

USEFULNESS OF COMPUTER SCINTIGRAPHY FOR DETECTING LIVER TUMOR WITH ^{67}Ga -CITRATE AND THE SCINTILLATION CAMERA

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A number of studies on tumor-specific scanning agents have been performed (1-3). In 1969 Edwards, et al (4) reported that carrier-free ^{67}Ga administered as citrate showed remarkable distribution in the palpable cervical lymph node which was histologically confirmed as Hodgkin's disease. In a further paper (5) they reported that 23 of 41 patients showed localization of the isotope in neoplastic tissue. Their series included only a few cases with liver tumors.

The purpose of this paper is to present the usefulness of scintiphotography, particularly computer scintigraphy, with ^{67}Ga -citrate and a scintillation camera for detecting the tumor of the liver.

MATERIALS AND METHOD

Thirteen cases with primary liver cancer and 16 cases with metastatic liver cancer have been examined by scintiphotography. In all the 29 patients, the localization of tumors was confirmed by surgical inspection and histopathological examination.

A Nuclear-Chicago Pho/Gamma III scintillation camera with a high-energy, 3-in., 1,000-hole collimator and an attached Polaroid camera for immediate imaging were used. In addition to the conventional Polaroid photographs, the data were also collected in a 1,600-channel multichannel analyzer and stored in the memory. Data stored in the memory were then transferred to a computer-compatible, seven-channel digitizing tape recorder*.

The patients were given 1-2 mCi of ^{67}Ga -citrate intravenously. Tumor images were displayed on the Polaroid camera integral with the scintillation camera, 48-72 hr after the injection of the isotope, at the 90-keV photopeak setting with a 20% window. The data were also stored in the memory of the

1,600-channel analyzer using a 40×40 array for later recording on digital tape.

Immediately after taking ^{67}Ga scintiphotos, we injected 100 μCi of ^{198}Au -colloid or 150 μCi of ^{131}I -bromsulphalein (BSP) into all these patients keeping them in the same position. The images of ^{198}Au -colloid or ^{131}I -BSP deposited in the liver were then obtained. All data were stored in the tape to provide later computer scintigraphy and to allow a subtraction procedure.

Figure 1 shows the scintiphotograms with ^{67}Ga -citrate and ^{198}Au -colloid in a 37-year-old male who was confirmed to have a huge mass in the right lobe of the liver at surgery. A marked increase in activity localized in the right lobe of the liver where it was shown with ^{198}Au -colloid as a cold area.

Figure 2 shows the results in a 54-year-old female who was confirmed to have multiple metastatic lesions in the right lobe. Any area with increased ^{67}Ga activity or with decreased ^{198}Au activity was not seen

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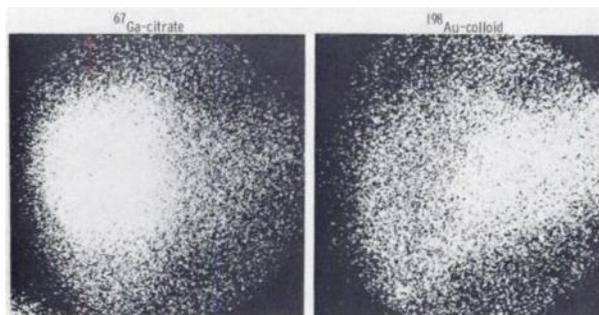


FIG. 1. 37-year-old male with hepatoma. There is increased concentration of ^{67}Ga radioactivity in right lobe of liver, where cold area is demonstrated with ^{198}Au -colloid, indicative of presence of tumor.

* TM-7, Toshiba-Ampex Corp., Suehiro-cho, Kawasaki, Kanagawa, Japan.

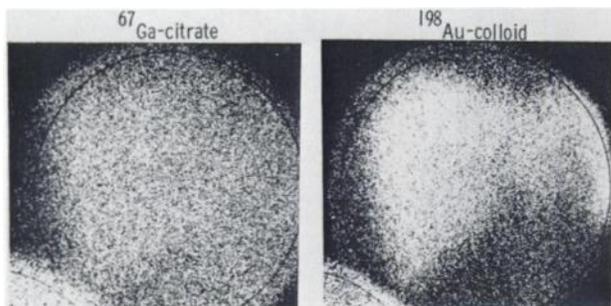


FIG. 2. 54-year-old female with metastatic liver tumor originating in pancreas. No unusual distribution of ⁶⁷Ga-citrate and ¹⁹⁸Au-colloid is shown on scintiphotograms.

Level (%)	Symbol	Level (%)	Symbol
below 5	blank	50—below 55	'
5—below 10	blank	55—below 60	Y
10—below 15	.	60—below 65	#
15—below 20	○	65—below 70	blank
20—below 25	▽	70—below 75	"
25—below 30	blank	75—below 80	?
30—below 35	'	80—below 85	W
35—below 40	=	85—below 90	blank
40—below 45	Q	90—below 95	=
45—below 50	blank	95—below 100	@

on scintiphotograms. Subtraction scintigram is shown in Fig. 8, in the case report.

The excretion of ⁶⁷Ga into the bowel and distribution within the normal liver tissue make it difficult to delineate tumors in the liver. To obtain good resolution of the tumor from the surrounding tissue, computer scintigraphy was performed. The tapes were fed into a FACOM 230-60 computer in the Kyoto University Data Processing Center for processing.

First, data defined by a 40 × 40 matrix were averaged to reduce the random fluctuation. The effect of computer averaging was examined by various configurations such as five-element cross arrays, and a block array of 9, 25, and 49 elements with and without weighting factors. It was found that the nine-element averaging was appropriate in our present system.

Next, to extract true information from the averaged data which were blurred because of the lack of resolution of the detecting system iterative approximations were performed according to Inuma's method (6,7). The observed image is expressed by the convolution of true radioisotope distribution with resolving power of the system. Utilizing a point source of ¹³¹I and ^{99m}Tc in water, we derived a system response function for the 1,000-hole collimator. A system response function with ¹³¹I was used for the restoration of images obtained by ¹³¹I-BSP or ¹⁹⁸Au-colloid and that with ^{99m}Tc was used for ⁶⁷Ga-citrate. From the results of phantom experiments, a resolving power matrix was chosen to be 7 × 7 = 49 elemental images at the central part of the matrix. The iteration procedure was terminated after two times to eliminate the noise in further approximations.

Finally, the computer sought the point of maximum intensity on the matrix and divided this value into 20 levels. The radioisotope image was printed out in a 120 × 80 array assigned by codes, symbols, and letters, as shown in Table 1. This 120 × 80

array was thought to show the liver on the computer scintigram with minimum distortion of the image.

The subtraction scintigram was obtained by subtracting ¹⁹⁸Au-colloid activity from ⁶⁷Ga activity in each matrix which was fed into the magnetic tape. Similar subtraction techniques have been employed in pancreatic scans, using ¹⁹⁸Au for liver and ⁷⁵Se-selenomethionine for liver and pancreas (8,9). In all the patients in this series, a ⁶⁷Ga-¹⁹⁸Au (or ¹³¹I-BSP) subtraction scintigram was obtained and selective angiography was performed. Scintigraphy with ⁶⁷Ga-citrate and ¹⁹⁸Au-colloid was performed and a subtraction scintigram was obtained in two healthy volunteers.

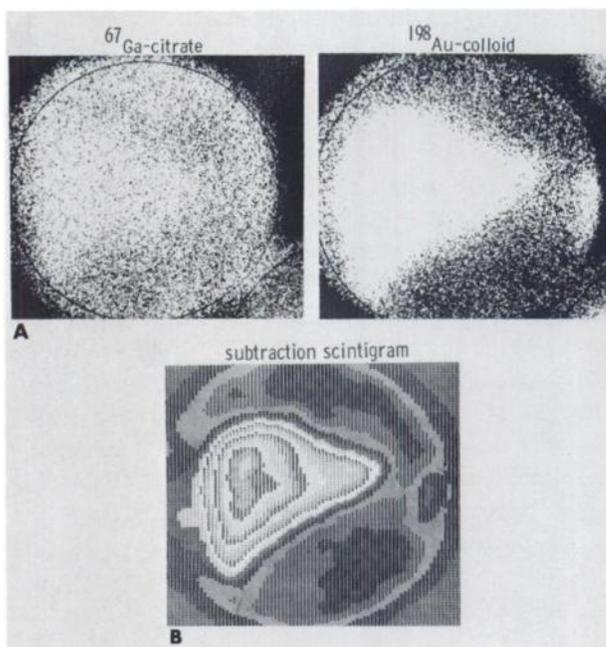


FIG. 3. Case 1. 23-year-old healthy volunteer. There is almost uniform distribution of ⁶⁷Ga-citrate and ¹⁹⁸Au-colloid within liver in scintiphotograms. Subtraction scintigram demonstrates definite margin of liver and smooth count levels in liver. Area with positive count levels in subtraction scintigram is shown as shadow.

The usefulness of computer procedures in detecting liver tumors was compared with conventional imaging with a scintillation camera and with selective angiography.

RESULTS

Results of scintiphotographic, angiographic, and computer scintigraphic examinations on primary and metastatic liver tumors are summarized in Table 2. In patients with primary liver cancer, positive findings were obtained in 12 out of 13 cases examined with ⁶⁷Ga-citrate scintiphotography, in 12 out of 13 cases with ¹⁹⁸Au-colloid (or ¹³¹I-BSP) scintiphotography, in 13 out of 13 cases with selective angiography, and in 13 out of 13 cases with subtraction scintigraphy. In patients with metastatic liver cancer, metastatic lesions were accurately delineated in 7 out of 16 cases with ⁶⁷Ga-citrate scintiphotography, in 10 out of 16 cases with ¹⁹⁸Au-colloid scintiphotography, in 12 out of 16 cases with selective angiography, and in 15 out of 16 cases with subtraction scintigraphy.

REPORT OF CASES

Case 1. Figure 3A shows the scintiphotos with ⁶⁷Ga-citrate and ¹⁹⁸Au-colloid in a 23-year-old healthy volunteer. Almost uniform distribution of ⁶⁷Ga and ¹⁹⁸Au-colloid within the liver was seen in scintiphotos. The subtraction scintigram shows the definite margin of the liver and smooth count levels in the liver (Fig. 3B).

Case 2. A 64-year-old male was admitted with a mass in the right upper abdomen. A selective celiac

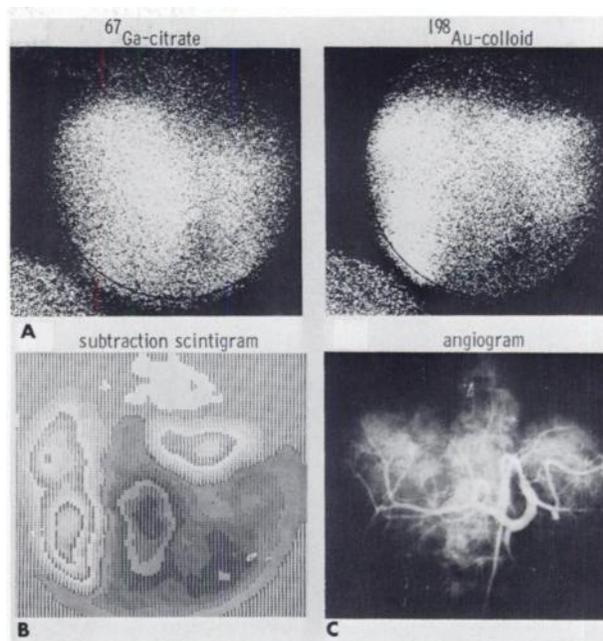


FIG. 4. Case 2. 64-year-old male with hepatoma. Area of increased radioactivity of ⁶⁷Ga is demonstrated to have diminished activity of ¹³¹I-BSP in scintiphotos. In subtraction scintigram this area is shown to have positive count levels shown as shadow. Large hypervascular mass in right lobe of liver in selective celiac angiogram corresponds anatomically to area with higher count levels in subtraction scintigram.

angiogram showed the presence of a mass in the right lobe of the liver (Fig. 4C). In scintiphotos, the area of increased activity with ⁶⁷Ga was shown as coinciding with a zone of diminished activity with ¹⁹⁸Au (Fig. 4A). In the subtraction scintigram this zone was shown to have high count levels (Fig. 4B). Surgery confirmed the presence of a mass, which was histologically hepatoma, in the right lobe of liver corresponding anatomically with the area of higher count levels in the subtraction scintigram.

Case 3. A 40-year-old male was admitted to the hospital for the evaluation of a painless mass of 3-month duration in the epigastric region. A selective angiography revealed that the common hepatic artery derived from the superior mesenteric artery in an aberrant fashion (Fig. 5C). Moderately increased vascularity of the tumor vessels was noted in the left lobe of the liver. Decreased radioactivity of ¹⁹⁸Au-colloid was seen in the left lobe of the liver, but equal distribution of ⁶⁷Ga activity was demonstrated in both lobes (Fig. 5A). The subtraction scintigram showed the positive count levels in this area (Fig. 5B). At the time of surgery, a mass which was histologically hepatoma with cirrhosis was confirmed in this area.

Case 4. A 43-year-old male was admitted with a 3-month history of general fatigue and anorexia. A selective celiac angiogram revealed no definite ab-

TABLE 2. SUMMARY OF SCINTIPHOTOGRAPHIC, ANGIOGRAPHIC, AND COMPUTER SCINTIGRAPHIC EXAMINATIONS ON PRIMARY AND METASTATIC LIVER TUMORS

	Num-ber of cases	Positive findings			
		Scintiphoto		Subtrac-tion scinti-gram	Angio-gram
		⁶⁷ Ga-citrate	¹⁹⁸ Au-colloid		
Primary liver cancer					
Hepatoma	11	10 (90.9%)	10 (90.9%)	11 (100%)	11 (100%)
Cholan-gioma	2	2 (100%)	2 (100%)	2 (100%)	2 (100%)
Metastatic liver cancer					
	16	7 (43.8%)	10 (62.5%)	15 (93.8%)	12 (75.0%)

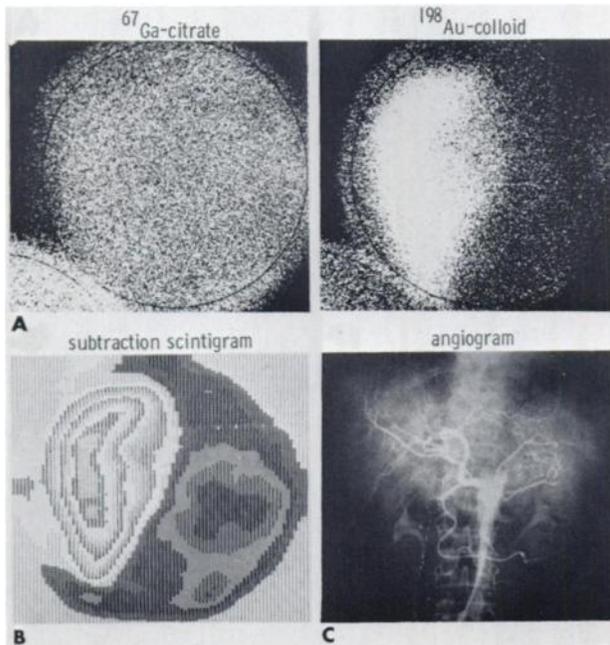


FIG. 5. Case 3. 40-year-old male with hepatoma. Corresponding with area of decreased radioactivity of ^{198}Au -colloid in left lobe of liver, normal, not increased, distribution of ^{67}Ga activity is shown in scintiphotograms. Area is demonstrated as positive in subtraction scintigram. Angiogram demonstrates presence of mass in left lobe of liver.

normal vessels in the liver (Fig. 6C). Both scintiphotograms with ^{67}Ga -citrate and ^{198}Au -colloid showed decreased activity in the left lobe of the liver (Fig. 6A). A mass in the left lobe of the liver which was histologically cholangioma was shown as an area of higher count levels on the subtraction scintigram (Fig. 6B).

Case 5. A 45-year-old male was admitted with a mass in the left upper abdomen and progressive jaundice, thought to be obstructive and due to a possible pancreatic tumor. A selective angiogram did not confirm the presence of tumor in the liver (Fig. 7C). No abnormal distribution of ^{67}Ga in the liver was shown on the scintiphotogram. A slight decrease in radioactivity in the left lobe of the liver, on the other hand, was shown with ^{131}I -BSP (Fig. 7A). A subtraction scintigram accurately delineated the extent of the disease in the border of left and right lobes of the liver (Fig. 7B). Surgery confirmed a small mass (2×2 cm) at the same site as shown on a subtraction scintigram.

Case 6. A 54-year-old female was admitted with progressive jaundice and weight loss. A selective angiogram demonstrated abnormal vessels in the upper margin of the right lobe of the liver (Fig. 8B). The scintiphotogram with ^{67}Ga did not delineate the presence of tumors. No unusual distribution of radioactivity in the liver was shown on the scintiphotogram with ^{198}Au -colloid (Fig. 2). Several areas with

higher count levels were shown on the subtraction scintigram (Fig. 8A). Surgery confirmed the presence of two metastatic lesions (2×2 cm) corresponding with areas of higher count levels on the subtraction scintigram (arrow). The other areas with high count levels could not be confirmed by the existence of foci at surgery.

DISCUSSION

It has been shown that ^{67}Ga administered as a citrate complex can concentrate in a wide variety of human tumors. This concentration, however, does not constantly occur in all kinds of tumor. The mechanism for the localization of ^{67}Ga -citrate in tumor is not known. We observed increased concentration of gallium in inflammatory lesions such as liver abscess. Swartzendruber and associates (10) pointed out from their light and electron microscopic autoradiography that the localization of ^{67}Ga in the liver was over both hepatic and Kupffer cells and suggested that the intracellular sites localizing ^{67}Ga were lysosomes or places of lysosomal enzymatic activity. Therefore ^{67}Ga cannot be regarded as an ideal scanning agent for malignant tumors. However, concentration of ^{67}Ga in liver tumors, especially in hepatoma, indicates the undoubted clinical value of this radionuclide.

In this study, 28 patients with primary or meta-

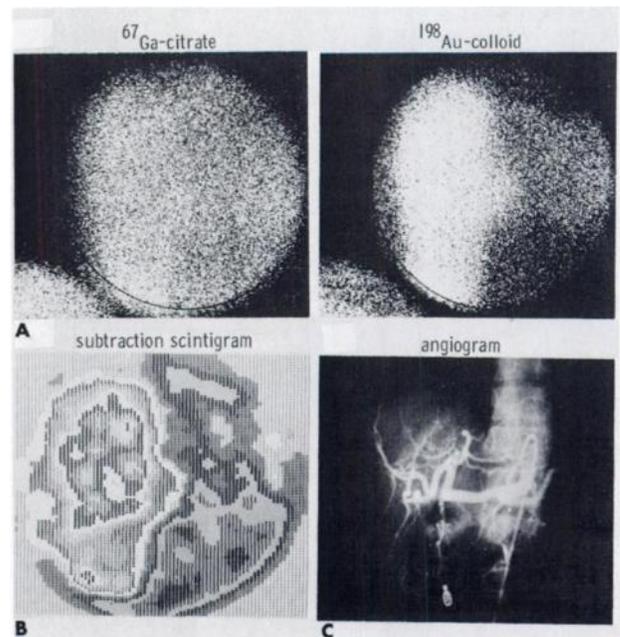


FIG. 6. Case 4. 43-year-old male with cholangioma. Scintiphotograms with ^{67}Ga -citrate and ^{198}Au -colloid show decreased radioactivity in left lobe of liver. Area is demonstrated as area of positive count levels on subtraction scintigram. Surgery confirmed mass that corresponded anatomically with subtraction scintigram. No abnormal vessels are shown on selective angiogram.

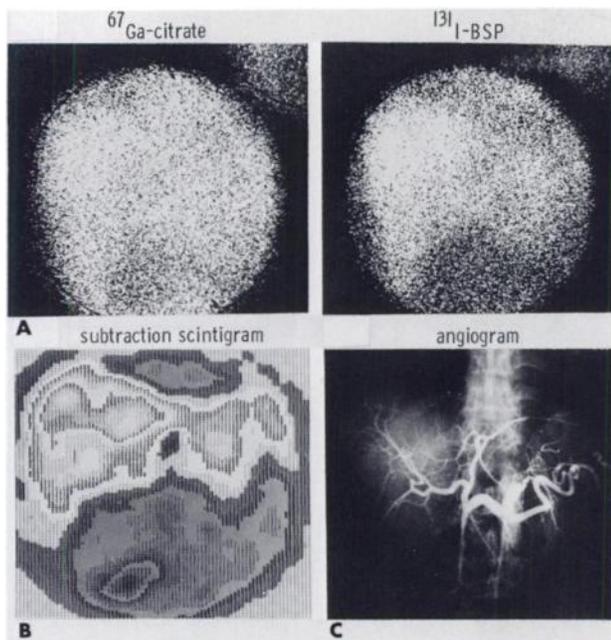


FIG. 7. Case 5. 45-year-old male with metastatic liver cancer of pancreatic cancer. Slight decrease in radioactivity of ^{131}I -BSP in left lobe of liver and almost normal distribution of ^{67}Ga in liver area is demonstrated on scintiphotograms. Angiogram does not demonstrate any abnormal vessels in liver. Subtraction scintigram accurately delineates extent of disease in border of left and right lobes of liver. Surgery confirmed presence of small mass (2×2 cm) on site.

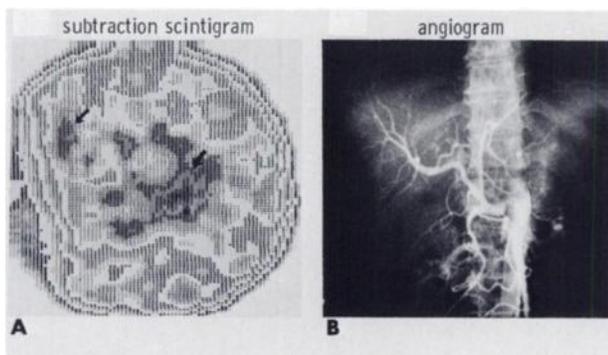


FIG. 8. Case 6. 54-year-old female with metastatic liver tumor originated in pancreas whose scintiphotograms with ^{67}Ga -citrate and ^{198}Au -colloid were shown in Fig. 2. Selective angiogram demonstrates abnormal vessels only in upper margin of right lobe of liver. Several areas show positive count levels which are revealed on subtraction scintigram. Surgery confirmed two metastatic lesions (2×2 cm, respectively) corresponding to areas indicated by arrows.

static liver tumors were examined by scintiphotography with ^{67}Ga -citrate, ^{198}Au -colloid or ^{131}I -BSP, and scintillation camera. Distribution of ^{67}Ga within the normal liver tissue may mask a small hot lesion with a high level of radioactivity in the liver. To obtain good resolution of the tumor from the surrounding tissue, subtraction scintigraphy was performed. Our comparative studies of scintiphotography, subtraction procedure, and selective angiography

showed that subtraction scintigraphy was of great value in detecting the liver tumors. The subtraction scintigram has enhanced the contrast so that tumors in the liver which are invisible on conventional read-outs become obvious. Cases 5 and 6 exemplified this. In these two cases, the metastatic foci 2 cm in diameter were shown on the subtraction scintigrams. An example of false positive subtraction scintigram was shown in Fig. 8. Nonuniformity of the ratio of between ^{198}Au -colloid and ^{67}Ga -citrate in liver might be expected in patients with cirrhosis to cause falsely positive scans.

Our results would indicate that subtraction scintigraphy with ^{67}Ga -citrate and ^{198}Au -colloid is a superior method of detecting tumors in the liver.

SUMMARY

The usefulness of scintiphotography, particularly computer scintigraphy using ^{67}Ga -citrate and the scintillation camera for detecting the tumors of the liver, was evaluated.

Twenty-nine patients with liver tumors were examined by the scintillation camera coupled to a 1,600-channel analyzer and tape data storage for computer processing using ^{67}Ga -citrate, ^{198}Au -colloid, and ^{131}I -BSP.

Gallium-67 administered as the citrate was excreted into the bowel and distributed within the normal liver tissue. This made it difficult to delineate the tumor image in the liver. The dual isotopes, ^{67}Ga -citrate and ^{198}Au -colloid (or ^{131}I -BSP), allowed computer-subtraction scintigraphy to be applied which enabled us to delineate the tumor image in two cases with metastatic liver tumor invisible on conventional scintiphotography with these isotopes.

These results suggested that ^{67}Ga -citrate scintigraphy, particularly computer scintigraphy, was clinically useful in evaluating the presence and distribution of tumors of the liver.

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