Relationship Among ^{201}T1 Uptake, Nuclear DNA Content and Clinical Behavior in Metastatic Thyroid Carcinoma

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A prospective study of ^{201}Tl uptake was performed to compare ^{201}Tl uptake with nuclear deoxyribonucleic acid (DNA) content and clinical behavior of tumors in metastatic thyroid carcinoma and to assess the significance of ^{201}Tl uptake in evaluating clinical characteristics of thyroid carcinoma. **Methods:** Fifty-six patients with metastases of differentiated thyroid carcinoma had ^{201}Tl scintigraphy. Grade of ^{201}Tl uptake was semiquantitatively assessed according to tumor-to-background ratio on 2-h late scan. Nuclear DNA content was analyzed within 3 wk of ^{201}Tl study by flow cytometry using biopsy material and was classified as diploidy or aneuploidy. Patients were followed up to examine incidence of tumor growth and/or anaplastic transformation. **Results:** DNA content was diploidy in 48 patients and aneuploidy in 8 patients. ^{201}Tl uptake in the DNA-aneuploid group (2.61 ± 0.29) was significantly higher than that in the DNA-diploid group (1.82 ± 0.35, $P < 0.01$ for both groups). Tumor growth was observed in all patients with DNA aneuploidy but in only 5 of 48 patients with DNA diploidy ($P < 0.01$). Anaplastic transformation was observed in 3 patients in the DNA-aneuploid group but in none of the patients in the DNA-diploid group. **Conclusion:** High ^{201}Tl uptake indicates greater incidence of abnormal DNA content with aggressive clinical behavior of metastatic tumors. Thus,^{201}Tl scintigraphy may be useful in characterizing metastatic thyroid carcinoma and in identifying those patients with poorer prognoses.

Key Words: ^{201}Tl; thyroid carcinoma; DNA content; flow cytometry

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Differentiated thyroid carcinomas generally show slow growth and have a favorable prognosis. However, some show a more aggressive clinical course with poor outcome. Thus, predicting the clinical behavior of a tumor and identifying high-risk patients are of clinical importance for adequate patient management. Some classification systems have been established for determining high-risk patients (*1–3*) on the basis of clinical and tumor characteristics such as patient age, size or extent of tumor, presence of distant metastasis and histologic grade. In addition to these classification systems, deoxyribonucleic acid (DNA) content has been accepted as a significant prognostic indicator for differentiated thyroid carcinoma (*4–10*). Abnormal DNA content indicates poor prognosis. Some reports suggest that ^{201}Tl scintigraphy may reflect the biological characteristics of thyroid carcinoma (*11,12*). However, this has not been clinically confirmed. We prospectively investigated the relationship among ^{201}Tl uptake, nuclear DNA content and clinical behavior in metastatic thyroid carcinoma.

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MATERIALS AND METHODS

Patients and Tumors

The study population consisted of 56 patients (48 women, 8 men; age range 19–74 y, mean age 50.3 ± 11.7 y; 51 papillary carcinomas and 5 follicular carcinomas) with metastatic differentiated thyroid carcinoma who had undergone total thyroidectomy and radioiodine therapy before this study. Tumors were located in the neck or the mediastinum. Patients were treated with 3.7–5.55 GBq ^{131}I. However, none had responded to the treatment. Of the 56 patients studied, 41 showed poor ^{131}I uptake on post-treatment scintigrams. ^{131}I uptake was good for the other 15 patients. However, the tumor size did not significantly reduce. Patients underwent ^{201}Tl scintigraphy and ultrasonography-guided needle biopsy. ^{201}Tl scintigraphy was performed 6–9 mo after ^{131}I therapy. Biopsy was performed within 3 wk of ^{201}Tl scintigraphy to confirm histologic tumor findings and analyze flow cytometry. To eliminate significant partial-volume effects, tumors >1.5 cm but <4.0 cm in diameter were selected for this study. None of the tumors were associated with dominant cystic changes or massive calcification. When a patient had more than two metastatic tumors, the largest tumor was used for evaluation of ^{201}Tl uptake and needle-biopsy sampling.

^{201}Tl Scintigraphy

Planar anterior images were acquired 10 min (early) and 120 min (late) after intravenous injection of 37–74 MBq ^{201}Tl using a LVOF gamma camera (Searle, Des Plaines, IL) with a low-energy, all-purpose collimator. Data were acquired for 10 min in a 64 × 64 matrix into an online computer (Scintipac 1200; Shimadzu, Kyoto, Japan). A 3 × 3 pixel region of interest was drawn over the center of the tumor and the contralateral cervical area or mediastinum. Tumor ^{201}Tl uptake was semiquantitatively determined as tumor-to-

background ratio (TBR) on the late scan, as previously described (*13*).

Flow Cytometry

Fresh biopsy specimens were used for analysis. Nuclear DNA content was analyzed in accordance with the procedure described by Isobe et al. (*14*) with minor modification. In short, the tumor was minced into small pieces. Then 5 mL phosphate-buffered saline (Japan Pharmacia, Tokyo, Japan) with 0.1% ribonuclease (Sigma Chemical Co., St. Louis, MO) and 0.1% tritonX-100 (Sigma) were added and mixed with the minced tissue using a vortex mixer. The resulting suspension was passed through a 40-μm nylon mesh and stained with 50 mg/mL propidium iodide (Wako, Tokyo, Japan). To determine DNA profiles, human lymphocytes were used as control cells because all patients had undergone total thyroidectomy and therefore had no normal thyroid tissue for comparison. A FACSCAN flow cytometer (Becton-Dickinson, Franklin Lakes, NJ) was used for analysis. The relative DNA content was expressed as DNA index (DI) from the DNA histogram (*14,15*). When the DNA histogram showed only symmetrical G_0/G_1 cells (DI = 1.00) with a coefficient value <7%, it was classified as normal DNA content (diploidy). When one or more G_0/G_1 peaks were clearly observed (DI > 1.00) in the histogram, it was classified as abnormal DNA content (aneuploid). More than 10,000 cells were analyzed in each specimen.

Assessment of Tumor Clinical Behavior

Incidence of tumor growth and anaplastic transformation were examined as clinical behaviors of the metastatic tumors. Patients were followed up for 10–58 mo (mean 29.7 ± 5.6 mo). Tumor diameter was measured by CT scan and/or ultrasonography at regular intervals. Tumor growth was defined as an increase in tumor diameter of >25% over the initial volume. When a tumor showed growth, needle biopsy was repeated to determine the presence of anaplastic transformation.

Data Analysis

Data are expressed as mean ± SD. The non-paired *t* test was used to compare ^{201}Tl uptake. The F test was used to check the difference of variance in ^{201}Tl uptake. Chi-square analysis was used to compare the incidence of clinical events. *P* values < 0.05 were considered significant.

RESULTS

TBRs ranged from 1.35 to 3.23 (mean 1.96 ± 0.48). Tumor growth was observed in 13 patients (23.2%). Anaplastic transformation was observed in 3 (5.4%).

DNA content was successfully determined in all patients. Of the 56 patients studied, 48 (85.7%) showed DNA diploidy. The remaining 8 (14.3%) showed DNA aneuploidy.

Patients were classified into two groups according to nuclear DNA content (Table 1). Mean TBR was 1.82 ± 0.35 in the DNA-diploid group and 2.61 ± 0.29 in the DNA-aneuploid group. Tumors with DNA aneuploidy had significantly higher TBRs than those with DNA diploidy ($P < 0.01$). There was no significant difference in the variance of TBR between the two groups ($F = 0.726$, $P = 0.569$). This ensured that use of the non-paired *t* test was appropriate. Only 5 of 48 patients (10.4%) in the DNA-diploid group showed tumor growth (Fig. 1). In contrast, all patients in the DNA-aneuploid group showed tumor growth. Incidence of tumor growth obviously was significantly higher in the DNA-aneuploid group ($P < 0.01$). Anaplastic transformation was observed in 3 patients with DNA aneuploidy (Fig. 2) but in none with DNA diploidy. These patients died of their cancer within 1 y of confirmation of anaplastic transformation.

TABLE 1
Relationship Among Nuclear DNA Content, ^{201}Tl Uptake and Clinical Behavior

DNA content	^{201}Tl uptake	Tumor growth		Anaplastic transformation	
		n	%	n	%
Diploidy (n = 48)	1.82 ± 0.35*	5	10.4*	0	0.0
Aneuploidy (n = 8)	2.61 ± 0.29*	8	100.0*	3	37.5

*$P < 0.01$.

DISCUSSION

All of the patients in this study did not respond to radioiodine. Therefore, they were potentially high-risk patients and were not representative of typical differentiated thyroid carcinoma patients. However, their clinical outcomes varied. Although the incidence of abnormal DNA content was relatively low, our observations confirmed that aneuploid tumors grew significantly during the follow-up period and that anaplastic transformation occurred only in the DNA-aneuploid group. In contrast, the majority of DNA-diploid tumors showed nonaggressive clinical courses despite the ineffective radioiodine therapy. Moreover, ^{201}Tl uptake correlated significantly with clinical outcomes and DNA-ploidy patterns. These results suggest that high ^{201}Tl uptake indicates high risk of abnormal DNA content as well as aggressive tumor clinical behavior.

^{201}Tl scintigraphy has been proven to be useful for detecting radioiodine-negative metastatic thyroid carcinomas (*16–21*). However, the relationship between grade of ^{201}Tl uptake and patients' clinical outcomes has not yet been fully discussed. On the other hand, although nuclear DNA content has prognostic value in thyroid carcinoma (*4–10*), assessment of abnormalities in nuclear DNA content has been difficult using conventional diagnostic images such as radiographs, sonograms or CT scans. When ^{201}Tl uptake is linked with nuclear DNA content and clinical behavior of metastatic thyroid carcinoma, it may prove valuable to visualize the abnormal DNA content and to predict clinical evolution of the tumor. When ^{201}Tl uptake is low in radioiodine-ineffective tumors, most patients will have good prognoses. On the other hand, when ^{201}Tl uptake is high in such tumors, patients will have a much more difficult clinical course and will need more intense management. Takekawa et al. (*22*) suggested that ^{201}Tl uptake may be one of the

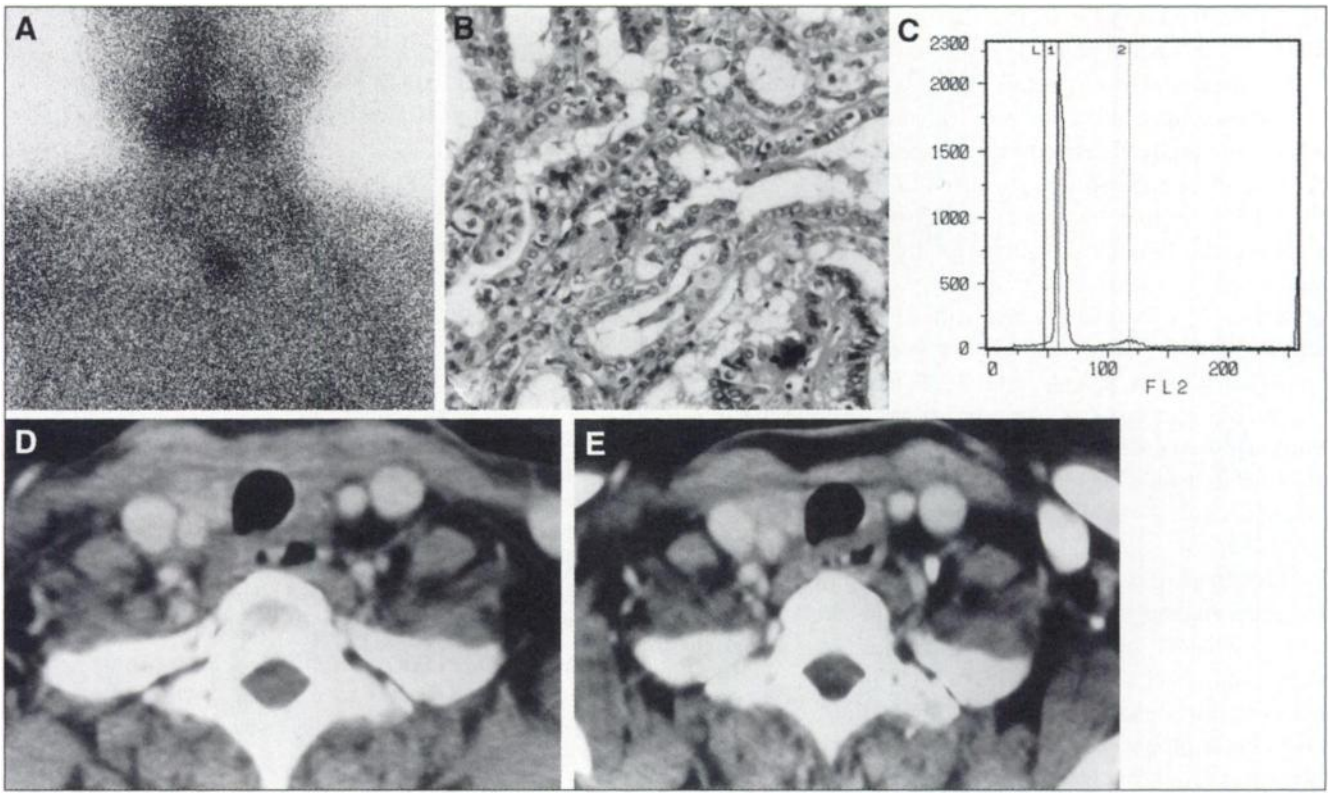

FIGURE 1. A 63-y-old woman with DNA-diploid papillary carcinoma. (A) ^{201}Tl scintigram shows relatively low uptake in right neck tumor. TBR = 1.50. (B) Microscopic examination shows well-differentiated thyroid carcinoma. (C) DNA histogram shows diploidy pattern (DI = 1.00). (D) Baseline CT scan shows metastatic tumor in right paratracheal region. (E) Follow-up CT scan 4.6 y later shows that tumor did not increase in size during follow-up period.

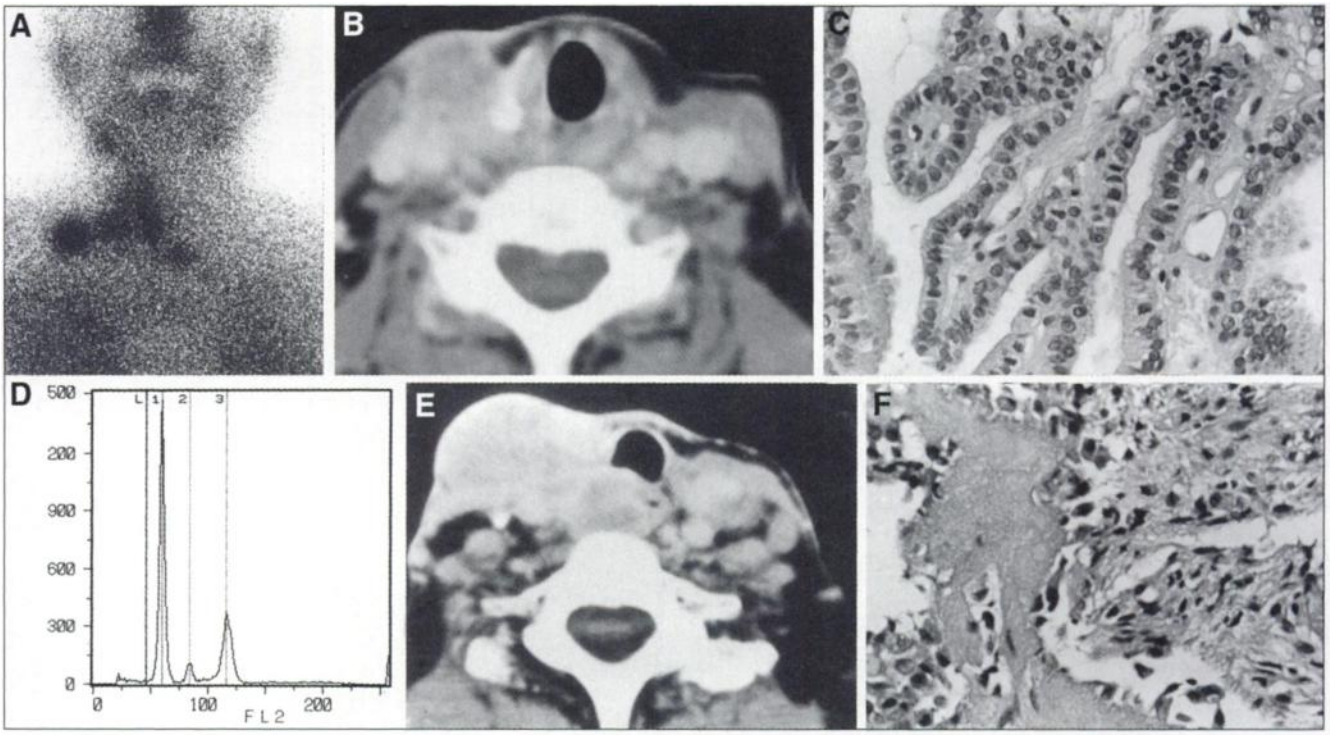

FIGURE 2. A 62-y-old woman with DNA-aneuploid papillary carcinoma. (A) ^{201}Tl scintigram shows high uptake in right anterior neck. TBR = 2.90. (B) Baseline CT scan. (C) Microscopic examination of initial biopsy specimen shows well-differentiated papillary carcinoma. (D) DNA histogram shows aneuploid peak (DI = 1.40). (E) Follow-up CT scan 1.4 y later shows rapid and remarkable increase in tumor size and number. (F) Microscopic examination from second biopsy specimen shows that anaplastic transformation has occurred.

independent prognostic factors for lung cancer survival. Although the studied population was small and the duration of follow-up was short in this study, it is anticipated that ^{201}Tl uptake may affect the survival rate of patients with radioiodine-ineffective metastatic thyroid tumors.

Although some findings are related to prognosis (*23–26*), microscopic characteristics do not have absolute value in assessing the biological features of differentiated thyroid carcinomas because cellular atypia generally is mild or moderate. More recently, biochemical markers such as activity of adenylyl cyclase (*27*) or telomerase (*28,29*) or expression of glucose-transporter 1 (*30*) have been discussed as possible indicators of aggressiveness of thyroid carcinoma. However, abnormalities in these markers were also observed in benign disorders, and the relationship between a patient's clinical course and these markers has not been established.

Assessment of nuclear DNA content using flow cytometry in various human cancers including thyroid carcinomas is a well-established technique (*4–10,14,15,31,32*). Although aneuploidy is not always specific in malignant tumors, it is well recognized that human cancers with DNA aneuploidy have poorer prognoses than do those with diploidy. Therefore, we analyzed nuclear DNA content in metastatic thyroid carcinoma to correlate with in vivo ^{201}Tl uptake. Our results suggest that ^{201}Tl scintigraphy may be an alternative to flow cytometry to some extent. Fresh biopsy specimens were used in flow-cytometric analysis to reduce the appearance of debris and acquire DNA histograms with small coefficient of variation. S-phase fraction cells are also regarded as independent prognostic indicators for thyroid cancer (7) and can be estimated using a DNA histogram. Although we did not calculate S-phase fraction cells in this study, it has been reported that ^{201}Tl uptake is significantly correlated with expression of proliferating cell nuclear antigen, a direct marker of S-phase reaction cells, in thyroid tumors (*11,12*).

^{67}Ga accumulates in anaplastic thyroid carcinomas (*33,34*). Higashi et al. (*34*) showed that DNA content and proliferative index in anaplastic carcinoma and malignant lymphoma of the thyroid were significantly higher than in well-differentiated carcinoma and that increased ^{67}Ga uptake in a thyroid tumor indicates a more highly malignant tumor (*34*). However, there is considerable variance in DNA content in anaplastic thyroid carcinoma (*35*), and the study population of Higashi et al. seems too small to determine the role of ^{67}Ga uptake in assessment of aggressiveness of thyroid tumors. It seems that tumor uptake of ^{67}Ga is not parallel with that of ^{201}Tl. Plasma transferrin and its receptors play an important role in ^{67}Ga uptake (*36,37*), whereas ^{201}Tl uptake depends on blood perfusion, Na^+, K^+-adenosinetriphosphatase (ATPase) activity (*38–40*) or mitochondrial development (*41*). As for cell cycle, high ^{201}Tl uptake is supposed to reflect a high population of S-phase cells. On the other hand, ^{67}Ga uptake in tumor cells is supposed to peak at the G_2 phase (*42*). Therefore, it is likely that ^{201}Tl uptake is related to proliferative activity more directly than ^{67}Ga. ^{201}Tl uptake is less affected by coexisting inflammatory processes.

In addition, this study showed that ^{201}Tl scintigraphy distinguishes microscopically differentiated but potentially anaplastic tumors from other differentiated tumors before histologic changes become apparent. Although we did not compare ^{201}Tl and ^{67}Ga uptake in our DNA-aneuploid group, it is believed that ^{201}Tl scintigraphy has advantages over ^{67}Ga in assessing tumor aggressiveness and follow-up in differentiated thyroid carcinoma. Recent reports suggest that whole-body ^{18}F-fluorodeoxyglucose (FDG) PET is also useful for detecting recurrent or metastatic thyroid carcinomas when ^{131}I scintigraphy is negative (*43,44*). Although the mechanism of ^{201}Tl uptake is somewhat different from that of ^{18}F-FDG (*45,46*), ^{201}Tl scintigraphy may provide information similar to that provided by FDG PET (*47*) that cannot be assessed by other imaging modalities.

We focused on radioiodine-ineffective tumors because there has been no established prognosis predictor for them. Our previous study (*13*) and this one indicate that ^{201}Tl scintigraphy is a simple and reliable means to distinguish patients with poor prognoses from those with good prognoses. It also is expected that ^{201}Tl scintigraphy may add a predictive value to previously reported classification systems for thyroid carcinoma, as DNA-content analysis does (*9*). The combined use of ^{201}Tl scintigraphy with clinical classification systems will be helpful in assessing the characteristics of primary tumors.

It is considered that early ^{201}Tl scans reflect primarily perfusion and blood pool in the cancer tissue. In contrast, delayed ^{201}Tl scans may reflect some cellular mechanism or function that retains ^{201}Tl longer and may be closely related to DNA abnormality rather than vascularity. DNA-aneuploid cells may have higher Na^+, K^+-ATPase activity or may have more mitochondria than DNA-diploid cells. Further study is needed to clarify the mechanism of increased ^{201}Tl uptake in relation to DNA content.

CONCLUSION

The clinical characteristics of metastatic thyroid carcinoma can be determined by ^{201}Tl scintigraphy. ^{201}Tl scintigraphy may be useful not only in detecting metastatic thyroid carcinoma but also in identifying high-risk patients.

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