ORIGINAL RESEARCH ARTICLE

Prospective Evaluation of Small Hepatocellular Carcinoma

Prem Chand P[1], Sachin AN[2], Gurivi Reddy C[3], Aswith Kumar P[4], Vedaraju KS[5], Bhargavi Chunduru[6], Vamshi Kiran D[7]

[1]Assistant Professor, Department of Radiology, Narayana Medical College and Hospital, Nellore, A.P, [2]Consultant Radiologist, Krisnaa Diagnostics, Chicmangalore, Karnataka, [3]Senior Resident, Department of Radiology, Narayana Medical College and Hospital, Nellore, A.P, [4]Assistant Professor, Department of Radiology, Narayana Medical College and Hospital, Nellore, A.P, [5]Professor and Head, Department of Radiology, Narayana Medical College and Hospital, Nellore, A.P, [6]Post Graduate, Narayana Medical College and Hospital, Nellore, A.P, [7]Post Graduate, Narayana Medical College and Hospital, Nellore, A.P, India

Corresponding author: Dr Gurivi Reddy C, Senior Resident, Department of Radiology, Narayana Medical College and Hospital, Nellore, A.P, India.

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A B S T R A C T

Introduction: Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide with an estimated 500,000 to 1 million new cases per year. Current study was designed to assess sensitivity of 128-slice CT in detection of small hepatocellular carcinoma in comparison to ultrasound and also to determine the value of equilibrium phase (delayed phase) in diagnosing small hepatocellular carcinoma.

Material and Methods: As per these guidelines all the patients underwent ultrasound and serum AFP levels as the initial screening modality. Despite the absence of lesion on ultrasound, patients in whom there was a strong clinical suspicion of HCC in view of AFP levels in the diagnostic range (> 400 NG/ML) or serial raise in AFP levels but less than the diagnostic range underwent CT; and if the lesion size (on CT) ranged from 1 to 2 cm they underwent MRI.

Results: Our study group consists of 32 patients with small HCC. Age of the patients ranged from 45 to 76 years with mean age of 63 years. 30 out of 32 patients in our study were male. The number of patients without any etiological factors was 15.The number of patients who were alcoholic are 12, and the number of patients who were positive for HEP – B sag are 3, and the number of patients who were positive for HEP – C sag were 2. The number of patients who were having AFP less than 20 was 16, between 20-200 was 10, between 200 – 400 was 3, and more than 400 was 3.

Conclusion: MDCT is a superior tool for diagnosing small HCC and to identify the multifocal nature of HCC in comparison to US. MRI is a second level imaging modality and should be used in lesions with equivocal findings on CT or when the lesion size is less than 2 cm in size.Arterial phase is mandatory, and delayed phase helps in detecting more lesions than portal venous phase alone.

Key words: Hepatocellular Carcinoma**,** CHILD'S CRITERIA, MDCT, Arterial Phase

INTRODUCTION

The incidence ranges from four cases per 100,000 populations in USA to 150 cases per 100,000 populations in parts of Africa and Asia where HCC is responsible for a large proportion of cancer deaths.[1] A rise in the incidence of mortality from HCC has been observed in different countries.[2] Approximately 77% of deaths from HCC occur in developing countries. The prognosis of HCC is dismal with 5-year survival being 1–4 %.[3]

The global distribution of HCC is very variable. According to the age adjusted HCC incidence per 100,000 population per annum, different geographic regions can be divided into three incidence zones: low (<5), intermediate (between 5 and 15), high (>15).[4] Most Asian countries are in intermediate or high incidence zones of HCC. In India, the mean incidence of HCC in four population-based registries is 2.77% for males and 1.38% for females. The prevalence of HCC in India varies from 0.2% to 1.6 %.[5,6]

The geographic model of HCC occurrence is frequently correlated with the etiologic factors. Hepatitis B virus (HBV) infection is the most common etiologic factor in high incidence areas, while hepatitis C (HCV) infection is more prevalent in the low incidence areas.[7,8]

Unlike other low incidence zones, in India HBV is the main etiological factor associated with HCC.[9-13] In the west, majority of HCC are diagnosed incidentally during routine evaluation. However, in India, most of the patients in clinical practice present at an advanced stage ruling out curative treatment in most cases. Despite India being a low incidence zone for HCC, there were an estimated 12,750 HCC cases in 2001.[5] However, there is paucity of published literature on

profile of HCC patients in India, making formulation of a proper health care strategy difficult.

Due to the relative paucity of symptoms in the early stages and the rapid doubling time of the tumor, most HCCs are detected late in advanced stages at presentation. The prognosis of large, symptomatic HCC is poor and only palliative treatment is available. In contrast small tumors are now amenable to several modes of treatment including liver transplantation, surgical resection and loco regional ablation with acceptable 5-year survival rates. Therefore, the identification of small lesions through screening should prolong survival.

Okuda et al, used the term "minute" HCC, which was defined as a solitary tumour smaller than 4.5 cm or a few tumour nodules smaller than 3.5 cm in diameter.[14] Chen et al described the term "small" HCC to denote a tumour smaller than 3.0 cm in diameter. In our study we have considered lesion less than 3 cm as small HCC.[15]

Recommendations for HCC surveillance as per AAASLD (American Association for the Study of Liver Diseases) are: Surveillance for HCC should be performed using ultrasonography. AFP alone should be used for screening only if ultrasound is not available. Patients should be screened at 6 to12 month intervals. The surveillance interval does not need to be shortened for patients at higher risk of HCC.

AFP level is neither sensitive nor specific if used alone. Moreover, with dysplastic nodules and small HCC, the level of AFP is usually in the normal range and imaging plays an important role in the early detection of dysplastic nodules and HCC.

Sonography has variable sensitivity in the detection of HCC in the cirrhotic liver ranging from 33 to 96% with a high sensitivity of 80% if HCC is suspected clinically. However, there are no specific features to distinguish dysplastic nodules from HCC and it has low sensitivity for the detection of dysplastic nodules (0–1.6%) and also for small HCC less than 1 cm.[16] Sonographic contrast agents may improve detection of the lesions.[17,18,19]

Once an abnormality is detected on a screening test, a recall test is performed to determine the presence of HCC. The tests used to diagnose include radiology (triple-phase spiral CT, dynamic MRI), biopsy and AFP serology.

Magnetic resonance imaging (MRI) helps to identify the characteristic imaging features of HCC such as pseudocapsule, internal septa and mosaic appearance. CT arterio-portography and CT hepatic arteriography are more sensitive for the detection of HCC but the false positive rate is high due to benign hypervascular lesions like arterioportal shunts.[20,21]

Multidetector CT has the advantage of increased speed, improved spatial and temporal resolution, which is particularly useful in cirrhotic patients with small transiently enhancing nodules. Hence study was undertaken to evaluate the role of 128-slice CT in the detection of small hepatocellular carcinoma.

MATERIAL AND METHODS

Study was done in the Department of Radiology, Narayana medical college hospital, Nellore, A.P, India for the period of two and half years after taking the informed consent from the subjects and ethical clearance from the ethical board.

Inclusion criteria

Cirrhotics who underwent US and MDCT as part of follow up or with suspected HCC.

All patients who had arterial phase enhancing lesion with washout in venous or delayed phases on CT with size being ≤ 3cm.

Exclusion criteria

- Enhancement pattern not characteristic of HCC on CT.
- Lesion size > 3 cm.

740 Patients (patient population), satisfying the said criteria over a period of 30 months underwent screening with serum AFP and US. 212 patients were diagnosed as having hepatocellular carcinoma by different modalities (CT, MRI, and biopsy) applied according to the guidelines provided by AASLD criteria. Among them (212 patients), 32 patients (study population) were diagnosed as small hepatocellular carcinoma according to AASLD criteria. Reccomendations for HCC diagnosis as per AASLD are:

Nodules between 1-2 cm found on ultrasound screening of a cirrhotic liver should be investigated further with two dynamic studies, either CT scan, contrast ultrasound or MRI with contrast. If the appearances are typical of HCC (i.e., hypervascular with washout in the portal/venous phase) in two techniques the lesion should be treated as HCC. If the findings are not characteristic the lesion should be biopsied.

If the nodule is larger than 2 cm at initial diagnosis and has the typical features of HCC on a dynamic imaging technique, biopsy is not necessary for the diagnosis of HCC. Alternatively, if the AFP is >200 ng/mL biopsy is also not required. However, if the imaging findings are not characteristic or if the nodule is detected in a non-cirrhotic liver, biopsy should be performed.

Biopsies of small lesions should be evaluated by expert pathologists. If the biopsy is negative for HCC patients should be followed by ultrasound or CT scanning at 3-6 monthly intervals until the nodule either disappears, enlarges, or displays diagnostic characteristics of HCC. If the lesion enlarges but remains atypical for HCC a repeat biopsy is recommended.

As per these guidelines all the patients underwent US and serum AFP levels as the initial screening modality. Despite the absence of lesion on US, patients in whom there was a strong clinical suspicion of HCC in view of AFP levels in the diagnostic range (> 400 NG/ML) or serial raise in AFP levels but less than the diagnostic range underwent CT; and if the lesion size (on CT) ranged from 1 to 2 cm they underwent MRI.

In this study out of 32 cases, 3 patients showed AFP levels diagnostic for HCC; 22 were found to be suspicious for HCC by ultrasonography and 32 cases were diagnosed by CT as classical for HCC and in 5 cases confirmed by MRI as in these patients the lesion size ranged from 1 to 2 cm on CT. Out of the ten patients who underwent CT directly, two patients had AFP levels in the diagnostic range and eight patients had serial rise in AFP levels however with absolute values less than the diagnostic range.

Equipment

1. Sonography was performed with:
   - GE Voluson P8.
   - 2-6 MHZ curvilinear probe.
   - 8-10 MHZ linear probe
2. MDCT was performed with:

–GE 128 slice CT.

Imaging analysis

MDCT: Patients who fulfill the said criteria were selected and their hepatic lesions are imaged according to the protocol. Multiphase contrast scans include late arterial phase [15 sec delay], portal venous phase [20 sec delay], and delayed phase [90 sec delay- after a trigger threshold of 100 HU has reached in the upper abdominal aorta]. Based on enhancement in comparison to surrounding liver, the nodules were characterized as hyper /hypo/iso attenuating in different phases. Positive enhancement of the nodule was defined as when a hypodense nodule in unenhanced scan becomes isodense or hyperdense in arterial dominant phase or when an isodense nodule in unenhanced scan turns hyperdense in arterial dominant phase. The window levels of images were kept constant during interpretation. The criteria for diagnosing hepatocellular Carcinoma is, lesion enhancement in late arterial phase and contrast washout in venous, delayed phases. Contrast washout was defined as when a hyperdense nodule in arterial phase turns isodense or hypodense in either portal or delayed phases in comparison to the adjacent hepatic parenchyma.

MRI: The nodule was considered positive for small HCC if it showed characteristic hypo intense signal on T 1 MPGR weighted image, hyperintense signal on T 2 SSFSE image and the lesion on dynamic contrast study showed arterial phase enhancement and venous washout.

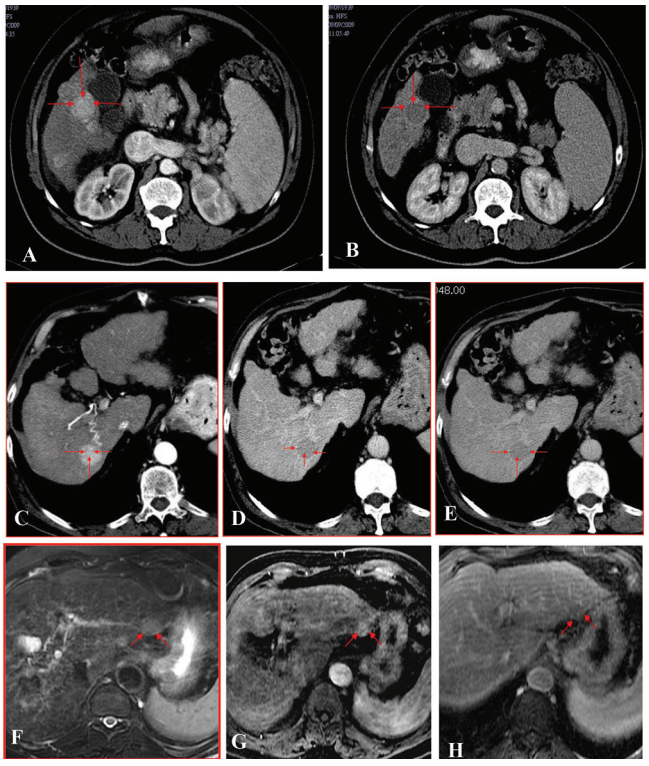

Figure-1: A. A 61 year old male with chronic liver disease showing Enhancing lesion in arterial phase in segment 5/6. B. - Delayed phase scan showing washout of contrast from the lesion. C. A 59 year old male with chronic liver disease. Small enhancing lesion in arterial phase in segment 6. D and E. (Portal venous and delayed phase respectively) showing washout of contrast from the lesion. F. MRI of 65 year old male with chronic liver disease with lesion size ranged 1 to 2 cm. - T2 (fat suppressed) axial image showing the bright lesion. G. Dynamic post-contrast scan in arterial phase showing enhancement of the lesion. H. Delayed phase – showing washout of contrast from the lesion.

RESULTS

Our study group consists of 32 patients with small HCC. Age of the patients ranged from 45 to 76 years with mean age of 63 years. 30 out of 32 patients in our study were male. The number of patients without any etiological factors was 15.The number of patients who were alcoholic are 12, and the number of patients who were positive for HEP – B sag are 3, and the number of patients who were positive for HEP – C sag were 2. The number of patients who were having AFP less than 20 was 16, between 20-200 was 10, between 200 – 400 was 3, and more than 400 was 3. In CHILDS CRITERIA, A score were of 14, B score were of 11, and C score were of 7.

Total number of lesions (including multifocal) detected on ultrasound were in 26 cases. Among them, 12 lesions were

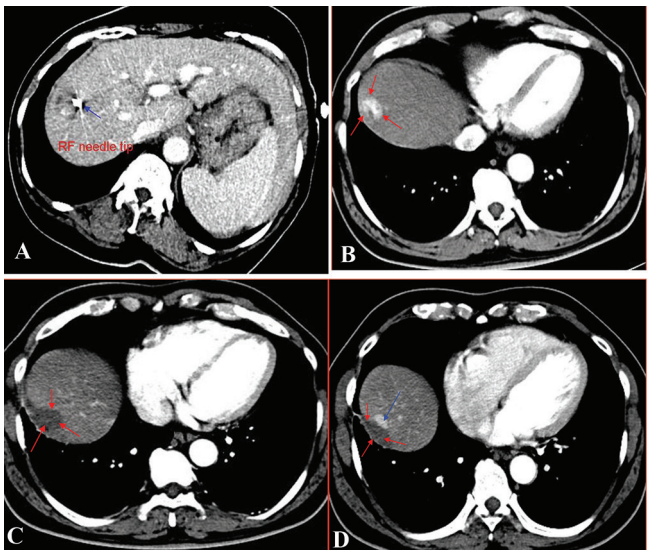

Figure-2: A. Case 4-CECT of a 69 year old patient with small HCC in the right lobe- planned for RFA. The Radiofrequency ablation needle tip is placed in the outer aspect of the lesion under CT guidance. B. Case 20- 64 year old male with chronic liver disease – before and after Radiofrequency ablation of small HCC. Small enhancing lesion in arterial phase in segment 8 (subdiaphragmatic surface). C. Post-contrast scan arterial phase 1 month after RFA of the lesion showing no enhancement consistent with total ablation of the lesion. D. Post-contrast scan arterial phase 3 months after the above scan showing nodular enhancement in the margin of the ablated lesion consistent with recurrence.

hypoechoic, 9 showing heterogenous, 4 showing hyperechoic and 1 was isoechoic. There are US detected multifocal lesions in 3 patients and CT detected multifocal lesions in 7 patients. Total number of lesions (including multifocal) detected on CT was 45.

a) On unenhanced CT number of isodense lesions were 26, hypodense-14, hyperdense-5
b) During arterial phase 24 lesions showed homogenous enhancement, 21 lesions showed heterogenous enhancement.
c) 27 lesions showed washout in portal venous phase and 40 lesions showed washout in delayed phase.

DISCUSSION

Out of 740 patients, 212 were diagnosed as HCC and among them only 32 were diagnosed as small HCC. So the detection of small HCC cases in cirrhotics was 4.3%. Consequently we have a small study population. The growing awareness among the physicians and surgeons regarding the therapeutic options available for small HCC will probably lead to an increase in the number of cirrhotic patients screened with MDCT in the near future.

We found male predominance among HCC patients and that the incidence is more common in older age group. These findings were in agreement with that reported by Parkinet al.[22] and Bosch et al.[23] who found that the incidence of HCC increases progressively with advancing age in all populations and that males are more affected than females, and male predominance is more obvious in populations at high risk of the tumor than those in low or intermediate risk. These differences in sex distribution are thought to be due to variations in hepatitis carrier states, exposure to environmental toxins, and the trophic effect of androgens.

In India HBV is supposed to be the main etiological factor associated with HCC,[24] however in our study we found more patients with alcoholic etiology than HBV. Among the 32 patients included in the study, the number of patients in Childs classification A was 14, B-11, and C- 7. AFP levels were within normal range in 50 % of the cases, between normal range and diagnostic levels (21to400ng/mL) in 31.25 % and above 400ng/mL in 9.37 %. Oka et al also reported that in patients who were diagnosed with HCC, AFP levels may be normal in up to 40% of patients, particularly during the early stages.[25]

As mentioned earlier, in the cirrhotic patients who underwent screening by AFP, only 3 patient's showed values in the diagnostic range; whilst 22 patients were diagnosed as suspicious for HCC by US screening. Thus it can be concluded that US is a more sensitive screening test than AFP. US technique also frequently detects false positive or benign lesions and careful differential diagnosis is required as reported by Choi et al.[26] One may consider lowering the screening level of AFP to increase the sensitivity. However, this would result in a lot of false positive cases, because most of the mildly elevated AFP cases were due to chronic liver disease rather than HCC. In such cases, real time ultrasound provides a good tool to make a differential diagnosis. However, the advantage of AFP determination is that it takes less time for examining a large number of subjects and it is technically easier as compared to US screening. Furthermore, if a tumor detected by US is accompanied with elevated AFP over the diagnostic level, invasive procedures for differential diagnosis, such as biopsy or angiography, can usually be avoided. Thus, AFP assay is a good complementary tool to US in the detection of HCC.

Lesions could be detected in 22 patients by US. Among them 19 patients showed unifocal lesion, the rest of the 3 patients showed multifocal lesions. Multinodularity may result from either intrahepatic metastases from a primary focus or the occurrence of synchronous tumors. Synchronous tumors occur more frequently in chronic HBV infection, accounting for half of the multinodularcases.Yoshida et al in an ultrasonography study found 68.8% as unifocal lesion.[27] Sarder et al found 71.4% unifocal and 27.6% multifocal lesions.[28] Colombo et al found 71% HCC lesion as unifocal in sonography and 28% as multifocal.[29] Our study is in concordance with these studies with 86.3% unifocal and 13.6% multifocal lesions.

Among the 3 patients with multifocal lesions, 1 patient had three lesions and the other 2 patients had two lesions each. So the total number of lesions detected by US was 26. Among these 26 lesions, 12 lesions were hypoechoic, 4 lesions were hyperechoic, 9 lesions were heterogenous (mixed) and only 1 lesion was isoechoic with hypoechoic halo on US. In isoechoic HCC, the tumor may easily be missed on sonography, and care must be taken in looking for hypoechoic halo representing the capsule and lateral shadow. 15 lesions were located in the right lobe, 11 lesions were located in the left lobe. Saad et al found 59% right lobe lesion and 41% left lobe lesion. Similarly our study showed 57.6% right lobe lesion and 42.3% left lobe lesion.[30]

In comparison to CT, USG showed more ambiguity in the allocation of lesion to a particular segment. Ultrasonography detected multifocal lesions in 3 patients; CT detected multifocal lesions in 9 patients. Among the 9 patients with multifocal HCC on CT, 5 patients had 2 lesions each and the rest 4 had 3 lesions each. So the total number of lesions detected by CT including multifocal are 45.

No lesions were detected in 10 patients on US. In 5 of these patients the lesion size ranged between 2-3 cm and in 5 patients the lesion size ranged from 1-2 cm. 5 lesions (In 4 size ranged from 1-2 cm and in 1 size ranged between 2-3 cm) located in the anterosuperior sector of right lobe were especially difficult to detect on US. The shrunken right lobe allows very little acoustic window for satisfactory interrogation of the liver. CT and US were almost equally accurate in detecting HCC according to the study conducted by Tsutomu Takashima et al.[31] However Tsunetomi et al reported that US was found to be superior to CT for lesions under 2 cm.[32] Our study reveals that CT is more accurate than US in detecting lesions under 2 cm and for lesions located in the anterosuperior segment.

Computed tomography has been shown to be an accurate method for the detection of small HCC, by Inamoto et al[33] particularly when used with dynamic CT studies. It is not operator dependant like US and can not only define more accurately the extent of the HCC, but it can also better define extra hepatic spread of disease as reported by La Berge.[34]

Detectability of small HCC by CT in our data is superior to that of previous reports of Takashima et al.[35] This is because of a new generation CT machine and bolus injection of a large amount of contrast medium. Detectability of small HCCs on CT scans will vary depending on the X-ray attenuation of the lesion. In our series, contrast-enhanced CT was superior to non-contrast-enhanced CT in identifying small HCCs; detecting 100 % in comparison with 42.22 % by non-contrast-enhanced CT.

Portal venous phase is the most valuable in the detection of metastatic tumor because liver–tumor contrast is maximal in this phase.[36] However, in the detection of hypervascular hepatocellular carcinoma, most investigators agree that arterial phase images are superior to portal and delayed phase images.[37] Therefore, the arterial phase imaging is mandatory in multiphasic dynamic CT. Regarding the relative value of portal venous and delayed phase imaging, Choi et al. reported that the detection rates of hepatocellular carcinoma with a combination of all three phases (arterial, portal venous, and delayed) (92%) and with a combination of arterial and portal venous phases (92%) were equal.[38] They concluded that the combination of arterial and portal venous phase is enough and that the delayed phase imaging can be omitted to decrease scanning time and radiation dose. However, patients in their series had hypervascular hepatocellular carcinoma, and their gold standard for diagnosis was iodized-oil CT and the presence of neovascularization on angiography. In clinical practice, there are many cases of hypovascular hepatocellular carcinoma, such as well-differentiated hepatocellular carcinoma or early hepatocellular carcinoma.[39] Furthermore, in cirrhotic patients, most premalignant lesions such as dysplastic nodules are hypovascular. Therefore, Hwang et al recommended triple-phase helical CT for the detection and characterization of hepatocellular carcinoma.[40]

Delayed phase imaging is important; especially for the detection of small hepatocellular carcinomas less than 2 cm. Small hepatocellular carcinomas can be treated either by surgical resection or nonsurgical methods such as radiofrequency ablation or alcohol injection. If we detect an additional small hepatocellular carcinoma in the other lobe of the liver that might have been missed on dual-phase CT, we choose a nonsurgical method of treatment because hepatocellular carcinoma in both lobes of the liver precludes surgical resection. It is valuable in confirming or increasing the confidence level in the detection of equivocal nodules on arterial or portal venous phase images because those nodules are usually more conspicuous on delayed phase than on portal venous phase imaging or are detected only on delayed phase CT. In our study, 13 additional lesions could be detected only in delayed phase as they showed complete washout, which appeared isodense in portal phase.

Triple phase CT, including delayed phase imaging, has additional value in the characterization of hepatic masses because of better visualization of a capsule or the mosaic pattern of hepatocellular carcinoma than with dual-phase CT.[41]

One may question the benefit of triplephase CT, considering the added radiation dose to the patients and the increased scanning time compared with dual-phase CT.[42] The most important implication of our study is that triple-phase helical CT is better than dual-phase CT for the detection of small hepatocellular carcinomas. Small hepatocellular carcinomas are much easier to treat at surgery or by local ablation therapy, and when treated, the prognosis of those patients is much better than that of patients with hepatocellular carcinomas larger than 3 cm.[43] During follow- up imaging of cirrhotic patients, the initial presentation of hepatocellular carcinoma is usually a small nodule less than 3 cm, but there may be multiple small nodules in patients with advanced cirrhosis, such as regenerative nodules or dysplastic nodules, which must be differentiated from hepatocellular carcinoma. Delayed phase imaging is helpful in the differential diagnosis of those small nodules. Additionally, in advanced liver cirrhosis, small arterioportal shunts mimic hepatocellular carcinoma on hepatic arterial phase imaging. MRI was done in patients when the lesion size ranged from 1-2 cm as detected on MDCT. Among these four patients showed arterial phase enhancement with corresponding venous washout. In the remaining one patient, arterial phase enhancement was noted, however due to respiratory motion washout was not clear. Respiratory motion artifacts are more in MRI as each phase requires 13 sec breathe hold unlike in MDCT which requires only 5-6 sec breath hold.

MRI should be used as a second level imaging modality, in case of equivocal findings on CT or when the lesion size is less than 2 cm. The practical difficulty we felt in using MRI was the patient compliance. Most patients with HCC tend to be aged and debilitated with poor breath hold. Consequently poor quality images results in equivocal findings.

Of the 32 patients, 10 patients underwent RFA, guided by US or CT. RFA could not be done in the remaining 22 patients due to severe ascites and associated comorbidities. The triple phase CT protocol was found to be very useful for picking up and in precisely locating nodular lesions for local ablative therapy.

CONCLUSION

MDCT is a superior tool for diagnosing small HCC in comparison to US. For identifying the multifocal nature of HCC, MDCT is more useful than US. This is critical from a therapeutic point of view.MRI is a second level imaging modality and should be used in lesions with equivocal findings on CT or when the lesion size is less than 2 cm in size.Triple phase CT imaging, is essential to evaluate small HCC. Arterial phase is mandatory, and delayed phase helps in detecting more lesions than portal venous phase alone.

REFERENCES

1. Wands JR, Blum HE. Primary hepatocellular carcinoma.N Engl J Med 1991;325(1):729–31
2. El-serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999;340(3):745–50.
3. Pisani P, Parkin DM, Ferlay J. Estimates of the worldwide mortality from eighteen major cancers in 1985. Implications for prevention and projections of future burden. Int J Cancer 1993;55(6):891–3.
4. Bosch FX. Global epidemiology of hepatocellular

carcinoma. In: Okuda K, Tabor E, eds. Liver Cancer. New York, Churchill Livingstone; 1997:13-27.
5. Annual Report 1987. National Cancer Registry Programme.New Delhi, Indian Council of Medical Research,1990.
6. Jayant K, Rao RS, Nene BM, Dale PS. Rural Cancer Registry at Barshi- Report 1988-92. Barshi, Rural Cancer Registry, 1994.
7. Park YM. Hepatocellular carcinoma in Asia. In: SarinSK, Okuda K, eds. Hepatitis B and C. Carrier to Cancer. India, Elsevier Sciences 2002:268–71.
8. Pyrsopoulos N, Reddy RK. Hepatocellular carcinoma in Asia. In: SarinSK, Okuda K, eds. Hepatitis B and C. Carrier to Cancer. India, Elsevier Sciences, 2002:363–4.
9. Sarin SK, Thakur V, Guptan RK, Saigal S, Malhotra V, Thyagarajan SP, et al. Profile of hepatocellular carcinoma in India: an insight into the possible etiologic associations. J Gastroenterol Hepatol 2001; 16(3):666–73.
10. Durga R,Muralikrishna P.Viral markers in hepatocellular carcinoma. Ind J Gastroenterol1994;13(1):A57.
11. Sundaram C, Reddy CRRM, Venkataramana G, Benerjea S, Venkatratnam G, Swarnakumari G, et al. Hepatitis B surface antigen, hepatocellular carcinoma and cirrhosis in South India-an autopsy study. Indian J PatholMicrobiol1990;33(3):334–8.
12. Kumar A, Sreenivas DV, Nagarjuna YR. Hepatocellular carcinoma. The Indian scenario.Ind J Gastroenterol1995;14(4):A95.
13. Kar P, Budhiraja S, Narang A, Das BC, Panda SK, Chakravorty A. Comparative evaluation of serology and polymerase chain reaction for hepatitis C viral infection in liver diseases. Ind J Gastroenterol 1997;16(6):118–9.
14. Okuda K, Nakashima T, Obata H. Clinicopathologic studies of minute hepatocellular carcinoma: analysis of 20 cases, including 4 with hepatic resection. Gastroenterology 1977;73(3):109-115.
15. Chen D, Sheu S, Sung J.C, Lai J.L. Small hepatocellular carcinoma- a clinicopathological study in thirteen patients. Gastroenterology 1982; 83(1):1109-1119.
16. Bennett GL, Krinsky GA, Abitbol RJ, Kim SY, Theise ND, Teperman LW. Sonographic detection of hepatocellular carcinoma and dysplastic nodules in cirrhosis. Correlation of pretransplantationsonography and liver explant pathology in 200 patients. AJR 2002;179(5):75–80.
17. Hann LE, Bach AM, Cramer LD, et al. Hepatic sonography: comparison of tissue harmonic and standard sonography techniques. AJR 1999;173(6):201–6.
18. Wilson SR, Burns PN, Muradali D. Harmonic hepatic US with microbubble contrast agent: initial experience showing improved characterization of hemangioma, hepatocellular carcinoma, and metastasis. Radiology 2000;215(3):153–61.
19. Harvey CJ, Blomley MJ, Eckersley RJ. Hepatic malignancies: improved detection with pulse-inversion US in late phase of enhancement with SH U 508A – early experience. Radiology 2000;216(2):903–8.
20. Jang HJ, Lim JH, Lee SJ. Hepatocellular carcinoma: are combined CT during arterial portography and CT hepatic arteriography in addition to triple-phase helical CT all necessary for preoperative evaluation? Radiology 2000;215(3):373–80.
21. Kim TK, Choi BI, Han JK.Nontumorousarterioportal shunt mimicking hypervascular tumor in cirrhotic liver: two-phase spiral CT findings. Radiology 1998;208(5):597–603.
22. Parkin DM. Global cancer statistics in the year 2000. Lancet oncology 2001;2(9):533-543.
23. Bosch FX. Primary liver cancer: worldwide incidence and trends. Gastroenterology 2004; 127(5):S5-S16.
24. Kumar R, Kumarsaraswati M, Chander Sharma B, Sakhuja P Sarin SK. Q J Med 2008; 101(5):479–485.
25. Oka H, Tamori A, Kuroki T, Ko bayashi K. Prospective study of á -fetoprotein in cirrhotic patients monitored for development of hepatocellular carcinoma. Hepatol. 1994;19(1): 61-66.
26. Choi BI, Kim CW, Han MC, Kim CY, Lee HS, Kim ST, Kim YI. Sonographic characteristics of small hepatocellular carcinoma. Gasterointest Radiol. 1989;14(3): 255-61.
27. Yoshida T, Matsu H, Okazaki N, Yoshino M. Ultrasonographic differentiation of hepatocellular carcinoma from metastatic liver cancer. J Clin Ultrasound 1987;15(5):431 -37.
28. Sardar MK, Shamsuddin AKM, Kundu SS. Hepatocellular carcinoma and metastatic liver cancer: ultrasonographic differentiation- Study of 19 cases. BJRI 1997; 5(5): 26-29.
29. Colombo M. Hepatitis C virus and hepatocellular carcinoma. SeminLiv Dis. 1999; 19(3): 263-69.
30. Saad AMH, Alam SZ, Alam J. Evaluation of liver mass by ultrasound, CT scan and FNAC- A study of 22 cases. BJRI 1996; 4(6): 7-10.
31. Tsutomu T, Matsui O, Suzuki M. Diagnosis and screening of small hepatocellularcarcinomas. Comparisonofradionuclideimaging, ultrasound, computedtomography, hepatic angiography, and alpha-fetoprotein assay. Radiology 1982;145(1):635-638
32. Tsunetomi S. Ohto M. Ultrasonography in the evaluation of hepatocellular carcinoma in comparison with computed tomography Jpn J Med Ultrasonics 1981;1(5): 235-236.
33. Inamoto K, Tanaka S, Yamajaki H. Computed tomography in the detection of small hepatocellular carcinomas.Gastrointestinal Radiology 1983;8(2):321-326.
34. Labertge J.M, Laing F. Hepatocellular carcinoma: assessment of resectability by computed tomography and ultrasound.Radiology 1984;152(1): 485-90.
35. Takashima T. Diagnosis and screening of small hepatocellular carcinomas. Comparison of radionuclide imaging, ultrasound, computed tomography, hepatic angiography, and alpha-fetoprotein assay. Radiology 1982;145(6):635-638.
36. Baron RL, Oliver JH, Dodd CD, Nalesnik M, Holbert BL, Carr B. Hepatocellular carcinoma: evaluation with biphasic, contrast enhanced, helical CT. Radiology 1996;199(3):505-511.
37. Iannaccone R, Laghi A, Catalano C, Rossi P, MangiapaneF,Murakami T. Hepatoceellularcarcinoma: role of unenhanced and delayed phase multi-detector row helical CT in patients with cirrhosis. Radiology 2005;234(2):460-467.

38. Hwang GJ, Kim M-J, Yoo HS, Lee JT. Nodular hepatocellular carcinomas: detection with arterial-, portal-, and delayed-phase images at spiral CT. Radiology 1997;202(6):383–388.
39. Takayasu K, Shima Y, Muramatsu Y. Angiography of small hepatocellular carcinoma: analysis of 105 resected tumors. AJR 1986;147(2):525–529.
40. Kim T, Murakami T, Takahashi S. Optimal phase of dynamic CT for detecting hepatocellular carcinoma: evaluation of unenhanced and triplephase images. Abdom Imaging 1999;24(1):473–480.
41. Heiken JP, Brink JA, McClennan BL, Sagel SS, Forman HR, DiCroce J. Dynamic contrast-enhanced CT medium injection rates and uniphasic and biphasic injection protocols. Radiology 1993;187(6):327–331.
42. Honda H, Matsuura Y, Onitsuka H. Differential diagnosis of hepatic tumors (hepatoma, hemangiomaandmetastasis) with CT: value of two-phaseincrementalimaging. AJR 1992;159(2):735–740.
43. Choi BI, Lee HJ, Han JK, Choi DS, Seo JB, HanMC. Detection of hypervascular nodular hepatocellularcarcinomas: value of triphasic helical CT compared with iodized-oil CT. AJR 1997;168(4):219–224.

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