Truth and Fancy in the Management of the
Solitary Thyroid Nodule

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Received January 21, 1980

Although there is considerable controversy about the proper management of the solitary
nodule, certain information may be useful in reaching this decision. Age, sex, and a previous
history of external irradiation to the head and neck are helpful as are the clinical characteristics
of the thyroid gland. Whether the nodule is functioning or "cold" on thyroid scan, and cystic or
solid on thyroid ultrasound is also helpful. Based on these findings, the physician must decide
whether to recommend surgery or thyroid hormone suppressive therapy.

SOLITARY THYROID NODULES

Proper management of the solitary thyroid nodule is perhaps the area of greatest
controversy among thyroidologists. This controversy continues because it is possible
to obtain statistics to support any stand one wishes to take.

One of the major problems in estimating the risk of malignancies in thyroid
nodules is to eliminate bias in case selection. We attempted to do this by studying
patients with thyroid nodules who were referred for radioisotopic scan of the thyroid
gland [1]. Presumably, most physicians would obtain a radioisotopic scan before
making any therapeutic decision. There were 130 patients with solitary “cold” thyroid
nodules and 68 of these patients came to thyroid surgery. Thyroid carcinoma was
found in 18 percent of patients at surgery. Whether case selection occurred to any
significant extent in the patients referred to surgery is not clear. However, even if no
further malignancies were found, the incidence of thyroid carcinoma in these
presumably unselected patients with solitary cold thyroid nodules would be about 9
percent.

Factors Predisposing to Thyroid Cancer

The possibility of malignancy is clearly increased in solitary “cold” thyroid nodules
and it is important to obtain further criteria to select those patients most at risk.

Sex

All forms of thyroid disease are more common in females and this is true of thyroid
malignancy as well. However, non-toxic nodular goiter is even more common than
malignancy in females than in males. As a consequence, a solitary thyroid nodule
occurring in a male is more likely to be malignant than a solitary nodule occurring in
a female.
Age

Estimates have indicated that one-half the thyroid nodules appearing in children may be malignant. The implication is not that thyroid cancer is more common in childhood but, rather, that thyroid nodules in general are uncommon in this age group. Eighty percent of the children with carcinoma of the thyroid who formed the basis of this estimate had a past history of radiation [2,3]. The chance of malignancy in the thyroid nodule of children needs to be reappraised now that this type of irradiation has been practically discontinued.

In one study of 30 children with solitary thyroid nodules, only four children had a previous history of neck irradiation [4]. Nevertheless, there was still a 40 percent incidence of carcinoma in the series including the four irradiated children. These data would suggest that thyroid carcinoma continues to be a significant risk in children with solitary thyroid nodules. However, in a study of 5,179 school children in Grades 6 through 12, nodularity of the thyroid was found in 93, 1.8 percent [5]. The nodularity represented adolescent goiter in 34 children and thyroiditis in 31. Benign adenomas were found in 20 and only two thyroid cancers were found. The 28 thyroid nodules that proved to be neoplasms were discrete, solitary, of firm consistency, and without changes in the rest of the thyroid.

Previous Irradiation of the Head and Neck

Previous irradiation of the head and neck markedly increases the chances of malignancy in a thyroid nodule. The observation in 1950 that nine of twenty-eight children with carcinoma of thyroid had been given radiotherapy to the thymus in infancy first highlighted this association, which was later confirmed in prospective studies [6,7]. Most instances of thyroid malignancy following neck radiation had been reported within 10 years after radiation therapy. Since this type of radiation therapy to the neck had been virtually discontinued, a degree of complacency developed among many physicians. However, recent reports indicating an increased incidence of thyroid carcinoma, an average of 25 years after radiation exposure to the head and neck, have dispelled this illusion [8]. Despite direct questioning, few patients with a thyroid nodule were able to give a history of radiation during infancy. Public awareness increased dramatically after the relationship was featured in a television drama.

The exact magnitude of the increase in thyroid carcinoma after irradiation to the neck is unknown because appropriate age-matched control data are sparse. However, the increase in thyroid carcinoma is significant, and estimates have ranged from a twofold to a one hundredfold increase in the frequency of thyroid cancer.

Physical Characteristics

Careful examination of the thyroid can be extremely helpful in determining the proper degree of suspicion of underlying malignancy. A history of recent thyroid growth, dysphagia, or dyspnea should make the examiner suspicious of malignancy. Palpation of the thyroid should be done carefully with particular attention to the regularity and hardness of the nodule, whether the gland is fixed to surrounding structures and whether there are palpable regional lymph nodes. On the other hand, the presence of a multinodular goiter would decrease the suspicion of malignancy.

A group of patients with thyroid nodules were first classified clinically and these results were compared to the findings at surgery [9]. Thyroid cancer was found in 76 percent of cases thought to be malignant clinically, 12 percent of cases thought to be benign clinically but symptomatic as indicated by pain, recent change in goiter size,
or dysphagia and 3 percent of patients thought to be benign and asymptomatic. In this particular study of 53 patients, there were only two patients with thyroid carcinoma who were free of symptoms.

The most important physical sign is the presence of a hard, irregular thyroid nodule. Extreme hardness may be due to hemorrhage into a cyst with subsequent calcification. If the thyroid cancer has spread beyond the capsule and invaded surrounding structures, the clinical diagnosis becomes comparatively simple although Riedel's struma can also extend beyond the gland. Fixation to the strap muscles, trachea, or larynx is easily detected on physical examination. Recurrent laryngeal nerve paralysis is not a common presenting symptom in thyroid carcinoma but does occur.

LABORATORY DIAGNOSIS

The presence of a solitary thyroid nodule raises the question of thyroid malignancy and the above predisposing factors may strengthen or allay suspicions in the individual patient. The next step in the evaluation is to use the laboratory to discriminate which nodules may be malignant and which may be benign.

Radioactive Scan of the Thyroid

Scanning of the thyroid after the administration of a tracer dose of radioactive iodine or Technetium-$^{99m}$Tc permits the delineation of functioning and non-functioning areas of the thyroid. Since even well-differentiated thyroid carcinomas do not concentrate iodine as efficiently as normal thyroid, hypofunctioning or "cold" thyroid nodules have been considered to harbor a greater risk of malignancy. This classification is established by assessing the amount of radioactivity within the nodule. The "cold" nodule must be approximately one centimeter in diameter. Large nodules may produce a well-defined focal defect, marginal indentation, or locally reduced parenchymal activity. Demonstration of a "cold" thyroid nodule is significant but unfortunately non-specific. The majority of clinically detectable thyroid nodules are less functional than the extra-nodular thyroid tissue [10].

Iodine$^{131}$ has been the radionuclide most widely used for imaging the thyroid. Although the high absorbed radiation doses were recognized with concern, this concern has heightened with the recurrence of interest in the delayed effects of neck irradiation [11]. The administration of 100 μC of $^{131}$I for a thyroid scan can result in a dose of 80 rads to the thyroid [12]. Since several scans would deliver a dose of radiation to the thyroid which has been associated with subsequent thyroid cancer with external radiation, alternative methods of thyroid imaging are highly desirable.

Iodine$^{123}$ is perhaps the ideal isotope for in vivo diagnostic studies of thyroid function and structure. The short half life of 13.3 hours is suitable for routine uptakes. Scans superior in resolution than those afforded by $^{99m}$Tc or $^{131}$I can be obtained with a radiation dose 1/85 that for a comparable I$^{131}$ scan. However, high purity I$^{123}$ is not generally available, and technetium is probably the most readily available isotope of choice for thyroid scanning at the present time. Technetium-$^{99m}$ would deliver about 0.6 rads to the thyroid during a scanning period. The pertechnetate ion ($^{99m}$TcO$_4$) is rapidly trapped by the thyroid but is not organically bound and does not remain in the gland. The difference between the two radioisotopes has clinical significance because some thyroid malignancies have trapped pertechnetate but not I$^{131}$ because of a defect in organization.

The findings in most studies have been consistent with the physiological considerations discussed above. Most of the thyroid cancers were "cold" but benign thyroid
nodules were also predominantly "cold." This lack of discrimination makes it difficult to use the thyroid scan to differentiate between benign and malignant thyroid nodules. Certainly, no patient with a solitary thyroid nodule should be either selected for surgery or screened from surgical consideration by a thyroid scan although the scan would be helpful in eliminating the minority of solitary nodules with increased uptake from serious consideration of malignancy.

**Ultrasound**

The presence of a cold nodule on thyroid imaging may indicate either a solid nodule that does not trap the radionuclide or a cystic area in the gland. Analysis of the echoes produced by and ultrasonic beam directed into the thyroid nodule may permit differentiation of the solid nodule from the cystic nodule. Diagnostic ultrasound employs acoustic properties to distinguish different soft tissues by passing ultra-high sound frequencies into the nodule and analyzing the reflected echoes. In solid thyroid nodules, multiple echoes are generated with high sensitivity levels, while this does not occur in a thyroid cyst.

The thyroid gland is not as acoustically dense as the surrounding tissue. Tracheal cartilage represents the most dense structure in the area. In addition to distinguishing between solid and cystic thyroid nodules, enlargement of the thyroid due to tumor growth can be differentiated from enlargement due to cystic or hemorrhagic degeneration [13].

Cysts have been reported to occur in 20 percent of solitary thyroid nodules [14]. Although the possibility of malignancy is significant, particularly in a partially cystic lesion, the incidence is less than in a solid lesion. The use of ultrasound to evaluate solitary nodules over 4 cm is limited because both solid and cystic lesions of this size will demonstrate heterogeneous echoes. Small nodules are also difficult, and cystic lesions less than one centimeter in size may not be identified. Substernal goiters are difficult to study because the sternum reflects the sound. Despite the useful information that can be obtained, ultrasound does not differentiate between a benign and a malignant thyroid nodule.

**Thyroid Biopsy**

Although various diagnostic procedures may heighten suspicion that a particular solitary thyroid nodule is malignant, only a tissue diagnosis will ultimately diagnose or exclude thyroid cancer. Needle biopsy of the thyroid has been considered as an alternative to surgery, but fear that cancer might be disseminated along the track delayed acceptance of this procedure. Although a consideration, possible seeding of the needle track should not be a major deterrent to needle biopsy of the thyroid. The most difficult thyroid lesions to diagnose are follicular carcinomas, because their identification often rests on the demonstration of vascular and capsular invasion. The small amount of tissue obtained means these areas may be missed. Papillary carcinoma on the other hand is usually easily identified due to its unique histological characteristics.

Since the majority of patients who have had a biopsy of the thyroid do not have a subsequent thyroidectomy, comparison of the biopsy specimen with the entire thyroid gland is frequently impossible. In a series of 81 cases where 93 percent of needle biopsy diagnoses were confirmed by thyroid surgery, the errors were due to lymphoma complicating Hashimoto's disease, undifferentiated carcinoma diagnosed as non-specific thyroiditis, and follicular carcinoma mistaken for follicular adenoma
No serious complications occurred with the needle biopsy procedure and in none of the primary cancers was there evidence of tumor implantation in the needle track. However, there was a single example of seeding in a renal cell carcinoma metastatic to the thyroid. If there is a significant clinical suspicion of thyroid cancer, a negative needle biopsy should not deter immediate surgery and is probably not indicated in such cases.

Thyroid biopsy with a cutting needle has the potential for complications which have made many physicians cautious about the procedure. Aspiration thyroid biopsy with a fine needle obviates the risk of serious complications that may occur with cutting needles like the Vim-Silverman. The amount of tissue obtained is not as great which may make accurate diagnosis more difficult. However, despite the random nature of the sampling, the accuracy of the thyroid cytology has been high [16]. Adequate aspirate for cytologic diagnosis can be obtained in 95 percent of cases and may agree with the histology at surgery in as many as 80 percent of cases. Nevertheless, the possibility of sampling error is large, and a negative aspiration biopsy should not influence the therapeutic decision.

**MANAGEMENT OF THE SOLITARY THYROID NODULE**

A therapeutic decision must be made about the management of the solitary thyroid nodule, and a decision tree for management is outlined in Fig. 1. A solitary thyroid
nodule occurring in a child or individual with a history of neck irradiation should be operated upon immediately as should the patient who has a clinically "malignant" thyroid on physical examination. Before surgery, it is important to be sure that a solitary nodule does not represent a single thyroid lobe with compensatory hypertrophy. In the absence of these immediate indications for surgery, the patient should have a thyroid scan. If the nodule is functioning, and if fine needle aspiration biopsy is non-diagnostic, the gland should be suppressed with thyroid hormone for three months. Disappearance of the nodule is an indication for continued thyroid hormone suppression. An occasional patient may have an autonomous nodule and become thyrotoxic on thyroid hormone suppression. Therefore, thyroid function tests should be done several weeks after suppressive therapy has been started. If the response is incomplete and the patient is a young male, surgery is indicated. Otherwise, thyroid hormone suppression can be continued for another three-month trial period.

If the solitary thyroid nodule is non-functioning, then ultrasound should be used to determine whether it is solid or cystic. If it is cystic and aspiration does not reveal evidence of malignancy, then thyroid hormone suppression can be attempted for three months. Complete disappearance of the nodule would be an indication for continued thyroid hormone suppression therapy. A solid non-functioning thyroid nodule should have a fine needle aspiration biopsy. If malignancy were not found, the gland would be suppressed with thyroid hormone and managed like the functioning nodule with treatment depending upon the response.

Thus, although the degree of function in the thyroid nodule is used to separate patients into two tracks, the tracks are treated in similar manner. The difference between thyroid hormone suppressive therapy for a diffuse or multinodular goiter and the solitary nodule is one of degree. The attempt should be made to treat the solitary nodule with the suppressive dose of thyroid hormone so that the serum TSH concentration is suppressed as much as possible. Regardless of the dose of thyroid hormone administered, it is extremely difficult to totally suppress pituitary TSH secretion. Whether these low circulating levels of TSH actually stimulate the thyroid is not clear. However, it seems desirable to decrease the circulating concentration of serum TSH to lowest possible levels.

The question has been raised about the practice of using thyroid hormone suppression in solitary "cold" nodules with the implication that "cold" means inactive. Actually, "cold" nodules have been shown to be more active biochemically than "warm" nodules [17]. They appear to have a defect in iodine trapping but other parameters such as glucose oxidation and cyclic AMP levels are actually increased. In one study, 50 percent of the "cold" nodules did decrease in size with thyroid hormone therapy [18].

**Dose of Thyroid Hormone**

The usual suppressive dose of L-thyroxine will range between 200 to 300 μg/day. The amount of thyroxine for suppression of a solitary thyroid nodule can be adjusted to a dose just below that giving rise to thyrotoxic symptoms like palpitations, sleep disturbance, or excessive sweating. However, with elevated thyroid hormone concentrations, subclinical hyperthyroidism may result and may be undesirable over the long term. The TRH test may be helpful in this situation. By adjusting the dose of thyroxine until the TSH response to TRH is inhibited, hyperthyroidism should be avoided with effective suppression of TSH. This is probably unnecessary for initial suppression of the nodule and arbitrary dose of 200 to 250 μg/day will suffice.
**Duration of Suppression**

If the patient with a solitary thyroid nodule is to have a trial of thyroid hormone suppression, it is important to know how long thyroid hormone should be administered before deciding that the nodule will not regress with suppression of circulating TSH. Some patients have not had regression in their goiter until the treatment was continued for a year or longer. Half the patients receiving thyroid hormone suppressive therapy for non-toxic goiter had a decrease in the size of their thyroid nodules after three months. When patients who had not responded were treated for another four months, one-third of the nodules decreased in size, and it made no difference whether the dose of thyroid was increased or not. The data suggest a course of therapy for at least three months and preferably six months before deciding that the thyroid nodule will not respond to suppression. Re-evaluation at three-month intervals would allow a management decision based on factors such as sex and age in addition to response to thyroid hormone.

If the thyroid nodule disappears completely, then thyroid hormone suppression should be continued indefinitely. Regression of the solitary nodule does not rule out cancer but does indicate that the nodule is responsive to TSH. Thyroid hormone should be continued as long as there is no change in the size of the nodule and immediate surgery advised if the nodule should enlarge while on suppressive therapy. If the nodule does not regress completely, then the decision whether or not to operate will depend on the other factors already discussed.

**Surgery**

If the decision is made to operate, both lobes of the thyroid should be totally exposed even though the nodule is palpable preoperatively in only one lobe. Multiple thyroid nodules are discovered at surgery in as many as 60 percent of cases diagnosed as a single nodule preoperatively by careful palpation and scan. If multinodular goiter is discovered at operation, the risk of carcinoma in the thyroid nodule lessens dramatically but the surgeon should probably go on to remove the lobe thought to contain the single nodule.

**REFERENCES**

1. Burrow GN, Mumtaba Q, Livolsi V, et al: The incidence of carcinoma in solitary “cold” thyroid nodules. Yale J Biol Med 51:13, 1978
2. Hempelmann LH: Thyroid neoplasms following irradiation in infancy. In Radiation-Associated Thyroid Carcinoma. Edited by LJ DeGroot. New York, Grune & Stratton, 1977, p 221
3. Winship T, Rosvoll RV: Childhood thyroid carcinoma. Cancer 14:734, 1961
4. Kirkland RT, Kirkland JL, Rosenbert HS, et al: Solitary thyroid nodules in 30 children and report of a child with a thyroid abscess. Pediatrics 51:85, 1973
5. Rallison ML, Dobyns BM, Keating FR Jr, et al: Thyroid nodularity in children. JAMA 233:1069, 1975
6. Duffy BJ Jr, Fitzgerald PJ: Cancer of the thyroid in children: A report of 28 cases. J Clin Endocrinol Metab 10:1296, 1950
7. Refetoff S, Harrison J, Karanfilski BT, et al: Continuing occurrence of thyroid carcinoma after irradiation to the neck in infancy and childhood. N Engl J Med 292:171, 1975
8. Bowens OM, Vander JB: Thyroid nodules and thyroid malignancy. Ann Intern Med 57:245, 1962
9. Miller JM, Hamburger JI, Mellinger RC: The thyroid scintigram II—The cold nodule. Radiology 85:702, 1965
10. DeGroot LJ (ed): Radiation-Associated Thyroid Carcinoma. New York, Grune & Stratton, 1977
11. Esser PD: Absorbed radiation doses in adults. In Clinical Scintillation Imaging, ed 2. Edited by LM Freeman, PM Johnson. New York, Grune & Stratton, 1975, p 799
13. Blum M: Enhanced clinical diagnosis of thyroid disease using echography. Am J Med 59:301, 1975
14. Miller JM, Zafar SU, Karo JJ: The cystic thyroid nodule. Radiology 110:257, 1974
15. Vickery AL Jr: Needle biopsy and the thyroid nodule. In Radiation-Associated Thyroid Carcinoma. Edited by LJ DeGroot. New York, Grune & Stratton, 1977, p 339
16. Walfish PG, Hazani E, Strawbridge HTG, et al: An evaluation of combined ultrasound and needle aspiration cytology in the assessment of the hypofunctioning thyroid nodule. In Radiation-Associated Thyroid Carcinoma. Edited by LJ DeGroot. New York, Grune & Stratton, 1977, p 315
17. Field JB, Larsen PR, Yamashita K, et al: Demonstration of iodide transport defect but normal iodide organification in nonfunctioning nodules of human thyroid glands. J Clin Invest 52:2404, 1973
18. Shimaoka K, Sokal JE: Suppressive therapy of nontoxic goiter. Am J Med 57:576, 1974