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Original Article

Radiology Section

# Radiological Outcome of Subcentimeter Arterially Enhancing Nodules Detected during Surveillance for Hepatocellular Carcinoma- A Cohort Study

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## ABSTRACT

**Introduction:** Hepatocellular Carcinoma (HCC) is the sixth most diagnosed cancer and the fourth leading cause of cancer-related death globally. The male:female ratio for HCC in India is 4:1 with age of presentation ranging from 40-70 years. There is limited clinical information on the course of Subcentimeter-Sized Nodules (SCSNs) detected during surveillance for HCC.

**Aim:** To evaluate the serial outcome of subcentimeter arterially enhancing nodules evolving into HCC and henceforth, to identify specific radiological features which can prognosticate and, if possible, predict which SCSNs will turn into HCC.

**Materials and Methods:** A prospective cohort study was conducted in a tertiary care centre in Delhi, India, in the Department of Radiodiagnosis between 1st May 2018 and 30th April 2019. Total of 72 lesions in 59 patients were evaluated during the study period of one year, which included images spanning over a mean duration of three years (range 2-6.5 years). Dynamic contrast enhanced imaging was done as per Liver Imaging Reporting and Data System version 2018 (LI-RADS version 2018) using either Magnetic Resonance Imaging (MRI) or Computed Tomography (CT). The gold standard for HCC diagnosis was LR 5 lesion. Size cut-off, rate of growth, enhancement features were studied and calculated. Student's t-test was used for comparison of quantitative outcome parameters.

**Results:** A total of 59 patients were analysed with mean age 53±12 years, of which 85% were males. The cumulative HCC development rate was 47.5%. A 60.9% of the SCSNs which turned into HCCs showed an increase in size, 31.6% of the non HCC-SCSN lesions also showed an increase in size. Upon baseline comparison, the growth difference was more in the HCC group (8.2±12.24 mm) than in the non HCC group (3.37±7.39 mm). The optimal cut-off points after which the likelihood of an arterially enhancing lesion turning into HCC increased significantly was 8.5 mm on CT and 10.5 mm on MRI.

**Conclusion:** Around 47.5% of arterially enhancing SCSN converted into HCC; this percentage is much higher than quoted literature. A six monthly follow-up may be considered as 52.2 percent of lesions turned into HCC in a span of 1 year. The optimal cut-off points after which the likelihood of an arterially enhancing lesion turning into HCC increases can be taken as 8.55 mm on CT and 10.5 mm on MRI. Among the lesions showing washout, 80.8% on CT and 91.3% nodules on MRI changed into HCC.


**Keywords:** Computed tomography, Diffusion restriction, Hepatobiliary contrast, Magnetic resonance imaging, Washout

## INTRODUCTION

The HCC is the sixth most diagnosed malignancy and the fourth leading cause of cancer-related death globally [1]. In India, the age adjusted incidence rate of HCC ranges from 0.7-7.5 and 0.2-2.2 per 100,000 of population per year for men and women respectively. The male: female ratio for HCC in India is 4:1 with age of presentation ranging from 40-70 years [2].

The most reliable diagnostic examinations for diagnosis of HCC are multiphasic CT and MRI, which includes late arterial, portal venous, hepatic venous, and delayed/equilibrium phase imaging at about 3-5 minutes after contrast injection [3,4]. The presence of arterial enhancement followed by washout has a sensitivity of 90%, specificity of 95%, and a positive predictive value of approximately 100% among the group having high chances of developing HCC, e.g., cirrhotics [5]. Washout is defined by the appearance of a hypoattenuating area in the portovenous or delayed phase on a triphasic CT liver scan that was hyperdense compared with the rest of the liver in the arterial phase [6].

Hepatobiliary contrast agents are extracellular gadolinium chelates that are now routinely employed in MR liver scanning. Apart from renal excretion, these agents also have a component excreted by the liver depending upon the functional hepatocytes in the parenchyma. A significant benefit of these agents is that they can detect early HCC that shows relative hypoenhancement on the Hepatobiliary Phase (HBP) when there is no appreciable arterial enhancement or venous washout. This can increase the sensitivity and accuracy for HCC diagnosis [7,8]. HBP hypointensity favours a premalignant or a malignant lesion rather than a low-grade dysplastic or a cirrhotic nodule in studies with hepatitis B and C patients [9,10].

Diffusion-Weighted Imaging (DWI) can enhance the diagnostic performance of MRI for small HCCs by demonstrating higher cellularity of HCCs. Other ancillary imaging features favouring HCC diagnosis include the presence of intralesional fat, mild to modest hyperintensity on T2-weighted images, and morphologic findings such as intratumoural haemorrhage, fatty transformation, and nodule-in-nodule configuration [11].

Accordingly, the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases advocate performing screening for HCC in patients at risk. There are imaging criteria for HCC diagnosis if lesions are 1 cm or larger, but a wait and watch policy is recommended for nodules smaller than 1 cm owing to a high false positive rate. However, there is a high possibility that minute hepatic nodules detected during surveillance may become malignant over time [12-14]. Nevertheless, there is limited information on the clinical course of SCSNs detected during surveillance.

Arterially enhancing lesions are mostly benign and include primary liver tumours like focal nodular hyperplasia, adenoma, and small hemangiomas that rapidly fill with contrast. These have to be differentiated from the most common hypervascular malignant liver tumour, which is HCC; and metastasis from hypervascular neoplasms like melanoma, renal cell carcinoma, breast, sarcoma and neuroendocrine tumours (carcinoid, pheochromocytoma, islet cell tumours).

Meanwhile, according to the LI-RADS classification, which endorses a conservative approach, even though a definitive diagnosis of HCC cannot be established, "probable" HCC can be given for subcentimeter nodules showing one finding among "threshold growth," "washout," or "capsule," [15]. Korean Liver Cancer Study Group-National Cancer Centre (KLCSG-NCC) practice guidelines suggests that HCCs can be diagnosed by a combination of the typical features of HCCs in ≥2 imaging modalities and increased serum α-fetoprotein levels with an increasing trend over time for liver nodules <1 cm in patients with suppressed hepatitis activity [16].

The diagnosis of subcentimeter HCC can be clinically helpful by providing two different options, i.e., immediate treatment and intense follow-up. The key to achieving long-term survival is promptly implementing effective treatment strategies, including locoregional ablative therapy, hepatic resection, and liver transplantation [17,18].

Therefore, the current evidence is not concrete in discretely triaging subcentimeter hypervascular nodules in the cirrhotic liver. Also, there is no data from the Indian subcontinent. Furthermore, the rate of growth of SCSN and imaging predictive markers of hypervascular SCSN, which turn into HCC, is also not clear.

This study aimed to evaluate the incidence of arterially enhancing subcentimeter nodules evolving into HCC. To identify any specific size cut-off, rate of growth, or specific radiologic features which can prognosticate and, if possible, predict which subcentimeter arterially enhancing nodule will turn into HCC.

## MATERIALS AND METHODS

A prospective observational cohort study was conducted in all cirrhotic patients who presented to the Department of Radiodiagnosis at Medanta The Medicity, Gurgaon, Haryana, India, for dynamic CT or MRI during the study period from (1st May 2018 to 30th April 2019) The study was undertaken only after the approval from Institutional Review Board.

**Inclusion criteria:** Patients with liver cirrhosis of any aetiology or chronic liver disease, including chronic hepatitis B and C viral infection, without a prior history of HCC in whom a SCSN was identified during HCC surveillance with either CT or MRI were included.

**Exclusion criteria:** Patients with lesions size more than 1 cm or known HCC on the first scan were excluded from the analysis. Also, patients who had only a single imaging study were eliminated from the research group.

**Sample size calculation:** Cochran formula was used for sample size calculation which yielded a minimum number of 51 lesions [19]. The final study was done on 72 lesions in 59 patients.

After the inclusion in the study, the patients were further followed for at least one year. The retrospective previous cross-sectional imaging, if available, was also included in the study.

LI-RADS is a system to categorise liver lesions used in patients with liver cirrhosis and chronic hepatitis B without cirrhosis, as these patients are at an increased risk of HCC. LI-RADS staging reflects the probability of HCC and is based on the typical CT and MRI findings in HCC. LI-RADS is currently not to be used in patients <18 years or patients with cirrhosis due to other causes like congenital hepatic fibrosis or vascular disorders. This is because these patients have lower chances of developing HCC [20].

### Imaging Analysis

The multiphasic imaging was done in-house CT and MRI scanners:

1. Siemens Somatom Definition Flash- 128 dual source MDCT scanner (Siemens Healthineers, Erlangen, Germany).
2. Siemens Magnetom Verio-3 Tesla (Siemens Healthineers, Erlangen, Germany).

Scans were independently and retrospectively reviewed on a Picture Archiving and Communication System workstation by two Radiologists with more than 10 years' experience in hepatobiliary imaging, who evaluated the lesions at different time points for above criteria on dynamic CT and MRI. A definitive interobserver disagreement between the assessors, which occurred in 7 cases, required consensus of the radiology team.

The gold standard for HCC diagnosis was LR 5 lesion. An LR 5 lesion is more than 20 mm in size, showing arterial phase hyperenhancement and washout on portovenous phases/enhancing capsule/threshold growth.

The findings were collected in a tabulated form. The following outcomes were assessed: percentage of lesions turning into HCC, size specific cut-off, rate of conversion, and imaging criteria suspicious for HCC.

## STATISTICAL ANALYSIS

The analysis involved profiling of patients on different demographic, clinical and radiological findings. Quantitative data sets were presented in terms of means and standard deviation. Qualitative/categorical data were presented as absolute numbers and proportions. Crosstables were constructed and Chi-square test was used for testing of association. Student's t-test was used for comparing quantitative parameters. The Area Under the Curve (AUC) was measured using ROC curve analysis. The cut of points has been calculated as a minimum of $(1\text{-Sensitivity})^2+(1\text{-Specificity})^2$. The cut-off values along with corresponding sensitivity and specificity was also calculated. The p-value <0.05 was considered statistically significant. Statistical Package for Social Sciences (SPSS) software version 20.0 was used for statistical analysis.

## RESULTS

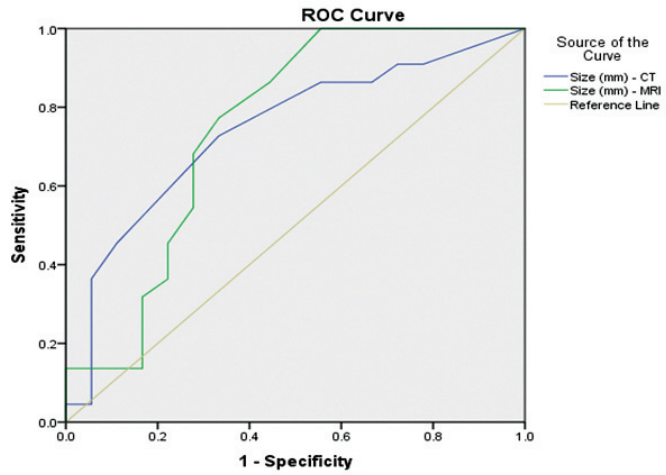
A total of 59 patients were analysed, of which 85% were males, and 15% were females between ages of 22-81 (Mean±standard deviation: 53±12 years). Many of the patients were scanned using both modalities at different time points. Out of 59 patients, 96.6% (n=57) underwent CT examination and 71.2% (n=42) were scanned using MRI. Out of 59 patients, 28 (47.5%) developed HCC during the study period. Of those who developed HCC, 74.1% had an increase in size on CT. With MRI as an imaging modality, 58.3% of the HCC lesions showed an increase in size while only 33.3% of the non HCC lesions increased in size [Table/Fig-1].

| Direction of change | CT findings | | | MRI findings | | |
|---|---|---|---|---|---|---|
| | HCC n=27 n (%) | Non HCC n=30 n (%) | Total N=57 n (%) | HCC n=24 n (%) | Non HCC n=18 n (%) | Total N=42 n (%) |
| Decrease | 0 | 2 (6.7) | 2 (3.5) | 0 | 2 (11.1) | 2 (4.8) |
| No change | 7 (25.9) | 17 (56.7) | 24 (42.1) | 10 (41.7) | 10 (55.6) | 20 (47.6) |
| Increase | 20 (74.1) | 11 (36.7) | 31 (54.4) | 14 (58.3) | 6 (33.3) | 20 (47.6) |
| Total | 27 (100) | 30 (100) | 57 (100) | 24 (100) | 18 (100) | 42 (100) |

**[Table/Fig-1]:** Change in size of lesions on CT and MRI and HCC status.

The nodules' mean size, when labelled as HCC, was 13.6±15 mm on CT and 18.1±11.8 mm on MRI. Upon baseline comparison, the growth difference was more in the HCC group (8.2±12.24 mm) than in the non HCC group (3.37±7.39 mm). None of the lesions turning into HCC showed a decrease in size.

There was a substantial increase in size in the nodules that later evolved into HCC compared with nodules that did not. Using CT as an investigation modality, the mean size of an arterially enhancing SCSN at first scanning, which later turned into HCC, was 5.0±3.5 mm, while which did not turn into HCC was 5.4±3.4 mm. Upon continuous follow-up, the lesions that ultimately transformed into HCC had a difference in growth size between first and last CT was of 8.4±14.0 mm vis a vis non HCC group, which had a growth of 1.4±3.6 mm with a p-value of 0.011, which was statistically significant. The optimal cut-off points after which the likelihood of an arterially enhancing lesion turning into HCC increase was 8.5 mm in CT with a sensitivity of 72.7% and a specificity of 66.7% (AUC 0.741); and 10.5 mm in MRI with a sensitivity of 77.3% and a specificity of 66.7% (AUC 0.749) [Table/Fig-2].




| Size on (mm) | Area | Standard error | Asymptomatic 95% Confidence Interval (CI) | |
|---|---|---|---|---|
| | | | Lower bound | Upper bound |
| CT (mm) | 0.749 | 0.080 | 0.584 | 0.899 |
| MRI (mm) | 0.741 | 0.084 | 0.585 | 0.914 |

**[Table/Fig-2]:** Receiver operating characteristic curve showing MRI has better sensitivity towards detection of SCSN as it is located on the left upper corner of the image with an AUC of 0.749. In contrast, CT has an AUC of 0.741.

Washout was demonstrated in 40.4% of the lesions on CT scan and 50% on MRI scan. Of these, almost 80.8% of nodules on CT and 87.7% on MRI changed into HCC (p-value <0.001), which is statistically significant [Table/Fig-3].

| CT parameters | HCC n=26 n (%) | Non HCC n=31 n (%) | Total N=57 n (%) | Odds ratio (95% CI) |
|---|---|---|---|---|
| Washout (Chi-square value=32.448; p-value=0.0001) | | | | |
| Yes | 21 (80.8%) | 2 (6.5%) | 23 (40.4%) | 60.9 (0.76-344.67) |
| No | 5 (19.2%) | 29 (93.5%) | 34 (59.6%) | |
| Rim enhancement (Chi-square value=5.1; p-value=0.023) | | | | |
| Yes | 6 (23.1%) | 1 (3.2%) | 7 (12.3%) | 9 (1.01-80.52) |
| No | 20 (76.9%) | 30 (96.8%) | 50 (87.7%) | |

**[Table/Fig-3]:** Comparison between HCC status and various parameters of SCSN on CT.
The p-value <0.05 was considered statistically significant

In patients having nodules that later changed into HCC and were scanned using MRI, 45.8% showed diffusion restriction (p-value 0.004), and 83.3% demonstrated non uptake of hepatobiliary contrast (p-value <0.001), which was statistically significant [Table/Fig-4].

| MRI parameters | HCC n=24 n (%) | Non HCC n=18 n (%) | Total N=42 n (%) | Odds ratio (95% CI) |
|---|---|---|---|---|
| Diffusion (Chi-square value=8.176; p-value=0.004) | | | | |
| Yes | 11 (45.8) | 1 (5.6) | 12 (28.6) | 14.38 (1.64-126.08) |
| No | 13 (54.2) | 17 (94.4) | 30 (71.4) | |
| Washout (Chi-square value=31.5; p-value=0.0001) | | | | |
| Yes | 21 (87.5) | 0 | 21 (50) | 227.28 (11.01-4693.5) |
| No | 3 (12.5) | 18 (100) | 21 (50) | |
| Rim enhancement (Chi-square value=1.287; p-value=0.257) | | | | |
| Yes | 6 (25) | 2 (11.1) | 8 (19) | 2.667 (0.46-15.13) |
| No | 18 (75) | 16 (88.9) | 34 (81) | |
| Non uptake of hepatobiliary contrast (Chi-square value=15.685; p-value=0.0001) | | | | |
| Yes | 20 (83.3) | 4 (22.2) | 24 (57.1) | 17.5 (3.73-82.04) |
| No | 4 (16.7) | 14 (77.8) | 18 (42.9) | |

**[Table/Fig-4]:** Comparison between HCC status and various parameters of SCSN on MRI.
The p-value <0.05 was considered statistically significant

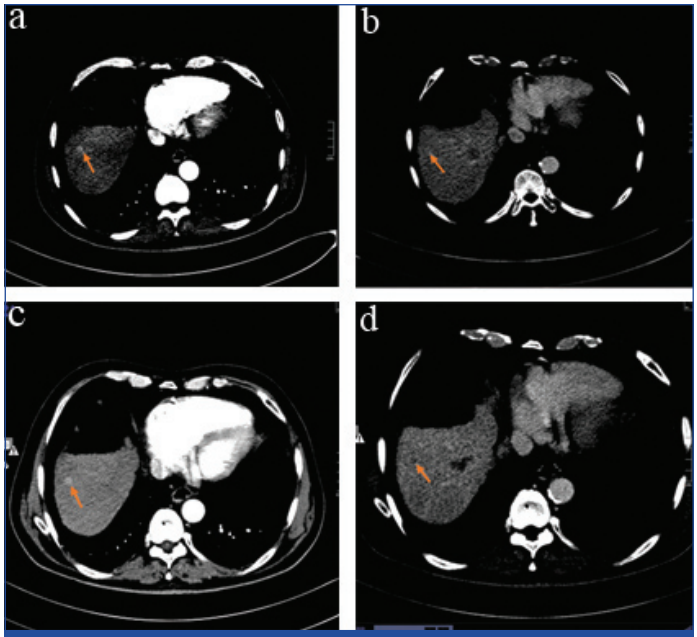
For arterially enhancing SCSN, the mean HCC free interval was 3.3 years and the median HCC free interval was 2.1 years. At a time interval of 1 year, 47.8% of lesions did not change into HCC and at an interval of 4 years, 45.2% of lesions did not convert into malignancy. (The retrospective previous cross-sectional imaging, if available, was also considered in the study. Some of the included patients had previous imaging reaching upto, 4-6 years, so their 4 years' worth of investigation and imaging was included in the study).

## DISCUSSION

In our study, the incidence of development of HCC was 47.5% from arterially enhancing subcentimeter nodules, with upto 52.2% of lesions changing into HCC within the first year. This percentage is relatively higher than the reported literature; a plausible explanation for this could be the inclusion of cirrhotics or patients of chronic liver disease due to any aetiology rather than patients only of hepatitis B or C virus infection. In the study by Min YW, the yearly incidence was 4.9% for the development of HCC from nodules in patients with chronic hepatitis B or C infection [12]. Other researchers have also reported a similar incidence of 2-8% for subcentimeter nodules changing into HCC within a year, in patients with chronic hepatitis B or C infection [13,21]. Park MJ et al., reported that small (5-10 mm) arterially enhancing nodules on CT in surveillance for HCC have a 29.5% probability of developing into HCC over a mean 35.7 month of follow-up [22]. According to a study by Forner A et al., 15.4% of subcentimeter lesions turned into HCC over a median follow-up period ranging from 23-30 months [23]. Jeong YY et al., reported that 13% of arterial enhancing nodules less than 2 cm were HCC in patients with cirrhosis [24]. Holland AE et al., who evaluated 45 arterial phase enhancing nodules smaller than 2 cm in cirrhotic livers, found that 35% of patients with cirrhosis had these enhancing nodules and that only 7% of lesions were neoplastic [25]. There is wide variation in the current cited literature regarding subcentimeter nodules' incidence of evolving to malignancy. Still, it is coherent to consider that arterially enhancing lesions show a higher propensity to convert into HCC, as demonstrated in the present study [Table/Fig-5].

The optimal time for follow-up of the patient should be every six months as upto 52.2% of lesions might convert into HCC within one year. Also, lesions can convert into HCC even after remaining stable for 3-4 years. Therefore, hypervascular lesions should be followed-up for at least 6 years [12]. Min YW, recommended follow-up of SCSNs every few months to detect growth suggestive of malignant transformation [12].

Song KD et al., reported that the initial size of hypervascular SCSN was a significant predictor of progression to overt HCC, with a cut-off value of 5.5 mm [26]. As per his findings, most SCSNs (89.9%)




**[Table/Fig-5]:** Temporal evolution of subcentimeter arterially enhancing nodule to HCC. Images a and b: On CT at time point 1, there is a 5 mm nodule in segment 8 of the liver without any definite washout in image b. Images c and d: On CT at time point 2, there is an increase in the size of the arterially enhancing nodule to 9 mm with definite washout on delayed phases.

progressed to overt HCCs within 12 months, and all SCSNs larger than 5.5 mm, progressed to overt HCCs within 12 months. Our statistical analysis revealed that the optimal cut-off points after which the likelihood of an arterially enhancing lesion turning into HCC increased was 8.5 mm in CT and 10.5 mm in MRI. So, it concurred that once the lesion nears these cut-off points, they need to be more aggressively followed-up. In addition, in this study, the rate of change of size was a better predictor than baseline size for predicting LR 5 HCC on CT.

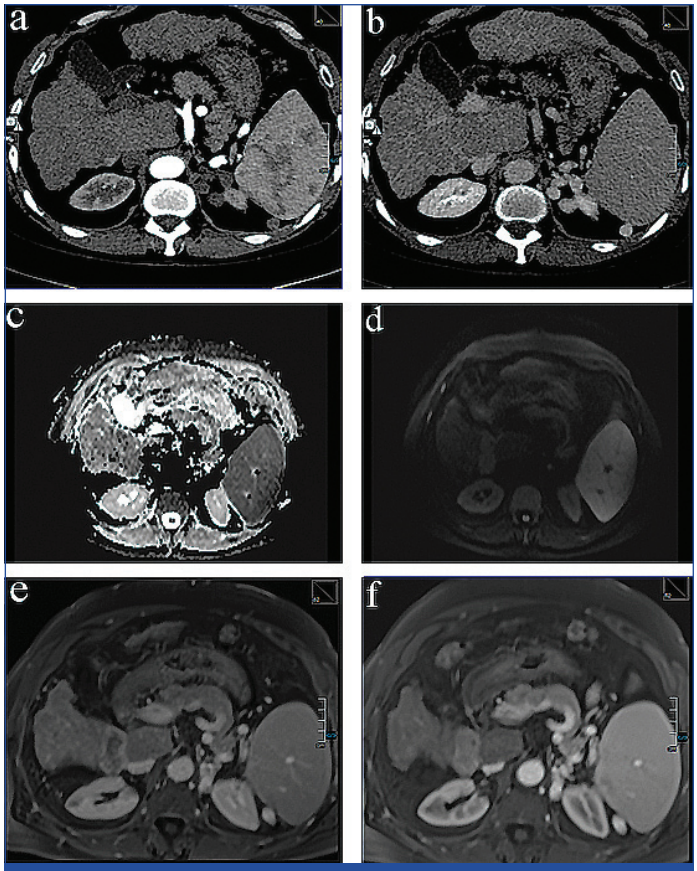
In current study, none of the lesions that changed into HCC decreased in size. Of the nodules that changed into HCC over time, only 23.1% on CT and 25% on MRI showed rim enhancement [Table/Fig-6]. This is partially explained because when the tumours become 1.5-2 cm in diameter, they tend to dedifferentiate, becoming moderately differentiated and growing in an expansile fashion with the formation of a fibrous capsule [27]. A surrounding tumour capsule can be detected in lesions of any size, but because of increasing capsule thickness with increasing tumour size, capsules are better seen with bigger HCCs [28]. They are typically thin and discontinuous and show progressive delayed enhancement. Capsular enhancement may represent contrast material retained in the fibrous and vascular elements of the tumour margin [29]. Capsular enhancement is seldom seen in tumours less than 1 cm in diameter [30]. Ishigami K et al., noted that HCCs with histologic fibrous capsules were larger than 1.2 cm in size and that approximately one-half of well-differentiated HCCs had no enhancing capsule [31].

The DWI may improve the diagnostic performance of MRI for malignant SCSNs by demonstrating higher cellularity of HCC [11]. In this study, 45.8% of small HCCs had restricted diffusion [Table/Fig-6]. Albin N, elucidated that on DWI, 79% of dysplastic nodules are iso- or hypointense, whereas 97% of HCCs are hyperintense [32].

The HBP hypointensity is a strong indicator of premalignancy or malignancy, and its presence favours early HCC over a cirrhotic nodule [10]. Out of all who developed HCC, 83.3% of patients showed HBP hypointensity, which was statistically significant (p-value <0.001).

### Limitation(s)

The present study had some limitations. There was a lack of histologic confirmation for the lesions, which were defined on the basis of radiologic images. However, it is unlikely that HCCs were mistakenly categorised, as previous imaging was also considered.




**[Table/Fig-6]:** Temporal evolution of subcentimeter arterially enhancing nodule to HCC. Images a and b: On CT at time point 1, there is a 7 mm nodule in segment 6 of the liver without any definite washout in image b. Images c and d: On MRI at time point 2, there is an increase in the size of the arterially enhancing nodule to 15 mm, which now shows rim enhancement and definite washout on delayed phases. Image e and f: in the same patient there is subtle diffusion restriction with fall in ADC values on MRI.

Additionaly, pathological validation of these lesions would not be practical in routine clinical settings. Lastly, our assessments regarding the number, nodule pattern, location, and size of SCSNs had a component of subjectivity due to the small nodule sizes and sometimes ill-defined margins. To overcome this limitation, all radiologic images were reviewed by two experienced radiologists. Future large multicentre prospective studies are needed to refine our research findings and confirm our proposed cut-off values.

## CONCLUSION(S)

Thus, around 47.1% of subcentimeter arterially enhancing nodules have the potential to turn into HCC. The size specific cut-off for CT was 8.5 mm, and for MRI was 10.5 mm with a sensitivity of 72.7% and 77.3%. The optimal time for following-up the patient should be every six months as upto 52.2% of lesions might turn into HCC in less than one year. None of the lesions that changed into HCC decreased in size on imaging. Diffusion restriction and HBP hypointensity are strong predictors of premalignancy or malignancy, and their presence favours early HCC over cirrhotic nodule. This study can be used to power other large multicentric trials with larger sample sizes to further develop recommendations for subcentimeter arterially enhancing nodules in HCC surveillance.

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