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Assessment of the follow-up interval changes of the less than 2 cm arterial phase enhancing hepatic nodules in correlation with Liver Imaging Reporting and Data System (LI-RADS) classification version 18 using contrast-enhanced multidetector computed tomography

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Abstract

Background: Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and the second leading cause of cancer death in the world. It is the only tumor that can be diagnosed by imaging only, without a need for histopathological confirmation. CT and MR are the imaging techniques that often allow making a definite diagnosis.

This study is a prospective study done by multiphasic contrast-enhanced computed tomography on 25 patients with liver cirrhosis showing 30 hepatic arterial phase hyper-enhancing nodule. Follow-up CT studies for these nodules were performed 4 to 6 months after the initial study

Results: In the follow-up study, 14 (46.66%) lesions showed size progression; however, only 4 of them had a progression which was more than 50% (threshold progression as described in LI-RADS version18). Nine (30%) lesions showed stationary size, and 7 lesions (23.33%) disappeared. Regarding the enhancement dynamics, 2 lesions developed delayed non-rim washout. By application of the LI-RADS classification, LI-RADS 3 category was noted in 25 lesions, and only 2 lesions evolved in the follow-up to LI-RADS 5 (using version 17 of the LI-RADS), while using LI-RADS version 18, only 3 lesions evolved. Five lesions were classified as LI-RADS 4 category by LI-RADS version 20017, and all these lesions progressed in size with 2 of them (40%) exceeded the growth threshold in the follow-up and progressed to LI-RADS 5. Using version 18 of the LI-RADS system, these lesions are classified as LI-RADS 5 category in the initial study.

Conclusion: The findings of the current study support the modification of the LI-RADS scoring system in the LI-RADS version 2018 upgrading arterial hyper-enhancing lesions with non-peripheral washout ranging from 1 to less than 2 cm from LI-RADS 4 to LI-RADS 5.

Keywords: Liver cirrhosis, Tomography, X-ray computed, Carcinoma, Hepatocellular, Liver neoplasms

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Background

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and the second leading cause of cancer death in the world. CT and MR are the imaging techniques that often allow making a definite diagnosis of HCC without a need to biopsy the lesion. HCC is one of the tumors that can be diagnosed by imaging only, without the need for histopathological confirmation [1, 2].

Ultrasonography remains a first-line examination, and it has recently gained increasing capabilities due to the implementation of dynamic contrast-enhanced studies and elastography [3]. However, the diagnostic role of DCE ultrasonography relative to DCE-CT and MR imaging remains debated [4, 5], and also, there is a significant overlap of lesion stiffness in elastography between benign and malignant lesions [6].

The role of MR imaging has been substantially increased due to the recent updates in MRI technology. The pulse sequences at MR imaging can be adjusted to produce images that assess different tissue characteristics to differentiate benign from malignant lesions such as diffusion, perfusion, and viscoelasticity [7, 8].

There are many guidelines that try to facilitate and unify HCC diagnosis in imaging studies, for example, American Association for the Study of Liver Diseases (AASLD) [9], European Association for the Study of the Liver (EASL) [10], and Asian Pacific Association for the Study of the Liver (APASL) [11] guidelines.

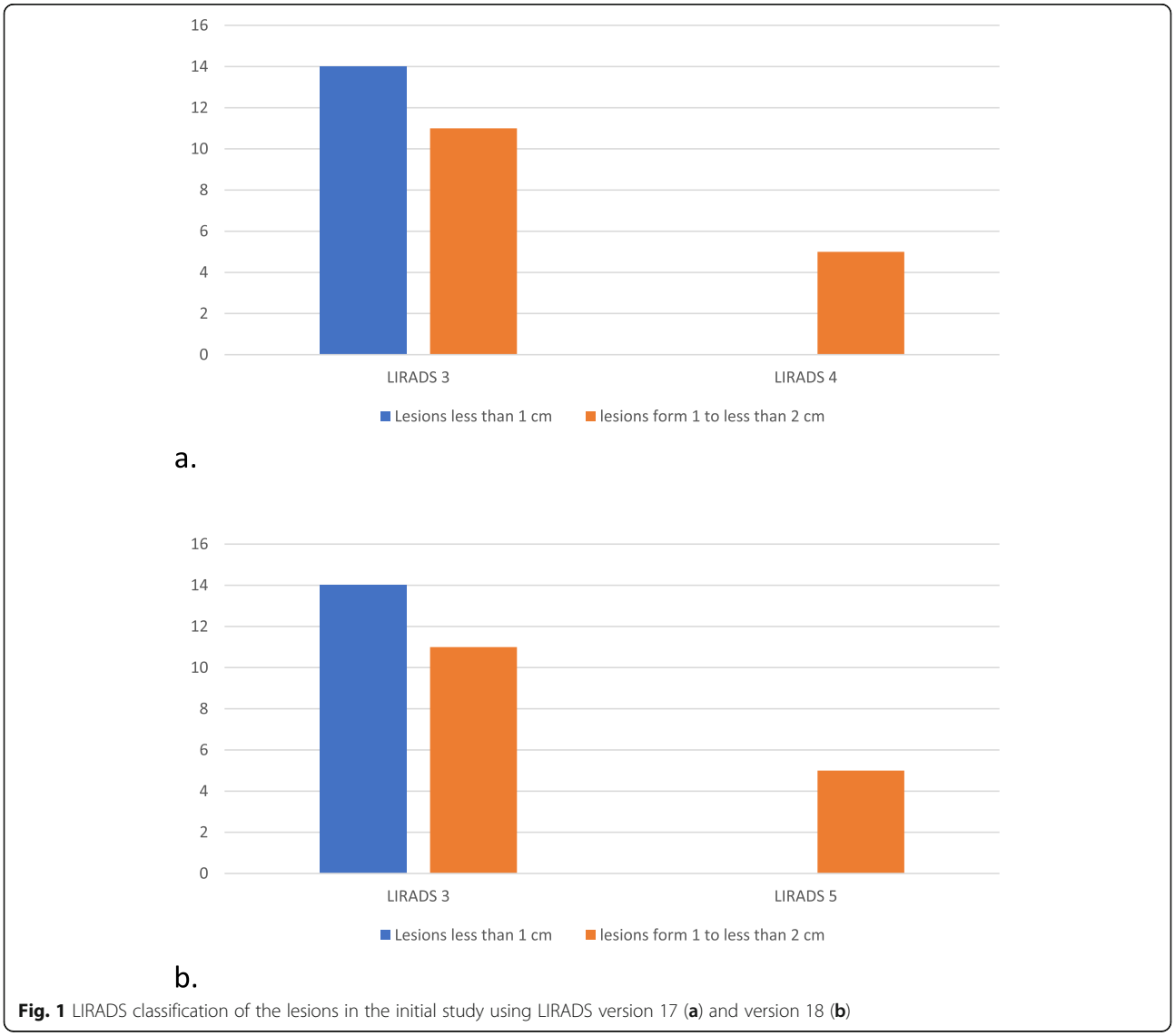


Fig. 1 LIRADS classification of the lesions in the initial study using LIRADS version 17 (**a**) and version 18 (**b**)

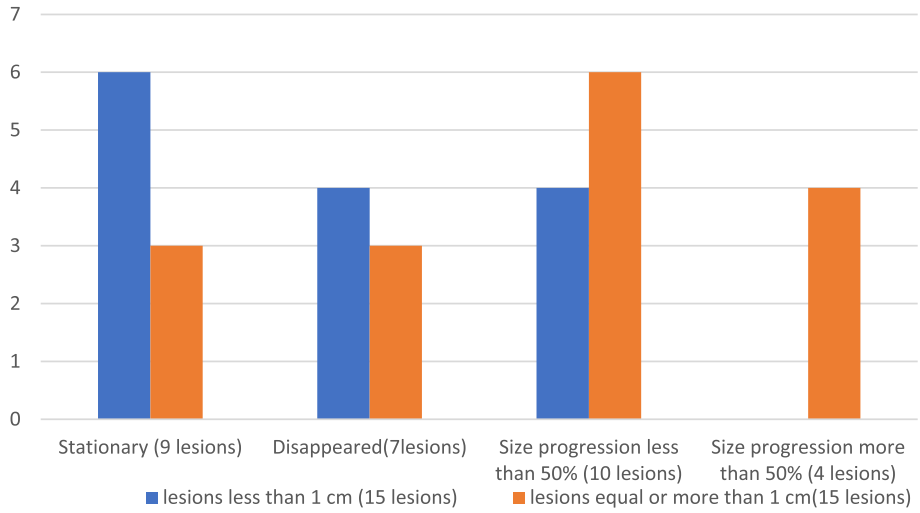


Fig. 2 Interval changes of the lesions in the follow-up study

In 2008, the first Liver Imaging Reporting and Data System (LI-RADS) committee convened, with support from the American College of Radiology, with the primary aim of standardizing the lexicon, interpretation, and reporting of imaging findings to improve communication related to the diagnosis of HCC in high-risk patients. The major features include non-rim arterial phase hyper-enhancement (NRAP), observation diameter, non-peripheral washout appearance, enhancing capsule appearance, and threshold growth [12].

The initial version of LI-RADS was released in 2011 with a standardized five major categories for classifying observations in the liver: LI-RADS 1 (definitely benign), LI-RADS 2 (probably benign), LI-RADS 3 (intermediate probability for HCC), LI-RADS 4 (probably HCC), and LI-RADS 5 (definitely HCC) [13].

In the 2014 LI-RADS update, the diagnostic algorithm was modified. A split cell was introduced into the algorithm for 10–19 mm observations with NRAP and one additional major feature for HCC, and all other observations in this cell were assigned as LI-RADS 4 [14]. LI-RADS v2017 added new algorithms for US surveillance, CEUS diagnosis, and CT/MRI treatment response assessment. The category LR-non-categorizable (LR-NC) was added to describe observations that cannot be categorized due to image degradation or omission [15].

In LI-RADS version 2018, a change in LR-5 criteria was introduced: lesions 10–19 mm in size with NRAP and washout are categorized as LR-5. In prior LI-RADS versions, such observations were categorized as LR-4 or, if visible on antecedent US images, as LR-5us, and also, it simplified the threshold growth definition to a size increase of at least 50% in 6 months or less [16].

Objective

The objective of this study is to identify the interval changes in size and enhancement dynamics of NRAP hepatic nodules measuring less than 2 cm in correlation to LI-RADS version 18.

Patients

Inclusion criteria

During the period from February 2016 to April 2017, this prospective study was performed on 25 patients with cirrhotic liver who referred to our institution showing in the initial study a less than 2 cm NRAP nodule/s with a time interval between the 2 studies of 4 to 6 months.

Exclusion criteria

The exclusion criteria are as follows:

1. Patients with targeted lesions managed in the time interval between the initial study and the follow-up study
2. Patients with incomplete medical records

Table 1 Size progression of the lesions in the current study with assessment of sensitivity and specificity of size progression in more than 1 cm NRAP lesions using MedCalc's statistical test

	Total number	Progressed lesions
Lesions more than 1 cm	16	10
Lesions less than 1 cm	14	4
Sensitivity		62.5%
Specificity		71.4%
Positive predictive value		71.4%
Negative predictive value		62.5%

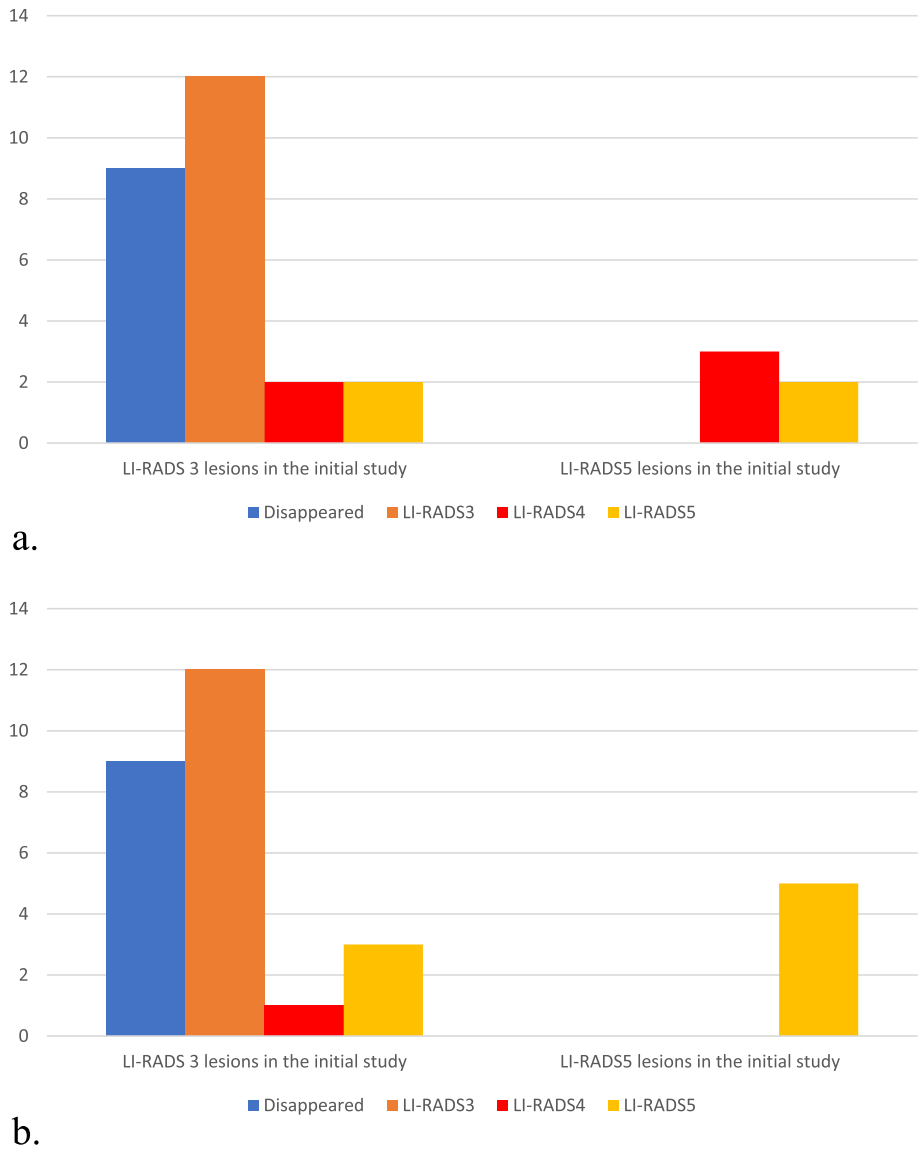


Fig. 3 LIRADS classification of the lesions in the follow-up study using LIRADS version 17 (**a**) and version 18 (**b**)

3. Lesions with indistinct outlines or wedge shape subcapsular lesions (probably representing areas of transient hepatic attenuation difference)

Patient consent was waived by the Research Ethics Board, assuring respect of the confidentiality of the medical record.

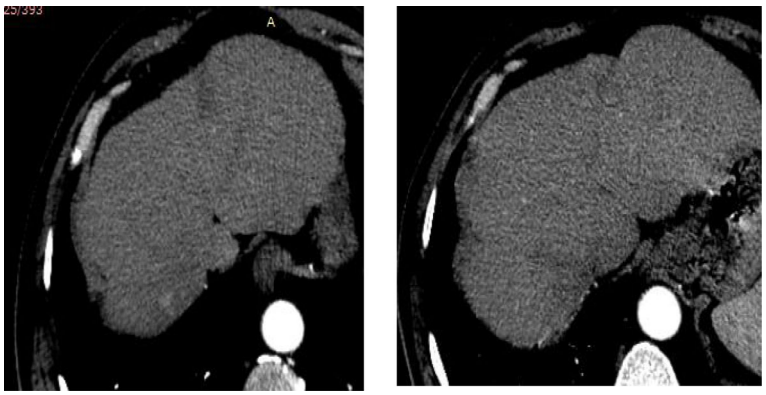
Methods

All patients were subjected to the following:

1. Full history taking
2. Laboratory investigations including liver and renal function tests as well as serum alpha-fetoprotein level
3. Assessment of previous radiological studies in patients with previous radiological imaging
4. Pre- and post-contrast MDCT abdomen with multiphasic assessment of the liver using GE optima aquilion 16 slices. The CT technique parameters include 1.5 mm thickness, interval of 0.625, pitch of 1.751, rotation speed of 3500, matrix size of 512, detector configuration 16 × 1.25, beam collimation of 200 mm, and coverage time of 10.35 s using large field of view.

A pre-contrast study covers a range from the tracheal bifurcation to the pelvic outlet.

A post-contrast study following non-ionic water-soluble contrast medium was injection using an



a. b.

Fig. 4 Case 1: a 58-year-old male patient with cirrhosis. **a** MDCT in the arterial phase dated February 2017 reveals a small right hepatic lobe segment VII hyper-enhancing nodule measuring 11 mm showing no washout in the venous nor the delayed phases (not shown); this lesion is categorized as LIRADS-3. **b** MDCT in the arterial phase for the same patient 5 months later showing disappearance of the lesion

automated injector (1.5 ml/kg body weight) 25 s, 70 min, and 180 min following contrast administration using the same parameters.

Result

The current study included 30 lesions in 25 cases, of those 22 were male patients and 3 were females. Their ages ranged from 48 to 76 years with mean age of 62 years.

In the initial study, 14 lesions were less than 1 cm, and in 16 lesions, the size was between 1 and less than 2 cm.

A total of 25 lesions (83.33%) showed NRAP with neither washout nor pseudo-capsule and were classified as LI-RADS 3 category (by LI-ARDS version 17 and version 18), including 14 cases with less than 1 cm in maximum diameter(100%) and 11 out of 16 cases with diameter equal or more than 1 cm (68.75%).

While 5 cases (17.66%) showed washout in the delayed phase and were classified as LI-RADS 5 category by version 18 of LI-RADS and LI-RADS 4 category by version 17, all of them were more than 1 cm (Fig. 1).

In the follow-up study, 7 lesions disappeared (23.3%) from which 4 were less than 1 cm and 3 were with diameter equal or more than 1 cm.

A total of 9 cases (30%) showed stationary course regarding their size and enhancement, and 8 showed NRAP only with a single lesion showing washout in both the initial study and follow-up.

A total of 14 lesions (46.66%) showed progression in size, from which 4 lesions were initially less than 1 cm and 10 lesions were initially more than 1 cm (4 of them showed size progression more than 50% from which 2 progressed to more than 2 cm), and 5 lesions showed delayed washout in the initial study and follow-up, while 4 cases developed delayed enhancement washout in the follow-up (Fig. 2, Table 1).

In the follow-up study using LI-RADS system version 17 (Figs. 3, 4, 5, 6, 7, and 8).

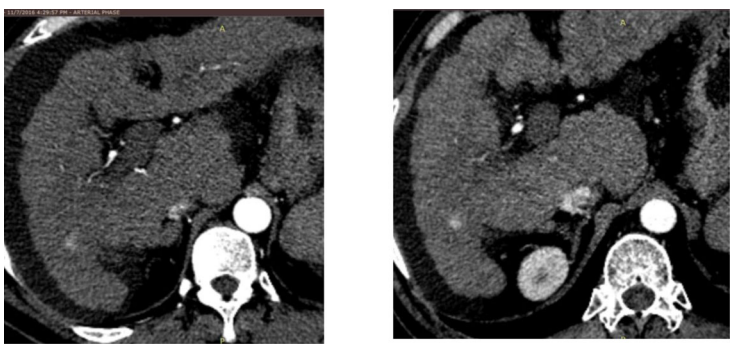
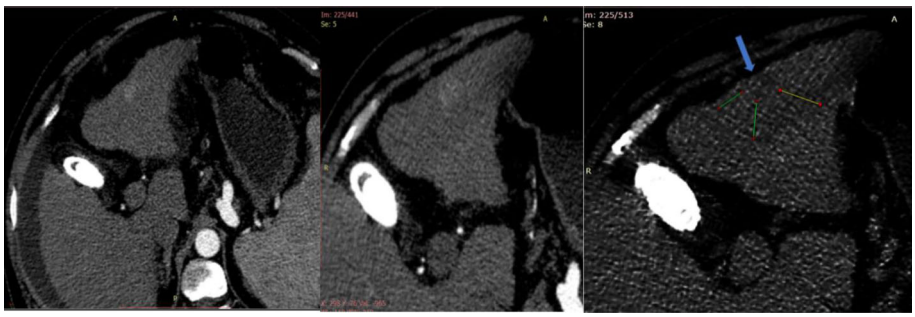


Fig. 5 Case 2: a 63-year-old male patient with cirrhosis. **a** MDCT in the arterial phase dated January 2017 reveals a small right hepatic lobe segment VI hyper-enhancing nodule measuring 8 mm showing no washout in the venous nor the delayed phases (not shown); this lesion is categorized as LIRADS-3. **b** MDCT in the arterial phase for the same patient 6 months later showing stationary size of the lesion



a. b. c.

Fig. 6 Case 3: a 55-year-old male patient with cirrhosis. **a** MDCT in the arterial phase dated August 2016 reveals a small left lobe hyper-enhancing nodule measuring 11 mm showing no washout in the venous nor the delayed phases (not shown); this lesion is categorized as LIRADS-3. **b**, **c** MDCT in the arterial and delayed phases for the same patient 4 months later showing size progression of the lesion measuring 22 mm with development of mild washout; in the second study, the lesion is classified as LI-RADS 5

For LI-RADS 3 category lesions, 9 lesions disappeared (36%), 12 lesions remained as such (50%), 2 upgraded to LI-RADS 4, and 2 upgraded to LI-RADS 5.

For LI-RADS 4 category, all the lesions progressed in size, and 2 lesions (40%) evolved to LI-RADS 5 while the remaining 3 lesions remained in LI-RADS 4 category. Based on these data, size progression of LI-RADS 4 lesions in the current study showed sensitivity of 100% and specificity of 80.6% while LI-RADS 4 progression to LI-RADS 5 showed sensitivity of 40% and specificity of 92.6% (Tables 2 and 3).

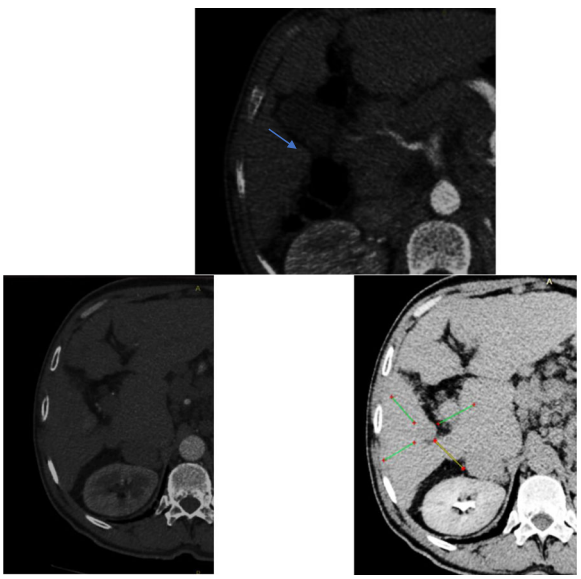


Fig. 7 Case 4: a 63-year-old male patient with cirrhosis. **a** MDCT in the arterial phase dated November 2016 reveals a small segment V right lobe hyper-enhancing nodule measuring 12 mm showing no washout in the venous nor the delayed phases (not shown); this lesion is categorized as LIRADS 3. **b**, **c** MDCT in the arterial and delayed phases for the same patient 6 months later showing size progression of the lesion measuring 21 mm with development of mild washout; in the second study, the lesion is classified as LI-RADS 5

In the follow-up study using LI-RADS system version 18 (Figs. 3, 4, 5, 6, 7, and 8).

For LI-RADS 3 category lesions, 9 lesions disappeared, 14 lesions remained as such (50%), 1 upgraded to LI-RADS 4, and 3 upgraded to LI-RADS 5. The remaining lesions were initially classified as LI-RADS 5 category.

Discussion

Small enhancing hepatic nodules are problematic, indeterminate lesions that are commonly encountered during interpretation of contrast-enhanced CT and MR imaging studies of cirrhotic liver [17]. Most of these findings are benign pseudo-lesions due to underlying diseases that severely alter perfusion, such as Budd-Chiari syndrome and, less commonly, chronic portal venous occlusion and large arterio-portal fistula [12].

Given their enhancement pattern, these nodules may be difficult to differentiate from HCC. Many therefore are categorized as LI-RADS 3 or 4. If a well-defined homogeneously hyper-enhancing nodule without a capsule appearance remains stable for longer than 1 year, particularly in a patient with the underlying conditions described, a diagnosis of benign hyperplastic nodule becomes increasingly likely [18].

When the hyper-enhancing observation is subcapsular and shows a triangular shape, it can be confidently labeled as definitely benign (LI-RADS 1) or probably benign (LI-RADS 2). In contrast, the more central lesions with a round or oval shape, in the absence of comparison studies, are more likely to be labeled as indeterminate (LI-RADS 3) [19].

The LI-RADS category may, therefore, evolve from 4 to 3, or occasionally to 2. Conversely, if the patient presents with a history of viral hepatitis, alcoholism, non-alcoholic steatohepatitis, or other chronic liver diseases, NAPH should be followed to ensure it does not represent HCC or its precursors [20].

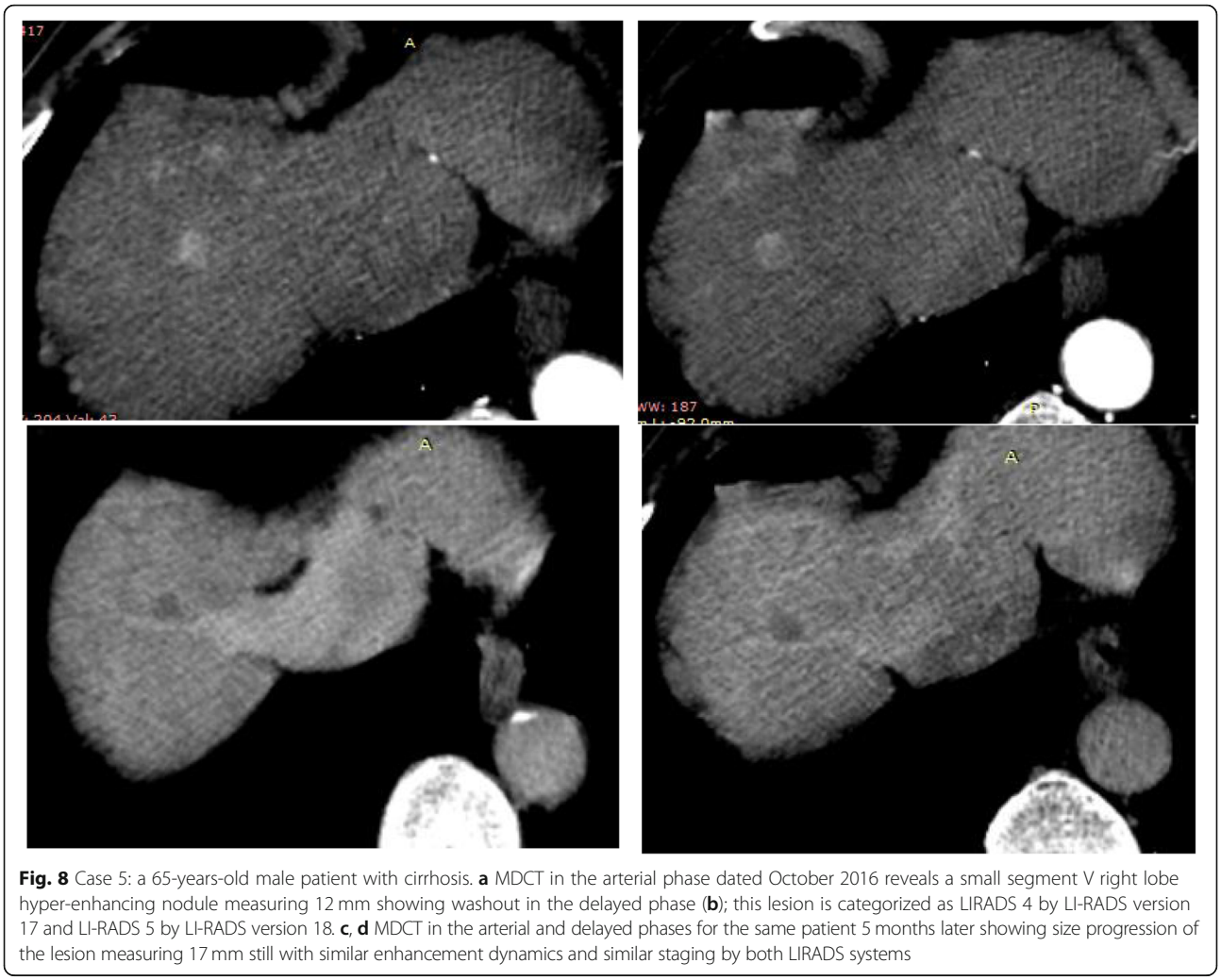


Fig. 8 Case 5: a 65-years-old male patient with cirrhosis. **a** MDCT in the arterial phase dated October 2016 reveals a small segment V right lobe hyper-enhancing nodule measuring 12 mm showing washout in the delayed phase (**b**); this lesion is categorized as LIRADS 4 by LI-RADS version 17 and LI-RADS 5 by LI-RADS version 18. **c**, **d** MDCT in the arterial and delayed phases for the same patient 5 months later showing size progression of the lesion measuring 17 mm still with similar enhancement dynamics and similar staging by both LIRADS systems

In the current study, 25 lesions initially showed NRAP with neither washout nor delayed capsular enhancement and were described as LI-RADS 3 category, from which 2 lesions (8%) were evolved in the follow-up to LI-RADS 5 category (using version 17 of the LI-RADS), while using LI-RADS version 18, 3 lesions evolved (12%).

The current study results match with the findings described by Holland et al. [18] who found that the majority (93%) of NRAP-only lesions are non-neoplastic, even in patients with pathologically proved HCC.

Matching results were also described by Choi et al. [21], who reported that 94% of LI-RADS 3 identified at

Table 2 Size progression of LI-RADS 4 lesions in the current study compared with LI-RADS 3 with the assessment of sensitivity and specificity in more than 1 cm NRAP lesions using MedCalc's statistical test

	Total number	Progressed lesions
LIRADS 4	5	5
LIRADS 3	25	6
Sensitivity		100%
Specificity		80.6%
Positive predictive value		45.4%
Negative predictive value		100%

Table 3 Sensitivity and specificity of progression of less than 2 cm LI-RADS 4 to LI-RADS 5 by LI-RADS 17 scoring system compared with LI-RADS 3 using MedCalc's statistical test

	Total number	Progressed lesions
LIRADS 4	5	2
LIRADS 3	25	2
Sensitivity		40%
Specificity		92.6%
Positive predictive value		50%
Negative predictive value		89.3%

gadoxetic acid-enhanced MR imaging remained stable or decreased during imaging follow-up.

There is partial discrepancy between the current study results and the results described by Quaia et al. [22] who found in their study on 151 NRAP hepatic nodules a percentage of 24% HCC.

Using LI-RADS version 17 and older versions, 5 lesions in the current study were described as LI-RADS 4 category, and all the lesions showed progression in size, 2 of which progressed to LI-RADS 5.

In the literature, similar results were encountered by Tanabe et al. [19] who found that 38% of LI-RADS 4 lesions progressed to a malignant category (LI-RADS 5 or LI-RADS M) within 6 months to 3 years, and 43% remained stable in category, while the remainder decreased in category, only 4% of LI-RADS 3 observations progressed to LI-RADS 5, and most remained stable or decreased in category.

Partial validation also is provided by Darnell and colleagues [23], who showed that 96% of LR-4 with a histologic reference standard were HCC. The LI-RADS 4 ("probably HCC") category is intended to convey high probability of HCC, and this was confirmed by these investigators.

In the current study, all the lesions (five lesions) between 1 and 2 cm in diameter with NRAP and delayed washout progressed in size compared with 36% of the other less than 2 cm lesions; from these five lesions, two of them had growth exceeding 50% of their size. These findings are matching with the recent update of the LI-RADS system version 18 [16] which upstaged these lesions from probable HCC to definite HCC.

We acknowledge the limitation in the current study; first, there were relatively a limited number of cases, and this is attributed to the exclusion of some cases, either due to loss of contact with the patients of the study population or interventional management that was done in some cases with lesions less than 2 cm with NRAP and delayed washout out of our institution. The second limitation was the interval follow-up duration which was in the current study between 4 and 6 months; we think that if the time interval was above 6 months, there would be more progression of the lesions with delayed washout. Further studies using larger study population and longer follow-up interval are recommended to confirm the results of the current study.

Conclusions

The current study findings support the modification of the LI-RADS scoring system in the LI-RADS version 2018 upgrading arterial hyper-enhancing lesions with non-peripheral washout ranging from 1 to less than 2 cm from LI-RADS 4 category to LI-RADS 5 category [16].

Abbreviations

AASLD: American Association for the Study of Liver Diseases; APASL: Asian Pacific Association for the Study of the Liver; EASL: European Association for the Study of the Liver; HCC: Hepatocellular carcinoma; LI-RADS: Liver Imaging Reporting and Data System; MDCT: Multidetector computed tomography; NRAP: Non-rim arterial phase hyper-enhancing

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Not applicable

Authors' contributions

Not applicable (single author). The author read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of the Medical Research Institute, Alexandria University, on 13 August 2019 (reference number of approval: 10rg0008812). All patients included in this study gave written informed consent to participate in this research (all the patients were older than 16 years old).

Consent for publication

All patients included in this research gave written informed consent to publish the data contained within this study.

Competing interests

The author declares that there are no competing interests.

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