

# A Prospective Study of Ultrasound Guided Fine Needle Aspiration Cytology of Focal Lesions in Liver

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## ABSTRACT

**Introduction:** Many hepatic lesions which are detected clinically or by imaging technique are easily accessible to Fine Needle Aspiration Cytology (FNAC). Swift diagnosis by FNAC helps to save precious time and allow clinicians to duly plan treatment. Ultrasound guided FNAC of the liver is a safe, cheap, relatively non invasive procedure with minimum complication and can be routinely done for evaluation of liver diseases.

**Aim:** To evaluate hepatic lesions by ultrasound guided FNAC and classifying into inflammatory or non inflammatory, benign or malignant, primary or secondary tumour and also to find novel cytological features.

**Materials and Methods:** The present two year descriptive cross-sectional prospective study was carried out in the Department of Pathology, Karnataka Institute of Medical Sciences, Hubli, India. A total of 90 patients who satisfied the inclusion criteria during the two years study (August 2012 to July 2014) were assessed for clinical history and subjected to FNAC under ultrasound guidance. Descriptive statistical analysis was performed to calculate the percentage and frequency for the categorical variable included in the study.

**Results:** Out of 90 cases, majority 73 (81.1%) cases were neoplastic and 11 (12.2%) cases were non-neoplastic and the remaining 6 (6.6%) cases were inconclusive. Out of 73 cases, four cases were benign tumours and 69 cases were malignant tumours. Out of 69 cases, 33 cases were Hepatocellular Carcinoma (HCC), 32 cases were metastatic deposits, three cases were cholangiocarcinoma, one case was suggestive of malignancy. Among 33 cases of metastatic deposits, adenocarcinoma was most common (32 cases) and Squamous Cell Carcinoma (SCC) the least (one case). The most consistent cytological findings in HCC were macronucleoli (32 cases) and trabecular pattern of arrangement (32 cases). The most consistent finding in metastatic adenocarcinoma was coarse clumping of nuclear chromatin (32 cases).

**Conclusion:** The study concludes that the ultrasound-guided FNAC of the liver is a safe, simple, cost-effective, and accurate method that permits the categorisation of non-neoplastic (inflammatory) and neoplastic lesions (non inflammatory), primary and secondary malignancy in a simple and rational manner which is helpful for the management of hepatic lesions.

**Keywords:** Hepatic lesions, Hepatocellular carcinoma, Ultrasonography

## INTRODUCTION

Fine needle aspiration cytology is accepted as the first line of investigation and an excellent method of confirming diagnosis of hepatic lesions [1]. Among all hepatic lesions, neoplastic lesions were diagnosed more accurately when compared to non-neoplastic lesions [2]. Diagnostic accuracy is increased by cytomorphological analysis of FNAC of liver lesions as Ultrasonography (USG) alone has its own limitations [3].

The liver is associated with many non-neoplastic and neoplastic diseases. Pertinent clinical management is required for the accurate diagnosis of hepatic lesions as most of the liver masses present a relatively common clinical dilemma [4]. Hepatic lesions range from cysts and inflammatory process to neoplasms which may be benign or malignant, primary or secondary [5].

Now and then, the hepatic lesions such as inflammatory lesions or diffuse liver diseases may impersonate mass-like lesions. Such lesions should be sampled by FNAC to differentiate benign and malignant tumours of liver [6].

Major cytological diagnostic issues arise in benign hepatocellular lesions, reactive hepatocytes, Well-Differentiated HCC (WD-HCC), Poorly Differentiated HCC (PD-HCC), cholangiocarcinoma, metastatic carcinomas and, determination of the primary site of metastatic tumour. These lead to indeterminate reports on FNAC. The advantage of cytodiagnosis is, it obviates the need for diagnostic laparotomy, especially in inoperable cases, and allows specific chemotherapy to be instituted without delay [7].

The main goal is to help the clinicians in the management of patients who present with an abnormal mass [8]. Accurate diagnoses of hepatic masses are very important because treatment ranges from supportive care for advanced metastatic lesions to partial hepatectomy for primary carcinoma [7].

Hence, the present study was carried out to accurately diagnose focal lesions of liver which helps the clinicians to plan the treatment accordingly within a short time frame.

## MATERIALS AND METHODS

The present descriptive cross-sectional prospective study was conducted in the Department of Pathology, Karnataka Institute of Medical Sciences, Hubli, India, from August 2012 to July 2014. Before the commencement, the study was approved by the Ethical and Research Committee, Karnataka Institute of Medical Sciences, Hubli.

**Inclusion criteria:** Patients who presented with hepatic mass confirmed by radiological examination were included in the study. Since it was a time-bound study, all the samples received during the study period fulfilling the selection criteria were included in the study.

**Exclusion criteria:** Patients with haemorrhagic diathesis, Patients with a skin infection at the site of aspiration, critically ill patients, non-co-operative patients were excluded from the study. All the patients fulfilling the selection criteria were explained about the nature of the study and written informed consent was obtained before enrollment. Data such as age, sex, presenting complaints were recorded on a predesigned and pretested proforma.

## Study Procedure

The needle of length 15-20 cm and 22-23 G bore disposable needle was fixed on the 10 mL syringe. Under the ultrasound guidance the needle was introduced and was checked before aspirating over the screen. Patients were instructed to hold their breath during the procedure. The needle was moved back and forth and directed into different areas of the lesion, along with vacuum in the syringe. The piston of syringe was slowly released to reduce the vacuum and the syringe with the needle is withdrawn. The puncture site was immediately sealed with gauze soaked in iodine. The needle was detached, the syringe filled with air and then the needle reintroduced again. The contents were gently blown out on to the clean glass slides. Smears were quickly prepared with the help of another slide surface, putting gentle pressure to obtain thin and evenly spread smears. At least 2 to 4 smears of the aspirate from each patient were prepared. Smears were immediately fixed in ethyl alcohol and were stained by using Haematoxylin and Eosin (H&E) stain.

## STATISTICAL ANALYSIS

The categorical data was expressed as rates, ratios and proportions and continuous data was expressed as mean±Standard Deviation (SD).

## RESULTS

A total of 90 patients satisfied the inclusion criteria. Patients were assessed for clinical history and FNAC was done under ultrasound guidance.

In the present study, 48 (53.33%) cases were males and 42 (46.67%) cases were females. The commonest age group at presentation was sixth decade (50-59 age) that is 26 (28.89%) cases followed by fifth decade (40-49 age) that is 23 (25.56%) cases. The most common presentation was pain abdomen 73 (81.11%) cases followed by fever 15 (16.67%) cases. On physical examination, only hepatomegaly was present in 81 (90%) cases. A 9 (10%) cases showed combined hepatomegaly and splenomegaly.

On cytological examination, 73 (81.12%) cases were neoplastic and non-neoplastic lesions accounted for 11 (12.22%) cases, 4 (4.44%) cases were inadequate and the remaining 2 (2.22%) cases were inconclusive [Table/Fig-1a].

Hepatic lesions	Number of cases	Overall percentage
Non-neoplastic	11	12.22%
Neoplastic	73	81.12%
Inconclusive	02	2.22%
Inadequate	04	4.44%
Total	90	100%

**[Table/Fig-1a]:** Distribution of hepatic lesions on ultrasound-guided Fine-Needle Aspiration Cytology (FNAC) in the present study.

Five cases of the non-neoplastic lesions (inflammatory) were pyogenic abscess (45.45%) and remaining 4 (36.36%) cases and 2 (18.18%) cases were diffuse parenchymal lesion and granulomatous lesion respectively [Table/Fig-1b].

Diagnosis	Number of cases	Percentage
Pyogenic abscess	5	45.46%
Granulomatous lesion	2	18.18%
Diffuse parenchymal lesion	4	36.36%
Total	11	100%

**[Table/Fig-1b]:** Cytologic diagnosis of hepatic non-neoplastic (inflammatory) lesions in the present study.

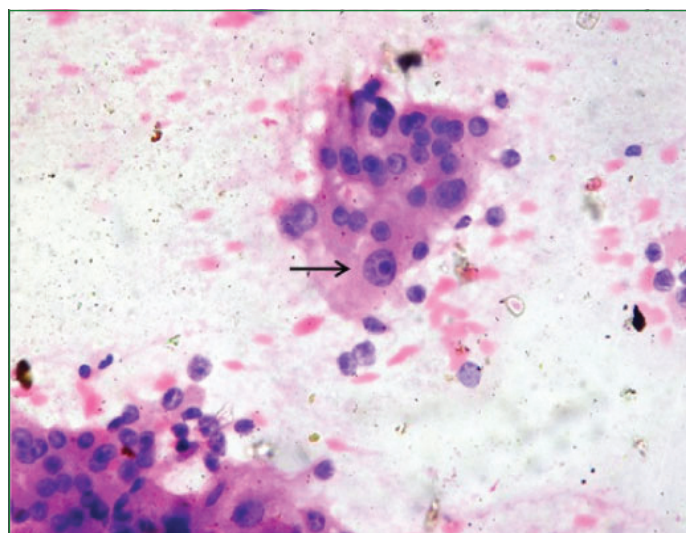
A total of 69 (94.52%) cases of the neoplastic lesions were malignant and remaining 4 (5.48%) cases were benign. Of the most common malignant lesions were metastatic adenocarcinoma and primary HCC

(32 cases each, 43.83%) followed by cholangiocarcinoma (4.12%), and least was metastatic squamous cell carcinoma and suggestive of malignancy (1 case each, 1.37%) [Table/Fig-1c].

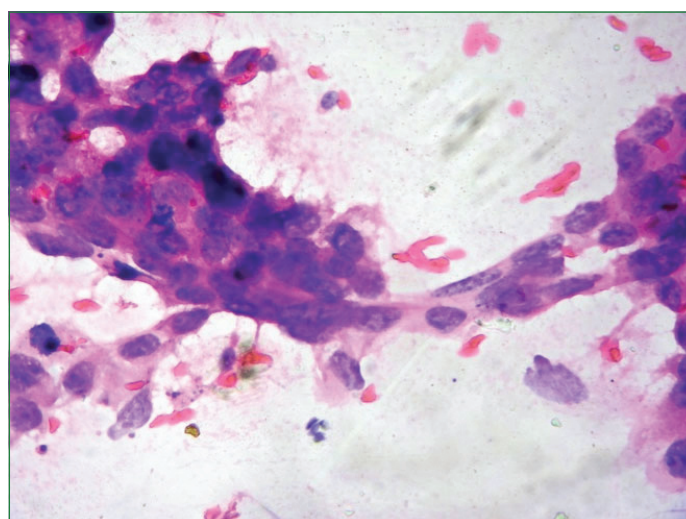
Diagnosis	Number of cases	Percentage
Benign		
Focal nodular hyperplasia	04	5.48%
Malignant		
Hepatocellular carcinoma	32	43.83%
Metastatic adenocarcinoma	32	43.83%
Metastatic squamous cell carcinoma	01	1.37%
Cholangiocarcinoma	03	4.12%
Suggestive of malignancy	01	1.37%
Total	73	100%

**[Table/Fig-1c]:** Cytologic diagnosis of hepatic neoplastic (non inflammatory) lesions in the present study.

The most consistent cytological findings in HCC were macronucleoli [Table/Fig-2] and trabecular pattern of arrangement followed by a hyperchromatic nucleus, increased nuclear-cytoplasmic ratio, pleomorphism, traversing blood vessels [Table/Fig-3], endothelial rimming [Table/Fig-4], bare nuclei, intranuclear inclusions [Table/Fig-5] and hypercellularity. The least common findings were binucleation/multinucleation, intracytoplasmic inclusions, tumour giant cells, and intracytoplasmic bile [Table/Fig-6].

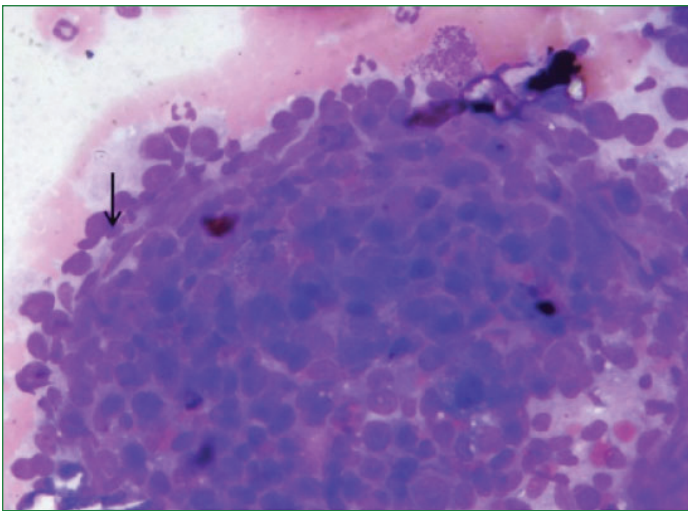


**[Table/Fig-2]:** Hepatocellular carcinoma showing macronucleoli (H&E stain 100X).

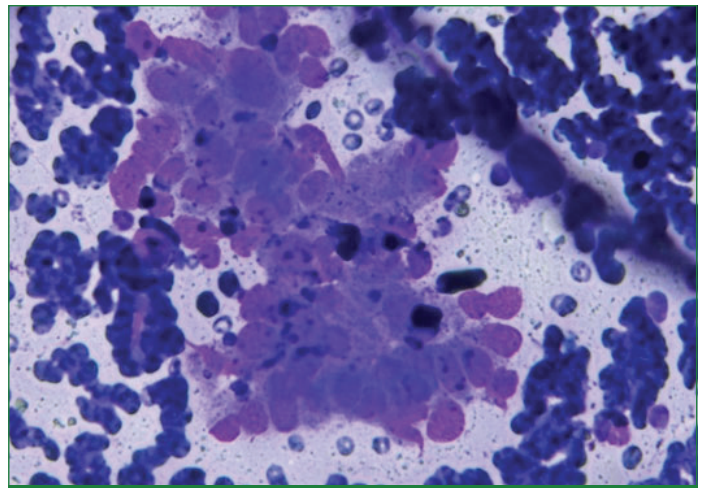


**[Table/Fig-3]:** Hepatocellular carcinoma showing traversing blood vessels (wright's stain, 400X).

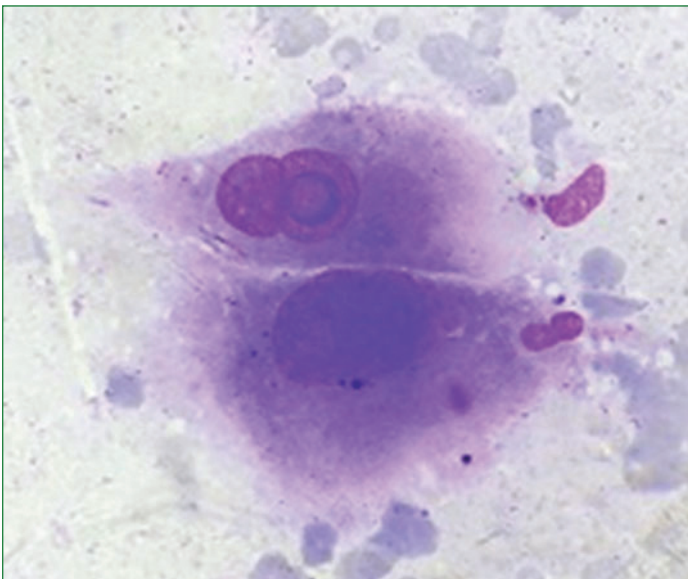
On cytological examination, coarse clumping of nuclear chromatin was the most consistent finding in metastatic adenocarcinoma



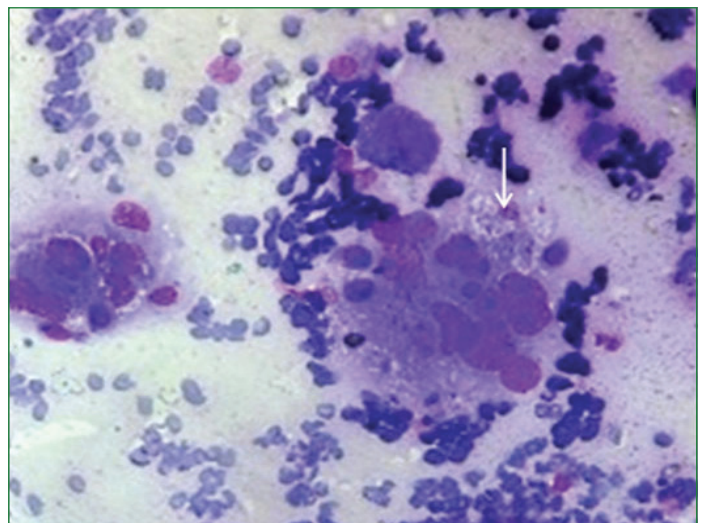
[Table/Fig-4]: Hepatocellular carcinoma showing endothelial rimming (Wright's Stain, 400X).



[Table/Fig-7]: Metastatic adenocarcinoma showing acinar pattern with coarse chromatin (Wright's stain, 100X).



[Table/Fig-5]: Hepatocellular carcinoma showing intranuclear inclusion (Wright's stain, 400X).



[Table/Fig-8]: Metastatic adenocarcinoma showing cytoplasmic vacuolation and mucinous background (Wright's stain, 400X).

Diagnosis	Distribution (n=32)	
	Frequency	(%)
Macronucleoli	32	100
Trabecular pattern	32	100
Hyperchromatic nucleus	31	96.88
Increased nuclear:cytoplasmic ratio	30	93.75
Pleomorphism	28	87.50
Traversing blood vessels	23	71.87
Endothelial rimming	21	65.62
Bare nuclei	20	62.50
Intranuclear inclusions	18	56.25
Hypercellularity	16	50.00
Binucleation/multinucleation	11	34.38
Intracytoplasmic inclusions	8	25.00
Tumour giant cells	6	18.75
Intracytoplasmic bile	5	15.62

[Table/Fig-6]: Cytological features of hepatocellular carcinoma in the present study.

[Table/Fig-7] followed by vacuolated cytoplasm [Table/Fig-8], eccentric nucleus, prominent nucleoli, increased nuclear-cytoplasmic ratio, benign hepatocytes, mucinous background [Table/Fig-8] and pleomorphism. The least common findings were normal bile ductular epithelial cell clusters; bile plugs, nuclear inclusion, and least were inflammatory cells and hypercellularity [Table/Fig-9].

Diagnosis	Distribution (n=32)	
	Frequency	Percent
Coarse chromatin	32	100.00
Vacuolated cytoplasm	28	87.50
Eccentric nucleus	22	68.75
Prominent nucleoli	22	68.75
Increased nuclear-cytoplasmic ratio	16	50.00
Benign hepatocytes	15	46.88
Mucinous background	9	28.12
Pleomorphism	9	28.12
Bile duct epithelium	3	9.37
Bile plugs	3	9.37
Nuclear inclusions	3	9.37
Inflammatory cells	2	6.25
Hypercellularity	2	6.25

[Table/Fig-9]: Cytological features of metastatic adenocarcinoma in the present study.

### DISCUSSION

Diagnosis of hepatic masses is very important for treatment. Clinically and radiologically, we cannot certainly distinguish benign and malignant tumours of liver but they help to narrow down our differential diagnosis. USG guided FNAC is an accurate method for arriving at a definite tissue diagnosis in focal liver lesions without major complications and minimal invasion at less cost.

Tumours, primary or secondary, may undergo extensive necrosis, with cavitations mimicking abscesses. Most of the times, abscesses

go along with proliferative reactive changes, thus making it difficult to differentiate it from neoplastic process radiologically. In such instances, FNAC plays an important role in attempt to categorise the lesions of the liver [8].

In this study, over half of the patients were male (53.33%) with male to female ratio being 1.14:1 suggesting near equal distribution. Similar near equal sex distribution was noted in study by Siddalingareddy and Andola SK [10]. Siddalingareddy and Andola SK observed slight female preponderance [10]. The mean age was 52.58±12.70 years and the median age was 52.5 years with the youngest patient being 26 years and the oldest being 80 years. The mean age observed in the present study was comparable with a study done by Franca AVC et al., and Talukder SI et al., [11,12].

The common clinical presentation found in present study was pain in the abdomen. The other presentations included fever, loss of appetite and abdominal distension, jaundice and vomiting, mass per abdomen, and loss of weight. Ahuja A et al., in their study also observed, pain in the abdomen as the commonest clinical presentation followed by loss of weight and anorexia, jaundice, fever, and lump [13].

In present study among 90 cases, FNAC diagnosis was available in 84 cases, and in six cases diagnosis could not be established as four cases were inadequate and two cases were inconclusive [Table/Fig-1a]. There were no follow-up details as well as non availability of those patients for a further needle biopsy. Reason could not be established for the above-said cases. In all those cases secondary change such as fibrosis might be the reason for inadequate material or inconclusive smears. Siddalingareddy and Andola SK; Ahmed SS et al., and Khan N et al., also observed similar unsatisfactory smears (6.5%, 6.5%, and 6%, respectively) [10,14,15].

In the present study, 11 cases (12.22%) were categorised as non-neoplastic lesions. The most common non-neoplastic lesion was a pyogenic abscess (5 (45.4%) cases) followed by diffuse parenchymal lesion (4 (36.36%) cases) and granulomatous lesion (2 (18.18%) cases). Diffuse parenchymal diseases accounted for 36.36% which was similar to the value found by Khurana U et al., [16].

Neoplastic lesions were the most easily and frequently diagnosed in most studies including Arathi S, Girijyan S, Khurana U et al., and Pupulim LF et al., [Table/Fig-10] [3,16,17]. Most of the neoplastic lesions (94.52%) in the present study were malignant, and remaining (5.48%) were benign. Over half of all malignant lesions were primary hepatic tumours (47.93%) and the remaining were secondary metastatic lesions (46.57%). The most frequent primary hepatic malignancy on ultrasound-guided FNAC of the liver was hepatocellular carcinoma. The most frequent secondary hepatic tumour was metastatic adenocarcinomas. Similar observations were found in a study done by Salamao DR et al., [18].

Author	Total cases	Neoplastic	Non-neoplastic
Present study	90	81.12%	12.22%
Khurana U et al., [16]	50	94%	6%
Pupulim et al., [17]	472	73.3%	26.7%
Arathi S and Giriyan S [3]	102	81.37%	9.8%

**[Table/Fig-10]:** Showing comparison of neoplastic (non-inflammatory) and non-neoplastic (inflammatory) cases in the present study with other studies [3,16,17].

The above observations showed that ultrasound-guided FNAC of the liver is the most valuable, cheapest, and fastest means of distinguishing primary hepatocellular carcinoma and secondary adenocarcinoma without much difficulty than USG alone or FNAC alone. Ultrasound guiding allows proper location and sampling of lesions thus enhancing the proper yield of diagnostic material.

In the present study, the most consistent cytological feature of hepatocellular carcinoma was macronucleoli and trabecular pattern of cells, which was followed by hyperchromatic nuclei, increased

nuclear-cytoplasmic ratio and pleomorphism. Some cases showed traversing blood vessels, endothelial rimming, malignant bare nuclei and occasionally intranuclear inclusions. Wee A, Nilsson B, and Balani S et al., both observed increased nuclear-cytoplasmic ratio as the most consistent cytological feature [Table/Fig-11] [19,20].

Cytological features	Wee A and Nilsson B, [19]	Balani S et al., [20]	Present study
Macronucleoli	75.14	85.7	100.00
Trabecular pattern	88.57	65	100.00
Hyperchromatic nucleus	75.71	100	96.88
Increased n:c ratio	100	100	93.75
Pleomorphism	80.00	71.4	87.50
Traversing blood vessels	82.85	57.1	71.87
Endothelial rimming	35.71	35.7	65.62

**[Table/Fig-11]:** Showing comparison of cytological features of HCC in the present study with other studies.

In the present study, metastatic hepatic tumours constituted 46.57% of total neoplastic lesions. Most of them (43.83%) were metastatic adenocarcinoma, and the least was metastatic SCC and metastatic malignancy unclassifiable (1.37% each). Metastatic adenocarcinoma deposits revealed high cellularity. The malignant cells were arranged in flat monolayered sheets, acinar pattern, palisading forms and in singles. Individual tumour cells were columnar or round to oval in shape with majority having vacuolated cytoplasm and some with eosinophilic cytoplasm. These cells showed mild to moderate anisonucleosis with a central or eccentrically placed nucleus with fine to coarsely granular chromatin. Some cases showed prominent nucleoli. An altered nuclear-cytoplasmic ratio was noted. Mitotic figures were seen in few cases. Nine cases showed mucinous background. In many cases normal benign hepatocytes were present and inflammation, necrosis, and fibrosis were prominent in some cases. Similar features were noted by Nasit JG et al., and Barbhuiya M et al., [7,9].

None of these metastatic tumours showed 'endothelial rimming' and 'traversing blood vessels'. Hence, in all metastatic hepatic epithelial tumours, it is important to note the presence or absence of "endothelial rimming or traversing blood vessels".

### Limitation(s)

The present study used FNAC as the sole diagnostic method and needle biopsy was not done for confirmation. However, in six cases diagnosis could not be established as there were no follow-up by patients for further needle biopsy and also there might be sampling error that can occur due to abundant fibrosis of tissue, extensive necrosis and prominent inflammatory reactions.

### CONCLUSION(S)

Ultrasound/Computed Tomography guided FNAC of the liver is a safe, simple, cost-effective method and plays an important role in getting sample from the lesion proper which helps in accurate diagnosis with high rate of sensitivity and specificity. FNAC of hepatic lesions categorically differentiates inflammatory or non-inflammatory, benign or malignant, primary or secondary lesions and it can be safely adopted during diagnostic evaluation of hepatic lesions.

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**PLAGIARISM CHECKING METHODS:** [Jain H et al.]

- Plagiarism X-checker: Oct 12, 2020
- Manual Googling: Jan 09, 2021
- iThenticate Software: Mar 15, 2021 (12%)

**ETYMOLOGY:** Author Origin**AUTHOR DECLARATION:**

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Oct 10, 2020**Date of Peer Review: **Dec 11, 2020**Date of Acceptance: **Feb 17, 2021**Date of Publishing: **Jul 01, 2021**