Relationship of Uptake of Technetium-99m(Sn)-N-Pyridoxyl-5-Methyltryptophan by Hepatocellular Carcinoma to Prognosis

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The relationship of technetium-99m(Sn)-N-pyridoxyl-5-methyltryptophan (^{99m}Tc-PMT) uptake by hepatic tumors to survival was studied in 162 cases of hepatocellular carcinoma (HCC). The median survival of 82 patients in whom hepatic tumors showed increased uptake in delayed ^{99m}Tc-PMT imaging was 1013 days, which was significantly longer than the survival time of 398.5 days of 80 patients in whom hepatic tumors did not show increased uptake of radioactivity ($p < 0.002$). The relationship between the ability of hepatic tumors to take up ^{99m}Tc-PMT and survival was also analyzed in patients with HCC showing filling defects in ^{99m}Tc-colloid liver images and, in relation to the therapy, serum values of bilirubin and alpha-fetoprotein. Results indicated that the degree of ^{99m}Tc-PMT uptake by hepatic tumors is closely correlated with the prognosis of patients with HCC.

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Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in many countries in Asia and Africa, and as its prognosis is poor (*1–3*), urgent factors include the establishment of efficient systems for prevention, detection, and treatment. Recently, the prognosis of HCC has been reported to have improved due to the development of new diagnostic techniques, such as ultrasonography (US), computed tomography (CT), selective arteriography, and better therapeutic treatments such as surgical techniques, new chemotherapeutic agents, and transcatheter arterial embolization (TAE) therapy (*4–7*). The survival of patients with HCC is reportedly influenced by various factors, such as sex, age, treatment, the presence of liver cirrhosis, the serum levels of bilirubin and AFP, encapsulation, and histologic conditions (*8–14*). In general, the prognosis is worse in cases of less differentiated malignant tumor (*15*), and there are reports of a positive correlation between the degree of differentiation of HCC and the prognosis (*14,16*).

Recently, we reported the value of delayed hepatobiliary imaging with technetium-99m(Sn)-N-pyridoxyl-5-methyltryptophan (^{99m}Tc-PMT, Nihon Medi-physics, Takarazuka, Japan) for increasing the specificity of diagnosing HCC, correlating the extent of ^{99m}Tc-PMT uptake by hepatic tumors, and differentiating tumor cells (*17–18*). Calvet et al. also observed a relationship between ^{99m}Tc-diisopropyl iminodiacetic acid uptake by hepatic tumors and the extent of their cytologic differentiation (*19*). Thus, survival of patients with HCCs that actively take up hepatobiliary imaging agents may be better than that of patients with carcinomas that do not take up these agents. In this study, we examined the relationship of delayed ^{99m}Tc-PMT imaging and survival of patients with HCC.

MATERIALS AND METHODS

Between February 1983 and December 1987, 162 patients with HCC (134 men and 28 women, ages 36–75 yr) were examined by ^{99m}Tc-PMT imaging. In 63 of these patients, a diagnosis of HCC was made by histologic examination of specimens obtained by necropsy, surgery, or biopsy, and in the remaining 99 patients, the diagnosis was based on typical arteriographic findings (*20–22*) as well as findings on ultrasonography, CT scanning, and radionuclide imaging using ^{99m}Tc-PMT, gallium-67-citrate, or ^{99m}Tc-colloid, and/or on serum AFP levels. The patients were classified into three groups in terms of hepatic functional reserves according to Child's classification as follows: A—108 patients with good hepatic function; B—35 patients with moderately impaired hepatic function; C—19 patients with advanced hepatic dysfunction (*23*). Survival times were calculated from the day when ^{99m}Tc-PMT imaging was performed.

In this study, the minimum observation period of survival was 13 mo. Images were obtained at 5 and 10 min and at 1, 3, and 5 hr after i.v. injection of 4.9–15.0 mCi of ^{99m}Tc-PMT. Uptake of radioactivity by hepatic tumors was evaluated on delayed ^{99m}Tc-PMT images taken 3–5 hr after injection of the

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radioisotope as reported (*17*), in comparison with ^{99m}Tc-colloid liver images. In four patients who showed filling defects in ^{99m}Tc-PMT images taken 5–10 min after injection, these early images were used instead of the ^{99m}Tc-colloid images. In 45 patients, who did not show filling defects in either of the liver images, we assessed whether focal increase of ^{99m}Tc-PMT was in the tumor area in the liver, which was determined by CT scanning and selective arteriography.

The uptake of ^{99m}Tc-PMT radioactivity by hepatic tumors was grouped as follows: Group 1—increased uptake (radioactivity in the tumor was more than that in the surrounding normal liver in 82 patients) or Group 2—no increased uptake (radioactivity in the tumor was similar to or less than that in the surrounding normal liver in 80 patients). Group 2 was then subdivided on the basis of ^{99m}Tc-PMT uptake by the hepatic tumor as follows: (a) equilibrated uptake, (b) less uptake than that in surrounding normal liver, and (c) unassessable uptake (UA); that is, patients with tumors showing no filling defect in ^{99m}Tc-colloid images and no increased uptake of radioactivity in delayed ^{99m}Tc-PMT images. In the patients with multiple hepatic tumors, ^{99m}Tc-PMT uptake by the tumors was evaluated in the largest tumor in the liver.

Hepatocellular carcinomas were treated after ^{99m}Tc-PMT imaging as follows: surgically (48 patients), ranging from enucleation to extended lobectomy; TAE therapy (85 patients) using ethiodized oil, anticancer drugs (Doxorubicin, Kyowa Hakko Co., Tokyo, Japan or Cisplatin, Nihon Kayaku Co., Tokyo, Japan), and a gelatin sponge (Upjohn Co., Kalamazoo, MI) (*6*); and systemic chemotherapy (29 patients) by oral or rectal administration of tegafur or tegafur-uracil (Taiho Pharmaceuticals Co., Tokyo, Japan). The differences in age, sex, serum levels of albumin, bilirubin and AFP, therapeutic modalities, the presence of liver cirrhosis, Child's classes (*23*), maximum tumor size, and tumor numbers in the Group 1 and 2 patients were assessed by the chi-square test with Yate's correction. The survival of patients was analyzed by the method of Kaplan and Meier (*24*) and the generalized Wilcoxon test (*25*).

RESULTS

Technetium-99m-PMT Uptake by HCC

In 82 patients (Group 1), the HCCs showed increased uptake of ^{99m}Tc-PMT. In the remaining 80 patients (Group 2), 25 tumors showed equilibrated uptake, 27 decreased uptake, corresponding to filling defects seen in the ^{99m}Tc-colloid liver images or ^{99m}Tc-PMT images taken soon after injection of the radioisotope, and 28 did not show filling defects in either the colloid images or early ^{99m}Tc-PMT images, nor was there increased uptake in the delayed ^{99m}Tc-PMT images.

Clinical Characteristics

There was no significant difference in the mean ages or serum albumin levels between Group 1 and Group 2 patients (Table 1). Sex, frequency of liver cirrhosis, Child's classes, tumor size classified as less and more than 5.0 cm in diameter, and tumor numbers, classified as solitary and multiple, were also not significantly different in the two groups (Table 1). The mean serum bilirubin level was, however, definitely less in Group 1

TABLE 1
Clinical Data on Patients with HCC Examined by ^{99m}Tc-PMT Imaging

Data	Tc-99m PMT imaging: Increased uptake	Tc-99m PMT imaging: Not increased uptake
Number	82	80
Age (mean ± s.d.)	59.62 ± 0.81	58.08 ± 0.81
Sex		
Male (no.)	64	70
Female (no.)	18	10
Liver cirrhosis		
With (no.)	59	62
Without (no.)	22	18
Serum albumin (mean ± s.d., g/dl)	3.71 ± 0.05	3.63 ± 0.06
Serum bilirubin (mean ± s.d., mg/dl)*	1.05 ± 0.05	1.26 ± 0.09
No. of patients		
< = 1.2 mg/dl	58	51
1.3–2.0 mg/dl	23	24
2.1–3.0 mg/dl	1	1
3.0 mg/dl <	0	4
Child's class		
A (no.)	57	51
B (no.)	18	17
C (no.)	7	12
Tumor size		
5.0 cm < (no.)	39	34
< = 5.0 cm (no.)	43	46
Tumor numbers in the liver		
Solitary (no.)	31	26
Multiple (no.)	51	54
Serum AFP*		
< 20 ng/ml (no.)	29	24
20–399 ng/ml (no.)	33	19
400–999 ng/ml (no.)	8	12
1,000 ng/ml =,< (no.)	12	25
Treatment		
Resection (no.)	23	25
TA chemoembolization† (no.)	44	41
Systemic chemotherapy (no.)	15	14

* Significant difference between the distribution of numbers or mean values in the two groups with hepatic tumors showing increased and not increased uptake ($p < 0.05$).
† Transcatheter arterial chemoembolization.

patients (1.05 mg/dl) than in Group 2 patients (1.26 mg/dl) (Table 1, $p < 0.05$). Furthermore, serum AFP was either not detectable or was present at low levels (<400 ng/ml) in 62 (75.6%) Group 1 patients and in only 43 (53.8%) Group 2 patients (Table 1, $p < 0.05$).

Relationship Between PMT Uptake and Survival

Colloid-Liver and PMT Images. Of the 117 HCCs showing filling defects in the colloid images or the early PMT images, 65 (Group 1) showed increased uptake, 25 equilibrated uptake (Group 2), and 27 decreased uptake of ^{99m}Tc-PMT (Group 2). The median survival of the 65 patients with tumors showing increased uptake was 958.5 days, 331.0 days for 25 patients with tumors showing equilibrated uptake, and 270.0 days for 27 patients with tumors showing decreased uptake. The survival of the first group of 65 patients was significantly longer than those of the other two groups ($p < 0.0002$), in which survival was not significantly different.

Comparison of Survival Between Groups 1 and 2. Of the 162 patients with HCC, Group 1 patients lived significantly longer than Group 2 patients. The median survival times were respectively 1013 days and 398.5 days ($p < 0.002$, Fig. 1).

Median Survival of Patients Treated Surgically or with TAE Therapy. Forty-eight patients were treated surgically. Tumors in 23 of these patients showed increased PMT radioactivity uptake; there was no increase in PMT uptake in the remaining 25 patients. The former group, with a survival rate of 57.5% on Day 2137, lived significantly longer than the latter, in whom the median survival was 1576 days ($p < 0.05$, Fig. 2). Moreover, one year after ^{99m}Tc-PMT imaging, the survival rate of the former group was 100%, while that of the latter was 76% ($p < 0.05$).

Of the 85 patients treated with TAE therapy, tumors in 44 patients showed increased ^{99m}Tc-PMT uptake, whereas tumors in the other 41 patients did not. The survival of the former group was definitely longer than that of the latter: median survival was 958 days and 358 days, respectively ($p < 0.002$, Fig. 3).

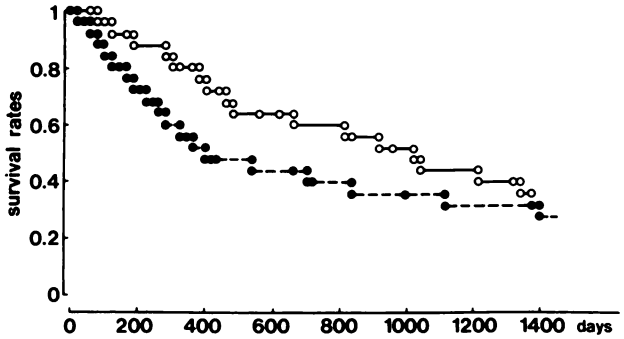

FIGURE 1
Survival curves for 162 patients with hepatoma. Of the patients studied, 82 had hepatic tumors that showed increased ^{99m}Tc-PMT uptake (open circles). These patients lived significantly longer than the other 80 in whom tumors did not show increased PMT uptake (solid circles) ($p < 0.002$). Double circles represent overlapping values.

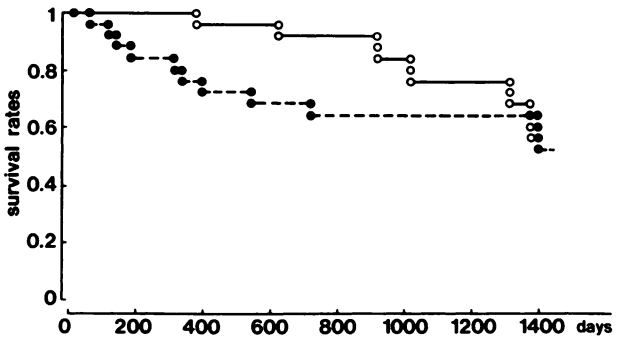

FIGURE 2
Survival curves for 48 patients treated with hepatic resection. Of the 48 patients, the 25 in whom tumors showed increased PMT uptake (open circles) lived significantly longer than the 23 in whom tumors did not show increased uptake (solid circles) ($p < 0.05$). Double circles represent overlapping values.

Relationship of ^{99m}Tc-PMT Uptake and Serum AFP Levels. The serum AFP level was more than 400 ng/ml in 57 of the 162 patients with HCC and less than 400 ng/ml in the other 105 patients. Of the 57 with an increased AFP value, 20 patients in whom tumors showed increased ^{99m}Tc-PMT uptake tended to live slightly longer than the other 37 in whom the tumors did not show increased radioactivity uptake, although the difference was not statistically significant. Median survival of the two groups was 396 days and 254 days, respectively. Of the 105 patients showing little or no increase in serum AFP level, 62 patients in whom tumors showed increased ^{99m}Tc-PMT uptake survived significantly longer than the 43 in whom tumors showed no increased uptake. Median survival was 1038 days and 702 days, respectively ($p < 0.05$).

Prognosis of Patients with Hepatoma and Normal Serum Bilirubin Levels. Of 109 patients with serum bilirubin less than 1.2 mg/dl, 60 patients with tumors that showed increased ^{99m}Tc-PMT uptake had a median survival time of 1013 days, whereas 49 patients with tumors that did not show increased radioactivity uptake had a median survival time of 407 days ($p < 0.02$).

CASE REPORTS

The following three cases illustrate the prognostic benefits of ^{99m}Tc-PMT imaging for HCC.

Case 1

A 57-yr-old man suspected of having a hepatic tumor was admitted to this hospital. Delayed ^{99m}Tc-PMT imaging (Fig. 4A) showed localized, increased uptake of radioactivity in a large area corresponding to the filling defect shown in the left hepatic lobe with ^{99m}Tc-phytate liver imaging (Fig. 4B). A giant, hypervascular tumor was revealed in the left hepatic lobe on selective arteri-

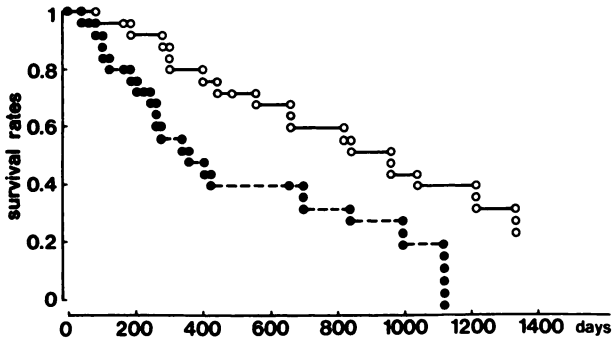

FIGURE 3
Survival curves for 85 patients treated with TAE. Forty-four patients with tumors that showed increased PMT uptake (open circles) lived significantly longer than the other 41 in whom tumors did not show increased uptake (solid circles) ($p < 0.002$). Double circles represent overlapping values.

ography (Fig. 4C). After lateral segmentectomy of the liver, a tumor of 12 × 11 cm was found. Histologic diagnosis of HCC was made after examination of resected tumor specimens. The patient survived for 5 yr and 10 mo after ^{99m}Tc-PMT examination and died due to esophageal varices rupture aggravated by the relapse of the hepatic tumor.

Case 2

A 61-yr-old man suspected of having a hepatic tumor was referred to this hospital from another hospital, in which he had been treated for liver cirrhosis for about 10 yr. His serum AFP value was 58.2 ng/ml. Delayed ^{99m}Tc-PMT imaging (Fig. 5A) showed localized accumulation of radioactivity in a large area corresponding to a filling defect shown in the right hepatic lobe with ^{99m}Tc-phytate liver imaging (Fig. 5B). Selective arteriography revealed a giant, hypervascular tumor of 14 × 13 cm, which was strongly suggested to be HCC (Fig. 5C). TAE therapy using cisplatin, ethiodized oil, and gelatin sponge was performed. He survived for 3 yr and 3 mo after the ^{99m}Tc-PMT study and died of hepatic failure caused by relapse of the hepatic tumor.

Case 3

A 63-yr-old man suspected of having HCC was admitted to this hospital. Technetium-99m-phytate liver imaging (Fig. 6A) showed a filling defect in the right hepatic lobe, where no increase in radioactivity uptake was seen on delayed ^{99m}Tc-PMT imaging (Fig. 6B). Selective arteriography revealed the presence of a nodular tumor in the right hepatic lobe (Fig. 6C). Anterior segmentectomy of the right hepatic lobe revealed a 3 × 3.5-cm tumor in segment 5 and several small metastases in segment 8. Histologic diagnosis of HCC was made on specimens obtained at surgery. The patient died of hepatic failure caused by recurrence of the hepatic tumor about one year after the ^{99m}Tc-PMT study.

DISCUSSION

In general, the degree of differentiation of a malignant tumor is thought to provide a clue to the prognosis:

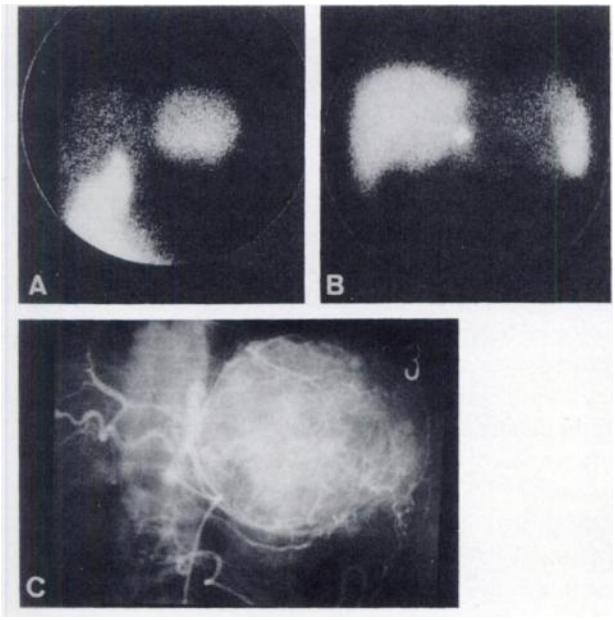

FIGURE 4
A delayed ^{99m}Tc-PMT image (A) showing increased radioactivity uptake in the left hepatic lobe, corresponding to a large filling defect seen in a ^{99m}Tc-phytate liver image (B). A selective arteriogram showing a hypervascular tumor in the left hepatic lobe (C).

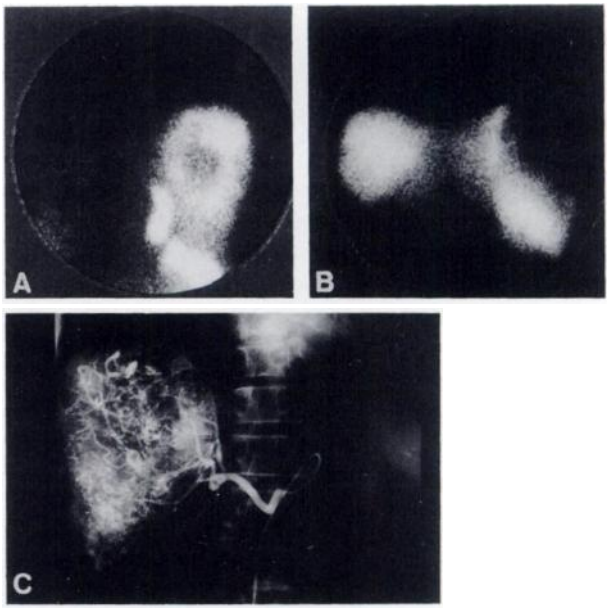

FIGURE 5
A posterior view of a delayed ^{99m}Tc-PMT image (A) showing increased uptake of radioactivity in a large area corresponding to the filling defect seen in the right hepatic lobe in a posterior view of the ^{99m}Tc-phytate image (B). A selective arteriogram (C) showing a large, hypervascular tumor in the right hepatic lobe.

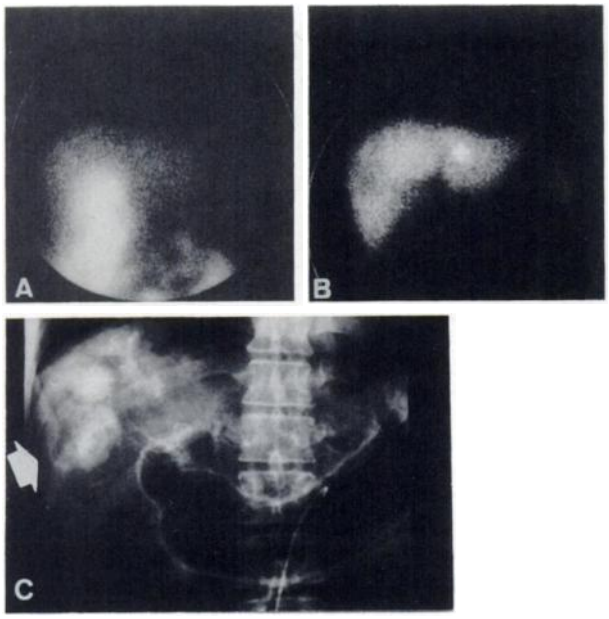

FIGURE 6
A delayed ^{99m}Tc-PMT image (A) shows no increased uptake of radioactivity in the tumor site corresponding to the filling defect in the right hepatic lobe seen in the ^{99m}Tc-phytate liver image (B). A selective arteriogram (C) shows a nodular tumor that was stained with contrast medium (arrow) in the capillary phase in the right hepatic lobe.

the less differentiated the tumor, the poorer the prognosis (*15*). There are reports that the prognosis of patients with HCC is closely related with the macroscopic, histologic, and cytologic characteristics of the tumor (*10–14,16*). Some of these reports noted that HCCs showing morphologic features associated with differentiation indicated a favorable prognosis (*12,14,16*). However, it is difficult to determine the exact relationship between the characteristics of hepatomas and survival from the microscopic features of tumor tissues, because both the histologic type and the degree of cytologic differentiation often vary in different parts of a single tumor (*14*). Thus, a simple, objective method is necessary for assessing the characteristics of a tumor. Hepatoma cells often show some functionally differentiated characters, such as ability to produce glycogen, fat, or bile (*13,26–27*). Positive imaging of HCCs using hepatobiliary agents is the only easy method available for determining the hepatocytic function of tumor cells. Furthermore, the degree of hepatobiliary uptake by hepatic tumors reportedly correlates with the extent of morphologic differentiation of the tumor cells (*18,19*). Therefore, we studied the relationship between the results of delayed ^{99m}Tc-PMT imaging and the survival of patients with HCC.

In the present study, 162 patients with HCC were classified into two groups on the basis of the degree of ^{99m}Tc-PMT uptake by their tumors. In 82 patients (Group 1), the tumors showed increased uptake of radioactivity, and in the other 80 (Group 2), the tumors did not show increased uptake. We found that Group 1 patients lived significantly longer than Group 2 patients. In assessing ^{99m}Tc-PMT uptake by hepatic tumors, it was difficult to distinguish between hepatic tumors showing equilibrated uptake and decreased uptake when the hepatic tumors were small and, if at all, barely detectable in ^{99m}Tc-colloid images or early ^{99m}Tc-PMT images. Accordingly, we combined the three subgroups showing equilibrated, decreased, and unassessable uptakes into one group classified as tumors not showing increased uptake. In our series, many of the patients in whom the tumors showed increased uptake of ^{99m}Tc-PMT lived longer than those in whom the tumors showed equilibrated or decreased uptake of radioactivity, but there was no significant difference between the survival of patients with tumors showing equilibrated and decreased uptake of ^{99m}Tc-PMT.

Many factors affect the prognosis of patients with hepatocellular carcinoma (*8–15*). We examined whether the distributions of various parameters were different in the two groups in whom tumors showed increase and no increase in radioactivity uptake. We found no significant difference between the groups in age distribution, sex, therapeutic treatments, serum albumin levels, tumor sizes, tumor numbers, or Child's classes. However, the mean serum bilirubin level and the frequency of patients with an increased serum AFP level were significantly higher in the group in which tumors did not show increased ^{99m}Tc-PMT uptake.

The uptake of hepatobiliary agents by liver parenchymal cells is known to be inhibited in hyperbilirubinemia (*28*). Furthermore, the capacity of hepatoma tissues to take up ^{99m}Tc-PMT is generally thought to be less than that of normal liver tissues, because in early images taken 5 min after injection of ^{99m}Tc-PMT the radioactivity taken up by the tumor area was less than that in the adjacent normal liver (*29*). Therefore, the ability of hepatic tumors to take up ^{99m}Tc-PMT might be inhibited more than that of normal liver by hyperbilirubinemia. However, among the 16 patients with serum bilirubin levels of more than 1.2 mg/dl in our series, increased tumor uptake of ^{99m}Tc-PMT was seen in three patients with hepatoma of Edmondson's Grade I, and in only two with hepatoma of Edmondson's Grades II–III. In patients with hyperbilirubinemia, therefore, well-differentiated hepatomas also tend to show increased uptake of ^{99m}Tc-PMT more frequently than intermediately differentiated hepatic tumors. The prognosis of hepatoma patients with hyperbilirubinemia is reportedly poor (*9–10*). In this study, we could not clarify the relationship between the results of ^{99m}Tc-PMT imaging and the survival of patients with hyperbilirubinemia, because very few patients in whom tumors showed increased uptake of ^{99m}Tc-PMT had elevated serum bilirubin levels. Our results showed, however, that ac-

tive uptake of ^{99m}Tc-PMT by hepatic tumors is an indication of good survival of patients with a normal serum bilirubin level.

In our series, the frequency of patients with a low serum AFP level of less than 400 ng/ml was higher in the group in which tumors showed increased uptake of tumor, and conversely the frequency of patients with a high AFP level of more than 400 ng/ml was higher in the other group. Among the patients with AFP levels of more than 400 ng/ml, there was no significant difference in survival between the groups in which the tumors did and did not show increased radioactivity uptake. Ihde et al. and Alpert et al. have found poor prognoses for patients with HCC showing a high serum AFP level (*10,30*). Furthermore, experimental studies have shown that cell lines of rapidly growing hepatomas produce high titers of AFP and that AFP production rate correlates with the degree of tumor cell malignancy (*31–32*). Moreover, serum AFP levels correlate with the total number of tumor cells producing and excreting AFP. Accordingly, a highly elevated serum AFP level also appears to be an indication of poor survival for patients with hepatoma unrelated to the degree of ^{99m}Tc-PMT uptake by hepatic tumors. Patients with serum AFP levels of less than 400 ng/ml and hepatomas that showed increased uptake of ^{99m}Tc-PMT survived significantly longer than those with tumors that did not show increased ^{99m}Tc-PMT uptake. These results, therefore, indicate that in patients with HCCs, in whom serum AFP was undetectable or low, the results of ^{99m}Tc-PMT imaging closely correlated with the prognosis.

Okuda et al. reported that the gross pattern of HCCs, classified on the basis of their growth in relation to nontumorous liver parenchyma, is different in Japan from that in the U.S. and South Africa. In Japan, the expanding type is the most frequent and is often associated with encapsulation, whereas in the U.S. and South Africa the spreading type is the most frequent (*33*). Furthermore, patients with the expanding type generally survive better than those with the spreading type (*14*). On the other hand, Kiriyama et al. reported that the frequency of hepatic tumors showing increased radioactivity uptake of ^{99m}Tc-PMT was higher among patients with hepatomas of the nodular type than among those with other types, such as massive or diffuse (*34*). Among the gross patterns of HCCs, the expanding and nodular types are distinct entities classified by different criteria (*33,36*). On the basis of these criteria, the nodular type seems to be included in the expanding type and constitutes a large proportion of cases (*33,36*). Therefore, based on these reports (*12,33–35*), one reason for the longer survival of patients in whom the tumors showed increased uptake of ^{99m}Tc-PMT may be due to a difference in the gross anatomical features of their tumors.

Various kinds of hepatobiliary imaging agents have been reported to accumulate in HCC (*17,37–46*). There are several reports that ^{99m}Tc-PMT imaging is useful for detection of hepatic tumors (*17–18,34,44,46*). The positive rate of detection of hepatic tumors by hepatobiliary imaging in our current series using ^{99m}Tc-PMT (50.6%) was higher than in other studies, in which it was determined to be 3.8%–42.1% by ^{99m}Tc-iminodiacetic acid imaging (*18,41–43*). In a comparative study on the detection of HCC by imaging, the rate of increased uptake of radioactivity of ^{99m}Tc-PMT (56%) was higher than that of increased uptake of ^{99m}Tc-diethyl iminodiacetic acid (11%) (*47*). Gallium-67-citrate imaging has also been widely used for detection of intrahepatic tumorous lesions (*48–52*). This imaging method was, however, reported to be less specific for diagnosis of HCC than ^{99m}Tc-PMT imaging (*18*). Therefore, we often use ^{99m}Tc-PMT imaging for evaluating the nature of hepatic masses, that were detected by US or ^{99m}Tc-colloid liver imaging and were suspected of HCCs.

For accurate prognosis of patients with HCC, it is important to evaluate several independent factors. Technetium-99m-PMT imaging is an easy noninvasive method for objective evaluation of hepatic tumors on the basis of the hepatocytic function of the tumor cells. This function is closely associated with the degree of differentiation of the tumor cells. Thus, this method provides specific information for evaluating the prognosis of patients with HCC.

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EDITORIAL

Prognosis of Hepatocellular Carcinoma: Known to Be Poor: Yet Difficult to Predict

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in the world today and approximately one million individuals develop this disease per year (*1*). Recent advances in early detection and treatment of HCC have improved the prognosis, and long-term survival has been reported particularly in those individuals who have small encapsulated subclinical HCC (*2–4*). In general, however, the prognosis of HCC is poor (*5,6*). Survival of patients with HCC is influenced by many complex factors such as the presence of hepatic cirrhosis, location of tumor, and extent of disease (*7*). Other important considerations in the response to therapy include the serum bilirubin and AFP levels (*8*) as well as the biologic behavior of the tumor with respect to its growth characteristics (*9*). Another important prognostic indicator is the histologic type and grade of the tumor at the time of diagnosis (*10,11*). There is a general need to develop reliable, sensitive, and specific techniques that will aid the clinician in assessing the prognosis of the disease at the time of clinical presentation.

In this issue of the *Journal*, Hasegawa et al. (*13*) have shown that late imaging of HCC by a technetium agent, namely, ^{99m}Tc(Sn)-N-pyridoxyl-5-methyltryptophan (^{99m}Tc-PMT) may be useful for predicting long-term survival of patients with HCC. The authors have demonstrated in a carefully performed study of 162 patients with HCC that increased uptake of ^{99m}Tc-PMT in the tumor was associated with a significantly longer survival (n = 82, median survival: 1013 days) as compared to those who did not show a similar increased uptake of the imaging agent (n = 80, median survival: 398.5 days). This finding is of considerable clinical interest since increased uptake of ^{99m}Tc-PMT into the tumor appears to be an independent marker different from most of the other parameters used to assess the prognosis of the disease. First, the two study groups that showed increased and decreased uptake of ^{99m}Tc-PMT had comparable clinical characteristics and it is important to note that no significant differences in age, sex, distribution, treatment received, serum level of albumin, tumor size, or degree of hepatic dysfunction as assessed by Child's classification were found. It is especially noteworthy that their finding of improved survival with increased uptake within the tumor was independent of the type of therapy, which included such approaches as hepatic resection and transarterial embolization. Thus, the prognosis of HCC patients was clearly correlated with the tumor concentration of ^{99m}Tc-PMT. However, these differences in survival between the two groups (Figs. 1 and 2) had a tendency to disappear and, indeed, the two groups merged with time following the initial diagnosis. Nevertheless, the availability of a reliable and simple test to predict early survival of patients with this disease may be an important prognostic indicator for the choice of various therapeutic interventions.

Recently, hepatobiliary imaging agents have been widely used in nuclear medicine in the diagnosis of liver diseases. Many investigators have taken advantage of the fact that some HCCs maintain a high degree of differentiated hepatic function since such tumors retain the capability to take up these agents. The previous observations have stimulated the development of hepatic scintigraphy as a diagnostic aid to determine the localization of HCC with the liver. Many other radionucleotide-conjugated hepatobiliary agents have also been reported to be useful in this regard as well (*14–18*).

Identification of HCC as measured by regions of increased uptake has been an attractive feature of this approach even though there has been a low detectability rate of HCC by this method (*15–18*). Calvet et al. have reported of a relationship between the uptake of hepatobiliary agents and tumor cell differentiation. Thus, the sensitivity of liver scintigraphy using ^{99m}Tc-labeled agents were related to this important biologic property of the tumor (*18*). For example, these investigators found that most of the well-differentiated HCCs that concentrate radiolabeled hepatobiliary agents are usually well visualized as "hot areas" by scintigraphic scanning images. In contrast, moderately or poorly differentiated HCCs are usually not visualized by this approach. This clinical pathologic correlation is especially important since

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