Original Articles

Non-imaging-guided fine-needle aspiration of liver lesions: a retrospective study of 279 patients

Yeouda Edoute[1,4], Ehud Malberger[2,4], Orly Tibon-Fishe[2] and Nimer Assy[3,4]

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Abstract

AIM **To determine the value of nonimaging-guided (direct) fine-needle aspiration cytology in diagnosing liver lesions.**

METHODS **Detection by technetium-99m, ultrasound or computed tomographic scanning of the liver was made in 279 patients with 332 aspirations.**

RESULTS **Based on histologic, cytologic and clinical findings, final liver diagnoses were reached in 265 patients, of whom 171 had malignant and 94 benign liver disease. Among the 171 patients with malignant liver disease, the cytologic findings indicated suspected malignancy in 8 patients, suggested definite malignancy in 130, but failed to disclose malignancy in 33 patients. In 93 of the 94 patients with benign liver disease, the cytologic findings were reported as benign, while in one patient the report of malignancy was false. The overall sensitivity, specificity, and positive and negative predictive values for cytologic results were 80.7%, 98.9%, 99.3% and 73.8%, respectively. The diagnostic accuracy of fine-needle aspiration cytology was 87.2%. The only major complication attributable to the procedure consisted of one case of pneumothorax.**

CONCLUSION **Direct fine-needle aspiration of palpable liver mass and blind fine-needle aspiration of non-palpable liver lesions for cytodiagnosis are simple, safe, and cost-effective diagnostic method for evaluating the nature of liver lesions. The aspiration procedure including potential complications could be cut short by early finding of abnormal cells.**

Department of [1]Internal Medicine C, [2]Diagnostic Cytology, [3]Liver Unit, Rambam Medical Center, Haifa, and [4]The Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel.
Correspondence to: Nimer Assy, MD., Fassouta, Upper Galilee 25170, P.O.B. 428, Israel
Tel. +972 • 4 • 9870-080,   Fax. +972 • 4 • 9870-080
E-mail. drnimer@netvision.net.il
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INTRODUCTION

Imaging-guided fine-needle aspiration (FNA) for cytodiagnosis is well establis hed as a reliable and cost-effective method for diagnosing malignant lesions in all systems and organs of the human body. FNA of liver lesions guided by ultrasound (US) or computed tomography (CT) has proven to be a safe, very sensitive and specific method for diagnosing hepatocellular carcinoma[1-8] and liver metastases[3,9-11]. A sensitivity between 66.9% and 100% has been reported in major centers[12-28]. However, its value in small peripheral centers remains to be determined. From 1976, and before the US and CT imaging methods were introduced in our hospital, we performed direct FNA of palp able ab do minal[29] and liver mass and blind FNA of nonpalpable lesions detected by technetium-99m, US and CT liver scan. Our findings encouraged us to use this method as the initial diagnostic tool in patients suspected of having malignant liver disease (MLD). To date, a large retrospective evaluation describing the ac curacy of direct FNA or the safety of the technique has not been reported.

The aspiration procedure using guided needle aspiration seems excessive for routine use with potential for complications. Whether the procedure could be cut short by early finding of abnormal cells remains to be determined. The aim of this study was to report our experience gained with nonguided FNA of palpable and non palpable liver and to compare our results with the method of imaging guided FNA as reported in the literature.

MATERIAL AND METHODS

During the years 1976-1988 we performed 332 direct FNAs of liver in 279 patients at Rambam Medical Center. Of the 332 aspirations, 50 (45 patients) were direct aspirations of palpable liver lesions, and 282 (234 patients) were blind aspira tions of non-palpable liver lesions. The aspirations were made in order to either confirm or rule out suspicions of primary or metastatic malignancy in the liver, based on clinical findings and supported by the presence of unifocal or mult ifocal liver lesions on a radioisotope, US or CT scan. Informed consent was obtained from each patient, and the study protocol conformed to the ethical guidelines of the Declaration of Helsinki as reflected in a priori approval by the hospital's Human Research Committee.

Technique

The specimens for cytologic examination were obtained by direct insertion of a long (0.8 mm×80 mm) 22-gauge needle. All aspirations were performed by one operator, and the penetrating sites of the liver were subcostal. An attendant cytopathologist was present in all cases to verify that adequate numbers of cells of the expected type were present in the sample. In cases of palpable liver mass, or of hepatomegaly arousing a strong suspicion of liver malignancy but without any palpable mass, the aspiration was usually performed prior to any imaging exploration of the liver. In cases of unifocal or multifocal lesion (s) demo nstrated by imaging methods (with or without an enlarged liver), the puncture sites and directions of the needles were blindly directed towards the estimated site of the lesion. Three to five aspirations from different insertion points were made in each FNA procedure, with six to eight needle passes for each aspiration. The aspirate was expelled onto glass slides, smeared and fixed with 95% ethyl alcohol, and later stained by Papanicolaou's method. One slide was air-dried for May-Grünwald/Giemsa staining.

Exclusion

The only contraindications for FNA were a history of marked hemorrhagic tendency, a high increase in D-dimers, reduced platelet count, or prolonged prothrombin or partial thromboplastin time.

Cytopathologic interpretation

Cytologic findings were reported as follows: acellular,unsatisfactory, no malignancy,atypical-reactive,malignancy cannot be ruled out (inconclusive), suspected malignancy and definite malignancy. The tumor cell type was specified whenever possible. The clinical, laboratory, radiologic, imaging, operative, histologic and cytologic data were compiled in each patient. Follow up information for each patient was obtained in order to reach a final diagnos is and to evaluate the diagnostic role played by FNA. Data were obtained by revi ewing Rambam Medical Center charts, the discharge summaries of other hospitals and telephone communication.

Statistical analysis

To determine the sensitivity and specificity of cytologic diagnoses, it is necessary to classify cytologic findings for each patient as either malignant or benign. For this purpose, patients with cytologic findings of 'no malignancy' and 'atypical-reactive' were classified as having benign cytologic diagnoses, while patients with cytologic findings in liver aspirations from the right or left side of 'suspected' and 'definite malignancy' were diagnosed as having malignancy. The cytologic findings of FNA were categorized as true-positive, true-negative, false-positive and false-negative. The accuracy of true and false cytologic diagnoses was verified against histologic, cytologic and clinical categories. A cytologic diagnosis was defined as true-positive if a patient with malignant cytologic diagnosis had one or more of the followings:

Histologic findings Histologic findings of malignancy based either on liver tissue obtained by liver needle biopsy, surgery or autop sy or on histologic findings of malignancy from another site revealing malignant cells similar to those obtained by FNA of the liver.

Cytologic findings Malignant cells from other organs or from body fluids, exhibiting malignant cells similar to those obtained by FNA of the liver.

Clinical findings A combination of the followings: ① palpable liver mass, hepatomegaly or elevated serum alkaline phosphatase; ② imaging scan of the liver suggesting malignancy and ③ steady deterioration, with survival time not exceeding 12 months, with or without indication of MLD on death certificate.

A cytologic diagnosis was defined as true-negative if a patient with negative cytologic diagnosis also had benign histologic diagnosis of a liver biopsy or no evidence for MLD during surgery and/or his subsequent clinical course was considered characteristic of a benign disease (improvement either spontaneously or following therapy). Specificity was determined by dividing true-negatives by the number of lesions ultimately found to be benign. Basing on histologic, cytologic and clinical findings, we reached final diagnoses in 308 aspirations from 265 patients.

RESULTS

Twenty-four out of 332 aspirations were excluded from the study: ten because the aspirates were unsatisfactory, five because the cytological findings were inconclusive, and nine because the conclusive cytology findings could not be verified by histology, adequate clinical follow-up, or autopsy. The study included 265 patients (308 aspirations) with final diagnosis, of whom 171 (203 aspirations) had a malignant liver disease and 94 (105 aspirations) had a benign liver disease. Sixty-one (21.9%) patients had histories of prior malignancy, 56 with one prior tumor and 5 with two prior tumors.

Table 1 lists the patients' clinical characteris-

tics. All the patients underwent at least one of the following liver imaging explorations: technetium-99m scanning, US or CT. Among 94 patients with BLD, the imaging scans suggested malignancy in less than 20%.One hundred and fifty-five of the 171 patients with malignant liver disease underwent at least liver imaging scanning, malignancy was suggested in 134 (86.5%) patients. In patients with malignant liver disease, malignant multifocal lesions were found in 79% and unifocal lesions in only 21%.

Table 2 shows the conclusive cytological findings from FNA according to the final diagnosis of liver disease. Among 130 patients with definite cytological findings of malignancy, primary liver carcinoma was diagnosed in 26 (20%), 24 of whom had hepatocellular carcinoma. Adenocarcinoma was specified in 59 (64.1%) of 92 patients (70.8%) with cytologically diagnosed liver metastases. Other cytologic diagnoses included anaplastic carcinoma, lymphoma, sarcoma, etc. Histologic fi ndings verified the cytologic diagnosis of malignancy in 62 (36.3%) patients. In 35 (20.5%) patients the cytologic diagnosis of malignancy was verified by matching with cytologic tumor cells obtained from other organs or from body fluids, and in 74 (43.2%) patients by clinical findings alone. Clinical findings sugge sting malignancy were observed in only two (2.1%) of 94 patients with benign liver disease and corresponding cytologic findings. In these two patients, the survival time was shorter than 12 months due to cardiovascular events.

Table 3 shows the relationship between nonguided FNA cytodiagnosis in patients with MLD and type of suspected malignant liver lesion detected by various kinds of liver imaging scanning. Among 230 liver scans suggesting malignancy, 166 (72%) were suggestive of multifocal lesions, and 64 (28%) of unifocal lesions. The pr oportion of true-positive cytologic diagnosis was 73.5% (122/153) among patients with liver scans suggesting multifocal lesions, while 68.8% (44/66) indicated unifocal lesions. The final clinical diagnoses in the benign liver lesions were liver cirrhosis, various types of chronic hepatitis, liver abscess, and he mangioma. Using the defined histologic, cytologic, and clinical criteria for malignant and benign liver diseases, the sensiti-vity of FNA cytology for the diagnosis of malignancy was 80.7%, while the specificity and positive and negative predictive values were 98.9%, 99.3% and 73.8% respectively. The overall diagnostic accuracy rate of FNA cytology was 87.2%.

Sensitivity = proportion of correctly diagnosed malignant lesions.

Specificity = proportion of correctly diagnosed benign lesions.

Table 4 shows the effect of repeated FNA on

the accuracy of liver disease diagnosis. In 37 patients clinically suspected of having malignant liver disease, nondiagnostic or benign cytologic diagnosis was made in 18 patients, thus increasing the sensitivity and decreasing the false-negative rate. The one case originally classified as malignant (false-positive cytologic finding) was, on review of the cytologic slides, subsequently classified as benign lesion with marked cellular atypia.

One case of non-fatal pneumothorax was the only major complication following the procedure, while pain and tenderness at the puncture site was not an infrequent complaint.

The median survival of patients with malignant liver disease was 2 months (range, 1-19 months), whereas the median survival of patients who died of benign liver disease was 12 months (range, 1-95 months).

Table 1 Characteristics of patients with final diagnosis of liver disease

	Malignant	Benign
Number of patients	171	94
Male	99	46
Female	72	48
Age (years)		
Median	69	67
Range	22-99	7-86
Symptoms (% of patients)		
Weight loss	71.3	48.9
Abdominal pain	64.7	51.0
Jaundice	18.8	19.4
Signs (% of patients)		
Hepatomegaly	74.3	45.7
Palpable liver mass	19.9	5.3
Ascites	16.5	15.3
Abdominal mass	7.6	5.1
Abnormal liver tests (% of patients)		
Alkaline phosphatase	88.9	60.6
Aspartate aminotransferase	48.2	22.4
Bilirubin	44.1	36.7

Table 2 Direct fine-needle aspiration (FNA) diagnosis for liver lesions compared with the final diagnosis

Direct FNA cytology	Final diagnosis	
	Malignant	Benign
Non-malignant	49	99
Atypical-reactive	03	05
Suspicious	16	0
Malignancy	135	1
Total	203	105

Table 3 Relationship between nonguided fine-needle aspiration cytodiagnosis and type of suspected malignant liver lesions demonstrated by different kinds of imaging liver scanning among patients with malignant liver disease

Type of imaging and lesions *	No. of imagings	True-positives	False-negatives	True-negatives	False-positives
Radioisotope					
Unifocal	35	23	5	7	0
Multifocal	96	71	17	7	1
US					
Unifocal	21	15	2	4	0
Multifocal	61	46	11	3	1
CT					
Unifoca	18	6	1	1	0
Multifocal	9	5	3	1	0

* Patient may have more than one imaging scanning.

Table 4 Accuracy of non-guided FNA cytodiagnosis according to first FNA (number of FNAs) or most meaningful FNA when it was repeated (number of patients)

	FNAs No. (%)	Patients No. (%)
True positive	151(74.4)	138(80.7)
True negative	104(99.0)	93(98.9)
False positive	1(1.0)	1(1.1)
False negative	52(25.6)	33(19.3)
Non-diagnostic	24(7.2)	14(5.0)
Total	332	279

DISCUSSION

FNA is a procedure available for more than two decades. FNA of the liver guided by US or CT has proven to be a safe and accurate method for diagnosing hepatocellular carcinoma[1-8] and liver metastases[3,9-11]. The most important requirement for such cytodiagnosis is a representative sample from the lesion. Except for some cases of well-differentiated hepatocellular carcinoma, the?identification of malignancy in liver aspirate can be made by any experienced cytopathologist (our cytopathologist has a high expertise in obtaining an accurate diagnosis by FNA). The reported sensitivity of US- and CT-guided FNA ranges between 66.9% and 100%[12-28]. In the present study, the sensitivity, specificity, and positive and negative predictive values of nonguided FNA for cytodiagnosis of liver lesions were 80.7%, 98.9%, 99.3% and 73.8%, respectively. The overall accuracy rate was 87.2%. These data indicate that the diagnostic accuracy of nonguided FNA of liver lesions is similar to imaging-guided FNA.

What, in the present study, produced representative tissue sampling by nonguided FNA ① Sampling representing a larger liver volume: this was achieved by a num ber of aspirations in various directions (multiple insertion points) and by mult iple (6-8) long passes in each aspiration; ② direct sampling by aspiration of palpable liver masses including cleaning of the needle with saline solution after each pass to remove residual cellular material and/or debris: this explanation applies to 19.9% of patients (34 out of 171) with malignant liver diseases; and ③ large parts of the liver being affected: imaging scannings suggesting malignant multifocal lesions were more prevalent than those indicative of unifocal lesions. Thus, among 230 liver scans suggesting malignancy, 166 (79%) pointed to multifocal lesions and only 64 (21%) to unifocal ones.

Furthermore, nondetection of pathologic find ings by imaging liver scans does not preclude the presence of malignancy. Heiken *et al*[30] prospectively evaluated the ability of CT to detect malignant lesions in eight patients who subsequently underwent hepatic lobectomy or transplantation. Among the 37 malignant lesions demonstrated by

pathologic evaluation, only 14 (38%) were detected by contrast-enhanced CT, but none of the 18 lesions smaller than 1cm in diameter were detected by the CT. We therefore suggest that actual malignancy is more frequent than its on-screen appearance.

Histopathologic examinations of patients with rectal carcinoma showed that the depth and distance involvement of the tumor exceeds the macroscopically defined tumor border[31,32]. Consequently, although the aspirating needle does not necessarily aspirate the actual imaged lesion, it certainly aspirates some surrounding malignant cells since the enlarged liver is accessible to needles and do not require radiological visualization. This argument may be supported by the facts that 74.3% of patients with MLD had hepatomegaly which could only be attributed to malignancy and that the rate of malignant cytologic findings in patients with unifocal malignant liver lesion was only slightly less than that of patients with multifocal lesions (69% vs 73%).

The present study was conducted in order to establish the cytologic examination as a reliable diagnostic method. Evaluation of the diagnostic accuracy of our cytologic findings was carried out on three levels. In 62 (36.3%) of the 171 patients with MLD, the cytologic diagnosis was verified by histologic findings obtained by liver needle biopsy, at surgery, at autopsy or on histologic findings of malignancy from another site revealing malignant cells similar to those obtained by FNA of the liver. This constituted the highest level of verification. The cytologic diagnosis of malignancy was confirmed in 35 (20.5%) patients by matching with cytologic tumor cells obtained from other organs or from body fluids, and in 74 (43.2%) by clinical findings alone. The defined clinical findings suggesting malignancy were observed in only two (2.1%) of 94 patients with BLD and corresponding cytologic findings. In these two patients the survival time was shorter than 12 months due to cardiovascular events. The validity of the cytologic findings is also supported by the survival time. The median survival for patients in whom the cytologically diagnosed MLD was verified against histologic, cytologic and clinical findings was 2, 3 and 2 months, respectively.

There were 33 (19.3%) patients with false negative cytologic findings, which was due to fai lure to obtain a representative malignant sample rather than to misinterpretation of the smears. It has been shown that superficial nonrepresenta tive FNA of a malignant tumor may reveal only necrotic material, degenerative changes or in flammatory reactions, which are frequently observed but do not reveal the presence of an underlying tumor[19]. In order to lower the rate of false-negative cytologic findings, we suggest that FNA should be repeated in patients c linically suspected of having malignancy despite negative cytologic findings. In doing so, we were able to increase the sensitivity of the cytologic

findings from 74.4% to 80.7%. Negative cytologic findings must be viewed with caution because of their false-negative rate (19.2%). However, because a malignant cytologic diagnosis is considered to be equivalent to a malignant histologic diagnosis, high specificity is a necessary requirement. In our series one false-positive cytologic diagnosis due to marked cellular atypia was reported. False-positive cytologic diagnoses have been reported in the literature[9,13,19,20], ranging from 4% (20) to 20% (9). One case of pneumothorax is the only major complication reported following the procedure [33], while pain, tenderness and local skin hemorrhage at the puncture site were not infrequent. In general, use of a thin (23 gauge) needle is usually safe and is less likely associated with m ajor complications such as bleeding.

The results of this retrospective study may lead to the impression that FNA is easy and accurate for use by physicians who perform FNA. However, it does not mean to replace the current general practice of ultrasound guided needle biopsy in major centers, and does not provide rejection of available and more useful methods, particularly in the diagnosis of localized lesions of the liver. The aspiration procedure seems excessive for routine use with potential for complications and this study indicates that the procedure could be cut short by early findings of abnormal cells. Moreover, as funding for health care becomes increasingly a global issue of paramount importance, a less-time consuming and less ex pen sive procedure with high clinical benefit for both diagnosis and therapy will be the goal of clinicians, health care policymakers, and patients. Our data suggest that nonguided (direct and blind) FNA of palpable and nonpalpable liver lesions is a simple, accurate and cost-effective method that allows rapid microscopic diagn osis. When repeated nonguided FNA fails to demonstrate malignancy, guided FNA should be considered.

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