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Original Research Article

Utility of FNAC in Conjunction with Cell Block for Diagnosing Space-Occupying Lesion (SOL) of Liver with Emphasis on Differentiating Hepatocellular Carcinoma from Metastatic SOL

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Conflict of interest: Nil

Abstract

Background: The present study was undertaken to differentiate HCC from metastatic adenocarcinoma by conventional cytology, and cell block preparation and to evaluate whether there is any diagnostic advantages of cell block over conventional image guided FNAC. The present study was aimed to compare the efficacy of cell block with FNAC smears in liver neoplasms.

Materials and Methods: Following parameters was studied during imaging like size of the mass and number of mass (es) in liver; echotexture, vascularity, margin of the mass; site of origin of mass outside liver (if possible) and whether any lymphadenopathy is associated with the mass. Following parameters was studied during cytology, cell block and IHC like cytomorphology of the different cell population on smears stained with routine Leishman-Giemsa (LG) and H&E stains; architecture and morphology of cells in cell block preparation and dentification and differentiation of HCC and metastatic adenocarcinomas.

Results: In case of HCC, majority of patients were sixth decade of age with male female ratio 2.33:1. In case of metastatic carcinoma, age ranged from 30-79 with male female ratio 1.28:1. The majority of patients were in fifth decade of age. Although serum α feto protein is widely used as biochemical marker of HCC but it is not specific for HCC. It may be evaluated in many tumors other than HCC. Its normal level also does not exclude the chance the HCC. In our study, serum α feto protein level was elevated in 85% HCC (25% mild, 45% moderate, 15% marked) & 21.88 % (15,63% mild, 6.25% moderate) metastatic carcinoma. There was no elevation in 15%% HCC. Cell block having high sensitivity (90%) and specificity (93.75%) can be able to provide more information than conventional smear (sensitivity 88.89% and specificity 91.18%).

Conclusion: Cell block having high sensitivity (90%) and specificity (93.75%) can be able to provide more information than conventional smear (sensitivity 88.89% and specificity 91.18%).

Keywords: Space-Occupying Lesion (SOL) of Liver, Hepatocellular Carcinoma, Metastatic SOL, fine needle aspiration cytology (FNAC), Cell Block, Diagnosis.

Introduction

The basic idea of fine needle aspiration cytology (FNAC) i.e., to obtain cells and tissue fragments through a needle introduced into the abnormal tissue was by no means new. In the mid-nineteenth century, Kün (1847) [1], Lebert (1851) [2] and Menetrier (1886) [3] employed needles to obtain cells and tissue fragments todiagnose cancer. Leyden (1883) [4] used the same method toisolate pneumonic microorganisms. But the technique, FNAC as we know it today began to flourish in Europe in the 1950s and 1960s. [5] In the following years, experience accumulated rapidly and pathologists and oncologists from many other countries came to study the technique, which subsequently spread to the rest of Europe, the Americas, Asia and Australia. FNAC is now part of the service of all sophisticated departments of pathology. [6] FNAC was initially conceived as a means to confirm a clinical suspicion of local recurrence or metastasis of known cancer. Following success in this area, the interest focused on preliminary preoperative diagnosis of all kinds

of neoplastic processes, benign or malignant, in any organ or tissue of the body.The clinical value of FNAC is not limited to neoplastic conditions only. It is also valuable in the diagnosis of inflammatory, infectious and degenerative conditions, in which samples can be used for microbiological and biochemical analysis in addition to cytological preparations [7].

Liver is an important site for neoplasm-both primary and metastatic,the later being more common. Hepatocellular carcinoma (HCC) is the most important primary liver cancer and its incidence is expected to rise rapidly over the next decade. The annual global incidence of HCC is approximiately 6,26,000 cases with male to female ratio approximiately 2.4:1. [8] Age standardized incidence rates of HCC in India for men and women are 0.9-3.4 and 0.2-1.8 per 100000 person respectively. Among patients with background cirrhosis, the incidence rate increases to 1.6 per 100 person per-year. [9] In case of liver neoplasm both primary and secondary metastasis, a documentary evidence of the nature of the pathology is mandatory before the institution of therapy or intervention. FNAC can perform a brilliant role here. It is a rapid, less hazardous and easy to perform diagnostic modality. In a majority of cases diagnosis obtained by FNAC is so accurate that it can be a substitute for surgical procedures like diagnostic laparotomy. [10]

But in most of the liver neoplasm (both primary and secondary metastasis) , their exact size, shape, consistency and extent of the lesion cannot be defined clinically. [9] Image guided FNA has an important role to differentiate hepatocellular carcinoma (HCC) from secondary metastasis. Various imaging modalities like USG, CT or fluoroscopy can be used as a guide for FNAC. [11]

The advantage of ultrasound guided FNA is that it provides sectional images in any plane and three dimensional information based on acoustic property of the tissue. Ultrasound is safe and does not use any ionising radiation. It does not require any contrast agent, provides good to excellent spatial and contrast resonation. It is portable, takes less time and is cost effective and has low complication rate. [12]

Most studies have shown guided FNAC as a highly sensitive, highly specific, accurate and a cost effective diagnostic procedure with a negligible complication rate. Severe coagulopathy is an absolute one among various other contraindications for this investigation. [13, 14] However according to the view of Zito and others FNAC sometimes does not yield information for precise diagnosis and the risk of false-negative and indeterminate diagnosis is always present. The diagnostic failure rate of FNAC may be as high as 45%. [15] An inconclusive diagnosis on FNAC may be due to poor spreading, air drying artefact and presence of thick tissue fragments despite aspiration of adequate material.[16] However distinguishing a well-defined differentiated HCC from regenerative hepatocyte nodule may be very difficult in some cases,especially on cytology. Furthermore some of the unusual morphologic variants including fibrolamellar, clear cell, and pleomorphic variants may be mistaken for metastasis. Similarly metastasis from various primary tumors to the liver may be mistaken for primary hepatic tumors.

In order to overcome these problems, cell block technique has been resorted to make the best use of the available material. Various methods for preparing paraffin embedded cell blocks from fine needle aspiration cytology have been reported. These methods mainly include direct transfer of all centrifuged cellular material wrapped in lens paper or embedding in plasma or agar and then processing as a routine histological specimen. Cell block preparation in a way mimics the histopathological sections, thus help in sub classifying various neoplastic lesions. [17, 18]

The benefit of cell block technique is the recognition of histologic pattern of diseases that sometimes cannot be reliably identified in smears. They are also useful for categorization of tumors that otherwise may not be possible from smears themselves. [15] Richardson et al have shown that additional diagnosis of cancer can be obtained in 5% of fluid specimens if smear technique is supplemented by cell block sections of residual material. [19] In this overview we used selective IHC markers on cell block preparation to differentiate HCC from metastatic adenocarcinoma in liver. We also used core needle biopsy as a gold standard method to corroborate the results of FNAC, and cell block in our study.

Aims and Objectives: The present study was undertaken to differentiate HCC from metastatic adenocarcinoma by conventional cytology, and cell-block preparation and to evaluate whether there is any diagnostic advantages of cell block over conventional image guided FNAC. The present study was aimed to compare the efficacy of cell block with FNAC smears in liver neoplasms.

Materials and Methods

This study was performed after obtaining approval from Institutional Ethics Committee of North Bengal Medical College and Hospital and after taking proper consent of the patients participating in this study. The study was performed in the Department of Pathology after collection of the sample following image guided FNAC in the Department of Radio Diagnosis of North Bengal Medical College and Hospital. It is one of the

tertiary care units of West Bengal. Patients usually come from six districts of North Bengal like, Darjeeling, Jalpaiguri, Coochbehar, Malda, Uttar and Dakshin Dinajpur and also from surrounding states and neighbouring countries like, Nepal, Bangladesh, and Bhutan. Patients who are being referred to Department of Radio Diagnosis of North Bengal Medical College and Hospital for image guide FNAC of liver mass lesions during the study period (July 2014- June 2015). About 100 cases who were referred to Department of Radio Diagnosis for image guided FNAC of intra-abdominal mass lesions during the study period.

Inclusion Criteria

All the patients referred to the Department of Radiodiagnosis with liver mass lesions for USG guided FNAC and suspected to be hepatocellular carcinoma or adenocarcinoma on cytolgoy.

Exclusion Criteria:

1. Patients who refuse to give consent for this investigation.
2. All lesions other than hepatocellular carcinoma or adenocarcinoma will be excluded from the study.

Following parameters was studied during imaging like size of the mass and number of mass (es) in liver; echotexture, vascularity, margin of the mass; site of origin of mass outside liver (if possible) and whether any lymphadenopathy is associated with the mass.

Following parameters was studied during cytology, cell block and IHC:

- Cytomorphology of the different cell population on smears stained with routine Leishman-Giemsa (LG) and H&E stains.
- Architecture and morphology of cells in cell block preparation and dentification and differentiation of HCC and metastatic adenocarcinomas.

Different tools have been used during different phase of this study

1. Performa to note the clinical epidemiological and imaging profile of the patient along with the findings of aspirate and also the interpretation of conventional smear cytology and cell block histopathology.
2. For the purpose of image guidance during performing FNAC of liver mass: Imaging modalities like USG by using 3.5 to 5 MHz curvilinear trans-abdominal transducer

The present study was conducted in the Department of Pathology in association with the Department of Radio diagnosis of North Bengal Medical College and Hospital covering a period of 12 months (June, 2012–May, 2013) over all the patients presenting with intra-abdominal mass lesions after taking the approval of Institutional ethical committee. After thorough work up of patients, including detailed clinical history and examination, FNAC was done under ultrasound guidance.

Procedure of guided FNAC of liver SOL: The area is sterilized with surgical spirit. The depth of the lesion was noted with the help of the imaging modality operated by the radiologist. In each case 27-22 gauge needle attached to a 10 ml syringe for superficial masses and 22 gauge spinal needles for deep seated masses was used. Under the guidance of ultrasound, in the presence of the radiologist, the needle was introduced and was checked before aspiration over the screen. Then suction was applied and multiple passes were done. The suction was released and the needle was removed. The specimen within the needle lumen was ejected on the slides. Detaching the needle to introduce air into the syringe and then reattaching it enhances the cellular expulsion. The aspirate was spread thinly and evenly by a second slide. Minimum of 4 smears were prepared. In cases where fluids were aspirated, it was centrifuged and decanted and the sediment was sent for preparation of smears as well as cell block preparation. Air dried and alcohol fixed smears were prepared for staining with Leishman-Giemsa and hematoxylin and eosin (H&E) stain respectively. The remaining material in the aspirating syringe and needle hub were collected and preserved in 10% Normal Buffer Formalin for cell block preparation overnight. Results of conventional smear, cell block and combination of cell block were compared with available histopathological diagnosis regarding diagnostic sensitivity and specificity.

Results

Table 1: Hepatocellular carcinoma, metastatic deposit and age distribution

Age	Hepatocellular carcinoma (n=20)	Metastatic carcinoma (n=32)
30-39	-	2(6.25%)
40-49	2(10%)	7(21.875%)
50-59	3(15%)	13(40.625%)
60-69	10(50%)	6(18.75%)
70-79	3(15%)	4(12.5%)
80-89	2(10%)	-

Table 2: Hepatocellular carcinoma, metastatic deposit and sex distribution

Sex	Hepatocelllar carcinoma (n=20)	Metastatic carcinoma (n=32)
Male	14(70%)	18(56.25%)
Female	6(30%)	14(43.75%)

Hepatocellular carcinoma: Male: Female==> 2.33:1; Metastatic carcinoma: Male: Female==> 1.28:1 [Table 2].

Table 3: Hepatocellular carcinoma, metastatic carcinoma and serum α-feto protein

Serum α-feto protein	Hepatocellular carcinoma (n=20)	Metastatic carcinoma (n=32)
No elevation(<20 ng/ml)	3 (15%)	25 (78.12%)
Mild elevation (20-100 ng/ml)	5(25%)	5(15.63%)
Moderate elevation (>100-500 ng/ml)	9(45%)	2(6.25%)
Marked elevation (>500 ng/ml)	3(15%)	-

Table 4: Result of FNAC, cell block, cell block and Core needle biopsy

Diagnosis	FNAC	Cell block	Core needle biopsy
HCC	19	20	20
Metastatic carcinoma	33	32	32
Total	52	52	52

Table 5: Sensitivity and specificity of FNAC

Test (FNAC)	HCC	Metastatic carcinoma
Positive	16	3
Negative	2	31

- True positive= No of HCC properly detected =16;
- False positive-=No of metastatic carcinoma reported as HCC=3;
- False negative= No of HCC reported as Metastatic carcinoma=2;
- True Negative= No of Metastatic carcinoma properly detected=31
- Sensitivity of FNAC=True positive x100/ (True positive + False negative) = 16x100/(16+2)= 88.89%
- Specificity of FNAC= True negative x100/(True negative + False positive) = 31x100/(31+3)=91.18%
- Positive predictive value (PPV)= True positive x100/(True positive+False Positive) =16x100/ (16+3)=84.21%
- Negative predictive value (NPV)= True negative x100/(True negative+False negative) = 31x100/(32+2)=93.94%
- Diagnostic accuracy =(True positive + True negative) x 100/Total case =(16+31) x 100/52=9 0.38%

Table 6: Sensitivity and specificity of cell block

Test (Cell block)	HCC	Metastatic carcinoma
Positive	18	2
Negative	2	30

- True positive= No of HCC properly detected = 18
- False positive =No of metastatic carcinoma reported as HCC= 2
- False negative = No of HCC reported as metastatic carcinoma= 2
- True negative = No of Metastatic carcinoma properly detected = 30
- Sensitivity of Cell block = True positive x 100/(True positive + False negative) = 18x100/(18+2) =90%
- Specificity of Cell block =True negative x 100/ (True negative + False positive) = 30 x 100/(30+2) = 93.75%
- Positive predictive value (PPV)= True positive x 100/(True positive+False Positive) = 18x100/(18+2) =90%
- Negative predictive value (NPV)= True negative x100/(True negative+False negative) = 30x100/(30+2)=93.75%
- Diagnostic accuracy = (True positive + True negative) x 100/Total case= (18+30) x 100/5 2=92.30%

Table 7: Sensitivity and Specificity of AFP (α- feto protein)

AFP	HCC	Metastatic carcinoma
Positive	11	3
Negative	9	29

- Sensitivity of AFP =True positive x 100/(True positive + False negative)= 11 x100/(11+9)= 55%
- Specificity of AFP = True negative x 100/(True negative + False positive) = 29 x100 (29+3) = 90.62%
- Positive predictive value = True positivex100/(True positive+ False positive)= 11 x100/(11+3)=78.57%
- Negative predictive value = True negative x 100/(True negative+ False negative) = 29 x100 /(29+9) = 76.31%
- Diagnostic accuracy =(True positive + True negative) x 100/Total no case = (11+29) x100/52 = 76.92%

Discussion

The present study was undertaken to differentiate HCC from metastatic carcinoma in liver by conventional smear cytology and cell block preparation as well as to assess whether there is any diagnostic advantages of cell block over conventional USG guided FNAC or cell block alone. For these purpose, core needle biopsy (CNB) of liver has been taken as a gold standard method.

Age and sex distribution: In this study, comparative evaluation of cell block with IHC over conventional smear cytology or cell block alone was assessed over 52 patients presenting with liver SOL. In case of HCC, the age of the patient ranged from 40-89 yrs with male female ratio of 2.33:1. The majority of patients were in sixth decade of age. In case of metastatic carcinoma of liver, the age ranged from 30-79 yrs with male female ratio of 1.28:1. The majority of patients were in fifth decade of age. Hepatocellular carcinoma, matastatic carcinoma and age sex distribution were given in Table 1& 2.

Serum α feto protein (AFP): In present study, serum AFP was measured in every patient presenting with liver SOL. Although serum AFP is widely used as a biochemical marker of HCC, its usefulness in early detection and diagnosis of this malignancy is limited by several factors. While markedly elevated levels (>500) are diagnostic of HCC, a significant proportion of patients with HCC either do not have raised levels or have only mildly raised levels. [20] Mildly to moderately elevated serum AFP levels are commonly seen in patients with liver diseases other than HCC, particularly in acute and chronic viral hepatitis, small bowel carcinoma, gastric carcinoma, germ cell tumors etc. [21] Our study showed that 15% (3/20) of HCC patients had levels of serum AFP diagnostic of lesion (>500 U/ml). 15% (3/20) of patients had serum AFP levels within normal limit (<20 U/ml), while remaining of 45% (9/20) and 25% (5/20) of patients had moderately (>100-500 U/ml) and mildly (>20-100 U/ml) elevated level respectively. 6.25% (2/32) and 15.62% (5/32) of metastatic carcinoma also showed moderately and mildly elevated level of serum AFP. Results of HCC, metastatic carcinoma and serum AFP level were given in Table 3.

Liver SOL: In our study, metastatic carcinoma [Fig 1-4] was the most commonly found malignancy (32 cases, 61.54%) in liver followed by HCC (20 cases, 38.46 %).There were also one cases of secondary deposit of squamous cell carcinoma of cervix in liver along with two cases of secondary deposit of germ cell tumors of ovary. In a study done by Shah A et al [23] metastatic deposits in liver found to be more common than primary malignancy as in this study. Similar to this study, in a recent study done by Singh S et al [24] found secondary deposits in liver in majority (65.7%) of the cases and adenocarcinoma was the commonest type (32.8%).

Histopathological Corroboration of liver SOL: Histopathological correlation (core needle biopsy) were available in every case as a gold standard procedure and to corroborate the results of FNAC, cell block. Twenty cases of HCC and 32 cases of metastatic deposit were found in core needle biopsy. FNAC, cell block and cell block and core needle biopsy results were given in Table no 4.

FNAC: In present study, FNAC diagnosis were HCC in 19 cases and metastatic carcinoma in 33 cases. In 47 cases (16 HCC, 31metastatic deposit), FNAC and core needle biopsy diagnosis were concordant. Among remaining 5 cases, 3 were false positive and 2 were false negative. FNAC results were shown in Table 5. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy of FNAC were 88.89%, 91.18%, 84.21%, 93.94% and 90.38% respectively. This result corresponds to the study done by Samaratunga et al [25] in hepatic lesion suspicious for malignancy, in which sensitivity and specificity of FNAC were 90% and 87%. Jitendra G Nasit et al in their study found 86% sensitivity and 98% diagnostic yield of FNAC. [26] Guo Z et al showed that conclusive diagnostic materials were available in majority of conventional smear with 94% sensitivity and 92% specificity. [27] Similarly, Franca AV et al showed that sensitivity and specificity of FNAC were 94% and 92%. [28]

Cell block: Although cell block provides us more information than conventional smear, in some cases it may fail to provide the specific diagnosis because of small quantity of sample. Sometimes it may give false positive or false negative results due to changing of cellular arrangement after centrifugation. In our study, cell block diagnosis were HCC in 20 cases and metastatic deposit in 32 cases. In 48 cases (18 HCC. 30 metastatic deposit),

both cell block and core needle biopsy were similar with 2 false positivity and 2 false negativity.

Cell block results were given in Table 6. Sensitivity, specificity, PPV, NPV and diagnostic accuracy of cell block were 90%, 93.75%, 90%, 93.75% and 92.30% respectively. Basnet et al in their study also found that the diagnostic accuracy and specificity were high in cell block in comparison to the smear ranging from 83% in the smear and 100% in the cell block. [29] Shivkumarswamy et al also experienced that the cell block yielded more cellularity and better architectural patterns which improved the diagnosis of malignancy by 15%. [30] Keyhani-Rofaga et al reported that in a study of 85 cases, 55% of the original smear diagnoses were improved after the cell block was examined. [31] Kern and Haber studied 393 cases of cell block preparation. [32] In 237 cases (60.3%), the findings were confirmatory, and in 103 cases (26.2%), cell blocks provided additional information for diagnosis. Similarly, Nathan et al showed that conclusive diagnostic material was available in 296 (89.4%) cell blocks from 331 cases. [33] However, Wojcik and Selvaggi showed that 84% of the cases had identical results on both smears and cell blocks. [34]

Alpha feto protein (AFP): AFP showed positivity in 11 cases out of 20 cases of HCC. Among them 1 was poorly differentiated, 10 were well to moderaely differentiated HCC. In 3 cases of metastatic carcinoma, positivity was also noticed. Among them 2 were germ cell tumor of ovary one was poorly differentiated metastatic adenocarcinoma with focal hepatoid differentiation. Results of AFP were shown in Table 10.

Sensitivity, specificity, PPV, NPV and Diagnostic accuracy of AFP were 55%, 90%. 78.57%, 76.31% and 76.92%. Jasirwan COM et al study have revealed that the sensitivity and specificity of AFP in the surveillance of HCC in Indonesia with a cut-off of 10 ng/ml were 82.6 and 71.2%, respectively.

The parameters most associated with the increase of AFP ≥10 ng/ml according to multivariate analysis were the etiology of hepatitis B, the stage of Barcelona Clinic Liver Cancer (BCLC) B and C, and the presence of cirrhosis, respectively. [35]

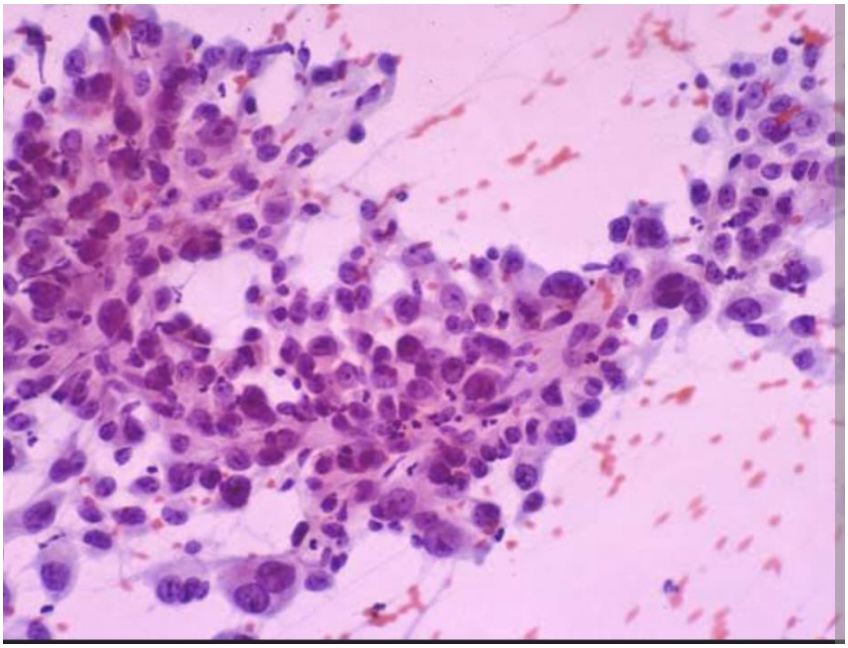

Fig 1: FNAC picture of hepatocellular carcinoma

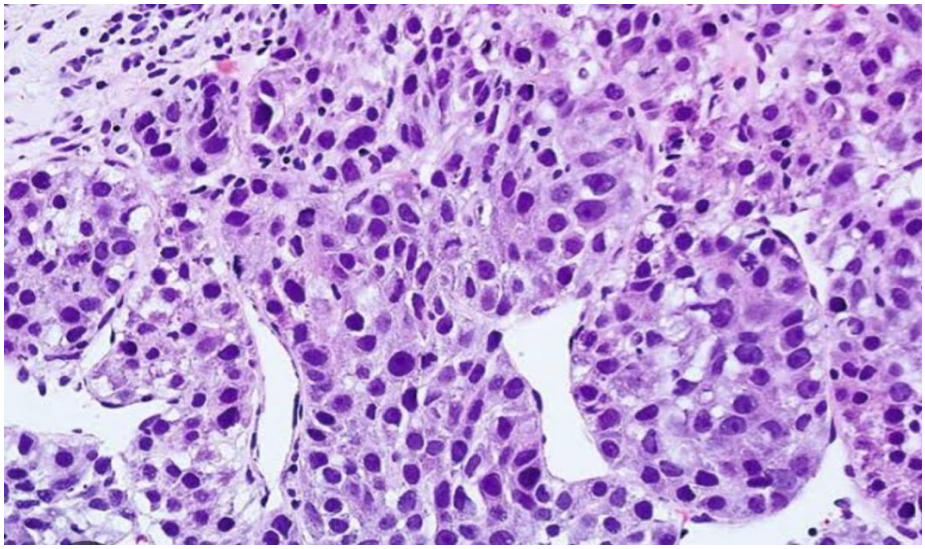

Fig 2: Cell block picture of hepatocellular carcinoma

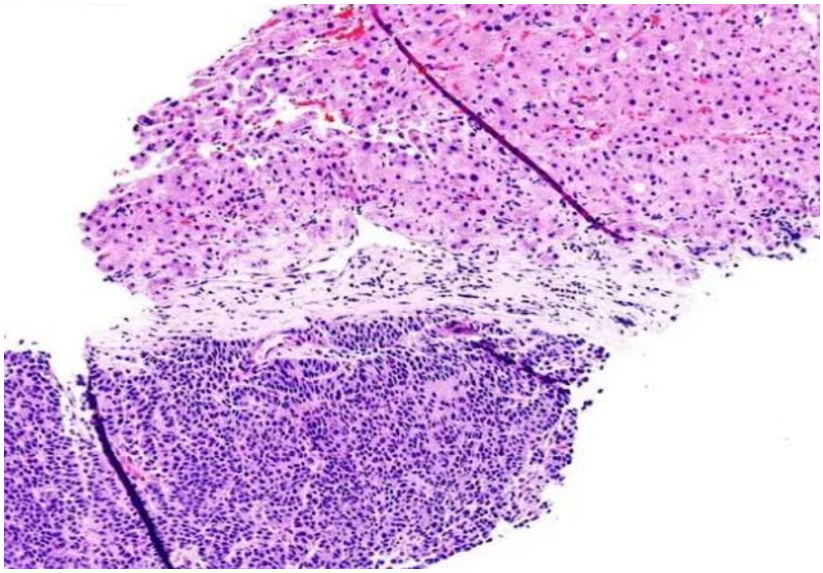

Fig 3: Metastatic adenocarcinoma cell block picture

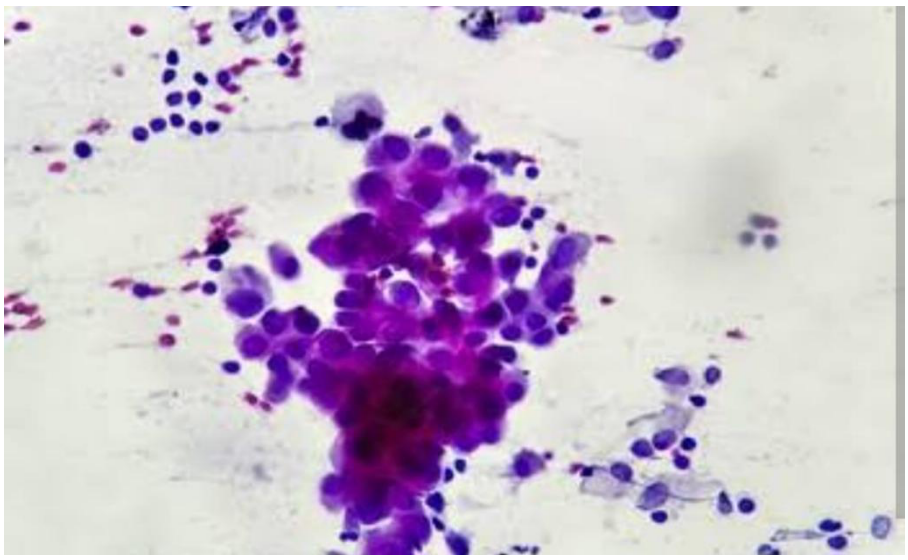

Fig 4: FNAC picture of metastatic adenocarcinoma

Conclusion

This study was undertaken to differentiate HCC from secondary tumors in liver with help of conventional smear cytology, cell block technique. The result that have emerged from the present study can be summarized as follows. In case of HCC, majority of patients were sixth decade of age with male female ratio 2.33:1. In case of metastatic carcinoma, age ranged from 30-79 with male female ratio 1.28:1. The majority of patients were in fifth decade of age.

Although serum α-feto protein is widely used as biochemical marker of HCC but it is not specific for HCC. It may be evaluated in many tumors other than HCC. Its normal level also does not exclude the chance the HCC.In our study, serum α feto protein level was elevated in 85% HCC (25% mild, 45% moderate,15% marked) & 21.88 % (15,63% mild, 6.25% moderate) metastatic carcinoma.There was no elevation in 15%% HCC. Cell block having high sensitivity (90%) and specificity (93.75%) can be able to provide more information than conventional smear (sensitivity 88.89% and specificity 91.18%).

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