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Diagnostic Accuracy of Fine-Needle Aspiration Biopsy in Patients with Hepatocellular Carcinoma

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The present study was undertaken to investigate the diagnostic usefulness of fine-needle aspiration biopsy (FNAB) in a large series of patients with hepatocellular carcinoma (HCC) seen over a 1-year period. During 1986, ultrasonographically guided percutaneous FNAB was performed in 72 patients with suspected HCC. A final diagnosis of HCC was made in 58 patients. The presence or absence of HCC was ascertained by histological examination and/or by other diagnostic procedures (α_1-fetoprotein, computed tomography, arteriography) and by clinical follow-up (repeated ultrasonographic controls) and/or by surgery or necropsy. A total of 61 FNABs were carried out in these 58 patients. Only 42 (69%) of the 61 FNABs allowed the diagnosis of HCC. This moderate diagnostic sensitivity was not related to tumor size. Only one false positive result was observed in the non-HCC group. Therefore, the diagnostic specificity of FNAB for HCC was 93%, with a positive predictive value of 97% and a negative predictive value of 40%. These results show that FNAB is a useful diagnostic technique in patients with HCC. However, these data also show that there is a large proportion (31%) of subjects with false negative results. Therefore, we suggest that further efforts should be made to improve the diagnostic accuracy of this procedure.

KEY WORDS: hepatocellular carcinoma; fine-needle aspiration biopsy.

Hepatocellular carcinoma (HCC) represents a major health problem, particularly in countries from the Far East and Central Africa (1). This has led to the development of mass screening programs aimed at achieving early detection of this disease, thus allowing surgical treatment. Usually the presence of HCC is sought by periodic ultrasonography and α_1-fetoprotein (AFP) (2–5). Fine-needle aspiration biopsy (FNAB) is the diagnostic technique currently used to establish the histological diagnosis in those subjects found to have focal hepatic lesions (5). This technique is an easy and harmless procedure for diagnosing both thoracic and abdominal tumors. Its diagnostic sensitivity in large series of patients with abdominal malignancies varies between 70% and 100% (6–17). However, most of these studies include only a small number of HCC patients, do not take into account the size of the tumors, and are performed over several years (6–17). The results published by Okuda (5) in a recent overview on hepatic cancer, suggesting a diagnostic sensitivity of this technique of only 60% in small HCC, prompted us to carry out this study, which was aimed at determining the diagnostic accuracy of ultrasonographically guided FNAB in a large

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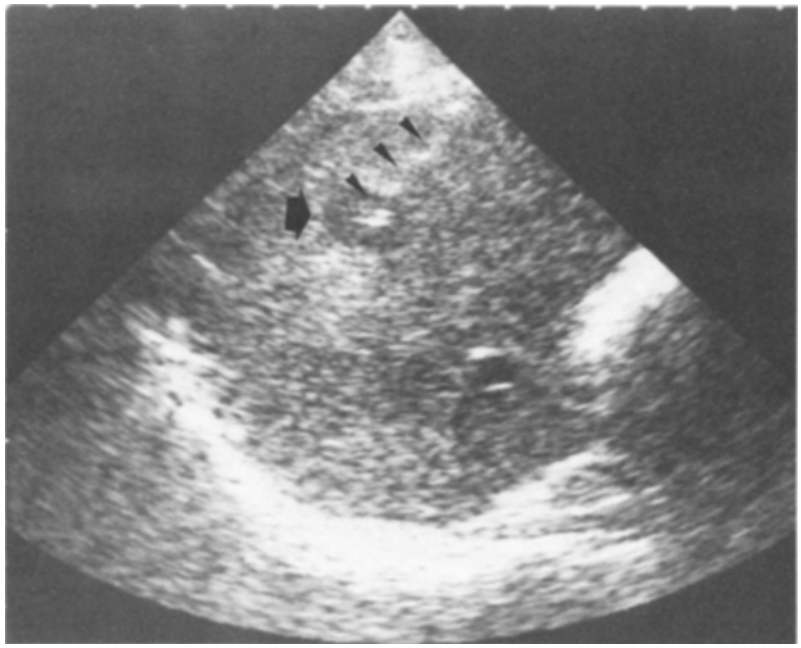

Fig 1. FNAB of a hypoechoic hepatocellular carcinoma (arrow). The needle is identified as a thin hyperechogenic line (arrow heads).

series of HCC patients seen over a 1-year period and stratified according to the size of the tumor.

MATERIALS AND METHODS

All the patients with suspected HCC who underwent FNAB during 1986 were included in the study. The focal liver lesion was identified using a gray-scale real-time scanner with a sectorial transducer of 3.75 MHz. Sonograms of each patient were recorded, and the longest axis of the lesion was taken as its size. FNAB was performed using a 22-gauge spinal-type needle, under continuous ultrasound control of the needle tip (Figure 1). Upon placement of the needle into the suspected tumoral area, a sustained aspiration with small displacements of the needle tip was made with a syringe. Half the aspired material was fixed, and the rest was air dried on several plates, thus allowing cytological examination using Papanicolaou and May-Grünwald-Giemsa staining techniques.

A final HCC diagnosis in patients with FNAB positive for malignancy was established when there was complete agreement with clinical follow-up and other diagnostic procedures (AFP, CT, peritoneoscopy) or when surgery or necropsy confirmed this diagnosis. A nonmalignant diagnosis was considered to be true when other diagnostic procedures (repeated FNAB, large-bore hepatic biopsy, peritoneoscopy) performed during the same hospitalization or during the 1-year clinical and ultrasonographic follow-up excluded HCC diagnosis.

RESULTS

Percutaneous FNAB of suspected HCC was performed in 72 patients during 1986. Fifty-eight of the 72 patients who underwent FNAB had a final diagnosis of HCC. In the remaining patients, final diagnoses were: benign hepatic tumor (one adenoma and one focal nodular hyperplasia), focal fatty liver infiltration (two patients), severe architectural distortion due to hepatic cirrhosis (nine patients), or secondary to hepatic regeneration following liver surgery (one patient).

Forty-five HCC patients were male and 13 female, with ages ranging between 22 and 89 years. In 42 of the 58 HCC patients the diagnosis was based on the positivity of FNAB associated to increased plasma levels of AFP and/or progressive tumoral growth in sequential explorations or necropsy. In the remaining 16 patients with negative FNAB the final diagnosis was based on arteriographic and CT findings (three patients), surgery or necropsy (three patients), large bore hepatic biopsy (two patients), high plasma AFP levels (two patients), bone metastasis biopsy (one patient), and clinical, echographic, or CT events in the follow up (five patients). In three HCC patients, the first FNAB was not diagnostic and a second FNAB was indicated. This second FNAB was diagnostic of HCC in only one of these three patients. Therefore, in order to calculate the diagnostic sensitivity of this technique a total of 62 FNABs in 59 HCC patients were taken into account.

TABLE 1. REASONS FOR NEGATIVE RESULTS OF FNAB (19 OF 61 PROCEDURES

Necrotic/hemorrhagic material	2
Noncytological criteria of malignancy	17
Total	19

As previously mentioned, only 42 FNABs were positive for HCC. Thus, the sensitivity of FNAB in this series of patients with HCC was 69%. In 19 procedures (31%) the diagnosis of HCC could not be established due either to necrohemorrhagic specimen (two occasions) or to the absence of cytological criteria of malignancy despite a large sample (Table 1).

FNAB sensitivity was not related to tumor size. In fact, 57% of the HCCs smaller than 3 cm could be confirmed by this technique, whereas this percentage rose to 68% in the tumors between 3 and 5 cm and to 71% in HCCs bigger than 5 cm (Table 2).

Only one false positive was observed. It was secondary to the reactive cellular abnormalities related to hepatic regeneration in an alcoholic patient who was previously submitted to liver surgery for carcinoid hepatic tumor. Therefore, the diagnostic specificity of FNAB for HCC was 93%, with a positive predictive value of 97% and a negative predictive value of 40%. The overall accuracy of FNAB was 73%.

DISCUSSION

For many years, HCC has been diagnosed by peritoneoscopy and biopsy. This technique is able to confirm 72% of those patients with clinical suspicion of HCC (18), and their false negatives are due to the attainment of a hemorrhagic and nondiagnostic biopsy and/or to the deep location of the tumor, which in some cases may be impossible to visualize. FNAB under continuous ultrasound guidance was expected to overcome these problems. Theoretically, all the tumors, including those deeply located, would be able to be visualized and punctured. In addition, it was thought that the use of a fine needle would allow an aspiration biopsy to be performed even in highly vascularized lesions. However, this technique also has some handicaps.

TABLE 2. RELATIONSHIP BETWEEN HCC SIZE AND FNAB DIAGNOSTIC SENSITIVITY

Size (cm)	*N*	*Sensitivity (%)*
0–3	7	57
3–5	22	68
>5	32	71
Total	61	69

The results of the present study show that FNAB is able to confirm only 69% of the HCC submitted to this diagnostic procedure. This percentage is clearly lower than those previously reported in other studies performed by ourselves and by other authors (6–17). In these previous investigations FNAB was found to be very useful, since it was able to set the diagnosis of malignant liver involvement in nearly 90% of the cases. However, the majority of these studies include a large proportion of metastatic tumors and a reduced number of patients with HCC (6–11, 16, 17) and therefore, cannot offer adequate information about FNAB sensitivity in this kind of malignancy. In addition, some of these investigations may be hampered by an important bias, since FNAB positivity is frequently an inclusion criteria and, therefore, HCC patients with negative results may be lost to follow-up and not considered.

The reason for our negative results of FNAB in confirming HCC diagnosis may be attributed to several factors. It may be supposed that it is very difficult to puncture small HCC located in the liver parenchima, yet is must be stressed that none of the previously published investigations offer data about the relationship between the size of the tumor and FNAB diagnostic accuracy. However, with the echographic equipment usually employed, the needle tip can be continuously controlled, therefore ensuring that FNAB is performed in the central part of the tumor. In that regard, the results of this study demonstrate that there is no definite relationship between HCC diameter and FNAB positivity, thus suggesting that tumor size is not the unique factor in determining FNAB diagnostic accuracy. In HCC bigger than 5 cm, negative FNAB cases could be due to the necrosis and hypervascularization of the tumor, which would result in the attainment of necrotic or hemorragic material. This circumstance was observed in two cases of the present series, both being bigger than 5 cm. However, this cannot explain all the false negative results in large tumors. Probably, the most important factor in determining the sensitivity of FNAB is the degree of differentiation of the tumor and the fact that it usually develops in patients with liver cirrhosis (5, 12, 19). Moreover, it is known that small HCCs are mainly formed by well-differentiated hepatocytes and that large HCCs may contain areas with different degrees of differentiation (20). FNAB using 22-gauge

needles obtains a reduced tissue specimen that is processed for cytological examination and perhaps minor changes observed in well-differentiated tumors may impede the cytological distinction with reactive changes due to the underlying liver disease (21, 22).

This diagnostic problem is especially relevant in those lesions discovered in early detection plans or during clinical follow-up in patients with liver disease. In these subjects the suspected HCC is frequently smaller than 3 cm (23) and anatomopathological confirmation may be mandatory before initiation of treatment. In patients suitable for surgical resection, the histological study may be performed during surgery (24), and it may be argued that ultrasonography and CT sensitivity and specificity are similar or greater than that of FNAB. Therefore, surgical ablation of a suspected neoplastic nodule may be proposed if the echographic findings are in agreement with those of arteriography or computed tomography. In nonsurgical patients, the administration of chemotherapy or the ethanol injection of the tumor should be based on a very sure diagnosis. Because in these cases with small HCC α_1-fetoprotein is frequently within normal values (5, 25), tumor confirmation relies exclusively on anatomopathological examination.

Efforts should be made to improve the sensitivity of FNAB. It is probable that ongoing studies investigating the diagnostic usefulness of immunohistochemistry, histochemistry, and cytochemistry will lead to better diagnostic accuracy of FNAB.

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