Iranian Journal of Pathology (2012) 7 (2): 70 - 79

Original Article

Cytomorphological Patterns of Nodular Lesions of Liver

Alpana Banerjee[1], Rajesh Singh Laishram[1], Ahongshangbam Meina Singh[2], Moirangthem Kulachandra Singh[3], Durlav Chandra Sharma[1]

1. Dept. of Pathlology, Manipur University, Imphal, India
2. Dept. of Pathlology, Aligargh Muslim University, Imphal, India
3. Depet. Of Medicine, Manipur University, Imphal, India

ABSTRACT

Background and Objectives: Nodular lesions of liver are usually neoplastic (primary or metastatic), although inflammatory lesions can occur. The objectives of this paper were to study the cytomorphological changes in various nodular lesions of liver and to correlate the cytomorphological findings with biochemical parameters especially serum alpha-fetoprotein.

Materials & Methods: A cross-sectional study consisting of 40 patients with nodular liver lesions was carried out at Regional Institute of Medical Sciences (RIMS) during the period from August 2008 to July 2010 (2 years). A detailed clinical history and relevant data were collected. Fine needle aspiration cytology (FNAC) findings were correlated with clinical and biochemical parameters especially alpha-fetoprotein (AFP). Statistical analyses of the results were done and discussed.

Results: Out of these 40 patients, 28 (70%) were male and 12 (30%) were female with a male female ratio of 2.3:1. Age of the patients ranged from 13 years to 85 years with a mean age of 47.5 yr. Regarding the FNAC diagnosis, 18 cases (45%) were non-neoplastic and 22 cases (55%) were neoplastic. Out of the total 22 malignant lesions, majorities were metastases with 14 cases (63.6%) and 8 cases (36.4%) were hepatocellular carcinoma (HCC). 75% of HCC patients (6 cases) had markedly elevated serum AFP level (> 500 ng/ml). The association of hepatic malignancy with serum alpha-fetoprotein level was found to be statistically significant.

Conclusion: This study emphasized on unique cytomorphological patterns of distinctive liver lesions for the diagnosis by FNAC and importance of the interpretation of FNAC results along with serum alpha-fetoprotein level in the cases of malignancy.

Keywords: Fine needle aspiration, Hepatocellular carcinoma, Alpha Fetoprotein, Metastases

Received: 11 June 2011
Accepted: 13 November 2011
Address communications to: Dr Rajesh Singh Laishram, Department of Pathology, Regional Institute of medical sciences, Imphal, Manipur, India
Email: rajeshlaishr@gmail.com

Introduction

Liver is the second largest organ of the body (1). The majority of malignancies in the liver are metastases. Adenocarcinomas are the most common metastatic tumors to the liver (2). Hepatocellular carcinoma (HCC) is the most common primary malignant tumor in the liver. It is the fifth most common malignant tumor in men and eighth most common in women worldwide (3).

Alpha-fetoprotein (AFP), a glycoprotein, normally produced during embryonic life in the foetal yolk sac and liver is widely used as a biochemical marker of liver cell cancer (4). Elevation of its level up to pathological range in adults correlates with the appearance of several malignant and chronic conditions, such as HCC, germ cell tumor, chronic liver disease etc (5). A serum AFP level of >1000 ng/ml is highly suggestive of HCC (or hepatoblastoma in the appropriate age group), but a mild increase in serum AFP (<500ng/ml) can be seen in many other liver disorders particularly in acute and chronic viral hepatitis. The hepatocellular malignancies can also present without elevated serum AFP; e.g., fibrolamellar variant of HCC is seldom associated with a very high AFP level (2).

Liver is the most commonly aspirated abdominal organ, accounting for 55% of the abdominal aspirates and 36% of all aspirates performed by radiologist (6). Ultrasonography has been used in combination with fine needle aspiration biopsy in the diagnosis of liver diseases since 1970s (7). Malignancy in the liver, primary or metastatic, is usually inoperable at the time of diagnosis, and as such portends an ominous prognosis. A diagnostic modality such as FNAC, which offers accuracy without complications and which requires minimal intervention at low cost, warrants consideration early in the investigative sequence (8).

The present study was taken up to describe the cytomorphological changes in different nodular lesions of liver and to find out the distribution of various lesions with regards to age, sex, ethnicity and socio-economic status of the patients. The importance of FNAC in the diagnosis of liver diseases will also be evaluated by correlating with clinical and biochemical parameters, particularly estimation of serum alpha-fetoprotein (AFP).

Materials and Methods

The present study was a hospital based cross-sectional study, carried out in the Department of Pathology, in collaboration with Department of Medicine, Regional Institute of Medical Sciences (RIMS), Imphal. RIMS is the major referral centre in north eastern India. The study was conducted during the period from August 2008 to July 2010 (2 years) and included a total of 40 patients, having nodular hepatic lesions. Patients having nodular liver lesions (including solitary, multiple and diffuse), irrespective of age, sex, race and socio-economic status as detected by the clinicians and/or radiologists, were included in the study. Patients with hemorrhagic tendency such as those with hepatic surface hemangioma, prolonged prothrombin time, those who fail to cooperate and inadequate aspirates/material were not included in the study.

Fine needle aspiration cytology (FNAC) of the liver lesions was conducted using the standard procedure of FNA (both guided and unguided) followed worldwide. After taking an informed consent, a detailed history, thorough clinical examination, swelling characteristics/measurements, routine hematological and urine examination, biochemical tests

such as blood sugar, kidney function tests and particularly liver function tests were carried out. Estimation of serum alpha-fetoprotein was also done in selected cases.

Estimation of prothrombin time (PT) was performed in all patients prior to the FNAC of the liver mass. Patients with normal PT were selected for the study. Patients with PT value 5 seconds more than the control were excluded in the study.

The fine needle aspiration procedure was performed following the method described by Zaman MB in those patients with palpaple nodular liver (6). Aspirations were repeated whenever necessary to reduce diagnostic errors. Multiple FNA was done when there were multiple nodules. Deep seated hepatic nodule/mass aspirations were carried out in the Department of Radiology, RIMS with the help of radiologist following the procedure described by Zaman MB (6).

At least 6 smears were made, two air-dried for Giemsa stain and another alcohol fixed for Papanicolaou (PAP) staining which gives better nuclear details. Remaining slides were used for special stains whenever necessary.

Besides routine laboratory tests, liver function tests including serum aspartate transaminase (AST), serum alanine transaminase (ALT), serum alkaline Phosphatase (ALP), serum bilirubin (total & conjugated) and serum protein (total, albumin & globulin) were done. Serum alpha-fetoprotein (by Fluoroimmuno assay) in some selected cases was also done.

The stained FNAC smears were examined and evaluated for the cytomorphological changes and diagnosis. The cytomorphological findings were analyzed and correlated with the clinical and biochemical parameters. Distribution of the cases with regards to age, sex, race and socio-economic status of the patients was also done in the study. Socio-economic status was categorized according to the modified Kuppuswami's Scale (9).

Descriptive statistics and significance testing were carried out whenever and wherever appropriate. SPSS 13.0 was used for statistical analysis.

Prior informed consent was obtained from the patient as per the guidelines of Institutional Ethical Committee (ICE), RIMS, Imphal.

Results

During the study, 4707 patients attended RIMS OPD for FNAC. Out of which 40 patients presented with palpable/nodular liver lesions and were taken up for the study. FNAC of the liver constituted 0.85% of all aspirates in the study period.

Out of these 40 patients, 28 (70%) were male and 12 (30%) were female. The male to female ratio was 2.3:1. Age of the patients ranged from 13-85 yr. Regarding the ethnic groups, 26 cases (65%) were Meiteis (local ethnic group of the valley), 12 (30%) were Tribals (local ethnic group of the hill) and 2 (5%) were Manipuri Muslims. Accounting the socio-economic status, 60% of the patients were in the lower socio-economic class and rest in the middle class (i.e., 40% of the patients). There was no patient in the upper class.

Solitary mass and diffuse nodular hepatomegaly accounted for 37.5% of the cases each, as the most common presentations of the nodular liver lesions. Regarding the FNAC diagnosis, 18 cases (45%) were non-neoplastic and 22 cases (55%) were neoplastic. The non-neoplastic lesions were pyogenic abscess which constituted 50% of the entire non-neoplastic lesions, followed by fatty liver (33.3% of the cases). Others include one case (5.6%) each of amoebic liver abscess and tubercles lesion. All the neoplastic lesions were malignant. Out of the total 22 malignant lesions, majorities were

metastases (14 cases, i.e., 63.6% of the cases) and 8 cases (36.4% of the cases) were HCC. Among the metastatic lesions, metastatic adenocarcinoma was the commonest tumor comprising 85.8% of all the metastatic tumors. Both metastatic lymphoma and metastatic renal cell carcinoma accounted for 7.1% of the cases each.

Sixty percent of the patients presenting with solitary liver mass and 60% with diffuse nodular hepatomegaly, were diagnosed as non-neoplastic lesions. Most of the cases with multiple hepatic nodules (70% of the cases) were found to be metastatic tumors (Table 1).

Table 1- Distribution of patients by clinical presentations and FNAC* diagnosis

Clinical findings	Non-neoplastic lesions		HCC**		Metastatic tumors		Total
	No.	%	No.	%	No.	%	
Solitary mass	9	60.0	3	20.0	3	20.0	15
Multiple nodules	0	0	3	30.0	7	70.0	10
Diffuse nodular hepatomegaly	9	60.0	2	13.3	4	26.7	15

* Fine Needle Aspiration Cytology

** Hepatocellular Carcinoma

Most of the non-neoplastic lesions (61.1% of the cases), HCC (75% of the cases) and metastatic tumors (71.4% of the cases) were having serum bilirubin level within the range of >1 mg% but ≤ 10mg%. There was no significant correlation between different liver lesions and serum bilirubin level. It was found that 66.7% of non-neoplastic cases, 75% of HCCs and 64.3% of metastatic tumors were having serum aspartate level within the range of 41-200 U/L. The association was statistically not significant (Table 2). The serum ALT level within the range of 31-200 U/L was found in 66.7% of non-neoplastic cases, 75% of HCCs and 78.6% of metastatic tumors. The association of FNAC results with serum ALT level was statistically not significant.

This study also shows that 55.6% of the non-neoplastic liver lesions were having a serum ALP level within the range of 151-300 U/L whereas, 50% of the HCC cases and 42.8% of the metastatic tumors were associated with a level > 300 U/L. But the association was not significant (Table 3). Table-4 shows that 75% of HCC patients (6 cases) had markedly elevated serum AFP level (> 500 ng/ml). Out of which 4 cases having AFP level ≥ 1000 ng/ml. In case of metastatic liver tumors, 78.6% of the cases were having AFP level within normal range. Only 21.4% of the cases showed mild elevation (11-200 ng/ml). The association of hepatic malignancy with serum alpha-fetoprotein level was found significant (*P*-value=0.02; Fisher's exact test).

Table 2- Association of FNAC* diagnosis with serum bilirubin and serum aspartate amino transferase (AST) level

FNAC diagnosis	Serum Biliribin			Serum AST		
	0.1-1mg% (normal)	>1 but ≤10 mg%	>10 mg%	5-40U/L (normal)	41-200 U/L	>200 U/L
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Non-neoplastic lesions	7(38.9)	11(61.1)	0	6(33.3)	12(66.7)	0
HCC**	0	6(75.0)	2 (25.0)	1(12.5)	6(75.0)	1(12.5)
Metastatic tumors	3(21.4)	10(71.4)	1 (7.2)	3(21.4)	9(64.3)	2(14.3)

* Fine Needle Aspiration Cytology

** Hepatocellular carcinoma; AST- Aspartate amino transferase

Table 3- Association of FNAC* diagnosis with serum alanine amino transferase (ALT)** and serum alkaline phosphatase (ALP)*** level.

FNAC diagnosis	Serum ALT			Serum ALP		
	5-30 U/L (normal)	31-200 U/L	>200 U/L	40 – 150 U/L (normal)	151 – 300 U/L	>300 U/L
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Non-neoplastic lesions	6(33.3)	12(66.7)	0	7(38.9)	10(55.6)	1(5.5)
HCC****	1(12.5)	6(75.0)	1(12.5)	1(12.5)	3(37.5)	4(50.0)
Metastatic tumors	3(21.4)	11(78.6)	0	4(28.6)	4(28.6)	6(42.8)

* Fine Needle Aspiration Cytology

** Alanine amino transferase; *** Alkaline phosphatase ****Hepatocellular carcinoma;

Table 4- Association of malignant liver tumors with serum alpha-fetoprotein (AFP)* level

FNAC** diagnosis	Serum AFP							
	0-10ng/ml (normal)		11-200ng/ml (mild↑)		201-500ng/ml (moderate↑)		> 500ng/ml (marked↑)	
	No.	%	No.	%	No.	%	No.	%
HCC***	0	0	0	0	2	25	6	75.0
Metastatic tumors	11	78.6	3	21.4	0	0	0	0

*AFP- Alpha-fetoprotein;** Fine Needle Aspiration Cytology

***Hepatocellular carcinoma;

Discussion

Fine needle aspiration cytology (FNAC) has proven to be a very effective means of obtaining tissue from many different body sites for cytological diagnosis (10). FNAC is used predominantly for diagnosing mass lesions when there is a question of a neoplastic process, either primary or metastatic (2). Not many studies on this subject have been reported from this part of the country.

The finding of a male to female ratio of 2.3:1 in the present study is consistent with those of Nggada *et al.* (11) where M: F=2.5:1. Similarly, Hao *et al.* (12) found that the incidence rates for males and females were 27.4/100000 and 11.5/100000 respectively, which constituted M: F = 2.4:1. The finding of Talukder *et al.* (13) where the mean age of diagnosing hepatic mass lesions was 53 years was similar to the present study.

Regarding the ethnicity of the patients, 65% of the patients were Meiteis. This is explicable from the fact that the population of the Meiteis exceeds the rest of the ethnic group in the valley area of Manipur and RIMS is a referral centre located at the heart of the valley. In the view of socio-economic status, it was found that 60% of the patients were in the lower socio-economic class and rest in the middle class (40%). Similar findings had been reported by Sobhonslidsuk *et al.* (14) and it was also mentioned that low socio-economic status may keep the patients from appropriate treatment; hence deterioration of liver disease is likely to happen.

In the present study, 45% of the cases were diagnosed as non-neoplastic and 55% as neoplastic which were all malignant. Similarly, Rasania *et al.* (10) identified 23.3% of the cases as benign and 67.7% as malignant. Cohen *et al.* (15) also reported 63.4% cases as malignant and 36.6% as benign.

Regarding the non-neoplastic lesions, males were affected more (72.2%) than the females. These lesions were commonly seen in the age group of 41-50 years (6 out of 18 cases). Rasania *et al.* (10) observed that non-neoplastic lesions were common between 20-40 years. Assy *et al.* (16) reported that more than 20% of solid liver lesions were non-neoplastic. Similarly, Bahirwani *et al.* (17), in the evaluation of solitary liver masses mentioned that most incidentally noted liver masses were non-neoplastic. Again, Tchelepi *et al.* (18) concluded that most of diffuse liver diseases were diagnosed as non-neoplastic.

In the present study, the non neoplastic lesions include pyogenic abscess, fatty liver, tuberculous lesions and one amoebic liver abscess. Ziehl-Neelsen (ZN) staining was positive in both the tuberculous lesions and diagnosis of abscess was confirmed by microbiological investigations. Nggada *et al.* (11) reported one case each of amoebic liver abscess, liver storage disease and large cell dysplasia using this investigative tool. Rasania *et al.* (10) also diagnosed cirrhosis, abscess, parenchymal liver diseases and regenerative nodule from cytomorphological findings.

Cytological methods are considered to lack precision necessary to be of real diagnostic value in benign/diffuse parenchymal diseases of liver. However, cytological diagnosis by FNAC of liver can be useful for indicating the presence and severity of the disease and excluding infiltrating malignancies(19). Roy *et al.* (20) concluded that in benign lesions, diagnosis may be clinched after due consideration to the clinical, ultrasonographic and other radiologic findings.

Neoplastic liver lesions:

The findings in the present study is similar to those of Talukder *et al.* (13) where out of 101 samples only one was non-neoplastic and 100 malignant. Among the 22 malignant cases 14

(63.6%) cases were metastatic and 8 (36.4%) were HCC. This observation was similar to the findings of Mondal (21) where metastatic deposits were found in 61.22% of hepatic malignancies.

Hepatocellular carcinoma

In the present study, 36.4% of the cases were diagnosed as HCC all occurring in males. The most common age group of the patients was 51-60 years. In a comparable study, Talukder *et al.* (13) observed that most of the hepatocellular carcinomas occurred in males (7 in 8 cases). Ahuja *et al.* (22) reported that mean age of the patients with HCC was 58.84±11.93 years, which is consistent with the present study. The authors have also found a male to female ratio was 7.3:1. Assy *et al.* (16) concluded that a liver mass in a cirrhotic liver should be viewed as HCC until proved otherwise and multiple liver masses in a cirrhotic liver indicates diffuse HCC.

In this study, HCC was differentiated from other non-malignant conditions of the liver by different distinctive cytological features such as high cellularity, trabecular pattern, acinar pattern, endothelial cells lining or transgressing cell clusters, round to polygonal cells with centrally located hyperchromatic nuclei, single or multiple prominent nucleoli, many atypical stripped nuclei in the background, intracytoplasmic eosinophilic inclusions, intranuclear cytoplasmic inclusions and sinusoidal stroma etc. Cells clusters mainly the trabeculae are seen in better differentiated tumors. With decreasing differentiation single-lying cells become more prominent and endothelial relationships with HCC cell groups are diminished. Cohen *et al.* (15) put forward that high N/C ratio, trabecular pattern of arrangement and atypical naked hepatocytic nuclei were the three primary criteria for diagnosis HCC and when these three criteria were used, the sensitivity of diagnosing HCC by FNAC was 100% and the specificity was 87%. Kung *et al.* (23) suggested that more attention should be paid to the sinusoidal stroma for diagnosis of HCC by FNA. Soyuer *et al.* (24), in their stepwise regression analysis showed that multinucleated tumor giant cells, cytoplasmic hyaline and central sinusoidal stroma as the three most predictive parameters to differentiate reactive hepatocytes from HCC.

In the present study, 14 metastatic cases were diagnosed with majority occurring in 51-60 years age group (5 in 14 cases). Male to female ratio was 1:1. Most of the cases presented with multiple hepatic nodules (7 in 14 cases). In a comparable study, Talukder *et al.* (13) observed that the frequency of metastatic carcinoma was more in males (M:F=1.14:1). Ahuja *et al.* (22) reported that the mean age of the patients with metastatic carcinoma was 50.28±14.88 years and male to female ratio was 2.6:1. Assy *et al.* (16) concluded that multiple liver lesions in a normal liver usually indicate liver metastasis (most commonly from adenocarcinoma of the colon, stomach, lung or prostate).

Metastatic adenocarcinoma was the commonest tumor metastasizing to the liver which is comparable to findings by Das *et al.* (25) and Ahuja *et al.* (22). In the present study, metastatic adenocarcinoma showed malignant columnar epithelial cells in microglandular groups, clusters or palisaded rows, often with evidence of mucin secretion. Metastatic renal cell carcinoma showed cells with clear/vacuolated cytoplasm; well defined round to slightly irregular nuclei and majority of cells exhibited low nuclear to cytoplasmic ratio. Smears from metastatic lymphoma showed poorly differentiated malignant cells in a lymphoid background. Metastatic anaplastic carcinoma demonstrated highly cellular smears with large bizarre malignant cells with promi-

nent nucleoli and high nuclear to cytoplasmic ratio. These cells could not be differentiated.

Features used favoring the diagnosis of liver cell carcinoma over metastatic carcinoma were polygonal cells with centrally placed nuclei, trabecular pattern of growth, cells separated by sinusoidal stroma, nuclear pseudoinclusions, giant cells and bile secretion. Bottles *et al.* (26) reported the key criteria for the diagnosis of HCC over metastatic malignancies which included polygonal cells with centrally placed nuclei, cells separated by sinusoidal capillaries and bile. Similarly, Soyuer *et al.* (24), by stepwise logistic regression analysis showed that centrally located nucleus in an atypical cell, intranuclear inclusion and bile were the three most predictive parameters for the differentiation of metastatic carcinoma from HCC.

In the correlation of FNAC diagnosis and biochemical parameters, no significant association was found between liver lesions and serum bilirubin, AST, ALT or ALP level. Biochemical parameters are nonspecific in the diagnosis of liver diseases, but might suggest an underlying chronic hepatitis, cirrhosis or an infiltrative process (16). Thapa and Walia A (27) described the uses and limitations of biochemical parameters. The uses are screening for liver dysfunction, to recognize the pattern of disease, assess severity and follow-up of certain liver diseases and the limitations are lack of sensitivity and specificity.

Laboratory liver function tests help to elucidate the alteration of markers which reflect the liver disease. But a single laboratory liver function test is of little value in screening for liver diseases as many serious liver diseases may be associated with normal levels and abnormal levels might be found in asymptomatic healthy individuals. But the pattern of enzyme abnormality, interpreted in the context of patient's characteristics, can aid in directing the subsequent diagnostic work-up (27).

The association of hepatic malignancy with serum alpha-fetoprotein level was found significant (*P*-value=0.02; Fisher's exact test). These findings are comparable to those of Yap *et al.* (4) where 70% cases of HCC (35 cases out of 50 cases of HCC) showed elevation of serum AFP level and 28 of whom had levels ranging from 500 to over 10,000 ng/ml.

Among the various biochemical markers employed in the diagnosis of HCC, AFP is the most widely used (4). AFP is helpful in assessing problems in management of HCC and monitoring treatment regimens (5).

From the various results obtained in this study, it can be concluded that FNAC is a valuable tool for identification of malignant diseases of the liver and helpful as an accessory tool in benign and inflammatory liver diseases. In cases of poorly differentiated HCC, AFP estimation can certainly supplement the FNAC results. Serum AFP is the significant biochemical marker of HCC. A markedly elevated level (>500 ng/ml) of AFP when associated with a liver mass is diagnostic of HCC and it helps in the distinction of primary liver cell carcinoma from metastatic carcinoma.

In the present study, no complication was encountered in patients undergoing FNAC. FNAC is a less invasive, relatively inexpensive, reliable diagnostic tool with minimal complications and without absolute contraindications. Cytological diagnosis in conjunction with serum AFP (in cases of suspected malignancy) increases the diagnostic accuracy. Considering the overall advantages cited above, FNAC can be used as the initial modality of choice for the diagnosis of palpable/nodular liver lesions in many clinical settings.

Conclusion

Cytological diagnosis depends largely on the recognition of distinct cytomorphological features of various liver lesions. A marked increase in serum AFP level when associated with liver mass is diagnostic of HCC and helps in the differentiation of HCC from metastatic carcinoma. This study emphasized on unique cytomorphological patterns of distinctive liver lesions for the diagnosis by FNAC and importance of the interpretation of FNAC results along with serum alpha-fetoprotein level in the cases of malignancy. The present study was limited to a total number of 40 cases. Further study with higher number of cases and longer duration supported by more parameters would prove more helpful in the evaluation of cytomorphological changes and in the differentiation of a wide spectrum of liver masses.

Acknowledgements

There was no financial and material support for this study. We would like to thank Mr. Balaraj Sharma, cytotechnician for his help and all the patients who co-operated during the study. The authors declare that there is no conflict of interests.

References

1. Junqueira LC, Carneiro J. Organs Associated with the Digestive Tract. Basic Histology. 11th ed. New York: MacGraw Hill; 2011.

2. Tsui W, Cheng F, Lee Y. Fine needle aspiration cytology of liver tumors. Ann Contemporary Diag Pathol 1998;(2):79-93.

3. Fletcher C. Diagnostic Histopathology of Tumours. 3rd ed. Philadelphia: Churchill Livingstone; 2007.

4. Yap SF, Peh SC. Alpha-fetoprotein in hepatocellular carcinoma: a serological and histochemical study in Malaysian patients. Malays J Pathol 1991;13(2):115-8.

5. Baig JA, Alam JM, Mahmood SR, Baig M, Shaheen R, Sultana I, *et al.* . Hepatocellular carcinoma (HCC) and diagnostic significance of A-fetoprotein (AFP). J Ayub Med Coll Abbottabad 2009;21(1):72-5.

6. Koss L, Melamed M. Diagnostic Cytology and Its Histopathologic Bases. 5th ed. Philadelphia: Lippincott Williams and Wilkins; 2006.

7. Ji XL. Fine-needle aspiration cytology of liver diseases. World J Gastroenterol 1999;5(2):95-7.

8. Orell S, Sterrett G, Whitaker D, Leiman G. Liver and Spleen. Fine Needle Aspiration Cytology. 4 ed. New Delhi: Elseiver; 2005.

9. Patel AB, Prabhu AS, Dibley MJ, Kulkarni LR. A tool for rapid socioeconomic assessment. Indian J Pediatr 2007;74(4):349-52.

10. Rasania A, Pandey C, Joshi N. Evaluation of FNAC in diagnosis of hepatic lesion. J Cytol 2007;24(1):51-4.

11. Nggada HA, Ajayi NA, Ahidjo A, Pindiga UH, Tahir A, Mustapha SK, *et al.* . Fine needle aspiration cytology diagnosis of liver diseases in the University of Maiduguri Teaching Hospital, Maiduguri. Afr J Med Med Sci 2004;33(3):255-7.

12. Hao XS, Chen KX, Wang PP, Rohan T. Changes in survival patterns in urban Chinese patients with liver cancer. World J Gastroenterol 2003;9(6):1212-5.

13. Talukder SI, Huq MH, Haque MA, Rahman S, Islam SM, Hossain GA, *et al.* . Ultrasound guided fine needle aspiration cytology for diagnosis of mass lesions of liver. Mymensingh Med J 2004;13(1):25-9.

14. Sobhonslidsuk A, Silpakit C, Kongsakon R, Satitpornkul P, Sripetch C, Khanthavit A. Factors influencing health-related quality of life in chronic liver disease. World J Gastroenterol 2006;12(48):7786-91.

15. Cohen MB, Haber MM, Holly EA, Ahn DK, Bottles K, Stoloff AC. Cytologic criteria to distinguish hepatocellular carcinoma from nonneoplastic liver. Am J Clin Pathol 1991;95(2):125-30.

16. Assy N, Nasser G, Djibre A, Beniashvili Z, Elias S, Zidan J. Characteristics of common solid liver lesions and recommendations for diagnostic

workup. World J Gastroenterol 2009;15(26):3217-27.
17. Bahirwani R, Reddy KR. Review article: the evaluation of solitary liver masses. Aliment Pharmacol Ther 2008;28(8):953-65.
18. Tchelepi H, Ralls PW, Radin R, Grant E. Sonography of diffuse liver disease. J Ultrasound Med 2002;21(9):1023-32.
19. Gatphoh ED, Gaytri S, Babina S, Singh AM. Fine needle aspiration cytology of liver: a study of 202 cases. Indian J Med Sci 2003;57(1):22-5.
20. Roy M, Bhattacharyya A, Dasgupta S, Sanyal S. Fallacies of the fine needle aspiration cytology of surgical lesions of liver. J Indian Med Assoc 1994;92(9):285-7.
21. Mondal A. Cytodiagnostic accuracy of hepatic malignancy by fine needle aspiration biopsy. J Indian Med Assoc 1991;89(8):222-4.
22. Ahuja A, Gupta N, Srinivasan R, Kalra N, Chawla Y, Rajwanshi A. Differentiation of hepatocellular carcinoma from metastatic carcinoma of the liver – clinical and cytological features. J Cytol 2007;24(3):125-9.
23. Kung IT, Chan SK, Fung KH. Fine-needle aspiration in hepatocellular carcinoma. Combined cytologic and histologic approach. Cancer 1991;67(3):673-80.
24. Soyuer I, Ekinci C, Kaya M, Genc Y, Bahar K. Diagnosis of hepatocellular carcinoma by fine needle aspiration cytology. Cellular features. Acta Cytol 2003;47(4):581-9.
25. Das DK, Tripathi RP, Kumar N, Chachra KL, Sodhani P, Parkash S, *et al.* . Role of guided fine needle aspiration cytology in diagnosis and classification of liver malignancies. Trop Gastroenterol 1997;18(3):101-6.
26. Bottles K, Cohen MB. An approach to fine-needle aspiration biopsy diagnosis of hepatic masses. Diagn Cytopathol 1991;7(2):204-10.
27. Thapa BR, Walia A. Liver function tests and their interpretation. Indian J Pediatr 2007;74(7):663-71.