FROM THE DEPARTMENTS OF ONCOLOGY, RADIATION PHYSICS, OTORHINOLARYNGOLOGY AND CYTODIAGNOSTICS, UNIVERSITY HOSPITAL, S-221 85, LUND, SWEDEN.

KINETICS OF ^{201}Tl UPTAKE IN ADENOMAS AND WELL-DIFFERENTIATED CARCINOMAS OF THE THYROID

A double isotope investigation with $^{99}Tc^{m}$ and ^{201}Tl

J. TENNVALL, J. PALMER, A. BIÖRKLUND, T. MÖLLER, J. RANSTAM and M. ÅKERMAN

Abstract

A visually increased uptake of ^{201}Tl chloride corresponding to a 'cold' (^{131}I or $^{99}Tc^{m}$) thyroid nodule is mostly seen in well-differentiated carcinomas but also often in follicular adenomas. Since a visually increased uptake of ^{201}Tl can be due to an increased initial uptake and/or a delayed elimination, an extended dynamic investigation was performed in patients with well-differentiated carcinomas or with follicular adenomas. Data were collected in a dynamic simultaneous double isotope ($^{99}Tc^{m}+^{201}$Tl) study up to 50 min after intravenous administration. Adenomas could be significantly separated from carcinomas by the elimination ($p=0.0001$), but not by the initial uptake.

The incidence of thyroid carcinomas in scintigraphic solitary 'cold' thyroid nodules (viz. with $^{99}Tc^{m}$ or ^{131}I) is usally reported as relatively high, approximately 20 per cent (2, 6). However, the high incidence of carcinoma found in solitary 'cold' nodules can often be attributed to a bias of case selection (7). To avoid this selection process and to analyse how often a carcinoma does present itself as a 'cold' nodule, the findings in the preoperative scintigraphy of 83 consecutive histophatologically confirmed thyroid carcinomas have recently been reported (12). A solitary reduced uptake was observed in 70 per cent of the entire group (in 65% of well-differentiated carcinomas) wich supports the statement that a solitary reduced uptake is the most frequent scintigraphic appearance of a thyroid carcinoma.

Preoperative aspiration cytology of the thyroid is not seldom inconclusive, and therefore there is a need for complementary investigations to make the preoperative diagnosis as correct as possible to reduce the number of unnecessary operations.

Evaluation of thallium scintigraphy of the thyroid has been reported by several authors. In these reports there is agreement on the general indications and findings. The aim has been to improve the preoperative diagnosis of solitary 'cold' areas in technetium or iodine scintigrams, since malignant thyroid tissues show an accumulation of thallium. The sensitivity appears to be in the order of 90–95%, while the specificity is insufficient (36–54%) to allow a distinction between benign lesions and carcinomas (4, 11, 15). In previous reports (9, 14) it was found that carcinoma as a group might have a slightly decreased disappearance rate of thallium compared with adenomas. Thus, kinetic analysis might increase the specificity.

The aim of this investigation was to further evaluate the kinetics of ^{201}Tl in order to define condi-

Accepted for publication 23 December 1983.

tions (in terms of initial uptake and disappearance rate) for optimum separation between well-differentiated carcinoma and adenoma.

Material and Methods

The criteria for inclusion in the investigation was a histopathologically confirmed well-differentiated thyroid carcinoma or a follicular adenoma with a preoperative $^{99}Tc^{m}$ or ^{131}I thyroid scintigram showing a solitary reduced uptake and a ^{201}Tl scintigram showing uptake in the same lesion (Fig. 1). Medullary and undifferentiated tumours have not been included in this series, because the sensitivity of preoperative aspiration cytology is high in these tumours (10, 13).

Patients with visibly reduced thallium uptake in the lesion were excluded from the study as these thallium negative lesions mostly represent benign conditions (4, 11, 15).

From August 1981 to March 1983, 33 patients fulfilled these criteria, 9 patients had a papillary thyroid carcinoma and 24 patients a follicular thyroid adenoma. The size of the smallest tumour was 18 mm in diameter.

Scintigraphic procedure. Patients were given intravenous injections of 30 MBq $^{99}Tc^{m}$ pertechnetate and, after a delay of 10 to 15 min, 55 MBq ^{201}Tl chloride. Data acquisition was started 6 min before the thallium injection and continued for 50 min. Data were collected by a gamma camera (G. E.) equipped with a pinhole collimator and dedicated computer (Digital Equipment Corp GAMMA-11). Sequential 64×64 element images were recorded simultaneously in two channels in order to provide identical positioning for the thallium and technetium images. The kinetics was evaluated by fitting single-exponential functions, C exp($-\lambda$t), to the background-subtracted count-density curves generated from the pathologic (p) and normal (n) regions of interest (Fig. 2). The kinetics was interpreted in terms of relative uptake (C_p/C_n) and relative disappearance rate (λ_p–λ_n). The clinical presentation is shown in Fig. 3.

The average curve from two regions enclosing the thyroid was used as background. This background amounted to about one third of the initial thyroid uptake, but usually did not differ significantly in the two regions, except during the injection phase. Data were fitted in the interval 6 to 44 min after injection of thallium. Data were also corrected for the channel cross-talk by a first-order correction, thus:

$$(R_i)_{corrected} = R_i - (E_{ij}/E_{jj})\, R_j,$$

where R_x is the count-rate in channel x, and efficiency E_{xy} the count-rate per unit activity of isotope y in channel x, as determined by phantom measurements. The efficiency ratio is of the order of 5 to 10 per cent. The cross-talk is due to scattered events from the ^{201}Tl 167 keV and $^{99}Tc^{m}$ 140 keV gamma rays and to the ^{201}Tl 135 keV gamma rays.

In the absence of this correction, the analysis of the kinetics of thallium is affected if the uptake in the nodule is compared with a normal region with high technetium uptake, the obtained relative disappearance rate (λ_p–λ_n) being incorrectly increased by the order of 0.01 min^{-1}.

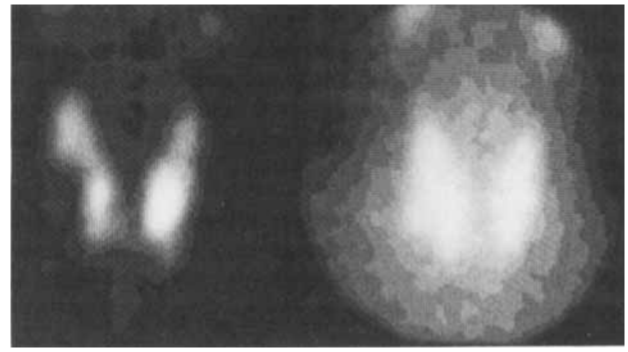

Fig. 1. Comparison between technetium and thallium scintigram in the same patient. The technetium scintigram (left) shows a defect in the caudal lateral part of the right lobe while the thallium scintigram (right) shows an uptake of thallium on the corresponding site. Histopathology revealed a papillary carcinoma measuring 25 mm in its largest diameter on this location.

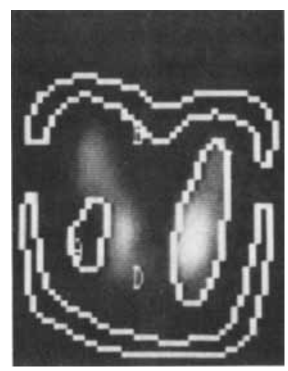

Fig 2. From the simultaneous technetium scintigram (Fig. 1, left) the pathological, normal and background areas are primarily defined for the subsequent kinetic analysis of recorded thallium uptake.

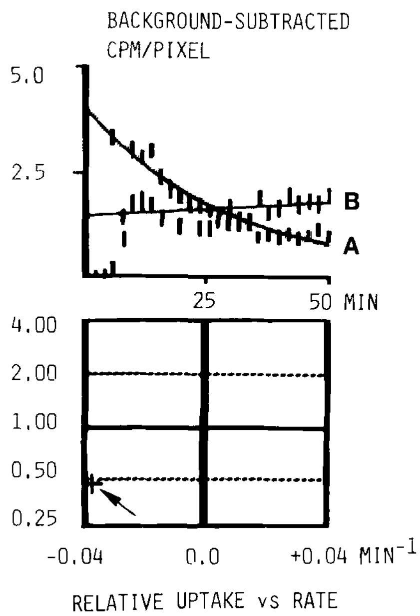

Fig. 3. Example of kinetics of thyroid ^{201}Tl uptake for the same patient as in Figs 1 and 2. Above: Elimination curves in normal (A) and cancerous tissue (B). The areas below the curves are directly proportional to the visual thyroidal scintigraphic uptake of thallium. Below: Diagram showing the extrapolated zero-times uptake ratio ln (C_p/C_n) and relative disappearance rate (λ_p–λ_n). The current values show a decreased initial uptake but a delayed elimination.

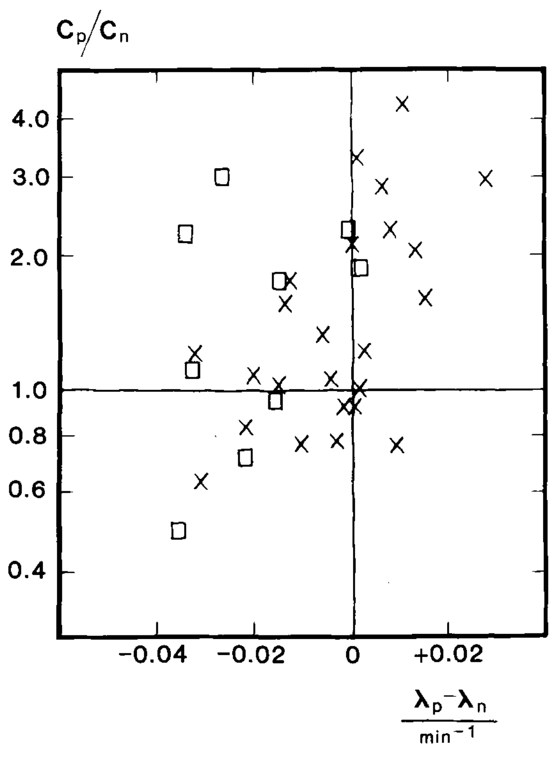

Fig. 4. The extrapolated zero-time uptake ratio ln (C_p/C_n) vs. relative disappearance rate (λ_p–λ_n) in 24 patients with follicular adenomas (×) and in 9 patients with papillary carcinomas (□).

Results

The initial thallium uptake ratio ln (C_p/C_n) and relative disappearance rate (λ_p–λ_n) for all 33 patients are presented in Fig. 4. The carcinomas occupy the left half of the diagram, indicating lower disappearance rates, whereas there is no obvious separation in initial uptake values between carcinomas and follicular adenomas.

The mean value of the disappearance rates for carcinoma and adenoma were −0.021 (SD 0.014) min^{-1} and −0.003 (SD 0.015) min^{-1} respectively ($p<0.01$). The corresponding values for the uptake ratio were 0.316 (SD 0.598) and 0.317 (SD 0.522), respectively.

The present measurements have been pooled with corresponding data from a prevoiusly reported series of 36 patients with solitary 'cold' thyroid nodules in conventional scintigraphy, subject to a dynamic ^{201}Tl examination. Out of these patients, 24 fulfilled the criteria for inclusion in the present series (14). The pooled data are presented in Fig. 5.

Discriminant analysis of adenomas and carcinomas of the pooled material in respect to the disappearance rate and the uptake showed that the disappearance rate could be used to separate the two groups statistically ($p=0.0001$). The optimum value for discrimination was found to be at a disappearance rate of −0.01 min^{-1}.

The uptake was a poor discriminator ($p=0.45$). There was no interaction between the two rates ($p=0.86$).

All p-values have been calculated by F-tests and multivariate F-tests (16).

Testing the optimum value for discrimination from the clinical point of view (Fig. 5) a vertical line, drawn at a value of −0.01 min^{-1} divides the patient material in a high-risk group (11/23 patients with carcinomas) to the left and a low-risk group (5/34 patients with carcinomas) to the right.

Discussion

When complementary thallium scintigraphy is performed in patients with solitary 'cold' nodules (viz. with $^{99}Tc^m$ or ^{131}I) a visually reduced uptake of thallium corresponding to the examined nodule mostly represents a benign lesion. On the other hand, a visually increased uptake is mostly found in well-differentiated thyroid carcinomas of papillary and follicular types but also often in benign thyroid adenomas (4, 11, 15).

In a previous report (14) the elimination of thallium was found to be generally delayed for different types of pathologic tissues. In these tissues thyroid carcinoma as a group was distinguished from various benign lesions by a lower disappearance rate. Among the benign disorders a delayed elimination of thallium was most marked for follicular adenomas.

In the present investigation the difference in rate of elimination between well-differentiated carcinomas and adenomas was evaluated for clinical use in the differential diagnosis.

It is apparent from Figs 4 and 5, that the initial uptake values of thallium alone are of no value for differentiation between benign and malignant lesions. However, it is possible to obtain a good separation between follicular adenomas and well-differentiated carcinomas only by an analysis of thallium elimination. In our data, this differentiation could not be improved by using both parameters in conjunction.

Thus, it was possible (Fig. 5), to divide the patients with a visual thallium uptake in a high-risk group (48% carcinomas) and a low-risk group (15% carcinomas). The possibility of defining a high-risk group of patients having a carcinoma is of value in the progress of surgical decision making.

The mechanism of thallium accumulation in vivo is not fully understood neither in malignant cells nor in normal cells. The disappearance of thallium from blood is extremely rapid and intracellular deposition is nearly immediate (1, 5). Therefore the concentration of thallium in the thyroid is related to factors besides blood flow.

Since the thallium uptake in the thyroid gland is ouabain sensitive (18), parts of the thallium uptake is mediated by Na-K-ATPase, where potassium is replaced by thallium (3, 8). This conclusion is also supported by the analogous biological distribution of thallium and potassium (5). Since the behaviour of thallium is related, but not identical, to that of potassium, the thallium accumulation is certainly to some extent an expression of tissue cellularity. This is in agreement with the observations that follicular adenomas with low or absent uptake of thallium are usually cystic, saturated with colloid or showing signs of bleeding, while follicular adenomas with increased thallium uptake usually belong to the microfollicular or the Azkanazy-cell group (9, 14).

VENUTA et coll. (17) have shown in in vitro studies on transformed thyroid cells that the increased

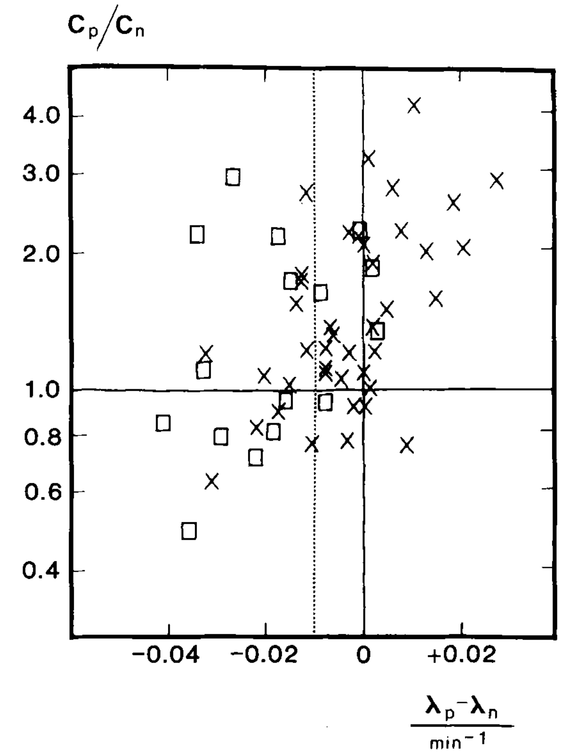

Fig. 5. Present data (as in Fig. 4) combined with corresponding data from a previous report (14). Optimum discrimination between benign and malignant diseases was obtained at a value of -0.01 min^{-1} (dashed line) which divides the patient material in a high-risk group (11/23 patients with carcinomas) to the left and a low-risk group (5/34 patients with carcinomas) to the right.

uptake of thallium may be related to both cell transformation and to growth rate.

To our knowledge, no special study of the elimination of thallium from thyroid cells has been published.

The present kinetic analysis of ^{201}Tl demonstrated that a delayed elimination of the isotope from a thyroid lesion might indicate a malignant thyroid tumour. This finding is important in preoperative investigation when fine needle aspiration biopsy only has given a picture of a follicular neoplasm.

REFERENCES

1. ATKINS H., BUDINGER T., LEBOWITZ E., ANSARI A., GREENE M., FAIRCHILD R. and ELLIS K.: Thallium-201 for medical use. Part 3: Human distribution and physical imaging properties. J. Nucl. Med. 18 (1977), 133.
2. BURROW B. N., QAIYM M., LIVOLSI V. and CORNOG J.: The incidence of carcinoma in solitary 'cold' thyroid nodules. Yale J. Biol. Med. 51 (1978), 13.

3. GEHRING P. and HAMMOND P.: The uptake of thallium by rabbit erythrocytes. J. Pharmacol. Exp. Ther. 145 (1964), 215.
4. HISADA K., TONAMI N., MIYAMAE T. et coll.: Clinical evaluation of tumour imaging with ^{201}Tl chloride. Radiology 129 (1978), 497.
5. ITO Y., MURANAKA A., HARADA T., MATSUDO A., YOKOBAYASHI T. and TERASHIMA H.: Experimental study on tumor affinity of ^{201}Tl-chloride. Eur. J. Nucl. Med. 3 (1978), 81.
6. KENDALL K. W. and CONDON R. E.: Prediction of malignancy in solitary thyroid nodules. Lancet I (1969), 1071.
7. LO GERFO P., COLACCHIO T., CAUSHAJ F., WEBER C. and FEIND C.: Comparison of fine-needle and coarse-needle biopsies in evaluating thyroid nodules. Surgery 92 (1982), 835.
8. OSTER Z., STRAUSS W., HARRISON K., BURNS D. and PITT B.: Thallium-201 distribution in the thyroid. Relationship to thyroid trapping function. Radiology 126 (1978), 733.
9. PALERMO F., SAITTA B., COGHETTO F., TIBERIO M. and CALDATO L.: Computerized study with ^{201}Tl of the cold thyroid node. Nuklearmedizin 21 (1982), 23.
10. SÖDERSTRÖM N., TELENIUS-BERG M. and ÅKERMAN M.: Diagnosis of medullary carcinoma of the thyroid by fine needle aspiration biopsy. Acta Med. Scand. 197 (1975), 71.
11. TENNVALL J., PALMER J., CEDERQUIST E. and ÅKERMAN M.: The kinetics of thallium^{201} uptake in thyroid carcinoma. *In:* COX P. H., Progress in radiopharmacology, p. 81. Proceedings of the third European Symposium on Radiopharmacology. Martinus Nijhof Publishers. The Hague 1982.
12. — CEDERQUIST E., MÖLLER T., NAVERSTEN Y. and ÅKERMAN M.: Preoperative scintigraphy with correlation to cytology and histophatology in carcinoma of the thyroid. Acta radiol. Oncology 22 (1983), 183.
13. — ANDERSSON T., ASPEGREN K. et coll.: Undifferentiated giant and spindle cell carcinoma of the thyroid. Report on two combined modalities. Acta radiol. Oncology 18 (1979), 408.
14. — PALMER J., CEDERQUIST E. et coll.: Scintigraphic evaluation and dynamic studies with thallium-201 in thyroid lesions with suspected cancer. Eur. J. Nucl. Med. 6 (1981), 295.
15. TONAMI N., BUNKO H., MICHIGISHI T., KUAWAJIMA A. and HISADA K.: Clinical application of ^{201}Tl scintigraphy in patients with cold thyroid nodules. Clin. Nucl. Med. 3 (1978), 217.
16. VAN DE GEER J. P.: Introduction to multivariate analysis for the social sciences. W. H. Freeman, San Francisco 1971.
17. VENUTA S., FERRAJUOLO R., MORRONE G., AMBESIIMPIOMBATO F., MANSI L. and SALVATORE M.: The uptake of ^{201}Tl in normal and transformed cell lines. J. Nucl. Med. Allied Sci. 23 (1979), 163.
18. WOLF J.: Transport of iodine and other anions in the thyroid gland. Physiol. Rev. 44 (1964), 45.