Early and Late Lesion-to-Non-Lesion Ratio of Thallium-201-Chloride Uptake in the Evaluation of "Cold" Thyroid Nodules

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Forty-nine consecutive patients with "cold" thyroid nodules were studied using early and late visual and semiquantitative measurements of ^{201}Tl uptake in the nodule to differentiate benign from malignant nodules. The visual method compared ^{201}Tl uptake in the nodule to the normal thyroid tissue. The semiquantitative method used a lesion-to-non-lesion (L/N) ratio of the same areas. Both measurements were carried out early (15 min) and late (3 hr) following ^{201}Tl injection. The reproducibility of the method for the early and late measurements was tested for intraobserver and interobserver variability as well as for repeatability coefficients. The visual method resulted in 43% sensitivity and 79% specificity for the detection of malignant nodules. The L/N method showed that an early threshold of 1.55 chosen by receiver characteristic analysis had a sensitivity of 57% and a specificity of 86%, while the late ratio of 0.99 had a sensitivity of 100% and a specificity of 62%. It is concluded that a L/N ^{201}Tl uptake method performed 3 hr following ^{201}Tl injection is superior to a visual scoring method as well as to the early L/N ^{201}Tl uptake in detecting malignant thyroid nodules.

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The differentiation of benign from malignant thyroid "cold" nodules (visualized on [^{99m}Tc] pertechnetate or ^{131}I) has been attempted unsuccessfully using various radioisotopes such as ^{131}Cs (*1*), ^{67}Ga (*2*), and ^{201}Tl (*3*). To improve the results of thallium scintigraphy, early (15 min) postinjection and late (3 hr) thyroid scintigrams were obtained by Ochi et al. (*4*). The majority of carcinoma cases demonstrated persistent 3-hr uptake as judged visually, while benign lesions were relatively diminished in the late images as compared to the normal thyroid tissue. The investigators claimed that slow thallium washout from a thyroid nodule was characteristic of thyroid cancer and therefore thyroid uptake was still prominent 3 hr following the injection of the isotope. Since visual interpretation of thallium uptake in the nodule may be inconsistent and cannot depict different ranges of uptake, we carried out a prospective study with semiquantitative thallium uptake measurements in thyroid cold nodules and normal thyroid tissue (L/N ratios) at 15 min and 3 hr injection. Thus measurements were made to determine if different uptake patterns in thyroid nodules could differentiate malignant from benign lesions.

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MATERIALS AND METHODS

From October 1988 to March 1989, 49 consecutive patients (5 males, 44 females, age 17–69 yr, mean ± s.d., 43 ± 11 yr) were referred for surgery by the Department of Endocrinology. These patients had a single cold nodule demonstrated by [^{99m}Tc]pertechnetate thyroid scintigraphy.

One or 2 wk before surgery, ^{201}Tl scintigraphy was performed. Following the intravenous administration of 2.5–3.0 mCi of ^{201}Tl, 15-min (early) and 3-hr (late) images were obtained. A digital large field of view gamma camera (Apex 009, Elscint Ltd, Haifa Israel) fitted with a pinhole collimator and an energy setting of 75 keV with a 15% window were used. Each image was recorded for a present count of 100K with an imaging time of approximately 20 min. The early and the late images were obtained at the same distance and patient's position in relation to the collimator.

Two different methods of assessment were used: a visual scoring method based on Ochi et al. (*4*) and a L/N semiquantitative technique.

Images were assessed visually by two observers (RH, EB) by consensus using the following scoring method: 0—no thallium uptake visualized in the nodule; +1—thallium uptake equal to the adjacent normal thyroid tissue; +2—increased thyroid uptake as compared to the normal thyroid tissue.

Following the reading, a L/N semi-quantitative assessment was performed. The early and the late nodule and normal thyroid were measured from images displayed on a 256 × 256 matrix. A rectangular elongated region of interest was drawn over the area of the thyroid nodule and then moved to the opposite normal lobe (Fig. 1). The size and location of the region were identical for the early and late thyroid images. The number of counts in the lesion (L) and the non-lesion (N) regions were recorded for the early and late images. Early and late L/N ratios were then calculated (Figs. 2–4).

Measurements were performed by the same observers (RH, EB) before surgery without knowledge of the histologic results. The intraobserver, interobserver variability and repeatability coefficients (*5*) were calculated for both early and late images.

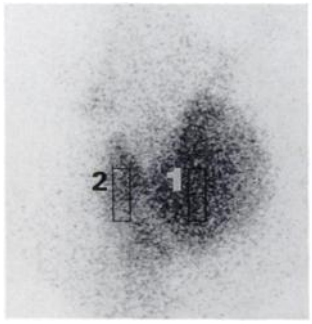

FIGURE 1. A rectangular region of interest is demonstrated drawn over the thyroid nodule (1) and then moved to the opposite unaffected lobe (2).

All patients underwent surgery, the longest diameter of the nodule was measured, and the histologic results were recorded.

RESULTS

Nodule size ranged from 1.3 cm to 6 cm (mean ± s.d. 3.62 ± 1.37 cm). Thirty-six patients had adenomatous goiter, five patients had follicular adenomas, one patient had Hürtle cell adenoma, and seven patients had papillary carcinoma.

Scintigraphic Results

Visual Interpretation. Table 1 summarizes the various patterns of early (15 min) and late (3 hr) scintigraphy, according to the visual scoring method (*4*). Using the persistence of thallium uptake in thyroid nodules (early +2, late +2) as a pattern consistent with a malignancy, there were 3 true-positive, 33 true-negative, 9 false-positive, and 4 false-negative cases. This resulted in a sensitivity of 43%, specificity of 78.5%, and accuracy of 73%. The remaining patients with thyroid cancer showed increased uptake with complete washout (one patient), no thallium uptake (one patient), and persistent uptake equal to the normal thyroid tissue (two patients). When including patients with early +1 and late +1 patterns in the malignant nodule group, there were 5 true-positive, 26 true-negative, 16 false-positive, and 2 false-negative cases. This resulted

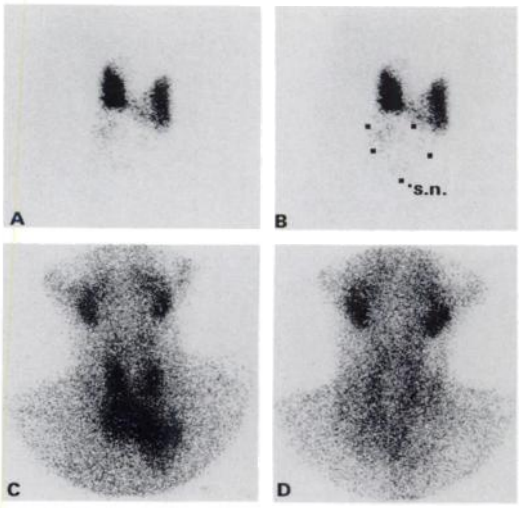

FIGURE 3. Technetium-99m and ^{201}Tl thyroid scintigraphy in a 34-yr-old female. A cold nodule in the right lower lobe and isthmus is visualized (A,B, s.n.-sternal notch). An increased ^{201}Tl uptake is demonstrated in the nodule in the early (15 min, C) image. It includes a large retrosternal portion which could not be appreciated on the ^{99m}Tc image. The late image (3 hr, D), demonstrates complete washout of ^{201}Tl. The visual score was +1 and 0, and the L/N 0.95 and 0.75 respectively. The diagnosis was colloid nodule.

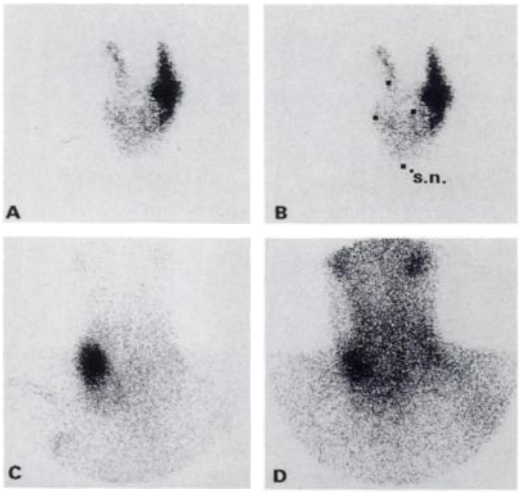

FIGURE 2. Technetium-99m and ^{201}Tl thyroid scintigraphy in a 54-yr-old female. A cold nodule of the right lower lobe (A,B, s.n.-sternal notch) is visualized on the ^{99m}Tc image. An increased ^{201}Tl uptake is demonstrated in the early (15 min, C) and the late (3 hr, D) images with a visual score of +2 and +2, and a L/N of 3.68 and 1.58, respectively. The diagnosis was papillary carcinoma.

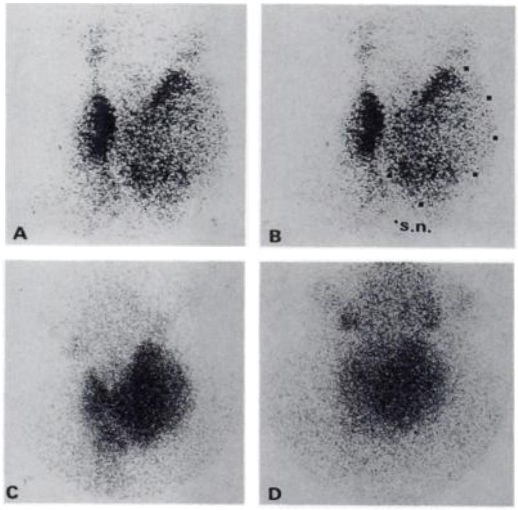

FIGURE 4. Technetium-99m and ^{201}Tl thyroid scintigraphy in a 64-yr-old female. A large cold nodule in the left lobe is visualized (A,B, s.n.-sternal notch). An increased ^{201}Tl uptake is demonstrated in the nodule as compared to the right lobe in the early as well as the late images. The visual score was +2, +2, and the L/N 1.24 and 1.28 respectively. The diagnosis was colloid nodule.

TABLE 1
Early (15 Minutes) and Late (3 Hours) Thyroid Scores in Various Thyroid Nodules

Histology	Thallium score		No. of patients
	Early	Late	
Adenomatous nodule, n = 36	+2	+2	6
	+2	+1	10
	+2	0	2
	+1	+1	7
	+1	0	4
	0	0	7
Follicular and Hürtle cell adenoma, n = 6	+2	+2	3
	+2	+1	2
	+2	0	1
Papillary carcinoma, n = 7	+2	+2	3
	+2	0	1
	+1	+1	2
	0	0	1

in a sensitivity of 71%, specificity of 62%, and accuracy of 63%.

Early and Late L/N Ratios. Early and late L/N ratios were measured in 49 patients. These ratios were then correlated wtih the final diagnosis (Fig. 5). The early L/N ratio for benign nodules was 1.12 ± 0.37 and 1.92 ± 0.96 for malignant nodules. The late L/N ratio of benign nodules was 0.95 ± 0.20 and 1.31 ± 0.27 for malignant nodules. The Student's t-test demonstrated a significant difference between the two groups for both the early ($p < 0.001$) and late ($p < 0.001$) ratios.

The reproducibility of the early and late tests was measured for intraobserver and interobserver variability. A good correlation was found for the intraobserver variation: $r = 0.99$ for the early images with a regression line defined as $y = 0.901x + 0.111$ and $r = 0.69$ with a regression line defined as $y = 0.969x \pm 0.020$ for the late images. Interobserver variability was $r = 0.99$, $y = 0.964x - 0.012$ for the early images and $r = 0.93$, $y = 0.864x + 0.111$ for the late images. The repeatability coefficients (*5*) were 0.074 and 0.036 for the early and late images, respectively.

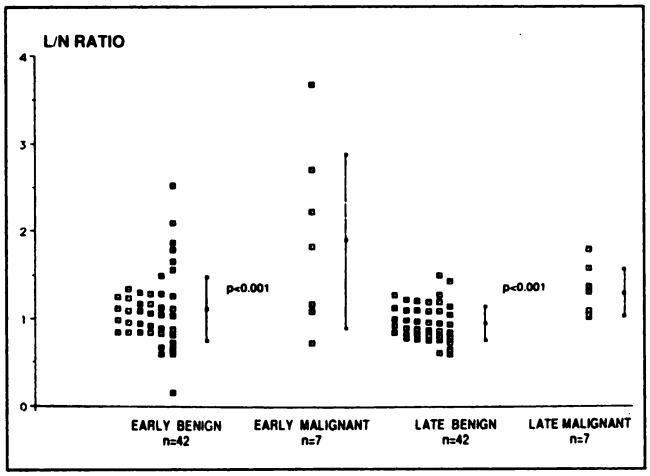

FIGURE 5. L/N ratios in benign and malignant thyroid nodules early (15 min) and late (3 hr) following the injection of ^{201}Tl.

Table 2 summarizes the results of the visual and the quantitative assessments. In order to detect the threshold above which malignant thyroid nodules can be detected, a receiver operating characteristic analysis was used. Following this analysis, a L/N ratio of 1.51 was selected for the early images. With this ratio, there were 4 true-positive cases, 36 true-negative cases, 6 false-positive cases, and 3 false-negative cases, resulting in a sensitivity of 57%, specificity of 86% and accuracy of 82%.

For the late images, a L/N ratio of 0.99 was selected, resulting in 7 true-positive, 26 true-negative and 16 false-positive cases. No false-negative case was detected using this ratio. The sensitivity was therefore 100%, specificity 62% and accuracy 67%.

No correlation was found between thallium uptake and the diameter of the nodule either in the 15-min or 3-hr study.

DISCUSSION

Thyroid nodules are very common (*6*). It is customary to image these nodules with either radioactive iodine or [^{99m}Tc]pertechnetate (*7*). When the nodule is cold and demonstrates adherence to the trachea and adjacent neck tissues on palpation, or when there are enlarged lymph nodes, the probability for thyroid cancer is high. When all these features are missing, it is almost impossible to differentiate between benign and malignant nodules.

Several reports have been published that claimed that early (*3,8,9*) or early and late ^{201}Tl thyroid scintigraphy (*4, 10,11*) were helpful in differentiating benign from malignant thyroid nodules. Tonami et al. (*3*), who performed early ^{201}Tl imaging, found that ^{201}Tl accumulated in 94% of the carcinomas, 40% of the adenomas in one of two patients with adenomatous goiter and in five patients with thyroiditis. Hermans et al. found that early ^{201}Tl images have a sensitivity of 85% and a specificity of 80% for the detection of thyroid carcinoma. Ochi et al. (*4*) found similar results with early images. Increased uptake was observed in 97% of thyroid carcinomas and in 56% of adenomas in five patients with adenomatous goiter. Delayed images demonstrated unchanged uptake in 69% of the carcinomas with some washout in 25%. These studies used a subjective impression, comparing nodule uptake to the normal thyroid tissue. Fading of thallium concentration was determined by comparing the late concentration to the background activity (*4*), judging them to be either equal, moderately or markedly increased compared to the background. Since no quantitation was carried out on the images, it is unclear whether an overlap of uptake occurs in the last two entities.

Tennvall et al. (*10*) performed dynamic ^{201}Tl thyroid studies for 40 min. The uptake measurements could not differentiate between malignant and benign lesions. The

TABLE 2
Detection of Thyroid Carcinoma Using Visual and Quantitative Methods

	TP	TN	FP	FN	Sensitivity	Specificity	Accuracy
Visual scoring							
+2 early, +2 late	3	33	9	4	43%	79%	73%
+2 early, +2 late 1+ early, 1+ late	5	26	16	2	71%	62%	63%
Quantitative analysis							
Early L/N ratio threshold 1.51	4	36	6	3	57%	86%	82%
Late L/N ratio threshold 0.99	7	26	16	-	100%	62%	67%

TP = true-positive; TN = true-negative; FP = false-positive; and FN = false-negative.

relative disappearance rate separated cancer from benign lesions as a group, but could not do so in individual cases.

The above studies performed scintigraphic studies on selected cases, and therefore their series had a high proportion of carcinoma and adenoma cases, while adenomatous goiter which is the most common cause for cold nodules were seldom present.

In this study, we assessed early and late thallium uptake prospectively in consecutive cases of cold thyroid nodule. The majority of cases were diagnosed as adenomatous goiter, and only 7 of the 42 cases (17%) studied were carcinomas, representing the population seen in this clinic. This percentage is within the 9%–26% incidence of thyroid carcinoma in cold thyroid nodules reported in the literature (*6,12*). It was found that the scoring method detected only three of seven carcinoma cases. The early L/N ratio was also unreliable in detecting malignant nodules, however, the 3-hr L/N ratio with a threshold above 0.99 differentiated benign from malignant nodules by detecting all carcinoma cases, resulting in 100% sensitivity of the test but at the cost of falsely detecting 16 of 42 (38%) benign nodules. This L/N ratio may vary depending upon the equipment used, imaging techniques or patient population. Each laboratory is therefore advised to establish its own threshold. In trying to differentiate benign from malignant thyroid nodules, the aim is to correctly diagnose all carcinoma cases. Therefore, the sensitivity of the test used for this purpose is far more important than its specificity, and one is willing to accept the fact that there are always patients with benign nodules who undergo "unnecessary" operations. This report presents only seven carcinoma cases. A larger series of patients should be examined using this semi-quantitative technique to further validate its findings.

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