

Comparison of Multidetector computed tomography with Digital Subtraction Angiography and lipidol CT in detection of small hepatocellular carcinoma

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Abstract: Objectives: this study aims to compare the sensitivity of MDCT, DSA and lipidol CT in detection of small HCC. **Back ground:** hepatocellular carcinoma (HCC) is a common malignancy in Egypt, their management depend greatly on the size and number of the lesions so they should be precisely defined. Multiple imaging modalities can be very helpful in this purpose, as MDCT, DSA and lipidol CT. **Methods:** fifty patients known to have HCC were evaluated for more small (<3cm) nodules by MDCT (as base line CT study), DSA with lipidol injection and 2 weeks later by post embolization CT study, then the number of the small HCC detected in every modality is calculated and further categorized according to their size into (A<1cm, B1-2cm and C2-3cm) to be compared. **Results:** the total number of small HCCs detected by DSA (142 =86,6%) is higher than those detected by base line CT study (97=59,15%), but both are less than lipidol CT (post embolization study) =100%. DSA has higher Sensitivity (87%) than Baseline CT study (78%) and higher specificity (94%) relative to ((73%) by baseline CT study. And for categorization of the lesions according to their size into; (A <1cm, B=1-2cm, C=2-3cm), DSA detected higher number of focal lesions than those detected by base line CT study in every category as follows; category A(50fl=75.75%):(22fl=33.33%), category B(65 fl=92.6%):(52 fl=74.3%) and category C(27fl=96.43%):(23fl=82.14%) respectively. **Conclusion:** DSA has higher Sensitivity and specificity than Baseline CT study in detection of small hepatic focal lesions and this sensitivity is more in category A>B>C.

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Key Words: multidetector computed tomography (MDCT), digital subtraction angiography (DSA), hepatocellular carcinoma (HCC), transarterial chemoembolization (TACE).

1.Introduction:

Hepatocellular carcinoma (HCC) is one of the most common malignancies, ranking third in frequency among all malignancies in the world. HCC is characterised by rapid tumor growth and a high propensity of vascular invasion. (1)

Unlike most other organs, the liver is unique in that it has a dual blood supply via the portal vein and the hepatic artery. Normally, the portal vein is responsible for supplying most of the blood to the liver (75%–83%) with the hepatic artery providing only a supportive role (20%–25%). However, this balance is profoundly altered in cases of HCC, in which the hepatic artery practically becomes the sole supplier of blood to the tumor (90%–100%). (2)

HCC has a typical tendency to produce small or minute satellite nodules (daughter lesions), frequently located in the vicinity of the main tumour. (3)

Several factors are relevant to the pathogenesis of HCC. Three major etiological associations have been established: Viral infection (HBV, HCV), chronic alcoholism and food contaminants (primary aflatoxins), other conditions include tyrosinemia and hereditary hemochromatosis. (4)

Hepatocellular carcinomas range from well differentiated to highly anaplastic undifferentiated lesions. (5)

Early diagnosis of small HCC has become a principal objective because several potentially curative treatment options, such as liver transplantation, surgical resection, and local ablation therapy, can be successfully used to improve outcome if the HCC detected is small. (6)

Staging is essential for the management of HCC, as the choice of therapy depends on the functional state of the liver and the extent of tumour growth. The functional status of the liver in a patient with cirrhosis is usually assessed by the Child-Pugh classification. (7)

It is currently accepted that imaging techniques may confidently establish the diagnosis, without needing biopsy confirmation. (8)

A complete evaluation of the entire liver parenchyma to detect the smallest tumor is important in the management of HCC. Spiral CT, with the introduction of multidetector- row scan technology, plays a fundamental role in the diagnosis and staging of HCC. (3) The visibility of hepatic tumors depends

on their enhancement relative to normal parenchyma. Tumor enhancement varies with the vascularity of each tumor and the phase of contrast at the time of scanning. (9)

The typical HCC shows an intense enhancement in the arterial phase and a contrast wash-out in late venous contrast phases.(8)

Digital subtraction angiography (DSA) is a way of taking images of the hepatic artery using complex computerised X-ray equipment. (10) Angiography has long been used to diagnose HCC through the demonstration of abnormal arterial tumour vessels and nodular tumour stain using the digital subtraction technique (DSA) (11). Digital Subtraction Angiography procedure uses the image intensifier and computers to obtain rapid digital information as the contrast medium passes through the arteries. The computer is able to subtract the bones and other tissues, leaving only the vessels filled with contrast medium in the image, thus improving greatly the clarity and detail of the examination. (11) Lipidol is a lipid compound containing iodine and has been used for many years as a lymphatic contrast agent. Lipidol has been introduced into chemoembolization regimens as a result of its affinity to and prolonged retention in liver tumors (12). In Lipidol CT, iodized oil is injected into the hepatic artery through angiographic catheterization. Most of the iodized oil droplets flow into HCCs by virtue of the increased blood supply to the tumour and, once deposited in the tumour, disappears at a far slower rate compared with those deposited in the normal liver tissue. Hence, on CT scans acquired 3-4 weeks later, HCCs appear as highly hyper-attenuating areas compared with non-tumorous liver tissue.(13)

The method of choice for the early diagnosis of HCC should have high validity (sensitivity and specificity), efficacy, and cost-effectiveness.(14)

2. Patients and Methods

This study includes assessment of 50 patients discovered to have hepatic focal lesions on top of cirrhotic liver by US examination in the out-patient clinic of (National liver institute, Menoufiya University) starting in October 2011 till October 2013. Patient acceptance was ensured for all cases. The study was approved by the Research Ethics Committee of National Liver Institute and the Research Ethics Committee of the Faculty of Medicine, Menoufiya University.

ALL OUR PATIENTS WERE SUBJECTED TO THE FOLLOWING:

- Full history sheet and Full Clinical examination.

- Laboratory blood samples examination. (Liver function tests & complete blood picture, AFP...etc).

- Ultrasonography and color Doppler examination of the liver.

- Abdominal triphasic CT scan as a base line study.

- Digital subtraction angiography (DSA) and lipidol injection.

- Abdominal triphasic CT scan 2weeks after DSA and lipidol injection as a post embolization study.

Technique of triphasic CT scan of the liver:

Twenty patients were examined by (Siemens 20 Somatom Definition AS 2010) used in the National Liver Institute and the other thirty patients examined by different outside MDCT machines, this scan was done twice: (first; before DSA as base line study then; 2weeks after DSA as post embolization study).

With the following parameters 120 kVp, 350 mAs, 0.5 second tube rotation time, 16x1.25mm collimation, pitch of 1.375, 5mm slice thickness for axial images, and 1.25mm reconstruction slice thickness, 1.25mm reconstruction interval.

Patient preparation:

- Fasting for 6 hours before scan.
- No oral contrast was used.
- Creatinin clearance should be >30
- Vigorous Oral hydration.
- Intravenous catheter introduced through antecubital vein.

Patient position:

- The patient lies supine, head first, scanning start from the lung bases down to the inferior border of the liver in all phases except in the porto-venous phase where the scan extend to perineum.

CT scan Protocol

1) Non-contrast phase:

Used for identification of calcifications in the base line study, and in post embolization study: to identify the lipidol deposition in the focal lesions.

Then a nonionic contrast agent (300 mg of iodine per mL) was administered intravenously (2 ml /kg), through the intravenous catheter. then the helical acquisition started(8sec) after a threshold level of (140 HU) was reached in the abdominal aorta then the arterial phase acquired(20-30sec) after injection of contrast media, the porto-venous phase acquired (50-60sec) after the injection of contrast media, Lastly the delayed phase acquired (5-10min) after injection of the contrast media.

2) Contrast enhanced phases:

It includes arterial, porto-venous and delayed phases. Diagnosis of the focal hepatic lesion depend on its pattern of enhancement.

Ex; hypervascular HCC lesions will show typical criteria of enhancement (wash-in at the

arterial phase and wash-out at the porto-venous and delayed phases).

Post procedure care:

Vigorous Oral hydration

Technique of hepatic DSA and lipiodol injection:

The cases were decided to perform DSA and lipiodol injection after fulfillment of the inclusion criteria, as follows:

- Only Patients with Child-Pugh class A or B with absolute exclusion of class C.
- Absence of extra hepatic spread.
- Absence of vascular and biliary invasion.
- Absence of portal vein thrombosis (main trunk or its branches).
- Absence of marked bleeding diathesis (prothrombin concentration should be over 60% and platelet count not be less than 50,000).

Patient Education

Before the procedure, all patients were informed about the side effects and risks as; bleeding, fever and pain.

Patient preparation

Patients fast overnight and admitted to the hospital in the morning of the procedure. Vigorous hydration (normal saline solution at a rate of 500 mL/8hrs), and prophylactic antibiotics (1g of cefotaxime Na, IM) are initiated.

Parameters used:

The examination was done for the 50 patients using (Toshiba Infinix) with 70 kV, 800 mA, the acquisition time 2 frames/sec, the effective field of view 14, the images were acquired by injection of (20) ml bolus of optiray300 (ioversol injection 64% & 300mg/ml organically bowel iodine), (5) French introducer sheath & (5) French catheter were used & (10) ml of lipiodol were injected.

Technique

In the angiography suite, with the patient under conscious sedation. After infiltration of local anaesthetic, the Seldinger technique is used to gain access to the common femoral artery through femoral artery puncture.

Then 5-French vascular sheath is passed into the common femoral artery over a 0.035-inch Guide-wire. Under fluoroscopic guidance, a 5-French glide Cobra catheters (Cordis) is advanced into the aorta and then used to select the celiac axis and SMA. Over

the guide-wire, diagnostic visceral arteriography is performed to determine the arterial anatomy of the liver and tumoral lesions. Then the catheter is advanced into the hepatic artery for injection of lipiodol. patients were asked to perform another abdominal triphasic CT 2weeks after the procedure.

Post Procedure Care:

- Bed rest for 24 hours.
- The puncture site must be carefully observed during this period.
- Vital signs must be taken periodically up to 24 hours.
- Patients are discharged after 24-hour admission.

Then total number of the lesions seen at both (base line CT study and DSA) with further categorization according to their size into (A<1cm, B=1-2cm and C=2-3cm) are compared, taking post embolization CT study as the gold standard of this comparison.

3.Results

The total number of small lesions detected by post embolization CT study (lipiodol CT) = (164) was higher than those detected by DSA= (142) and base line CT study (MDCT) = (97) which detected the lowest number of lesions. (Table 1)

According to categorization of the lesions regarding their size into A<1cm, B1-2cm and C2-3cm Post embolization CT study discovered higher number of focal lesions than those detected by base line CT study or even by DSA in every category A,B and C. Also DSA detected higher number of lesions than those detected by baseline CT study in all categories but its superior ability is more in category A than B than C.(Table2)

So DSA has higher Sensitivity (87%) than Baseline CT study (78%) and higher specificity (94%) relative to ((73%) by baseline CT study in detection of small<3cm lesions (Table3).

Table (1): Descriptive statistics of the total number of small focal lesions detected by base line CT study, DSA and post embolization CT study.

Type of study	No of focal lesions
Baseline CT study	97
DSA	142
Post embolization CT study	164

Table (2): Descriptive statistics of the Number of focal lesions detected by Baseline CT study, DSA and Post embolization CT study according to the size of lesion.

The study	Number of focal lesions according to the size			
	A < 1cm No (%)	B = 1 to 2 cm No (%)	C = 2to 3 cm No (%)	Total
Baseline CT study	22(33.33%)	52(74.3%)	23(82.14%)	97(59.15%)
DSA	50(75.75%)	65(92.6%)	27(96.43%)	142(86.6%)
Post-embolization CT study	66(100%)	70(100%)	28(100%)	164(100%)

Table (3): Sensitivity and specificity of Baseline CT study (triphasic CT) and DSA in detection of small HCC <3cm.

Test Result Variable(s)	Sensitivity	Specificity
DSA	87%	94%
Baseline CT study (Triphasic CT)	78%	73%

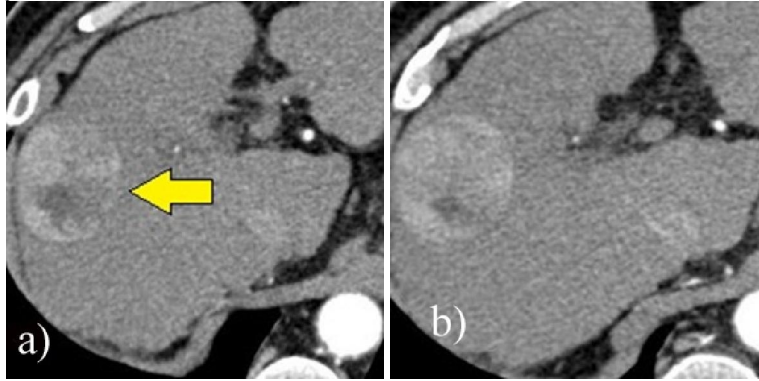
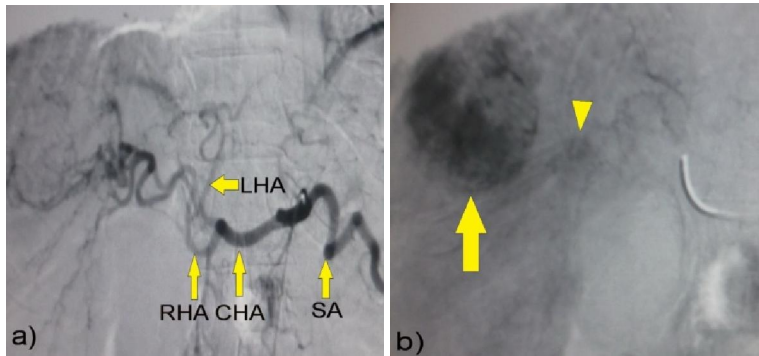
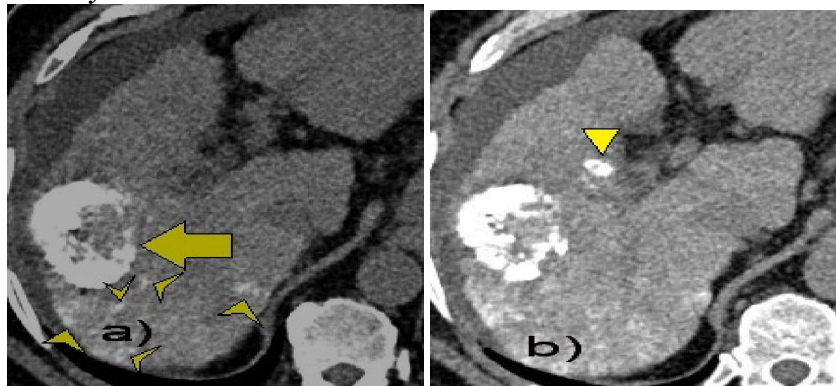
Baseline CT study:**DSA:****Post embolization CT study:**

Figure 1: Female patient 60 years old diagnosed to have right lobe mass during follow up of HBV cirrhosis, AFP= 32 ng/ml, Child –Pugh Class A, Hepatic artery is type I (Michel's classification). Baseline CT study (arterial phase) revealed Right lobe single sub capsular enhancing lesion measuring 6x5cm at segment VIII with No other lesions seen.

DSA images: a) DSA through the celiac trunk revealed that the CHA arises from the celiac trunk. b) DSA through the RHA revealed tumor blush at the previously described HCC at segment VIII (arrow) with another small tumor blush is seen at its medial aspect measures 22 mm in diameter (arrow head). Post embolization CT study revealed lipiodol deposition at the previously described lesion at segment VIII (arrow) as well as multiple new small focal lesions, up to 6 in number, less than 2cm (arrow heads).

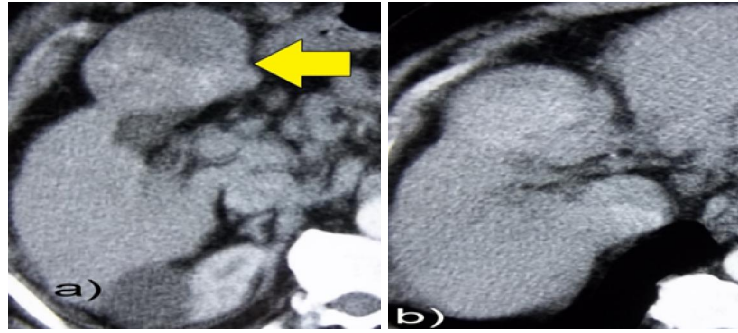
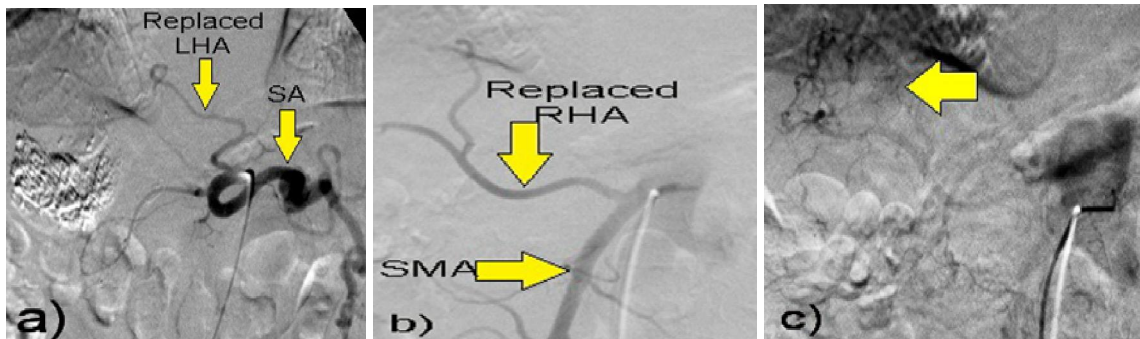
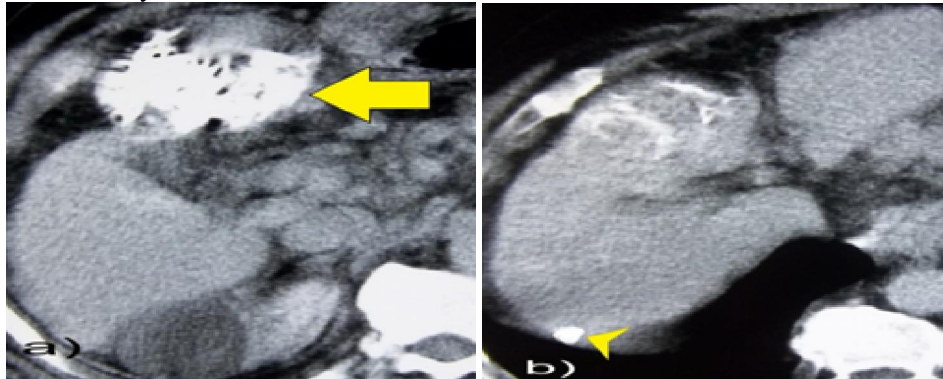
Baseline CT study:**DSA:****Post embolization CT study:**

Figure 2: Male patient 51 years old has focal lesion on top of cirrhotic liver with hepatitis B, AFP= 522 ng/ml, Child –Pugh Class B. Hepatic artery is type III (Michel's classification). Baseline CT study shows The left hepatic lobe (segment IV) showed solitary large enhancing focal lesion measures 8x8 cm with areas of breakdown. DSA images a) DSA through the celiac trunk revealed replaced LHA arising from the left gastric-left hepatic trunk. b) DSA through the SMA revealed replaced RHA arising from the SMA. c) It shows single tumor blush (arrow). Post embolization CT study: CT lipidol revealed a) Partial lipidol deposition within the large HCC described before. b) Dense lipidol deposition within single new small lesion at segment VII measures 12 mm in

4. Discussion

Hepatocellular carcinoma (HCC) is now the third leading cause of cancer deaths worldwide (15). Early diagnosis of small HCC has become a principal objective in abdominal imaging because several potentially curative treatment options, such as liver transplantation, surgical resection, and local ablation therapy, can be successfully used to improve outcome

if the HCC detected is small, that is, less than 2–3 cm in diameter (6). The method of choice for the early diagnosis of HCC should have high validity (sensitivity and specificity), efficacy, and cost-effectiveness (14). The purpose of this study is to compare the sensitivity of DSA and MDCT (baseline CT study) in detection of small HCC <3cm taking lipidol CT (post embolization CT study done 2 weeks

after DSA and lipidol injection) as the gold standard in this comparison. For this purpose 50 patients known to have hepatic focal lesions on top of cirrhotic liver were further assessed for number and size of other small FIs by base line CT study, DSA and post embolization CT study, then data collected and compared. In our study, the total number of small HCCs detected in the 50 cases by post embolization CT study (lipidol CT) = 16 was higher than those detected by DSA= 142 or base line CT study (MDCT) = 97, And according to categorization of the lesions regarding their size into A <1cm, B=1-2cm, C=2-3cm:

For category A; the post embolization CT study discovered higher number of focal lesions= 66 than those detected by base line CT study=22 or even by DSA= 50.

Also for category B; post embolization CT study detected higher number of focal lesions= 70 than DSA= 65 or base line CT study =52.

Lastly for category C; post embolization CT study detected a higher number of focal lesions =28 than by DSA =27 or base line CT study=23.

These results confirm the superior ability of post embolization CT study (lipidol CT) to discover small HCC nodules more than DSA or MDCT.

In agreement with these results **Iwazawa, et al.**, (16) and **Meyer et al.**, (17) proved that lipidol CT showed a high sensitivity for detection of small HCCs than MDCT. Also **Tognolini et al.**, (18) concluded that lipidol CT provided information not apparent or discernible at DSA, resulted in a change in diagnosis and treatment planning. The additional information included visualization of additional or angiographically occult tumors and identification of incomplete treatment. Also **El-Serag et al.**, (19) reported that Lipidol CT has been reported to be the most sensitive preoperative imaging modality for HCC especially in detecting small HCCs. And the reason of its high sensitivity and accuracy is explained by **Choi et al.**, (12) who states that Lipidol has a preferential uptake in tumor tissue because of its ability to target and remain fixed in HCC as It is normally removed by the reticuloendothelial (RES) cells of the liver. Normal liver usually removes Lipidol in 1 to 30 days. RES cells are missed in hepatic tumors.

Lastly **Bartolozzi et al.**, (20) proved that significant histological changes are present with or without evident arterial supply of the nodule. So the very small size of the lesion with immature vascular structure is one of the causes that make the lesion ill defined or even occult by modalities depend only on the vascular supply without the histological structure of the lesion.

Also our study resulted that; the total number of small focal lesions detected by DSA (142) is higher than those detected by base line CT study = 97 And as post embolization CT study is the reference =100% so; DSA=86.6% while base line CT study=59.15%, So DSA has higher Sensitivity 87% than Baseline CT study 78% and higher specificity 94% relative to 73% by baseline CT study in detection of small<3cm.

And for categorization of the lesions according to their size into A <1cm, B=1-2cm, C=2-3cm, DSA detected higher number and percent of focal lesions than those detected by base line CT study in every category as follows; category A(50fl=75.75%):(22fl=33.33%), category B(65 fl=92.6%):(52 fl=74.3%) and category C(27fl=96.43%):(23fl=82.14%).

These results can be explained by the following studies **Kojiro**, (21) who state that for small tumors, the risk of false negative diagnosis in contrast enhanced CT could be as high as 50% due to immature arterial vascularization of the nodule and as vascular supply of the lesion is the key for diagnosis as mentioned by **Bartolozzi et al.**, (20) and explained by **Andreana et al.**, (3) as follows: Normally, the portal vein is responsible for supplying most of the blood to the liver 75%–83%with the hepatic artery providing only a supportive role 20%–25%. However, this balance is profoundly altered in cases of HCC, in which the hepatic artery practically becomes the sole supplier of blood to the tumour 90%–100%.

So in MDCT the visibility of hepatic tumors depends on their enhancement relative to normal parenchyma. Enhancement varies with the vascularity of each tumor and the phase of contrast at the time of scanning (9). So, the inaccurate timing of scan (very early or very late scan)leads to inaccurate phase also inaccurate dose of contrast (even if tumoral vascular supply is mature) will lead to false negative diagnosis of the lesion in the different phases of the scan as discussed by **Bachir et al.**, (22), on the other hand the classic angiographic criteria of HCC as mentioned by **Masatoshi et al.**, (23) include; neovasculation, increased vascularity, tumor stain, dilated feeding arteries and arterio-portal shunts. So DSA can visualize the malignant vascular changes inside the lesions in real time avoiding the conflicts facing MDCT as inaccurate timing of scan as discussed by **Kwang et al.**, (24) and even for tiny lesions with immature vascular structure, they are diagnosed mainly by tumor stain as proved by **Kwang et al.**, (24).also the high ability of DSA in diagnosis of hypervascular HCC even of tiny sizes is mentioned by **Jin et al.**, (25), which lower the incidence of missed lesions by DSA.

Unlike these result (26) and (27) resulted that MDCT has superior ability in diagnosis of HCC.

Conclusion

DSA has higher Sensitivity and specificity than Baseline CT study in detection of small<3cm lesion and this sensitivity is more in smaller lesions.

We recommend future studies to optimize and adjust MDCT technique, including; timing of scan as the best phase to detect enhancing hepatic focal lesion is the late arterial phase to avoid missing lesions especially tiny lesions with immature vasculature.

Also we recommend future studies to consider the role of lipidol CT and DSA in detection of small hepatic lesions especially in cirrhotic patients without obvious focal lesions to exclude the possibility of hidden malignancy and increase the predictability of small lesions.

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