Early Recognition of Recurrent Hepatocellular Carcinoma Utilizing Gallium-67 Citrate Scintigraphy

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Gallium-67 scintigraphy is a valuable test together with other screening tests such as alpha feto-protein (AFP) and other imaging modalities in following up recurrent hepatocellular carcinoma (HCC). Three patients were followed in our institution for intervals varying from 2–24 mo after successful resection of uninodular localized hepatomas. In the first patient, gallium scan showed abnormal localized activity while the computed tomography (CT) scan and the magnetic resonance imaging were negative. Liver function tests and AFP were also normal and the patient was operated upon only on the basis of the gallium scan. The second patient had a follow-up gallium scan 2 mo after the first operation that showed an area of increased activity along the inferior aspect of the right lobe. A CT scan done after that showed no evidence of recurrence, but subsequently became positive when repeated 4 mo later. The third patient had abnormal simultaneous gallium scan and CT scan demonstrating a recurrence in the left adrenal gland while both AFP and carcinoembryonic antigen were normal. This has led us to consider every patient a candidate for a baseline and follow-up gallium scan for evaluation for recurrence following HCC.

J Nucl Med 29:712–716, 1988

The pre-operative diagnosis of early primary hepatic carcinoma remains a diagnostic challenge and various reports have appeared discussing the clinical and radiographical difficulties encountered in making this diagnosis (*1–8*). In the past, many cases of hepatocellular carcinoma (HCC) remained undiagnosed until the time of autopsy (*9*). Prognosis often is poor and may be related to a number of factors including that these tumors arise in cirrhotic livers, that many are multicentric, and that often patients are diagnosed late (*10–11*). Early diagnosis is important because surgical resection offers the only practical chance for a cure (*12*).

Although several blood tests have been described to be abnormal with HCC, none are sensitive enough to serve as the sole screening test. Alpha feto-protein (AFP) is known to be a relative specific test for hepatocellular carcinoma among high risk patients particularly as levels tend to increase on follow up examinations of patients with advanced HCC. As a screening test, it has limited sensitivity in the detection of patients with early hepatocellular carcinoma (*13–15*). In addition, elevated AFP findings may also be transiently present in cirrhosis and hepatitis (*16–17*).

Recent advances in the newer multiple imaging modalities have made it possible to diagnose cases of primary HCC at an earlier stage (*18*). Limited reports appear in the literature regarding the clinical and radiographic detection of early recurrent or metastasizing hepatocellular carcinoma following surgery (*19–26*). With improvements in the control of the primary tumor with newer treatment modalities, the significance of recurrence due to metastasis becomes increasingly important if prognosis in these patients is to improve (*20*).

During the last five years, we have had the opportunity of following at our institution an increasing number of patients who underwent surgery for localized or solitary hepatocellular carcinoma. The following three cases were evaluated postoperatively in our Medical Center for intervals varying from 4–30 mo following

Received Aug. 18, 1987; revision accepted Dec. 8, 1987.

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primary resection of a solitary HCC. During this period, various imaging and laboratory studies were performed in addition to their clinical evaluations. All three patients showed gallium-67 scan evidence of metastatic recurrence. Clinical, laboratory, and other radiographic modalities proved not to be as useful for the detection of metastasis or local recurrence in the post-operative evaluation of these patients. These findings have led us to conclude that every post-operative patient is a candidate for a baseline and follow-up gallium scan. This may be the earliest marker of post-operative local or distal recurrence and is likely to facilitate further resection and increase the survival rate in this group of patients in whom the overall long term survival has been low with nonsurgical modalities of treatment (*27, 28*).

CASE REPORTS

Case 1

A 28-yr-old woman had a past history of oral contraceptive ingestion for several years. She presented with abdominal pain and was clinically and radiographically (angiogram and CT scan) suspected of having a benign hepatic adenoma in the lateral segment of the liver. A base-line gallium-67 (^{67}Ga) citrate scan revealed a hot spot in the region of the left lobe of the liver, AFP was normal. A left lateral segmentectomy of the liver was performed in June of 1985, and a fibrolamellar HCC was diagnosed. At follow-up examinations in June and September of 1986, clinical and laboratory examinations were unremarkable. A follow-up gallium scan performed on these dates revealed no abnormalities other than the post-surgical changes secondary to the resection (Fig. 1A). Subsequently, the patient started to complain of intermittent right upper quadrant abdominal pain associated with headaches. Clinical and laboratory studies, including serum liver function tests and AFP were normal.

In March of 1987, due to persistence in symptoms, a gallium scan was performed. A localized area of increased ^{67}Ga activity was found in the midline in the inferior aspect of the liver, underlying the region from which the left lobe had been resected (Fig. 1B). A CT, MR, and US scan of the area were interpreted as showing no evidence of recurrence (Fig. 2). One month later, in April, a repeat gallium scan was performed which once again visualized the abnormal concentration of gallium activity in the epigastrium. Technetium-99m sulfur colloid (Fig. 1C) and a ^{99m}Tc hepatobiliary scan performed at this time showed that the focus in the epigastrium was not due to functioning liver tissue. Liver function tests were slightly abnormal and showed the serum glutamic oxaloacetic (SGOT) and serum glutamic pyruvic transaminase (SGPT) to be 202 international units (normal 3 to 35) and 46 international units (normal 7 to 56), respectively. Serum AFP was recorded as being 4 ng/ml (normal less than 15 ng/ml). The patient underwent a laparotomy in April 1987, on the basis of the positive gallium scans. Hepatoma recurrence metastatic to a 2.5-cm lymph node in the superior aspect of the pancreas was demonstrated and was surgically resected. Post-operative evaluations have been unremarkable.

Case 2

A 42-yr-old woman with a 14-yr history of oral contraceptive use, presented with symptoms of right upper quadrant pain and on evaluation was found to have a 13-cm space-occupying lesion involving the right lobe of the liver on, [^{99m}Tc]sulfur colloid liver scan and selective coeliac arteriogram. At surgical biopsy in August 1977, the lesion was diagnosed as being a large hepatic adenoma. Following discontinuance of oral contraceptives, the patient clinically improved and was periodically reevaluated. She demonstrated a decreasing size of the right hepatic lesion on several follow up [^{99m}Tc]sulfur colloid scintigrams performed over the years. In February 1984, the patient presented with an acute onset of right upper quadrant abdominal pain and an elevated white cell count. Ultrasonography performed at this stage showed cholelithiasis. A cholecystectomy was performed, and a necrotic hemorrhagic mass 4 cm in diameter was found and removed from the inferior aspect of the right lobe of the liver, precisely at the site of the previous adenoma. Post-operative surgical biopsy reports revealed that this was a poorly differentiated hepatoma. Tests of serum AFP, ferritin, and hepatitis B surface antigen were negative. A gallium scan was performed which showed a limited area of increased activity along the inferior aspect of the right lobe which was thought to represent residual disease (Fig. 3A). The patient underwent a partial right hepatic lobectomy for tumor found in this region. Four months later in August 1984, the clinical and laboratory findings were unremarkable and a repeat gallium scan showed disappearance of the previously described abnormalities in the inferior aspect of the right lobe. However, a new abnormality was demonstrated in the caudal area of the liver (Fig. 3B). This appeared separated from the liver in the infrahepatic structures presumably around the colon. A CT scan done at this time was interpreted as normal. On reevaluation in December 1984, 4 mo later, a repeat CT scan was performed and now demonstrated a 10-cm mass arising from or in very close relationship to the hepatic flexure of the colon. At this

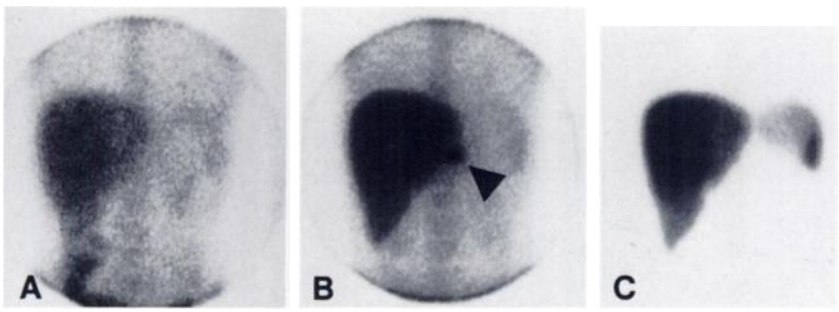
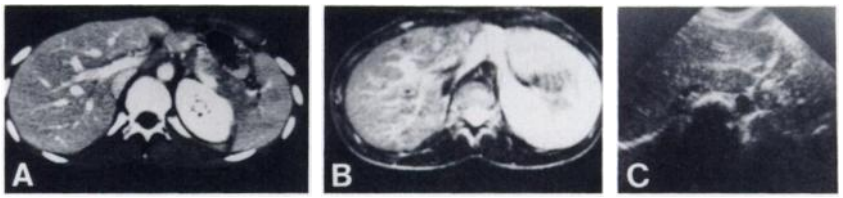


FIGURE 1
A: Case 1 patient demonstrates normal anterior postoperative gallium scan in this patient after left lateral segmentectomy. B: Arrow demonstrates recurrence in the gallium scan 22 mo after the surgery in the upper abdomen which appears extrinsic to the liver. C: Anterior [^{99m}Tc]sulfur colloid scan on this patient shows no abnormalities within the liver.

FIGURE 2
Demonstrates representative CT scans (A); MRI (B); and ultrasound scans (C); Case 1 patient, all studies were interpreted as being normal although gallium scan was called positive for recurrence on two occasions (before and after these studies).



stage, a third laparotomy was performed which revealed a tumor implant on the transverse colon which was resected. Patient has been followed since for approximately two years. Clinically she remains asymptomatic and laboratory and roentgenographic studies, including three follow up gallium scans performed during this period, have shown no evidence of recurrence (Fig. 3C).

Case 3

A 62-yr-old male underwent a hepatic resection in October 1985 for a right lobe primary HCC proven pre-operatively by an US guided needle biopsy. A baseline gallium scan was positive in the area of the mass lesion. A serum alpha fetoprotein AFP in December 1985 was 5 ng/ml (normal less than 15 ng/ml) and a serum carcinoembryonic antigen (CEA) was 1.2 ng.ml (normal 0–3 ng/ml).

Four months later, repeat serum studies showed AFP of 0.4 ng/ml, and a CEA of 1.7 ng/ml. A follow-up CT study showed a left adrenal mass. As there was uncertainty if this was a benign adrenal mass or a metastatic HCC, a gallium scan was done. The gallium scan was positive, confirming a metastatic lesion. At this stage, all other liver function tests were normal. In May 1986, the patient underwent a left adrenalectomy for a single metastatic hepatoma. Follow-up evaluations of this patient, including gallium and CT scans and AFP have been normal.

DISCUSSION

Hepatocellular carcinoma is the most common primary hepatic malignancy in adults and is known to have a poor prognosis (*27,28*). Although a close association of hepatocellular carcinoma with cirrhosis, particularly due to chronic B hepatitis has been known (*16,17,29,30*), screening programs in this high risk group have met with some difficulties, and many cases remain undiagnosed until the time of autopsy (*9,10*) or detected when already inoperable. Serum markers such as AFP, when measured by even the most sensitive methods, may not be abnormally elevated in the detection of early hepatocellular carcinoma.

In recent years, various imaging modalities have been advocated for the detection of focal disorders of the liver. Their overall reported sensitivity and specificity has varied with certain limitations and advantages being advocated for each imaging modality (*5,6,18,22,31,32, 38*).

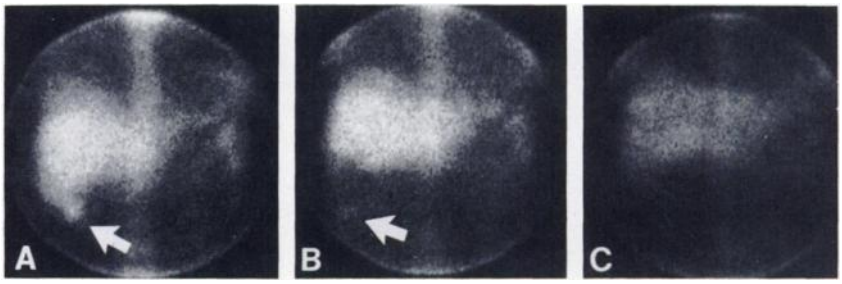
Advances in methods for early detection and identification of operable candidates has resulted in improved prognosis. Because of the better control of the primary tumor and the availability of newer treatment modalities, the significance of detecting early local recurrence would also be important in improving final outcome.

Since hepatoma spreads locally and metastasizes distantly by hematogenous and lymphatic routes (most commonly, to lung, lymph nodes and bone), an imaging modality that can be used for this purpose would be desirable.

The ideal imaging modality should have the prerequisite of being noninvasive, have low cost, be easily repeated, and be able to identify residual or recurrent disease at an early stage both locally and distally with a high degree of sensitivity and specificity.

In the evaluation of patients successfully operated on for hepatocellular carcinoma, no large controlled series exists comparing the relative role of the various imaging modalities. The postoperative patient may be more difficult to evaluate since normal anatomical relationships of both hepatic and extrahepatic structures are often altered. Such factors, as displaced loops of bowel, surgical clips, compensatory hypertrophy of liver lobes, regenerating nodules, and associated liver disease may affect image quality.

FIGURE 3
A: Demonstrates a [^{67}Ga]citrate scan in Case 2 patient; arrow demonstrates site of recurrence 3 mo after resection of the primary hepatocellular carcinoma. B: Demonstrates postoperative scan after second partial lobectomy for residual disease in the liver; arrow shows site of recurrence caudal to the liver. C: Demonstrates follow-up scan 1 yr after last operation which serves as a baseline for this patient.



Previous reports have indicated that most hepatomas show a strong avidity for gallium both in the evaluation of the primary hepatic lesion and also for detecting metastatic lesions. Only a small fraction of hepatomas has been described to be non-gallium-avid (*38*). A baseline study is recommended in every patient, since a follow-up study would be expected to detect any recurrence, if the hepatoma was gallium-avid on the baseline study. Prospective studies are available, evaluating the role of [^{67}Ga]citrate and other imaging modalities in the post-operative follow-up evaluation of patients who have had their primary hepatic tumors resected. Our study allowed us to evaluate a number of imaging modalities in this setting.

SUMMARY

Although multiple imaging modalities are being utilized in the evaluation of primary hepatocellular carcinomas and their metastasis, limited prospective studies are available in evaluating the role of these imaging modalities in the post-operative follow-up evaluation of these patients. Three case studies are reported that demonstrate the usefulness of a post-operative gallium scan. Baseline and follow-up studies are indicated when evaluating patients for recurrence or metastasis or hepatocellular carcinoma. The presence of a positive gallium scan even in the absence of serum markers of additional radiographic evidence of recurrence should still be considered as a sign of recurrence and the need for further evaluation and therapy. Alpha fetoprotein tests may be negative and when positive, the hepatocellular carcinoma lesions found at surgery are usually four to five centimeters in size and are often not resectable (*14*).

Early recognition of recurrence (distant or local) is important to maximize successful surgical resection and increase the overall survival of patients with hepatocellular carcinoma.

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