CT.

Almost all (94.5%) lesions were found in the right lobe of liver predominantly involving the segments 4, 5, 6, 7, and 8 Most commonly lesions were distributed in segment IV and VIII.

These 110 lesions were further characterized as either heterogeneous or homogenous on gross appearance.

Eight one (73.6%) lesions appeared as heterogeneous on contrast enhanced triple phase CT. Sixty five percent of patients had heterogeneous lesions followed by 18.3 % patients with mixed lesions.

These 110 lesions were categorized as small, medium and large on the basis of size in centimeters as already described. Sixty-seven of these were of medium sized lesions and 33 were categorized as large Average lesion size was 4.22±2.13 cm. Most of the patients were having solitary lesion while maximally we detected five lesions in any patient.

We also calculated total number of lesions detected on each phase of scan. Maximum lesions were detected by delayed phase followed by hepatic arterial phase. Portal venous phase missed 5% of heterogeneous and 11% of homogenous lesions.

Heterogeneous lesions (n = 81)

Eighty-one heterogeneous lesions detected collectively by all scan phases were further sub-classified on the basis of attenuation characteristics.

Fifty five percent lesions were hyper-attenuating on hepatic arterial phase followed by 32 % lesions grouped as hypoattenuating. Further these lesions were classified on internal distribution of the contrast as mosaic, tumor capsule (ring) as wavy or irregular and additional patterns. Mosaic pattern of enhancement were leading and were documented in 75 % of patients on hepatic arterial phase followed by tumor capsule or ring in 23.8 % of patients.

Most of the tumor lesions (61.7%) were hypoattenuating on portal venous phase with further characterizing mosaic pattern in 77 % of the reported lesions. Significant number of lesions (11%) was isoattenuating to parenchyma; a major cause of missed lesion when only portal venous phase were analyzed.

Fifty nine lesions on delayed phase were hypoattenuating which is dominant pattern of this phase. In this phase we further analyzed the classic ring formation, which we recorded in 54 % of these lesions. We were unable to find any heterogeneous lesion, which remained hyperattenuating on delayed phase imaging.

Enhancement characteristic on all three phases were further categorized. Well-differentiated lesions were largely hyperattenuating on HAP and PVP and almost hypoattenuating on delayed phase. While moderately well differentiated lesion had

Table 5: Tumor Grades and CT patterns distribution

Scan Phase	Attenuation	Histopathology		
		Well Differentiated	Mod. Well Differentiated	Poorly Differentiated
HAP (n=81)	Hyper	20	16	11
	Iso	4	4	4
	Hypo	5	10	7
PVP (n=81)	Hyper	13	12	9
	Iso	2	02	3
	Hypo	14	16	10
DP (n=81)	Hyper	0	0	0
	Iso	4	10	4
	Hypo	25	20	18
Heterogeneous lesions				
Mosaic		2	22	18
Tumor Capsule		1	11	7
Tumor Necrosis		0	1	15
Venous Invasion		0	0	4
AP shunt		0	4	6

significant hypoattenuating component on HAP, PVP and delayed phase scanning. Finally poorly differentiated heterogeneous lesions remained hypoattenuating on all scan phases except HAP which shows a significant number as hyperattenuating.

The frequency of distribution of lesion characteristics and correlated them with histopathological grade. Almost all tumor grades showed mosaic pattern of internal enhancement. Poorly differentiating tumors had significant number of lesions (15) showing tumor necrosis. Additionally portal venous thrombosis and arterioportal shunting were more common in higher tumor grades.

Tumor lesion size was also compared with pattern of enhancement of heterogeneous lesions. We found medium and large tumors had predominantly mosaic pattern of contrast distribution while irregular tumor capsule, necrosis and venous invasion were mostly seen in the larger lesions. Arterioportal shunting was equally noted in medium and large sized lesions.

Homogenous lesions (n=29)

Twenty nine homogenous lesions were also further analyzed for pattern of enhancement considering attenuation qualities. Twenty six of these lesions showed hyperattenuation on HAP with significant number on PVP also were hyperattenuating (37.9%). Delayed phase showed dominant pattern of hypoattenuation in 23 lesions.

We also compared these attenuation characteristics with tumor grade. Well-differentiated lesions were predominantly (12/29) hyperattenuating followed by moderately differentiated lesions. Largely tumor lesions were isoattenuating on early tumor grades on PVP and almost hypoattenuating on delayed phase.

DISCUSSIONS

The advances in CT technology have resulted in improvement in the ability to detect liver tumors. Many of the early studies suggested that contrast enhanced imaging technique will increase the detection of hypervascular liver tumors. [13]

Lesions that show greater component of enhancement than surrounding hepatic parenchyma on arterial phase are classified as hypervascular. Because more patients with cirrhosis liver and focal lesions are scanned during arterial phase of enhancement as a part of dual or triple phase CT scans protocols. [14, 15]

Mean age of the patients in our study was

53.9 years which is well correlated with Lee HM (56.8 years), Iannaccone R (56 years), Hwang GJ (52 years), and Lee KHY had mean age of 57.6 years. We have nearly same age range as been published by Sharaif et al (56.2 years). [5, 11, 14, 16]

Gender distribution of our study showed 38% females and was almost correlated with Li CI (32%), and Baron RL (29%); while other studies have dominated male sample population. [17, 18]

In our study 66% patients had shown positive HCV serology and only single patient with alcoholic liver cirrhosis, while most of the non Asian studies were dominated by HBV positive serology and alcoholic liver cirrhosis. AS HCV preventive measures are highly sophisticated in the European countries and US, and alcohol consumption is much more than our territory so our data included more patients with positive HCV serology.[19, 20]

We had 63% of patients with high AFP levels with similar occurrence as been reported by Sharief et al. i.e., 65% patients with high AFP levels. Lee KHY reported only 20% patients having normal AFP levels and another 15% having borderline results. [5, 19]

We have higher number of moderately well differentiated tumors while two previously published studies have studied well differentiated tumors. [18, 20] This disparity in patient selection is due to lack of early presentation of our population with tumor lesion in the tertiary care hospital. Another justification for this is lack of early sophisticated investigation with multislice CT.

Total number of lesion in our study was 110. This is comparable with the study of Stevens WR who studied 100 lesions, Lee HM (58 lesions), Murakami T (96 lesions), Hwang GJ (81 nodular HCC lesions) and Lee KHY with 79 lesions. Most of our patients were having single lesion with only 10 patients having more than 3 lesions. [14, 16, 19, 21]

Lee HM showed 2 to 10 lesions with average number of 3 per patients. Maximum number of lesions detected and interpreted with confidence is reported as 15 in any patient. In this regard we were in safe limits with maximum lesions in any patient of 5. [14, 22]

We in our study included all three size groups of nodular HCC including small, medium and large size with more than 5 cm. Various group of authors focused especially on smaller lesions suggesting utility of CECT in early detection of tumor lesion. [23, 24]

Average lesion size in this study was 4.22 cm while average size of lesion in single Asian study reported by Yaqoob et al. was 3.1 cm and median size in Steven WR study was 7.5 cm. [10, 21]

Tumor lesion size range in our study was 1.3 to 11.2 cm which similar as reported by Steven WR and Lee HM whose data showed 1.2 to 12 cm size range with mean size 2.9 cm. Most of our lesions are in right lobe with dominance of segments 4a, 4b, and VIII. We were unable to find any published data especially mentioning segmental distribution of lesions. Right lobe tumor distribution was similar as been already reported. [14, 21, 25]

Stevens WR showed 65% lesions as heterogeneous while in our study this figure was 73 %. Lee HM et al reported as 78 % lesions as heterogeneous as their tumor size was 7.5 cm. This data suggested that larger is the size of tumor more heterogeneous is appearance of tumor on contrast enhanced CT. [14, 21]

We in our study shown those lesions seen at hepatic arterial phase are more confirmed on additional delayed phase while purely portal venous phase study slightly under estimated total number. So adding additional delayed phase with biphasic CT is helpful to detect small isodense lesions on HAP. These results are consistent with those reported by Iannaccone R et al who showed improved sensitive from 89.2 to 92.8 with addition of delayed phase in routine biphasic scan protocol. Similar extra detection of lesions is reported by the Monazawa S et al who were able to pick 3 more lesions with additional delayed phase scanning. [11, 23]

Although our results regarding lesion detection are almost similar with only 2 more lesions on delayed phase which when retrospectively analyzed were also found on HAP. So adding one more phase adds more confidence for lesions detection especially those, which were small isoattenuating lesions.

Most 55% of our lesions were hyper-attenuating followed by a medium hypoattenuating group same as Baron RL et al reported more number of lesions as hyperattenuating. Similar results are reported by the Monazawa and Yaqoob et al. As we

had significant number of hypoattenuating lesions and ultimate cause may be large size of lesions in our study. These larger lesions have more necrotic component and poor central vascularity which may result there hypoattenuating appearance. We noted that medium and small lesions predominantly hyperattenuating followed by isoattenuation. [10, 23]

These large hypoattenuating lesions significantly contributed in portal venous phase which showed a dominant group of hypoattenuation. As most of the lesion in our study showed hypoattenuation on delayed phase scanning. Possible explanation may be increased cellularity or decreased interstitium in these lesions when compared to surrounding liver parenchyma.

When we further classified internal contrast distribution of these heterogeneous lesions we found mosaic pattern of enhancement as dominant. Seventy five percent lesions showed this type of enhancement.

Lee KH reported 86% lesions as mosaic appearing, Stevens WR showed 46% mosaic enhancements. In our study medium and large sized lesions significantly showed mosaic enhancement. These results are consisting with reported by van Leeuwen et al. [26]

Lalonde et al. studied 34 patients with nodular HCC. They got CECT and MRI of all patients. They concluded that mosaic and capsule patterns are dominant morphologic patterns on imaging. They further concluded that delayed phase CT are much valuable for capsule depiction. In our study most of the patients (75%) showed mosaic pattern and 23% showed ring pattern on HAP. While delayed phase showed 54 % lesions showing classical capsule pattern which is said to be subtype of HCC with good prognosis. [27]

CT studies in Asian population have reported a large proportion of capsulated lesions especially on delayed phase scanning as many as 67%. We have consistent results as in our study this figure was 54%. While only 23% patients showed capsule on HAP; so additional delayed phase helps for better characterization of encapsulated lesions. [28]

Portal venous invasion reported by these authors is higher than our data. This may be explained by the different population group of patient studied as they had seen this finding more in alcoholic liver cirrhosis and we had only single patient in this category. Secondly location of the tumors may different which resulted in direct invasion the portal vein.

Steven WR reported 31 % lesion with complete or partial encapsulization while in our study only 23 % lesions showed such property.

Arterioportal shunting was similarly detected as been reported by Honda H et al. [23]

Well differentiating tumors in our study had mainly homogenous appearance and hyperattenuation on HAP. These lesions were equally hyper and isoattenuating on PVP and predominantly hypoattenuating on delayed phase. Lee J et al also showed 43 % tumors as hyperattenuating and significant group as isoattenuating. They mainly studied tumors smaller than 2 cm while our group also included tumor in the range of 3 cm. [24]

Monazawa et al. showed hyperattenuation of well differentiated lesions (15/44) and 13/93 lesions showed hyperattenuation which were moderately or poorly differentiated. We in our study showed dominant hyperattenuating pattern in the well differentiating group while a significant large number of lesions were also hypoattenuating besides hyperattenuation and showed moderate to poor differentiation on histopathology. [23]

Li et al. also reported equal number of hyper and iso attenuation of lesions with dominating hyperattenuation. Again largest tumor they included was 2.7 cm with mean of 1.5 cm. [18]

AS in our study, well differentiated tumors are usually small and have variable vascular supply and vascular. These tumors with low grade malignancy usually receive poor arterial supply and frequently have a significant venous supply.

The above mentioned disparity reflects differences in vascular supply and development of neovascularity and might have a different grade of malignancy. [29]

Conclusively internal tumor vascularity which in turn depends on grade of tumor is the mainstay of contrast distribution in the lesions which ultimately is portrayed by enhanced CT giving variable pictures of these lesions.

CONCLUSION

We concluded from this work that most the HCC lesions are heterogeneous in appearance and hyperattenuating on triple phase MDCT. Mosaic internal distribution was the leading pattern followed by capsule formation. Homogenous lesions are smaller and show hyperattenuation on contrast enhanced CT.

STUDY LIMITATIONS

In this study we had histopathological results of single largest lesion in each patient that was approachable by ultrasound guided FNAC. But in the mean time same patients had variable sized lesions. These lesions might have variable grades of differentiations so enhancement pattern was not individually applicable as it was not possible to get histopathology of every lesion. This might added some bias in our selection criteria.

These results are only applicable to nodular HCC lesions as it is difficult to characterize infiltrating type lesions.

Most of our patients were of HCV serology so result might be different from those published by western studies with a large group of alcoholic cirrhosis and non B, non C cirrhosis.

The dose of contrast material, injection speed, and scanning time were not individualized in this study, which might have impact on lesion characterization.

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