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Clinical Significance of Hepatic Visualization on Iodine-131 Whole-Body Scan in Patients with Thyroid Carcinoma

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The purpose of this study was to evaluate the frequency and clinical significance of diffuse hepatic uptake on ^{131}I whole-body scan in 399 patients (53 males, 346 females) with well-differentiated adenocarcinomas of the thyroid. **Methods:** Two hundred and ninety-one diagnostic scans were performed 2 days after the administration of 74–370 MBq (2–10 mCi) ^{131}I, and 824 post-therapy scans were done 3–5 days after the administration of 1.11–7.4 GBq (30–200 mCi) ^{131}I. There was no evidence of liver metastasis in these patients. Liver and thyroid visualization on each ^{131}I scan were graded from 0–4. To evaluate the incorporation of radioiodine to thyroglobulin and thyroid hormones, a patient's serum was extracted by 80% ethanol/20% trichloroacetic acid solution and analyzed by silica gel thin-layer chromatography. **Results:** Diffuse hepatic uptake (>Grade 2) was definitely seen in 239 of 399 (59.9%) of the patients and 397 of 1115 (35.6%) of the studies. In the diagnostic scans, 36 (12.0%) showed uptake in the liver. In post-therapy scans, however, the incidence of liver uptake increased according to increased doses of ^{131}I (39.1% with 1.11 GBq, 61.5% with 2.775–3.7 GBq and 71.3% with 5.55–7.4 GBq). The more that uptake appeared in the residual thyroid, the more it appeared in the liver. There were 13 patients whose scans showed metastatic and liver uptake without any thyroid uptake. Fifteen patients showed diffuse liver uptake without uptake by the thyroid or metastasis. Follow-up studies of seven of these patients revealed metastatic lesions. Liver uptake on scan related to the fraction of ^{131}I-labeled thyroglobulin in the serum. **Conclusion:** Diffuse liver uptake indicated functioning thyroid remnant or metastasis. In a few cases, liver uptake without uptake by the thyroid or metastasis on whole-body scans suggests hidden metastases.

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Whole-body ^{131}I scan has been used to evaluate patients with well-differentiated thyroid adenocarcinomas after operation and ablation therapy. Normally, radioactive iodine accumulates in organs, including residual thyroid tissue, the stomach, intestine, salivary gland and urinary bladder that secrete and concentrate iodide (*1*). Several studies have been published reporting diffuse liver uptake of ^{131}I in thyroid carcinomas after surgery, detected either during diagnostic procedures or after the administration of ablative doses of ^{131}I (*2–6*). Pochin suggested that diffuse liver uptake was mainly due to the metabolism of

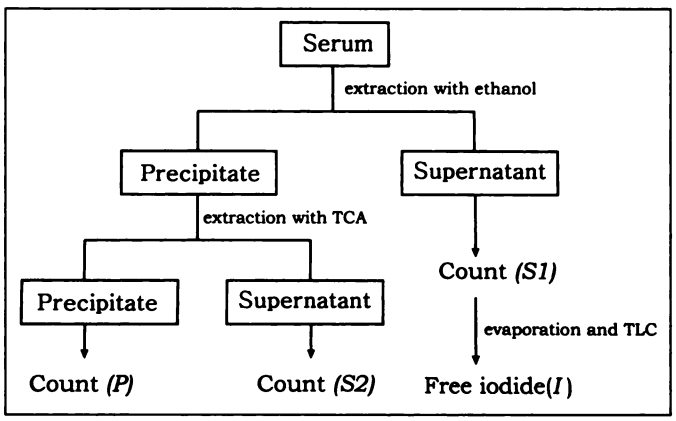

FIGURE 1. Scheme and interpretation of patient's serum analysis.

TABLE 1
Percentage of Each Extracted Fraction Measured by Standards

Fraction	T3	T4	Tg	I-131
Precipitate (P)	3.9 ± 0.2	17.5 ± 0.8	93.8 ± 3.6	1.4 ± 0.7
Ethanol (S1)	91.9 ± 0.9	66.4 ± 0.5	4.7 ± 3.1	96.2 ± 3.4
20% TCA (S2)	4.2 ± 0.7	16.1 ± 0.3	1.5 ± 0.6	2.4 ± 3.0
Total	100	100	100	100

Each value shows mean ± s.d. TCA = trichloroacetic acid.

TABLE 2
Distribution of Liver Visualization in Iodine-131 Whole-Body Scan

Liver uptake	Number of scans	Number of patients
Grade 0	461 (41.4%)	97 (24.2%)
Grade 1	257 (23.1%)	63 (15.8%)
Grade 2	304 (27.2%)	159 (40.0%)
Grade 3	68 (16.1%)	56 (14.0%)
Grade 4	25 (2.2%)	24 (6.0%)
Total	1115	399

labeled thyroid hormones in the liver and therefore indicated hormonification (*7*). There is still controversy, however, concerning the mechanism of ^{131}I liver uptake, especially in patients with ablated thyroid tissue.

Ziessman et al. demonstrated that liver visualization in ^{131}I whole-body scan was more common than generally appreciated (*4*). Schober et al. reported several cases of diffuse liver uptake with functioning metastases. He concluded that this indicates either functioning thyroid remnants, recurrence of the tumor, functioning metastases or a combination of these (*5*). Although ^{131}I whole-body scan is used as a routine imaging method to detect metastatic lesions, false negatives accounting for 13%–23% of total scans were reported (*8–11*). It is possible that liver uptake of ^{131}I offers additional information for the detection of metastasis.

Diffuse liver uptake without remnant thyroid or functioning metastases on ^{131}I whole-body scan had not been reported. But we encountered several cases with these findings. We performed this study to evaluate the frequency and clinical significance of this diffuse pattern of liver uptake on ^{131}I whole-body scan.

MATERIALS AND METHODS

Patients

Included in our study were 401 patients examined between 1983 and 1995. Two patients with liver metastasis were excluded, leaving 399 patients (346 females and 53 males). Well-differentiated adenocarcinomas of the thyroid were confirmed in all patients by biopsy or surgical pathology.

Iodine-131 Whole-Body Scan

Of a total of 1115 scans, 291 were diagnostic and performed 2 days after oral ingestion of 74–370 MBq (2–10 mCi) ^{131}I, whereas 824 were post-therapy and performed 3–5 days after ingestion of 1.11–7.4 GBq (30–200 mCi) ^{131}I. All patients had discontinued thyroid hormone replacement 4 wk earlier and had elevated levels of thyroid stimulating hormone (>30 IU/ml). A large field-of-view gamma camera (ON 410) with medium-energy parallel hole collimator was used for imaging. A 20% symmetric window was centered at 364 keV. Anterior images of the neck, chest and abdomen were obtained, each accumulating 100,000 counts.

Images were evaluated retrospectively by two experienced nuclear physicians for diffuse liver uptake, remnant thyroid uptake and the presence of metastases. The uptake of the liver or thyroid was subjectively graded by consensus on a scale from 0 to 4: 0, no uptake; 1, equivocal uptake; 2, definite but faint uptake; 3, moderate uptake; 4, intense uptake.

Analysis of Patient's Serum

Just before ^{131}I whole-body scan, blood was drawn from 46 patients, and the distribution of radioactivity was analyzed. Each 0.5 ml of serum was extracted with 2.5 ml of ethanol three times, and the precipitate and supernatant were separated by centrifugation (3000 × g for 30 min). Each sample of supernatant was dried by blowing nitrogen gas at 37°C and analyzed by thin-layer chromatography (TLC) (chloroform:MeOH:ammonium hydroxide = 6:4:0.5) after radioactivity was measured by a γ scintillation counter (S1). Standards for TLC, including 3-monoiodotyrosine (MIT), 3,5-diiodotyrosine (DIT), 3,3′,5-triiodothyronine (T3) and 3,3′,5,5′-tetraiodothyronine (T4) were purchased from Sigma Chemical Co., St. Louis, MO. Although we were able to separate all possible standard iodine-containing components by TLC, amounts of radioactivity in the serum of some patients were not clearly separated. Instead, we quantitatively measured the percentage of free iodide (I) in S1 fraction by TLC using a BAS1500 image analyzer. Each ethanol precipitate was extracted with 2.5 ml of 20% trichloroacetic acid (TCA) twice to completely extract protein-bound T4. Radioactivity of the final supernatants (S2) and precipitates (P) was measured by a gamma scintillation counter (Fig. 1).

We measured the extraction percentage of standards using ^{131}I-labeled T3, T4, thyroglobulin (Tg) and ^{131}I-iodide. The percentage of each extracted fraction measured by standards is summarized in Table 1. From these results, we were able to estimate the radioactivity of each component in a patient's serum according to the following equations.

1. Radioactivity in Tg = P.
2. Radioactivity in organic component (T3, T4, MIT, DIT, etc.) = S1 + S2 − I * S1.
3. Free iodide = I * S1.

Statistical Analysis

Statistical analysis on the relationship between liver uptake and ^{131}I dose or thyroid uptake was done using χ^2 test. Differences in

TABLE 3
Relation Between Iodine-131 Dose and Liver Visualization

Liver uptake	≤370 MBq (n = 300)	1.11 GBq (n = 672)	2.775–3.7 GBq (n = 26)	5.55–7.4 GBq (n = 108)
Grade 0	235 (78.3%)	205 (30.5%)	5 (19.2%)	16 (14.8%)
Grade 1	33 (11.0%)	205 (30.5%)	5 (19.2%)	15 (13.9%)
Grade 2	25 (8.3%)	221 (32.9%)	11 (42.3%)	37 (34.3%)
Grade 3	5 (1.7%)	36 (5.3%)	3 (11.6%)	24 (22.2%)
Grade 4	2 (0.7%)	5 (0.8%)	2 (7.7%)	16 (14.8%)

χ^2 = 311.55, df = 12, $p < 0.001$.

TABLE 4
Relation between Visualization of the Thyroid and Liver

Liver uptake	Thyroid uptake				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Grade 0	135 (66.8%)	81 (54.7%)	60 (36.4%)	69 (29.4%)	107 (33.8%)
Grade 1	29 (14.4%)	33 (22.3%)	51 (30.9%)	81 (34.4%)	60 (18.9%)
Grade 2	30 (14.8%)	30 (20.3%)	47 (28.5%)	71 (30.4%)	101 (31.9%)
Grade 3	7 (3.5%)	1 (0.7%)	6 (3.6%)	12 (5.1%)	36 (11.3%)
Grade 4	1 (0.5%)	3 (2.0%)	1 (0.6%)	2 (0.9%)	13 (4.1%)

$\chi^2 = 165.65$, df = 16, $p < 0.001$.

the fraction percentage of ^{131}I-labeled thyroid hormones and Tg among grades of liver uptake were tested using the Kruskal–Wallis test. The entire statistical procedure was done by PC-SAS. Values lower than 0.05 were considered significant.

RESULTS

Diffuse hepatic uptake (>Grade 2) was definitely seen in 239 of 399 (59.9%) patients and 397 of 1115 (35.6%) studies (Table 2). In diagnostic scans, 36 (12.0%) showed uptake in the liver. In post-therapy scans, however, the incidence of liver uptake increased significantly ($p < 0.001$), according to doses of ^{131}I (39.1% with 1.11 GBq, 61.5% with 2.775–3.7 GBq and 71.3% with 5.55–7.4 GBq) (Table 3). The more uptake that appeared in the residual thyroid, the more intense uptake appeared in the liver ($p < 0.001$) (Table 4).

There were 13 patients whose scans showed metastatic and liver uptake without any thyroid uptake. Fifteen patients showed diffuse liver uptake without uptake by the thyroid or metastasis. Follow-up studies of seven of these patients revealed metastatic lesions. Profiles of these patients are summarized in Table 5. In all seven patients, the serum level of Tg was elevated; in four follow-ups, ^{131}I whole-body scan showed lung metastasis, which in three patients was confirmed by computed tomography (CT). In the other three patients, enlarged cervical lymph nodes were palpable, and reoperation with neck dissection confirmed the recurrence of cancer in these lymph nodes. All except one of the eight other patients showed normal serum Tg levels and no evidence of metastasis or recurrence.

Patient 2, shown in Figure 2, is a typical case. Initial ^{131}I whole-body scan (Fig. 2A) showed Grade 2 liver uptake with neither uptake by the thyroid nor metastasis. However, the serum level of Tg was 58.8 ng/ml at that time. Follow-up whole-body scan (Fig. 2B), 15 mo later, revealed lung uptake and chest CT (Fig. 2D) showed lung metastasis. Results for Patient 5 are shown in Figure 3. Iodine-131 whole-body scan showed Grade 2 liver uptake and no metastatic lesion. This patient's serum concentration of Tg was very high (152.3 ng/ml). However, a whole-body scan, obtained 31 mo later, showed only liver uptake. On physical examination, cervical lymph nodes were palpable. Lymph node dissection was performed, and metastatic papillary carcinoma was confirmed by pathology.

We compared the distribution of ^{131}I in serum with grades of liver uptake in 46 patients. We examined the incorporation of radioiodine to Tg and organic components, including thyroid hormones, in the sera of patients. Liver uptake on scan did not relate to the fraction of ^{131}I-labeled organic components. But the fraction of ^{131}I-labeled Tg increased according to the increase of liver uptake ($p < 0.01$) (Table 6).

DISCUSSION

After operation, patients with well-differentiated thyroid carcinoma are evaluated by chest radiograph, ^{131}I whole-body scan and serum Tg determination. Iodine-131 whole-body scan is the usual method for evaluating patients after ablative thyroid therapy (*11*). However, only about 50%–80% of recurrent or metastatic lesions will concentrate sufficient ^{131}I for therapy, and false-negative ^{131}I whole-body scan was found in 13%–23% of all cases (*8–10*). Several groups have reported abnormally elevated serum Tg levels in patients with negative radioiodine scans (*9,12*). False-positive results of Tg tests have also been reported, however (*13*). For the detection of residual-functioning thyroid carcinoma, the combination of serum Tg and ^{131}I whole-body scan is therefore superior to either method alone (*10,11*).

Several articles have reported diffuse hepatic uptake on ^{131}I whole-body scan (*2–6*). In particular, Ziessman et al. demonstrated that liver visualization was common and related to the dose of ^{131}I and indices of thyroid function (*4*). In this study, diffuse hepatic uptake was seen in 59.9% of patients and 35.6%

TABLE 5
Profiles of Patients Who Showed Metastases after Liver Visualization on Iodine-131 Whole-Body Scan

Patient no.	Age (yr)	Sex	Follow-up I-131 scan	Serum Tg (ng/ml)	Length of follow-up (mo)	Tumor extent	Confirmation of metastases	Pathology
1	67	F	Lung uptake	45.0	12	Lung	F/U ^{131}I scan	Papillary
2	21	F	Lung uptake	58.8	15	Lung, cervical L/N	CT, neck dissection	Papillary
3	39	F	Lung uptake	26.7	3	Lung	Chest CT	Papillary
4	54	F	Lung uptake	483.0	1	Lung, cervical L/N	Chest CT	Papillary
5	62	F	Negative	152.3 31	10	Lung, cervical L/N	Neck dissection	Papillary
6	70	F	Negative	38.9	4	Cervical L/N	Neck dissection	Papillary
7	37	F	Negative	71.9	11	Cervical L/N	Neck dissection	Papillary

L/N = lymph node; CT = computed tomography; F/U = follow-up.

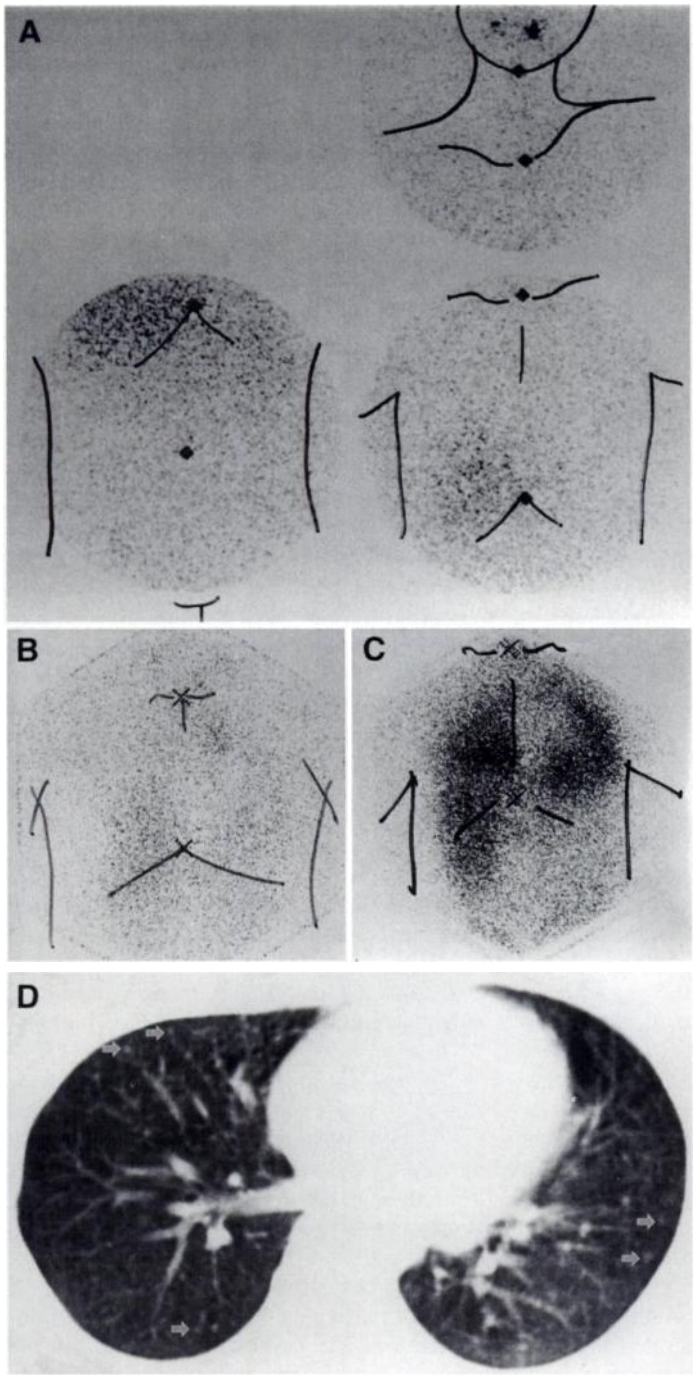

FIGURE 2. Anterior images of ^{131}I whole-body scan in Patient 2. (A) Whole-body scan showed Grade 2 liver uptake and no metastatic lesion. (B) Whole-body scan 15 mo later revealed faint metastatic lesions in the lung. (C) Whole-body scan after 1 yr showed intense uptake in both lung fields and liver. (D) CT showed hematogenous metastatic lesions in both lungs (arrows).

of all studies, and this agreed with the results of previous studies (*4–6*).

It is sometimes difficult to differentiate diffuse hepatic uptake and true liver metastasis. True hepatic metastases are typically seen as focal uptakes; the uptake by hepatic metastasis occurs earlier, with a time sequence similar to that of uptake by the thyroid or other metastases. Albert and Puliafito suggested that physiologic accumulation in the liver occurs later, after labeling of thyroid hormone and its release into the circulation (*13*).

The first report on diffuse hepatic uptake of ^{131}I suggested that this activity was due to ^{131}I-labeled thyroid hormones, especially thyroxine (*7*). The liver actively concentrates T4.

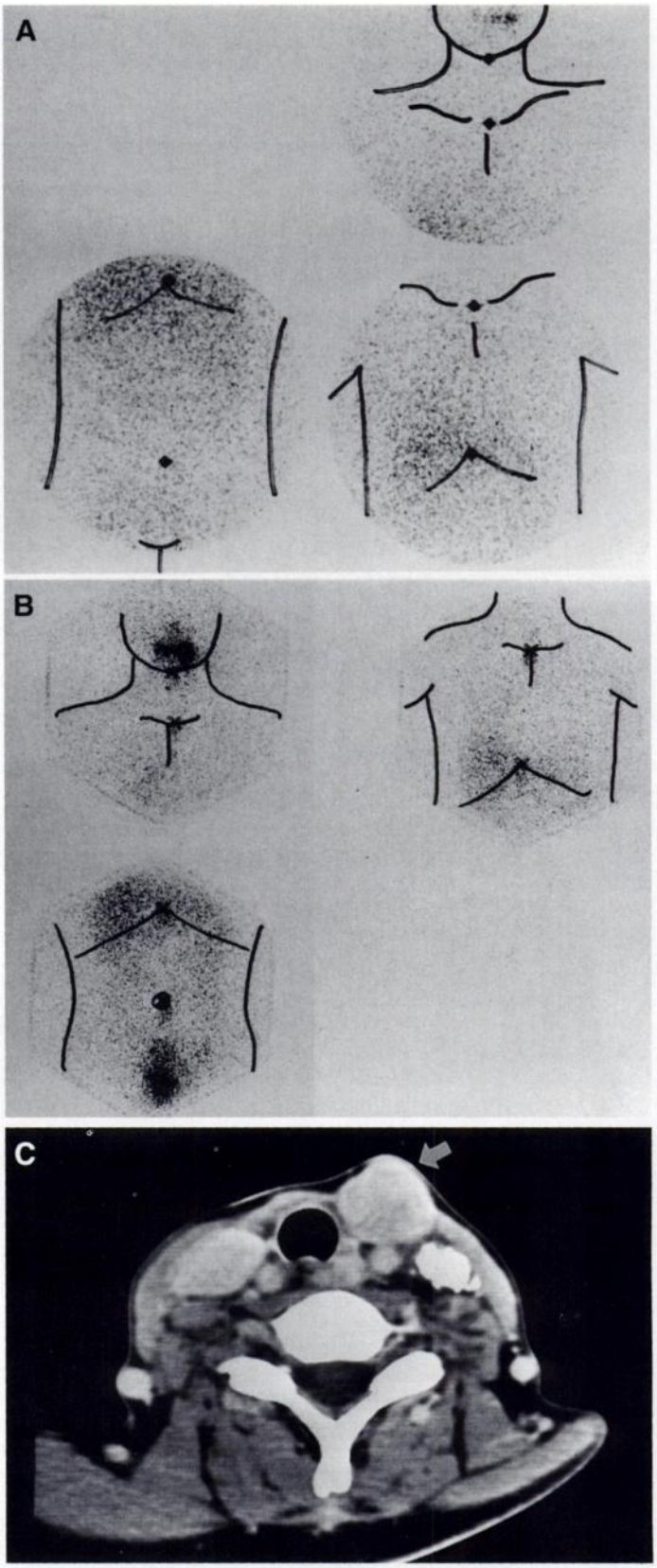

FIGURE 3. Anterior images of ^{131}I whole-body scan in Patient 5. (A) Whole-body scan showed Grade 2 liver uptake and no metastatic lesion. (B) Thirty-one months later the whole-body scan still showed liver uptake only. Serum level of Tg was very high, 152.3 ng/ml. (C) CT of the neck revealed enlargement of left cervical lymph nodes (arrow), which during reoperation was confirmed as metastases.

TABLE 6
Comparison of Liver Uptake in Whole-Body Scan and Fraction of Iodine-131-Labeled Thyroglobulin and Thyroid Hormones

Liver uptake	Number	Percent of fraction		
		Tg*	Organic components	Free I
Grade 0	8	12.9 ± 9.2	72.9 ± 14.9	13.7 ± 12.0
Grade 1	9	30.2 ± 13.3	63.1 ± 15.4	6.6 ± 10.0
Grade 2	23	35.1 ± 16.4	62.9 ± 14.7	6.3 ± 6.1
Grade 3	6	48.2 ± 27.3	47.5 ± 25.4	4.3 ± 5.6

*Kruskal–Wallis test.
Each value shows mean ± s.d. $\chi^2 = 14.66$, df = 3, p = 0.002.

Hepatic localization of labeled T4 occurred within hours of injection, and an equilibrium of T4 distribution between plasma and hepatocytes was rapidly established (*14*). Maayan et al. performed a chromatography of serum in three patients with hepatic uptake and found that ^{131}I-labeled T4 was the only identified iodoamino acid in two of these (*3*). We evaluated a large number of patients, however, and found that ^{131}I-labeled Tg was related to hepatic uptake.

We used extraction and chromatographic methods to evaluate the mechanism of liver uptake. According to the results of serum extraction, the majority of radioactivity in the precipitate was Tg. T4 seems to bind serum protein, e.g., thyroxine-binding protein, so strongly that it is hard to extract with ethanol or TCA solution. Other radioactive matter, including free iodide, T3 and small iodine-containing molecules, was almost completely extracted by ethanol and TCA. Although it was difficult to separate each iodine component, we were able to successfully measure by TLC the proportion of free iodide and all other small iodine-containing molecules, such as T3, T4, MIT, DIT and small peptides.

The liver is the major organ in the metabolism of thyroid hormones. It actively concentrates T4 and deiodinates it to T3 (*15*). The liver is responsible for 40% of T4 deiodination occurring in the whole of the body and 70% of T3 production. Approximately 35% of exchangeable body T4 and approximately 5% of T3 are within the liver (*14*). Radiolabeled thyroid hormones are accumulated in the liver in patients with remnant thyroid tissues, and the high incidence of diffuse hepatic uptake in cases of high doses of ^{131}I and intense uptake in the thyroid can be explained by this finding. Radiolabeled Tg might, however, have a role in patients without remnant thyroid. When ^{131}I is used for ablation of thyroid cancer tissue, Tg is released from functioning cancer tissue and absorbed by the liver. In addition, nonspecific iodinated protein, identified in the serum of patients with thyroid cancer, may be responsible for liver visualization. Many factors such as thyroid function status, fasting, stress, acute illness and some medications can of course change thyroxine metabolism and liver uptake (*4*).

In this study there were 13 patients whose scan showed metastatic and liver uptakes without any thyroid uptake. It rarely happened that metastatic cells could manufacture thyroid hormones from administered ^{131}I. Specifically and/or nonspecifically, ^{131}I bound to Tg in cancer cells and appeared as a main peak in our chromatographic study.

We found seven cases of metastatic adenocarcinoma in which ^{131}I whole-body scan showed only diffuse liver uptake; as far as we know, there has been no previous report of this kind. In four patients, follow-up scan revealed uptake in metastatic lesions. All patients showed elevated concentration of serum Tg, and the presence of metastases was confirmed. This particular finding increased the detectability of metastasis in ^{131}I whole-body scan. We speculated that ^{131}I was first taken into metastatic cells and subsequently washed out as forms of ^{131}I-labeled Tg and organic components. These ^{131}I-labeled components accumulated in the liver. Earlier whole-body imaging could be helpful in detecting metastatic lesions in these cases.

We found that diffuse liver uptake of ^{131}I is common in ^{131}I whole-body scan; this uptake indicates functioning thyroid remnant or metastasis. When there is liver uptake without uptake by the thyroid or evidence of metastasis, hidden metastases may be suspected. In one-half of these cases, however, liver visualization did not imply metastatic disease.

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