# Thyroid Nodules and Thyroid Cancer

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*A review of clinical and laboratory features of thyroid cancer, designed to help in a more precise selection of patients for operation, showed that factors contributing to a high index of suspicion of cancer include previous exposure to low doses of radiation, the presence of a firm, solitary thyroid nodule clearly different from the rest of the gland, a young patient, nodules that are "cold" on scan with radioiodine, and nodules that fail to regress after an adequate trial of thyroxine therapy. Factors contributing to a low index of suspicion of thyroid cancer include soft or cystic lesions, multinodular goiters, nodules that are "hot" on $^{131}I$ scan, and those that regress during thyroxine treatment.*

*When these factors are used to select patients for surgical operation, about 30 percent are found to have thyroid cancer.*

*Until more precise methods for preoperative diagnosis are established, it is suggested that this type of clinical selection may be very helpful in the management of patients with thyroid nodules or nontoxic goiter.*

THE THYROID GLAND is unique in that it is easily visible and easily palpable in its location anterior to the trachea. This gland has a tendency to develop nodules, usually benign but occasionally malignant. Although most thyroid cancers are indolent and slow-growing, widespread local metastasis can develop, as well as distant metastasis, resulting in considerable disability and, occasion-

ally, death.[1,2] There have been several excellent reviews on the management of nodular goiter and thyroid cancer.[3-12] Therefore, I intend to review here the clinical differentiation of benign from malignant thyroid nodules.

There has been considerable confusion about the actual prevalence of thyroid cancer. Surgical statistics are particularly unsatisfactory as a source of information. For example, in 1925 at the University of California Medical Center, San Francisco, thyroidectomy was done in approximately 290 patients, and ten cancers were found. This is an incidence of about 3.5 percent. In 1966 thyroidectomy was carried out in 100 patients and 20 cancers were found. This is an incidence of 20
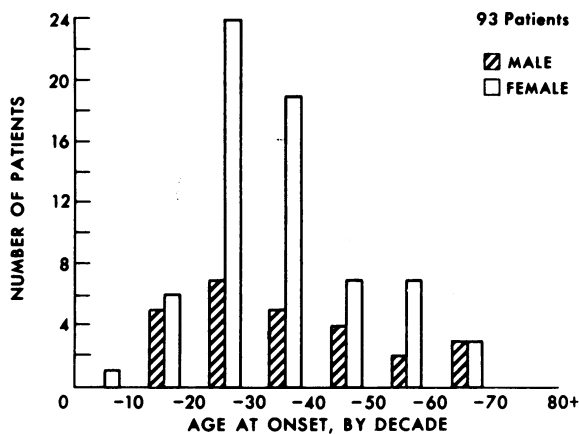
Chart 1.—Distribution by age and sex in a group of 93 patients with proven thyroid cancer.

TABLE 1.—*Summary of Clinical Characteristics of 93 Patients with Proven Thyroid Cancer*

| | |
|---|---|
| Sex ratio ............ | Male to female, 1:3 |
| Age at onset ......... | 4 to 66 years |
| History ............. | Recent growth (71%) |
| | Lesion present more than one month (65%) |
| | Previous radiation therapy (33%) |
| | Familial history of thyroid disease (24%) |
| Physical examination .. | Firm nodule (92%) |
| | Solitary nodule (86%); multinodular (10%) |
| | Nodule larger than 2 centimeters in diameter (67%) |
| | No palpable nodule (6%) |
| | Palpable lymph nodes (33%) |
| Uptake of ¹³¹I ........ | "Cold" (92%; 34 of 37) |
| Response to therapy .. | Did not regress after thyroxine therapy (100%; 21 of 21) |

percent (Goldman L: personal communication). Does this mean that the incidence of cancer has increased? On the contrary, it suggests that the indications for thyroidectomy are changing, and that more of the patients who have thyroid cancer are being selected for operation, whereas fewer who do not have cancer are operated upon.

In the state of Connecticut, all malignant diseases are reported, and excellent statistics are available. Between 1935 and 1970, there has been a gradual increase in the incidence (newly diagnosed cases per year) of thyroid cancer in females, from about 1.5 to 4 per 100,000, and in males, from 0.5 to 1.5 per 100,000.[13,14] Mortality figures from 24 countries, gathered between 1952 and 1963, indicate a drop in deaths from thyroid cancer from about 1.5 per 100,000 in 1952 to 1 per 100,000 in 1963.[15] Interestingly, the death rates in males and females are equal despite the higher incidence of thyroid malignant disease in females. Although the prevalence (total number) of patients with nodular goiter in the United States varies in different geographical locations, Sokal has estimated a minimum prevalence of nodular goiter in the United States at 4 percent, or 4,000 cases per 100,000 population.[4] Mustacchi and Cutler have estimated the incidience of thyroid cancer in the United States as about 0.0025 percent, or 2.5 cases per 100,000.[16] Thus, only a small fraction of patients with nodular goiter will have cancer of the thyroid gland. Although thyroid cancer is an indolent disease and survival is measured in years rather than days or months, it can be a lethal illness.[1,2,17] The question, then, is which nodular lesions are malignant?

## Clinical Characteristics of a Group of Patients with Cancer of the Thyroid

I recently reviewed the clinical characteristics of a group of 93 patients with proven thyroid cancer diagnosed during the past ten years. The ratio of male to female patients was about 1 to 3. The age at diagnosis ranged from 4 years to 66 years (Chart 1). There is a peak incidence in the age range of 20 to 40 years in the female group, whereas the number of male patients was relatively constant for each decade. (These data are not adjusted for the percentage of each age group represented in the population.) Age-adjusted data on the incidence of thyroid cancer, presented by Christine et al,[14] showed a peak incidence between the ages of 20 and 40 in female patients, with secondary peaks at age 60 and age 80. We did not see the late peaks in thyroid cancer in our smaller group.

Clinical characteristics of these 93 patients (Table 1) may be summarized as follows:

Although the goiter had been present in most patients for more than a month, 71 percent had evidence of recent growth, either by patient observation or by physician evaluation. In one series,[18] most of the goiters containing cancer had been present more than one year before operation. Thus, recent growth is probably a more significant finding than total duration of the goiter. One-third of the patients had received therapeutic irradiation to the face or neck area. Therapy was administered as early as the first week of life or as late as 30 years of age, and the thyroid cancer was

diagnosed from six to forty years after exposure to radiation. Indications for radiation therapy were reported to have been thymic irradiation for respiratory distress of the newborn, treatment of recurrent tonsillitis or adenoiditis, treatment of cervical lymphadenopathy, or treatment of the face and upper chest for severe acne.

The most striking physical finding indicative of thyroid malignant disease was a large (more than 2 centimeters), firm, solitary nodule, clearly different from the rest of the gland. Cancer in multinodular goiter was rare, and usually involved a "dominant" nodule, which was different from the rest of the gland. A few patients presented with a large, diffuse goiter that was unusually firm; this was the presentation of anaplastic carcinoma or lymphoma. In a few patients, no nodule was palpable at all; either these patients presented with metastatic lesions in lymph nodes as the first symptom of the disease, or the cancer was found as a microscopic focus, as it was, for example, in one patient with Graves' disease. About one-third of this group of patients had palpable lymph nodes at the time of initial examination.

In patients who had radioiodine scans, the nodules were almost all "cold"; in the few that were not clearly "cold," the nodule was too small to delineate on the scan. In 21 patients, thyroxine had been administered in an attempt to reduce the size of the lesion; in none of these patients was this therapy effective.

Most of the patients had papillary carcinoma or mixed papillary and follicular carcinoma (Table 2). The incidence of metastatic lesions, either intraglandular or to regional lymph nodes, was remarkably high.

## Radiation Exposure and Thyroid Cancer

Duffy and Fitzgerald in 1950 reported upon 28 patients less than 18 years old who had cancer of the thyroid gland. Ten of them had received radiation therapy to the neck or chest in infancy.[19] Winship and Rosvoll[20] looked at records of a large group of children under the age of 15 who had had carcinoma of the thyroid gland. Eighty percent of them had received x-ray therapy to the thymus, tonsils, skin, or cervical lymph nodes. A peak incidence of cancer occurred around 1955. Although this epidemic of thyroid cancer has subsided, deGroot and Paloyan recently reported that 20 of 50 adult patients with thyroid cancer had received radiation therapy at some time in the past.[21] Similarly, in our group, 22 of 66 had a history of previous x-ray therapy.

Several types of radiation exposure have been investigated (Table 3). In a retrospective study, Pincus et al reviewed 2,878 patients who had received radiation therapy to the thymic area in infancy.[22] The incidence of nodular goiter was 28 percent, and of thyroid cancer 4 percent. After exposure to radiation fallout in the Marshall Islands in 1954, there was a very high incidence of nodular goiter, particularly in the exposed children, and the incidence of thyroid cancer was again about 4 percent.[23] The incidence of thyroid cancer among the survivors of the Nagasaki-Hiroshima atom bombs was much lower, about 0.4 percent, although it was higher in persons less than 20 years of age at the time of exposure, and in those exposed to 50 or more rads of atomic radiation.[24] On the other hand, after radioiodine therapy for hyperthyroidism, which results in a

TABLE 2.—Pathologic Classification of Thyroid Cancer in a Group of 93 Patients

| Type | Number | Percentage with Metastasis |
|------|--------|-----------------------------|
| Papillary | 51 | 57 |
| Follicular | 18 | 67 |
| Papillary and follicular | 17 | 88 |
| Anaplastic, lymphoma | 5 | 100 |
| Medullary | 2 | 50 |

TABLE 3.—Incidence of Thyroid Lesions After Irradiation

| Type of Irradiation | Estimated Dose to Thyroid | Lesion |
|---------------------|---------------------------|--------|
| Thymic irradiation | 335 R | Nodular goiter—28% Carcinoma—4% |
| Radiation fallout | Gamma, 175 R; beta, 700 to 1400 R | Nodular goiter Children—80% All—27% Carcinoma—4% |
| Radioiodine therapy | 10,000 R | Hypothyroidism—70% Nodular goiter in children—16% Cancer—rare |

much higher dose of radiation to the thyroid, the occurrence of hypothyroidism is very high,[25] but the incidence of thyroid cancer is very low, about 0.1 percent.[26] There was, however, a significant incidence of thyroid nodules in patients treated with radioiodine before their twentieth birthday.[27]

Even tiny doses of radiation administered to the scalp of children for treatment of ringworm, where the estimated dose to the thyroid was only 5 to 6 R, was associated with five-fold increase in the incidence of thyroid cancer over that of sibling controls.[28] Larger doses of external radiation, which were used to treat adults with Graves' disease in the early 1940's, were followed in ten to twenty years with malignant lesions in the pharynx in some patients, but cancer of the thyroid was not reported.[29] Similarly, high-dose external radiation for malignant lymphoma was associated with later development of hypothyroidism in many patients, but not with development of thyroid carcinoma.[30]

These data suggest an increasing incidence of nodular goiter and hypothyroidism with increasing doses of radiation therapy, and a decidedly increased susceptibility in children as compared with adults. The risk of thyroid cancer seems to be related to age and to dose in a lower dose range (50 to 500 R). At higher doses, 2,000 R or more, the risk of thyroid cancer is reduced.[31] This may be due to injury to thyroid cells at high radiation doses with failure of the cell to replicate.

Thus, irradiation induces nodular goiters in many patients, and cancers in a few.[32] A history of radiation therapy in a child, or even in an adult, makes one more strongly suspicious of the possibility of cancer.

## Major Factors in Clinical Suspicion of Thyroid Cancer

Table 4 summarizes factors to be considered in differential diagnosis. A familial history of goiter usually suggests a benign lesion such as Hashimoto's thyroiditis or dyshormonogenesis. Similarly, residence in an endemic goiter area might be expected to be associated with a high incidence of nontoxic goiter, but not necessarily a high incidence of cancer. The incidence of malignant lesions in older women is relatively low. Cancer is not usually found in diffuse or multinodular goiters. Soft nodules are usually not malignant. In contrast to this, a nodule in a child, a young adult, or a male patient of any age would have a higher index of suspicion of malignant

change. The most common presenting malignant thyroid lesion is a solitary, firm, or dominant nodule in the thyroid gland. The presence of vocal cord paralysis, hoarseness, palpable lymph nodes, or distant metastatic lesions would certainly be highly suggestive of malignant disease of the thyroid gland. A high antithyroid antibody titer would be more suggestive of Hashimoto's thyroiditis than of malignant disease.

## Scanning Techniques in Evaluation of Nodules

Measurement of the uptake of radioiodine by scanning has been very helpful in the differential diagnosis of thyroid nodules. A nodule that picks up more radioiodine than surrounding tissue—a "hot" nodule—is rarely malignant, whereas malignant lesions occur in 5 to 20 percent of patients with "cold" nodules. Displacement of normal thyroid tissue suggests fixation of the nodule, and this is frequently found in large neoplastic lesions. It is important that the nodule be carefully marked under the scanner to clarify its position in relationship to the scan.[33-36]

Newer scanning techniques have become very useful in differential diagnosis. The vascular flow pattern of thyroid nodules has been evaluated with [99m]TcO$_4$. Nodules that have a nonvascular flow pattern are almost never malignant, whereas malignant lesions are associated with an early blood flow pattern of the vascular type.[37] Other scanning agents, such as [75Se]methionine, [131]cesium, [67]gallium citrate, and [^{99m}Tc]bleomycin, have also been investigated. These agents are taken up by malignant lesions, but are also frequently taken up in significant amounts by benign lesions; therefore, they have not proved as useful for differentiating benign from malignant lesions as had been hoped.[38-41]

The echo scan has been particularly helpful in the diagnosis of cystic lesions. Such lesions are almost always benign, and can be satisfactorily treated by needle aspiration. On the other hand, a lesion that appears solid by echo scan is more likely to be a tumor.[42] Thermographic techniques are also useful in that cystic lesions are usually cold and solid tumors are warm on thermography. Although this is helpful in differentiating cysts from solid tumors, thermography cannot differentiate between benign and malignant lesions.[43] Soft tissue roentgenograms of the neck may show shell-like calcification, suggesting a benign cyst, or punctate calcification, which is more suggestive

TABLE 4.—*Differential Diagnosis of Thyroid Nodules*

| Clinical Evidence | Low Index of Suspicion for Thyroid Cancer | High Index of Suspicion for Thyroid Cancer |
|---|---|---|
| History .................. | Familial history of goiter<br>Residence in area of endemic goiter | Previous therapeutic irradiation of head, neck, or chest<br>Hoarseness |
| Physical characteristics ..... | Older women<br>Soft nodule<br>Multinodular goiter | Children, young adults, men<br>Solitary, firm, dominant nodule<br>Vocal cord paralysis<br>Enlarged lymph nodes<br>Distant metastatic lesions |
| Serum factors ............. | High titer of antithyroid antibody | Elevated serum calcitonin |
| Scanning techniques | | |
| Uptake of ¹³¹I ........... | "Hot" nodules | "Cold" nodule |
| Echo scan .............. | Cystic lesion | Solid lesion |
| Thermography .......... | Cold | Warm |
| Roentgenogram ........ | Shell-like calcification | Punctate calcification |
| Technecium flow study ... | Avascular | Vascular |
| Thyroxine therapy ........ | Regression after 0.3 mg per day for three months or more | No regression |

of cancer.[44] Metastatic lesions on scan or x-ray are strongly suggestive of malignant disease (Table 4).

## Effects of Thyroxine Therapy

Nontoxic goiters are probably caused by impaired synthesis of thyroxine and hyperplasia secondary to excessive secretion of thyroid-stimulating hormone (TSH). Therefore, administration of thyroxine in sufficient doses to suppress secretion of TSH should allow regression of nontoxic goiters. This certainly occurs in most diffuse nontoxic goiters and in some multinodular goiters, whereas large cystic nodules will regress poorly.[45-47] There is evidence that many thyroid cancers, particularly papillary and follicular carcinoma, can be stimulated by TSH, and this technique is used in radioiodine therapy of advanced thyroid cancer.[48] There have been a few instances where metastatic lesions in the neck or in the lung have actually decreased in size or disappeared on suppressive thyroxine therapy.[49] On the other hand, most thyroid cancers, although they may not grow as rapidly during suppression of TSH by thyroxine, do not completely regress on such therapy. Therefore, the "suppression test" may be useful. In this procedure, L-thyroxine, 0.3 mg per day or its equivalent, is given for a period of three to six months, and the nodule is observed and measured carefully. If the nodule regresses in size and disappears, it is reasonably certain that it was not malignant. If it does not regress or grows during thyroxine therapy, then the suspicion of malignant disease is greater (Table 4).

Factors that contribute most to a high index of suspicion of malignancy are: history of previous therapeutic irradiation, a solitary firm nodule in a young person or a male patient of any age, a "cold" nodule on ¹³¹I scan, and failure to regress on thyroxine therapy. Factors that suggest a benign lesion are: a soft nodule or a multinodular goiter, a "hot" nodule on scintiscan, and significant regression after thyroxine therapy.

## Clinical Applications

Recently I had opportunity to summarize the records of a group of 158 patients who were treated according to the above plan (Table 5). In almost all patients who had diffuse goiter, regression occurred after thyroxine therapy. One patient could not tolerate thyroxine and could not be treated. One patient presented with a large, firm, diffuse goiter that increased in size during thyroxine therapy; on surgical excision the lesion was found to be lymphosarcoma of the thyroid gland. In most of the patients with multinodular goiters, regression occurred during therapy with thyroxine. Of the four patients in whom regression did not take place, malignant disease was found in one. About half the patients who had a dominant nodule in a multinodular goiter responded to thyroxine; three cancers were found among the six goiters that did not regress.

The patients with solitary nodules were divided into three groups—those with "hot" nodules, those with "cold" nodules highly suspicious of malignant change, and those with "cold" nodules not highly suspicious of malignant change. Three patients

TABLE 5. *Results of Therapy with Thyroxine in Patients with Thyroid Lesions*

| Type of Lesion | Number of Patients | Thyroxine Therapy | | Surgical Excision | |
|---|---|---|---|---|---|
| | | Number Treated | Number Regressed | Number of Patients* | Number with Cancer |
| Diffuse | 49† | 48 | 47 | 1 | 1 |
| Multinodular | | | | | |
|   No dominant nodule | 29 | 29 | 25 | 4 | 1 |
|   Dominant nodule | 13 | 13 | 7 | 6 | 3 |
| Single nodule | | | | | |
|   "Hot" | 11‡ | 8 | 5 | 1§ | 0 |
|   "Cold" and highly suspicious | 24 | 0 | | 24 | 8 |
|   "Cold" and less suspicious | 32 | 32 | 19 | 13 | 2 |
| TOTAL | 158 | 130 | 103 | 49 | 15 |

*None of the patients with "cold" single nodules and a high index of suspicion of cancer received thyroxine; all other patients who had surgical excision had received thyroxine and the lesion had not regressed.
†One patient not treated with thyroxine.
‡Three patients not treated with thyroxine.
§Excision for cosmetic purposes.

with "hot" nodules received no treatment. Only one of the "hot" nodules was surgically removed; it was an adenoma. The incidence of malignant change among the "cold," suspicious nodules was 33 percent. About half the "cold," less suspicious, nodules responded well to thyroxine. Of the remainder, two of 13 were malignant. The total incidence of malignant change in the group operated upon was about 30 percent. The other lesions that were found were mostly adenomata.

## Other Diagnostic Aids

The development of a simple blood test for the presence of thyroid cancer would be a great aid in diagnosis. Van Herle reported elevated levels of thyroglobulin in some patients with thyroid cancer.[50] Calcitonin, a hormone secreted by the parafollicular cells of the thyroid gland, has been found in high concentrations in the serum of patients with medullary carcinoma of the thyroid gland, and has been very useful in detecting patients with this rare type of thyroid cancer.[51,52] Needle biopsy of the thyroid has been proposed as a diagnostic technique,[12,53,54] but it has been more useful for the diagnosis of chronic thyroiditis than for thyroid cancer.[55,56] Thus, we are still left with largely clinical criteria for the differentiation of benign from malignant thyroid lesions before operation.

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