MANAGEMENT OF THYROID NODULES

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I. Introduction

Although thyroid nodules are common, clinically significant thyroid cancer is much less common. In approaching a patient with a clinically solitary thyroid nodule one would like to be able to select appropriately for excision biopsy those patients with a greater likelihood of cancer and avoid subjecting the majority of patients in whom the nodule is a sign of a benign process to an unnecessary operative procedure. Not only would it be desirable to have a management scheme that would result in patients having minimal morbidity and mortality, but in this time of rising health care costs such a scheme should also be cost effective.

II. Prevalence of Thyroid Nodules

In an autopsy study of 1000 patients at the Mayo Clinic during 1951-53 Mortensen et al reported that a little less than half of patients with "clinically normal" thyroids were found to have single or multiple macroscopic thyroid nodules (1). In this study three-fourths of thyroid glands with nodules had multiple nodules. Interestingly, in a recent study of 1000 patients at the Mayo clinic high resolution sonography (see below) was used to evaluate the thyroid glands of patients undergoing neck sonography for hyperparathyroidism with similar conclusions (2). The thyroid sonogram was abnormal in 46% with 41% of all patients having nodules, approximately equally divided between single and multiple (2). Of these 1000 patients, 709 had neither a history of previous thyroid disease or operation, nor any current clinical evidence for nodular thyroid disease or thyroid function abnormality and were considered clinically normal. Even in this selected group the sonogram was abnormal in 41% and detected a nodule in 38% (2). The relationship of the age of the patient to the prevalence of nodules in both the older autopsy study and the recent sonography study is shown in Fig. 1.

Figure 1

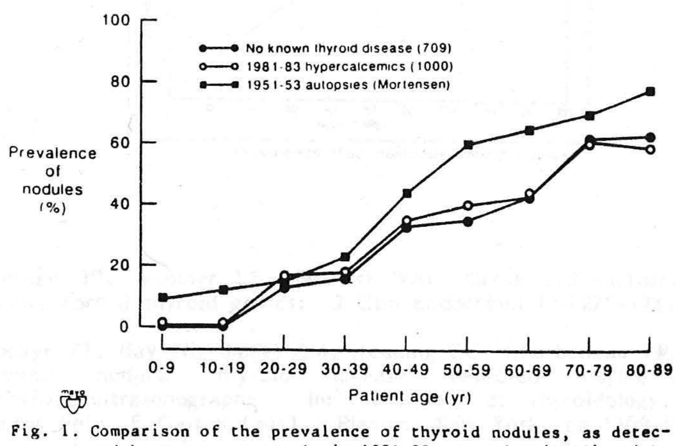
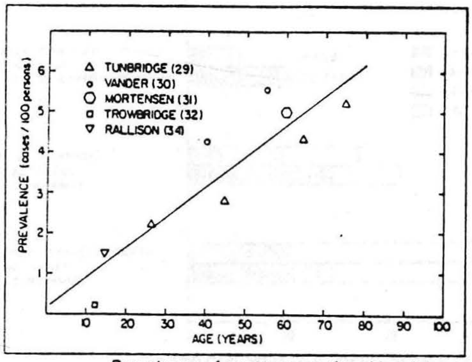


Fig. 1. Comparison of the prevalence of thyroid nodules, as detected by Mortensen et al. in 1951-53 autopsies (1,12), with that determined by high-resolution sonography in 1981-83 ambulatory outpatients.

As can be seen from the figure the prevalence of thyroid nodules is low in children and increased progressively with each decade so that by the eighth decade from 60 to 80% of individuals have detectable nodules depending on the method of assessment. The size of the dominant nodule in the sonography study was less than 1 cm diameter in half of the subjects and thus probably not theoretically palpable even if on the surface of the gland.

In contrast to the 40 to 50% actual prevalence of thyroid nodules is the 10-fold less prevalence on clinical exam. In the above mentioned sonography study of 1000 patients with hyperparathyroidism, only 8% of patients had nodules detected on neck palpation with again approximately half having a solitary nodule (4.2%) (2). This is in agreement with studies only reporting results of physical exam (3, 4). The classic Framingham study of 5127 adults detected nodules in 4.2% with three-fourths of them clinically solitary (3). A similar size study of 5179 school children found a low prevalence of 1.8% (4). Maxon et al summarized results of several studies and was able to suggest a linear relationship of prevalence as a function of age of the population (Fig. 2) (5). As is true for all thyroid diseases, nodular thyroid enlargement is more common in women than in men. The Framingham study found a 4:1 ratio of women to men in the group with thyroid nodules.

Figure 2



Prevalence of spontaneous thyroid nodules.

1. Mortensen JD, Woolner LB, Bennett WA: Gross and microscopic findings in clinically normal thyroid glands. J Clin Endocrinol 15:1270-1280, 1955.

2. Horlocker TT, Hay JE, James EM, Reading CC, Charboneau JW: Prevalence of incidental nodular thyroid disease detected during high-resolution parathyroid ultrasonography. In: Frontiers of Thyroidology. Vol. 2. G Medeiros-Neto, E Gaitan (eds). Plenum, New York, pp 1309-1312, 1986.

3. Vander JB, Gaston EA, Dawber TR: The significance of nontoxic thyroid nodules. Final report of a 15-year study of the incidence of thyroid malignancy. Ann Intern Med 69:537-540, 1968.

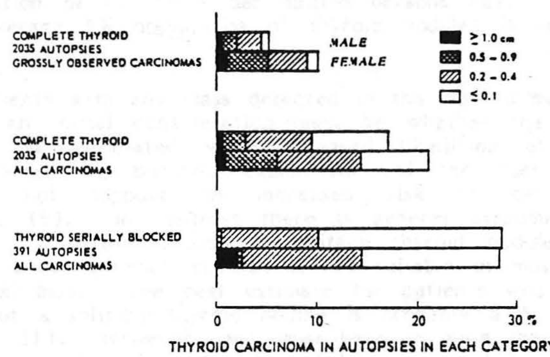
4. Rallison ML, Dobyns BM, Keating Jr FR, Rall JE, Tyler FH: Thyroid nodularity in children. JAMA 233:1069-1082, 1975.

5. Maxon HR, Thomas SR, Saenger EL, Buncher CR, Kereiakes JG: Ionizing irradiation and the induction of clinically significant disease in the human thyroid gland. Am J Med 63:967-978, 1977.

III. Prevalence of Thyroid Cancer

In considering the prevalence of thyroid cancer a distinction must again be made between studies using sensitive means of detecting all cancers and studies of clinically apparent thyroid cancer. In autopsy series in this country thyroid carcinoma is usually reported to be present in almost 2% of adults (6, 7). The problem in interpreting these data is that the number of occult tumors (i.e. less than 1.5 cm diameter) varies depending on the thoroughness with which the thyroid is examined pathologically (Fig. 3) (7). Often these occult cancers are only detected microscopically with serial sectioning of the gland.

Figure 3



Frequency and size distribution of thyroid carcinoma found in each thyroid category.

A comparison of the thyroid cancer death rates in three populations with the prevalence of occult thyroid cancer in autopsy studies using similar methods of detection suggests that an increased prevalence of occult thyroid carcinoma is not correlated with increase in the death rate for thyroid carcinoma (Table I) (7).

Table I Thyroid Cancer Death Rates and Prevalence of Occult Thyroid Cancer in Three Populations

	Thyroid Cancer Death Rates/ 100,000/Year		Occult Thyroid Cancer
	Men	Women	%
Switzerland	1.51	1.56	1.2
United States	0.4	0.8	5.7
Japan	0.21	0.46	17.9

(From Ref. 7)

Since the biological risk of this occult minimal papillary carcinoma is probably negligible, these tumors rarely are a cause of death. Such tumors are responsible for the disparity between thyroid cancer as a cause of death and thyroid cancer prevalence. Since the overall annual U.S. death rate from thyroid cancer is about 0.5 per 100,000 population, deaths from thyroid cancer are uncommon compared with deaths from other cancers. The presence of occult tumors of little biological significance detected at operation makes it difficult to discuss incidence. The Third National Cancer Survey reported an age adjusted incidence of thyroid cancer at approximately 0.004% per year for the general population or 40 cases per million persons (8). Expressed in the same terms the average 4% prevalence of thyroid nodules is 40,000 per million persons.

Since most patients with any mass detected in the thyroid might be concerned about malignancy, an initial consideration must be whether the common nontoxic multinodular goiter is associated with increased likelihood of thyroid cancer. As discussed in detail by Burrow, examination of the question from several perspectives does not support an increased risk of cancer in nontoxic multinodular goiters (9). In contrast there is general agreement that there is an increased risk of thyroid cancer in solitary thyroid nodules (6, 10, 11). The frequency of cancer in such nodules is not reliable in most surgical reports because of selection bias. The best estimate for patients who come to medical attention because of a solitary thyroid nodule is probably a 5 to 10% frequency of cancer (6, 10, 11). However, one must keep in mind that in most surgical series an occult cancer found in the thyroid lobe resected but distant from the palpated nodule will be reported as a cancer found.

6. Silverberg SG, Vidone RA: Carcinoma of the thyroid in surgical and postmortem material. Analysis of 300 cases at autopsy and literature review. Ann Surg 164:291-299, 1966.

7. Sampson RJ: Prevalence and significance of occult thyroid cancer. In: Radiation-associated thyroid carcinoma. LJ DeGroot, LA Frohman, EL Kaplan, S Refetoff (eds). Grune and Stratton, New York, pp 137-153, 1977.

8. Cutler SJ, Young JL (eds): Third National Cancer Survey: Incidence Data, National Cancer Institute Monograph 41, US DHEW publication (NIH) 75-787. Bethesda, pp 107, 111, 1975.

9. Burrow GN: The thyroid: Nodules and neoplasia. In: Endocrinology and Metabolism. P Felig, JD Baxter, AE Broadus, LA Frohman (eds). McGraw-Hill, New York, pp 473-507, 1987.

10. Vieth FJ, Brooks JR, Grigsby WP, Selenkow HA: The nodular thyroid gland and cancer. A practical approach to the problem. N Engl J Med 270:431-436, 1964.

11. Burrow GN, Mujtaba Q, LiVolsi V, Cornog J: The incidence of carcinoma in solitary "cold" thyroid nodules. Yale J Biol Med 51:13-17, 1978.

IV. Pathophysiology of Thyroid Nodules

A. Role of Thyrotropin (TSH)

The cause of thyroid nodules in man is not known. Studies in rats suggest a role of TSH. Iodine deficiency tends to enhance TSH secretion in rats and is associated with the development of thyroid nodules, some of which are malignant (9). Hypophysectomized animal or animals given exogenous thyroxine do not develop nodules. In man the role of TSH in thyroid nodule formation is less clear. In vitro studies of both benign and malignant thyroid nodules demonstrate presence of TSH receptors in similar quantity to that detected in adjacent normal thyroid tissue (12). Moreover, these TSH receptors were shown to be functionally active in that they respond to TSH with stimulation of adenylate cyclase activity (12). In fact, the neoplastic thyroid tissue had a fourfold greater maximal adenylate cyclase response to TSH than the nonneoplastic thyroid tissue in one study (12). As will be discussed in greater detail below, the response of benign nodular thyroid enlargement to thyroxine therapy (13) as well as the improved prognosis of patients with papillary thyroid cancer treated with thyroxine (14) suggest a role of TSH in human thyroid neoplasia.

12. Clark OH, Gerend PL, Davis M, Goretzki PE, Hoffman Jr PG: Estrogen and thyroid-stimulating hormone (TSH) receptors in neoplastic and nonneoplastic human thyroid tissue. J Surg Res 38:89-96, 1985.

13. Greer MA, Astwood EB: Treatment of simple goiter with thyroid. J Clin Endocrinol Metab 13:1312-1331, 1953.

14. Mazzaferri EL, Young RL, Oertel JE, Kemmerer WT, Page CP: Papillary thyroid carcinoma: The impact of therapy in 576 patients. Medicine 56:171-196, 1977.

B. In Vitro Studies of Nodule Function

In contrast to the metabolic activity of human thyroid nodules described above is the observation that most thyroid nodules (both benign and malignant) appear to be hypofunctioning as assessed by the ability to concentrate radionuclide on scintiscans (i.e., they are "cold" nodules) (see additional discussion below). This hypofunction of the nodules in vivo corresponds to a defect in vitro in iodide transport (15, 16). Any defect in iodide organification was thought to be secondary to the defect in iodide trapping (15). The transport defect in nodules was not associated with any reduction in total Na^{+}-K^{+}- or Mg^{++} ATPase activities or the concentration of ATP.

15. Field JB, Larsen PR, Yamashita K, Mashiter K, Dekker A: Demonstration of iodide transport defect but normal iodide organification in nonfunctioning nodules of human thyroid glands. J Clin Invest 52:2404-2410, 1973.

16. Shiroozu A, Inoue K, Nakashima T, Okamura K, Yoshinari M, Nishitani H, Omae T: Defective iodide transport and normal organification of iodide in cold nodules of the thyroid. Clin Endocrinol 15:411-416, 1981.

C. Radiation Induction of Thyroid Nodules

For several decades beginning in the early 1920s external irradiation of the head, neck, or upper thorax was a common treatment for nonmalignant conditions such as tonsillitis, cervical adenitis, enlarged thymus or acne. When the thyroid gland was included in the radiation fields, such therapy has now been recognized as being associated with the subsequent development of a variety of thyroid problems including both benign and malignant thyroid nodules. Maxon et al have summarized several prior reports to derive an estimate of the dose response for thyroid nodularity and external irradiation (Fig. 4) (5).

Figure 4

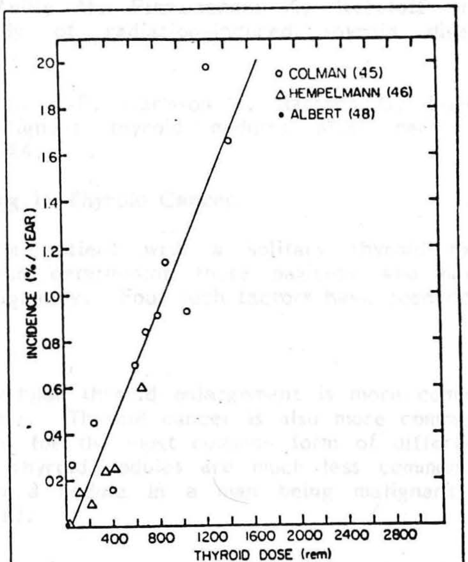


Figure 4. Estimated dose response for total thyroid nodularity and external radiation.

Based on a linear dose response curve an estimate of the absolute risk for the development of thyroid nodules was calculated to be 12.3 patients with nodules per million persons per rem per year. Note that these calculations are for low doses (<1500 rem) from external radiation. High doses of external radiation (>2000 rem) are thought to result in destruction of the thyroid gland with no increased risk of benign or malignant nodules. Low dose ^{131}I exposure from radioactive fallout in the Western US was not associated with increased thyroid nodularity in children in one controlled study (4). Maxon et al concluded that ratios of ^{131}I risk to external radiation risk in children suggest that ^{131}I is about 1/50 as effective as external radiation in the induction of total thyroid nodules. Data from the persons exposed to fallout from an atomic test in the Marshall Islands suggests that adults are less susceptible to the induction of thyroid nodules than children (5).

In typical populations examined an average of 25-43 years later for effects of childhood external radiation, a 25 to 30% prevalence of thyroid nodules on palpation was observed (17-19). The frequency of palpable thyroid abnormalities appeared to be increased with follow up time after radiation in one study (17). Physical exam alone was found to be sufficient for identifying significant thyroid pathology (17, 18, and see additional discussion below). In one study women appeared to have a threefold increased likelihood of developing benign nodules after neck irradiation than do men (19). This ratio is not dissimilar to that of nodules in persons not exposed to radiation.

17. Kaplan MM, Garnick MB, Gelber R, Li FP, Cassady JR, Sallan SE, Fine WE, Sack MJ: Risk factors for thyroid abnormalities after neck irradiation for childhood cancer. Am J Med 74:272-280, 1983.

18. DeGroot LJ, Reilly M, Pinnameneni K, Refetoff S: Retrospective and prospective study of radiation-induced thyroid disease. Am J Med 74:852-862, 1983.

19. Fjalling M, Tisell L-E, Carlsson S, Hansson G, Lundberg L-M, Oden A: Benign and malignant thyroid nodules after neck irradiation. Cancer 58:1219-1224, 1986.

V. Factors Predisposing to Thyroid Cancer

In approaching the patient with a solitary thyroid module certain factors should be considered in determining those patients who have a greater risk of the nodule being a malignancy. Four such factors have been considered useful.

A. Gender

As noted above nodular thyroid enlargement is more common in women than in men (about a 4:1 ratio). Thyroid cancer is also more common in women than men with about a 2:1 ratio for the most common form of differentiated thyroid cancer (20). Since solitary thyroid nodules are much less common in men than women, the likelihood of such a nodule in a man being malignant is two- to threefold that in a woman (9, 21).

20. McConahey WM, Taylor WF, Gorman CA, Woolner LB: Retrospective study of 820 patients treated for papillary carcinoma of the thyroid at the Mayo Clinic between 1946 and 1971. In: Advances in Thyroid Neoplasia 1981. M Andreoli, F Monaco, J Robbins (eds). Field Educational Italia, Rome, pp 245-262, 1981.

21. Messarias G, Evangelou GN, Tountas C: Incidence of carcinoma in cold nodules of the thyroid gland. Surgery 74:447-448, 1973.

B. Age

Solitary thyroid nodules in children are more likely to be malignant than such nodules in adults. This is not because thyroid cancer is more common in children, but rather because thyroid nodules in general are much less common in children (see above). A study of thyroid nodules in children noted a 40% prevalence of cancer in 30 children operated upon for solitary thyroid nodules (22). However, this high prevalence of malignancy might represent some selection of patients since in the large survey of school children referenced above (4), only 2 of 66 children with a solitary nodule (or 3%) were found to have carcinoma. Two subsequent retrospective surgical series reported 36% and 18% prevalence of cancer in smaller groups of children with solitary nodules (23, 24). Compared to the 5 to 10% prevalence of cancer in solitary nodules in adult surgical series with minimal selection, the prevalence in children estimated by the same approach averages about 30% or a 3- to 6-fold increased risk in children.

22. Kirkland RT, Kirkland JL, Rosenberg HS, Harberg FJ, Librik L, Clayton GW: Solitary thyroid nodules in 30 children and report of a child with a thyroid abscess. Pediatrics 51:85-90, 1973.

23. Silverman SH, Nussbaum M, Rausen AR: Thyroid nodules in children: A ten year experience at one institution. Mt Sinai J Med 46:460-463, 1979.

24. Hung W, August GP, Randolph JG, Schisgall RM, Chandra R: Solitary thyroid nodules in children and adolescents. J Pediatr Surg 17:225-229, 1982.

C. Radiation Exposure

As described above radiation to the head and neck is associated with an increased prevalence of both benign and malignant thyroid nodules (5). Calculation of the incidence of thyroid cancer as a function of low dose external thyroid radiation gives a linear relationship as found for total thyroid nodularity (Fig. 5) (5). The calculated absolute risk is 4.2 cases of thyroid cancer per million persons per rem per year or about one-third that for total nodules.

Figure 5

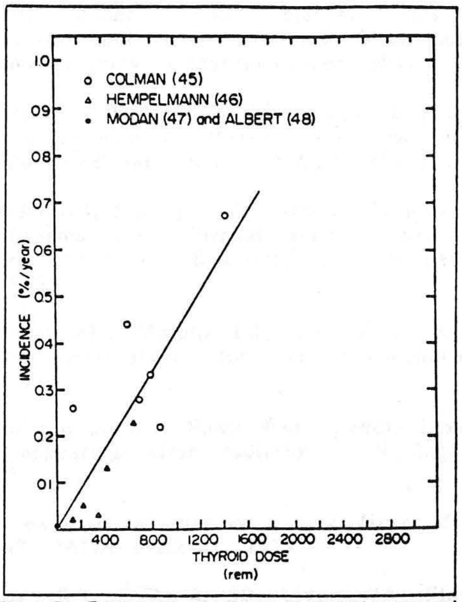


Figure 5. Estimated dose response for thyroid cancer and external radiation.

In trying to assess the frequency of thyroid cancers in patients with nodular thyroid disease and a history of head and neck irradiation, care must be taken in reading surgical series because of the inclusion of occult papillary carcinoma of questionable significance (see above). Thus two reports appeared to conclude a 46 and 33% incidence of malignancy in thyroid glands of irradiated patients with palpable abnormalities (25, 26). However, in the first of these reports no statement of size of the cancer is given, and of the seven cancers found only two were in patients with solitary nodules and not stated to be in the nodules (25). In the second larger study of 1056 examined subjects at risk, 82% of the cancers reported to be found were occult (26). Only 11 more than occult cancers were found in 182 patients with nodular disease for a 6% frequency of cancer (in the same range as the 5-10% malignancies in nodules in nonirradiated subjects). Similar analyses can be made of a 34% frequency of cancer in 124 patients with a "palpable abnormality" reported by Swelstad et al (27).

Crile et al and Utiger have noted in editorials the problem of inclusion of occult cancer in most of these series along with the lack of control groups and questioned the conclusion that external irradiation actually increases the risk of clinical thyroid cancer (28, 29). Crile concludes that the experience of the Mayo Clinic, Henry Ford Hospital, and Cleveland Clinic is relatively consistent and suggests that the frequency of cancer in patients with nodules is no greater in an irradiated group than in those who were not irradiated (28). Since thyroid nodules in general are about threefold more common in subjects exposed to head and neck irradiation (see above), one would suspect about a threefold increased risk of thyroid cancer in such subjects. This corresponds well to a 2.8 odds ratio for prior radiotherapy to the head and neck in a recent population-based case-control study of thyroid cancer (30).

25. Refetoff S, Harrison J, Karanfilski BT, Kaplan EL, De Groot LJ, Bekerman C: Continuing occurrence of thyroid carcinoma after irradiation to the neck in infancy and childhood. N Engl J Med 292:171-175, 1975.

26. Favus MJ, Schneider AB, Stachura ME, Arnold JE, Ryo UY, Pinsky SM, Colman M, Arnold MJ, Frohman LA: Thyroid cancer occurring as a late consequence of head-and-neck irradiation. Evaluation of 1056 patients. N Engl J Med 294:1019-1025, 1976.

27. Swelstad J, Scanlon EF, Murphy ED, Garces R, Khandekar JD: Thyroid disease following irradiation for benign conditions. Arch Surg 112:380-383, 1977.

28. Crile Jr G, Esselstyn Jr CB, Hawk WA: Needle biopsy in the diagnosis of thyroid nodules appearing after radiation. N Engl J Med 301:997-999, 1979.

29. Utiger RD: Is external irradiation a risk factor for thyroid disease and thyroid carcinoma? JAMA 242:2702, 1979.

30. Ron E, Kleinerman RA, Boice Jr JD, LiVolsi VA, Flannery JT, Fraumeni Jr JF: A population-based case-control study of thyroid cancer. JNCI 79:1-12, 1987.

D. Physical Exam Characteristics

A history of recent thyroid nodule growth, hoarseness, or local compressive symptoms should make the examiner suspicious of malignancy. The neck should be carefully inspected in indirect light so that slight shadowing can be seen. The patient should be instructed to swallow, and the neck observed for size and symmetry of the gland. Palpation of the thyroid may be performed from in front or behind the patient, but the patient should again swallow during palpation so that the entire contour of the gland can be outlined by the examiner's fingers. Attention should be given to how regular and hard a nodule is, whether the gland is fixed to surrounding structures, and whether there are palpable regional lymph nodes. An important physical sign of thyroid malignancy is the presence of a hard, irregular nodule. Extreme hardness may be due to hemorrhage into cyst with subsequent calcification. [Extremely rapid growth is more likely due to hemorrhage into a cyst than cancer.] None of these characteristics is absolutely reliable (31). However, cervical adenopathy with firm discrete, usually movable, nontender, 1-2 cm size nodes may be fairly reliable in predicting malignancy (31), and in one study cervical adenopathy in the presence of a thyroid nodule was associated with a 65% frequency of cancer (32).

One older study of 179 patients with thyroid nodules classified on clinical grounds as likely having benign or malignant thyroid nodules, found a reasonable predictive value to history and physical exam alone (Table II) (33).

Table II Comparison of Preoperative Clinical Diagnosis and Final Histological Diagnosis in Patients with Thyroid Nodules

Preoperative Diagnosis	Number	Histologically Malignant No.	%
Clinically malignant	39	29	74.3
Clinically benign (symptomatic)	82	10	12.2
Clinically benign (asymptomatic)	58	2	3.4
	179	41	

(From Ref. 33)

Those patients listed as having clinically benign but symptomatic nodules had pain, recent change in size in an old goiter, appearance of the mass during the previous year, or dysphagia.

31. Ashcraft MW, Van Herle AJ: Management of thyroid nodules. I: History and physical examination, blood tests, X-ray tests, and ultrasonography. Head Neck Surg 3:216-230, 1981.

32. Haff RC, Schecter BC, Armstrong RG, Evans WE: Factors increasing the probability of malignancy in thyroid nodules. Am J Surg 131:707-709, 1976.

33. Bowens OM, Vander JB: Thyroid nodules and thyroid management. The risk involved in delayed surgery. Ann Intern Med 57:245-253, 1962.

VI. Laboratory Evaluation

Given the presence of a solitary thyroid nodule and a certain degree of suspicion of cancer based on the factors just discussed, the next consideration is what laboratory evaluation might add.

A. Serum Studies

Routine thyroid function tests are not particularly useful in evaluating the patient with a solitary thyroid nodule (31). The occasional patient with a toxic adenoma of the thyroid causing thyrotoxicosis will be identified by such studies, but other patients with solitary autonomously functioning thyroid nodules have normal routine thyroid function tests. Autonomously functioning thyroid nodules with or without thyrotoxicosis are much less likely to be malignant (see below) (34).

There are two serum tumor markers worth mentioning: calcitonin and thyroglobulin. Calcitonin should be measured in all patients with a family history of medullary thyroid carcinoma or multiple endocrine neoplasia, type II

(35). However, it is not a cost effective screening test for the routine assessment of patients with a thyroid nodule. If one assumed that 6% of thyroid cancers are medullary thyroid carcinoma (36) and 5-10% of solitary nodules are malignant, then only about one in 200 to 300 persons with a solitary nodule would have this form of thyroid cancer.

Although serum thyroglobulin is a useful marker for recurrence of differentiated thyroid cancer following appropriate treatment (37), it is not useful in deciding which patients with a solitary thyroid nodule have a malignancy (31). Two recent studies reexamining the usefulness of thyroglobulin measurement could not confirm its reliability (38, 39). Although serum thyroglobulin levels were increased in subjects exposed to childhood neck irradiation, it provided no greater information than the finding of a nodule on physical exam (38). Another group evaluated the level of serum thyroglobulin basally and following an injection of TSH in a group of patients with solitary thyroid nodules and divided the patients on the basis of final histopathological diagnosis (39). Although patients with malignant nodules had significantly lower increments in serum thyroglobulin following TSH injection compared with those subjects with benign nodules, there was considerable overlap (39).

34. Hamburger JI: The autonomously functioning thyroid nodule: Goetsch's disease. Endocr Rev 8:439-447, 1987.

35. Leshin M: Multiple endocrine neoplasia. Department of Internal Medicine Grand Rounds. Sept 15, 1983.

36. Leeper RD: Thyroid cancer. Med Clin North Am 69:1079-1096, 1985.

37. Refetoff S, Lever EG: The value of serum thyroglobulin measurement in clinical practice. JAMA 250:2352-2357, 1983.

38. Hildreth NG, Schneider AB, Cave Jr WT: A comparative study between individuals receiving thymic irradiation in infancy and their nontreated siblings: Clinical and laboratory thyroid abnormalities. Radiat Res 110:458-467, 1987.

39. Leite Z, Carneiro P, Halpern A, Medeiros-Neto G: Reduced serum thyroglobulin response to bovine TSH in malignant hypofunctioning solid thyroid nodules: Comparison to benign nodular disease. J Endocrinol Invest 10:255-259, 1987.

B. Isotope Scans

The thyroid can be scanned after the administration of radioactive iodine or technetium 99m to detect functioning or nonfunctioning areas of the gland. Thyroid carcinomas do not concentrate iodine as efficiently as the normal thyroid gland, and thus hypofunctioning or "cold" thyroid nodules have been considered to have a greater likelihood of being malignant. A cold nodule must be at least 1 cm in diameter to be detectable under optimal conditions as a "defect" in the surrounding normal tissue. Scans are limited in their ability to outline nodules at the periphery or near the isthmus. If a nodule takes up radionuclide similar to the surrounding normal thyroid tissue it is said to be "warm". In contrast, if a nodule takes up radionuclide to a greater extent than the surrounding tissue so that it is the only aspect of the thyroid visualized on the scan, it is said to be a "hot" or hyperfunctioning nodule. Some of these latter "hot" or autonomously functioning thyroid nodules may cause thyrotoxicosis (34). Misclassification of the true functional status of a nodule can occur when functioning normal tissue overlies a nonfunctioning nodule. Also, hypofunctioning areas on a scan may represent an asymmetrical gland or thyroid lobe agenesis.

Initially, ^{131}I was the isotope of radioiodine utilized. Since ^{131}I administration in a dose of 100 μCi for a thyroid scan can result in a dose of 80 rem to the thyroid, several such thyroid scans could result in a significant radiation exposure. [However, recall that ^{131}I is only about 1/50 as potent as external radiation in inducing thyroid nodules.] The preferred radioiodine isotope for routine imaging is now ^{123}I which has a short half-life of 13.3 hours and results in 1/85 the radiation dose for a comparable ^{131}I study (9). Technetium 99m delivers about 0.6 rem to the thyroid during a scanning procedure. The pertechnetate ion ($^{99m}TcO_4^-$) is trapped by the thyroid but not organically bound and does not remain in the gland. This feature of technetium may be of clinical significance. Although technetium gives high quality images, it may fail to show some nodules to be hypofunctioning which appear cold on ^{123}I scans. Recall that many thyroid cancers appear to trap iodine normally but have defective organification (see above). It appears that defective organification with normal trapping leads to increased uptake of technetium-pertechnetate when the scan is made at 30 minutes but washout of radioiodine by the time the iodine scan is performed at 24 hours (40).

As originally noted by Miller _et al_ the scan appearance of most thyroid nodules is that of a hypofunctioning or cold nodule (41). In the comprehensive review of the literature concerning thyroid scanning techniques of Ashcraft and Van Herle, 84% of nodules were cold, 10.5% were warm, and 5.5% were hot (42). All patients had radioiodine scan and underwent surgical excision. Malignancy was found in 16% of the cold, 9% of the warm nodules, and 4% of the hot nodules. Thus a cold nodule has the greatest probability of being malignant but is most often benign (42). Although this review and others cite a small incidence of malignancy in hot nodules, the significance of this is doubtful (34). Careful examination of the reports of carcinoma in hyperfunctioning thyroid nodules usually discloses that it is either elsewhere in the gland or a hypofunctioning focus of occult papillary carcinoma embedded in a hot nodule (e.g. Ref. 43).

In summary a thyroid scan of a solitary thyroid nodule is only really useful if it demonstrates the presence of a hot nodule since this finding markedly decreases the likelihood of malignancy. Another benefit may result if the scan performed for evaluation of a solitary nodule discloses a multinodular goiter not detected on physical exam. As noted above multinodular goiters are not associated with an increased risk of cancer.

40. Keyes Jr JW, Thrall JH, Carey JE: Technical considerations in in vivo thyroid studies. Semin Nucl Med 8:43-57, 1978.

41. Miller JM, Hamburger JI, Mellinger RC: The thyroid scintigram. II. The cold nodule. Radiology 85:702-710, 1965.

42. Ashcraft MW, Van Herle AJ: Management of thyroid nodules. II: Scanning techniques, thyroid suppressive therapy, and fine needle aspiration. Head Neck Surg 3:297-322, 1981.

43. Hoving J, Piers DA, Vermey A, Oosterhuis JW: Carcinoma in hyperfunctioning thyroid nodule in recurrent hyperthyroidism. Eur J Nucl Med 6:131-132, 1981.

C. Sonography

Ultrasound examination of the thyroid adds to the evaluation determined by isotope scans since it can reveal unsuspected multinodularity and distinguish a solid from a cystic lesion. In one study using high resolution real-time ultrasonography, 40% of 73 patients with a clinical diagnosis of solitary nodules were found to have multinodular glands (44). The sensitivity of the technique allows for detection of solid lesions as small as 3mm diameter. In the previously mentioned review by Ashcraft and Van Herle 16 studies were analyzed for the sonography findings, and 69% of nodules were solid, 19% were cystic and 12% were mixed solid and cystic (31). At operation, 21% of the solid lesions, 12% of the mixed lesions, and 7% of the cystic lesions were malignant. A solid nodule is thus most often benign, although it has a greater likelihood of being malignant than a cystic nodule. And not all cystic lesions are benign. Attempts at determining sonographic criteria of malignancy have not been successful. Initially it was thought that a characteristic sonolucent rim or "halo" occurred around benign adenomas (44). However, subsequent reports have shown the lack of specificity of this sign (45, 46).

In summary sonographic examination of the thyroid is primarily useful in demonstrating the unexpected presence of a multinodular gland. As will be discussed below the presence of a cyst can be determined by other means.

44. Scheible W, Leopold GR, Woo VL, Gosink BB: High-resolution real-time ultrasonography of thyroid nodules. Radiology 133:413-417, 1979.

45. Propper RA, Skolnik ML, Weinstein BJ, Dekker A: The nonspecificity of the thyroid halo sign. J Clin Ultrasound 8:120-132, 1980.

46. Simeone JF, Daniels GH, Mueller PR, Maloof F, vanSonnenberg E, Hall DA, O'Connell RS, Ferrucci Jr JT, Wittenberg J: High-resolution real-time sonography of the thyroid. Radiology 145:431-435, 1982.

D. CT and MRI

As is true of most regions of the body CT can provide excellent images of the thyroid (47). The high iodine content of the thyroid results in it having CT numbers between 70 and 120 Hounsfield units and an "enhanced" soft tissue appearance prior to contrast, and the rich blood supply results in further enhancement with contrast. However the patient receives more radiation to the thyroid than with isotope scans, and the resolution of nodules is probably no better than with sonography.

Evaluation of thyroid tumors by magnetic resonance (MR) for T_1 and T_2 times was compared with normal adjacent thyroid tissue in an in vitro analysis (48).

The cancers in the study did not show a distinctive MR pattern in comparison with other benign nodular structures studied. Thyroid imaging with high-field strength surface-coil MR is relatively new (49). A thyroid MRI study of 53 patients including 10 patients with benign solitary nodules and 3 patients with carcinoma and 12 patients with multinodular goiter concluded that MRI was primarily useful in detecting cancer because of the ability to detect irregular edges of the carcinomas as well as the associated cervical lymphadenopathy. It is unclear from the report whether MRI provided more information than physical exam.

In summary available information does not support an advantage to CT and MRI in the evaluation of thyroid nodules.

47. Reede DL, Bergeron RT, McCauley DI: CT of the thyroid and of other thoracic inlet disorders. J Otolaryngol 11:349-357, 1982.

48. de Certaines J, Herry JY, Lancien G, Benoist L, Bernard AM, LeClech G: Evaluation of human thyroid tumors by proton nuclear magnetic resonance. J Nucl Med 23:48-51, 1982.

49. Gefter WB, Spritzer CE, Eisenberg B, LiVolsi VA, Axel L, Velchik M, Alavi A, Schenck J, Kressel HY: Thyroid imaging with high-field-strength surface-coil MR. Radiology 164:483-490, 1987.

E. Fine Needle Aspiration Biopsy (FNAB)

The reason for this overall review is the impact that fine needle aspiration biopsy has had on the management of thyroid nodules in the last ten years.

1. History of FNAB of the Thyroid

Although large cutting needle (e.g. Vim-Silverman) biopsy of the thyroid has been extensively used in some centers for more than 25 years (50), it has not gained wide acceptance. This is probably because of the experience needed to perform large needle biopsy safely and the fear of cancer spread along the needle track. The latter is probably without basis since there is only one report of such spread of a thyroid tumor (42).

Almost 25 years ago Soderstrom reported use of needle aspiration biopsy of the thyroid in Sweden (51). This technique was not rapidly accepted in this country, but its use at the Karolinska in Stockholm was such that by 1980 over 20,000 fine needle aspiration biopsies of thyroid nodules had been performed (52). Several reports of the comparative utility of fine needle and large needle biopsy by one group with extensive experience suggest that with experience using fine needle aspiration there was little or no need for large needle core biopsy (53-55). In fact, since only larger nodules are suitable for large needle biopsy, fine needle aspiration biopsy allows the possibility of a histological diagnosis without surgical excision on a greater number of patients (55). Another group has suggested that the two techniques might be complementary (56). However, with the ease of performance of FNAB I doubt that large needle biopsies will continue to be performed except in selected centers with extensive past experience.

50. Vickery Jr AL: Needle biopsy and the thyroid nodule. In: Radiation-associated thyroid carcinoma. LJ DeGroot, LA Frohman, EL Kaplan, S Refetoff (eds). Grune and Stratton, New York, pp 339-346, 1977.

51. Soderstrom N: Puncture of goiters for aspiration biopsy. A preliminary report. Acta Med Scand 144:237-244, 1952.

52. Lowhagen T, Willems J-S, Lundell G, Sundblad R, Granberg P-O: Aspiration biopsy cytology in diagnosis of thyroid cancer. World J Surg 5:61-73, 1981.

53. Miller JM, Hamburger JI, Kini S: Diagnosis of thyroid nodules. Use of fine-needle aspiration and needle biopsy. JAMA 241:481-484, 1979.

54. Miller JM, Hamburger JI, Kini SR: The needle biopsy diagnosis of papillary thyroid carcinoma. Cancer 48:989-993, 1981.

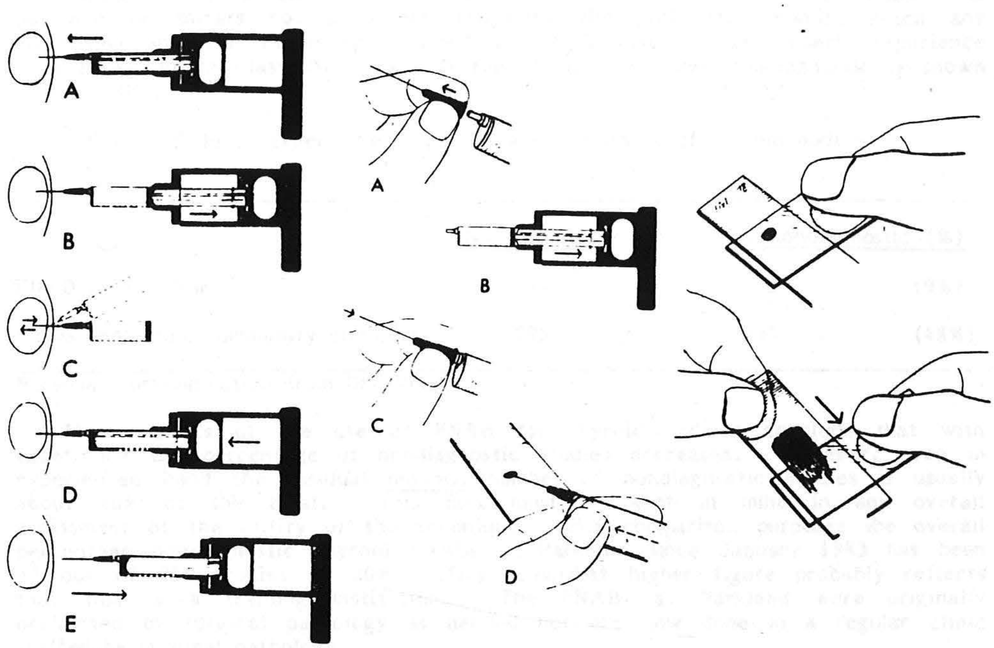
55. Miller JM, Kini SR, Hamburger JI: The diagnosis of malignant follicular neoplasms of the thyroid by needle biopsy. Cancer 55:2812-2817, 1985.

56. Nishiyama RH, Bigos ST, Goldfarb WB, Flynn SD, Taxiarchis LN: The efficacy of simultaneous fine-needle aspiration and large-needle biopsy of the thyroid gland. Surgery 100:1133-1137, 1986.

2. Technique of FNAB and Categories of Results

The technique of performing FNAB is relatively simple (Fig. 6). The requirements for successful fine needle aspiration are skillful palpation, aspiration of sufficient material, and adequate preparation of smears. The procedure is best done with the patient in a supine position with relaxed neck muscles. A disposable 10 ml syringe attached to special holder (Cameco syringe pistol, Precision Dynamics Corp., Burbank, CA) (52) is typically used with a 25 to 22 ga. needle. A syringe holder is useful since this allows the physician to stabilize the nodule with the free hand. Usually two, and occasionally more aspirations are needed for adequate sampling. Anesthesia is usually not necessary, and there are no common serious complications.

Figure 6



Left. Fine-needle aspiration (*FNA*) of thyroid. Materials and method used to obtain samples. **Middle.** Preparation of slides for cytologic evaluation. **Right.** Correct smearing technique. From Löwhagen and associates (22); reproduced by permission from *Surg Clin North Am.*

The needle is inserted into the nodule and suction obtained by retracting the syringe plunger. The needle is moved back and forth inside the nodule to collect small fragments of tissue. After a few seconds the plunger is released before the needle is removed from the nodule to keep the needle contents (the material of interest) from being aerosilized into the syringe. The needle is removed from the syringe, the syringe filled with air, the needle reattached, and the air used to expel the sample onto a glass slide. One or two drops of material from a solid lesion is desirable. Correct pressure must be applied in smearing the slide to avoid destruction of architecture or crushing cells (Fig. 6). Also, the smear must be made immediately, before clotting set in since cellular detail and architecture are lost if epithelial cells are trapped in clotted blood. The slides may be fixed in alcohol and/or air dried and stained appropriately. If a cyst is encountered, as much cyst fluid a possible should be aspirated and cells contained in the aspirate can be studied after filtration or preparation of a cell block. If a residual nodule remains following fluid aspiration, the solid component of the mixed cyst can be sampled by repeat FNAB.

The importance of adequate technique in performing FNAB and smearing the slide can be appreciated by some data supplied by Dr. Richard Voet formerly of UT Southwestern who is now in private practice in the community. Dr. Voet received special training in aspiration biopsy cytology and stresses the importance of preparation of the slides. When an inadequate aspirate is obtained or smears not performed properly, the pathologist cannot reach any conclusion and the FNAB is reported as nondiagnostic. Dr. Voet's experience with FNAB in the last two years in regard to percentage nondiagnostic is shown in Table III.

Table III Role of experience in performance of FNAB of thyroid nodules

	No. biopsies	No. nondiagnostic (%)	
FNAB by Dr. Voet	54	5	(9%)
Slides sent from community clinicians	295	143	(48%)

Personal communication from Dr. Voet

Most reports of the use of FNAB for thyroid nodules conclude that with experience the percentage of nondiagnostic studies decreases. However, even in experienced hand the residual minimal number of nondiagnostic studies is usually about 10% of the total. This fact must be kept in mind in any overall assessment of the utility of the technique. For comparison purposes the overall percentage nondiagnostic thyroid FNABs at Parkland since January 1983 has been 53 out of 261 studies or 20%. This somewhat higher figure probably reflects that this is a training institution. The FNABs at Parkland were originally performed by surgical pathology as needed but are now done in a regular clinic staffed by surgical pathology.

The successful application of FNAB to the evaluation of thyroid nodules requires not only skill in the performance of the aspiration and preparation of the slides but also specific training and experience on the part of the pathologist in interpreting the cytology. One cannot assume that any pathologist is qualified to interpret FNAB cytology, and lack of experience can result not only in equivocating about the category with an increased likelihood of assignment to the suspicious category but also an increased frequency of nondiagnostic studies. Of the 53 nondiagnostic studies in the Parkland series 19 patients subsequently had surgical excision of their thyroid nodules with final diagnoses of multinodular goiter in 10 patients, follicular adenoma in 7, papillary carcinoma in 1, and medullary carcinoma in 1. The follicular neoplasia category (see below) seems to be overrepresented.

Virtually any thyroid disease can present as a thyroid mass, and the categorization of FNAB results can thus be viewed differently by different cytologists. Excluding the nondiagnostic (or insufficient for diagnosis) category, I was given 5 categories of diagnoses from Dr. Voet and 7 from Dr. Sandstad for the Parkland experience. Most investigators agree that for the purpose of management decisions the various diagnostic categories can be grouped into three broad categories: benign, malignant, and follicular neoplasia (42, 57-62). The benign category typically includes colloid goiter, colloid cyst, and hemorrhagic cyst but may also include various forms of thyroiditis. The usual cytological picture is that of abundant follicular colloid. The malignant category is primarily composed of papillary carcinoma with a cytological picture of typical frondlike papillary lesions. Occasionally medullary thyroid carcinoma, undifferentiated carcinoma, and metastatic carcinoma are detected and included in this malignant category. The follicular neoplasia category is the suspicious category and the primary limitation of FNAB of the thyroid. This stems from the inability to differentiate between benign and malignant follicular neoplasm on the basis of cytology since histological evidence of the invasive characteristics of the lesion are the only satisfactory criteria. The cytological appearance of biopsies in this category is that of small follicular structures without the sheets of colloid seen in colloid goiters. The distribution of thyroid FNABs is generally found to be benign 60-80%, malignant 5-10%, and follicular neoplasia 10-30% (57-63). The experience of PMH and Dr. Voet in the distribution of FNAB biopsy results is shown in Table IV and is similar to the middle of the ranges just mentioned.

Table IV Distribution of the interpretable thyroid FNAB cytology categories in two Dallas series

	PMH		Dr. Voet	
Cytology Category	No.	(%)	No.	(%)
Benign	146	(70.2)	148	(73.6)
Malignant	16	(7.7)	14	(7.0)
Follicular neoplasia	46	(22.1)	39	(19.4)
	208		201	

Unpublished data supplied by Drs. Sandstad and Voet.

57. Miller TR, Abele JS, Greenspan FS: Fine-needle aspiration biopsy in the management of thyroid nodules. West J Med 134:198-205, 1981.

58. Norton LW, Wangensteen SL, Davis JR, Paplanus SH, Werner SC: Utility of thyroid aspiration biopsy. Surgery 92:700-705, 1982.

59. Ramacciotti CE, Pretorius HT, Chu EW, Barsky SH, Brennan MF, Robbins J: Diagnostic accuracy and use of aspiration biopsy in the management of thyroid nodules. Arch Intern Med 144:1169-1173, 1984.

60. Jayaram G: Fine needle aspiration cytologic study of the solitary thyroid nodule. Profile of 308 cases with histologic correlation. Acta Cytol 29:967-973, 1985.

61. Gharib H, Goellner JR, Zinsmeister AR, Grant CS, Van Heerden JA: Fine-needle aspiration biopsy of the thyroid. The problem of suspicious cytologic findings. Ann Intern Med 101:25-28, 1984.

62. Bugis SP, Young JEM, Archibald SD, Chen VSM: Diagnostic accuracy of fine-needle aspiration biopsy versus frozen section in solitary thyroid nodules. Am J Surg 152:411-416, 1986.

63. Rojeski MT, Gharib H: Nodular thyroid disease. Evaluation and management. N Engl J Med 313:428-436, 1985.

3. Reliability of FNAB

The calculation of false positive and false negative rates of thyroid FNAB cytology depends on how the follicular neoplasia category is handled. In general about 20% of thyroid cytologies will be on this suspicious category, and about 20-25% of such lesions will be finally diagnosed as malignant on histological examination at surgical excision (61). It is therefore necessary to proceed with histological examination to diagnose the nature of follicular neoplasia (42). This limitation also applies to large needle biopsy as well as frozen section (42). In most analyses of thyroid FNABs a cytologic diagnosis of follicular neoplasm which is histologically verified is considered a diagnosis correctly made and should not be considered as false negative.

The reliability of thyroid FNAB for 8 series totaling 1330 in which all patients underwent surgical resection regardless of cytological category as well as 20 series totaling 9912 patients in which selected patients were sent for surgery was similar as reviewed by Aschraft and Van Herle (42). The false positive rate of a malignant or suspicious (follicular neoplasia) cytology or percentage found to be benign at histology as 0.5% for the group in which all patients were operated. The false negative rate of benign cytology or the percentage found to be malignant at histology was 1.7% for this same group (42). This would translate into an overall reliability of 97.8%. Some of these individual studies had overall reliability in the 90-95% range (64, 65, 66), and in subsequent reports the false negative rate has ranged from 2 to 6% (67-72). In one study of 600 patients who underwent FNAB the 365 patients with benign cytology not operated were followed prospectively, and in the average 2.5 year followup only two patients were subsequently diagnosed as having cancer, both in recurrent cysts (69). In these same studies the calculated sensitivity ranged from 86 to 94% and specificity ranged from 92 to 99%.

The accuracy of FNAB in the subgroup of patients with thyroid nodules and a history of radiation exposure has also been evaluated in one report (73). The calculated false positive and negative rates are 8% and 16% respectively. However, it is difficult to interpret the degree of selection in this retrospective series since the number of patients not operated is unknown, and no description of the frequency of occult cancer is provided.

The accuracy of FNAB of thyroid nodules in the Parkland series has only been partially evaluated. Similar to published series the frequency of cancer in the follicular neoplasia group is 26% in those operated. In the group designated as having malignant cytology, 13 of the 14 who had surgical excision had confirmation of malignancy. The overall false positive rate was 10%. The false negative rate has not been accurately assessed by chart review and length of followup. Since no study was in progress, patients with clearly benign cytology have not been routinely sent for surgical excision. The surgical pathology records only disclose one subsequent surgical excision of malignancy for the 146 patients with benign cytology in Table IV.

64. Gershengorn MC, McClung MR, Chu EW, Hanson TAS, Weintraub BD, Robbins J: Fine-needle aspiration cytology in the preoperative diagnosis of thyroid nodules. Ann Intern Med 87:265-269, 1977.

65. Walfish PG, Hazani E, Strawbridge HTG, Miskin M, Rosen IB: A prospective study of combined ultrasonography and needle aspiration biopsy in the assessment of the hypofunctioning thyroid nodule. Surgery 82:474-482, 1977.

66. Walfish PG, Hazani E, Strawbridge HTG, Miskin M, Rosen IB: Combined ultrasound and needle aspiration cytology in the assessment and management of hypofunctioning thyroid nodule. Ann Intern Med 87:270-274, 1977.

67. Chu EW, Hanson TA, Goldman JM, Robbins J: Study of cells in fine needle aspirations of the thyroid gland. Acta Cytol 23:309-314, 1979.

68. Christensen SB, Bondeson L, Ericsson U-B, Lindholm K: Prediction of malignancy in the solitary thyroid nodule by physical examination, thyroid scan, fine-needle biopsy and serum thyroglobulin. Acta Chir Scand 150:433-439, 1984.

69. Boey J, Hsu C, Collins RJ: False-negative errors in fine-needle aspiration biopsy of dominant thyroid nodules: A prospective follow-up study. World J Surg 10:623-630, 1986.

70. Silverman JF, West RL, Larkin EW, Park HK, Finley JL, Swanson MS, Fore WW: The role of fine-needle aspiration biopsy in the rapid diagnosis and management of thyroid neoplasm. Cancer 57:1164-1170, 1986.

71. Hawkins F, Bellido D, Bernal C, Rigopoulou D, Valdepenas MPR, Lazaro E, Perez-Berrios A, de Agustin P: Fine needle aspiration biopsy in the diagnosis of thyroid cancer and thyroid disease. Cancer 59:1206-1209, 1987.

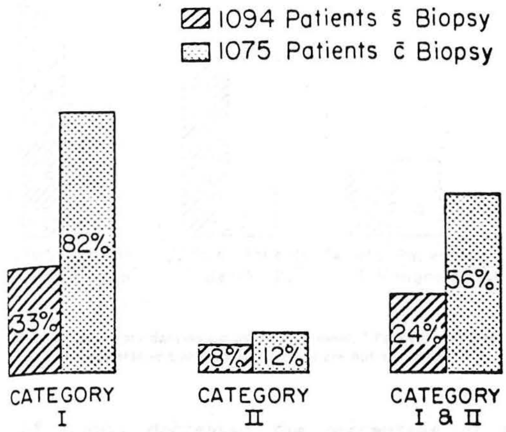
72. Anderson JB, Webb AJ: Fine-needle aspiration biopsy and the diagnosis of thyroid cancer. Br J Surg 74:292-296, 1987.

73. Rosen IB, Palmer JA, Bain J, Strawbridge H, Walfish PG: Efficacy of needle biopsy in postradiation thyroid disease. Surgery 94:1002-1007, 1983.

4. Impact of FNAB on Clinical Practice

At least seven papers have reported the impact of the use of FNAB of thyroid nodules on the surgical practice at a given institution (74-80). In general the observation is that addition of thyroid FNAB resulted in approximately a 50% decrease in operations for solitary thyroid nodules with a doubling in the frequency of malignancy detected at operation. The first of these reports is from the group with the largest experience and compares 1094 patients with thyroid nodules treated before the institution of needle biopsy in the practice and 1075 patients with satisfactory biopsies following the routine use of needle biopsy (74). The percentage of malignancy in surgical specimens for the two groups of patients is shown in Fig. 7. Categories I and II correspond to noninvasive diagnoses of probably malignant and possibly malignant respectively on clinical grounds for the first group or biopsy categories of malignant and follicular neoplasia for the second group.

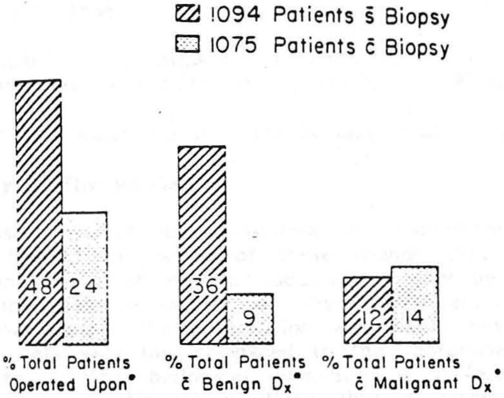
Figure 7



The impact of biopsy data on the percentage of malignancy in surgical specimens.

As can be seen from the figure, the most important comparison is for the combination of Categories I and II (in keeping with recommending surgical excision for suspicious lesions on FNAB as described above). The percentage malignancy more than doubled from 24% to 56%. Additional data on the impact of biopsy in patient management is shown in Fig. 8. The left column shows the percentage of total patients who were operated on for probable or suspected malignancy in the two groups. The center column shows the percentage of patients undergoing surgery found to have benign disease. The right column shows the percentage of total patients in whom malignancy was found.

Figure 8



The impact of biopsy data on patient management. * Patients who were in preoperative *Category III* (benign) are not included.

The availability of biopsy decreased the percentage of patients subjected to operation from 48% to 24% while simultaneously decreasing the percentage of patients operated on for benign disease from 36% to 9% (excluding preoperative benign or Category III electing operation) and increasing slightly the total number of cancers found from 12% to 14% of all patients.

74. Miller JM, Hamburger JI, Kini SR: The impact of needle biopsy on the preoperative diagnosis of thyroid nodules. Henry Ford Hosp Med J 28:145-148, 1980.

75. Hamberger B, Gharib H, Melton JL, Goellner JR, Zinsmeister AR: Fine-needle aspiration biopsy of thyroid nodules. Impact on thyroid practice and cost of care. Am J Med 73:381-384, 1982.

76. Al-Sayer HM, Krukowski ZH, Williams VMM, Matheson NA: Fine needle aspiration cytology in isolated thyroid swellings: A prospective two year evaluation. Br Med J 290:1490-1492, 1985.

77. Caplan RH, Wester S, Kisken WA: Fine-needle aspiration biopsy of solitary thyroid nodules. Effect on cost of management, frequency of thyroid surgery, and operative yield of thyroid malignancy. Minn Med 69:189-192, 1986.

78. Fitz-Patrick D, Navin JJ, Fukunaga BN: Fine-needle aspiration biopsy of thyroid nodules. A diagnostic method that minimizes the need for surgery. Postgrad Med 80:62-68, 1986.

79. Reeve TS, Delbridge L, Sloan D, Crummer P: The impact of fine-needle aspiration biopsy on surgery for single thyroid nodules. Med J Aust 145:308-311, 1986.

80. Baskin HJ, Guarda LA: Influence of needle biopsy on management of thyroid nodules: Reasons to expand its use. South Med J 80:702-705, 1987.

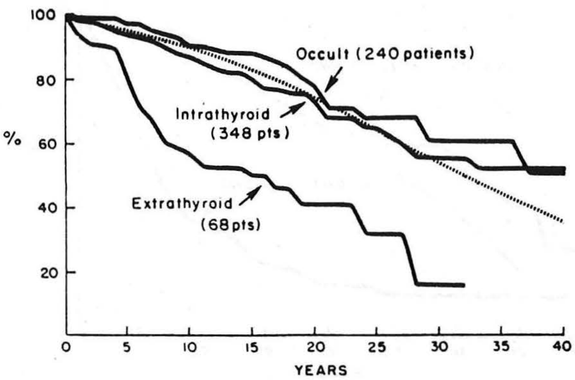
In summary, FNAB is quite useful in the evaluation of thyroid nodules.

VII. Natural History of Thyroid Cancer

A detailed discussion of the classification, management and prognosis of thyroid cancer is beyond the scope of these rounds (81, 82). However, the decisions about management of thyroid nodules can only be made in light of an understanding of the natural history of thyroid cancer. In the section on prevalence of thyroid cancer the observation was made that the death rate from thyroid cancer was relatively low compared to the approximate 2% prevalence for more occult disease. The biological behavior of different types of thyroid cancer varies markedly. Minimal papillary thyroid carcinoma has a negligible biological risk whereas undifferentiated or anaplastic thyroid carcinoma is one of the most malignant of all human cancers. Papillary carcinoma accounts for 60-70% of all thyroid cancer, and follicular carcinoma for 15-20%. These two forms of thyroid cancer are referred to as differentiated thyroid cancer and have a relatively benign course (see below). As mentioned above medullary thyroid carcinoma accounts for about 6% of all thyroid cancer. It has an intermediate degree of malignancy with about a 70% 5-year survival and is familial in about 20% of cases. Anaplastic carcinoma occurs in about 10% of patients with thyroid cancer and is usually inoperable at the time of diagnosis. It is seen primarily in elderly persons and has a mean period of survival from diagnosis of about 8 months (83).

Thus for the most part one should consider that the usual condition one is trying to diagnose accurately and in a reasonable time frame in patients with solitary thyroid nodules is papillary or follicular carcinoma. Woolner <u>et al</u> have provided valuable reports of long term followup of patients with papillary and follicular thyroid cancer seen at the Mayo Clinic (83). The survivorship curve for papillary carcinoma is shown in Fig. 9 (83).

Figure 9

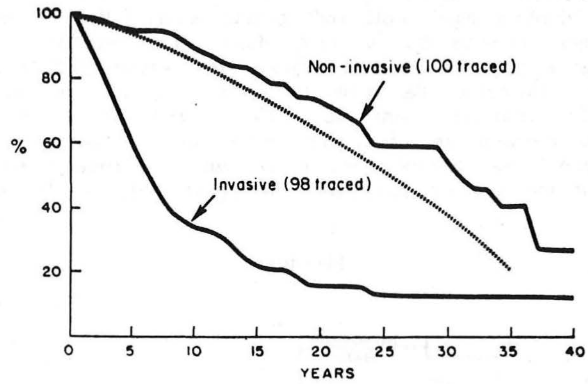


Papillary carcinoma: survivorship curves for occult, intrathyroid, and extrathyroid lesions; also, curve (dotted line) for normal persons of comparable age and sex.

The 240 patients with occult carcinoma included 95 patients with nodal metastases at the time of original surgery. Even in these latter patients none were found to have subsequently died from thyroid cancer (or to have developed distant metastases). The 348 patients labelled as having intrathyroid lesions are those with tumors greater than 1.5 cm diameter and what all concerned would agree is a "clinical" tumor. The survivorship for these patients is not statistically different than that for normal individuals of comparable age and sex. The group of 68 patients indicated as having extrathyroidal cancer had primary tumor spread beyond the capsule, and 60% of these patients had nodal metastases. In many cases the surgery was only palliative, and it is clear that overall survival is decreased by the lesion. However, even in this subcategory there was about a 50%, 15-year survival.

Those tumors found to have a mixed papillary-follicular histology primarily have a clinical behavior similar to papillary carcinoma. The most critical of prognostic indicators in true follicular carcinoma appears to be the degree of gross or microscopic capsular invasion (Fig. 10) (83).

Figure 10



Follicular carcinoma: survivorship curves (six operative deaths excluded) for patients with slight or equivocal capsular invasion and those with moderate or marked invasion (including recurrent and inoperable tumours); also, curve (dotted line) for normal persons of comparable age and sex.

The survivorship curve for 100 traced patients with encapsulated follicular carcinomas with minimal capsular invasion (which accounted for half of the 208 patients with follicular carcinoma) is similar to normals. In contrast 98 traced patients with tumors found to have moderate to marked invasion had a decreased survival with about a 20%, 15-year survival.

81. Block MA: Management of carcinoma of the thyroid. Ann Surg 185:133-144, 1977.

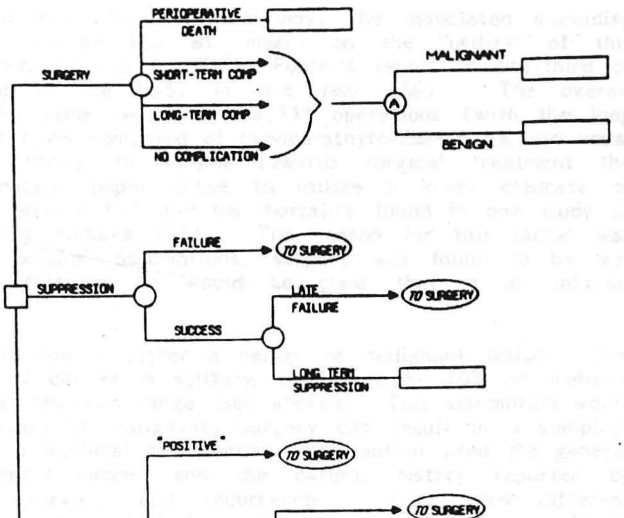
82. Block MA: Surgery of thyroid nodules and malignancy. In: Current Problems in Surgery. MM Ravitch (ed), Year Book Publishers, New York, pp 134-203, 1983.

83. Woolner LB, Beahrs OH, Black BM, McConahey WM, Keating Jr FR: Thyroid carcinoma: General considerations and follow-up data on 1181 cases. In: Symposium on Thyroid Neoplasia. S Young, DR Inman (eds), Academic Press, Long, pp 51-79, 1968.

VIII. An Application of Decision Analysis to Management Options - A "Tossup"

Although various management schemes have been presented for evaluation and treatment of thyroid nodules including considerations of cost effectiveness (see below), most do not consider suppressive or definitive surgical therapy and do not examine the issues of survival and quality of life. One review has employed the techniques of clinical decision analysis to evaluate the various approaches to solitary hypofunctioning thyroid nodules including all considerations (other than cost or psychological concerns of the patient) (84). Clinical decision analysis involves structuring a clinical problem as a "decision tree", which is simply a diagrammatic representation of therapeutic options and possible consequences (Fig. 11). While the choice of management strategy is under the physician's control, the actual outcome is determined by chance. With values from the literature the decision maker can assign likelihood or probabilities to the occurrence of all chance events that flow from a decision. Finally, the relative worths ("utilities") of each possible consequence can be quantified. The best option of the diagrammed choices is determined by summing the products of the likelihood and utility associated with all potential consequences of a particular therapeutic decision. One of the important advantages of the decision analytic approach is allowing systematic examination of the impact of variations in assumptions. This technique, known as "sensitivity analysis", allows evaluation of the full range of values of various parameters reported in the literature.

Figure 11



Decision tree. Three management plans for a cold thyroid nodule are delineated: immediate surgical extirpation (SURGERY), a trial of suppression with L-thyroxine (SUPPRESSION), and aspiration biopsy with cytopathologic analysis (ASPIRATION). By convention, *square nodes* indicate decisions, *circular nodes* indicate chance events, *rectangles* indicate terminal events, and *ovals* indicate transfer to another section of the decision tree. Subtree A, which contains the section of the tree devoted to the status of the nodule, is reached from each of the three nonfatal outcomes of surgery. See the text for details.

For their application of decision analysis Molitch et al have assumed the patient to have a hypofunctioning solitary noncystic nodule as defined by physical exam, thyroid function tests, sonography and radionuclide scan. [The appropriateness of using sonography or scans at all will be considered in the next section.] In addition the authors assume that history and physical findings do not disclose factors that markedly increase the likelihood of malignancy (e.g., history of familial medullary carcinoma or multiple endocrine neoplasia, type II, immobility of nodule, local adenopathy, or evidence of tracheal or recurrent laryngeal nerve invasion, see above). The three alternatives in initial management considered are: 1) definitive surgical removal of all nodules as classically recommended by many surgeons (85); 2) a trial of thyroid suppression with thyroid hormone with subsequent removal of nodules that do not regress; and 3) FNAB cytology with suspicious or malignant results being indications for surgery (Fig. 11). The second and third options may be viewed as "diagnostic tests"; malignant lesions are less likely to shrink and are more likely to have abnormal cytology than benign nodules.

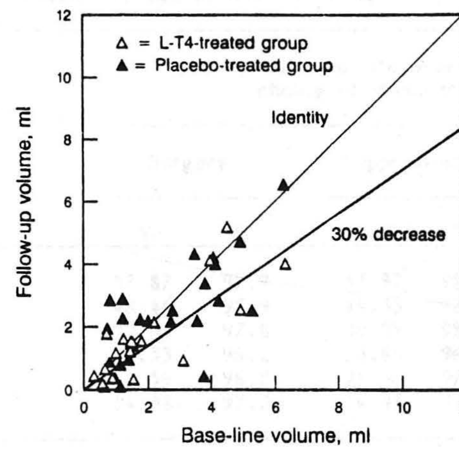
Although a detailed analysis of the "folding back" of this decision tree must be left for those interested in reading the paper, some description of the factors involved is appropriate before presenting the overall conclusions.

In considering subtotal or near total throidectomy, the associated morbidity and mortality of such a procedure has an impact on the "utility" of this approach. The operative mortality was 0.13% in Foster's report of one-third of all thyroidectomies performed in the U.S. in one year (86). The overall complication was 3.5% in this same report of 18,355 operations (with the long term morbidities component of 1.2% composed of hypoparathyroidism 0.9% and vocal cord paralysis 0.3%). In trying to weight towards surgical treatment the authors of the decisional analysis paper chose to utilize a lower estimate of operative complications (long term 0.3%) and 0% mortality found in one study of surgery specifically for solitary nodules (87). The reason for this tactic was that if, despite the "lower bounds" assumptions, surgery was found to be less efficiacious than competing strategies it would be clear that is an inferior strategy.

The result of surgical excision is either a benign or malignant lesion. The authors selected a frequency of cancer in solitary nodules to be 10% or probably on the high end of the actual unknown range (see above). This assumption would also favor surgery. If a nodule is malignant, surgery can result in a complete cure, a fatal recurrence, or a nonfatal recurrence. The author used the general distribution of type of thyroid cancer and the natural history reported by Woolner (83) to calculate survival and recurrence. They used different percentages of type of tumor and survival for patients under 40 and over 40 to account of the known increased frequency of anaplastic cancer in older individuals and decreased survival with papillary carcinoma in older subjects (14). They also assumed that any tumors were operable and intrathyroidal. [Recall the exclusion of patients with physical signs highly suggestive of cancer.] They also assumed that all patients would receive thyroid hormone suppression after surgery since this is known to reduce recurrence and mortality in papillary carcinoma (14). Since only some series have included ^{131}I therapy for ablation of the thyroid remnant after surgical resection (88), the authors did not assume it to be given.

The next question of utility in the tree is the role of thyroid suppression (Fig. 11). The authors assumed a six-month test period of suppressive therapy and defined a successful suppression as a lesion that shrinks to less than 50% of its original diameter. Although the classic report of Astwood et al found that 54% of 37 nodules had partial or complete response to thyroid (89) and Blum and Rothschild noted 69% response in 83 patients (90), other reports find a response rate as low as 9% (91). One study of 85 patients with radiation-related nodules noted a 28% complete regression on thyroid replacement (92). Some would question the use of anything less than complete disappearance since proven malignant nodules can regress temporarily on thyroid suppression (91). And only about 5-10% of nodules completely disappear with suppression (93). Additional criticisms of most of the literature on this subject is lack of monitoring actual suppression of TSH and inadequate measurement of the nodules size by relying on physical exam. A very recent report using TRH to monitor adequacy of suppression, high resolution ultrasound to quantitate size, and a double-blind placebo control format in 53 patients with a solitary colloid nodule confirmed at biopsy did not detect a significant effect on nodule diameters or volume in six months (Fig. 12) (94).

Figure 12



Nodule Volume at Follow-up Ultrasonography in Relation to Volume at Base Line in 28 Levothyroxine-Treated (L-T4) and 25 Placebo-Treated Patients.

Both the line of identity and that showing a hypothetical 30 percent decrease in size serve as reference lines and are not fitted to the data. Some of the open triangles represent more than one patient.

The authors of the decision analysis paper chose to use the average 21.8% suppressible calculated from results of studies describing patients who came to surgery. The sensitivity and specificity of thyroid suppression as a test for malignancy, is 83.8% and 22.3% respectively in these combined series (84). The revision of the probability of cancer based on suppression is not great. Using Bayes' rule and a critical assumption of 10% frequency of cancer, failure of suppression only slightly increases this probability to 10.7%. Successful suppression only slightly decreases the probability of cancer from 10% to 7.4%. No morbidity is assumed for the 6-month trial of suppression since delay of surgery for 6 months does not appear to have a deleterious effect in subsequent survival (14).

Finally, in the aspiration biopsy branch of the tree the authors assume an interpretable FNAB cytology because the procedure can be repeated. The authors note that a clearly malignant or benign aspirate has a much greater effect in revising the probability of cancer (89% and 1% respectively) than does the presence and absence of suppression (11% and 7% respectively). The authors point out that the finding of a suspicious aspirate changes the probability of cancer only slightly from 10% to 11.5%, and the revised probability of combining malignant and suspicious aspirates is only 33.4%.

The authors then assign a relative worth or utility to each outcome or terminal branch of the tree. They used a "quality-adjusted life expectancy" as a measure of utility. Aspiration biopsy provides the greatest quality adjusted life expectancy, but the gain over thyroid suppression is minuscule, ranging from 11 days for a 20-year old woman to 4 days for 70-year-olds (Table V).

Table V. Expected survival by age in white females

Age	LE (yr)	Quality-adjusted life expectancy (yr) choice of management					
		Surgery		Suppression		Aspiration	
		Yr	%	Yr	%	Yr	%
20	59.1	57.87	97.9	57.97	98.1	58.00	98.1
30	49.5	48.46	97.9	48.53	98.0	48.56	98.1
40	39.9	39.03	97.8	39.09	98.0	39.11	98.0
50	30.7	29.53	96.2	29.64	96.5	29.64	96.5
60	22.3	21.59	96.8	21.66	97.1	21.66	97.1
70	14.8	14.38	97.2	14.41	97.4	14.42	97.4

From Ref. 84

Immediate thyroidectomy is consistently inferior to the other two strategies. After a suspicious aspirate the best course of action is said to be a trial of thyroid suppression, because the likelihood of cancer is not increased sufficiently to warrant immediate surgery. The baseline values are minimum estimates for operative mortality and morbidity; any increase in these values further penalizes immediate surgery relative to the two non-surgical interventions. Variations of the 15-year survival parameter for malignancy to a lower percentage only result in suppression being slightly preferred to aspiration biopsy as initial management since some thyroid cancers would be permanently suppressed and also because a six month trial of suppression sends other malignancies to surgery. In another sensitivity analysis at the lowest, likelihood of success for suppression considered (9%), thyroid suppression was still slightly preferable to immediate surgery.

In other words when mortality and morbidity are used as outcome measures, all therapies are equally good, and the decision is a "tossup". Note that this analysis did not consider costs (which eliminates the choice of immediate surgery) and the psychological benefit afforded patients by the quick answers of FNAB (which makes FNAB preferable to thyroid suppression for initial management). The conclusions of this application of decision analysis do make the anxiety which most patients and many physicians have about approaching the management of the solitary thyroid nodule seem inappropriate.

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IX. A Cost-Effective Management Regimen

Although the early schemes for management of thyroid nodules centered on selection of patients for either immediate surgery or trial of thyroid suppression based on history and physical findings increasing the likelihood of malignancy (11, 95, 96), the experience with FNAB has been so positive that it is now the cornerstone of any management regimen. Perhaps the most cited reference on cost-effective evaluation of thyroid nodules is the paper by Van Herle et al describing the consideration of three different sequences of tests (97). In designing a cost effective approach to evaluation, the desired outcomes are the fewest malignancies missed, the fewest operations for benign conditions, and lowest cost. Van Herle et al compared scan followed by aspiration, scan followed by sonography, and aspiration followed by scan. Not surprising given the description of the utility of scan and sonography above, the two plans with FNAB had the fewest operations for benign lesions. Given the greater reliability of FNAB, the plan using FNAB prior to scan had the lower cost per nodule and per diagnosis. The average cost per correct diagnosis ($224) was considerably less than that for the traditional plan of scan followed by sonography ($517) (97). The authors suggest that a scan is useful in the patients with FNAB category of follicular neoplasia since most hot nodules are follicular lesions. As described in the paper, using reasonable assumptions one could estimate that as many as 29% of nodules in the FNAB category of follicular neoplasia will be hot or autonomously functioning and thus have a low probability of cancer.

Francis Greenspan in an unpublished postgraduate course syllabus has incorporated the conclusions of Van Herle et al into an overall decision matrix for diagnosis and management of a thyroid nodule (Fig. 13).

Figure 13

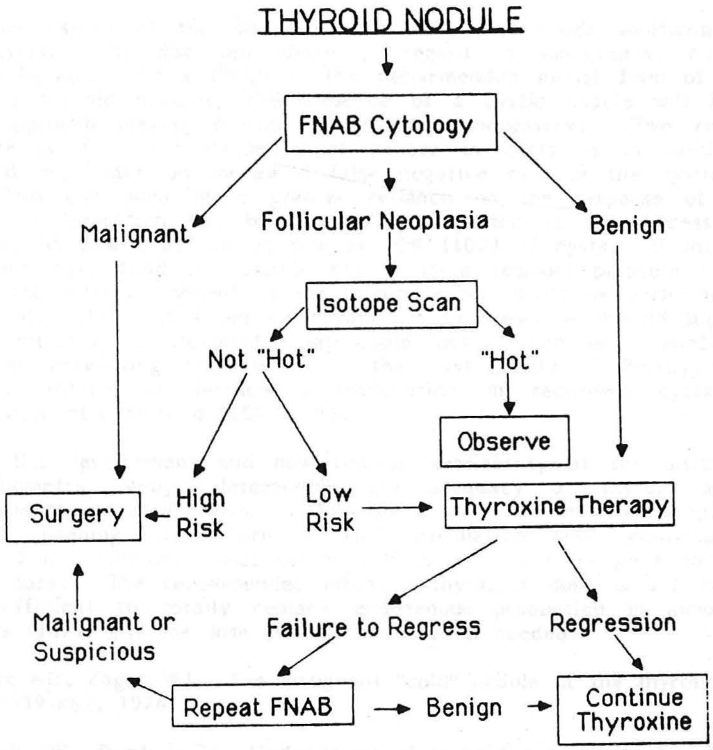

Fig. 13. Decision matrix for diagnosis and management of a thyroid nodule (Modified from Greenspan).

I feel that this scheme is quite reasonable and relatively self-explanatory. Several points should be stressed. All patients should have FNAB even if there is a high suspicion of cancer since the results may be useful to the surgeon in planning therapy. Perhaps the most controversial portion of the scheme is the decision of how to proceed in the patient with the FNAB cytology of follicular neoplasia and hypofunction on scan. Dr. Greenspan suggests that clinical criteria of relatively increased risk of malignancy (e.g., large lesion, young patient, firm nodule, etc.) can be used to favor immediate surgery rather than thyroid suppression. My initial reaction to this approach was negative. However, after considering the decision analysis model in the previous section and the minor differences in morbidity and morality, I think this is reasonable. The other aspect of this scheme that needs emphasis is the utility of sequential FNAB in following patients on thyroid suppression. Hamburger has recently reported the success of repeat needle biopsy in selecting patients on thyroid suppression for surgery (98). His evidence of correlation with surgical diagnoses is convincing for using repeat biopsy rather than automatic surgical referral for nodules that do not regress or thyroxine therapy. Repeat biopsies found to be benign were confirmed, and changes in biopsy result to malignant in six patients were confirmed in the five who had surgery.

Another aspect of the management scheme that needs additional comment is thyroid cysts. As discussed above in regard to sonography, not all thyroid cysts are benign. Since FNAB is the recommended initial form of evaluation in all solitary thyroid nodules, the presence of a cystic nodule will be determined by this approach making routine sonography unnecessary. Two reports suggest that there is a similar incidence of cancer in cysts as in solid nodules and that FNAB may have an increased false negative rate in the cystic lesion (99, 100). Thus one must place greater reliance on the response of the cyst to aspiration. Aspiration has been variously reported to be successful treatment in as many as 80% (101) or as few as 20% (102) of cysts. If initial aspiration of as much cyst fluid as possible results in a residual palpable nodule, repeat FNAB of the solid component of the mixed lesion should be performed as already recommended. Although I see no reason not to prescribe thyroid suppression, one placebo controlled double-blind trial could not detect any benefit of thyroid hormone in preventing recurrence of the cyst (103). Finally, two reports suggest a benefit of tetracyline installation in recurrent cysts to prevent reaccumulation of cyst fluid (104, 105).

With the development and now routine availability of the ultrasensitive TSH immunoradiometric assay, determining the adequacy of thyroid suppression in those patients treated with L-thyroxine is now greatly simplified (106). Instead of needing to perform a TRH stimulation test, confirmation of the presence of a suppressed basal serum TSH is sufficient evidence for adequacy of thyroxine dose. The recommended initial L-thyroxine dose is 0.1 mg daily since this is sufficient to totally replace endogenous production in almost two-thirds of subjects (107), and the dose may be increased if needed.

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X. Conclusions: Management Still Imperfect

Forty years ago decisions about what to do for the patient with a thyroid nodule were based entirely on clinical judgment. Although isotope scans and ultrasonography added new dimensions to the assessment, their limitations are clear. FNAB has had a major impact on management because of its greater sensitivity and specificity. The problem with the procedure is that the technique requires a great deal of expertise and is best performed by specialists who have become proficient in it. (My initial grumbling about our surgical pathologists wanting to keep the procedure for themselves has ceased.) Even more critical than the aspiration and preparation of the slides is their interpretation. Only pathologists with specific training in interpreting FNAB cytology and regular practice in the interpretation should be relied upon. In addition the 10% frequency of nondiagnostic aspirates needs to be kept in mind. This necessitates repeat aspiration or other diagnostic approaches. Even for the patient found to have a benign nodule on biopsy, there is the inconvenience of followup visits and the potential adverse effects of slight overtreatment with L-thyroxine with an increased risk of osteoporosis. In many cases the physician will suggest a repeat aspiration which increases the inconvenience and expense for the patient. If the nodule is greater than 2 cm in diameter it may present a cosmetic problem rivaling that of a neck scar from a surgical procedure. And Dr. DeGroot observes that approximately one-third of patients who have apparently benign lesions eventually undergo an operation, usually within a few years (108). This has caused him to question "how far have we come?" (108). I am not so pessimistic and feel that we have come a long way.

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