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Analysis of factors affecting uptake of Tc-99m Sn-N-pyridoxyl-5-methyltryptophan by hepatocellular carcinoma

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We performed Tc-99m PMT imaging in 176 patients with HCC and evaluated factors affecting ^{99m}Tc-PMT uptake by HCC with a logistic model. The probability of HCC showing increase in uptake of the radioisotope was 104.6 times higher in patients with the Ed I type than in those with the Ed III type and 12.1 times higher in patients with a tumor diameter of 5.0–7.9 cm than in those with a tumor diameter of 2.0–5.0 cm. Among the other variables, the serum AFP level and sex were suggested to have effects similar to those of the tumor size on Tc-99m PMT uptake by HCC. The grade of morphological differentiation of the tumor was therefore most markedly related to Tc-99m PMT uptake.

Key words: Tc-99m PMT, hepatocellular carcinoma, grade of tumor differentiation

INTRODUCTION

RECENT ADVANCES in various imaging techniques and treatment methods have markedly improved the prognosis of hepatocellular carcinoma (HCC).[1–4] For the diagnosis of HCC, selective arteriography and liver biopsy under ultrasonic guidance are often performed.[5–7] However, these techniques are invasive, and there is need for non-invasive imaging methods that allow differentiation of HCC from other liver tumors.

Hepatobiliary imaging is useful for the qualitative diagnosis of HCC.[8,9] Among agents used in this imaging, Tc-99m (Sn) N-pyridoxyl-5-methyltryptophan (Tc-99m PMT, Nihon Medi-Physics, Takarazuka, Japan) provides clear visualization of HCC in distinction from the surrounding liver areas.[10] However, the rate of clear visualization of HCC with Tc-99m PMT is only 51–56%.[8,10] In order to make clear the role of Tc-99m PMT imaging in qualitative diagnosis of HCC, it is important to clarify factors affecting Tc-99m PMT uptake by hepatic tumor, and further to determine the degree of their contribution if there are multiple factors.

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Logistic regression analysis has recently been used as a method of multivariate analysis to evaluate the causes of disease in the epidemiological field. When several factors are involved in the development of a certain result, the degree of enhancement of the probability of the result by one factor can be estimated by this method.[11]

In this study, we analyzed possible factors associated with HCC-positive findings in Tc-99m PMT imaging with a logistic model.

MATERIALS AND METHODS

The subjects consisted of 176 patients (143 males and 33 females) with HCC. Their age ranged from 36 to 76 years (mean, 58.7 years). The diagnosis of HCC was made by histological examination in 64 patients, and selective arteriography as well as ultrasonography, CT, and the serum AFP level in the other 112. In the 64 patients, the grade of differentiation of tumor cells was classified according to Edmondson and Steiner's criteria[12] by histological examination after evaluation of Tc-99m PMT uptake. For Tc-99m PMT imaging, 185–555 MBq (5–15 mCi) of Tc-99m PMT was intravenously injected, and imaging of the liver was performed after 5 minutes and 1, 2, 3, and 5 hours. Tc-99m PMT uptake by the tumor was measured on images 3–5 hours after injection. The tumor sites were determined by Tc-99m colloid imaging, CT

Table 1 Patient characteristics and Tc-99m PMT uptake by HCC diagnosed either histologically or clinically

Characteristics	No. cases	Tc-99m PMT uptake		p value
		Increased	Not increased	
		n = 95	n = 81	
Sex				0.044
Male	143 (100%)	72 (50.3%)	71 (49.7%)	
Female	33 (100%)	23 (69.7%)	10 (30.3%)	
Age				0.16
< 50	23 (100%)	8 (34.8%)	15 (65.2%)	
50–59	64 (100%)	33 (51.6%)	31 (48.4%)	
60–69	70 (100%)	42 (60.0%)	28 (40.0%)	
70 ≤	19 (100%)	12 (63.2%)	7 (36.8%)	
Serum bili.				0.92
≤ 1.2 mg/dl	121 (100%)	65 (53.7%)	56 (46.3%)	
1.2 mg/dl <	55 (100%)	30 (54.5%)	25 (45.5%)	
Serum AFP				0.026
< 20 ng/ml	55 (100%)	34 (61.8%)	21 (38.2%)	
20–399 ng/ml	61 (100%)	38 (62.3%)	23 (37.7%)	
400–999 ng/ml	21 (100%)	9 (42.9%)	12 (57.1%)	
1000 ng/ml ≤	39 (100%)	14 (35.9%)	25 (64.1%)	
Size				0.057
2.0–4.9 cm	93 (100%)	48 (51.6%)	45 (48.4%)	
5.0–7.9 cm	42 (100%)	29 (69.0%)	13 (31.0%)	
8.0 cm ≤	41 (100%)	18 (43.9%)	23 (56.1%)	

Table 2 Analysis of factors affecting Tc-99m PMT uptake by hepatic tumors in 176 patients with HCC diagnosed either histologically or clinically

Variables	PRR[a]	95% CI[b]	
		Lower	Upper
Female	1.00[c]		
Male	0.41*	0.17	0.99
Age (< 50)	1.00[c]		
Age (50–59)	1.56	0.54	4.49
Age (60–69)	2.36	0.81	6.91
Age (70 <)	1.41	0.35	5.69
Bili. (≤ 1.2 mg/dl)	1.00[c]		
Bili. (1.2 mg/dl <)	1.04	0.52	2.08
AFP (< 20 ng/ml)	1.00[c]		
AFP (20–399 ng/ml)	1.03	0.47	2.28
AFP (400–999 ng/ml)	0.42	0.14	1.27
AFP (1000 ng/ml <)	0.30*	0.12	0.76
Size (2.0–4.9 cm)	1.00[c]		
Size (5.0–7.9 cm)	2.99*	1.27	7.01
Size (8.0 cm ≤)	1.07	0.47	2.40

*Statistically significant
[a] Positive rate ratio
[b] Confidence interval
[c] Reference group

scan, and selective arteriography. When multiple tumors were present in the liver, the uptake by the largest tumor was measured. The Tc-99m PMT uptake by the tumor was compared with that by the non-tumor area of the liver and was classified into the following two groups. (1) increased uptake (more radioactivity in the tumor than in the surrounding liver tissues). (2) non-increased uptake (radioactivity in the tumor almost equal to or less than that in the surrounding liver tissues). The association between Tc-99m PMT uptake by HCC and various characteristics of the patient (sex, age, and serum bilirubin) and the tumor (the grade of histological differentiation, tumor size, and serum AFP) was evaluated. Patients with HCC less than 2.0 cm in diameter were excluded from the study, because

Table 3 Patient characteristics and Tc-99m PMT uptake by HCC diagnosed histologically

Characteristics	No. cases	Tc-99m PMT uptake		p value
		Increased	Not increased	
		n = 32	n = 32	
Sex				0.49
Male	54 (100%)	26 (48.2%)	28 (51.9%)	
Female	10 (100%)	6 (60.0%)	4 (40.0%)	
Age				0.17
< 50	11 (100%)	3 (27.3%)	8 (72.7%)	
50–59	21 (100%)	11 (52.4%)	10 (47.6%)	
60–69	23 (100%)	15 (65.2%)	8 (34.8%)	
70–79	10 (100%)	3 (30.0%)	7 (70.0%)	
Serum bili.				0.40
≤ 1.2 mg/dl	47 (100%)	25 (53.2%)	22 (46.8%)	
1.2 mg/dl <	17 (100%)	7 (41.2%)	10 (58.8%)	
Serum AFP				0.57
< 20 ng/ml	20 (100%)	12 (60.0%)	8 (40.0%)	
20–399 ng/ml	23 (100%)	12 (52.2%)	11 (47.8%)	
400–999 ng/ml	8 (100%)	3 (37.5%)	5 (62.5%)	
1000 ng/ml ≤	13 (100%)	5 (38.5%)	8 (61.5%)	
Size				0.21
2.0–4.9 cm	37 (100%)	18 (48.6%)	19 (51.4%)	
5.0–7.9 cm	13 (100%)	9 (69.2%)	4 (30.8%)	
8.0 cm ≤	14 (100%)	5 (35.7%)	9 (64.3%)	
Edmondson grade				0.01
Ed I	11 (100%)	10 (90.9%)	1 (9.1%)	
Ed II	36 (100%)	16 (44.4%)	20 (56.6%)	
Ed III	17 (100%)	6 (35.3%)	11 (64.7%)	

Table 4 Analysis of factors affecting Tc-99m PMT uptake by hepatic tumors in 64 patients with HCC diagnosed histologically

Variables	PRR[a]	95% CI[b]	
		Lower	Upper
Female	1.00[c]		
Male	2.57	0.19	34.00
Age (< 50)	1.00[c]		
Age (50–59)	1.86	0.26	13.30
Age (60–69)	6.09	0.73	50.68
Age (70 <)	0.42	0.03	5.47
Bili. (≤ 1.2 mg/dl)	1.00[c]		
Bili. (1.2 mg/dl <)	0.53	0.12	2.26
AFP (< 20 ng/ml)	1.00[c]		
AFP (20–399 ng/ml)	1.33	0.27	6.67
AFP (400–999 ng/ml)	0.37	0.04	3.70
AFP (1000 ng/ml <)	0.60	0.10	3.71
Size (2.0–4.9 cm)	1.00[c]		
Size (5.0–7.9 cm)	12.07*	1.76	83.00
Size (8.0 cm ≤)	2.72	0.38	19.31
Ed I	104.55*	2.70	4054.76
Ed II	1.78	0.37	8.50
Ed III	1.00[c]		

*Statistically significant
[a] Positive rate ratio
[b] Confidence interval
[c] Reference group

they showed a very low incidence of positive results in a Tc-99m PMT study. The significance of the relationship between Tc-99m PMT uptake by HCC and each variable was analyzed by chi-square test. In addition, to exclude the confounding effects among various variables, analysis was done with a logistic model.[11] At first, in all 176 patients, the association between radioactivity uptake by HCC and variables excluding the grade of histological differentiation was analyzed. A similar analysis was then done in 64 patients histologically examined. In the analysis with a logistic model, the covariate variables (sex, age, serum bilirubin, serum AFP, tumor size, and Edmondson's classification) were classified into 2–4 categories depending on the nature of each. For the covariate variables that have n categories, n–1 dummy variables, the values of which were set to be 0 or 1 for each patient, were made and included in the logistic model simultaneously. Odds ratios were calculated by taking the natural exponent of estimated beta coefficients for each dummy variable. In this study, the odds ratio indicates the ratio of the effect of a category on the increase in the incidence of positive results in Tc-99m PMT images to that of a designated baseline category for each factor (positive rate ratio) (Table 3). Analysis was done with PROC LOGISTIC of SAS.[13]

RESULTS

Tc-99m PMT uptake by HCC and various variables

The relationship between Tc-99m PMT uptake by HCC and various variables excluding the grade of histological differentiation was evaluated in the 176 patients with HCC. In Tc-99m PMT images, the incidence of positive results was higher in the females than in the males, in patients aged ≥ 60 years than in those < 60 years, in patients with an AFP level < 400 ng/m*l* than in those with a level ≥ 400 ng/m*l*, and in patients with a tumor 5.0–7.9 cm in diameter than in those with a tumor 2.0–4.9 cm or ≥ 8.0 cm in diameter. Among these variables, sex ($p = 0.044$), and the serum AFP level ($p = 0.026$) were significantly related to HCC-positive findings (Table 1).

In the 64 patients histologically examined, there were relationships similar to those observed in the 176 patients between HCC-positive findings and various variables excluding age and serum bilirubin. However, no significant differences were found in the chi-square test. Only the grade of histological differentiation was significantly related to HCC-positive findings ($p = 0.01$, Table 3).

Analysis with a logistic model

(1) *Tc-99m PMT uptake by HCC and various variables except the grade of histological differentiation in 176 patients with HCC:* Analysis with the logistic model showed a definite relationship between HCC-positive findings and sex, the serum AFP level and the tumor size. In Tc-99m PMT images, the probability of positive findings (positive rate ratio) was 0.41 in the males when the females were used as a reference (1.0), and 0.30 in patients showing an AFP level > 1,000 ng/m*l* when patients with an AFP < 20 ng/m*l* were used as a reference. Similarly, the positive rate ratio was 3.0 in patients with a tumor 5.0–7.9 cm in diameter when those with a tumor 2.0–4.9 cm were used as a reference, showing a significant difference (Table 2).

(2) *Tc-99m PMT uptake by HCC and various variables in 64 patients histologically examined:* Analysis with the logistic model showed a definite relationship between HCC-positive findings and the grade of histological differentiation as well as the tumor size. The probability of positive findings in Tc-99m PMT images (positive rate ratio) in patients with Edmondson I (Ed I) type HCC was 104.6 when those with Ed III HCC were used as a reference, being significantly high. On the other hand, the positive rate ratio in patients with Ed II HCC was 1.8, being only slightly high. The positive rate ratio in patients with a tumor 5.0–7.9 cm in diameter was 12.1, when those with a tumor 2.0–4.9 cm in diameter were used as a reference, showing statistical significance (Table 4).

CASES

Patient 1: a 59-year-old male

He visited our hospital due to general malaise persisting for 3 months. Since ultrasonography showed a tumor (about 6 cm in diameter) in the posterior segment of the right liver lobe, he was admitted. On admission, the serum bilirubin level was 1.2 mg/d*l*, and the serum AFP level was less than 20 ng/m*l*. A Tc-99m Sn colloid image (Fig. 1A) showed a defect in the posterior segment of the right lobe. Imaging 5 hours after a Tc-99m PMT injection (Fig. 1B) revealed marked uptake at the site of the defect. Selective arteriography showed a hypervascular tumor in S_7. Right lobectomy was performed, and the diameter of the resected tumor was 6.0 cm. Histopathologically, the tumor primarily consisted of Ed I type HCC.

Patient 2: a 55-year-old male

He visited our hospital due to decreased appetite persisting for about 1 month. Since ultrasonography showed a tumor (about 10 cm) in the right hepatic lobe, he was admitted. The serum bilirubin level was 0.9 mg/d*l*, and the serum AFP level was less than 20 ng/m*l*. Liver imaging with Tc-99m Sn phytate (Fig. 2A) demonstrated a large filling defect in the dorsal inferior portion of the right hepatic lobe. Tc-99m PMT imaging (Fig. 2B) showed an accumulation of radioactivity in this defect similar to that in the surrounding liver areas. Selective arteriography revealed a large hypervascular tumor extending from S_6 to S_7 (Fig. 2C). Right lobectomy was performed, and the size of the resected tumor was 13 cm. Histologically, the tumor primarily consisted of Ed III type HCC.

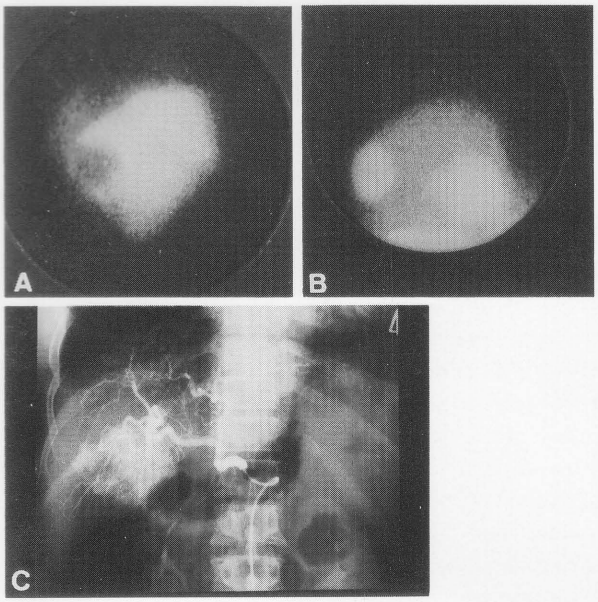

Fig. 1 A case of hepatoma. The right lateral view of Tc-99m Sn colloid image shows filling defect in the posterior portion of the right hepatic portion (A). The Tc-99m PMT image shows increased uptake of radioactivity in the same site (B). The selective arteriogram reveals a hypervascular mass in S_7 of the liver (C).

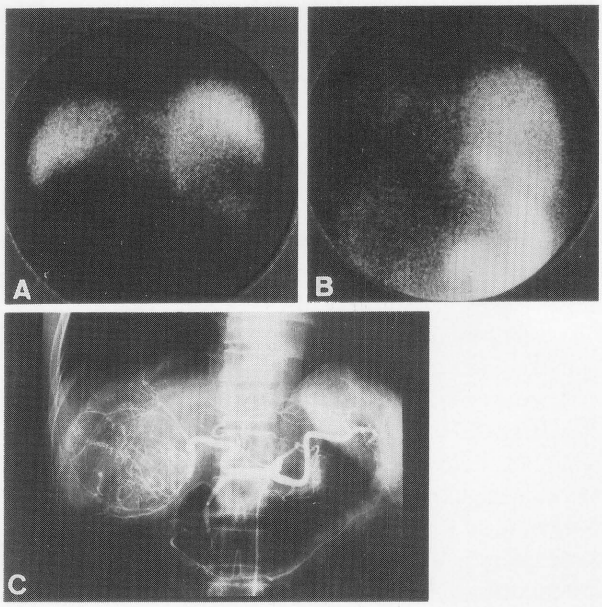

Fig. 2 A case of hepatoma. The posterior Tc-99m PMT image reveals equal uptake of radioactivity in the inferoposterior portion of the right liver (B), where a large filling defect is noted on the Tc-99m Sn phytate image (A), and a hypervascular tumor is seen on the selective arteriogram (C).

DISCUSSION

Hepatobiliary imaging is considered to be useful for the qualitative diagnosis of HCC.[8,9] Tc-99m PMT is superior to other agents for hepatobiliary imaging in clear visualization of HCC as a positive image. However, only about half of HCCs are positively visualized even by Tc-99m PMT imaging. The other HCCs are difficult to differentiate from other hepatic tumors. In this study, we analyzed patient and tumor factors affecting the results of Tc-99m PMT imaging of HCC. The possible association between Tc-99m PMT uptake by HCC and various variables excluding the grade of histological differentiation was evaluated with a logistic model in the 176 patients. The incidence of visualization of HCC as a positive image (positive rate ratio) was 3.0 times higher in patients with an HCC size of 5.0–7.9 cm than in those with an HCC size of 2.0–4.9 cm. The positive rate ratio was 0.30 times lower in patients with an AFP ≥ 1,000 ng/m*l* than in those with an AFP < 20 ng/m*l* and 0.41 times lower in the males than in the females. In analysis with a logistic model, when A in two categories (A and B) is used as a reference for a certain variable, the reciprocal of the positive rate ratio of the other (B) is considered to approximate the positive rate ratio of the former (A) when the latter (B) is used as a reference. Therefore, the probability of positive findings increased by 3.3 (1/0.30) times in patients with an AFP level < 20 ng/m*l* when patients with an AFP level ≥ 1,000 ng/m*l* were used as a reference and by 2.4 times (1/0.41) in the females when males were used as a reference. Analysis of HCC in the 176 patients showed that 3 variables (sex, serum AFP level and tumor size) were related to Tc-99m PMT uptake by the hepatic tumor to similar degrees.

On the other hand, in the 64 patients with HCC in whom the grade of histological differentiation could be determined, the probability of HCC-positive findings was 105 times higher in patients with Ed I type HCC than in those with Ed III type HCC, the difference being significant. The positive rate ratio was 12.1 times higher in patients with an HCC 5.0–7.9 cm in diameter than in those with an HCC 2.0–4.9 cm in diameter, the difference being significant. The ratio was also 2.7 times higher in patients with an HCC of more than 8.0 cm in diameter than in those with an HCC 2.0–4.9 cm in diameter, although the difference was not significant.

The uptake of a hepatobiliary imaging agent by the HCC is thought to be due to the hepatocytic function remaining in the hepatic tumor. A functionally differentiated HCC is also presumed to be morphologically differentiated. The degree of histologic differentiation of HCC has been reported to be significantly correlated with the uptake of hepatobiliary imaging agents by the hepatic tumor.[14] However, it is important to quantitatively estimate the pure effect of histological features on the tumor uptake of Tc-99m PMT after removing the effects of other factors. In the present study with a logistic model, the grade of morphological differentiation was shown to be the predominant determining factor in the taking up of Tc-99m PMT by HCC among the various factors studied. The tumor size was also an independent factor influencing the

Tc-99m PMT uptake by HCC after adjustment for the effects of other variables, even though it had a smaller effect on the tumor uptake of radioactivity than the histological findings. The lower incidence of HCC showing positive results on Tc-99m PMT imaging in patients with an HCC 2.0–4.9 cm in diameter than in those with an HCC 5.0–7.9 cm in diameter might partially be due to the limitation in detection of small HCC by this method. On the other hand, the lower odds ratio for positive visualization of HCC in patients with a tumor larger than 8.0 cm in diameter as compared with that in those 5.0–7.9 cm in diameter might be caused by the presence of hypovascularity and the necrotic tissues in the advanced tumors.[15]

Unlike the analysis in all the patients, analysis involving histological findings in the 64 patients showed no definite effects of serum AFP or sex on Tc-99m PMT uptake by HCC. This may be due to the smaller number of patients and addition of the grade of histological differentiation to the variables. In the 64 patients histologically examined, variables excluding Edmondson's classification were analyzed with a logistic model. The positive rate ratio between categories with different AFP levels and between the sexes was similar to that obtained in the analysis of the 176 patients, though it was not significant. In the 64 patients, sex and the AFP level may also have affected Tc-99m PMT uptake by HCC. In the animal experiments, the serum AFP level was found to be related to the grade of histological differentiation.[16,17] This relationship may explain why the serum AFP level affected the Tc-99m PMT uptake by HCC in the study of the 176 patients. However, in the analysis of the 64 patients, the marked effects of the grade of histological differentiation on ^{99m}Tc-PMT uptake by HCC might have resulted in underestimation of the effects of AFP. In contrast, the grade of morphological differentiation of HCC has not been reported to differ with the sex, to our knowledge. The reason why sex was seen to affect Tc-99m PMT uptake by HCC in the study of the 176 patients, therefore, is not yet clear. In order to determine whether AFP and sex are associated with HCC-positive findings in ^{99m}Tc-PMT imaging, additional cases of HCC at known grades of histological differentiation are needed.

Extrahepatic metastases of HCC taking up hepatobiliary imaging agents have been reported to frequently produce bile pigments in tumor cells.[18,19] However, it has not yet been clarified whether the uptake of a hepatobiliary imaging agent by the primary tumor of HCC is related to the bile formation in the tumor tissues or not. Of the 64 patients with HCC examined histologically, only 7 showed morphological evidence of bile formation in the tumor tissues of the liver. All 7 patients showed increased uptake of Tc-99m PMT by the hepatic tumors, whereas 32 (56.1%) of the remaining 57 patients who showed no bile pigments in the tumor tissues, did not take up a great deal of Tc-99m PMT ($p < 0.02$). The ability of hepatic tumors to produce bile was therefore also proved to be closely correlated with Tc-99m PMT uptake by the hepatic tumors. In the estimation of the effects of various factors including the effect of bile production on tumor uptake of Tc-99m PMT with a logistic model, the positive rate ratios for each level of variables did not converge into meaningful values as a whole. The difficulty in the analysis might be caused by the low frequency of HCC production of bile pigments despite the close relationship between the ability to form bile in the tumor cells and the tumor uptake of radioactivity. To accurately evaluate the effect of bile formation by HCC on Tc-99m PMT uptake by the hepatic tumor, it is necessary to analyze more cases of HCC examined histologically for the presence of bile pigments.

In our study, the grade of Tc-99m PMT uptake by the hepatic tumor was classified into two groups; "increased uptake" and "non-increased uptake". The latter group included two conditions of radioactivity uptake by the hepatic tumor; 1) equal uptake which showed radioactivity in the hepatic tumor equal to that in the surrounding liver tissues, and 2) decreased uptake showing less radioactivity in the hepatic tumor than in the surrounding liver. However, in patients with small hepatic tumors which did not show any filling defect on the liver images with Tc-99m colloid or Tc-99m PMT, it is difficult to differentiate the two conditions of Tc-99m PMT uptake by the hepatic tumor. Therefore, these two grades of Tc-99m PMT uptake by the hepatic tumor were combined into the group "non-increased uptake".

In the present study, the grade of morphological differentiation was most markedly related to Tc-99m PMT uptake by HCC. The tumor size was also related, but to a lesser degree. The serum AFP level and sex had effects similar to those of the tumor size. Thus, imaging of the hepatobiliary system not only is useful for qualitatively diagnosing HCC but also provides information associated with the grade of morphological differentiation.

A recent report suggested the usefulness of MRI for differentiating early stage Ed I type HCC from Ed II or III type HCC.[20] However, in about a half of Ed I liver tumors, the tumor and the surrounding areas were noted to be isointense on T_1- and T_2- weighted images.[20] On the other hand, there is a report that evaluated the grade of the differentiation of glucose metabolism of HCC by means of positron camera and ^{18}FDG.[21] This method is still very expensive. In future, however, the two methods may be used to determine the grade of HCC differentiation.

Even Ed III HCC incorporates Tc-99m PMT, though its incidence is lower than Ed I and II HCC. Therefore, the Tc-99m PMT uptake by HCC is not always in complete agreement with the grade of morphological differentiation. The uptake of a hepatobiliary agent by HCC originally represents the degree of functional differentiation of tumor cells. Tc-99m PMT imaging is a simple and inexpensive method. We hope that this method, which provides a specific index of the grade of HCC differentiation,

will be widely used.

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