⁷⁵Se-selenomethionine in the scintiscan diagnosis of primary hepatocellular carcinoma

A. L. W. F. EDDLESTON, M. O. RAKE, A. P. PAGALTSOS, S. B. OSBORN, AND ROGER WILLIAMS

From the Medical Research Council Group on the Metabolism and Haemodynamics of Liver Disease and the Department of Medical Physics, King's College Hospital, London

SUMMARY Forty-eight patients with 'cold areas' on ^{99m}Tc sulphur colloid liver scintiscans were scanned again using ⁷⁵Se-selenomethionine. In 11 patients with primary hepatocellular carcinoma considerable uptake of ⁷⁵Se-selenomethionine could be demonstrated in the area of the tumour and uptake of ⁷⁵Se-selenomethionine was also observed over extrahepatic metastases in two of these cases.

In contrast uptake was low in cholangiocellular carcinoma, Kupffer cell sarcoma, and secondary hepatic deposits (excepting melanoma metastases). No cause for the 'cold area' on the ^{99m}Tc scan could be discovered in 16 of 25 patients with cirrhosis and in these patients the uptake of the two isotopes in the area of the 'false positive' filling defect was almost equal. Positive identification of primary hepatocellular tumours using this dual scanning technique can be of value in determining and assessing treatment by surgery or cytotoxic therapy.

Scintiscanning has proved to be of value in the diagnosis of primary and secondary tumours in the liver (Wagner, McAfee, and Mozley, 1965; Poulouse, Reba, Deland, and Wagner, 1969). However, the colloidal substances most commonly used for scanning, namely, technetium (^{99m}Tc), gold (¹⁹⁸Au), and indium (^{113m}In), are taken up in the liver by Kupffer cells only and tumours, whatever their nature, are shown as 'cold areas'. Other space-occupying lesions—abscesses and cysts—may produce similar scanning appearances, and in patients with cirrhosis 'cold areas' may be evident on the scan for which no particular cause can be found on further investigation or at necropsy, the so-called 'false positive' filling defects (Johnson and Sweeney, 1967; Eddleston, Blendis, Osborn, and Williams, 1969). To identify tumour tissue positively would therefore be of considerable value, but no agent has yet been described which is taken up in a higher concentration in the neoplastic tissue than in surrounding normal liver tissue. However, ⁷⁵Se-selenomethionine (⁷⁵Se) is known to be taken up by normal hepatocytes, and in a patient with a primary hepatocellular carcinoma Ben-Porath, Clayton, and Kaplan (1967) showed equal concentration of this compound in tumour tissue and normal

liver tissue both on scintiscanning and subsequently at necropsy. This finding they subsequently confirmed in five of six patients with primary liver tumours (Kaplan and Ben-Porath, 1969). In this paper we report the findings in 48 patients found to have 'cold areas' on the routine ^{99m}Tc scans, with particular reference to the value of an additional ⁷⁵Se scan in the diagnosis of primary hepatocellular carcinoma.

Scanning Technique and Analysis

A Picker Magnascanner V was used with a 5 in. coarse focus collimator. One millicurie of ^{99m}Tc sulphur colloid was injected intravenously and 15 minutes later an anteroposterior scan was recorded. The positions of the costal margins, nipples, umbilicus, and palpable liver edge were marked on the scan. Scintiscanning was performed in the usual way and on completion the patient was given 500 microcuries of ⁷⁵Se selenomethionine intravenously. Thirty minutes later a repeat scan was performed using the same surface markings but with the scanner readjusted to detect ⁷⁵Se only.

The count rate in the 'cold area' was estimated from the colour dot scan. The machine is capable

of printing eight different colours in predetermined sequence (white, black, mauve, blue, green, yellow, red, and brown), and is so adjusted that brown-coloured dots are printed at the site of the maximum count rate which is located by moving the detector head over the lower thorax and upper abdomen. The range of count rate between 0 and 100% will then be automatically divided into eight steps of 12·5%, and the count rate in the 'cold area' can be easily determined as a percentage of the maximum count rate.

Results

The causes of the 'cold areas' seen on the ^{99m}Tc scans are given in the Table. These diagnoses were established after full clinical, biochemical, and radiological investigations supported by histological examination of percutaneous or surgical biopsy. In a number of cases the diagnosis was also confirmed at necropsy. Of the 48 patients, 25 had cirrhosis, nine were shown to have primary tumours of the liver, but in the other 16 no cause could be found for the 'cold area' seen on the scan. All the patients with primary hepatocellular carcinoma showed uptake of ⁷⁵Se in the area of the tumour

Diagnosis	Total No. of Cases	No. with Cirrhosis
Primary hepatocellular carcinoma	11	6
Cholangiocellular carcinoma	2	1
Kupffer cell sarcoma	3	2
Secondary deposits	4	0
Primary melanoma	12	0
Other secondary deposits	16	16
'False positive' filling defects in cirrhosis		

Table Final diagnosis of the 48 cases examined by both ^{99m}Tc sulphur-colloid and ⁷⁵Se-selenomethionine scintiscans

almost equal to that in the normal liver, and the appearances of the ⁷⁵Se scans were strikingly different from those of the ^{99m}Tc scans. This is illustrated by the following cases.

CASE 1
A woman, aged 76 years, presented with a blistering photosensitive skin eruption characteristic of porphyria cutanea tarda. Abdominal palpation revealed an enlarged liver with a large mass in the lower part of the right lobe. A 'cold area' corresponding with the mass was seen on the ^{99m}Tc

Fig. 1 (a) Primary hepatocellular carcinoma; ^{99m}Tc sulphur colloid scan showing large 'cold area' in lower part of right lobe, and (b) ⁷⁵Se-selenomethionine scan showing marked uptake of isotope in the 'cold area'.

Fig. 2 (a) $^{99\text{m}}\text{Tc}$ sulphur colloid scan showing 'cold area' in the left lobe of liver, and (b) ^{75}Se -selenomethionine scan with marked uptake of the isotope into the 'cold area'.

scan and there was considerable uptake of ^{75}Se in this area (Fig. 1). Histological examination of a percutaneous biopsy from the mass showed a well differentiated primary hepatocellular carcinoma.

CASE 2

A 29-year-old woman presented with epigastric pain. A mass was palpable in the epigastrium and a $^{99\text{m}}\text{Tc}$ scan showed a corresponding 'cold area' in the left lobe of the liver. Uptake of ^{75}Se in this area was equal to that in the normal liver (Fig. 2) and histological examination of the tumour, which was successfully removed by a left lobe hepatectomy, confirmed the diagnosis of primary hepatocellular carcinoma.

In each of these patients the diagnostic information came from the difference in uptake of the two isotopes in the area of the tumour. This could be quantitated by subtracting the count rate in the tumour area on the $^{99\text{m}}\text{Tc}$ scan (as a percentage of the maximum count rate) from that on the ^{75}Se scan. The difference between the uptake of the two isotopes was larger in the group of patients with primary hepatocellular carcinoma (with or without underlying cirrhosis) than in those with other primary liver tumours, secondary hepatic deposits, or cirrhosis with 'false positive' filling defects (see Fig. 4). The only other cases in which this occurred were

the four patients with secondary hepatic deposits from a primary melanoma of the eye.

In two patients uptake of ^{75}Se could also be demonstrated in extrahepatic metastases from a primary hepatocellular carcinoma. One of these, a man aged 74 years known to have cirrhosis, presented with a bony swelling at the right ankle. A $^{99\text{m}}\text{Tc}$ scan of the liver showed a 'cold area' in the right lobe. After giving ^{75}Se definite uptake of the isotope

Fig. 3. Extrahepatic uptake of ^{75}Se -selenomethionine in right ankle of a 74-year-old man; the three black circles are the surface markings indicating the posterior wall of the foot and the bony swelling.

Fig. 4 The count rate in the 'cold area' on the ^{75}Se -selenomethionine scan (as a percentage of the maximum count rate) minus that on the $^{99\text{m}}\text{Tc}$ sulphur colloid scan in the 48 cases studied.

could be demonstrated not only over the primary tumour in the liver but also at the site of the bony swelling (Fig. 3). At necropsy, the presence of the secondary deposit was confirmed, the histological appearances being similar to those of the primary hepatocellular carcinoma. In the other case, a girl of 18 years, scanning showed uptake of ^{75}Se , both over a large tumour in the liver and by a mass in the pouch of Douglas. Histological examination at necropsy of both the tumour in the liver and the mass in the pelvis showed a poorly differentiated primary hepatocellular carcinoma.

Discussion

Since ^{75}Se selenomethionine is derived by the substitution of ^{75}Se for the sulphur atom in the methionine molecule it is thought to follow the same metabolic pathways as methionine. Rapid incorporation into tissue and plasma proteins has been demonstrated (Awwad, Adelstein, Potchen, and Dealy, 1967), but relatively few studies are available on

the uptake of this compound by different organs and of the final distribution of an intravenous dose within the body. Uptake by the pancreas has made it of use for pancreatic scintiscanning (Blau, Manske, and Bender, 1962) although Ben-Porath and Kaplan (1969) found a higher concentration in the liver three hours after injection than in the pancreas (1.75 as compared with 1.35% of the total dose per 100 g of tissue).

The histological appearance of a primary hepatocellular carcinoma may closely resemble normal liver tissue, and indeed tumour cells may retain some of the functions of normal hepatocytes, including bile formation (Evans, 1966). The concentration of ^{75}Se in primary hepatocellular carcinoma might therefore be expected to approach that in normal liver tissue. Simple visual inspection of the scintiscans was often sufficient to show that a considerable amount of ^{75}Se had been taken up in areas of the liver in which $^{99\text{m}}\text{Tc}$ uptake was low. However, the actual count rate over the abnormal area on the ^{75}Se scan will depend not only on the uptake of the

compound by the tumour but also on the amount of normal liver tissue lying around the tumour; the latter was allowed for in the present study by subtracting the count rate over the filling defect on the ^{99m}Tc scan from that on the ⁷⁵Se scan. The development of an automatic subtraction scanning technique in which the differences in uptake of the two isotopes in the area of the tumour could be quantitated would be of considerable value.

Primary hepatomas are often classified according to histological appearances into two varieties, the cholangiocellular with structures resembling bile ducts and the hepatocellular with sheets of cells (Sherlock, 1968). However, mixed varieties occur and some authors consider both types to be variants of the same tumour (Weinbren, 1966). The finding of a considerable uptake of ⁷⁵Se only in tumours of the hepatocellular type shows a difference in the metabolism of these two varieties which might indeed indicate different cells of origin. In three of the present patients the histological appearances were those of Kupffer cell sarcoma. These tumours might be expected to take up ^{99m}Tc sulphur colloid, but in the cases studied the tumour mass was seen as a clear-cut 'cold area' on liver scintiscanning using this isotope, and the uptake of ⁷⁵Se was also low.

Markedly increased uptake of ⁷⁵Se was only found in one other tumour type—secondary hepatic deposits of melanoma. Why this occurred is uncertain. Methionine is not known to be a constituent of human melanin although it is found in 'squid' melanin (Shuster, 1970). The intermediary quinones which are involved in melanin synthesis could react with methionine but it is unlikely to be an important factor when very small doses are used, as in the present study. It is also possible that protein is synthesized at a high rate in melanoma tissue in a separate metabolic pathway from that involved in melanin synthesis.

In clinical practice, the diagnosis of secondary melanoma is usually not difficult and the finding of an increased ⁷⁵Se uptake relative to ^{99m}Tc in the area of a suspected tumour is very suggestive

evidence of a primary hepatocellular carcinoma. This is true whether or not there is underlying cirrhosis. The incidence of primary hepatoma in cirrhosis of about 15% in current necropsy series (Sherlock, 1968) may be increasing owing to the longer survival of patients with cirrhosis. However, if the primary tumour in patients with cirrhosis is of the cholangiocellular or Kupffer cell type positive identification is not possible. Nevertheless, the positive identification of primary hepatocellular carcinoma and the demonstration of the extent of both intra- and extra-hepatic spread can be of considerable help in the management of these patients, particularly in the selection of cases suitable for transplantation or partial hepatectomy.

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