

## The role of $^{201}\text{Tl}$ scintigraphy in evaluating proliferative activity in thyroid neoplasms

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To identify the relationship between the uptake of  $^{201}\text{Tl}$  and the proliferative activity in thyroid neoplasms,  $^{201}\text{Tl}$  scintigraphy was performed in 57 patients with thyroid neoplasms.  $^{201}\text{Tl}$  uptake ratio was calculated in both the early and the delayed images and then compared with factors representing cellular or practical proliferative activity of the lesions. The labeling index (LI) for proliferating cell nuclear antigen (PCNA) was determined quantitatively by flow cytometry. There was a significant correlation between the uptake ratio and LI for PCNA. The correlation coefficient for the delayed ratio (DR) vs. LI was better than that for the early ratio (ER) vs. LI. As parameters for practical proliferation, the surgical stage in primary thyroid carcinoma or  $^{131}\text{I}$  uptake in recurrent thyroid carcinoma was focused on. DR was strongly related to these parameters, regardless of the histopathological features or size of the lesions. Our results suggest that  $^{201}\text{Tl}$  uptake in delayed thyroid scan is useful in assessing proliferative activity in thyroid neoplasms.

**Key words:** cell cycle, proliferating cell nuclear antigen, flow cytometry,  $^{201}\text{Tl}$  scintigraphy, thyroid neoplasm

### INTRODUCTION

$^{201}\text{Tl}$  SCINTIGRAPHY has been used in diagnosing thyroid malignancies.<sup>1–8</sup> The high radioactivity of  $^{201}\text{Tl}$  in the delayed scan seems to be a sign of malignant nodules,<sup>2–4,7</sup> although positive uptake and retention of  $^{201}\text{Tl}$  have been described in benign nodules or chronic thyroiditis.<sup>3,6,8</sup> Although some authors have insisted that the sensitivity of  $^{201}\text{Tl}$  scintigraphy is low,<sup>5,6</sup> these results also suggest that  $^{201}\text{Tl}$  uptake is influenced by some factors which are independent of histopathological characteristics. Furthermore,  $^{201}\text{Tl}$  uptake has been reported to indicate the biological or histological aggressiveness in brain tumor.<sup>9–13</sup> Based on the above reports, we supposed that  $^{201}\text{Tl}$  scintigraphy has similar predictive value in assessing proliferative activity in thyroid tumor. Prospective studies were undertaken to identify the relationship between the  $^{201}\text{Tl}$  uptake and the proliferative activity in thyroid neoplasms.

### MATERIALS AND METHODS

#### *Patients*

For a period of 30 months between August, 1992 and January, 1995,  $^{201}\text{Tl}$  scintigraphy was performed on a total of 57 patients suspected of thyroid tumor. There were 44 females and 13 males with ages ranging from 17 to 84 years (mean  $57.0 \pm 14.1$ ). All patients satisfied the following criteria: a) Ultrasonogram (US) measurement of the longest diameter of the tumor was  $> 2.0$  cm long and  $\leq 5.0$  cm for the primary tumor, and  $> 1.5$  cm long and  $\leq 5.0$  cm for the recurrent tumor; b) Nodules were not associated with dominant cystic changes or massive calcification. US-guided needle biopsy was done within 3 weeks after  $^{201}\text{Tl}$  scintigraphy. Thirty-five patients (group M) had malignant tumors, and 22 patients (group B) had benign neoplasms. Histopathological diagnosis is listed in Tables 1 and 2. All carcinomas were well-differentiated in the epidermal grade. Chronic thyroiditis was classified as a benign nodule. Nineteen patients with primary thyroid cancer underwent surgery within 2 months after the study. Pathological determination of the *t* and *n* factor was done according to General Rules for the Description of Thyroid Cancer.<sup>14</sup> Five patients were classified as *t*<sub>4</sub> because of positive extrathyroidal involvement (ETI), and

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**Table 1** Histopathological diagnosis in group M

	PCA	FCA	MCA	ML	Total
P*	18		1	4	23
R**	10	2			12
Total	28	2	1	4	35

PCA: papillary carcinoma, FCA: follicular carcinoma, MCA: medullary carcinoma, ML: malignant lymphoma, \*: primary tumor, \*\*: recurrent tumor following total thyroidectomy.

**Table 2** Histological diagnosis in group B

FA	ADN	CH	Total
7	8	7	22

FA: follicular adenoma, ADN: adenomatous nodule, CH: chronic thyroiditis.

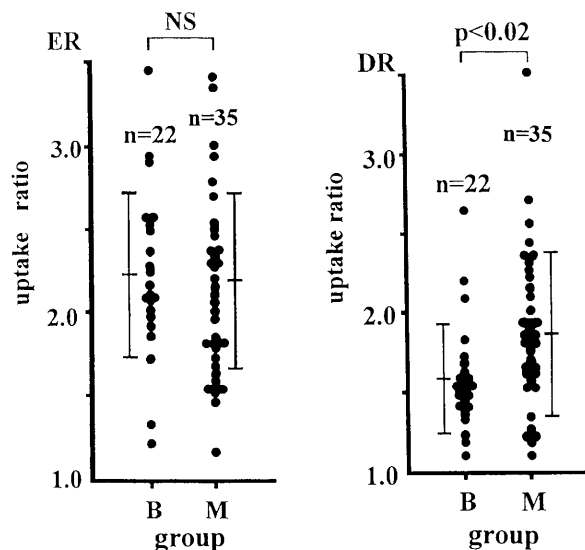
the rest were classified into  $t_2$ . Ten patients had positive lymph node (L/N) metastases. Twelve patients had recurrent thyroid cancer in the neck, the mediastinum, or the sternum. They received  $^{131}\text{I}$  therapy within 2 months after the study. Whole body  $^{131}\text{I}$  scintigram was obtained 4 to 7 days after the administration of the therapeutic dose (3.7 GBq–5.55 GBq).  $^{131}\text{I}$  uptake in tumor was good in 5 patients, and little or nil in the others.

#### $^{201}\text{Tl}$ scintigraphy

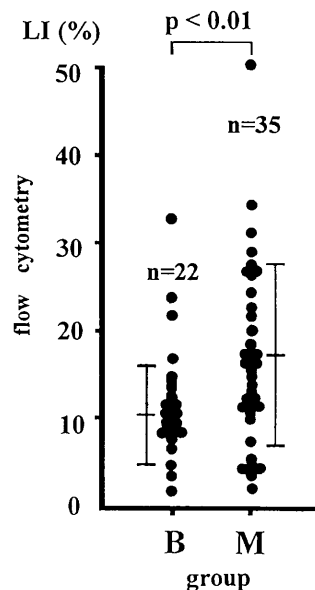
Static anterior images of the thyroid were obtained at 10 min (early scan) and 120 min (delayed scan) after intravenous administration of 3.7 MBq of  $^{201}\text{Tl}$  with a gamma camera (Searle, USA) equipped with low-energy-all-purpose parallel-hole collimator. Data were stored in an on-line computer Scintipac 1200 (Shimadzu, Japan) for 10 minutes in a  $64 \times 64$  matrix. The region of interest (ROI)  $3 \times 3$  pixel in size was drawn both for the nodular lesion and background regions (BG) in the contralateral cervical area of the lesion. The nodular lesion to BG ratio (early ratio; ER, delayed ratio; DR) was calculated from mean counts for each ROI. When nodularity was uncertain on the scintigram, the nodular ROI was set up according to US findings.

#### Flow cytometric analysis

The labeling index (LI) of proliferating cell nuclear antigen (PCNA) was determined as described by Landberg et al.<sup>15,16</sup> with minor modifications. The specimen was divided into 2 samples. One was incubated with mouse fluorescein isothiocyanate (FITC)-labeled PCNA antiserum (PC-10; DAKO Corporation, Glostrup, Denmark) before propidium iodide (PI) staining. The other was prepared as a negative control in incubation with mouse FITC-labeled IgG (Coulter Corporation, Hialeah, Finland). LI for PCNA in each specimen was calculated by subtracting the LI in negative control cells from that in PCNA-FITC-labeled cells. Flow cytometer FACS-CAN



**Fig. 1** Uptake ratio in  $^{201}\text{Tl}$  scintigraphy. ER: early ratio, DR: delayed ratio.



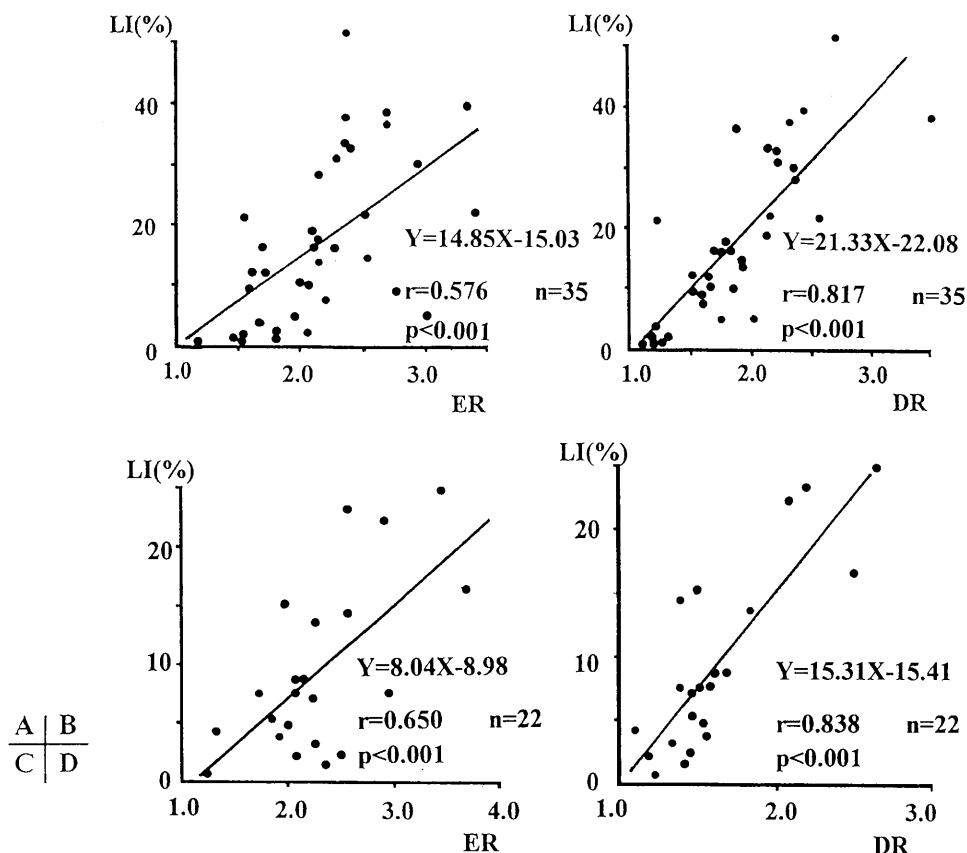
**Fig. 2** Results in flow cytometric analysis. LI: labeling index for PCNA.

(Becton-Dickinson, USA) and its application software were used for the analysis.

#### Comparative study

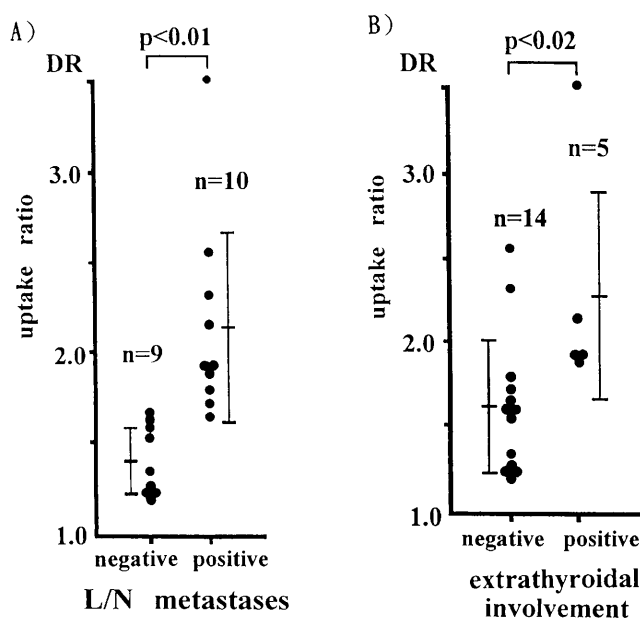
**A) Relationship between  $^{201}\text{Tl}$  uptake ratio and cellular proliferative activity:** The correlation between ER vs. LI for PCNA and between DR vs. LI for PCNA was determined in group M and group B.

**B) Relationship between  $^{201}\text{Tl}$  uptake ratio and practical proliferative activity in thyroid cancer:** In patients with primary cancer, DR was compared with surgically confirmed  $t$  and  $n$  factor. In patients with recurrent cancer, DR was compared with  $^{131}\text{I}$  uptake on the scintigram.



**Fig. 3** Correlation between  $^{201}\text{Tl}$  uptake and labeling index for PCNA. A) ER vs. LI in group M, B) DR vs. LI in group M, C) ER vs. LI in group B, D) DR vs. LI in group B.

In the text, figures are the means  $\pm$  s.d. Student's t-test was employed for between-group comparison. The difference was regarded as significant when the p-value was less than 0.05.



**Fig. 4** Comparison between DR and surgical stage in primary thyroid carcinoma. A) DR vs. lymph node (L/N) metastases. B) DR vs. extrathyroidal involvement.

## RESULTS

### $^{201}\text{Tl}$ uptake

ER ranged from 1.16 to 3.67 (mean  $2.24 \pm 0.56$ ). DR ranged from 1.10 to 3.51 (mean  $1.78 \pm 0.51$ ). ER and DR in group M were  $2.19 \pm 0.53$  and  $1.87 \pm 0.51$ , respectively. In group B, ER and DR were  $2.27 \pm 0.53$  and  $1.58 \pm 0.34$ , respectively. There was no statistical difference between the two groups in ER, but DR was significantly higher in group M than that in group B (Fig. 1).

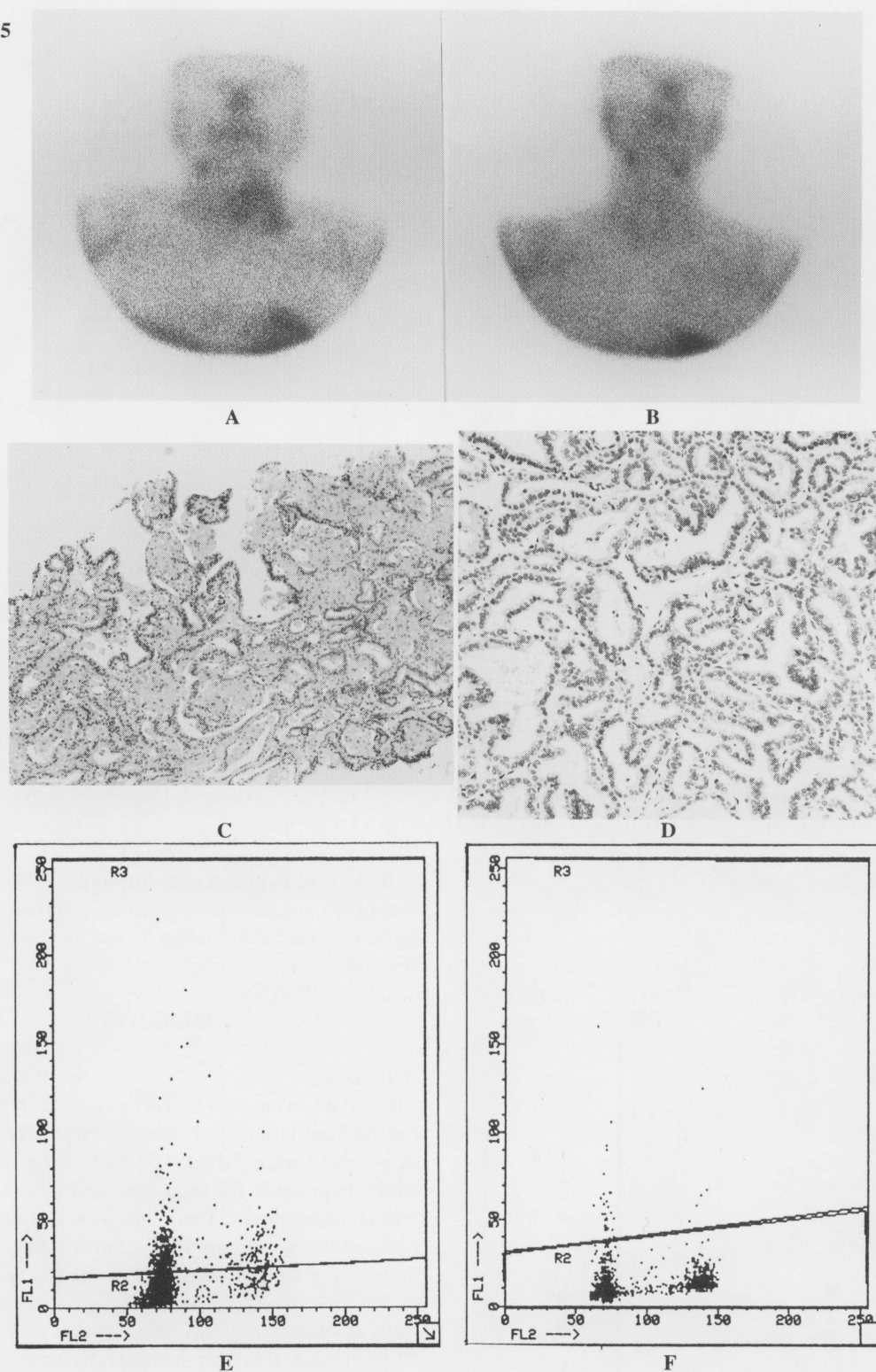
### Flow cytometric analysis

LI for PCNA (%) was successfully determined in all cases, and ranged from 0.5 to 51.2% (mean  $14.3 \pm 12.1$ ). LI was  $17.6 \pm 13.4\%$  in group M, and  $10.3 \pm 6.1\%$  in group B. Group M had significantly higher LI than group B (Fig. 2).

### Comparative study

A) Relationship between uptake of  $^{201}\text{Tl}$  and cellular proliferative activity: The correlation coefficients for

Fig. 5



ER vs. LI in group M and group B were 0.576 and 0.650, respectively (Fig. 3A, 3C). The correlation coefficients for DR vs. LI in group M and group B were 0.817 and 0.838, respectively (Fig. 3B, 3D). The correlation between  $^{201}\text{Tl}$  uptake and LI for PCNA was significant in the two groups.

*B) Relationship between uptake of  $^{201}\text{Tl}$  and practical*

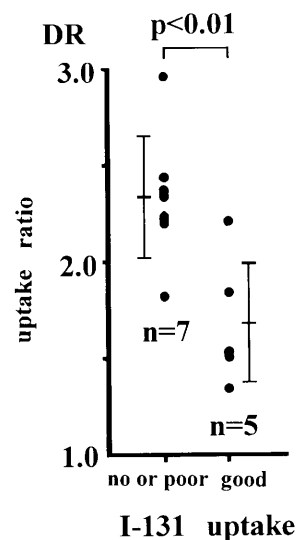
*proliferative activity in thyroid cancer:* DR was used for this purpose because of better correlation with PCNA. In primary thyroid cancer, DR was  $2.14 \pm 0.53$  in lesions with L/N metastases, and was  $1.41 \pm 0.18$  in those without L/N metastases (Fig. 4A). DR was  $2.28 \pm 0.62$  in lesions with positive ETI and  $1.62 \pm 0.39$  in those with negative ETI (Fig. 4B). DR was significantly higher in

◀ **Fig. 5** A–F. Primary thyroid papillary carcinoma. A) a 70-year-old male. He has a hard mass in the left lobe with 4.3 cm in the longest diameter. Cervical lymph nodes are palpable. Delayed  $^{201}\text{Tl}$  scan image demonstrates intense uptake in primary tumor and lymph node metastases. DR is 2.15. The data suggests that the tumor has high proliferative activity. Surgical stage is  $t_4n_2$ . B) a 39-year-old female. A solid tumor in the left lobe has been pointed out. The longest diameter of the tumor is 2.1 cm. Delayed  $^{201}\text{Tl}$  scan image shows no increased  $^{201}\text{Tl}$  activity in the tumor. DR is 1.19. The results shows the tumor has low proliferative activity. Surgical stage is  $t_2n_0$ . C) microscopic findings in case A ( $\times 20$ ). D) microscopic findings of case B ( $\times 30$ ). The epidermological grade is well-differentiated and the histological structure was similar in 2 specimens. E) cytogram in case A. F) cytogram in case B. The oblique bar is cut-off level in PCNA staining. Dots above the bar mean the positively stained cells. LI for PCNA is 22.1 (%) in case A and is 1.0 (%) in case B.

lesions which were accompanied by L/N metastases or ETI. Representative cases are presented in Figure 5. In recurrent carcinoma, DR was  $2.34 \pm 0.32$  in patients with no or poor  $^{131}\text{I}$  uptake, and was  $1.68 \pm 0.36$  in those with good uptake, respectively (Fig. 6). DR was noticeably higher in tumors which showed no or poor  $^{131}\text{I}$  uptake than in those with good  $^{131}\text{I}$  uptake. Representative cases are shown in Figure 7.

## DISCUSSION

The assessment of proliferating activity in thyroid tumor is difficult by morphological methods, such as microscopy, US, or CT scan. The possibility of  $^{201}\text{Tl}$  scintigraphy as a representative for  $^{18}\text{F}$ -FDG PET has been recently suggested for brain tumor.<sup>10–14</sup> Tumor uptake of  $^{201}\text{Tl}$  is regulated by various factors,<sup>17–20</sup> such as vascularity, activity of the  $\text{Na}^+\text{-K}^+\text{-ATPase}$ ,  $\text{Ti}^+\text{-Na}^+\text{-2Cl}$  co-transport system, or development of cellular mitochondria. These factors are not direct predictors of proliferative activity and there has been no study on the relationship between  $^{201}\text{Tl}$  uptake and proliferative factors in thyroid tumors. We focused on PCNA as a predictor of proliferative activity. PCNA is a nuclear protein which is produced in the late  $G_1$  and S phases in the cell cycle and acts as a co-protein of DNA polymerase  $\delta$ .<sup>21,22</sup> Like bromodeoxyuridine (BUdR), PCNA is regarded as a parameter for the cells in the S phase. One of the advantages of PCNA over BUdR is that there is no need of pre-administration at tissue sampling. PCNA is detectable by immunohistochemical staining,<sup>23–26</sup> but the results have been strongly influenced by the conditions in fixation of the materials.<sup>24–26</sup> The FCM technique is expected to make the results more reliable and objective with less artifacts. Biopsy specimens were fragmental but heterogeneity within the specimens may be less than with surgical ones. In our study, DR or LI for PCNA was higher in malignant tumors than in benign nodules. More importantly, there was a significant correlation between  $^{201}\text{Tl}$  uptake and LI for PCNA. This finding suggests that thyroid tumors which concentrate or retain more  $^{201}\text{Tl}$  include more cells in the S phase. The reason for the better correlation coefficient for DR vs. LI than for ER vs. LI is not clear. ER may be related to blood perfusion, but DR may represent a cellular mechanism to

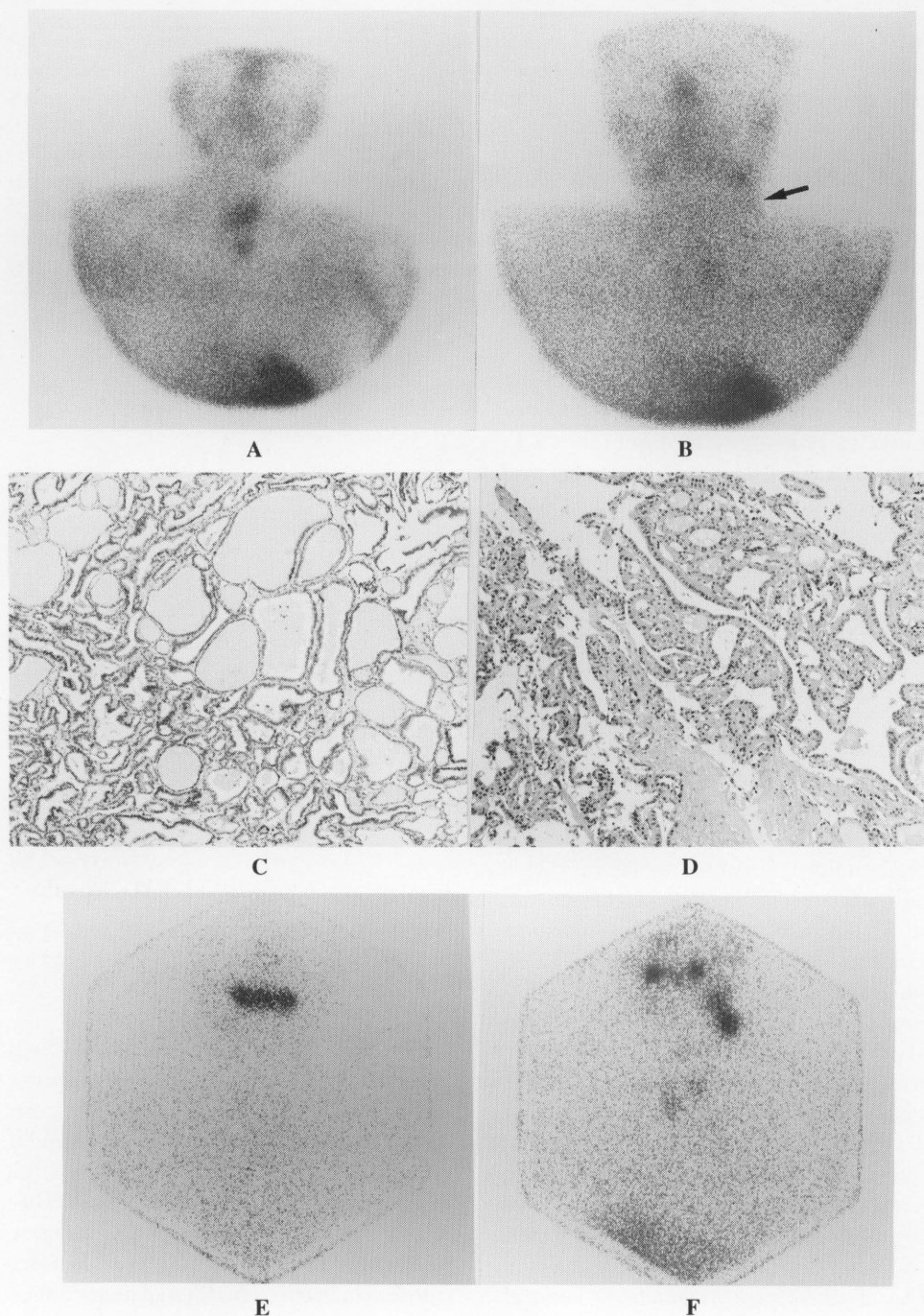


**Fig. 6** Relationship between DR and  $^{131}\text{I}$  uptake following radioiodine therapy in recurrent thyroid carcinoma.

retain  $^{201}\text{Tl}$  longer. The results may indicate that the vascularity of the tumor and the number of proliferating cells within the tumor do not always correlate. DR is a better representative in predicting cellular proliferative activity, and a thyroid tumor with high DR has the potential for rapid growth regardless of its histopathological classification. This may support the suggestion by Harada et al.<sup>8</sup> that the  $^{201}\text{Tl}$  scan is useful in determining the surgical indications for thyroid tumor rather than to differentiate between benign and malignant tumors, and that a case showing  $^{201}\text{Tl}$  accumulation on the scan has the possibility of further growth.

The objective in the comparative study was to identify the value of  $^{201}\text{Tl}$  scanning in characterizing thyroid carcinomas from the point of view of tumor proliferation. The surgical stage is a practical expression of the proliferative activity of thyroid carcinoma. Above all, the presence of ETI is one of the prognostic factors in thyroid carcinoma.<sup>27–29</sup> In this study, DR was significantly higher when ETI or L/N metastases were observed. In contrast, DR in thyroid cancer without ETI or L/N metastases did not differ from that in benign neoplasm. Moreover, there is positive correlation between  $^{201}\text{Tl}$  uptake and PCNA in

Fig. 7

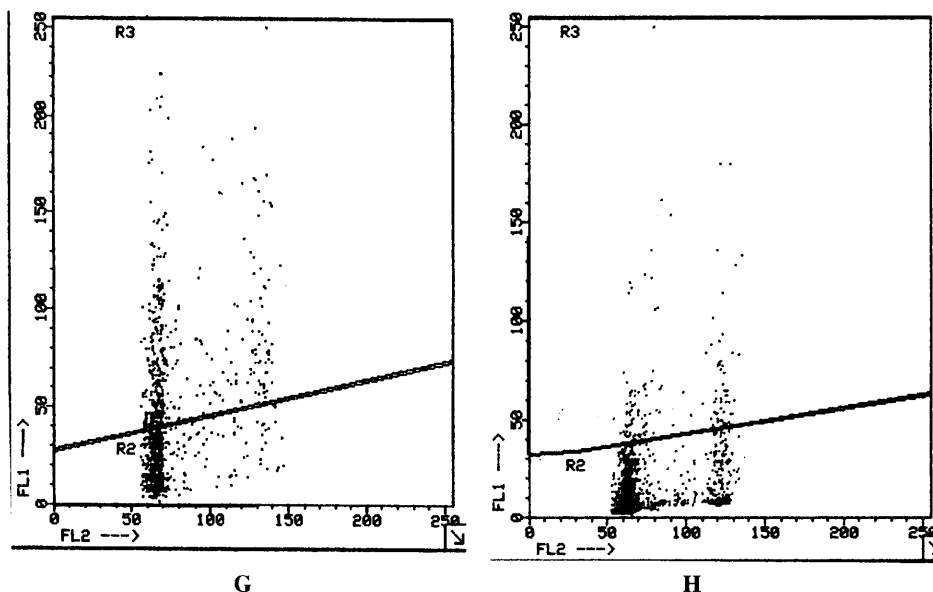


benign lesions as well as malignant tumors. These facts may help to resolve the controversy over the sensitivity and specificity of  $^{201}\text{Tl}$  scintigraphy.<sup>2-7</sup> The uptake of radioiodine is closely related to the prognosis of patients with recurrent thyroid carcinoma.<sup>30</sup> Some of the iodine-negative recurrent thyroid cancers rapidly grow in spite of thyroid hormone replacement. Our results show that although DR is higher in recurrent cancer with no or poor  $^{131}\text{I}$  uptake, it remains the same in the benign nodule in tumors with good  $^{131}\text{I}$  uptake.  $^{201}\text{Tl}$  scintigraphy has been reported to be useful in localizing metastatic tumors that do not concentrate  $^{131}\text{I}$ .<sup>31,32</sup> Our results may be interpreted

as indicating that DR demonstrates variations in the tendency for the tumor to concentrate  $^{131}\text{I}$ . Recurrent tumors with higher DR have more autonomously proliferating cells which may be independent of TSH regulation, resulting in less  $^{131}\text{I}$  uptake on the scintigram.

Differences among our subjects in the histological grade were small. Eighteen out of 19 primary lesions and all the recurrent lesions had "well-differentiated" epidermology. The greatest diameter in lesions were somehow arranged to reduce the partial volume effect on the uptake ratio. Since DR indicates the potentiality of thyroid cancer in invasive growth, in metastasizing, or in its





**Fig. 7** A–H. Recurrent thyroid papillary carcinoma. A) a 67-year-old male. Delayed  $^{201}\text{Tl}$  scan image shows strong uptake in the recurrent tumor in left paratracheal region. DR is 2.44. The data means that the tumor has many proliferating cells. B) a 21-year-old male. He has multiple recurrent tumors in the neck. Biopsy specimen is obtained from left cervical mass (arrow). Delayed  $^{201}\text{Tl}$  scan reveals weak uptake in the tumor. DR is 1.58. The data suggests that the tumor contains less proliferating cells. C) microscopic findings of case A ( $\times 20$ ). D) microscopic findings of case B ( $\times 20$ ). Both specimen show the same epidermal characters of well-differentiated carcinoma. E) therapeutic dose  $^{131}\text{I}$  scan in case A. There is no  $^{131}\text{I}$  uptake in the tumor. F) therapeutic dose  $^{131}\text{I}$  scan in case B.  $^{131}\text{I}$  uptake is good and coincides with  $^{201}\text{Tl}$  uptake. G) cytogram in case A. LI for PCNA is 39.4 (%). H) cytogram in case B. LI for PCNA is 7.6 (%). There is a wide difference in radioiodine uptake and proliferating activity between 2 cases in spite of similar histopathological findings.

resistance to radioiodine therapy, it provides important information for the management of thyroid cancer which cannot be assessed by other morphological studies. DR may also be helpful in determining indications for thyroid hormone administration in chronic thyroiditis or for surgery in benign nodules. In conclusion, this study strongly suggests that the delayed  $^{201}\text{Tl}$  scan is useful in predicting proliferative activity in thyroid neoplasms.

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