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RESEARCH ARTICLE

MULTIDETECTOR CT IN DETECTION OF HEPATOCELLULAR CARCINOMA MEETING THE MILAN CRITERIA BEFORE LIVER TRANSPLANTATION

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ABSTRACT

Background: Liver transplantation has been considered to be the only causal treatment for patients with liver cirrhosis and hepatocellular carcinoma (HCC) due to its theoretical advantage of eliminating both the tumor and liver disease. However, because of the shortage of donor organs, it is strongly recommended that liver transplantations should be performed on cirrhotic patients with HCCs only when the patients meet the predetermined criteria. Imaging is thus decisive in the patient inclusion or exclusion from transplantation lists.

Objective: The purpose of this study was to assess the diagnostic performance of MDCT in the detection of hepatocellular carcinoma in cirrhotic patients who are recommended for liver transplantation according to the Milan criteria.

Methods: This study included 35 patients (29 males and 6 females) with their age ranged from 39 years to 60 years old, presented to the transplantation unit of the National Liver Institute, Menoufia University in the period between May 2013 and December 2014. Potential recipients with focal lesion on their ultrasound underwent Triphasic CT and after liver transplantation the imaging findings were correlated with histopathological findings in the explanted livers on a patient-by-patient and a lesion-by-lesion basis.

Results: Histopathologic examination revealed 46 hepatocellular carcinomas in 31of 35 patients while MDCT revealed 42 hepatocellular carcinomas in 30 of 35 patients. Patient-by-patient analysis showed that the sensitivity of MDCT in detection of HCC was 90.3 %, its specificity was 50 % & its accuracy was 85.7%.

Conclusion: Multidetector CT (MDCT) has reasonable sensitivity and high diagnostic accuracy in the detection of hepatocellular carcinoma in patients with cirrhosis who will undergo liver transplantation according to the Milan criteria

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third most common cause of cancer-related deaths; the number of new cases per year is approaching 750,000 (Mazzaferro *et al*., 2011). Liver transplantation, recently, has become the ultimate solution for decompensating liver diseases and it has been considered to be the only causal treatment for liver cirrhosis in patients with hepatocellular carcinoma (HCC) due to its theoretical advantage of eliminating both the tumor and liver disease. However, because of the shortage of donor organs, it is strongly recommended that liver transplantations should be performed on cirrhotic patients with HCCs only when the patients meet the predetermined criteria in terms of number and extent of HCCs. Imaging is thus decisive in the patient inclusion or exclusion from transplantation lists. The imaging techniques used are CT, MRI and ultrasonography (Elkholy and Elshazly, 2014; Kim *et al*., 2008). The best indications for liver transplantation according to Milan criteria are known to be patients with a single tumor 5 cm or patients with fewer than three nodules not exceeding 3 cm in diameter and no macroscopic vascular invasion or extra hepatic metastases (Kim *et al*., 2008). MDCT is currently considered one of the most reliable techniques for evaluating hepatic cancer in the presence of cirrhotic liver disease and it is primarily involved in patient treatment strategies (Mortelé *et al*., 2001).

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HCC can be diagnosed radiologically, without the need for biopsy if the typical imaging features are present. This requires a contrast-enhanced study (dynamic CT-scan or MRI) (Bruix and Sherman, 2011). The long waiting time caused by the shortage of donor organs often results in tumor progression and dropout from transplantation candidacy. To that end, since, UNOS (United Network of Organ Sharing) has adapted the MELD (Model for End-stage Liver Disease) criteria favoring patients with HCC, in order to allocate organs according to the clinical urgency, thereby reducing the dropout rate , and the diagnostic performances of imaging modalities in evaluating the appropriateness of liver transplant candidates have become of major importance (Kim *et al*., 2008).

MATERIALS AND METHODS

The study was conducted in the National Liver Institute, Menoufia University in the period from May 2013 to December 2014. It included 35 patients (29 males and 6 females) with their age ranged from 39 to 60 years old, presented to the transplantation unit of National liver Institute, Menoufia University. The inclusion criteria were: Patients with advanced liver disease and focal lesions on their ultrasound, their Serum creatinine < 1.5 mg/dl. The exclusion criteria: Patients with renal impairment.

Consent was taken from patients or their relatives before CT study and they had the right to refuse at any time. The study was approved by the Research Ethics Committee of the National Liver Institute and the Research Ethics Committee of the Faculty of Medicine, Menoufia University. All individuals were subjected to clinical assessment including full history and clinical examination, laboratory investigation, ultrasound with Doppler study & Triphasic CT scanning.

CT was performed with a Siemens Somatome Definition scanner (20 detectors). Patient preparation for CT was as follows: 1- Fasting for 6 hours before scan. 2- No oral contrast was used. 3- Creatinine clearance >30. 4- Vigorous oral hydration. 5- Intravenous cannula introduced through the antecubital vein. The patient laid supine, scanning started from the lung bases down to the symphesis pupis in all phases. One scout was acquired in anteroposterior view. The examination was planned on these scouts from the level of the top of the right diaphragmatic copula (Hepatic Dome) till the symphesis pupis in the precontrast and post contrast sequences. The pre-contrast series were taken by using a 10mm section thickness, a slice pitch of 1.5, a gantry rotation period 0.6 second and a table speed of 15 mm per rotation. X –ray tube voltage was 120 KV and the current was 240-280 mA.

Multidetector CT scanner was applied to perform arterial, portovenous & delayed phases on all patients. All patients received 120ml of non ionic material (Ultravist 300) introduced intravenous with an infusion rate 4.0ml/sec using a single power injector. Arterial dominant phase images were acquired at 18 sec (collimation, 1.25 mm; pitch 0.6; kVp, 120; mA, 240–280). Portal dominant phase images were acquired at 60 sec (collimation 2.5 mm; pitch 0.6; kVp 120; mA 240–280). Delayed phase images also then taken through the entire liver and were acquired at 200 sec (collimation 2.5 mm; pitch 0.6; kVp 120; mA 240–280).

All further data were reconstructed with a standard algorithm and post-processing was performed on a commercially available workstation (Syngo work station) that equipped with software tool that allowed generation of 3D images. We used MIP technique for 3D image reconstruction that was helpful in detection of details and orientation of vessels. All scans were interpreted for the presence of HCC which was defined as an intensely enhancing nodule in the arterial phase followed by a well-defined area of hypo attenuation relative to surrounding liver parenchyma in the delayed phase, and for detection of the total number, the size & the location of nodules in liver segments in addition to the application of Milan criteria. Gross and histopathological analyses of the explanted livers of all our patients were performed by an experienced liver pathologist. All explanted livers were fixed in formalin and sectioned at 7-10 mm interval in the transverse plane. Each nodular lesion that was different from the background cirrhotic liver in the morphologic features, colours or size, was fixed in formalin, embedded in paraffin, and further sectioned for additional evaluation.

RESULTS

The histopathological examination of the explanted liver detected 46 focal lesions(HCC) from which 8 focal lesions (17.4%) were small in size (≤10mm), 13 focal lesions (28.3%) were of intermediate size (11-20mm) and the remaining 25 focal lesions (54.3%) were large in size (>20mm) , US detected 32 focal lesions from which 6 focal lesions (18.8%) were small in size, 10 focal lesions (31.2%) were of intermediate size and the remaining 16 focal lesions (50%) were large in size & MDCT detected 42 focal lesions(HCC) from which 8 focal lesions (19%) were small in size, 12 focal lesions (28.6%) were of intermediate size and the remaining 22 focal lesions (52.4%) were large in size. Table 1

Table 1. Different measurements for the size of HCC nodules among studied cases by US, MDCT and histopathological examination

Nodular size	US (n=32)	MDCT (n=42)	Histopathological findings (n=46)
Small (≤10mm)	6(18.8%)	8(19%)	8(17.4%)
Intermediate (11-20mm)	10(31.2%)	12(28.6%)	13(28.3%)
Large (>20mm)	16(50%)	22(52.4%)	25(54.3%)

US= ultrasound, MDCT= Multidetector CT, n= number of focal lesion (HCC)

In analysis based on lesion diameter, the sensitivity and positive predictive value (PPV) of MDCT were calculated for the three size groups (small, intermediate & large) detected at histopathological examination of the explanted liver. Table 2, Figure1

Table 2. Evaluation of MDCT in detection of different size of HCC nodules among studied cases

Nodular size	Sensitivity	Positive predictive value
Small (≤10mm)	5/8 (62.5%)	5/8 (62.5%)
Intermediate (11-20mm)	11/13 (84.6%)	11/12 (91.7%)
Large (>20mm)	22/25 (88%)	22/22 (100%)

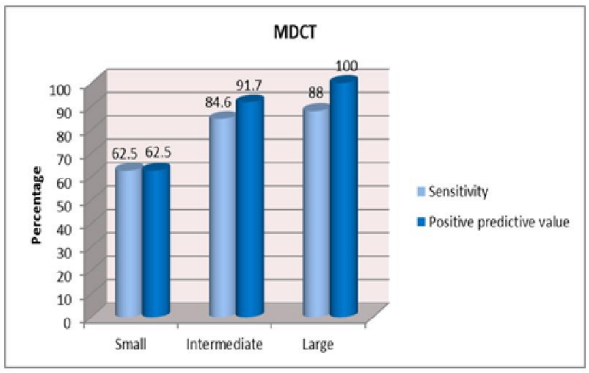

Figure 1. Evaluation of sensitivity and positive predictive value of MDCT in detection of different size of HCC nodules among studied cases

The results of patient by patient analysis were reported in table 3, which showed sensitivity, specificity, false positive result, false negative result, positive predictive value, negative predictive value & accuracy. Table 3, Figure2

Table 3. Evaluation of MDCT in detection of HCC among studied cases

	Patient by patient finding
Sensitivity (%)	90.3
No of patients	28/31
Specificity (%)	50
No of patients	2/4
False positive (%)	50
False negative (%)	9.7
Positive predictive value (%)	93.3
Negative predictive value (%)	40
Accuracy (%)	85.7

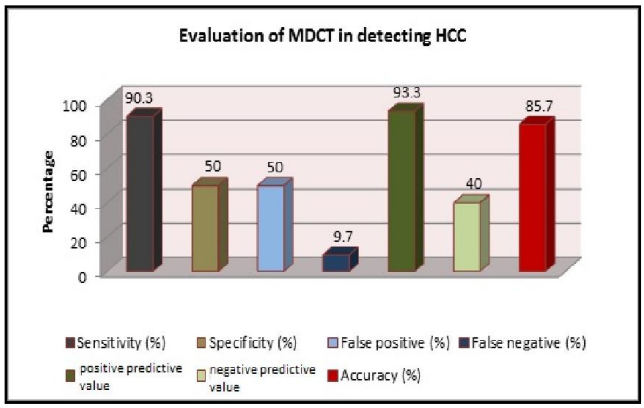

Figure 2. Evaluation of MDCT in detection of HCC among studied cases on patient by patient basis

Comparison between the histopathological results and MDCT results reavled that the number of HCC nodules that equal histopathological result regarding size were 34 (80.9%), the number of HCC nodules underestimated by MDCT were 7 (16.7%) and the number of HCC nodules that overestimated by MDCT were 1 (2.4%). Table 4 Application of Milan criteria according to CT results and after histopathological finding showed that five patients have no HCC nodules on their CT, three of them proved to have HCC nodules in their explant & the pathology report of the other two patients was identical to the result of CT. The other thirty patients with HCC nodules in their CT were within Milan criteria after correlation with pathology results. Twenty six patients had HCC nodules within Milan criteria (86.7%), two patients had HCC nodules beyond Milan criteria (6.7%) & two patients didn't have HCC nodules. After Comparison between Milan after CT and that after pathology we noticed that there were no significant difference (p value= 0.09). Table 5

Table 4. Measurements of CT for HCC nodules versus pathology among studied cases

CT nodular size	N=42	%
Equal to histopathological findings	34	80.9
Underestimated to histopathological findings	7	16.7
Overestimated to histopathological findings	1	2.4

Table 5. Comparison between Milan after CT and that after histopathological findings

MDCT	Milan after Histopathological findings: Within N	Within %	Beyond N	Beyond %	Not Applicable N	Not Applicable %	X^2 test	P value
Not applicable (n=5)	3	60	0	0.0	2	40	4.87	0.09
Within Milan (n=30)	26	86.7	2	6.7	2	6.7		

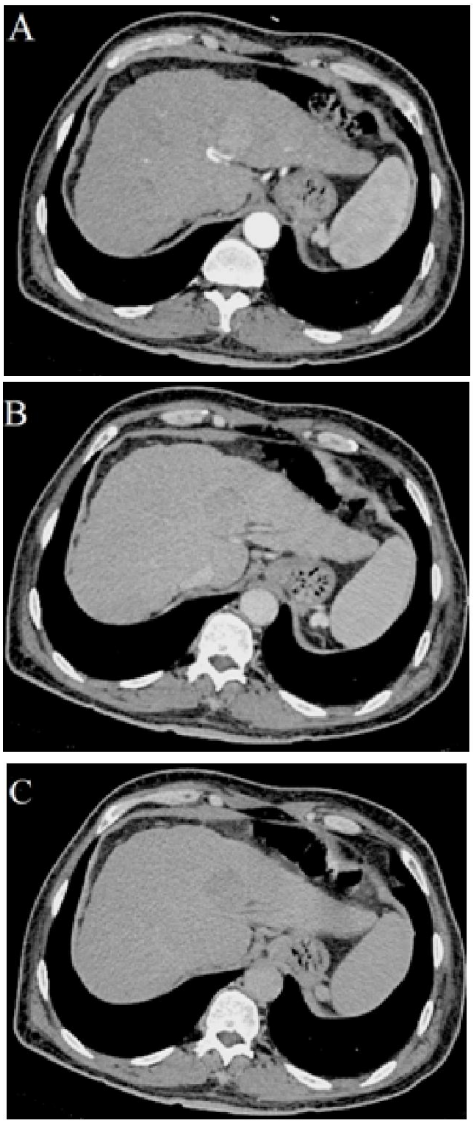

Figure 3. (A, B & C) axial images at arterial , portovenous &delayed phases respectively revealed left lobe focal lesion with enhancement at the arterial phase & wash out at the potovenous & the delayed phase

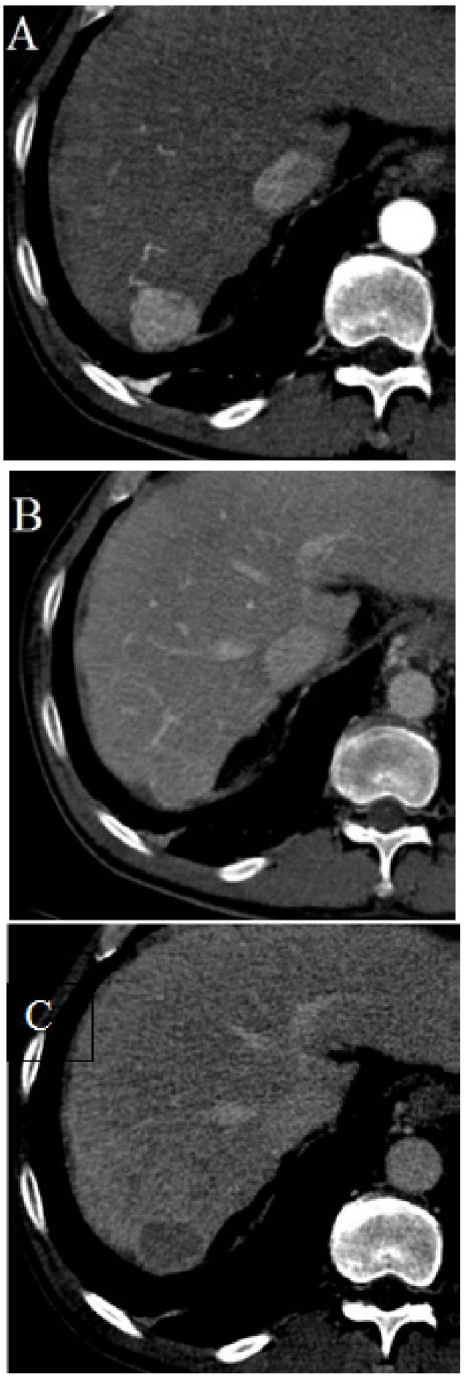

Figure 4. (A, B &C) CT axial images at arterial , portovenous &delayed phases respectively revealed right lobe focal with enhancement at the arterial phase & wash out at the potovenous & the delayed phase

DISCUSSION

Hepatocellular carcinoma (HCC) is a global health problem, with the burden of disease expected to increase in the coming years. Patients who are at increased risk for developing HCC undergo routine imaging surveillance, and once a focal abnormality is detected, evaluation with multiphasic contrast material–enhanced computed tomography or magnetic resonance imaging is necessary for diagnosis and staging (Purysko *et al*., 2012). MDCT is currently considered one of the most reliable techniques for evaluating hepatic cancer in the presence of cirrhotic liver disease and it is primarily involved in patient treatment strategies (Mortelé *et al*., 2001).

In our study comparison of imaging and histopathological findings showed that MDCT has acceptable diagnostic performance in the detection of HCC in patients with cirrhotic liver disease. The histopathological examination revealed 46 hepatocellular carcinomas in 31 of 35 patients, 8 of them were small in size (≤10mm), 13 were of intermediate size (11-20mm) and the remaining 25 were large in size (>20mm) while MDCT detected 42 hepatocellular carcinomas in 30 of 35 patients from which 8 HCC were small in size, 12 were of intermediate size and the remaining 22 were large in size. Kim *et al* histopathological examination revealed 139 hepatocellular carcinomas in 48 patients, 60 HCC were small in size, 42 were intermediate in size & 37 were large. MDCT correctly depicted 89 of 139 hepatocellular carcinomas (Kim *et al*., 2008). As expected, in our study the performance of MDCT was related to the lesion size. The sensitivity of MDCT for nodules decreased with lesion size.

We found very good sensitivity for HCCs larger than 20 mm (88%), acceptable sensitivity for nodules measuring 11–20 mm (84.6%), and low sensitivity for nodules 10 mm or smaller (62.5%). This finding may have been due to the altered hepatic structure from cirrhosis, which reduces the conspicuity of small HCC lesions and makes their characterization difficult. We noticed that not only sensitivity but also the positive predictive value (PPV) of MDCT decreased with lesion size, these values were quite low for small nodules (62.5%) increased to an acceptable level for nodules of intermediate size (91.7%) and were very good for nodules larger than 20 mm (100%). In comparison to Ronzoni *et al*. study, the results were as follows: the sensitivity for small nodules 47%, the sensitivity for intermediate nodules 76%, the sensitivity for large nodules 89%, the PPV for small nodules 53%, the PPV for intermediate nodules 61%, and the PPV for large nodules 97%.

So small nodules should be strictly monitored for size changes at follow up or should be studied with additional imaging & the histopathologic slice thickness shouldn't be greater than the CT slice Thickness (Ronzoni *et al*., 2007). This study revealed that the sensitivity of MDCT in detection of HCC using patient by patient analysis was 90.3 %, its specificity was 50 %, false positive results were 50%, false negative results were 9.7%, positive predictive value(PPV) was 93.3%, negative predictive value (NPV) was40% & its accuracy was 85.7%.previous study revealed 80 %, 50 %, 67 % and 85.5 % sensitivity and 96%,79%, 75% and 92.5% specificity by Lim *et al*, Libbrecht *et al*. Teefey *et al.* and Freeny *et al*. respectively (Lim *et al*., 2000; Libbrecht *et al*., 2002; Teefey *et al*., 2003; Freeny *et al*., 2003). Ronzoni *et al* study reported sensitivity 77% and specificity 75%, false-negative results 11%, false-positive results 10%, PPV 78.7%, NPV 73.1% & accuracy 76.1%,

The low sensitivity reported in this study can be due to fairly high slice thickness (5–10 mm) and imaging in the early arterial phase (Ronzoni *et al*., 2007). It is well known that to obtain the best conspicuity of lesions, arterial phase images should be acquired 30–35 seconds after injection of contrast material. On the other hand, the high false-positive rate in our study might have been related to overlooking nodules at histopathological examination, because the histopathological slice thickness was greater than the CT slice thickness.

This study revealed that application of Milan criteria on basis of CT results were as follows: 3 patients have no HCC nodules in their CT, had HCC nodules in their explanted liver histopathological findings, the other thirty patients with HCC nodules in their CT were within Milan criteria after correlation with histopathological results. Twenty six patients had HCC nodules within Milan criteria (86.7%), two patients had HCC nodules beyond Milan criteria (6.7%) & two patients didn't have HCC nodules, There was no significant difference in our study between Milan criteria on basis of CT results and that after histopathological findings (p value= 0.09) however small hyper vascular nodules should be strictly monitored for size changes at follow up or should be studied with MRI.

In our study after comparison between the histopathological results and MDCT results the number of HCC nodules were underestimated in 16.7% & overestimated in 2.4%. Ronzoni *et al* study showed that the number of HCC nodules was underestimated in 25% & overestimated in 19%. Some studies have shown that the Milan criteria may be too strict and that approximately 50% of patients receiving transplants outside the Milan criteria survive 5 years. Thus it is better that MDCT findings lead to an underestimation of disease extent rather than an overestimation, which would exclude patients from transplantation who would benefit from it [(7)].

Conclusion

At the end of this work, we concluded that MDCT has reasonable sensitivity and high diagnostic accuracy in the detection of hepatocellular carcinoma in patients with cirrhosis who will undergo liver transplantation according to the Milan criteria.

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