Role of Thallium-201 Total-Body Scintigraphy in Follow-Up of Thyroid Carcinoma

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To evaluate the reliability of total-body scintigraphy using [^{201}Tl]chloride in postoperative follow-up of thyroid carcinoma, this procedure was performed in 326 patients after total thyroidectomy for thyroid carcinoma. The results were compared with those of ^{131}I scintigraphy and thyroglobulin assays. ^{201}Tl total-body scintigraphy was found to have the greatest sensitivity (94%), whereas ^{131}I scintigraphy had the highest specificity (99%). It is shown that ^{201}Tl total-body scintigraphy is a useful procedure in follow-up of thyroid cancer, however, the combination of parameters provides the greatest reliability. In medullary thyroid carcinoma, which is usually ^{131}I negative, ^{201}Tl total-body scintigraphy can be of great value for the localization of metastases which are indicated by elevated serum levels of calcitonin and carcinoembryonic antigen.

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Until recently, follow-up of patients with thyroid carcinoma who had undergone a (sub)total thyroidectomy, with or without postoperative ablative therapy using iodine-131 (^{131}I), consisted of performing total-body scintigraphy with tracer doses of ^{131}I at regular intervals for many years. Although one was aware of the fact that dedifferentiation of the tumor can cause false-negative results, a negative ^{131}I scintigram was generally regarded as a proof of cure (*1*).

It was not until the introduction of tumor marker assays in thyroid carcinoma, when discrepancies between tumor marker levels and scintigraphic results were found, that it became clear that ^{131}I, although very effective in therapy of thyroid carcinoma metastases and selection of patients for this treatment, is not entirely reliable in excluding disease (*2*).

Thallium-201 (^{201}Tl) chloride, a radiopharmaceutical applied in nuclear cardiology, is reported to have tumor-seeking properties. Successful tumor imaging with this agent has been described in bronchial carcinoma (*3*), Hodgkin's (*4*) and non-Hodgkin lymphoma (*5*), liver cell carcinoma (*6*), esophageal cancer (*6*), breast carcinoma (*6*), Ewing's sarcoma (*7*), osteosarcoma (*7*), soft-tissue sarcoma (*7*), and in the majority of cases of thyroid carcinoma (*6, 8*).

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A comparative study of [^{201}Tl]chloride and gallium-67 (^{67}Ga) citrate in thyroid carcinoma showed that [^{201}Tl]chloride has a greater sensitivity in well-differentiated tumors, whereas [^{67}Ga]citrate is more useful in poorly differentiated and highly malignant forms of carcinoma and in lymphoma (*9*). Thallium-201 uptake has been described in a variety of thyroid abnormalities (*10*) and is not specific to differentiate between malignant and benign disease of the thyroid (*11*). However ^{201}Tl scintigraphy has been reported to be useful to detect metastases in patients who have had a total thyroidectomy for thyroid cancer (*12*). We have, therefore, evaluated the reliability of ^{201}Tl total-body scintigraphy in follow-up of thyroid carcinoma, comparing the results with those of ^{131}I total-body scintigraphy and thyroid tumor marker assays.

PATIENTS AND METHODS

Thallium-201 total-body scintigraphy was performed in 326 patients, 225 female and 101 male, who had undergone a total thyroidectomy for histologically proven thyroid carcinoma. In these patients 620 scintigrams were made. The histologic tumor type was papillary in 191, follicular in 110, anaplastic in six, and a giant cell carcinoma in one patient. Eighteen patients with medullary thyroid carcinoma (MTC) were also studied. Both anterior and posterior scintigrams were made 10–30 min after i.v. administration of 2 mCi (74 MBq) [^{201}Tl]chloride, using a dual head gamma camera

with parallel hole, high resolution collimators connected with a computer. Multiple digital images were made, acquiring counts over 5 min in a 256 × 256 matrix.

In 303 patients, the results were correlated with ^{131}I total-body scintigrams, made with a large field-of-view gamma camera fitted with a high-energy collimator. Multiple digital images, using a 256 × 256 matrix and an acquisition time of 10 min were made 48 hr after oral administration of 5 mCi (185 MBq) ^{131}I in most cases and 1 mCi (37 MBq) in some postoperative (within 1 mo) cases, 5 wk after discontinuation of l-thyroxin, and 2 wk after subsequent triiodothyronin medication had been stopped.

In 275 patients, the ^{201}Tl scintigrams could be correlated with tumor marker assays: in patients with papillary or follicular carcinoma thyroglobulin assays were performed in serum as was previously described (*13, 14*), and in MTC patients calcitonin and carcinoembryonic antigen (CEA) levels were determined. In thyroidectomized patients the following values were regarded as normal: thyroglobulin <10 ng/ml, calcitonin <0.012 nmol/l and CEA <3 ng/ml. In 262 patients, results of all parameters were available for comparison. In eight patients with ^{201}Tl positive MTC total-body scintigrams using [^{131}I]metaiodobenzylguanidine (MIBG) were made 24, 48 and 72 hr after administration of 37 MBq.

RESULTS

Pathological accumulations of [^{201}Tl]chloride were seen in 74 patients (23%). Table 1 gives the distribution of the ^{201}Tl results over the histological tumor types. Table 2 shows the correlative findings of ^{201}Tl and ^{131}I scintigraphy. In 237 patients with no clinical evidence of disease, both the ^{201}Tl and the ^{131}I scintigram were negative. However, 12 of these patients had moderately elevated thyroglobulin levels (14–74 ng/ml) and one patient had a level over 100 ng/ml. In five, this phenomenon could be explained by remnant thyroid tissue which was regarded to be normal.

TABLE 1
Distribution of ^{201}Tl Results over Histologic Tumor Types

Histological type	^{201}Tl positive	^{201}Tl negative	Total
Papillary carcinoma	30 (16%)	161	191
Follicular carcinoma	30 (27%)	80	110
Anaplastic carcinoma	4 (67%)	2	6
Giant cell carcinoma	1	0	1
Medullary carcinoma	9 (50%)	9	18
Total	74 (23%)	252	326

TABLE 2
Correlative Findings of ^{201}Tl and ^{131}I Scintigraphy in Thyroidectomized Patients

	^{201}Tl positive	^{201}Tl negative	Total
^{131}I positive	24	3	27
^{131}I negative	39	237	276
Total	63	240	303

In 24 patients, both ^{201}Tl and ^{131}I scintigraphy were positive. All these patients were confirmed to have thyroid carcinoma metastases. Fifteen of these patients had abnormal and seven normal tumor marker levels. In eight patients, the ^{201}Tl scintigram revealed more metastases than the ^{131}I scintigram did, in six other patients ^{131}I scintigraphy revealed more localizations. Figure 1 shows an example of a ^{201}Tl and ^{131}I positive metastasis from follicular carcinoma in the skull.

In 39 patients, ^{201}Tl scintigraphy revealed pathological accumulations which were not found on ^{131}I scintigrams, an example of which is shown in Fig. 2. Thirteen of these patients had papillary, 17 follicular, eight medullary and one a giant cell carcinoma. In this group, 14 patients had elevated thyroglobulin levels. All eight patients with MTC were calcitonin- and CEA-positive and two of these had positive [^{131}I]MIBG-scintigrams. Metastases were confirmed histologically in 26 (23 thyroid carcinoma, one bronchial carcinoma, one breast carcinoma, and one sarcoidosis) and radiologically in five patients. In eight patients no confirmation of disease has been obtained so far.

Negative ^{201}Tl scintigrams, despite positive ^{131}I scintigrams, occurred in three patients, of whom two had abnormal thyroglobulin levels and were confirmed to have thyroid carcinoma metastases. The comparative findings of ^{201}Tl scintigraphy, ^{131}I scintigraphy and thyroglobulin assays in 251 patients are shown in Table 3. It demonstrates that none of the parameters alone is completely reliable in detecting metastatic thyroid carcinoma. Table 4 shows the comparison of calcitonin, CEA, and ^{201}Tl scintigraphy in 18 MTC patients.

Table 5 sums up the characteristics of the three parameters. For these calculations, only patients who had all three tests were included. With an incidence of 50 cases of metastatic thyroid carcinoma in this group, ^{201}Tl scintigraphy was found to be the most sensitive (94%) method in follow-up of thyroid

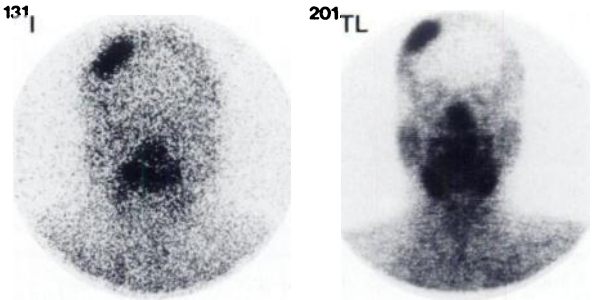

FIGURE 1
Both ^{131}I and ^{201}Tl positive skull lesion in patient with follicular thyroid carcinoma

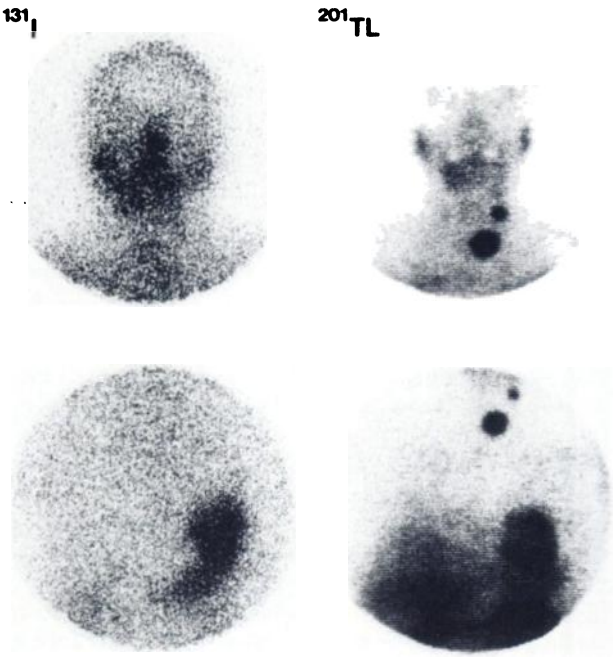

FIGURE 2
Scintigrams of patient with papillary thyroid carcinoma. 6 mo after total thyroidectomy and ablative ^{131}I therapy thyroglobulin level was 208 ng/ml; although ^{131}I scintigram (left) is negative, ^{201}Tl scintigram reveals two lymph node metastases, which were surgically removed and confirmed

carcinoma. Iodine-131 scintigraphy came out as the least sensitive (48%) but most specific (99%) procedure. The sensitivity can be increased up to 100% by combination of parameters, however, at the cost of loss of specificity.

DISCUSSION

Iodine-131 total-body scintigraphy is the most widely used method in postoperative follow-up of thyroid carcinoma. However, this procedure requires discontinuation of thyroid hormone medication and, dependent upon local legislation, admission to hospital isolation facilities; for a diagnostic procedure it gives a relatively high radiation burden to the patient and it is of limited value in patients who have remnant normal thyroid tissue and in medullary thyroid carcinoma. Although Tonami (*12*) had demonstrated ^{201}Tl scintigraphy to be a very sensitive technique in postoperative follow-up of 20 patients with thyroid carcinoma, Varma (*15*), who performed a comparative study of ^{131}I and ^{201}Tl scintigraphy in 40 patients, concluded that [^{201}Tl]chloride appeared to be useful only in patients with advanced metastatic thyroid carcinoma and could not replace ^{131}I in the management of this tumor.

Subsequent studies of combined use of ^{201}Tl scintigraphy and thyroglobulin assays by Müller-Brand (*16*) and Němec (*17*) again revealed a number of cases of thyroid carcinoma which did not concentrate ^{131}I. The present study, which compares all these parameters in a greater number of patients, shows that ^{201}Tl total-body scintigraphy is in fact the most sensitive method for detecting thyroid carcinoma metastases. Although ^{131}I scintigraphy is the procedure with the highest specificity, a considerable number of cases were missed using this technique. As in these patients ^{131}I therapy is not feasible, it is essential that the metastases can be localized by means of ^{201}Tl scintigraphy in order to facilitate surgical resection or radiotherapy with external beams.

Thallium-201 chloride also has advantages over ^{131}I for scintigraphic follow-up in that it is a simple and quick procedure, performed with a relatively low radiation burden and no inconvenience (i.e., discontinuation of medication, hospitalization) to the patient, that can produce images of superior quality. An additional advantage is, that ^{201}Tl scintigraphy, unlike ^{131}I scintigraphy, does not suffer from competitive tracer uptake by normal thyroid tissue, so that is can be used to exclude regional and distal metastases preoperatively as well (Fig. 3). Due to the attenuation of ^{201}Tl by overlying tissues it is essential that both anterior and posterior view images are recorded.

Of particular interest was the group of patients with

TABLE 3
Comparison of ^{201}Tl Scintigraphy, ^{131}I Scintigraphy and Thyroglobulin Assays in Thyroidectomized Patients

	Thyroglobulin positive		Thyroglobulin negative		
	^{201}Tl pos.	^{201}Tl neg.	^{201}Tl pos.	^{201}Tl neg.	Total
^{131}I pos.	15	2	7	1	25
^{131}I neg.	16	13	10	187	226
Total	31	15	17	188	251

TABLE 4
Comparison of ^{201}Tl Scintigraphy and Measurements of Calcitonin and CEA in Serum of MTC Patients, 11 of Whom Also Had ^{131}I Scintigrams, All Negative

	^{201}Tl pos.	^{201}Tl neg.	Total
Calcitonin/CEA pos.	9	1	10
Calcitonin/CEA neg.	0	8	8
Total	9	9	18

TABLE 5
Sensitivities and Specificities of Tests or Combinations of Tests in Postoperative Follow-up of Thyroid Carcinoma

	Sensitivity (%)	Specificity (%)
^{131}I scintigraphy	48	99
^{201}Tl scintigraphy	94	97
Tumor marker assay (TM)	74	93
^{131}I and TM	92	92
^{201}Tl and TM	98	90
^{131}I and ^{201}Tl	98	96
^{131}I + ^{201}Tl + TM	100	90

FIGURE 3
Left: ^{201}Tl positive lymph node metastasis in patient with medullary thyroid carcinoma (thyroid in situ). Right: Intense uptake of [^{131}I]MIBG in this metastasis

medullary thyroid carcinoma, which usually is ^{131}I negative. In ten of the 18 MTC patients calcitonin and CEA levels indicated disease, which was localized by ^{201}Tl scintigraphy and confirmed in nine of these patients. Beside [^{201}Tl]chloride recently other tracers have been reported to be useful in the detection of MTC, such as [^{99m}Tc]DMS (*18*), ^{131}I labeled monoclonal anti-CEA-antibodies (*19*), and [^{131}I]metaiodobenzylguanidine (*20, 21*). The last two tracers also have a therapeutic potential. The number of patients studied with these radiopharmaceuticals, however, are small. Figure 3 shows an example of a MTC patient with both [^{201}Tl] and [^{131}I]MIBG positive lymph node metastases in the neck.

It is concluded from this study that ^{201}Tl total-body scintigraphy is a valuable procedure in follow-up of thyroid carcinoma, especially when results of other parameters show discrepancies. It is of particular use in medullary thyroid carcinoma. Combination of parameters provides the greatest sensitivity. The introduction of tumor marker assays and ^{201}Tl total-body scintigraphy enable a more selective and efficient use of radioactive iodine and expensive isolation facilities.

At our institute, these findings have led to the following adjustment of postoperative management of thyroid carcinoma: following surgery or ablative/therapeutic ^{131}I doses all patients with differentiated thyroid carcinoma are screened both with a 5 mCi ^{131}I tracer dose and with ^{201}Tl scintigraphy; when the outcome is negative, further follow-up relies on both ^{201}Tl scintigraphy (yearly) and tumor marker assays (twice yearly), and ^{131}I scintigraphy is only performed when either test or any other clinical or radiological information suggests metastasis, in order to see if this is amenable to ^{131}I treatment.

REFERENCES

1. Blahd WH: Treatment of malignant thyroid disease. *Semin Nucl Med* 9:95, 1979
2. Hüfner M, Stumpf HP, Grussendorf M, et al: A comparison of the effectiveness of ^{131}I whole body scans and plasma Tg determinations in the diagnosis of metastatic differentiated carcinoma of the thyroid: A retrospective study. *Acta Endocrinol* 104:327–332, 1983
3. Cox PH, Belfer AJ, Van der Pompe WB: Thallium-201 chloride uptake in tumors, a possible complication in heart scintigraphy. *Br J Radiol* 49:767–768, 1976
4. Salvatore M, Carratu L, Porta E: Thallim-201 as a positive indicator for lung neoplasms: preliminary experiments. *Radiology* 121:487–488, 1976
5. Marks DS, Caroll KL: ^{201}Tl-chloride uptake by non-Hodgkins lymphoma: radiographic exhibit. *Henry Ford Hosp Med J* 26:56–57, 1978
6. Hisada K, Tonami N, Miyamae T, et al: Clinical evaluation of tumor imaging with ^{201}Tl-chloride. *Radiology* 129:497–500, 1978
7. Terui S, Oyamada H, Nishikawa K, et al: Tl-201 chloride scintigraphy for bone tumors and soft part sarcomas. *J Nucl Med* 25:P114, 1984 (abstr)
8. Tonami N, Bunko H, Mishigishi T, et al: Clinical application of ^{201}Tl-scintigraphy in patients with cold thyroid nodules. *Clin Nucl Med* 3:217–221, 1978
9. Senga O, Miyakawa M, Shirota H, et al: Comparison of Tl-201-chloride and Ga-67-citrate scintigraphy in the diagnosis of thyroid tumor: concise communication. *J Nucl Med* 23:255–228, 1982
10. Fukuchi M, Hyodo K, Tachibana K, et al: Uptake of Thallium-201 in enlarged thyroid glands: Concise communication. *J Nucl Med* 20:827–832, 1979
11. Harada T, Ito Y, Shimaoka K, et al: Clinical evaluation of ^{201}Thallium-chloride scan for thyroid nodule. *Eur J Nucl Med* 5:125–130, 1980
12. Tonami N, Hisada K: ^{201}Tl scintigraphy in postoperative detection of thyroid cancer: a comparative study with ^{131}I. *Radiology* 136:461–464, 1980
13. Ket JL, de Vijlder JJM, Bikker H, et al: Serum thyroglobulin levels: the physiological decrease in infancy and the absence of athyroidism. *J Clin Endocrinol Metab* 58:1301–1303, 1981
14. Bolk JH, Bussemaker JK, Nieuwenhuijzen Kruseman AC, et al: Thyroglobulin measurements in the follow up of patients with differentiated thyroid carcinoma: comparison with quantitative radioactive iodine uptake measurements and total body scans. *Neth J Med* 28:340–346, 1985
15. Varma V, Reba R: Comparative study of Tl-201 and I-131-scintigraphy in postoperative metastatic thyroid carcinoma. In *Nuclear Medicine and Biology*, Raynaud C., ed. Pergamon Press, I, 1982, pp 103–104
16. Müller-Brand J, Fridrich R, Spicher E, et al: Thyreoglobulin als Tumormarker und Thalliumszintigraphie zur Verlaufskontrolle beim differenzierten Schilddrüsenkarzinom. *Schweiz med Wschr* 113:325–327, 1983
17. Němec J, Zamrazil V, Pohunková D, et al: The rationale use of ^{201}Tl scintigraphy in the evaluation of differentiated thyroid cancer. *Eur J Nucl Med* 9:261–264, 1984
18. Ohta H, Yamamoto K, Endo K, et al: A new imaging agent for medullary carcinoma of the thyroid. *J Nucl Med* 25:323–325, 1984
19. Berche C, Mach JP, Lumbroso JD, et al: Tomoscintigraphy for detecting gastrointestinal and medullary thyroid cancers: First clinical results using radiolabelled monoclonal antibodies against carcinoembryonic antigen. *Br Med J* 285:1447–1451, 1982
20. Endo K, Shiomi K, Kasagi K, et al: Imaging of medullary thyroid carcinoma with ^{131}I-MIBG. *Lancet* II: 233, 1984
21. Sone T, Fukunaga M, Otsuka N, et al: Metastatic medullary thyroid cancer: localization with iodine-131 metaiodobenzylguanidine. *J Nucl Med* 26:604–608, 1985