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Abstract

The ultrasonographic characteristics of hepatocellular carcinomas (HCC) were investigated. Four typical features of HCCs, "mosaic internal echo pattern", "halo", "lateral shadow" and "posterior echo enhancement", were not recognized in minute HCCs smaller than 2 cm in diameter. These characteristics developed as the tumors grew. Only hypoechoic space-occupying lesions can be considered as small HCCs. In differentiating small HCCs from hypoechoic non-malignant space-occupying lesions in the cirrhotic liver, the ratios of short to long dimensions of the lesions seemed to be important since the ratios of HCCs were significantly larger than those of non-malignant lesions. The fact that 3 hyperechoic small HCCs could not be diagnosed even by celiac arteriography has suggested to us that ultrasonically guided biopsies should be performed in order to differentiate from small hemangiomas. Serum alpha-fetoprotein (AFP) levels of 1/3 of the patients with HCCs were below 100 ng/ml, indicating that it is impossible to detect small HCCs only by measuring serum AFP.

KEYWORDS: ultrasonography, hepatocellular carcinoma, alpha-fetoprotein

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Ultrasonographic Characteristics of Small Hepatocellular Carcinoma

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The ultrasonographic characteristics of hepatocellular carcinomas (HCC) were investigated. Four typical features of HCCs, "mosaic internal echo pattern", "halo", "lateral shadow" and "posterior echo enhancement", were not recognized in minute HCCs smaller than 2 cm in diameter. These characteristics developed as the tumors grew. Only hypoechoic space-occupying lesions can be considered as small HCCs. In differentiating small HCCs from hypoechoic non-malignant space-occupying lesions in the cirrhotic liver, the ratios of short to long dimensions of the lesions seemed to be important since the ratios of HCCs were significantly larger than those of non-malignant lesions. The fact that 3 hyperechoic small HCCs could not be diagnosed even by celiac arteriography has suggested to us that ultrasonically guided biopsies should be performed in order to differentiate from small hemangiomas. Serum alpha-fetoprotein (AFP) levels of 1/3 of the patients with HCCs were below 100 ng/ml, indicating that it is impossible to detect small HCCs only by measuring serum AFP.

Key words : ultrasonography, hepatocellular carcinoma, alpha-fetoprotein

Hepatocellular carcinoma (HCC) usually develops in the cirrhotic liver, and is one of the most prevalent malignancies in Japan (1). The frequency seems to be increasing concomitantly with advances in therapy for liver cirrhosis. The overall prognosis is very poor—21.5% survival in 1 year

(2)—probably because radical resections of large HCCs are impossible due to deteriorated liver functions. Therefore, the importance of detecting small HCCs has been stressed for complete healing. In recent advances in computed tomography (CT), ultrasonography (US) and celiac arteriography (CA) have made easy to detect small HCCs in the cirrhotic liver (3-5). Among these

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procedures real-time US is the most useful for localizing small HCCs (6-8), and periodic examinations by this method are routinely carried out in patients with liver cirrhosis in order to find HCCs when they are as small as possible. Although many papers have focused on US findings of HCCs (9-11), the sizes of the tumors have been relatively large. In the present paper, therefore, differences in ultrasonographic characteristics of HCCs of various sizes were analyzed, and the features of small HCCs less than 2 cm in diameter, which have been designated as small liver cancer by the Liver Cancer Study Group of Japan (12), were compared to those of non-malignant lesions of the same size.

Subjects and Methods

Forty-four cases of small space-occupying lesions (SOLs) less than 2 cm in diameter including HCCs, hemangiomas and non-malignant lesions, detected by US, and 55 HCCs diagnosed by CA were encountered from January 1984 to December 1986 in the First Department of Internal Medicine, Okayama University Medical School. All cases of hemangiomas and non-malignant SOLs were followed at least 18 months after the first detection by US. Diffuse type HCCs were omitted from this study.

The diagnostic criteria of small SOLs were set as follows: HCCs (16 cases), tumors diagnosed by CA or SOLs which increased in sizes during the follow-up period and were finally confirmed to be HCCs by either CA or surgery. Hemangiomas (19 cases), those hyperechoic SOLs diagnosed by CT and/or CA or those which did not enlarge during the following observation period. Non-malignant lesions (9 cases), hypoechoic lesions found in the cirrhotic liver in which characteristics of HCC were not obtained by CA and no tumor growth was recognized during the period.

Scanning in this study was performed with a Hitachi EUB 20 with a 3.5 MHz linear type probe or EUB 40 with a 3.5 or 5.0 MHz convex type probe. The US findings were judged by 4 ex-

aminers experienced in interpreting US images. Serum alpha-fetoprotein (AFP) levels were determined by RIA method. Statistical analysis was carried out by Student's *t*-test.

Results

Diagnosis of small HCCs. Among 16 cases of small HCCs less than 2 cm in diameter, 13 with a hypoechoic internal pattern were confirmed by CA, 1 of 3 cases which showed a hyperechoic pattern was confirmed by CT-arteriography and the remaining 2 were diagnosed by tumor growth during the follow-up period. CA and portography were performed in 7 cases of 9 non-malignant small SOLs, and characteristic findings of HCC (neovascularity and tumor stain by CA and shadow defect in portography) were not recognized in any of cases. Furthermore, during an 18-month follow-up period, the sizes of the lesions were unchanged in 8, and 1 of them disappeared. Of 19 hemangioma patients, CA was carried out in 6 cases with chronic liver diseases, and the diagnosis was confirmed. Thirteen other patients without liver diseases were followed-up at least 18 months, during which time the size of the tumor did not change.

Characteristic US findings of HCCs according to size. HCCs were divided into 3 groups according to size; 16 cases of tumors less than 2.0 cm in diameter, 23 of 2.1-3.0 cm, and 32 of 3.1-5.0 cm. With increasing size of tumor, the internal echo pattern changed from a hypoechoic homogeneous to an iso- or hyperechoic mosaic pattern. Only 2 small HCCs less than 2 cm in diameter showed a heterogeneous internal echo pattern. Other characteristic US features of HCCs generally observed, such as "halo", "lateral shadow" and "posterior echo enhancement" were not recognized in any of the small HCCs. The percentages of

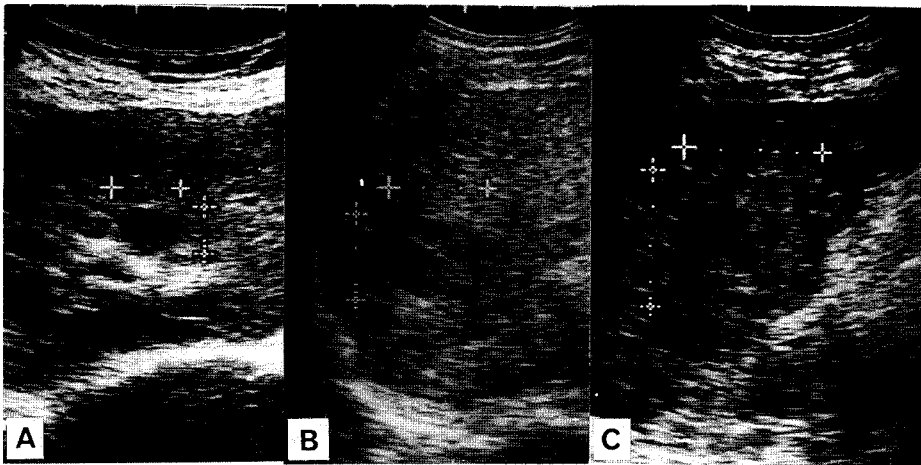


Fig. 1 Typical ultrasonographic changes of hepatocellular carcinomas (HCC) during tumor growth. A: A small HCC less than 2 cm in diameter which appears as a low space occupying lesion. B: An HCC with 2.5 cm in diameter which has a heterogeneous internal echo pattern, unclear halo, lateral shadow and posterior echo enhancement. C: An HCC larger than 3 cm in diameter with the 4 typical ultrasonographic characteristics.

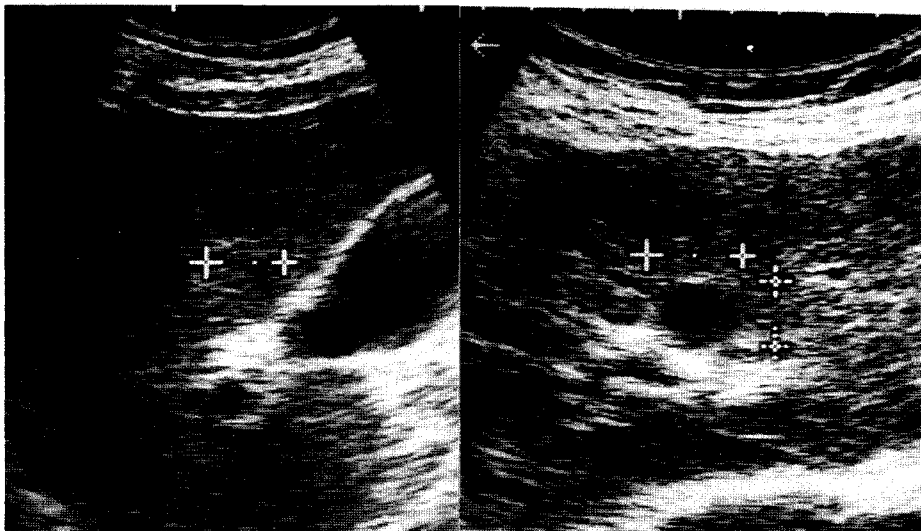


Fig. 2 A non-malignant lesion in the liver and a small hepatocellular carcinoma (HCC) smaller than 2 cm in diameter. The non-malignant lesion (left) is elliptic and the HCC (right) is globular.

Table 1 Ultrasonographic findings of hepatocellular carcinomas during their growth

| Size (cm) | No ^a | Halo | Lateral shadow | PEE ^b |
|-----------|-----------------|-------------------|-------------------|-------------------|
| <2 | 16 | 0(0) ^c | 0(0) ^c | 0(0) ^c |
| 2-3 | 23 | 8(35) | 2(9) | 6(26) |
| 3-5 | 32 | 25(78) | 4(13) | 12(38) |

a: Number of cases.

b: Posterior echo enhancement.

c: Percentage is shown in parentheses.

appearance of these 3 characteristics increased with increasing size of tumor (Table 1), and among these 3 characteristics, development of "halo" was the most frequent and diagnostically important. Typical changes in US characteristics of HCC during tumor growth are depicted in Fig. 1.

Comparison of US features of small non-

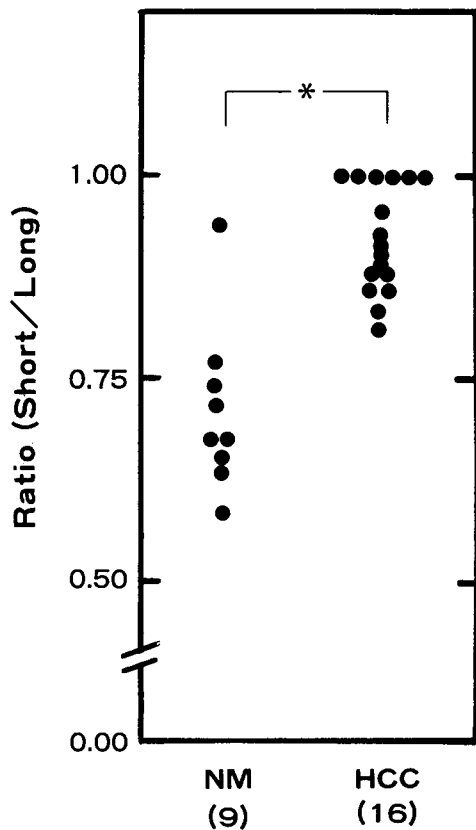


Fig. 3 Ratios of the short to long dimension of small space occupying lesions in the liver less than 2 cm in diameter. NM, Non-malignant lesion (9 cases). HCC, Hepatocellular carcinoma (16 cases). *, $p < 0.001$

malignant SOLs and HCCs less than 2 cm in diameter. Since small HCCs lack the 4 characteristic US findings of HCCs, other differences between small HCCs and non-malignant SOLs were investigated. We have noticed that all HCCs seemed round, while 6 of 9 non-malignant lesions were elliptic. Therefore, the sizes of both types of lesions were measured, and ratios of the short to long dimension were calculated. The ratios in non-malignant and HCCs were 0.71 ± 0.11 and 0.92 ± 0.07 , respectively, suggesting that HCCs were more globular than non-malignant lesions. The difference between the ratios was statistically significant (Figs. 2 and 3).

Hyperechoic small HCCs. Three among 16 small HCCs with a hyperechoic internal pattern are shown in Fig. 4. Although their spherical shape, irregular margin and slightly heterogeneous internal echo pattern suggested that 2 of them were HCCs, all cases were very difficult to distinguish from small hemangiomas because no informations were obtained by CA. One hyperechoic HCC was diagnosed as HCC by CT-arteriography, and it was surgically resected. The following

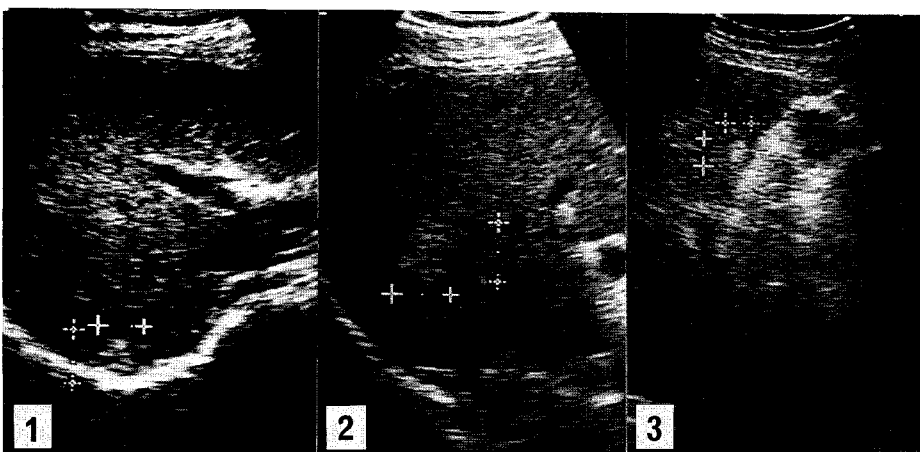


Fig. 4 Hyperechoic small hepatocellular carcinomas. Cases 1 and 2 show a irregular-marginal spherical shape with heterogeneous internal echo pattern. Case 3 shows a clearly discriminated margin with homogeneous internal pattern. Case 1 was diagnosed by CT-arteriography, and cases 2 and 3 were diagnosed by tumor growth.

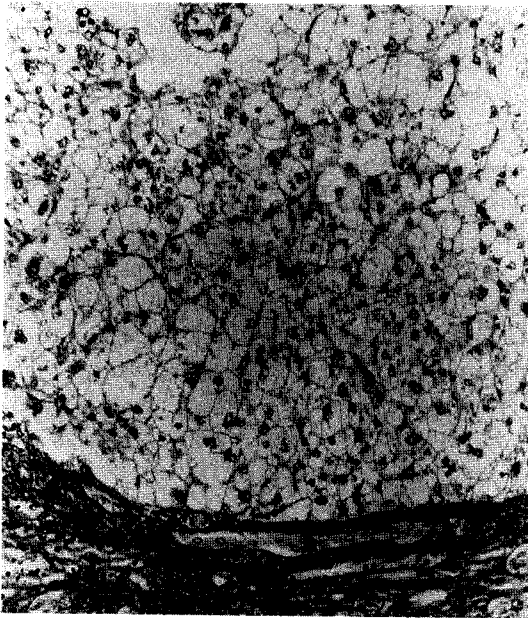


Fig. 5 Histological findings of a hyperechoic small hepatocellular carcinoma. Marked fatty deposition is shown in a clear cell carcinoma. (Hematoxyllin-Eosin, 5.5×15).

histological examination revealed marked fatty deposition in a clear cell carcinoma (Fig. 5).

Serum AFP levels in patients with HCCs of various sizes. Serum AFP levels in patients with HCCs ranged widely from very low to 10000 ng/ml irrespective of tumor size. The percentages of patients with relatively low serum concentrations below 100 ng/ml were 33, 52 and 34% among patients with HCCs less than 2 cm in diameter, 2.1-3.0 cm and 3.1-5.0 cm, respectively. This result indicates the difficulties in detecting HCCs in cirrhotic patients by measuring serum AFP concentrations alone (Fig. 6).

Discussion

Although serial determination of serum AFP has generally been useful for the detecting of HCCs in cirrhotic patients (13-

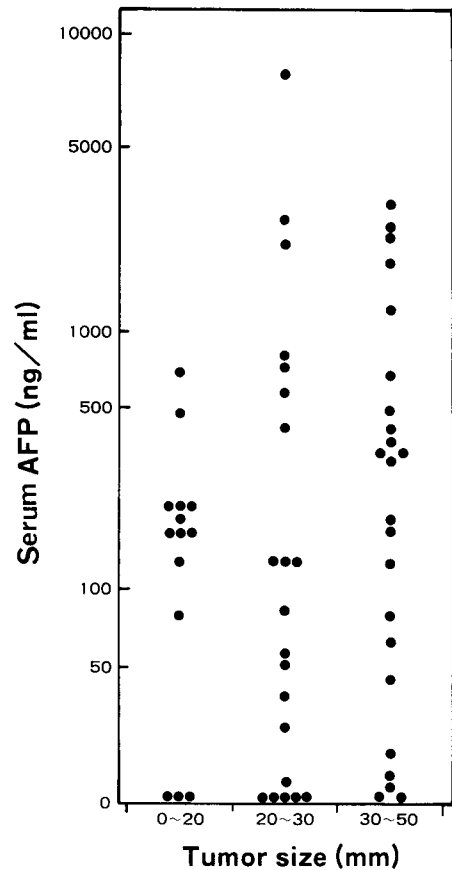


Fig. 6 Serum alpha-fetoprotein levels in patients with hepatocellular carcinomas of various sizes. A clear correlation between the levels and tumor sizes was not observed.

15), this study has clarified that levels were below 100 ng/ml are found in approximately 1/3 of HCC patients. Furthermore, the transient fall in serum elevated AFP in HCC patients (16) should be also mentioned.

Since the employment of real-time US scanning for detecting HCCs in cirrhotic patients, resectable small HCCs have been increasing in number (3). However, it has been revealed that typical US findings of HCCs, such as "mosaic internal echo pattern", "halo", "lateral shadow" and "posterior echo enhancement" were not recognized in minute HCCs smaller than 2 cm in diameter. These features become apparent

as the tumors enlarge, usually to larger than 3 cm in diameter. These natural and serial changes in US findings of HCCs have recently observed in one patient who denied any treatment (17). It should be emphasized that small HCCs less than 2 cm in diameter can be detected only as hypoechoic masses with globular shapes, and no characteristics of HCCs are found by US examination. The exact diagnosis should be positively confirmed by other methods, including ultrasonically guided aspiration biopsy or cytology (18-20).

The criterion we assumed for defining small non-malignant SOLs was probably appropriate because the sizes did not change even in 5 of 9 patients who have been followed-up longer than 42 months since the first detection. Gotoh *et al.* have reported that the overall diagnostic accuracy of US, CT and CA in foci lesions of HCCs less than 1 cm in diameter was only 45% by all 3 methods, and in HCCs of 1-2 cm, their sensitivities were 56, 81 and 56%, respectively (21). Therefore, it seems to be important to find differences in US features between malignant and non-malignant lesions smaller than 2 cm in diameter. The significant difference between malignant and non-malignant lesions in the ratios of short and long dimension (8 of 9 non-malignant SOLs showed a ratio of less than 0.80) indicates that the exact ratio should be calculated routinely. Although precise diagnoses of non-malignant lesions were not made in this study, the lesions may be regenerative nodule, focal nodular hyperplasia or hepatocellular pseudotumor as reported by Nagasue *et al.* (10).

Tanaka *et al.* have reported that 3 hyperechoic masses among 23 relatively small HCCs showed fatty deposition or severe dilated sinusoidal space (22). Chen *et al.* have also reported that one of 13 small HCCs was hyperechoic, and they have sug-

gested that severe tumor necrosis resulted in hyperechoic in US (4). Among their 13 HCCs, 3 cases were histologically of the clear cell carcinoma type. One of our 3 hyperechoic HCCs which was resected also showed marked fatty metamorphosis in a clear cell carcinoma, suggesting that fatty change contributes more to the hyperechoic picture in US than glycogen deposition.

The most impressive fact in this study was that all 3 small hyperechoic HCCs could not be diagnosed even by CA. In differential diagnosis of hyperechoic HCCs from small hemangiomas, Majima *et al.* have recently emphasized the importance of "bright loop phenomenon", which can be observed with 5.0 or 7.5 MHz probe and which corresponds the marginal fatty depositions of HCCs (23). A previous report, however, indicated the difficulty in differentiating between hyperechoic lesions, like HCC, hemangioma, liver cell adenoma, focal nodular hyperplasia and metastatic tumor, by US alone (24). Therefore, further examinations by CT-arteriography and/or needle biopsy should be carried out with strong suspicion of small HCCs when small hyperechoic SOLs are found in the cirrhotic liver and not diagnosed as hemangiomas by either CT or CA.

References

1. Munoz N and Linsell A: Epidemiology of primary liver cancer; in Epidemiology of Cancer of the Digestive Tract, Correa and Haenszel eds, Martinus Nijhoff, Dordrecht (1982) pp 161-195.
2. Okuda K and Liver Cancer Study Group of Japan: Primary liver cancers in Japan. *Cancer* (1980) **45**, 2663-2669.
3. Shinagawa T, Ohto M, Kimura K, Tsunetomi S, Morita M, Saisyō H, Tsuchiya Y, Saotome N, Karasawa E, Miki M, Ueno T and Okuda K: Diagnosis and clinical features of small hepatocellular carcinoma with emphasis of the utility of real-time ultrasonography—A study in 51 patients. *Gastroenterology* (1984) **86**, 495-502.
4. Chen DS, Sheu JC, Sung JL, Lai MY, Lee CS,

- Su CT, Tsang YM, How SW, Wang TH, Yu JY, Yang TH, Wang CY and Hsu CY: Small hepatocellular carcinoma—A clinicopathological study in thirteen patients. *Gastroenterology* (1982) **83**, 1109-1119.
5. Wang KL, Lai CL, Wu PC, Hui WM, Wong KP and Lok ASF: Ultrasonographic studies in hepatic neoplasia: Patterns and comparisons with radiological contrast studies. *Clin Radiol* (1985) **36**, 511-515.
 6. Maringhin A, Cottone M, Sciarrino E, Marceno Mp, Seta FL, Rinaldai F and Pagliaro L: Ultrasonographic and radionuclide detection of hepatocellular carcinoma in cirrhotics with low alpha-fetoprotein levels. *Cancer* (1983) **54**, 2924-2926.
 7. Shen JC, Sung JL, Chen DS, Yu JY, Wang TH, Su CT and Tsang YM: Ultrasonography of small hepatic tumors using high-resolution linear-array real-time instrument. *Radiology* (1984) **150**, 797-802.
 8. Shen JC, Sung JL, Chen DS, Chen DS, Lai MY, Wang TH, Yu JY, Yang PM, Chuang CH, Yang PC, Lee CS, Hsu HC and How AS: Early detection of hepatocellular carcinoma by real-time ultrasonography. *Cancer* (1985) **56**, 660-666.
 9. Tanaka S, Kitamura T, Ohshima A, Umeda K, Okuda S, Ohtani T, Tatsuya M and Yamamoto K: Diagnostic accuracy of ultrasonography for hepatocellular carcinoma. *Jpn J Clin Radiol* (1985) **30**, 257-262.
 10. Makuuchi M, Hasegawa H, Yamazaki S, Bandai Y, Watanabe G and Ito T: Ultrasonic characteristics of the small hepatocellular carcinoma. *Ultrasound Med Biol* (1983) **2**, 489-491.
 11. Kamijyo H, Hirosaka Y and Hata H: Ultrasonic findings of hepatocellular carcinomas in resectable cases (Engl Abstr). *Proc Jpn Soc Ultrasonics* (1980) **36**, 137-138.
 12. Kasai K and Suganami K: The general rules for the clinical and pathological primary liver cancer—Liver Cancer Study of Japan. *Nihon Rinsho* (1982) **40**, 15-25 (in Japanese).
 13. Okuda K, Kotoda K and Obata H: Clinical observations during a relatively early stage of hepatocellular carcinoma, with special reference of serum alpha-fetoprotein levels. *Gastroenterology* (1975) **69**, 226-234.
 14. Chen DS and Sung JL: Serum alpha-fetoprotein in hepatocellular carcinoma. *Cancer* (1977) **40**, 779-783.
 15. Kanematsu T, Sonoda T, Takenaka K, Matsumura T, Sugimachi K and Inokuchi K: The value of ultrasound in the diagnosis and treatment of small hepatocellular carcinoma. *Br J Surg* (1985) **72**, 23-25.
 16. Watanabe A, Sakata T, Shiota T and Nagashia H: Hepatocellular carcinoma of small size. *Am J Med Sci* (1984) **28**, 151-157.
 17. Gandolfi L, Solmi L, Bertoni F.: Small hepatocellular carcinoma: An Italian experience. *Hepato-Gastroenterology* (1987) **34**, 100-102.
 18. Ohto M, Karasawa E, Tsuchiya Y, Kimura K, Saisyo H, Ono T and Okuda K: Ultrasonically guided percutaneous contrast medium injection and aspiration biopsy using a real-time puncture transducer. *Radiology* (1980) **136**, 171-176.
 19. Noshier JL and Plafker J: Fine needle aspiration of the liver with ultrasound guidance. *Radiology* (1980) **136**, 177-180.
 20. Schwerk WB and Schmitz-Moormann PJ: Ultrasonically guided fine-needle biopsies in neoplastic liver diseases and echo pattern of lesions. *Cancer* (1981) **48**, 1469-1477.
 21. Gotoh H, Moriyama N, Shima Y, Muramatsu Y, Takayasu K, Ushio K, Matsue H, Sasagawa M and Yamada T: Diagnostic accuracy of CT, US and angiography in histologically verified hepatocellular carcinoma—Report on 125 foci in 84 cases. *Jpn J Clin Radiol* (1985) **30**, 257-262.
 22. Tanaka S, Kitamura T, Imaoka S, Sasaki Y, Taniguchi H and Ishiguro S: Hepatocellular carcinoma: Sonographic and histologic correlation. *Am J Roentgenol* (1983) **140**, 701-707.
 23. Majima Y, Fujimoto T, Iwai I, Tanaka M, Sakai T, Miura T, Abe M and Tanikawa K: Ultrasonographical characteristic finding "Bright Loop" in hyperechoic hepatocellular carcinoma without halo. *Jpn J Med Ultrasonics (Suppl I)* (1987) **14**, 47-49.
 24. Bree RL, Schwab RE and Neiman HL: Solitary echogenic spot in the liver: Is it diagnostic of a hemangioma?. *Am J Roentgenol* (1983) **140**, 41-45.

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