Hepatobiliary Imaging of Functional and Morphological Changes Following Hepatic Arterial Embolization in Hepatocellular Carcinoma

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Hepatic arterial embolization (HAE) is the treatment of choice for inoperable hepatocellular carcinoma. There are functional changes following HAE in the tumor and in the adjoining normal liver and biliary structures. We sought to determine if a ^{99m}Tc-HIDA hepatobiliary scan could evaluate the morphological and functional changes of the liver and biliary systems in patients with hepatocellular carcinoma undergoing HAE. **Methods:** Patients with hepatoma were evaluated by ^{99m}Tc-HIDA hepatobiliary scans before and after HAE. **Results:** Ten patients with histologically proven hepatomas had 44 ^{99m}Tc-HIDA scans over a 319-mo period. Liver uptake was good in all patients, none developed hepatic failure. Liver tumors were detected in five of the eight studies done before the first HAE. The HIDA scan failed to locate the tumor throughout the whole study period in only one patient. Two patients showed evidence of tumor uptake of the HIDA agent. In one of these two patients the hot uptake disappeared after the HAE but reappeared after tumor recurrence. Gallbladder filling time and contractility worsened in all eight patients the day after embolization. On the HIDA scans, the gallbladder was not visualized in three of four patients who survived longer than 40 mo after HAE. Bile stasis in the left intrahepatic duct was found in six of the eight patients who survived longer than 8 mo after HAE. **Conclusions:** Biliary complications were common in patients who received HAE, and HIDA scans may be useful for evaluating the biliary system and hot uptake in hepatocellular carcinoma in candidates for HAE.

Key Words: hepatocellular carcinoma; hepatic arterial embolization; hepatobiliary scintigraphy

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Hepatic arterial embolization (HAE) is the treatment of choice for inoperable hepatocellular carcinoma (*1,2*). Following HAE in patients with hepatocellular carcinoma, functional changes occur in the tumor and in the adjoining normal liver and biliary structures (*2–4*). Computed tomography (CT) and ultrasound (US) mainly provide morphological data, and the assessment of liver biochemical profile changes in the serum are only indirect measures of dysfunction. Serum liver function tests do not distinguish abnormalities due solely to the tumor from those resulting from HAE damage on the adjoining normal liver tissue. We report the preliminary results of a 4-yr prospective study of the morphological and functional changes in the normal liver, biliary tree, gallbladder and biliary tumor following HAE using ^{99m}Tc-HIDA agents (*5–10*).

METHODS

Over 4 yr, 35 patients with primary hepatocellular carcinoma were studied. Diagnosis of hepatocellular carcinoma was confirmed by a thorough clinical evaluation and laboratory investigation that included conventional liver function tests, alpha-fetoprotein (AFP), HBsAg, abdominal US, angiogram and CT studies. Histological confirmation was obtained in all patients. Patients selected for HAE underwent a pre-HAE HIDA study, which was repeated on the second day after HAE and at 3- to 6-mo intervals in the patients who lived that long and needed functional evaluation during follow-up. Of the 35 patients with hepatocellular carcinoma, 10 met the criteria of a minimum of 5 mo follow-up, successful HAE without technical complications, relatively good hepatic ^{99m}Tc-HIDA uptake in the pre-HAE study, and willingness to participate in a prospective study. The other 25 patients with hepatocellular carcinoma failed to meet these criteria and were excluded. Patient characteristics, AFP status, pre-HAE tumor size, number of HAE required and number of HIDA studies obtained and their outcomes are shown in Table 1.

A total of 20 HAEs were performed in the 10 patients and ^{99m}Tc-HIDA studies were obtained over 319 mo. Two patients received segmental resections after the first HAE. Eight patients received the first HIDA study before the first HAE. One patient received the first HIDA study before the second HAE, and another before the third HAE. Nine patients were were male and nine were HBsAg carriers. Abdominal US studies before the first HAE showed a normal gallbladder in 9 of the 10 patients and a gallstone in one patient (Patient 6).

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TABLE 1
Patient Data

Patient no.	Sex	Age	HBsAg	Highest AFP	Pre-HAE tumor size (cm)	No. HAE	No. HIDA scan	Outcome
1	M	62	+	2325	8	2	2	M(5)
2	M	51	+	1695	10	1	2	M(7)
3	M	41	+	<3	5	3	5	M(12)
4	M	55	+	2925	6*	3	6	M(16)
5	F	77	+	20	6	1	3	M(29)
6	M	69	−	<3	6	1	6	M(33)
7	M	59	+	270	2	2	4	M(41)
8	M	55	+	590	8	1	6	M(46)
9	M	32	+	<3	13	3	5	S(60)
10	M	62	+	306	10	3	5	S(70)

*Main tumor size; ten other small nodules were also present.
M = mortality; S = survival. Numbers in parentheses are total months of follow-up after the first HAE.

Each patient received 6 mCi ^{99m}Tc-HIDA. Anterior and right lateral liver scintigrams were obtained 5 min after injection, followed by anterior view imaging at 15-, 30-, 60- and 120-min intervals. Images were obtained with a multipurpose gamma camera at a preset count format of 400,000 cts/frame. If biliary stasis was found, biliary scans were obtained 3 and 4 hr after injection. In patients with metastatic lung tumors, chest scans were performed 3 and 4 hr after injection. The field of view included the thyroid, whole chest and abdomen. Lead shielding was used to cover the upper abdomen to decrease interference from intestinal activity.

For the first 2 yr of the study, liver functions were evaluated visually by comparing liver radioactivity to cardiac blood-pool radioactivity in the 5-min image. Clearance was graded from the 5-min image on a scale of 1 to 4 (10), grade 1 indicating normal liver uptake, grade 2 mild hepatocyte dysfunction, grade 3 moderate hepatocyte dysfunction and grade 4 severe hepatocyte dysfunction. Two years after initiation of the study, the liver-to-heart ratio was counted by the computer.

Intrahepatic bile stasis was defined as stasis of HIDA in the intrahepatic bile duct for more than 2 hr. Patients were asked to eat two eggs 2 hr after injection of HIDA. Gallbladder contractility was measured 1 hr after the eggs were eaten.

RESULTS

Hepatic Tumors

Liver uptake of HIDA was classified as grade 1 in the initial HIDA scans of all subjects. In the follow-up studies, the liver-to-heart ratio was good in all subjects (range 4.5 to 14.17) except Patient 10, whose liver-to-heart ratio on the last scan was 2.95.

Transient ischemic cold areas were noted in two of the

TABLE 2
HIDA Scan Results

Patient no.	Pre-HAE Mass (cm)	Pre-HAE Gallbladder F/min	Pre-HAE Gallbladder Cont.	One day post-HAE Gallbladder (F/min)	One day post-HAE Gallbladder (Cont.)	Sequential studies post-HAE Mass (cm)	Sequential studies post-HAE Gallbladder (F/min)	Sequential studies post-HAE Gallbladder (Cont.)	LIHD (mo)	RIHD
1	8	15	G	—		Unchanged	240(4)	F	−(3)	—
2	10	15	G	—		Enlarged	30(3)	F	−(3)	—
3	N-V	15	G	N-V		Enlarged	120–240	P	S(8)	—
4	N-V	15	F	120	P	—	30–240	F	−(14)	—
5	6	15	F	120	P	Unchanged	15(4)	G	S(1)	—
6	5	60	G	15	P	Metastasis	15–30	F	S(22)	S(4)
7	N-V	15	G	15	F	Enlarged	15–30	F	−(26)	—
8	8	15	G	15	P	Decreased	NV		S(24)	S(24)
9	4†	15	G	N-V		Decreased	NV		S(38)	—
10	4*	N-V	G	N-V		Disappeared, but new lesions occur	NV		S(18)	—

*† HAE done before second and third HAE, respectively. Numbers in parentheses are total months of follow-up after the first HAE.
F/min = minutes of initial gallbladder filling by HIDA; Cont. = gallbladder contractility after fatty meal; G, F and P = good, fair and poor gallbladder contractility; NV = nonvisualized; S = stasis of HIDA agent; LIHD and RIHD = left and right intrahepatic bile duct.

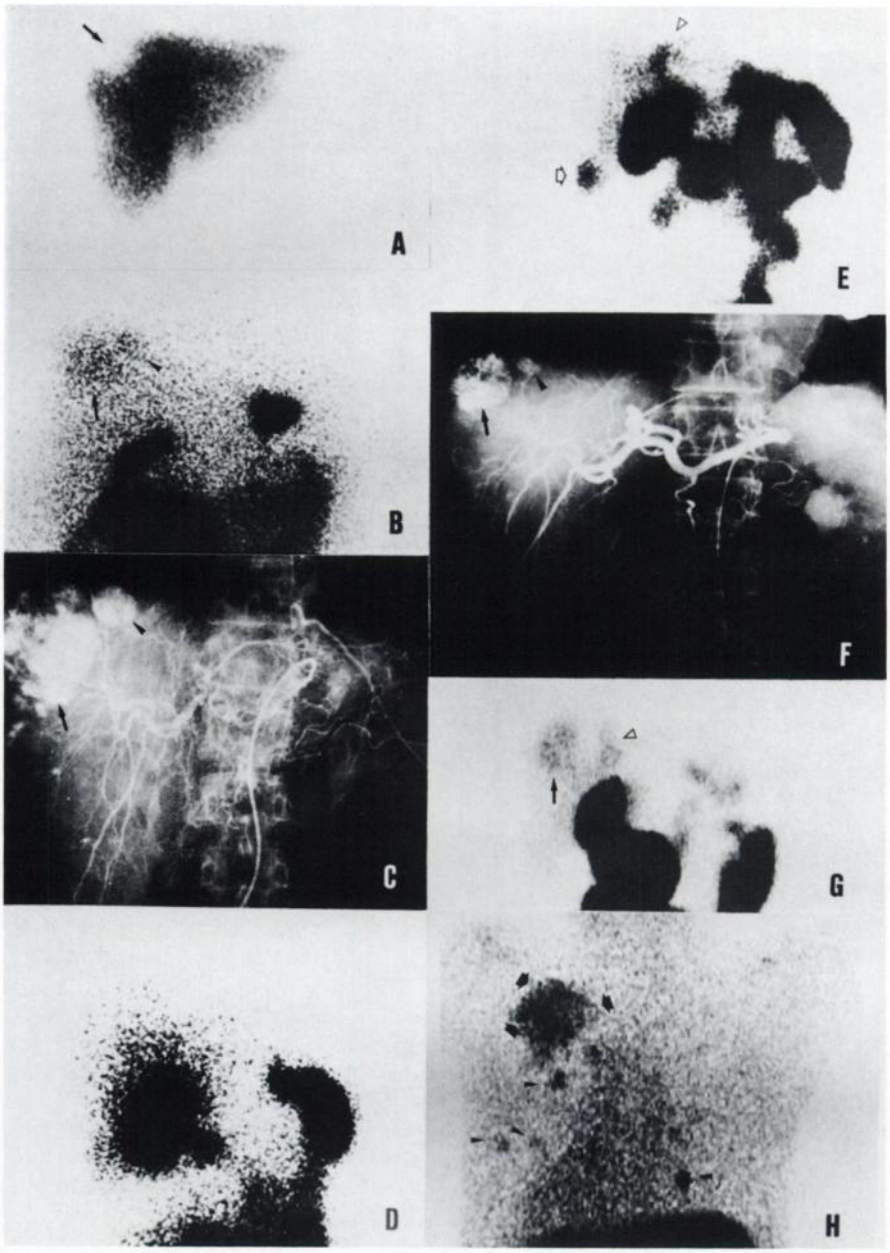

FIGURE 1. Serial images of Patient 6. (A) Cold tumor (arrow) on 5-min pre-HAE scan. (B) Hot uptake in the main tumor (arrow) and daughter nodule (arrowhead) on the 3-hr scan. (C) Celiac angiography shows a hypervascular tumor (arrow) and its daughter nodule (arrowhead). (D) Disappearance of hot uptake and gallbladder stasis on the 3-hr scan the day after HAE. (E) Stasis of the right (open arrow) and left (open arrowhead) intrahepatic bile duct on the 3-hr scan 4 mo later. (F) Second celiac angiogram 20 mo after HAE shows tumor shrinkage. (G) Reappearance of hot uptake (arrow) and persistence of left intrahepatic duct stasis (open arrowhead). (H) A 3-hr lung scan shows multiple lung metastases (arrowheads) and subcutaneous metastases in the left scapular area (arrows).

eight patients who received HIDA scans 1 day after HAE. HIDA scans revealed liver tumors in five of the eight patients before their first HAE (Table 2), with a detection rate of 62.5%. The tumor size ranged from 5 to 10 cm. Undetected tumors were 2 cm (Patient 7), 5 cm (Patient 3) and a 6-cm mass with multiple small nodules (Patient 4). In Patients 3 and 7, tumors were found in subsequent HIDA scan studies; in Patient 4, the tumors were not detected by the HIDA scan throughout the whole course of study.

On the pre-HAE HIDA scan (Fig. 1A) for Patient 6, the main tumor and its daughter nodule exhibited hot uptake, which corresponded well with the tumors detected by angiography (Fig. 1B). The nodule was absent the next day and 4 mo after HAE (Fig. 1C,D) but reappeared after tumor relapse (Fig. 1G). Abdominal US studies over the same period did not reveal the recurrent tumor, because there was no significant change in tumor size. The size of the tumor actually decreased significantly after HAE, as shown by the second angiogram taken 20 mo after HAE (Fig. 1F).

Tumor size increased or additional tumors developed in four patients. Tumor size decreased in two patients, and no significant change in tumor size was detected in two patients within a short HIDA-scan study period. Metastatic lung tumors were detected in one (Fig. 1H) of the two patients whose chest radiograph showed multiple lung metastases. A subcutaneous mass over the left scapular area was also detected on the same scan.

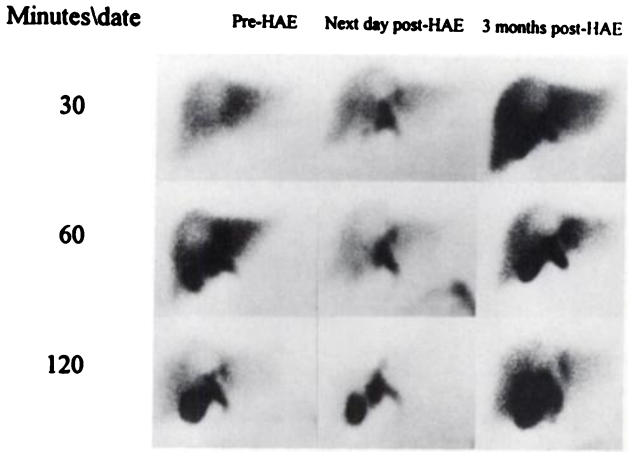

FIGURE 2. Serial 30-, 60- and 120-min HIDA scans pre-HAE, the day after HAE and 3 mo after HAE in Patient 5. Gallbladder filling time improved 3 mo after HAE.

Gallbladder

Patient 5 had a tumor located in the hilar area. Before the first HAE, gallbladder filling occurred 1 hr after injection (Fig. 2). One day after HAE, gallbladder filling was further delayed to 2 hr after injection. Three months after HAE, gallbladder filling time normalized.

Impaired gallbladder function was found in all eight patients who had HIDA scans the day after HAE. The gallbladder ejection fraction for Patient 4 pre-HAE, the day after HAE, 2, 4 mo (before the second HAE), 8 mo (before the third HAE) and 11 mo after HAE was 92.75%, 16.5%, 72.87%, 93.62%, 94.93% and 84.65%, respectively. His sequential HIDA scans also showed progressively decreased uptake of HIDA by the gallbladder (Fig. 3).

Four of the patients survived at least 40 mo after the first HAE. For three of these patients, the gallbladder was not visualized on the HIDA, US or CT scans. Two of these three patients demonstrated normal gallbladder function on the pre-HAE HIDA scan. Again, there was no visualization of the gallbladder 18 (Fig. 4A,B) and 24 and 38 mo after the first HAE in Patients 10, 8 and 9, respectively.

Ultrasound studies revealed gallstones after the first HAE in Patients 3, 7 and 8 at 6, 14 and 2 mo, respectively.

Bile Ducts

For Patient 5, intrahepatic bile stasis was found before the first HAE. Six of the eight patients who were studied for at least 8 mo showed persistent or transient bile stasis in the left intrahepatic duct (Fig. 1G, 4B). Two of these patients also demonstrated bile stasis in the right intrahepatic duct (Fig. 1E). Bile stasis developed as early as 4 mo after the first HAE. For Patient 10, endoscopic retrograde cholangiography and HIDA scan showed left intrahepatic duct stricture (Fig. 4A,B), with no visualization of the gallbladder.

DISCUSSION

Before HAE can be performed, one must first determine whether the patient's liver function reserve and gallbladder status are sufficient to withstand this treatment (*2–4*). Although conventional liver function tests may evaluate liver function reserve fairly well, pre-HAE HIDA scans provide a double check. In this study, all 10 patients showed good liver uptake on the pre-HAE HIDA scan studies, and none of them developed hepatic failure after HAE. It is important to note that we excluded two nonicteric study candidates for HAE because their uptake of HIDA was classified grade 3. In Patient 10, we also realized that we could not perform any additional HAE.

Our confidence in performing HAE is strengthened when a pre-HAE HIDA demonstrates a properly functioning gallbladder. We can avoid or postpone HAE in patients already suffering from gallbladder or biliary complications. Seven of eight patients had a functioning gallbladder before their first HAE. One patient's delayed gallbladder filling, due to tumor compression, was improved after HAE. Delayed gallbladder contraction was found in all HIDA scan studies the day after HAE. Although three patients developed gallstones after HAE, we observed no coexisting gallbladder disease to prompt us to postpone HAE. All our patients, including the patient with gallstones, had no severe gallbladder complication after HAE. Of course, addi-

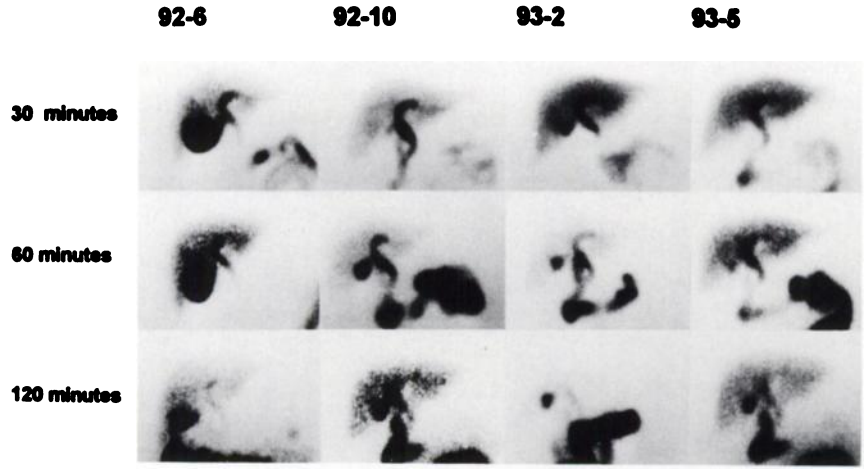

FIGURE 3. HIDA scans taken 30, 60 and 120 min postinjection of HIDA in Patient 4. Progressive decrease in gallbladder uptake of HIDA was found after three HAEs.

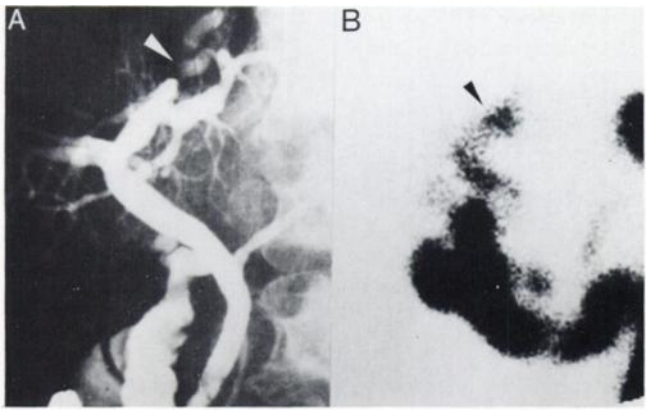

FIGURE 4. (A) Patient 10. Retrograde endoscopic cholangiography shows a stricture in the left intrahepatic duct (open arrowhead). The gallbladder was not visualized. (B) HIDA scan shows bile stasis in the left intrahepatic duct 3 hr postinjection (closed arrowhead). There is no sign of gallbladder filling.

tional studies are needed, especially of HAE candidates with associated gallstones.

For three of four patients who survived at least 40 mo after HAE, the gallbladder was not visualized on the HIDA scans. Abdominal US and CT scans revealed contracted gallbladders in these patients. As has been demonstrated, ischemic cholecystitis induced by HAE may cause delayed gallbladder emptying and fibrosis, a dysfunctional gallbladder may lead to gallstone formation (*11*) and gallbladder fibrosis, if severe enough, may scar and become indiscernible on imaging studies. Two of these three patients with contracted gallbladder are still alive, with no complications so far, and we will continue to observe them.

Intrahepatic duct bile stasis was the condition detected most often, and 6 of the 10 patients had persistent transient intrahepatic bile stasis. These findings suggest that bile duct damage was the rule rather than the exception (*4*). This situation is similar to the ischemic-type biliary complications seen after liver transplantation (*12*). None of the patients with bile stasis have had clinical symptoms or complications due to bile stasis. Further observation of the surviving patients' biliary system will be conducted.

Interestingly, the left intrahepatic ducts seem to be more susceptible to ischemia than the right. In Taiwanese patients, intrahepatic duct stones are more common in the left than the right intrahepatic duct (*13*). The etiology of intrahepatic duct stones is unknown, but one possibility is hemodynamic alteration.

Liver tumors were identified in only 62.5% of the patients who received a HIDA scan before their first HAE. Tumor size was not the only reason for the low detection rate. Patient 4 had one main tumor 6 cm in size and other 1–2-cm nodules in both lobes of the liver. These tumors were not detected in any of the six sequential HIDA studies. Multiple tumors and only slight differences in the uptake of HIDA between tumor and normal liver may make diagnosis difficult. The low detection rate precluded its use in the regular evaluation of tumors. If, however, tumor uptake can be shown clearly, as in Patient 6, sequential HIDA scans will be of great help in post-HAE evaluation and may help us understand tumor activity independent of changes in tumor size.

CONCLUSION

Gallbladder and bile duct damage was quite common in patients who received HAE. Further evaluation of the usefulness of HIDA scans in HAE candidates should be undertaken, especially in patients with gallstone or bile duct disease and those whose hepatocellular carcinomas have avid uptake of HIDA.

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REFERENCES

1. Lin DY, Liaw YF, Lee TY, Lai CM. Hepatic arterial embolization in patients with unresectable hepatocellular carcinoma: a randomized controlled trial. *Gastroenterology* 1988;94:453–456.
2. Liaw YF, Lin DY. Transcatheter hepatic arterial embolization in the treatment of hepatocellular carcinoma. *Hepatogastroenterol* 1990;37:484–488.
3. Jen KS, Ching HJ. The role of surgery in the management of unusual complications of transcatheter arterial embolization for hepatocellular carcinoma. *World J Surg* 1988;12:362–68.
4. Makuuchia M, Sukigara M, Mori T, et al. Bile duct necrosis complication of transcatheter hepatic arterial embolization. *Radiology* 1985;156:331–334.
5. Krishnamurthy S, Krishnamurthy GT. Technetium-99m-iminodiacetic acid organic anions: review of biokinetics and clinical application in hepatology. *Hepatology* 1989;9:139–153.
6. Reuland P, Kurtz B, Muller-Schauenburg W, Feine U. Comparative diagnosis of focal liver changes using computed tomographic and scintigraphic method. *Nuklearmedizin* 1991;30:43–54.
7. Hasegawa Y, Nakano S, Hashizume T, et al. Comparison of delayed imaging with Tc-99m PMT and Tc-99m DEIDA for visualization of hepatoma. *Clin Nucl Med* 1989;14:526–531.
8. Calvet X, Pons F, Bruix J, et al. Technetium-99m-DISIDA hepatobiliary agent in the diagnosis of hepatocellular carcinoma: relationship between detectability and tumor differentiation. *J Nucl Med* 1988;29:1916–1920.
9. Wang PW, Tai DI, Chen HY. Technetium-99m-HIDA hepatobiliary agent in the diagnosis of pulmonary metastasis from hepatocellular carcinoma. *Clin Nucl Med* 1991;16:120–123.
10. Gerhold JP, Klingensmith III WC, Kuni CC, et al. Diagnosis of biliary atresia with radionuclide hepatobiliary imaging. *Radiology* 1983;146:499–504.
11. Jen KS, Ching HJ. Delayed formation of gallstones after transcatheter arterial embolization for hepatocellular carcinoma: is elective cholecystectomy advisable during hepatectomy? *Arch Surg* 1989;124:1319–1322.
12. Sanchez-Urdazpal L, Gores GJ, Ward EM, et al. Diagnostic features and clinical outcome of ischemic-type biliary complications after liver transplantation. *Hepatology* 1993;17:605–609.
13. ChangChien CS, Wu CS, Chen PC, Liaw YF. Clinical study of primary intrahepatic stones. *J Formosan Med Assoc* 1983;82:936–940.