Diagnostic Accuracy of Percutaneous Cytodiagnosis of Hepatic Masses, by Ultrasound Guided Fine Needle Aspiration Cytology

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Objective: To evaluate the diagnostic accuracy, usefulness and limitations of ultrasound guided FNAC of hepatic masses.

Design: Cross – sectional analytical (comparative study).

Place and Duration: Department of histopathology, Sheikh Zayed Hospital, Lahore. Study period 1 year.

Material and Methods: A total of 32 patients with solitary or multiple hepatic masses underwent FNAC from March 1999 to March 2000. Adequate aspirates were obtained in all these cases. Smears were stained with May-Grunwald Giemsa, Haematoxylin and Eosin and Papanicolaou stain. Needle biopsies from the same cases were also obtained and processed. These were stained with routine Haematoxylin and Eosin staining. The blood clots obtained during FNAC were fixed in 10% neutral buffered formalin. The histopathology of these blood clots was used for cases whose needle core biopsy was not available. The screened FNAC smears were divided into 3 categories i.e., benign (group – I), malignant (group – II), non-neoplastic / inflammatory lesions (including cysts and abscesses) (group – III).

Results: Out of 32 cases, 6 were categorized as benign, 18 as malignant, and 8 as non-neoplastic inflammatory lesions. Three false negative diagnoses, including 1 for malignant tumour and 2 for benign tumours was obtained. There was 1 false positive diagnosis for malignancy. FNAC – histological correlation showed a 94.2% sensitivity and 92.3% diagnostic accuracy for malignant tumours, while benign tumours posed maximum diagnostic problems, giving a 66.67% sensitivity and 85.7% diagnostic accuracy. FNAC picked up correctly all the non-neoplastic lesions giving a 100% sensitivity and diagnostic accuracy.

Conclusion: Majority of the malignant tumours can be categorized on FNAC, with a high degree of accuracy, while benign tumours should be subjected to biopsy, as there is a relatively greater possibility of false negative diagnosis.

Key words: FNAC, benign, malignant, non-neoplastic.

Introduction

Blind liver biopsy is now almost obsolete. The main indications for fine needle aspiration cytology. (FNAC) of the liver is in the diagnosis of localized malignant deposits, including both primary hepatocellular neoplasm and metastatic tumours. Guiding the needle with diagnostic imaging techniques, particularly ultrasound or CT is usually recommended. Cytologic studies alone are more sensitive than histologic studies alone because the needle is longer, can be guided and the procedure can be easily repeated.[1]

Several studies have shown FNAC to be a more sensitive and specific technique for diagnosing malignancy, than conventional needle biopsy (Menghini or Trucut) with a low risk of complications like haemorrhage or biliary leak.[2] FNAC avoids these risks and is highly sensitive and specific in the diagnosis of malignant neoplasms, particularly metastatic disease. With the development of fine cutting needles used for aspiration (usually modified Menghini needles), FNAC has now largely replaced conventional large needle core biopsy in the diagnosis of focal lesions.[3,4] These fine needle cores obtained on FNAC, with the additional benefit of blood clot, has resulted in increased sensitivity.[5,6] The main advantage of FNAC is the possibility of multiple passes which increases the chances of obtaining adequate viable cells, specially in necrotic tumours. Sampling of those lesions which are relatively inaccessible by conventional biopsy, and a minimized risk of haemorrhage in vascular tumours like haemangiomas and hepatomas are additional advantages. Although the overall diagnostic yield may be higher with FNAC, wider bore needle biopsies for histology probably still confer advantages. These biopsies provide greater specificity and versatility and detailed information, specially in many benign lesions, well differentiated hepatocellular carcinoma, and the differentiation between primary and metastatic carcinoma.[7] They also allows special stains of subsequent sections and electron microscopy if required.[8] Cytologic and Histologic studies are therefore complementary, and using both can increase the diagnostic sensitivity.[9]

This study was carried out to ascertain the diagnostic accuracy, usefulness and limitations of FNAC of hepatic masses.

Materials and Methods

Thirty two (32) cases of hepatic masses were subjected to FNAC, and needle core biopsies from the same 32 cases were then obtained without any discrimination of age and

gender. The study period extended from March 1999 to March 2000. A clinical proforma was filled in each case to document the particulars of the patient including serologic tests like alpha – fetoprotein levels for hepatocellular carcinoma, clinical and radiological details including the site, size, consistency, extent of the mass and its vascularity. Aspirates were the obtained with a 21 or 22 gauge needles attached to a 10 ml syringe.[31] When adequate material appeared in the hub, the needle was withdrawn after releasing the suction pressure and 5 smears prepared including a clot, after fixation in 10% neutral buffered formalin. Two of these smears were air dried for Giemsa stain, 1 smear each for Papanicolaou and Haematoxylin and Eosin staining after wet fixation in 95% ethyl alcohol. After screening the smears results were categorized into 3 groups, benign (group–I), malignant (group – II) and non-neoplastic/ inflammatory lesions (group – III). Needle core biopsies from all these cases were also received and fixed in 10% formalin. The blood clots fixed in 10% neutral buffered formalin were also used for histopathology where needle core biopsies were not available. These biopsies were processed in an automatic tissue processor (Auto processor model 2LE, Shandon Germany). After processing, the tissue was embedded and paraffin blocks were made. Section cutting was done by rotary microtome (Model RM2125, Leica, Germany). Haematoxylin and Eosin (H&E) staining was done in each case. Results of FNAC and histological diagnosis were then correlated. The statistical analysis was done. The diagnostic accuracy / reliability was ascertained by calculating sensitivity, specificity, positive predictive values and negative predictive values in accordance with methods employed by Galen and Gambino.[10]

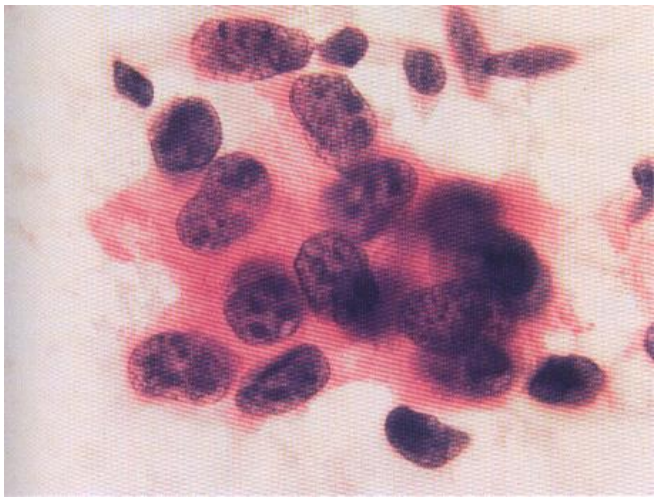

Fig. 1: *Photomicrograph of FNAC of liver showing hepatocellular carcinoma.*

Results

Of 32 cases 6 / 30 (18.5%) were benign, 18 / 32 (56.25%) malignant and 8/32 (25%) were non-neoplastic (inflammatory) lesions.

The 18 malignant cases included 10 (55.5%) primary hepatocellular carcinomas, and 8 (44.4%) metastatic tumours. Eight of the 10 (80%) cases of hepatocellular carcinoma were correctly picked up on FNAC (as shown in figure). One case was reported as atypical cells (false negative) on FNAC, while a diagnosis of well differentiated hepatocellular carcinoma was given on histology. The other misdiagnosed case reported as a metastatic carcinoma (false positive) on FNAC was histologically found to be a poorly differentiated hepatocellular carcinoma. In addition to a diagnosis of hepatocellular carcinoma on FNAC, an attempt was made to grade these tumours and then compared with histological grading (Table 1).

A 100% correct cytologic diagnosis was obtained in all of the metastatic tumours, comprising 6 adenocarcinoma and 2 malignant Melanomas. An attempt was also made to predict the primary source of the tumour on FNAC.

Six cases were placed in benign tumour group (group – I). Of these 6 cases 4 cases of haemangiomas, all of which were correctly diagnosed on FNAC. One case was reported as dysplastic cells (false negative) while the other case was reported as benign hepatocytes (false negative) with no definite diagnosis on FNAC. These were later confirmed on histology to be an adenoma and focal nodular hyperplasia respectively.

All the 8 non-neoplastic/inflammatory lesions were correctly reported on FNAC and included 3 cases each of hepatic abscess and fatty liver, 1 case each of hydatid cyst and a regenerating atypical hepatocytes, suggestive of a cirrhotic nodule. This was later confirmed on histology (Table 1).

Diagnostic accuracy of fine needle aspiration cytology (FNAC) was calculated taking histological diagnosis as the gold standard. The statistical analysis showed a 66.67% sensitivity, 85.7 diagnostic accuracy, 100% positive predictive value and 80% negative predictive value for benign tumours. While malignant tumours showed a 94.12% sensitivity 92.3% diagnostic accuracy, 94.12% positive predictive value and 88.9% negative predictive value. Non-neoplastic/ inflammatory lesions showed a 100% sensitivity and diagnostic accuracy (Table 2).

Discussion

The main indications for FNAC of the liver is in the diagnosis of solid space occupying lesions, including primary and metastatic tumours, haemangiomas, adenomas and focal nodular hyperplasia.[11] FNAC guided by diagnostic imaging has greatly facilitated early specific diagnosis of hepatocellular carcinoma.[12]

On FNAC a definite diagnosis was made in 28 (87.5%) of cases, with 3 false negatives, including 1 false negative for malignant tumours and 2 false negative for benign tumours. There was 1 false positive diagnosis for malignancy. (reported as metastatic carcinoma rather than hepatocellular carcinoma).

In our study the majority of hepatic masses were malignant neoplasms (56.25%), hepatocellular carcinoma being the commonest tumour, now seen with increased frequency in some Asian and African countries.[13] At least 80% of all primary liver cancers are hepatocellular carcinoma.

Four cases of benign tumours were haemangiomas (86.67%) which were later confirmed on angiocomputed tomography and histology. One case was reported as dysplastic cells (false negative) and was found to be an adenoma on histology. The other case was diagnosed as benign hepatocytes (false negative) without any specific diagnosis, and was confirmed on histology to be focal nodular hyperplasia. FNAC – histological comparison showed a 66.67% sensitivity and 85.7% diagnostic accuracy for benign tumours (Table 2, 3). FNAC is less useful in the diagnosis of localized benign lesions in the liver, including benign neoplasms. A specific tissue diagnosis is not usually possible. Nevertheless, FNAC may be helpful in excluding a malignant process, which cannot be readily distinguished from a benign lesion radiologically.[14] There were relatively less number of benign tumours 6 (18.75%), compared to malignant cases 18 (56.25%) and non-neoplastic/inflammatory lesions 8 (25%). This was probably because most of the obviously benign lesions were not referred for FNAC.

Table 1: *Comparison of FNAC with histology of suspected hepatic masses (n = 32)*

Category	FNAC		Histology	No. of cases
Benign 6	Haemangiomas		Haemangiomas	4
	Benign hepatocytes (FN)		Focal nodular hyperplasia	1
	Dysplastic cells (FN)		Adenoma	1
Malignant 18	Primary HCC			10
		Atypical cells (FN)	Well diff HCC	1
		Well diff HCC	Well diff HCC	3
		Mod diff HCC	Mod diff HCC	3
		Metastatic CA (FP)	Poorly diff HCC	1
		Poorly diff HCC	Poorly diff HCC	1
		Fibrolamellar CA	Fibrolamellar CA	1
	Metastatic tumours			
		Adenocarcinomas	Adenocarcinoma	6
		Malignant melanomas	Malignant melanomas	2
Non-neoplastic / inflammatory lesions 8	Hepatic abscesses		Hepatic abscesses	3
	Fatty liver		Fatty liver	3
	Hydatid cyst		Hydatid cyst	1
	Regenerating cirrhotic nodule		Regenerating cirrhotic nodule	1

HCC = Hepatocellular Carcinoma
CA = Carcinoma
FN = False Negative
FP = False Positive

Table 2: *Statical analysis of FNAC of hepatic masses (n = 32)*

FNAC Diagnosis					Accuracy
	TP	TN	FP	FN	FNAC
Benign	4	8	-	2	85.7%
Malignant	16	8	1	1	92.3%
Non-neoplastic / Inflammatory	8	8	-	-	100%

The majority of malignant tumours, in our study comprised 10 cases of hepatocellular carcinoma, 8 of which were correctly diagnosed on FNAC. One case reported as atypical cells (false negative) on FNAC was found to be well differentiated hepatocellular carcinoma on histology. This is one of the commonest cytologic pit falls, where well differentiated neoplastic hepatocytes can closely resemble the microscopic features of benign or reactive conditions like an adenoma, chronic hepatitis or active cirrhosis on FNAC.[15] Very well differentiated hepatocellular carcinoma may be difficult or impossible to diagnose.[16,17] Cell blocks/ clots for histology may be useful in such cases. On the other hand aspirates from lesions may show significant reactive atypia or even dysplasia. These may be mistaken for hepatocellular carcinoma.[18]

The other incorrect diagnosis on FNAC was metastatic

carcinoma (false positive) which was confirmed on histology to be a poorly differentiated hepatocellular carcinoma. However a strong morphological similarity occurs between the cell morphology of a poorly differentiated hepatocellular carcinoma and metastatic carcinoma. Although the diagnosis of malignancy is obvious the hepatocytic origin of the cells may not be clear.[19] Difficulty in recognizing the well and poorly differentiated hepatocytic morphology has also been highlighted in several previous studies.[15,20,21] Moreover the differentiation between primary and metastatic malignancy is difficult by cytological examination alone.[22] In many cases clinical correlation with AFP may be helpful. However alpha-feto protein levels which is a relatively specific, but rather insensitive marker for hepatocellular differentiation is present in only one quarter of cases.[23,24]

Table 3: *Indices indicating diagnostic reliability of ultrasound guided FNAC of hepatic masses (n = 32).*

	Benign Tumours (Group – I)	**Malignant Tumours (Group – II)**	**Neoplasms (Both benign and malignant)**
Specificity	100%	88.9%	88.88%
Sensitivity	66.67%	94.12%	86.96%
Diagnostic accuracy	85.7%	92.3%	87.50%
Positive Predictive Values	100%	94.12%	95.24%
Negative Predictive Values	80%	88.9%	72.73%

The diagnosis of fibrolamellar carcinoma on FNAC was made easier by an adequate blood clot and tissue cores, which revealed the characteristic oncocytic appearance of neoplastic hepatocytes with lamellar fibrosis as also seen in our smears. These features can also be appreciated on FNAC.[25] The main differential diagnosis is oncocytic variant of liver cell adenoma. Histologically adenoma has no fibrosis.

FNAC is being increasingly used for the diagnosis of liver metastasis with excellent results, and also can be sampled accurately with all needles and methods.[26] A study on the diagnostic role of FNAC of liver metastasis showed a sensitivity of 100% and specificity of 84.6%.[15]

In our study a 100% correct diagnosis for metastatic carcinomas was achieved. Also an attempt was made to predict the primary site of the tumour on FNAC, which in most cases is a great challenge for the histopathologist. FNAC is not only extremely useful in diagnosis but also for staging of tumours.[27] Major bulk of metastatic tumours in our study comprised 6 cases of metastatic adenocarcinoma, possibly of gastrointestinal tract (GIT) origin and 2 cases of malignant melanoma, which also frequently metastasize to this organ. Metastatic melanoma can closely mimic hepatocellular carcinoma. There are many cytological similarities. Even melanin pigment when present, may resemble various liver cell pigments. Single cells, eccentric nuclei pale peripheral cytoplasmic zone and some cells with double mirror image nuclei may help distinguish it from hepatocellular carcinoma. Immunohistochemistry may also be done to confirm the diagnosis.

Studies carried by Isler and Wittenberg showed an accuracy between 83 – 100%.[28,29] Another study carried by Droese[11] and Gabrijela[30] showed an accuracy of 94%, and 91.5% which is fairly comparable to the results obtained in our study (Table 3). In majority of the studies the specificity of diagnosis of hepatic malignancy was 100% whilst the sensitivity varied. Lack of sensitivity may have been due to sampling error, inadequate aspirates, giving false negative diagnosis.[31]

All the non-neoplastic/ inflammatory lesions showed a 100% cytohistologic correlation. FNAC is very helpful in making cytological diagnosis of hepatic masses in 90% of cases with a diagnostic yield of 83.4%[31] almost similar results were seen in the earlier studies by Shah and Jan[(32)]. Most studies comparing core needle biopsy and FNAC favour fine needle aspiration cytology for focal liver disease[(2)]. Our results are favourably comparable with other studies in diagnosing hepatic malignancies.[31,35] High diagnostic accuracy achieved in our study may be attributed to adequate/ diagnostic material, thorough screening of the smears, combined with relevant clinical, radiologic and serologic studies e.g., alpha-feto protein level.

Conclusion

Fine needle aspiration cytology offers a useful ancillary diagnostic procedure in combination with information derived from clinical, radiologic and serologic tests. It is safe, more sensitive and specific technique for diagnosing malignancy than conventional needle biopsy. However FNAC has its own limitations in diagnosing some benign lesions, well differentiated hepatocellular carcinoma and also in differentiating between a poorly differentiated hepatocellular carcinoma from a metastatic carcinoma and detection of the source of metastatic deposits.

Therefore to obtain maximum diagnostic information a cytohistological correlation combined with ancillary techniques should be used.

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