DIFFERENTIATION BETWEEN MALIGNANT AND BENIGN SOLITARY THYROID NODULES BY FLUORESCENT SCANNING

J. A. Patton, J. W. Hollifield, A. B. Brill, G. S. Lee, and D. D. Patton

Vanderbilt University Medical Center, Nashville, Tennessee

A quantitative fluorescent technique has been developed for making in vivo iodine content determinations of the total thyroid gland or of selected parts. In solitary thyroid nodules "cold" to radionuclide studies, the ratio of iodine content in the nodule to that in a corresponding area of the contralateral lobe has proven to be a good indicator of malignancy. In a preliminary study of 42 surgical patients, an iodine content ratio (ICR) below 0.60 (chosen a posteriori) proved to be an excellent indication of malignancy with a sensitivity of 100%, a specificity (predictive value) of 79%, and an overall accuracy of 90%. Further definitive studies are needed to verify these preliminary observations.

The first clinical system to be developed for in vivo mapping of the stable iodine distribution within the thyroid gland was reported by Hoffer, et al in 1968 (*1*). This fluorescent scanning technique involves the use of a collimated source of radiation (^{241}Am) and a high-resolution detector with the intersection of the field of irradiation and the field of view of the detector defining the area of response of the system. Thus, as the system scans in a rectilinear raster, if iodine atoms are present in the field of irradiation, then most of the 60-keV photons from ^{241}Am will be absorbed and the characteristic 28.5-keV x-rays of iodine would be emitted from the target and counted by the detector. The number of x-rays detected is proportional to the amount of iodine and therefore gross estimates of iodine content can be made from photoplotter images if speed and photoplotter intensity settings are standardized. The total radiation dose to the neck is about 50 mrads and is limited to that region. No radioactive materials are introduced into the body.

The fluorescent scanner was originally conceived by Hoffer as a device for diagnosing thyroid cancer (*2*). This diagnosis poses a serious dilemma for the clinician who must decide whether a palpable nodule is malignant or benign. Several nonsurgical techniques have been used in the preoperative assessment of thyroid nodules, e.g., the ^{99m}Tc thyroid vascular scan (*3*), ^{75}Se-selenomethionine scan (*4,5*), ^{67}Ga-citrate scan (*6,7*), B-mode ultrasound (*8,9*), thyroid angiography (*10*), and thermography (*11*). The degree of success has been variable. Hoffer conjectured that tumor tissue contained significant amounts of abnormal iodoproteins, and that these could be detected by fluorescent scans in regions that were "cold" in radionuclide scans. However, Hoffer found that "cold" nodules were almost always devoid of iodine on the fluorescent scan regardless of whether they were benign or malignant (*12*). Our studies have also shown that most nodules "cold" to radionuclides contain decreased amounts of iodine. However, there appeared to be varying degrees of "coldness" and we sought to explore the possibility of using the amount of iodine present in the nodule as an indicator of malignancy. This hypothesis was partially supported by the work of LeBlanc, et al (*13*) in which iodine content of nodules was determined by in vitro fluorescence techniques after surgery. The theory of quantitative fluorescent scanning has been presented in detail by Tinney (*14*) and applied to the measurement of regional cerebral blood flow and blood volume by Ter-Pogossian and Phelps (*15*) and to cardiac output by Kaufman (*16*). Hoffer (*17*) has pointed out the desirability of quantitative fluorescent scanning of the thyroid and described a means for determining gland depth. The work reported here is an attempt to replace the usual normal or "cold" nodule diagnosis with a quantita-

Received May 29, 1975; revision accepted July 31, 1975.

For reprints contact: James A. Patton, Div. of Nuclear Medicine and Biophysics, Vanderbilt University, Nashville, Tenn. 37232.

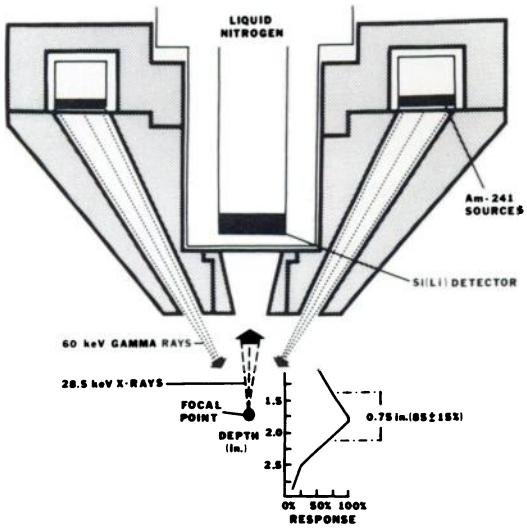

FIG. 1. Schematic of fluorescent scanning system, drawn to scale, showing detector–source geometry and system response to line source of stable iodine in air.

tive value that may be significant in establishing a clinical diagnosis.

METHODS

Our fluorescence system (shown schematically in Fig. 1) uses 16 individual disk sources, each containing 1 Ci of ^{241}Am, arranged in a circle. It is similar in design to a system now commercially available (*18*). Each source is individually collimated to a common focal point 1.75 in. from the face of the collimator. Situated concentric with the annulus of sources, but shielded from them, is a high-resolution lithium-drifted silicon [Si(Li)] detector (Ortec, 25 mm diam). The detector is coarsely collimated by a single hole tapered to the focal point of the field of irradiation. The intersection of the detector field of view and source field of irradiation provides a relatively uniform response over a depth of 0.75 in. centered at the focal point (Fig. 1). The system is mounted on the upper drive mechanism of a commercial rectilinear scanner (Ohio-Nuclear). Signal processing is handled by a linear amplifier (Ortec-716A) and single-channel analyzer (Ortec-455), and the resulting digital signals are recorded on the Ohio-Nuclear scanner photoplotter. Scan speed, line spacing, photoplotter intensity, and digitization frequency are standardized so that calibrations and meaningful comparisons between studies can be made from the film recordings themselves. The rectilinear scanner and detector electronics are also interfaced to our PDP-9 computer for on-line acquisition of digital data.

The computerized data analysis system made it possible to calibrate the technique in order to obtain

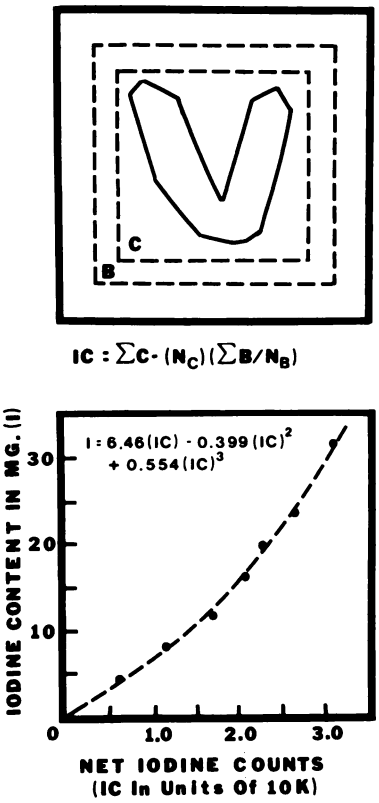

FIG. 2. Top: iodine quantitation technique. Average background count per data cell is determined by summing counts in Region B (ΣB) and dividing by number of data cells in this region (N_B). Net iodine counts (IC) are then determined by summing total counts in Region C (ΣC) and subtracting total counts in that region due to background ($N_C \Sigma B/N_B$), where N_C is number of data cells in Region C. Bottom: chemically determined iodine content (I) is related to net iodine counts (IC) by third-order polynomial.

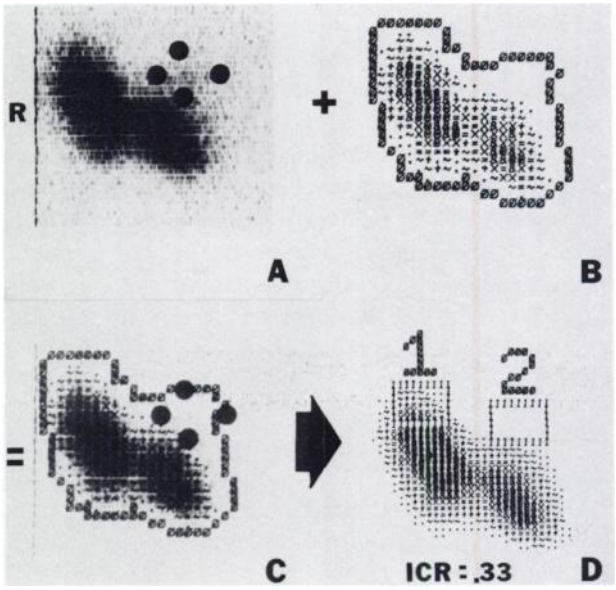

FIG. 3. Fluorescent scan of patient with solitary "cold" nodule illustrating marking of the palpable nodule on photoplot (A), computer generation of same-size image (B), overlay of both images to determine coordinates of nodule (2) and corresponding normal area (1) in contralateral lobe (C), and iodine content ratio (ICR) determination (D).

direct quantitative measurements of iodine content. Known quantities of stable iodine in a thyroid phantom were scanned using simulated neck geometry. After viewing the digitized image on a cathode ray tube, coordinates were entered into the computer to define a rectangular frame around the phantom (Fig. 2A). An area outside the frame was chosen to determine an average background for data cells. Using this average background, the net iodine counts within the frame were determined and plotted (Fig. 2B). A third-order polynomial was fitted to the data points in order to obtain a calibration equation for calculating iodine content based on net iodine counts. This is not a simple linear relationship, due to attenuation of the 60-keV photons as they enter the thyroid and attenuation of the 28.5-keV x-rays as they exit. Although neck and thyroid geometry varies from patient to patient, we have not seen significant variations from the polynomial relationship, probably due to the depth of the uniform field of irradiation of our system. In patient studies, net iodine counts are determined exactly as described for the phantom studies, and iodine content is then obtained from the calibration equation. A standardized collimator–thyroid geometry was maintained by assuming that the mid-depth plane of the thyroid lies 0.75 in. under the surface of the skin. The collimator-to-neck distance is maintained constant at 1 in. throughout the scan by means of a standard distance marker. Modifications in this procedure are made when palpation suggests an abnormal situation. After completion, in addition to the photoplot, a report is presented to the clinican. An explanation of the study is presented, accompanied by a computer-processed image of the iodine distribution and a report of the quantitative iodine content. Size measurements are made for euthyroid and hyperthyroid glands using the assumption that the gland includes all elements two standard deviations or more above background. Weight estimates are made by assuming the thyroid to be in the shape of two prolate ellipsoids with a density of 1 gm/cm^3.

In addition to measurements of total gland iodine, regional measurements of nodule iodine content can be made by comparing the nodule with normal thyroid with the same technique. Every patient diagnosed as having a solitary nodule that is "cold" on a radioactive study (either ^{131}I or ^{99m}Tc) receives a fluorescent scan. The nodule is outlined on the photoplot with the same marker techniques employed on most commercial rectilinear scanner systems (Fig. 3A). An image of the same size is generated by the computer using a border criterion of two standard deviations above background to outline the gland (3B). The images are then overlaid (3C) to determine the coordinates of the nodule (Region 2) and those of a corresponding normal area (Region 1) in the contralateral lobe (3D). The iodine content of each area is then determined using the techniques described earlier, and an iodine content ratio (ICR) —namely, the ratio of iodine content in the nodule to that in the corresponding normal area—is calculated and reported.

RESULTS

To date, fluorescence scans have been performed on 450 patients presented to our nuclear medicine clinic for thyroid work-up. To show the utility of the total-gland quantitative technique, Fig. 4 presents a summary of the measurements made on 80 patients who were clinically diagnosed as euthyroid, untreated hyperthyroid, or hypothyroid. Our measured normal iodine content of 10.7 ± 4.8 mg and normal thyroid weight of 28.7 ± 11.1 gm compare very well

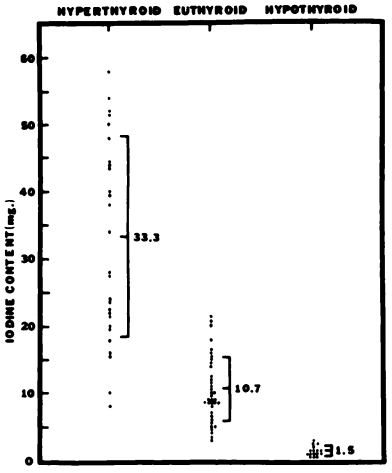

FIG. 4. Total thyroidal iodine determined by quantitative fluorescent scanning of 80 patients, with final clinical diagnosis of hyperthyroid, euthyroid, or hypothyroid state. Bars show mean value and one standard deviation.

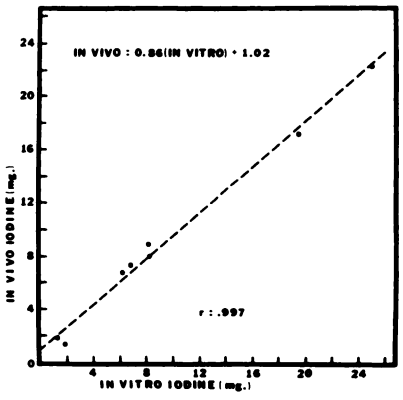

FIG. 5. In vivo compared with in vitro total-thyroid iodine measurements showing results of studies performed on eight patients, with in vitro iodine determined chemically after thyroidectomy.

with the normal ranges of 8–20 mg and 20–30 gm quoted in the literature (*19*). The iodine content of the untreated hyperthyroid group (33.3 ± 14.9 mg) overlaps slightly with the euthyroid group; however, there is a good separation of the hypothyroid group (1.5 ± 0.8 mg).

To verify the accuracy of the iodine estimates, fluorescent scans were performed on eight patients before thyroidectomy. Iodine content was determined in each case and compared with the results of in vitro measurements using accepted chemical procedures (Fig. 5). These data give a correlation coefficient of 0.997, clearly demonstrating the accuracy of the technique.

In addition to the total-gland iodine calculations, the iodine content ratios were determined in vivo on 42 patients presenting with solitary thyroid nodules that were "cold" on radioactivity studies and whose final histologic diagnoses were determined from surgical specimens. These data are summarized in Fig. 6, in the three categories of malignant, benign cyst, and benign solid. Fifteen of the 42 nodules were malignant, with an average ICR of 0.41, a standard deviation of 0.13, and a range of 0.19 to 0.58. Ten nodules were benign cysts with an average ICR of 0.91, a standard deviation of 0.36, and a range of 0.52 to 1.75. Seventeen of the patients had benign nodules with an average ICR of 0.78, a standard deviation of 0.29, and a range of 0.29 to 1.42. There was some overlap between the groups, with one cystic and three solid benign nodules falling into the "malignant" range. These four false positives were a hemorrhagic cyst, two nonfunctioning follicular adenomas, and one amyloid deposit (this patient had generalized amyloidosis and a family history of medullary carcinoma of the thyroid). No nodules classified as "benign" turned out to be malignant.

To verify the accuracy of the in vivo ratio determinations, the iodine concentration of both the nodule and the normal thyroid was determined chemically on surgically removed material in 14 cases. In vitro iodine content ratios were compared to the in vivo fluorescent ratios by least squares regression analysis (Fig. 7). The correlation is significant ($p < 0.001$) with a coefficient of 0.93.

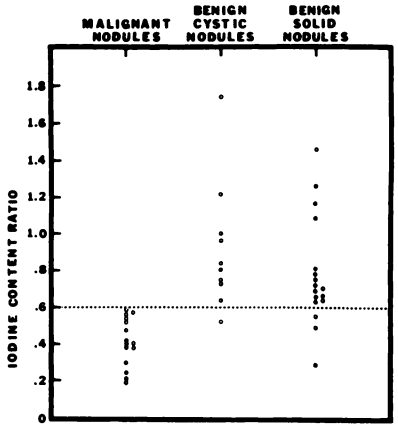

FIG. 6. Iodine content ratios determined before surgery on 42 patients with solitary "cold" thyroid nodule. Groupings are based on histologic study of surgical specimens.

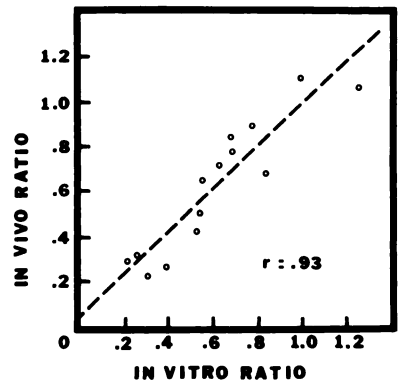

FIG. 7. Plot of in vivo ICR determined by fluorescent scanning against in vitro ICR determined chemically in surgical specimens from 14 patients with solitary "cold" thyroid nodules.

DISCUSSION

Hoffer (*12*) and the present authors (*20,21*) have previously reported that the fluorescent scan is a useful technique for evaluating the size, shape, and functional status of the thyroid, especially when the radiation dose must be kept as low as possible, such as in children and during pregnancy. Patients with a flooded iodine pool or those on short-term suppression who need evaluation of thyroid morphology will derive obvious benefit from this technique. The fluorescence scan may also be useful in predicting the effectiveness of ^{131}I therapy in hyperthyroidism; this is currently under study.

However, the most significant application of the quantitative fluorescent scan in our department has been in the "benign" or "malignant" classification of solitary thyroid nodules "cold" to radionuclide studies. By using the normal lobe of the patient's gland for comparison purposes, problems due to individual differences in iodine content and neck geometry are avoided. Since no malignant nodule has showed an ICR greater than 0.60, we have chosen a ratio of 0.60 to separate those patients who have a great potential for malignancy from those who do not. Based on the a posteriori selection of the 0.60 separation criterion, this indicator has a sensitivity (true positives/all verified positives) of 100%, a specificity or predictive value (true positives/all cases predicted to be positive) of 79%, and an overall accuracy [(true positives + true negatives)/all cases] of 90%. Of course, these studies are tentative and require

confirmation using the 0.60 separation as an a priori value.

The largest source of subjective error in this technique is in positioning the region of interest at the site of the nodule and adjusting its size to conform to the shape of the nodule. At present we are limited to a rectangular-shaped region of interest, but alternatives are being explored. We plan to modify the program to permit flagging the nodule with a light pen so that irregularly shaped areas can be better outlined. A corresponding area in the contralateral lobe can then be marked and the iodine content ratio determined. Another alternative is to measure the volume of the nodule by geometric techniques using the scan data (ultrasound may be necessary), then to determine the specific iodine content of the nodule (mg iodine/cc tissue), and finally to compare that value to the specific iodine content of the total gland. Both of these new techniques will be explored in the near future in hope of circumventing some of the positioning errors.

CONCLUSIONS

A quantitative fluorescent technique has been developed for making in vivo iodine content determinations of the total thyroid gland or of selected parts of it. This technique is now being used routinely to determine iodine content ratios of nodule to normal thyroid tissue in patients with solitary "cold" nodules. An experimental study performed on fluorescent scans from 42 patients has shown that an ICR (ratio of the iodine content in a nodule to that in a corresponding area of the contralateral lobe) of 0.60 serves to distinguish nodules that have a great potential for malignancy. Although these results are tentative and require further verification, the fluorescent technique appears to be superior to other noninvasive diagnostic tests in differentiating between malignant and benign thyroid nodules. The fluorescent scan, used in conjunction with careful clinical appraisal, should be a very useful tool in deciding which patients with solitary thyroid nodules should be treated by surgery.

ACKNOWLEDGMENTS

This work was supported in part by NIH Grant AM 17484-01. In addition the authors would like to thank Ortec, Inc., for their assistance in the design and fabrication of the fluorescence system, the Isotopes Development Group at Oak Ridge National Laboratory for the loan of the ^{241}Am source used in this work, Louis Rosenfeld for his assistance in obtaining surgical tissue specimens, and David Page for pathology assistance.

REFERENCES

1. HOFFER PB, JONES WB, CRAWFORD RB, et al: Fluorescent thyroid scanning: A new method of imaging the thyroid. *Radiology* 90: 342–344, 1968

2. HOFFER PB: Fluorescent thyroid scanning. *Am J Roentgenol Radium Ther Nucl Med* 105: 721–727, 1969

3. BLACK M: Tc-99m pertechnetate flow study for evaluation of "cold" thyroid nodules. *Radiology* 102: 705–706, 1972

4. THOMAS CG, PEPPER FD, OWEN J: Differentiation of malignant from benign lesions of the thyroid gland using complementary scanning with ^{75}selenomethionine and radioiodide. *Ann Surg* 170: 396–408, 1969

5. SPENCER R, HOLROYD AM: The value of ^{75}Se-selenomethionine scanning in solitary nodules of the thyroid gland. *Br J Radiol* 47: 457–463, 1974

6. EDWARDS CL, HAYES RL: Tumor scanning with ^{67}Ga-citrate. *J Nucl Med* 10: 103–105, 1969

7. HIGASI T, NAKAYAMA Y, MURATA K, et al: Clinical evaluation of ^{67}Ga-citrate scanning. *J Nucl Med* 13: 196–201, 1972

8. LELE PP: Application of ultrasound in medicine. *N Engl J Med* 286: 1317–1318, 1972

9. PERLMUTTER GS, GOLDBERG BB, CHARKES ND, et al: Ultrasound evaluation of non-functioning thyroid nodules. *J Nucl Med* 15: 523, 1974

10. DAMASCELLI B, CASCINELLI N. TERNO G, et al: Second thoughts on the value of selective thyroid angiography. *Am J Roentgenol Radium Ther Nucl Med* 114: 822–829, 1972

11. HOMESLEY J, KOVALESKI B, VANAGS K, et al: Thermography in the evaluation of cold thyroid nodules. *J Nucl Med* 16: 536, 1975

12. HOFFER PB, BECKERMAN C, BOWIE J, et al: Fluorescent thyroid scanning: What's new. In *Semiconductor Detectors in Medicine*, Oak Ridge, Tenn, USAEC CONF-730321, 1973, pp 238–248

13. LEBLANC AD, BELL RL, JOHNSON PC: Measurement of ^{127}I concentration in thyroid tissue by x-ray fluorescence. *J Nucl Med* 14: 816–819, 1973

14. TINNEY JF: In vivo x-ray fluorescence analysis—Concepts and equipment. In *Semiconductor Detectors in the Future of Nuclear Medicine*, New York, Society of Nuclear Medicine, 1971, pp 214–229

15. TER-POGOSSIAN MM, PHELPS ME, LASSEN M, et al: In vivo measurement of regional cerebral blood flow and blood volume by means of stimulated x-ray fluorescence. In *Semiconductor Detectors in the Future of Nuclear Medicine*, New York, Society of Nuclear Medicine, 1971, pp 240–257

16. KAUFMAN L, SHAMES DM, GREENSPAN RH: A new method of measuring cardiac output using fluorescent excitation. In *Semiconductor Detectors in Medicine*, Oak Ridge, Tenn, USAEC CONF-730321, 1973, pp 353–364

17. HOFFER PB, BECK R, STARK V, et al: Applications of fluorescent scanning in nuclear medicine. *IEEE Trans Nucl Sci* 20: 375, 1973

18. CLEMENTS D: Ortec, Inc., 100 Midland Road, Oak Ridge, Tennessee. Personal communication, 1974

19. BEIERWALTES WH, WAGNER HN, VOUGHT RL, et al: The thyroid gland. In *Principles of Nuclear Medicine*, Wagner HN, ed, Philadelphia, WB Saunders, 1968, p 312

20. PATTON JA, BRILL AB, BLANCO J, et al: Experiences with semiconductors in imaging and function studies at Vanderbilt. In *Semiconductor Detectors in Medicine*, Oak Ridge, Tenn, USAEC CONF-730321, 1973, pp 254–294

21. PATTON JA, HOLLIFIELD J, LEE GS, et al: Quantitative scanning of thyroidal iodine pools for assessment of thyroid disease. *J Nucl Med* 15: 522, 1974