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Quantitative Estimation and Clinical Significance of Accumulation and Washout of Thallium-201 Chloride in Follicular Thyroid Neoplasm

HIROSHI YADA, YASUO HOZUMI, KYOTARO KANAZAWA AND HIDEO NAGAI

Department of Surgery, Jichi Medical School, 3311–1 Yakushiji, Minami-Kawachi, Tochigi 329–0498, Japan

Abstract. Purpose: Uptake and washout ratios of thallium-201 chloride (^{201}TlCl) were studied to confirm their clinical applicability in the differential diagnosis of benign and malignant follicular lesions of the thyroid. Patients and Methods: Sixty-six patients with follicular tumor of the thyroid underwent preoperative thallium scintigram after an intravenous injection of 2 mCi (74 MBq) of ^{201}TlCl. The early accumulation and washout ratios of ^{201}TlCl were obtained by an online data-processing system. All tumors were surgically resected and histopathologically diagnosed as either follicular adenoma (49 patients) or follicular carcinoma (17 patients). Scintigraphic values in terms of the early accumulation and washout ratios were compared between follicular adenoma and follicular carcinoma. Results and Conclusion: Both the early accumulation and washout ratios were significantly higher in follicular carcinoma than in follicular adenoma. It was concluded that dynamic studies on accumulation and washout rates of ^{201}TlCl might be clinically reliable to differentiate between follicular adenoma and follicular carcinoma.

Key words: Thyroid follicular tumor, Thallium scintigraphy, ^{201}TlCl, Quantitative analysis

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FOLLICULAR tumor of the thyroid gland consists of follicular carcinoma (FC) and follicular adenoma (FA). Both conditions theoretically require different strategies for treatment. Despite its low-grade malignancy FC may be fatal to the host unless eradicated [1–4]. The benign lesion, FA, on the other hand, may allow the policy of "wait and see" in the absence of complications such as compression to the airway or esthetic problems [5], since malignant transformation from adenoma has not been reported. It remains difficult, however, to preoperatively differentiate the malignant type from its benign counterpart even under intraoperative investigations including histopathologic diagnosis of frozen sections [6–9].

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Correspondence to: Yasuo HOZUMI, M.D., Ph. D., Department of Surgery, Jichi Medical School, 3311–1 Yakushiji, Minami-Kawachi, Tochigi 329–0498, Japan

Our previous work demonstrated more blood flow in FC than in benign adenoma per unit volume of the neoplastic tissue, suggesting the utility of this characteristic for a preoperative differentiation of follicular neoplasms of the thyroid [10]. The present study focused on thyroid scintigraphy using thallium-201 chloride (^{201}TlCl), the accumulation and washout of which appear to be related to the blood flow of the lesions [11]. ^{201}TlCl uptake is also known to be associated with the activity of sodium-potassium (Na+-K+) ATPase in the tissue [10], which seems to indicate that the dynamic alterations of ^{201}TlCl may reflect the neoplastic nature of the lesion, thus enabling the differentiation between the benign and the malignant.

Despite a number of reports on the utility of ^{201}TlCl scintigraphy in differential diagnosis of thyroid tumors [13–18], results have been contradictory, mainly because of handling papillary carcinoma and follicular carcinoma under the same category [14–

18]. We therefore excluded papillary cancer and chose solely follicular tumors of the thyroid to determine factors distinguishing between FC and FA with quantitative evaluation of $^{201}TlCl$ accumulation and washout ratios.

Subjects and Methods

Patients and diagnostic criteria

Sixty-six patients with thyroid follicular neoplasm underwent preoperative $^{201}TlCl$ scintigraphy from May 1990 to November 1996. Details of the scintigraphy and methods of quantitative analyses are described in the next section. The patients comprised 58 females and 8 males with ages ranging from 17 to 75 years (mean: 45.9 years).

All patients had their tumor surgically removed. Resected specimens were subjected to histological examinations employing hematoxylin-eosin (HE) and elastica van Gieson (EVG) staining. Neoplasms with a basic structure of follicles were diagnosed as follicular tumor, although we excluded from the present study those cases of the follicular variant of papillary carcinoma that showed the typical nucleic findings of papillary carcinoma, in addition to the follicular pattern of the neoplastic structure. Also excluded were Hurthle cell tumors, small follicular neoplasms less than 2 cm in diameter, tumors undergoing cystic degeneration with cystic areas of more than approximately 10%, and lesions with coexisting pathological background conditions such as hyperthyroidism or Hashimoto's disease. The diagnosis of follicular cancer was made by experienced pathologists, stress being laid on histopathological evidence of vascular and/or capsular invasion in cases with minimal cytological and structural atypia. Lack of invasion and metastasis led to the diagnosis of adenoma. Using these criteria 17 of the 66 follicular tumors were diagnosed as FC and 49 as FA. The mean size of FC and FA was 34.1 mm and 33.2 mm, respectively (not significant). Of the 17 patients with FC, 8 had both vascular and capsular invasions, and 2 had vascular invasion without capsular involvement. Seven patients revealed capsular involvement without vascular invasion. Distant metastases were observed in 5 patients preoperatively, all of whom had both vascular and capsular invasion on histologic sections of the primary lesion. The follow-up period is only up to 4 years after surgery but distant metastasis was not observed in cases diagnosed as adenoma.

Quantitative analyses by $^{201}TlCl$ scintigraphy

After intravenous injection of 2 mCi (74 mBq) $^{201}TlCl$ (Nihon Mediphysics, Tokyo, Japan), the anterior cervical sites of the patients were scanned for 60 minutes by a gamma camera (GCA-501S, Toshiba, Tokyo, Japan) equipped with a pinhole collimator. Imaging was performed at the energy of 80 KeV, a window width of 30%, and 256×256 matrices.

The gamma ray values were continuously counted and expressed as counts per minute (CPM). Data were collected every 10 minutes to form 6 frames in total. Calculations were carried out using an online data-processor (GNS-55U, Toshiba, Tokyo, Japan) connected to the gamma camera.

Based on the $^{99m}TcO4$ scintigraphy of the thyroid performed immediately before the $^{201}TlCl$ scintigraphy, 3 regions of interest (ROI) were assigned: the neoplasm (ROI 1), the contralateral lobe of the thyroid (ROI 2), and the sternocleidomastoid muscle sufficiently apart from the thyroid gland (ROI 3) (Fig. 1). The mean of CPM/pixel for each ROI were calculated and designated as C1, C2 and C3, respectively.

For ROI 1 and ROI 2, we measured the maximum depth (a) and minimum depth (b) by ultrasonography. The mean of a and b was regarded as the mean depth (D) of ROI (D1 for ROI 1 and D2 for ROI 2).

Adjusted counts for ROI 1 (AC1) and those for ROI 2 (AC2) were calculated by the equations

$$AC1 = (C1\text{-}C3)/D1 \text{ and}$$

$$AC2 = (C2\text{-}C3)/D2.$$

AC1 and AC2 were measured for each frame. The ratio of AC1/AC2 for the first frame, i.e., during the first 10 minutes after administration of $^{201}TlCl$, was designated as early accumulation ratio (EAR) of the tumor. Therefore,

$$EAR = AC1\ (0\text{–}10\ \text{min})/AC2\ (0\text{–}10\ \text{min}).$$

The washout ratio (WR) of the tumor was calculated from the equation

$$WR = 1\text{-}AC1\ (50\text{–}60\ \text{min})/AC1\ (0\text{–}10\ \text{min}).$$

Correction of the data in consideration of attenuation of gamma rays was not performed because preliminary experiments using phantom models (thy-

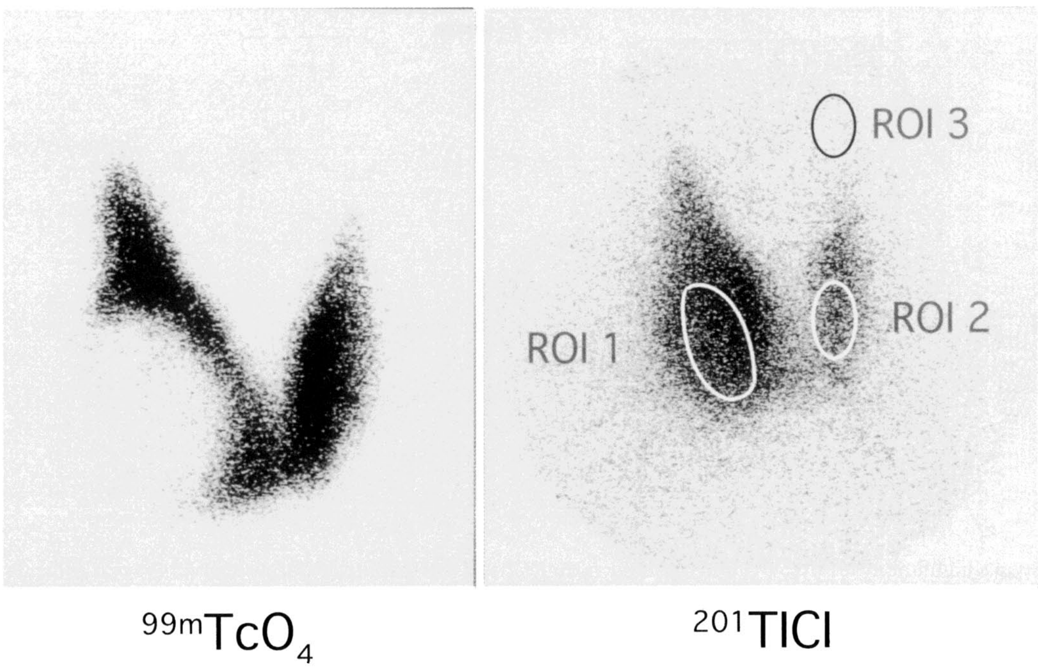

Fig. 1. Based on $^{99m}TcO4$ scintigrams of the thyroid, 3 regions of interest (ROI) were assigned: the neoplasm (ROI 1), the contralateral lobe of the thyroid (ROI 2), and the sternocleidomastoid muscle sufficiently apart from the thyroid gland (ROI 3).

roid phantom for nuclear medicine type TS, Kyoto Kagaku, Kyoto, Japan, and human muscle-equivalent phantom MIX-DP, Taisei Medical, Osaka, Japan) had shown negligibly low modifications of EAR and WR (data not shown).

Statistical analyses

Statistical analyses were carried out by the Mann-Whitney U test to compare the data of FC and FA. P values of less than 0.05 were considered significant.

Results

Figure 2 shows the results of EAR and WR. The mean ± SD of EAR was 1.99 ± 0.47 in FC and 1.04 ± 0.65 in FA. The difference between the two groups was significant ($p < 0.001$). All patients with FC had EAR of more than 1.0, whereas 55% (27/49) of those with adenoma had EAR of less than 1.0.

The mean ± SD of WR was 0.65 ± 0.09 in FC and 0.50 ± 0.16 in FA. The difference between the two groups was statistically significant ($p < 0.01$). All patients with FC had WR of more than 0.4 while 31% (15/49) of FA had WR of less than 0.4.

If the criteria for selection of FC were set up by employing both EAR > 1.0 and WR > 0.4, all FC cases would be harvested and 21 of the 49 patients with FA would be included in the selected group (Table 1). Therefore, the sensitivity of the criteria for FC would be 100% (17/17), whereas their specificity would be 57% (28/49).

Discussion

Several authors have reported the utility of $^{201}TlCl$ thyroid scintigraphy in the detection of thyroid malignancies. Tonami *et al.* [11] first reported the affinity of $^{201}TlCl$ to malignant thyroid tumors. Ochi *et al.* [14] and El-Desouki [17] found a sustained accumulation of $^{201}TlCl$ in the majority of carcinoma cases when early and delayed scans were compared. However, the specificity in predicting malignant thyroid tumors has generally proved to be low. Henze *et al.* [15], Bleichrodt *et al.* [16] and Derebek *et al.* [18] were unable to confirm the utility of $^{201}TlCl$

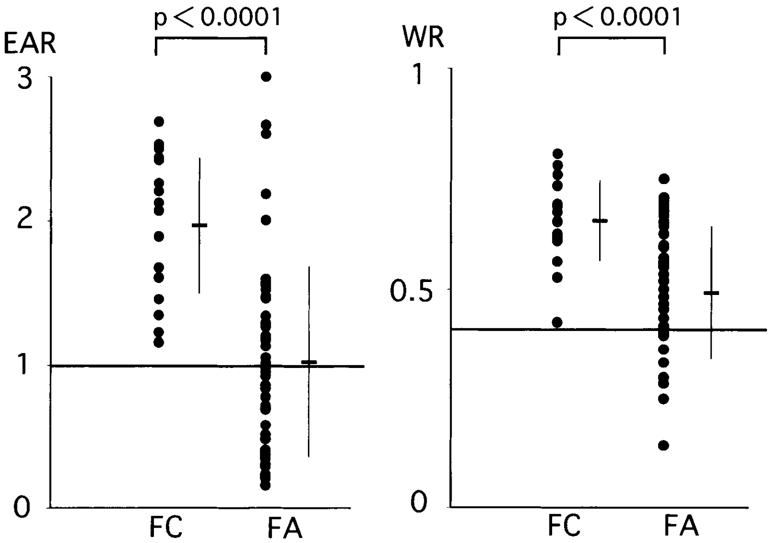

Fig. 2. Early accumulation ratio (EAR) and washout ratio (WR) of 201thallium chloride scintigraphy in follicular carcinoma (FC) and adenoma (FA) of the thyroid.

Table 1. Incidence of follicular cancer and adenoma categorized by early accumulation ratio (EAR) >1.0 or $\leqq 1.0$ and washout ratio (WR)>0.4 or $\leqq 0.4$

	EAR>1.0	EAR≦1.0	WR>0.4	WR≦0.4	EAR>1.0 plus WR>0.4
cancer	17	0	17	0	17
adenoma	22	27	34	15	21

scintigraphy. The reason for the inconsistency of these previous reports seems to be that they combined papillary carcinoma and follicular carcinoma under the same category of malignant thyroid neoplasm. Different degrees of cystic degeneration in the thyroid neoplasma might be another reason. In the present study, therefore, cystic neoplasms were excluded. We previously disclosed the mechanisms of ^{201}Tl accumulation in the late phase which are different between papillary and follicular carcinomas; that is high values in papillary adenocarcinoma are due to delayed washout of the radioisotope, while augmented incorporation in the early phase gives rise to a high residual amount at the late stage in follicular carcinoma [19].

The two types are known to have different histopathological and clinical features. Regarding the diagnosis of papillary carcinoma, ultrasonography-guided fine needle aspiration biopsy (FNAB) is considered reliable [8], hence, it is not necessary to carry out ^{201}TlCl scintigraphy as an adjunctive diagnostic modality. As for follicular carcinoma, on the other hand, preoperative differentiation between the benign and the malignant has been difficult even with FNAB unless unequivocal metastases exist. Accordingly, we investigated the applicability of ^{201}TlCl for preoperative assessment of the nature of follicular tumors.

To obtain the objective data on accumulation and washout of ^{201}TlCl, we analyzed the scintigram quantitatively using an online data-processing system. Since the visualized images of ^{201}TlCl scintigraphy represented two-dimensional data, we further estimated the values on a three-dimensional basis by taking into account the thickness of the tissue by conducting a concomitant ultrasonographic investigation. We also employed the relative values of scintigraphic counts in the lesion in relation to those in normal tissue, as the uptake of the radioisotope might depend on individual conditions, such as systemic blood pressure, circulating blood volume and body weight. We believe that these modifications made the raw data as objective as possible.

$^{201}TlCl$ is a monovalent cationic radioisotope with biological properties similar to those of potassium. The substance has been shown to be taken up by various normal and neoplastic tissues. Uptake rates of $^{201}TlCl$ are considered to be modified by multifactorial indices. The accumulation of the radioisotope appears to be related to the activity of Na+-K+ ATPase in the tissues [12]. In an in vitro study, Elligsen *et al.* [20] revealed that the Na+-K+ ATPase level in malignant tumor cells correlated with their proliferative ability. From an immunohistological investigation of proliferating cell nuclear antigen (PCNA), Kume *et al.* [21] and Nakada *et al.* [22] also suggested that $^{201}TlCl$ uptake in thyroid tumors might reflect proliferative activity. On the other hand, the uptake of $^{201}TlCl$ by tumor tissue is governed not only by the Na+-K+ ATPase of the tissue but also by blood flow: the higher the enzymatic activity and the more abundant the blood flow; that is, the higher the uptake of $^{201}TlCl$ by the tumor tissue [19]. In that study the author further demonstrated that follicular cancer had higher Na+-K+ ATPase activity and more blood flow than in the normal thyroid. The accumulation of $^{201}TlCl$ thus seems to express the proliferative ability of the tumor to some extent, which may be supported by our present data showing that the EAR of follicular carcinoma was significantly higher than that of follicular adenoma. Moreover, we showed a significant correlation between power-mode Doppler ultrasonography and EAR (unpublished data).

Besides EAR, we determined that the WR of $^{201}TlCl$ tended to differ between the patients with follicular adenoma and carcinoma. In a previous report [19], Kishida showed that the washout of the radioisotope is crucially related to the blood flow in the tissue, suggesting that the mechanism of $^{201}TlCl$ washout may be a passive one in contrast to its uptake. Differences in WR between FC and FA seem to be associated with those of blood flow in the two types of thyroid tumor.

It is to be noted that the combination of EAR and WR of $^{201}TlCl$ scintigraphy contributed to a decisive discrimination of follicular tumors of the thyroid. The criteria for selection of cancer with EAR of more than 1.0 plus WR of more than 0.4 had the sensitivity of 100% and specificity of 57%. Our new criteria could thus accurately select all the candidates for surgery and save more than 50% from unnecessary resections for adenoma of the thyroid. With regard to the role of ultrasonography, FA with low EAR tended to be associated iso- or hyperechogenicity of the tumor containing colloid rich follicles, and with cystic degeneration that can be differentiated from hypoechoic solid mass with relatively small follicles occasionally seen in FC. We should keep in mind that differentiation by US alone may not be reliable in some cases where $^{201}TlCl$ scintigraphy is helpful.

In conclusion, the quantitative estimation of $^{201}TlCl$ scintigraphy might be clinically reliable in differentiation between follicular adenoma and carcinoma of the thyroid. A future prospective investigation using the scintigraphic criteria of $EAR > 1.0$ plus $WR > 0.4$ is mandatory for definitive evaluation.

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