Prediction of Benignancy of the Solitary "Cold" Thyroid Nodule by Fluorescent Scanning

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A quantitative x-ray fluorescent scanning technique has been used routinely to determine iodine content ratios (ICR) of nodule to normal thyroid tissue in patients with solitary "cold" thyroid nodules. A study of 150 patients with histological diagnoses has shown that an ICR above 0.60 is an excellent indicator of benignancy with a sensitivity of 63% and a specificity of 99%. This technique, in conjunction with careful clinical judgment, can be used to identify those patients that are at low risk for malignancy and can probably undergo conservative clinical management.

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The management of patients with solitary "cold" thyroid nodules remains controversial due to the high incidence of nodules contrasted with the relative infrequency of cancer (*1–3*) and the low morbidity and mortality associated with thyroid malignancy (*3*). Radionuclide imaging serves to confirm the presence of the nodule within the thyroid, identifies the functional characteristics of the nodule, and may demonstrate the presence of multiple nodules (*3*). Although thyroid malignancies do not effectively concentrate radioisotopes, only ~20% or less of "cold" thyroid nodules are caused by cancerous lesions (*4–6*). The remaining 80% arise from thyroid adenomas, colloid nodules, degenerative nodules, nodular hemorrhage, simple cysts, inflammatory nodules (including Hashimoto's thyroiditis and De Quervain's thyroiditis), infiltrative disorders (including amyloid or hemachromatosis), or nonthyroid neoplasms. Surgery is generally required to provide a definitive diagnosis, although needle biopsies have been used in some major medical centers.

A preliminary report has suggested that quantitative x-ray fluorescent scanning can be used to differentiate between malignancy and benignancy in the solitary "cold" thyroid nodule (*9*). The report presented here examines the validity of the technique for this application.

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MATERIALS AND METHODS

The quantitative x-ray fluorescence system has been described in detail previously (*9*). The system is calibrated to yield measurements of regional or total gland iodine content and the accuracy has been validated in phantoms and in patients (*9*).

In our clinical studies, patients diagnosed as having a solitary nodule that was "cold" on a radioisotope study received a fluorescent scan. The nodule was carefully marked by a nuclear medicine physician and outlined on the scanner photoplotter. The area of the nodule was then identified on the computer image in addition to a corresponding area of the same size in the contralateral lobe. The iodine contents of the two regions were determined and an iodine content ratio (ICR) was then calculated by dividing the measured iodine content of the normal region into that of the abnormal region. In our preliminary retrospective study of 42 patients, an ICR of less than 0.60 tended to indicate a high probability for malignancy. In the prospective study reported here, the ICRs were reported to the referring physicians along with the results of our retrospective study. A histological diagnosis was obtained in those patients that subsequently were biopsied or went to surgery for nodulectomy.

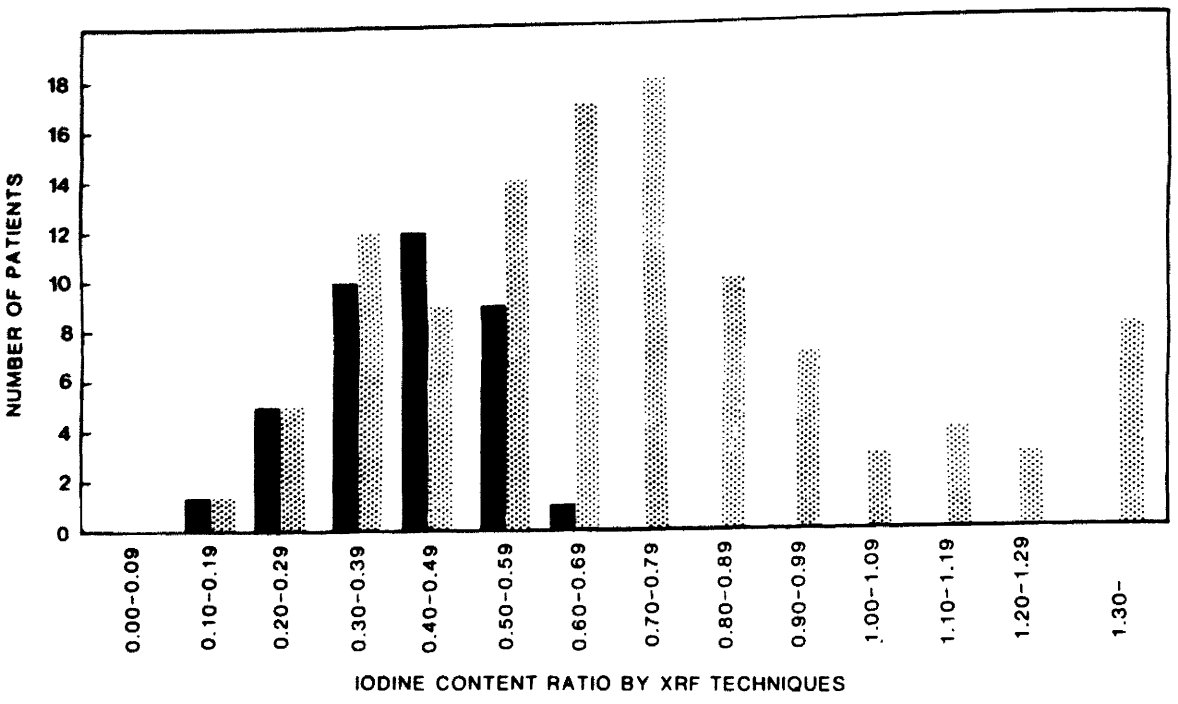

FIGURE 1
Bar graph of iodine content ratios determined before surgery from 150 patients with solitary "cold" thyroid nodules in which histological diagnoses were obtained from surgical specimens. (■) Malignant; (▩) Benign

RESULTS

Iodine content ratios were calculated using computerized x-ray fluorescent scanning techniques in 329 patients who were diagnosed as having a solitary "cold" nodule on a radioisotope scan. The values ranged from 0.10 to 2.83 with a mean of 0.63 ± 0.26. Of this group, a histological diagnosis was obtained in pathological specimens from 150 patients and the ICRs of these patients are shown in Fig. 1. These data are divided into two groups based on the histological determination of malignant (solid lines) or benign (dotted lines). In 145 patients, histology was determined by clinical pathology evaluations from surgical specimens. In five patients, clinical pathology review was performed on specimens obtained from needle biopsy. In four of the latter, no abnormal cells were found. The fifth case was diagnosed as a follicular carcinoma, a finding that was subsequently verified after nodulectomy. It can be observed from the figure that the data separate into two curves that roughly approximate Gaussian distributions. The malignant nodules had ICRs that ranged from 0.19 to 0.68 with a mean of 0.42 ± 0.11. The ICRs of the benign nodules ranged from 0.16 to 2.83 with a mean of 0.74 ± 0.41.

The remaining 179 patients were managed conservatively by their referring physicians and, therefore, no histological information was obtained. Of these studies, 105 were performed after the preliminary report with 44 having ICRs below 0.60 and 61 having ICRs above 0.60.

The validity of our original separation criterion of 0.60 was examined by displaying the ICRs from the 150 patients with histological data as shown in Fig. 2. The data points indicated by open circles correspond to the 42 patients in our preliminary study. From this figure, it can be observed that 37 of the 38 malignant nodules had ICRs below 0.60. The one exception was a value of 0.68. On the other hand, 71 of 112 benign nodules had ICRs above 0.60 (26 of 39 benign cysts and 45 of 73 benign solid nodules).

The malignant nodules were separated on the basis of their histological classifications and examined as a function of ICR. On the basis of these data, there appears to be no difference in the iodine content ratios of malignant nodules based on their categorization as papillary (0.44 ± 0.10), follicular (0.39 ± 0.14), mixed papillary/follicular (0.41 ± 0.12), and other (0.41 ± 0.03).

The four major classifications of benign nodules were also separated and examined as a function of ICR. The nodules classified as colloid cysts (18 cases) had ICRs that ranged from 0.36 to 1.75 with a mean of 0.79 ± 0.36, while those classified as hemorrhagic cysts (13 cases) ranged from 0.22 to 1.58 with a mean of 0.77 ± 0.41 indicating a virtually identical spread for the two distributions. The two major classifications of solid nodules were follicular adenomas (35 cases) and Hashimoto's thyroiditis (10 cases). The follicular adenomas were tightly grouped with ICRs that ranged from 0.29

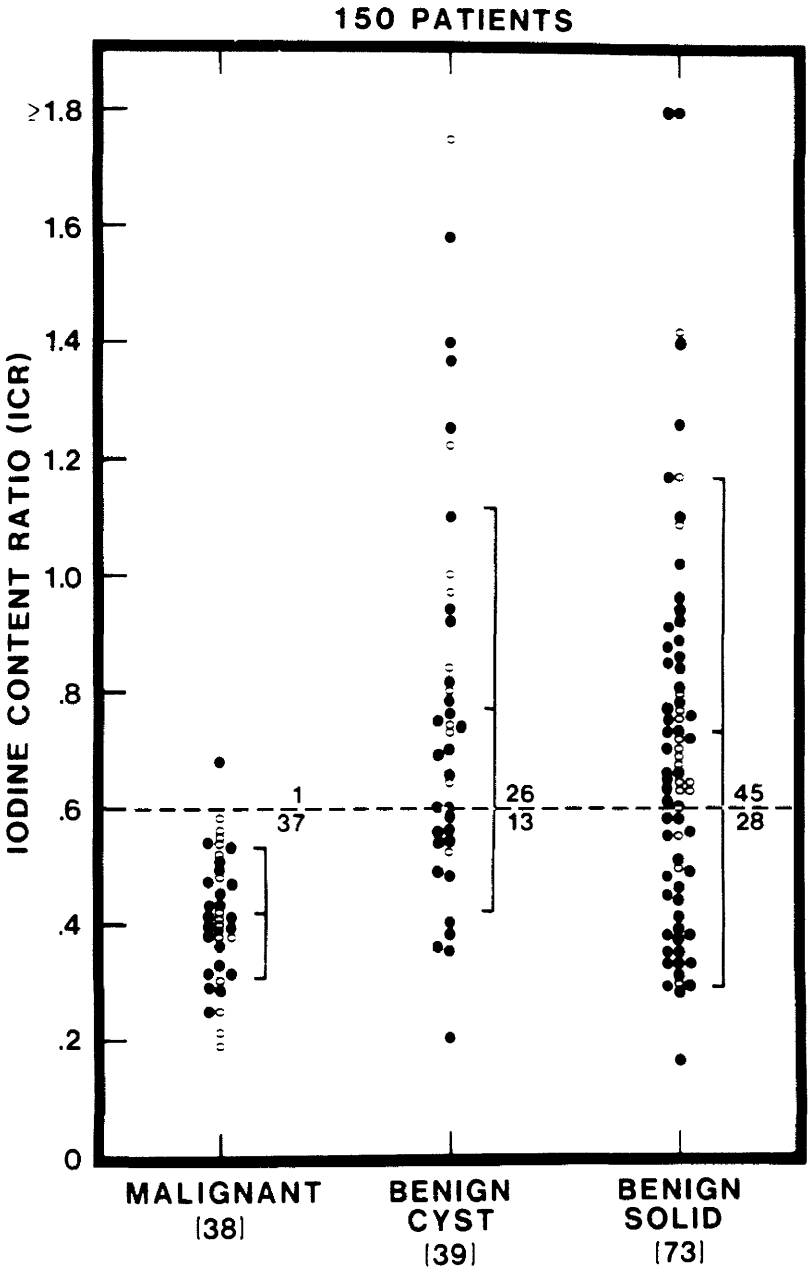

FIGURE 2
Iodine content ratios determined before surgery from 150 patients with solitary "cold" thyroid nodules. Groupings are based on histologic study of surgical specimens. Open circles correspond to 42 patients in our original retrospective study

to 1.10 with a mean of 0.55 ± 0.22. The nodules classified as Hashimoto's thyroiditis had a wide spread, ranging from 0.33 to 2.83 with a mean of 1.17 ± 0.91.

DISCUSSION

X-ray fluorescent scanning, introduced in 1968 (*7*), is an established technique for the investigation of thyroid disorders and we have found it to be especially useful in the evaluation of patients with solitary "cold" thyroid nodules (*9*). The fluorescent scanning technique involves the use of a collimated source of radiation (americum-241) and a high-resolution semiconductor detector mounted on a rectilinear scanner to obtain an intensity map of the stable iodine distribution in the thyroid using the principle of photoelectric absorption and x-ray emission. Quantitative measurements can be accomplished using dual-scaler counting methods (*8*) or computerized techniques (*9*). The total radiation dose to the neck is about 50 mrad and is limited entirely to that region. No radioactive materials are introduced into the body.

On the basis of the results from our original data base of 42 patients, it was concluded that an iodine content ratio of less than 0.60 could be used to distinguish nodules that have a high potential for malignancy. However,

in reviewing the current data base, we feel that we should change this conclusion to state that an iodine content ratio of greater than 0.60 can be used to distinguish nodules that have a high potential for benignancy. This change is warranted because the indicator has proven to be very sensitive for malignancy (true positives/all verified positives = 97%) but not very specific (true positives/all cases predicted to be positive = 47%). On the other hand, the indicator is not as sensitive for benignancy (true negatives/all verified negatives = 63%), but is very highly specific for benignancy (true negatives/all cases predicted to be negative = 99%). In other words, 47% of the nodules with ICRs below 0.60 were malignant, but 99% with ICRs above 0.60 were benign. The overall accuracy (true positives + true negatives/all cases) was 75%. It should be observed that the additional 108 patients added to the data base were weighted towards those with lower ICRs based on our previous experience (i.e., referring physicians were more inclined to treat patients with high ICRs conservatively, instead of performing thyroid biopsy or surgical removal of the nodule).

The ICR data from the diagnosed malignancies were examined to see if those nodules classified as follicular carcinoma had ICRs greater than the other malignant types. This possibility was based on the fact that follicular carcinomas often contain colloid and will concentrate iodine-131 (*10*). However, the data show no separation between the various classifications. It was also anticipated that hemorrhagic cysts would generally be iodine deficient and, therefore, have very low ICRs. However, there was no difference between the ICRs for hemorrhagic cysts, and those for the other benign nodules. This is possibly due to the difficulty in adequately resolving the cyst from surrounding thyroid tissue.

In conclusion, the quantitative x-ray fluorescent scan, used in conjunction with careful clinical judgment, can be used to identify those patients that are low risk for malignancy and can probably undergo conservative clinical management.

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