

Extrahepatic Uptake of Technetium-99m-Phytate: A Prognostic Index in Patients with Cirrhosis

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We examined the usefulness of technetium-99m-phytate (^{99m}Tc -phytate) hepatic scintigraphy in the evaluation of hepatic function, and the assessment of prognosis in patients with cirrhosis. Ninety-four patients with biopsy-documented cirrhosis had, at the time of entry into the study, a scintigraphy with ^{99m}Tc -phytate complexed with calcium in vivo. Extrahepatic uptake (EHU) of ^{99m}Tc -phytate on scintigraphy was graded from 0 (absent EHU) to 5 (important EHU) according to the relative distribution of the radiotracer between the liver, the spleen and the bone marrow. The severity of liver disease was also assessed according to the index of Child and Turcotte as modified by Pugh et al. Mean follow-up was 2 yr. EHU was correlated to the Pugh score ($r = 0.73$) and to survival. Survival at 2 yr was 97% for an EHU equal or inferior to 2.5, 62% for grades 3–4.5, and 31% for grade 5. In conclusion, hepatic imaging with ^{99m}Tc -phytate, in addition to its diagnostic value, also contains valuable prognostic information in patients with cirrhosis.

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Liver scintigraphy using Au-198-colloid (1), technetium-99m-sulfur colloid (2,3), or technetium-99m-Bida (4,5) is a commonly-used imaging technique for the diagnosis of liver diseases. Hepatic scintigraphy in cirrhosis shows delayed radiocolloid extraction by the liver, decreased and/or heterogeneous hepatic uptake, and increased uptake by the extrahepatic reticulo-endothelial system (RES). Few reports, however, have emphasized the value of liver scintigraphy in assessing the prognosis of patients with liver cirrhosis. The purpose of this study was to evaluate the value of technetium-99m-phytate (^{99m}Tc -phytate) complexed in vivo with calcium in the evaluation of hepatic function and to determine the prognostic value of this test, in compar-

ison with an already established prognostic indicator, the Pugh score.

MATERIALS AND METHODS

Patient Selection and Imaging Procedure

During a four-year period, ninety-four patients with cirrhosis as shown by liver biopsy were studied. Fifty patients had alcoholic cirrhosis, 24 post-hepatic cirrhosis, 12 cryptogenic cirrhosis, and 8 biliary cirrhosis. The mean age was 51 ± 13 (range = 20 to 79 yr). A ^{99m}Tc -phytate liver scintigraphy and a determination of the clinical index of Child-Turcotte (6), as modified by Pugh et al. (7) was carried out at the time of inclusion in the study.

Liver scintigraphies were performed using ^{99m}Tc -phytate complexed with calcium in vivo. Technetium-99m-phytate was prepared by labeling 10 mg of phytate and 1 mg of stannous chloride with 8 mCi of [^{99m}Tc]pertechnetate. No calcium was added to the preparation before injection. With this method, the formation of colloid occurs in vivo when the ^{99m}Tc -phytate is complexed to serum calcium. Images (500,000 cts) in the anterior, left lateral, right posterior oblique, right anterior oblique, and posterior views were obtained using a LFOV camera 20 min after injection. Both liver and spleen were imaged at the same time on the anterior and posterior views. The extrahepatic uptake (EHU) of ^{99m}Tc -phytate was determined on the posterior view. It was graded from 0 to 5 according to the summation of the relative distribution of the radiotracer between the liver, spleen, and bone marrow. The spleen uptake was graded from 0 to 3+ as following: 0: no uptake; 1+: uptake smaller than the liver; 2+: uptake equal to the liver; and 3+: uptake greater than the liver. The bone marrow was graded from 0 to 2 (0: no uptake; 0.5: visualization of part of the lumbar spine; 1: distinct visualization of the lumbar spine with no visualization of the ribs; and 2: good visualization of the lumbar spine and ribs). The score of the spleen and marrow uptake were added together to determine the EHU (Figs. 1, 2, and 3). The patients were divided in three subgroups according to their EHU: 0–2.5 ($n = 36$), 3.0–4.5 ($n = 45$), and 5 ($n = 13$). It should be noted that none of these patients had lung uptake of ^{99m}Tc -phytate.

The Child-Turcotte score, as modified by Pugh et al. (7) was determined within 2 wk of the liver scintigraphy. This index uses five clinical parameters: the presence of encephalo-

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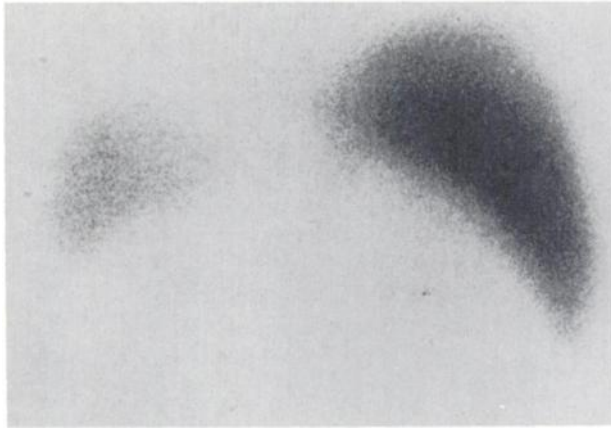


FIGURE 1
Liver spleen scintigraphy (posterior view) with splenic uptake smaller than the liver and no uptake by the bone marrow. The extrahepatic uptake equals 1.

lopathy and ascites, the determination of serum albumin, prothrombin time, and serum bilirubin (Table 1). Each variable was given a value of 1, 2, or 3, respectively, for increasing abnormality, and the value of the five parameters added together to calculate the score of each patient. Thus, the best possible score is 5 and the worst 15. The patients were categorized in three groups according to the Pugh score (5–6: Class A, $n = 34$; 7–9: Class B, $n = 37$; 10–15: Class C, $n = 23$).

After entry into the study, no patient was lost to follow-up, and four died of causes unrelated to their liver disease. Although survival analysis can handle deaths unrelated to the outcome under study (i.e., death from liver disease), we decided to exclude these four patients because the other types of analyses used in this paper cannot accommodate such occurrences. Thus, 90 patients were present in all types of analyses. The follow-up period averaged 810 days (range = 299–1151) until closure of the study.

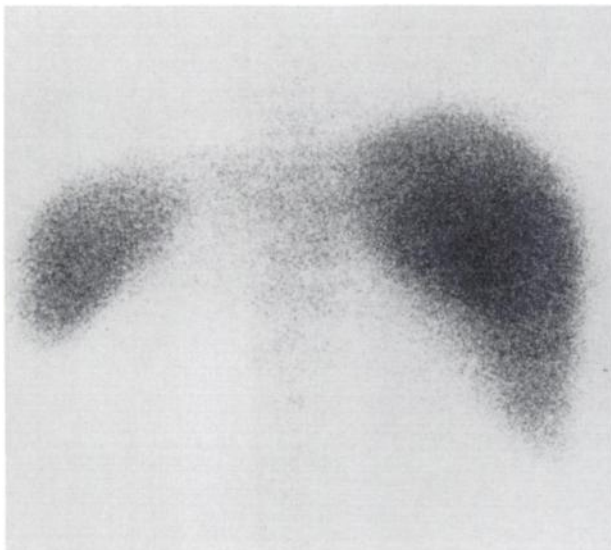


FIGURE 2
The extrahepatic uptake of this liver-spleen scintigraphy (posterior view) equals 2 (uptake by the spleen smaller than the liver, small uptake by the bone marrow).

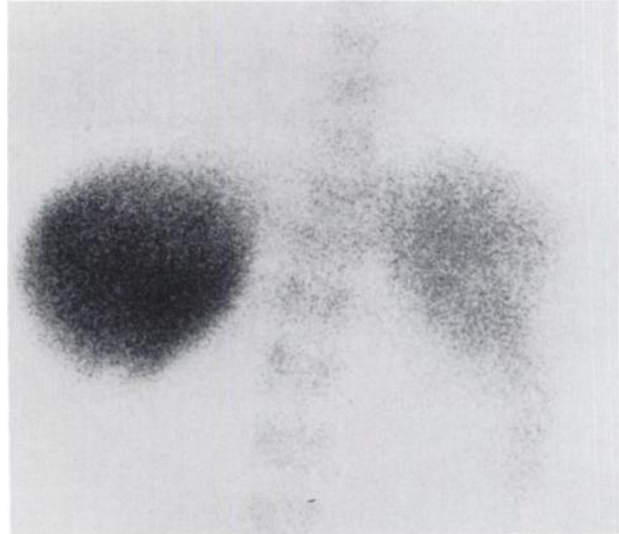


FIGURE 3
Liver spleen scintigraphy (posterior view) with an extrahepatic uptake of 5 (uptake by the spleen higher than the liver, good visualization of the bone marrow).

Data Analysis

The correlation between the EHU and Pugh's score was assessed by the Spearman rank-order test. Survival curves were constructed by the Kaplan-Meier's method, and the association between the EHU, the Pugh score, and survivorship was examined by the log-rank test (8), and with the Cox model (9). Two models of Cox regression analysis were compared: the first model (model A) included the Pugh score (from 5 to 15), whereas the second model (model B) included the EHU score (from 1 to 5). The likelihood (i.e., the probability of the observed data being explained by a model) of models A and B were compared with the likelihood of a model with no explanatory variables (model 0). The ratio of two likelihoods (for instance: model 0/model A) can be tested using a maximum likelihood chi-square (10). The model with the highest chi-square is the model with the greatest significance.

The sensitivity and the specificity of each model to the survival status were estimated using a receiver-operating characteristic (ROC) curve (11). This curve shows the capacity of the model to discriminate between those who die and those who survive, according to different cutoff points of the score.

RESULTS

Results of the EHU and the Pugh score in the 90 patients studied are shown in Figure 4. The correlation between ^{99m}Tc -phytate EHU and the Pugh score was significant ($r = 0.73$, $p < 0.001$).

During the follow-up period, 27 of 90 patients (30%) died from causes related to their liver disease (21 died of liver failure, 4 of variceal hemorrhage, and 2 of hepatocellular carcinoma). The proportion of patients who died in each diagnostic category was 40% in those with alcoholic cirrhosis, 37.5% in biliary cirrhosis, 25% in cryptogenic cirrhosis, and 9% in post-hepatic cirrhosis.

TABLE 1
Criteria for Child-Turcotte Classification (Pugh's Modification)

Variables (Grading)	A (1)	B (2)	C (3)
Ascites	Absent	Slight-moderate	Tense
Encephalopathy [*]	None	Grade I-II	Grade III-IV
Serum albumin (g/dl)	>3.5	2.8-3.5	<2.8
Serum bilirubin [†] (mg/dl)	<2.0	2.0-3.0	>3.0
Prothrombin time (seconds above control)	<4.0	4.0-6.0	>6.0

^{*} According to grading of Trey, Burns, and Saunders.

[†] For biliary cirrhosis: <4 mg/dl = 1; 4-10 mg/dl = 2, and >10 mg/dl = 3.

Survival curves of patients stratified according to their EHU showed a survival rate of 97% at 2 yr for grades 1-2.5, 62% for grades 3-4.5, and 31% for grade 5. There was a good discrimination between these groups (Fig. 5). The prognostic value of the Pugh score was similar to the EHU. The survival rate at 2 yr was 97% for a score of 5-6, 71% for a score of 7-9, and 27% for a score of 11-15 (Fig. 6).

Using the univariate analysis, survival in each group was significantly different between the three categories of the Pugh score ($\chi^2 = 44.9$, $p < 0.001$). Survival for the three groups of patients categorized according to their EHU was also significantly different between the groups ($\chi^2 = 25.7$, $p < 0.001$).

Using the Cox regression analysis, the maximum likelihood chi-square was 35.77 ($p < 0.0001$) for model A with the Pugh score, whereas it was 22.19 ($p < 0.0001$) for model B with the EHU score. This suggested that model A was a better model than model B, in the sense that it explained more of the risk of death. Accordingly, ROC curves indicated that the sensitivity and the spec-

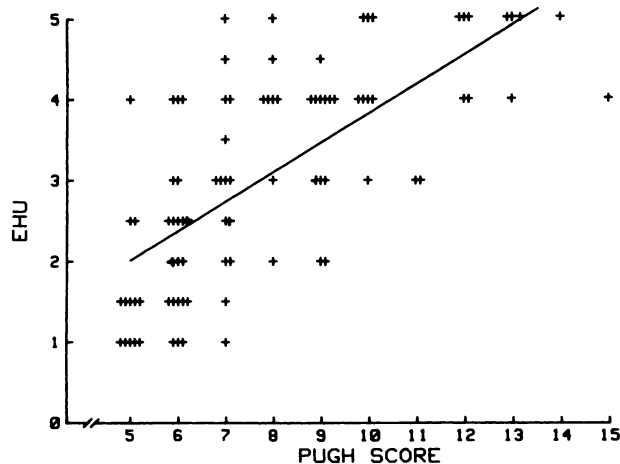


FIGURE 4
Correlation between the EHU of [^{99m}Tc]phytate and the Pugh score ($r = 0.73$, $p < 0.001$).

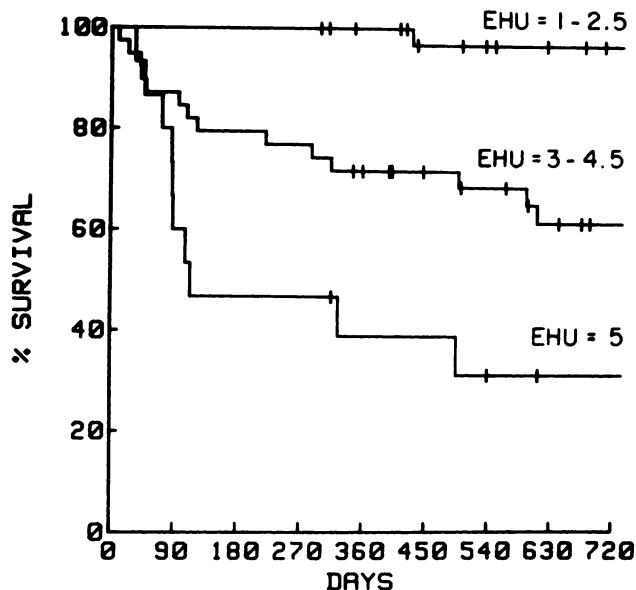


FIGURE 5
Cumulative survival in relation to the EHU of [^{99m}Tc]phytate. Patients were categorized in three groups according to their EHU: 1-2.5 ($n = 36$), 3-4.5 ($n = 39$) and 5 ($n = 15$). The short vertical bars indicate trial time for patients still at risk and with less than 720 days' follow-up when the study was closed.

ificity to an observed status of death was superior for the Pugh score at all cutoff points (Fig. 7). The maximum discrimination point [(sensitivity + specificity)/2] reached 79% with the Pugh score and 71% with the EHU score.

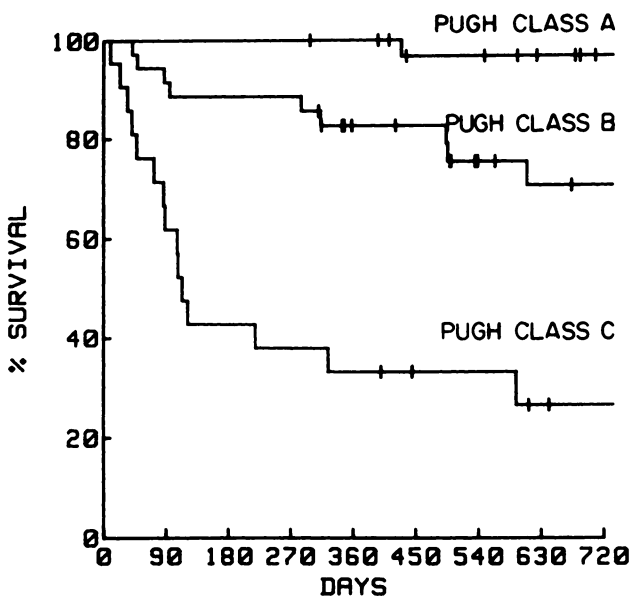


FIGURE 6
Cumulative survival in groups A, B, and C defined by the Pugh score. Scores of 5 or 6 defined as class A ($n = 34$), 7-9 as class B ($n = 35$), and 10-15 as class C ($n = 21$). The short vertical bars indicate trial time for patients still at risk and with less than 720 days' follow-up when the study was closed.

DISCUSSION

Technetium-99m-phytate (inositol hexaphosphate) is an imaging agent of the RES introduced in 1973 (12). After i.v. injection, ^{99m}Tc -phytate forms an insoluble calcium salt in vivo which undergoes RES localization. The spleen uptake of ^{99m}Tc -phytate colloid formed in vivo is less than that obtained with ^{99m}Tc -phytate colloid prepared in vitro or that of sulfur colloid (13). Since only a few milligrams of phytate are used for these studies, the depletion of serum calcium by chelation is negligible and the i.v. toxicity of the compound is very low (12).

We have evaluated liver function using ^{99m}Tc -phytate for over fifteen years. It is apparent from our experience that, in normal subjects, the EHU of ^{99m}Tc -phytate chelated in vivo is less than that observed with ^{99m}Tc -sulfur colloid. Similarly, Herzog *et al* (14) demonstrated that, in normal subjects, the mean liver and spleen uptake of phytate is respectively 75% and 3.5% at 20 min. For sulfur colloids, the mean uptake at 120 min is between 62%–74% for the liver and 15%–18% for the spleen. The spleen uptake is therefore five times lower with ^{99m}Tc -phytate than with ^{99m}Tc -sulfur colloid. These different patterns of distribution of ^{99m}Tc -phytate and ^{99m}Tc -sulfur colloid are probably related to the size of the particles. The particle size of ^{99m}Tc -phytate is smaller than that of ^{99m}Tc -sulfur colloid (4–12 μm against 500–2000 μm) (15). It also has been suggested that the electronegativity of the particles could affect the distribution of the radiopharmaceuticals and the handling of the colloids by the RES (16). The advantage

of ^{99m}Tc -phytate over ^{99m}Tc -sulfur colloid is its gradual redistribution from liver to spleen and bone marrow in the presence of increasing impairment of liver function. This allows easy quantitation of the redistribution of phytate on analogue images. In addition, in our experience, lung uptake of ^{99m}Tc -phytate is not observed in cirrhosis, whereas it occurs occasionally with ^{99m}Tc -sulfur colloid.

The uptake of ^{99m}Tc -phytate is dependent upon the colloid extraction by the liver, which is related to the function of the Kupffer's cells and to liver blood flow. The extrahepatic colloid uptake observed in patients with cirrhosis is consistent with a reduced hepatic ^{99m}Tc -phytate uptake due to failure of the diseased liver to remove the colloid. This reduced clearance is probably due to a reduced number of Kupffer's cells in cirrhosis or intrahepatic shunts (3,17), rather than a reduced function of the cells as the phagocytic capacity of Kupffer's cells is only modestly reduced in cirrhosis (18,19). It has also been demonstrated that EHU is not related to total hepatic blood flow or severity of portal hypertension (3,20).

Previous studies have evaluated the role of hepatic scintigraphy using ^{99m}Tc -sulfur colloid and/or ^{99m}Tc -diethyl-IDA in the evaluation of liver function (4,5,20, 21). We have previously reported a significant correlation between the EHU of ^{99m}Tc -phytate and the hepatic extraction of ICG, an organic anion removed by hepatocytes and used as a test of liver function (20). Sostre *et al.* (21) have demonstrated that liver-spleen scans using ^{99m}Tc -sulfur colloid provide a simple method to determine the extent of hepatic involvement and the probability of complications in chronic hepato-splenic schistosomiasis. Kim *et al.* (4) and Klingensmith *et al.* (5) showed that alterations of liver function tests are more closely related to Hida imaging changes than to sulfur colloid imaging changes. However, to our knowledge, no study has shown a relation between hepatic scintigraphy and survival in cirrhotic patients. In the present study, we have observed that the EHU of ^{99m}Tc -phytate is a moderately good prognostic indicator of survival in patients with cirrhosis, although somewhat inferior to the Pugh score.

CONCLUSION

The Pugh score, because of its simplicity, low-cost, widespread use, and excellent validity, remains in our opinion, the best method to assess the severity of the disease and prognosis in patients with cirrhosis. The variables that compose the score are measured routinely in patients with liver disease, and the capacity of the Pugh score to predict survival has been demonstrated repeatedly (10,22). Obviously, we do not think that hepatic scintigraphy using ^{99m}Tc -phytate should replace the Pugh score or be used routinely to assess prognosis in cirrhotic patients, but we wish to point out that

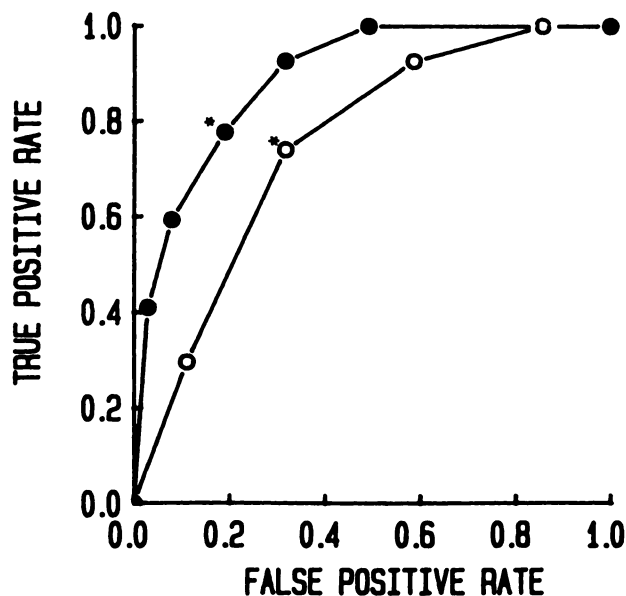


FIGURE 7
ROC curves showing the sensitivity (true-positive rate) and specificity (1-false-positive rate) for various cut-off points of the Pugh score (closed circles) and the EHU score (open circles). The asterisks indicate cutoff points with maximum discrimination.

abnormalities of hepatic scintigraphy are correlated with the severity of cirrhosis and that liver scans contain prognostic information. Thus, when scintigraphy is requested for diagnostic purposes, this additional information provided by the scan should be considered.

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