Thallium-201 Scintigraphy to Predict Therapeutic Outcome of Iodine-131 Therapy of Metastatic Thyroid Carcinoma

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We studied the relationship between ^{201}Tl uptake and the efficacy of radioiodine therapy in thyroid carcinoma. **Methods:** Forty-four patients with metastases of well-differentiated thyroid carcinoma received ^{201}Tl scintigraphy within the 2 mo before their initial ^{131}I therapy. Patients were classified into two groups according to the tumor-to-background (T/B) ratio on the late ^{201}Tl scan: high ^{201}Tl uptake (T/B $\geq$ 2.1) and low ^{201}Tl uptake (T/B $<$ 2.1). The therapeutic outcome was judged by the percent reduction in the tumor diameter at 6 mo after the treatment. The treatment was defined as effective when the tumor showed more than 50% reduction in the tumor diameter. The patients in whom radioiodine was ineffective were followed up to determine if the tumor showed further growth. **Results:** Of the 44 patients, 25 had high ^{201}Tl uptake and 19 had low ^{201}Tl uptake. The therapy was effective in 15 patients and was ineffective in 29. All the patients in whom radioiodine was effective had low ^{201}Tl uptake. On the other hand, 25 of 29 patients in whom radioiodine was ineffective had high ^{201}Tl uptake. Eight patients, in whom radioiodine was ineffective despite good ^{131}I uptake, had high ^{201}Tl uptake. There were no significant differences in the positive predictive value and the negative predictive value for effective treatment between ^{201}Tl scintigraphy and therapeutic dose ^{131}I scintigraphy. Among the 25 patients in whom radioiodine was ineffective and who had high ^{201}Tl uptake, the tumor diameter increased in 7 (28%). However, none of the tumors with low ^{201}Tl uptake increased in size during the follow-up period. **Conclusion:** Thallium-201 scintigraphy has a high predictive value for the efficacy of radioiodine therapy in metastatic thyroid carcinoma. Thus, it is helpful in determining the indication for radioiodine therapy and it seems to be an adjunct to tracer dose ^{131}I scintigraphy.

Key Words: thallium-201; thyroid carcinoma; radioiodine therapy; therapeutic outcome

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Radioiodine therapy is a treatment of choice for the metastatic tumors from differentiated thyroid carcinoma. About 70%–80% of the metastases of well-differentiated thyroid carcinomas concentrate radioiodine (*1*).

However, the radioiodine-positive metastatic thyroid tumors do not always respond to treatment (*2–4*). Thallium-201 has been discussed as an alternative to ^{131}I in detecting metastatic thyroid cancer (*5–7*). It is trapped by metastatic thyroid cancers that do not concentrate a significant quantity of radioiodine. However, some metastatic tumors concentrate both ^{201}Tl and ^{131}I. In addition, there was a controversy about the results of ^{201}Tl scintigraphy (*5–10*). We postulated that ^{201}Tl scintigraphy may add a predictive value to ^{131}I scintigraphy for forecasting the outcome of radioiodine therapy. This study was designed to investigate the relationship between ^{201}Tl uptake and the efficacy of radioiodine therapy in metastatic thyroid carcinoma.

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MATERIALS AND METHODS

Patients

The study population consisted of 44 patients (37 women, 7 men; age range 20–72 yr; mean age 52.9 yr) with metastatic well-differentiated thyroid carcinoma who had undergone total thyroidectomy.

Needle biopsy or aspiration cytology was performed on the metastatic tumors to confirm the histological findings. Thirty-nine patients had papillary carcinomas and five had follicular carcinomas. The tumors were located in the neck, the mediastinum or the sternum. To minimize partial volume effect on the scintigram, we selected tumors with a diameter greater than 1.5 cm and equal to or less than 4.5 cm. None of the tumors were associated with dominant cystic changes or massive calcification. Radioiodine therapy was planned for all patients.

Thallium-201 Scintigraphy

Patients underwent ^{201}Tl scintigraphy within 2 mo before radioiodine therapy. Thirty-seven patients were studied 5 days before treatment. The planar anterior images were acquired at 10 min (early scan) and 120 min (late scan) after intravenous injection of ^{201}Tl (37 MBq) using a gamma camera (LFOV, Searle, Des Plaines, IL) with a LEAP collimator. The data were acquired for 10 min in a 64 $\times$ 64 matrix in an on-line computer (Scintipac 1200, Shimadzu, Japan). The ^{201}Tl uptake in the tumor was semiquantitatively evaluated with the tumor-to-background (T/B) ratio on the late scan. The region of interest (ROI) of 3 $\times$ 3 pixel was drawn over the center of the tumor (tumor) and the contralateral cervical area or the mediastinum (background). The T/B was calculated from mean counts in each ROI. The patients were classified into two groups according to the T/B. Based on our previous study (*11*), a T/B of equal to or greater than 2.1 was regarded as high ^{201}Tl uptake, whereas a T/B of less than 2.1 was regarded as low ^{201}Tl uptake.

Radioiodine Therapy and Scintigraphy

The dosage of ^{131}I ranged from 3.7–5.55 GBq. Thyroid hormone replacement was stopped at least 3 wk before the treatment. All patients were hospitalized at least for 5 days before the treatment to receive a low-iodine diet containing less than 140 μg/day and to take diuretics. The thyroid-stimulating hormone (TSH) levels during treatment were measured using an IRMA kit (Dainabot, Japan; normal range 0.3–3.5 μU/ml). The TSH levels were elevated to more than 40 μU/ml in all patients. Whole-body and spot scintigrams were obtained 5–7 days after the ^{131}I administration using a gamma camera (Ohio-Nuclear, Solon, OH) with a high-energy collimator. Radioiodine uptake in the tumor was visually interpreted and was graded as good or poor by two independent observers. The final interpretation was derived by consensus.

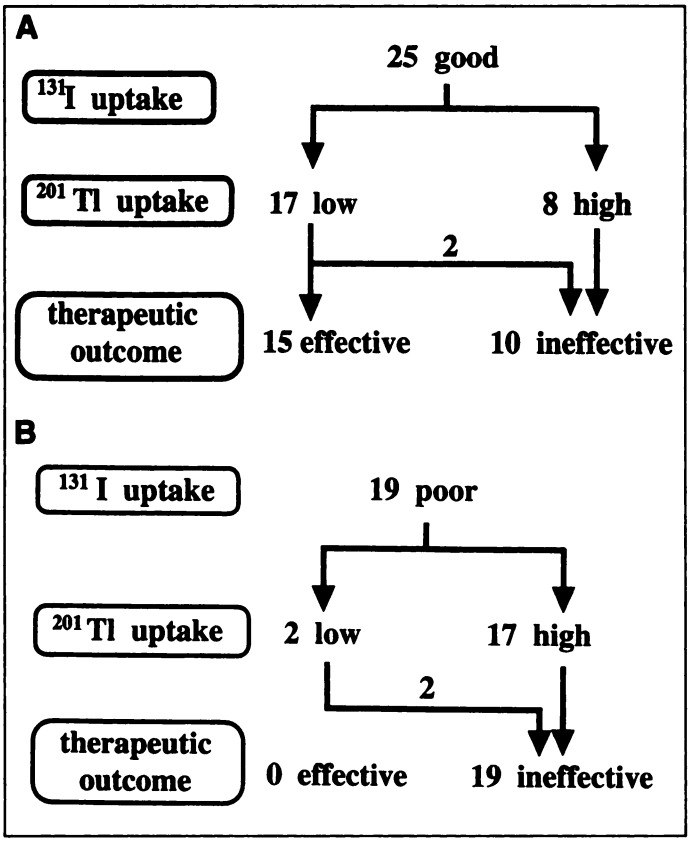

FIGURE 1. Relationship among ^{131}I uptake, ^{201}Tl uptake and the therapeutic outcome in metastatic thyroid carcinomas. (A) Patients with good ^{131}I uptake. (B) Patients with poor ^{131}I uptake.

Judgment of Therapeutic Outcome and Follow-Up

The therapeutic outcome was judged by the percent reduction in the tumor diameter at 6 mo after the treatment using CT scan or ultrasonography. When the tumor diameter decreased by more than 50%, the outcome was defined as effective. Otherwise, it was defined as ineffective. All the patients were followed up even further (range 9–55 mo with mean duration of 26.1 mo) so that the changes of the tumor diameter in patients in whom the radioiodine was ineffective could be evaluated. A tumor was defined as increased if its diameter was 25% greater than its pretreatment size.

Data Analysis

We defined low ^{201}Tl uptake or good ^{131}I uptake as an indicator of effective treatment and high ^{201}Tl uptake or poor ^{131}I uptake as an indicator of ineffective treatment. The positive predictive value (PPV) and the negative predictive value (NPV) of ^{201}Tl scintigraphy and therapeutic dose ^{131}I scintigraphy for effective treatment were determined. A chi-square test was used to examine whether there were significant differences in PPV and NPV between ^{201}Tl and ^{131}I.

RESULTS

Thallium-201 Uptake

The T/B ranged from 1.14–3.11 (mean 1.92 ± 0.51). Twenty-five patients showed high ^{201}Tl uptake. The remaining 19 patients showed low ^{201}Tl uptake.

Iodine-131 Uptake and Therapeutic Outcome

Iodine-131 uptake was good in 25 patients and was poor in 19. The treatment was effective in 15 and ineffective in 29.

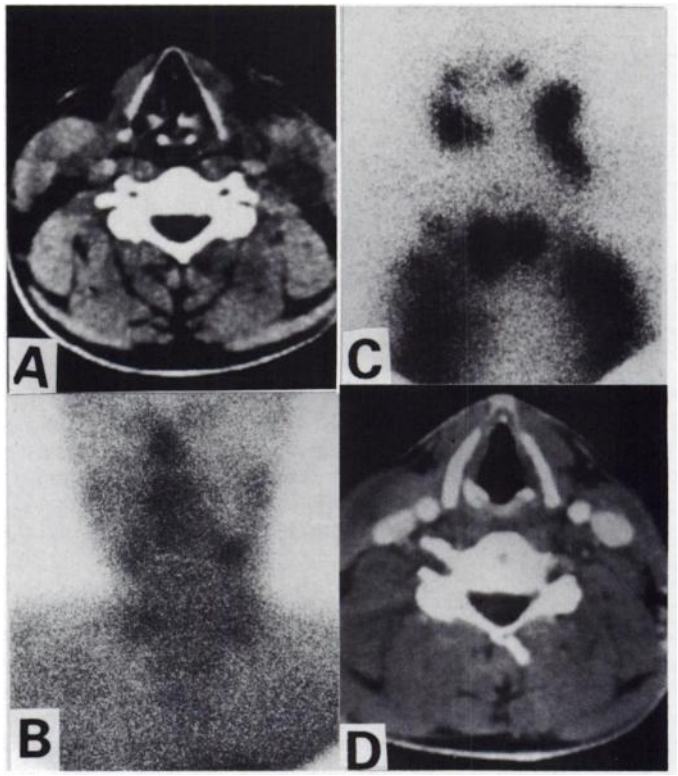

FIGURE 2. A 21-yr-old man with cervical lymph node metastasis from papillary carcinoma. (A) Pretreatment CT scan shows lymphadenopathy in the left neck. (B) Thallium-201 uptake in the tumor is low (T/B 1.24). (C) Iodine-131 uptake in the tumor is good. Unexpected uptake is also noted in the right neck and the lung field. (D) Post-treatment CT scan shows complete disappearance of the lymph node. The therapeutic outcome is effective.

Relationship Among Thallium-201 Uptake, Iodine-131 Uptake and Therapeutic Outcome

Seventeen of 25 patients with good ^{131}I uptake showed low ^{201}Tl uptake (Fig. 1A). The treatment was effective in 15

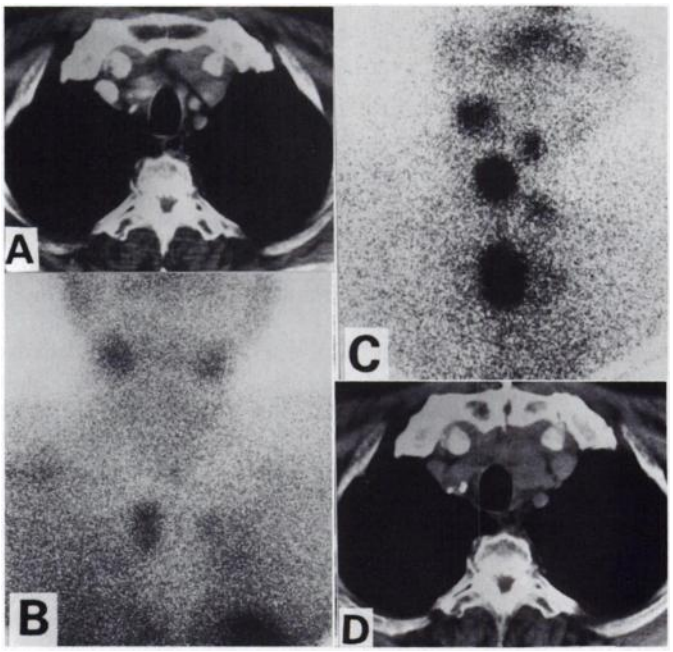

FIGURE 3. A 59-yr-old man with upper mediastinal lymph node metastasis from follicular carcinoma. (A) Pretreatment CT scan shows metastatic tumor. (B) Thallium-201 uptake in the tumor is high (T/B 2.45). (C) Iodine-131 scan shows good radioiodine uptake in the tumor. (D) However, post-treatment CT scan shows that tumor diameter has increased. The therapeutic outcome is ineffective.

TABLE 1
Scintigraphic Results for Predicting the Outcome of Iodine-131 Therapy

	TP	TN	FP	FN	PPV (%)	NPV (%)
^{201}Tl	15	25	4	0	78.9*	100.0*
^{131}I	15	19	10	0	60.0*	100.0*

* = ns.
TP = true-positive; TN = true-negative; FP = false-positive; FN = false-negative; PPV = positive predictive value; NPV = negative predictive value.

(88.2%) of them (Figs. 1A, 2). The remaining 8 patients showed high ^{201}Tl uptake. The treatment was ineffective in all of them (Figs. 1B, 3). Although 6 of the 8 patients received a second treatment, the tumors did not reduce in size. None of the patients with poor ^{131}I uptake were responsive to the treatment. Thallium-201 uptake was high in 17 (89.4%) of them.

Data Analysis

Thallium-201 scintigraphy had 15 true-positive cases and 4 false-positive cases, whereas ^{131}I scintigraphy had 15 true-positive cases and 10 false-positive cases. Neither ^{201}Tl scintigraphy nor ^{131}I scintigraphy had false-negative cases. The positive predictive value (PPV) and the negative predictive value (NPV) in ^{201}Tl for effective treatment were 78.9% (15 of 19) and 100% (25 of 25), respectively. Similarly, the PPV and the NPV in ^{131}I were 60% (15 of 25) and 100% (19 of 19), respectively. There were no significant differences in the PPV and NPV between ^{201}Tl scintigraphy and ^{131}I scintigraphy (Table 1).

Relationship Between Thallium-201 Uptake and Tumor Diameter

Among the 29 patients in whom radioiodine was ineffective, 25 showed high ^{201}Tl uptake and 4 showed low ^{201}Tl uptake (Fig. 4). The tumor diameter increased in 7 of 25 patients (28%) with high ^{201}Tl uptake. On the other hand, the tumor diameter did not increase in any of the patients with low ^{201}Tl uptake.

DISCUSSION

In this study, all the patients had well-differentiated carcinoma and their TSH levels at radioiodine therapy were sufficiently elevated. However, there were differences in their response to the therapy and in the tumor growth during the follow-up period. Our results show that the high uptake of ^{201}Tl indicates a poorer response to the radioiodine therapy regardless of the grade of ^{131}I uptake and a higher incidence of further tumor growth during the follow-up period. In contrast, low ^{201}Tl uptake in the tumor indicates a high probability of effective radioiodine therapy and a lower incidence of tumor growth thereafter.

Iodine-131 reveals functioning metastases from thyroid carcinoma. Thus, tracer dose whole-body ^{131}I scan has been used for determining the indications of radioiodine therapy. However, there are two drawbacks. First, the number of the lesions demonstrated on the tracer dose scan depends on the administered amount of ^{131}I (*12–14*). Second, patients must stop thyroid hormone replacement for several weeks to gain elevated serum TSH levels. This adds a risk of tumor growth to hypothyroidism during the preparation period.

The advantages of ^{201}Tl over ^{131}I are low radiation exposure and no patient preparation. With ^{201}Tl, there is also the capability of performing SPECT. However, most previous studies have focused on the ability of ^{201}Tl scintigraphy to detect metastatic thyroid cancers. It has not been established whether ^{201}Tl has a value in predicting the outcome of radioiodine therapy. Our results indicate a new role for ^{201}Tl as a predictor of the efficacy of radioiodine therapy. The similarity in the PPV and the NPV for effective treatment of ^{201}Tl and of therapeutic dose ^{131}I scan suggests that if ^{201}Tl uptake in the tumor is initially assessed, therapeutic results can be forecast before the treatment. Our results confirm that the tumors with high ^{201}Tl uptake are not eradicated by radioiodine, whereas those with low ^{201}Tl uptake are responsive to radioiodine therapy.

Various factors affect ^{201}Tl uptake in thyroid tumors (*15–19*). Recent reports show that ^{201}Tl uptake, especially in the late scan, is significantly correlated with the labeling index for proliferating cell nuclear antigen (PCNA) in a thyroid tumor (*11,20*). Based on these reports, we used the T/B ratio in the late scan to classify the patients. PCNA is generally regarded as a parameter for S-phase fraction cells (*21–23*), which is one of the significant prognostic predictors of human cancers (*24,25*). Metastatic thyroid cancers with high ^{201}Tl uptake may contain more S-phase fraction cells and may have high proliferative activity. Our results show that about one-third of the patients with high ^{201}Tl uptake had a further increase in the tumor diameter during the follow-up despite TSH suppression therapy. Thallium-201 uptake seems to indicate the biological aggressiveness of metastatic thyroid carcinomas.

The grade of radioiodine uptake is one of the important factors that influence the effects of radioiodine therapy. However, definitive radioiodine uptake does not always indicate the success of the treatment (*2–4*). Indeed, the tumor size did not significantly decrease in 40% of our patients with good ^{131}I uptake. Another important factor is the effective half-life of radioiodine in the tumor. Although we did not evaluate effective half-life quantitatively, post-treatment ^{131}I scans were obtained between 5–7 days after the administration and we supposed that tumors with good ^{131}I uptake might have sufficient effective half-life. Therefore, our results indicate that ^{201}Tl scintigraphy has a positive role in differentiating metastatic thyroid tumors that resist radioiodine from those with good ^{131}I uptake. This is very useful in managing post-thyroidectomized patients with differentiated thyroid carcinoma. In high ^{201}Tl uptake tumors,

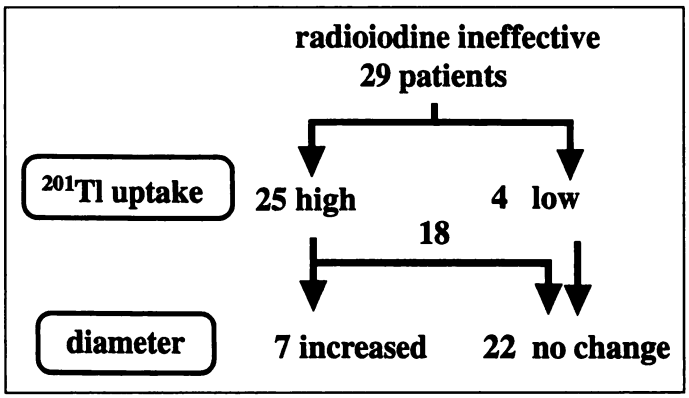

FIGURE 4. Relationship between ^{201}Tl uptake and the changes in the tumor diameter during the follow-up period in radioiodine-ineffective patients.

the precise mechanism of their tolerance to beta irradiation remains unknown. However, when the relationship between ^{201}Tl uptake and S-phase fraction is taken into consideration, two possibilities are hypothesized. First, in vitro studies have proven that the cells in the late S-phase are more radioresistant than they are in other phases of cell cycle (*26,27*). Higher ^{201}Tl uptake indicates that radioresistant cells are more abundant in the tumor. Second, the cells in S-phases have more proliferating activity and may be less dependent on TSH regulation. Therefore, serum TSH may not be a strong stimulator in increasing radioiodine uptake with high ^{201}Tl uptake tumor.

CONCLUSION

Thallium-201 does not reflect thyroid function. There is a size dependency for planar ^{201}Tl image to detect metastatic tumors. Therefore, evaluation of ^{201}Tl uptake is difficult in functioning but small or radiographically silent metastases. Thallium-201 is not a perfect alternative to radioiodine. However, in the case of a radiographically measurable tumor, ^{201}Tl scintigraphy has a predictive value for the efficacy of radioiodine therapy. It can detect metastatic thyroid tumors and can give physicians better discretion in managing metastatic thyroid carcinoma.

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Fluorine-18-Fluorodeoxyglucose Assessment of Glucose Metabolism in Bone Tumors

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In our study, we investigate the glucose metabolism of various types of bone lesions with ^{18}F-fluorodeoxyglucose (FDG) PET. **Methods:** Twenty-six patients showing clinical and radiographic symptoms of a malignant bone tumor were included. Histological examination after the PET study revealed 19 malignant and 7 benign tumors. PET images were corrected for attenuation. Arterial blood samples were taken to establish the input function. The metabolic rate of glucose consumption (MRglc) was calculated for the whole tumor, for the 10 pixels with maximum activity and for contralateral normal muscle tissue. **Results:** All lesions were clearly visualized with ^{18}F-FDG PET except for a small infarction of the humerus. All the other lesions had increased glucose metabolism compared to surrounding and contralateral muscle tissue. Both maximum and average MRglc for benign, as well as malignant, lesions were significantly higher than for contralateral normal tissue. The maximum and average MRglc were not higher for malignant as opposed to benign lesions. There was a large overlap between the MRglc of benign and malignant lesions. **Conclusion:** Fluorine-18-FDG PET appears suitable to visualize bone tumors. With the quantification of glucose metabolism, it is not possible to differentiate between benign and malignant bone tumors. There does not seem to be a clear correlation between the MRglc and the biologic aggressiveness of the neoplasms.

Key Words: bone neoplasms; glucose metabolism; PET; fluorine-18-fluorodeoxyglucose

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