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Thallium-201 scintigraphy in the evaluation of thyroid nodules
A retrospective study of 246 cases

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There is controversy at present concerning the value of Tl-201 scintigraphy in the diagnosis of malignant thyroid nodules. The usefulness of Tl-201 scintigraphy in differentiating benign from malignant nodules was evaluated retrospectively. Tl-201 scintigraphy was performed in 101 patients with malignant thyroid nodules and in 145 with benign nodules. Early and late images were examined to compare Tl-201 uptake in nodules and normal thyroid tissue. The visual method resulted in 74% of sensitivity and 58% of specificity for the detection of malignant nodules including incidental cancers. Excluding incidental cancers, 87% sensitivity and 58% specificity were achieved. Small cancers, including incidental cancers less than 1.5 cm in diameter and small number of viable tumor cells in a large tumor also gave negative Tl-201 scintigraphic results. Forty-two percent of the benign lesions gave false positive Tl-201 scintigraphic results.

It is concluded that Tl-201 scintigraphy is a sensitive and useful method to use in diagnosing malignant thyroid nodules, but is not a specific method even with late scan, for the detection of malignant thyroid nodules.

Key words: thallium-201, thyroid malignancies.

INTRODUCTION

Nowadays, thallium-201 (Tl-201) scintigraphy is used in tumor imaging for various diseases. Tl-201 scintigraphy of thyroid cancer is widely used in Japan. Since the application of Tl-201 scintigraphy to thyroid tumor diagnosis, several authors have reported the utility of the Tl-201 scan in diagnosing malignant thyroid tumors.[1–10] Tonami et al. have reported tumor affinity with thallium in malignant thyroid tumors,[1] but the specificity of thallium imaging in predicting malignant thyroid tumors has been proved to be low.[2,3] Ochi et al. have shown the usefulness of late scan. With a combination of early and late thallium scintigrams, they found that in the majority of carcinoma cases there was persistent accumulation of thallium, and therefore very high sensitivity and specificity could be obtained.[4] The investigators claimed that slow washout from a thyroid nodule was characteristic of thyroid cancer. However, controversy is continuing concerning the sensitivity and specificity of thallium scan for thyroid malignance.[8–10]

The purpose of this investigation was to clarify the utility of thallium scintigraphy in the diagnosis of thyroid malignancies in a larger number of cases. Thallium-201 images were evaluated for sensitivity and specificity along with information on their histology.

PATIENTS AND METHODS

From January, 1981 through December, 1991, patients who were examined by both technetium-99m (and/or Iodine-123) and thallium-201 thyroid scintigraphy were evaluated. One hundred and one patients with malignant lesion (62 with papillary cancer, 22 with follicular cancer, 3 with squamous cell cancer,

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7 with malignant lymphoma, one with medullary thyroid cancer, and 6 with undifferentiated cancer), and 145 patients with benign lesion (65 with follicular adenoma, 77 with adenomatous goiter and 3 with cyst) were histologically proven. Multiple nodules had been considered to have a low prevalence of malignancy compared with solitary nodules, but in recent studies the prevalence of malignancy in solitary nodules was 17%, while the prevalence of malignancy in multinodular glands was 13%.[10] Since the risk of malignancy in multinodular glands is not so low when compared with a solitary nodule, multinodular glands were also included in this study. There were 27 males and 74 females, aged 16–86 yr (mean age±S.D., 56.5±17.4 yr) in the malignant cases and fifteen males and 130 females, 19–88 yr (mean age±S.D., 49.9±15.8) in the benign cases.

Following intravenous administration of 74 MBq of thallium-201 chloride, 15 min (early) and 3 hr (late) images were obtained. An Anger type gamma camera (GCA-10A, Toshiba, Japan) fitted with a low energy converging collimator setting an energy at 80 KeV with 30% window was used. 650 K counts were collected for each image.

The thallium scan was assessed visually following procedures reported by Ochi et al.[4] For the early scans, the images were scored as follows: −, no thallium uptake or less than the uptake at non-tumor site of the thyroid, +, thallium uptake equal to non-tumor thyroid, and 2+, increased uptake compared with non-tumor site. For late images, the following scoring was used; −, less than or equal to non-tumor thyroid activity, +, slightly higher than non-tumor thyroid activity, 2+, markedly increased uptake as great as myocardial uptake. The images were obtained in the neck and chest field.

RESULTS

The results of thallium-201 scintigraphy and the findings on histological examinations are summarized in Table 1. When the criterion for malignancy was established as the uptake of Tl-201 in the late scan (2+/+, +/+, 2+/2+ and +/2+), 74% sensitivity and 58% specificity were obtained (Table 2). When malignancy was suspected, if the uptake in the late scan had increased and if no fading of activity had occurred compared with the early scan (+/+, 2+/2+, +/2+), 54% sensitivity and 77% specificity were obtained. In trying to differentiate a malignancy from a benign lesion, the aim is to correctly diagnose all carcinoma cases. High sensitivity is therefore more important than high specificity. The former criterion for the late scan (2+/+, +/+, 2+/2+, and +/2+) was used in this evaluation. Histological diagnosis is shown in Table 1. The malignant lesions were 62 cases of papillary cancer including 12 cases of recurrent tumor, 22 cases of follicular cancer including 3 cases of recurrent tumor, 3 squamous cell cancers, seven malignant lymphomas and 6 anaplastic cancers. Follicular adenomas (65 cases), adenomatous goiters (77 cases) and operatively confirmed cysts (3 cases) were taken as the control group.

Among malignant lesions, there were incidental tumors which were not suspected clinically, were found on the surgically resected specimen incidentally, and measured less than 1 cm in diameter. Ten cases of incidental cancer were included in the papillary cancers and were negative in both Tl-201 scintigraphy and technetium scintigraphy. And another type of cancer incidentally found at surgery was a sclerosing variant of papillary cancer. This

Table 1 Correlation of Tl-201 thyroid scintigrams with histopathology

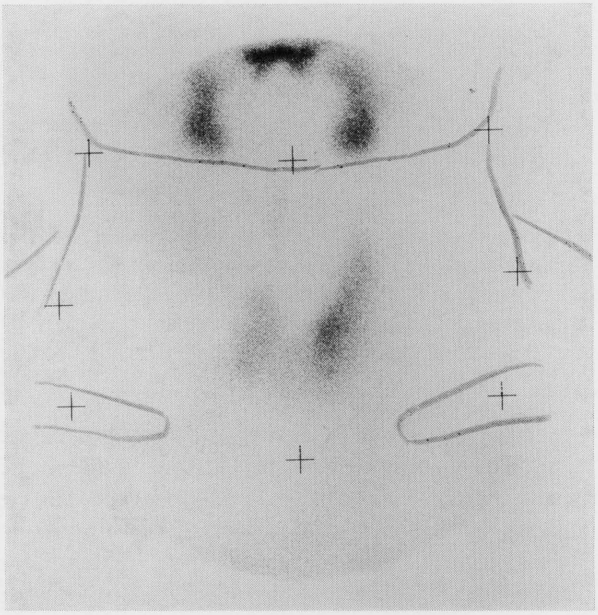
Histologic	−/−*	+/−	2+/−	2+/+	+/+	2+/2+	+/2+
Malignant lesion	16	9	1	11	16	37	11
Papillary ca**	13	7	1	4	7	15	3
recurrence					3	4	5
Follicular ca**		2		4	2	11	
recurrence				2		1	
Anaplastic ca				1	1	2	2
Malig lymphoma	1				2	3	1
Sq cell ca	2				1		
Medullary ca						1	
Benign lesion	57	25	2	27	7	27	
Follicular adenoma	22	9	1	16	4	13	
Adenomatous goiter	32	16	1	11	3	14	
Cyst	3						

*; early scan/late scan.
**; primary cancers only.

Table 2 The result of early and late Tl-201 scintigraphy with criterion based on late scan.

	Malignant	Benign	Total
Positive	75	61	136
Negative	26	84	110
Total	101	145	246

The sensitivity was 74%, specificity was 58%, accuracy was 65% positive predictive value was 55%, and negative predictive value was 76%.



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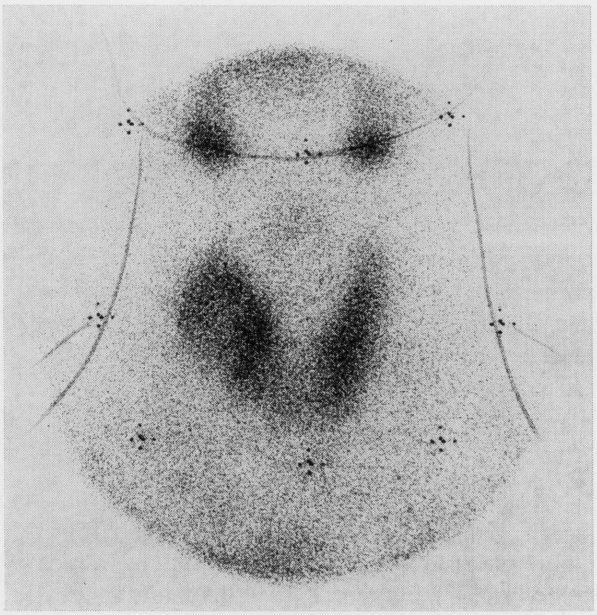

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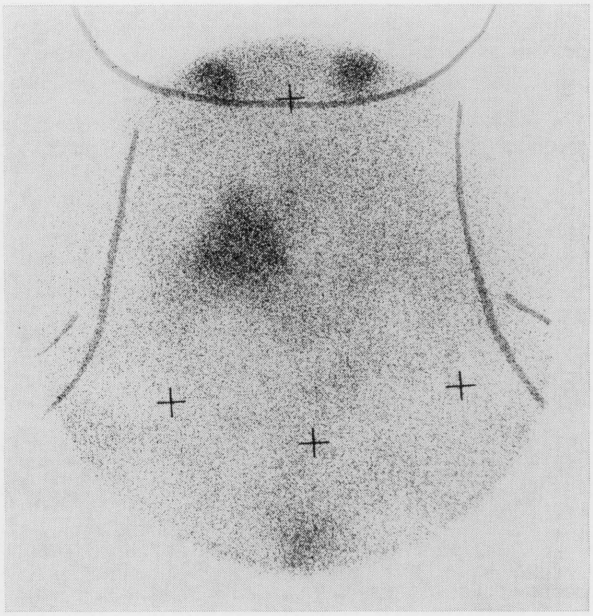

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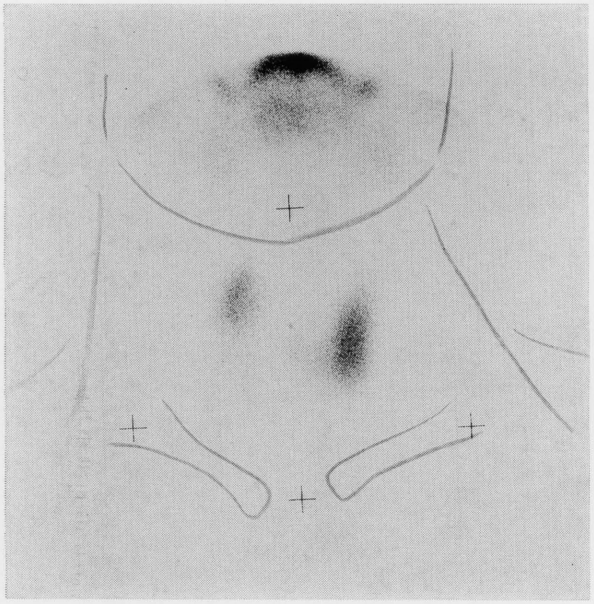
Fig. 1 A focal defect was shown in the right thyroid lobe on Tc-99m scan (A). Tl-201 uptake in the Tc-99m defect was similar to that of non-tumor portion on early scan (B), and a considerable Tl-201 retention was seen in tumor site on late scan (C). This tumor was operated and histological diagnosis was a papillary cancer.

type consisted of the diffuse scattered nests of cancer cells and proliferation of connective tissue between cancer nests. Five cases of a sclerosing variant of papillary cancer were included in the study. These cases gave negative Tl-201 results. Incidental small cancers and sclerosing variants of papillary cancers were not suspected preoperatively and were incidentally found when surgically treating other nodules. Excluding these cases, the sensitivity of thallium scintigraphy increased to 87% and the specificity remained at 58%.

The sensitivity of thallium scintigraphy for malignancy differed according to the cell type. Sensitivity for primary papillary cancer was 58% (29 out of 50), including incidental cancers, and was 83% (29 out of 35) excluding clinically occult cancers. Fig. 1 shows a typical positive case of papillary thyroid cancer. Lymph node recurrences of papillary cancers werd all detected (12 cases), but sensitivity for lymph nodes metastases accompanied with the primary cancer was only 38% (5 out of 13). Sensitivity for primary follicular cancer was 89% (17 out of 19) and all recurrent masses were also delineated (3 cases). Fig. 2 shows a scintigram of follicular thyroid cancer. All lymph node metastasis (5 cases) and hematogenous metastasis (2 cases) with primary follicular cancer was detected. Six cases of anaplastic thyroid cancer were positive in the Tl-201 scintigram.



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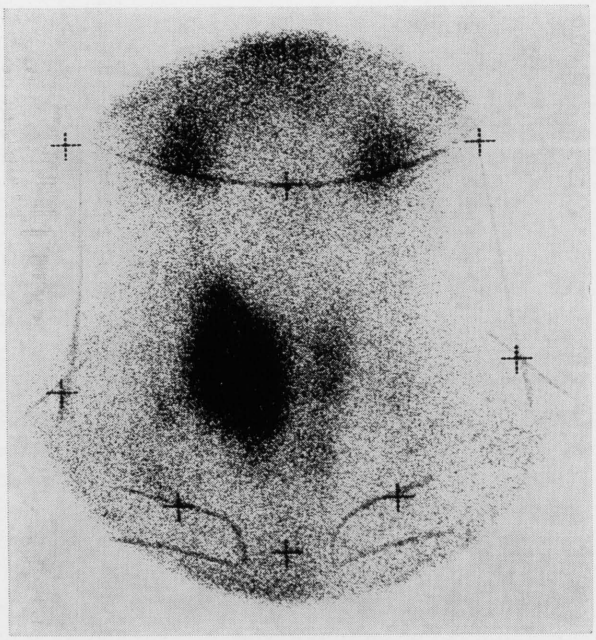

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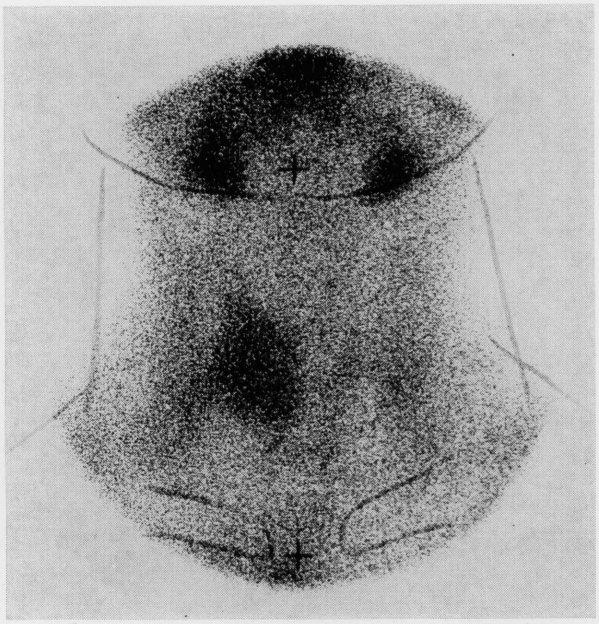

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Fig. 2 A case of follicular cancer was shown. A large defect was seen in the right thyroid on Tc-99m scan (A). An increased Tl-201 uptake was noted both in early (B) and late scan (C).

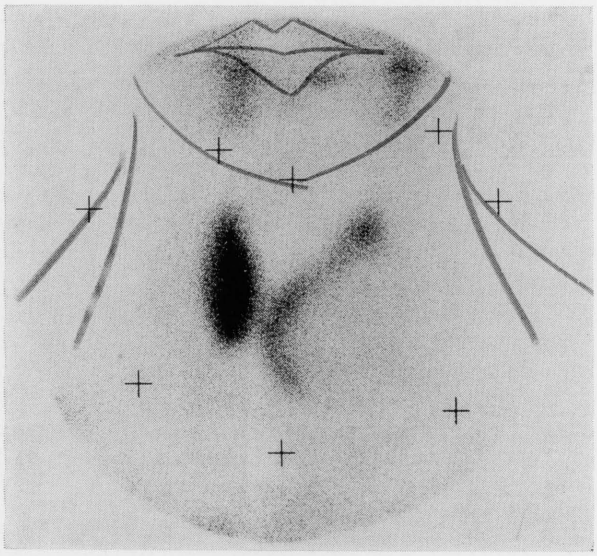
The number of thyroid malignant lymphoma patients was 7. Six patients were at stage IE and had positive Tl-201 scintigrams. One case of systemic disseminated tumor (stage IV) was Tl-201 negative. Three cases of squamous cell cancer of the thyroid were included in this study and one case had a positive scintigram, even though the degree of uptake was not so great. One case of medullary thyroid cancer had a positive Tl-201 scan.

There were 24 cases of Tl-201 negative differentiated papillary and follicular cancers including incidential cancers. As mentioned before, there were 15 cases of incidental cancers (10 cases with small papillary cancers and 5 cases with a sclerosing variant of papillary cancer). Two nodules (one papillary and the other follicular cancer) with Tl-201 negative, were 1.5 cm in diameter. There were large tumors in 7 patients and Tl-201 was negative. These large nodules had a minimal viable tumor portion because of necrosis and/or a cystic component, or contained a minimal cancer portion in a large follicular adenoma.

Figure 3 shows a false positive case of follicular adenoma. High intensity of Tl-201 accumulation was noted, and no or little fading of Tl-201 uptake was noted when the early and delayed scan were compared.

DISCUSSION

The information provided by Tl-201 scintigraphy is quite different from that provided by iodine and/or Tc-99m pertechnetate. The mechanism of iodine and Tc-99m pertechnetate uptake are known, but the mechanism of thallium accumulation in a tumor is not yet fully understood. A part of thallium uptake is mediated by Na-K-ATPase, because the thallium uptake in the thyroid gland is ouabain sensitive, where potassium is replaced by thallium.[12] Since the behavior of thallium is related, but not identical, to that of potassium, the thallium accumulation is certainly related to tissue cellularity to some extent. Other mechanisms of Tl-201 uptake in tumor are



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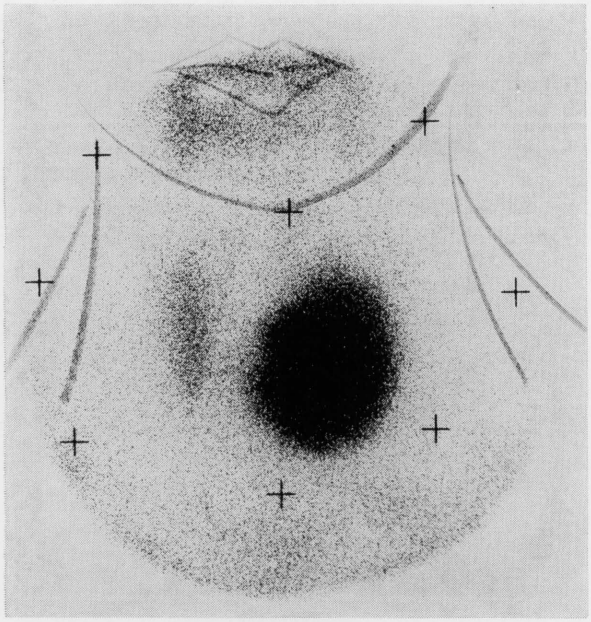

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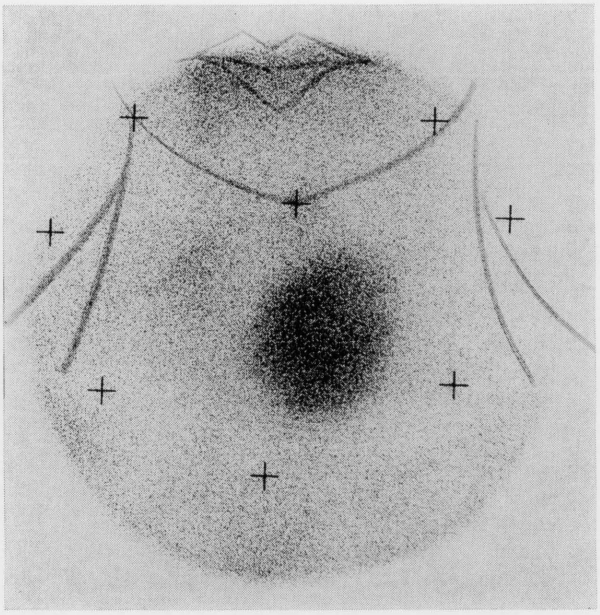

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Fig. 3 A false positive case of follicular adenoma was shown. A focal defect was seen in the left thyroid lobe on Tc-99m scan (A), and the increased Tl-201 uptake was observed both in early scan (B) and late scan (C).

related to blood flow, the co-transport system, immature tumor vessels with leakage into the extracellular spaces and the calcium ion channel. Although the underlying mechanisms are not fully known, the delayed Tl-201 elimination from thyroid cancer was shown by a kinetic analysis.[8]

Iodine-123 and Tc-99m pertechnetate scintigraphies are the common methods used in detecting thyroid nodular lesions. However, most nodules are shown as cold nodules in iodine and/or Tc-99m scan, no specific diagnosis can be made. Tonami et al. introduced Tl-201 scintigraphy as a tool for detecting malignant lesions of the thyroid. However, the specificity of Tl-201 was proved to be low.[2,3] Ochi et al. showed that a combination of early and late Tl-201 scintigraphy could greatly increase the reliability of this method. But some reports did not support these results.[8–10]. The numbers of patients reported were not so large. The present study compared early and late scintigraphic results, and the histology of a greater number of patients showed that Tl-201 scintigraphy with the early and late scans resulted in good sensitivity for malignancy, but specificity was not so high.

Small cancers less than 1.5 cm in diameter and sclerosing variants of papillary cancer gave negative Tl-201 results. Some large tumors with only small numbers of viable tumor cells also had a negative Tl-201 scintigram. Small nodules less than 1.5 cm in diameter and nodules with a large amount of cystic and/or necrotic components possibly give a false negative in Tl-201 scintigraphy.

All recurrent thyroid cancers were detected with Tl-201 scintigraphy in this study. Other reports also showed the reliability of Tl-201 scintigraphy for recurrent thyroid cancers.[13,14] Tl-201 scintigraphy plays a role in differentiating benign from malignant thyroid nodules, but its pitfalls have to be known.

Since our strategy for thyroid nodules was the use of positive Tl-201 scintigraphy in practice, cases of both malignant lesions and benign lesions were included. In addition, nodules with negative Tl-201 scintigraphic results were followed up unless other methods, including the fine needle aspiration and thyroglobulin measurement, indicated malignancy.

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