

TITLE: Evaluation of the Thyroid Nodule

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Background

Management of the thyroid nodule remains a challenge for the physician. Mazzaferri writes, "The trouble with thyroid nodules is that there are too many of them, and they tend to cause terrible apprehension because their behavior is so unpredictable. Thyroid nodules comprise a gamut of disorders with widely differing biologic behaviors, ranging from benign tumors with no malignant potential to aggressive thyroid cancers that may kill within a matter of months. Add to this the fact that concealed among the millions of nodules are only a relatively few thyroid cancers, most of which are completely curable, and one has woven the fabric of a serious diagnostic dilemma." ¹⁸ The otolaryngologist / head and neck surgeon encounters thyroid nodules commonly in practice, and an understanding of the diagnostic workup options is important.

Epidemiology

One of the most widely cited epidemiologic studies involves the population study of Framingham, Massachusetts. In this study palpable thyroid nodules were found, in adults between 30 and 59 years of age, in 6.4 % of women and 1.5 % of men. Additionally, the nodule accrual rate was found to be 1.3% at 15 years, or an annual accrual rate of 0.09%³³. However, the prevalence is much higher when assessed by autopsy, palpation at surgery, or by ultrasound. Mazzaferri pooled a number of studies and found that the prevalence of nodules by these methods is approximately ten times that of the prevalence by physical exam¹⁷. One autopsy study noted nodules in 65% of men and 80% of women in the ninth decade. Looking at numerous studies, one can draw a number of conclusions. First of all, thyroid nodules are more common in women. Also, the prevalence of thyroid nodules increases with increasing age. Physical exam alone is far less sensitive than other methods of detecting thyroid nodules, but the importance of nodules found by other methods has generally yet to be determined.

Thyroid cancer occurs at an incidence of approximately 12,000 cases per year with about 1,000 deaths per year. When one looks at autopsy series, however, the incidence of thyroid cancer can be as high as 35%. Currently there is no reliable way to distinguish *a priori* an aggressive thyroid cancer from an indolent one.

Histologically, thyroid cancer occurs as a number of different types. Papillary is the most common, accounting for around 70% of thyroid cancers. Follicular accounts for around 15%, medullary another 5-10%, and anaplastic another 5%. Additionally lymphoma may arise in the thyroid, especially in a setting of Hashimoto's thyroiditis. Metastasis to the thyroid may occur, usually from breast, lung, kidney, gastrointestinal sources, or from melanoma.

Pregnancy

One special circumstance that deserves comment is the thyroid nodule in the pregnant patient. Studies have shown that parity increases the incidence of thyroid nodules- in one study (using ultrasound) from 9.4% of nulliparous women to 25% of parous women³¹. Additionally, other investigators have cited the higher incidence of thyroid carcinoma in pregnant patients in whom a carcinoma arises^{19,26}. Some have reported increased biologic aggression of thyroid cancers in pregnant women. Other authors disagree and feel that pregnancy effects no changes on the pathophysiology of thyroid disease.²⁸ It has been suggested that human chorionic gonadotropin (HCG) may have thyroid-stimulating hormone (TSH) -like activity, acting as a growth promoter. Workup should include a fine-needle aspiration biopsy (FNAB), and perhaps an ultrasound, but radioactive scanning is contraindicated. Some have recommended surgery either before or after, but not during, the third trimester. Should I-131 ablation be needed postoperatively, the mother should avoid breast-feeding during this time. Also, given the potential exacerbating effects of pregnancy on thyroid cancer, some authors advocate avoidance of pregnancy in a woman who has had a thyroid cancer.³

Radiation

Ionizing radiation remains the only unequivocal environmental cause of thyroid cancer. Between the 1920's and the 1950's, an estimated one million Americans received head and neck irradiation for benign disease. Duffy, in 1950, recognized the association of childhood irradiation and thyroid cancer in a young man with thyroid cancer who had had thymic irradiation as an infant.³² This was borne out in other studies, as was the increased incidence of thyroid nodules and thyroid cancer in people exposed to radiation for other reasons. Some dramatic examples include Marshall Islanders accidentally exposed to nuclear fallout and Japanese persons exposed to irradiation from the atomic bombs at Hiroshima and Nagasaki.^{6,27} Persons receiving external irradiation therapeutically (e.g. for cancer) are also at increased risk. Some have found slightly increased risk in certain occupational exposures, such as X-ray technicians. Others have suggested background terrestrial sources or increased celestial sources at altitude as risk factors, but this association has not been demonstrated.²⁶

Children

Children represent a distinct population of thyroid nodules. As noted earlier, irradiation was commonly given in years past for benign conditions. In 1976, the National Institutes of Health (NIH) began a widespread effort to urge notification and examination of individuals exposed to irradiation as children. Some of these individuals and their parents were not aware of the exposure. Some hospitals routinely irradiated the thymus of all infants to prevent crib death. Other conditions treated with radiation include adenotonsillar hypertrophy, acne, eustachian tube dysfunction, bronchitis, hemangiomas, and tinea capitis.

Given this background, it is notable that in the 1950's approximately 70% of thyroid nodules in children represented cancer, whereas currently that number is closer to 20%. Ten percent of all thyroid cancer occurs before age 21, and thyroid cancer represents 1.5-2% of all pediatric malignancies.

Special mention should be made of medullary thyroid carcinoma (MTC). This neoplasm has been shown to have germ-line transmission, either alone (familial MTC), or as part of the multiple endocrine neoplasia type 2 syndromes (MEN2A and MEN 2B). Previously screened for with calcitonin levels following calcium-pentagastrin stimulation, this has been replaced with DNA screening for the RET proto-oncogene found on chromosome 10. Children with a family history positive for MTC who test positive for RET are recommended to undergo a prophylactic thyroidectomy in the first few years of life.

History & Physical

History

As with every clinical encounter, all new thyroid nodule patients begin with a history and physical. Beyond the usual questions, certain questions specific to the history of the thyroid patient should be included. Age less than 20 or greater than 60 has been suggested as having a higher incidence of cancer in a thyroid nodule. Gender is important- a nodule in a man is more likely to be cancer (although cancer overall is more common in women). Exposure to radiation is an important history item. Symptoms referable to hyper- or hypo- thyroidism should be elicited. Rapid enlargement of a mass is generally considered a poor sign unless there is associated pain which may indicate hemorrhage into a nodule.

Special history questions include history of Gardner's or Cowden's syndromes, as these have been linked to a higher incidence of thyroid carcinoma. As discussed previously, family history of medullary thyroid carcinoma is important to know in a child. Additionally, some have suggested family history of other types of thyroid cancer to be a soft risk factor. Hashimoto's thyroiditis can predispose a person to lymphoma, so this should be entertained during the history.

Although no element of the history is terribly sensitive or specific for thyroid carcinoma, certain history items may suggest invasion of local structures which, in turn, suggest malignancy. These include dyspnea, hoarseness, and dysphagia. Progressive enlargement and/or other high-risk factors should alert the clinician to the possibility of carcinoma.

Physical

As always, a complete head and neck examination in is order. The thyroid is best examined from behind. Both lobes and the isthmus should be palpated, and the patient should swallow to confirm that any masses are in the thyroid.⁴ Any nodules should be noted, as well as diffuse changes. With respect to the possibility of thyroid cancer, certain things should be emphasized. Vocal cord motion should be checked, and some advocate the use of preoperative videostrobolaryngoscopy to look for subtle abnormalities and for documentation. At our institution, this is not commonly done. It should be noted that the literature indicates that a fair number of benign masses may present with vocal cord paresis. The presence or absence of adenopathy should be noted. Lastly, in a patient with symptoms of hyperthyroidism, the eyes should be checked for exophthalmos and scleral show. Although physical examination is not very sensitive or specific for detecting thyroid cancer, certain findings such as fixation of a mass, induration, vocal cord fixation, adenopathy and stridor should raise the clinician's level of suspicion.

A classic study was done by Hamming *et al* compared physical examination finding to cytological findings obtained by fine-needle aspiration biopsy, ultimately with histological confirmation. In patients who were felt by clinical grounds to have a high suspicion of malignancy there was a 71% prevalence of malignancy. Criteria for high clinical suspicion included rapid growth of tumor, vocal cord fixation, very firm nodule, fixation to adjacent structures, enlarged regional lymph nodes, and distant metastasis. A small subset of patients had two of these findings, and all had malignancy. Patients were stratified to a moderate clinical suspicion if they were younger than 20 or older than 60, had a history of head and neck irradiation, were male with a solitary nodule, had dubious fixation, or had a lesion over four centimeters which was partially cystic. In this group the prevalence of malignancy was 14%. All other patients were considered to have a low clinical suspicion of malignancy, although 11% were ultimately found to have a malignancy.¹²

Workup & Management

After the history and physical, the clinician has a number of tools at his or her disposal for investigating the nature of the nodule. These include serum testing, needle biopsy, and imaging. The precise management of the workup of the thyroid nodule is controversial, balancing individual bias, the clinical picture, patient expectations, clinical availability, and cost-effectiveness. A thorough understanding of the options will allow the clinician to make appropriate decisions in a given clinical encounter.

Serum Testing

Many advocate serum testing of thyroid function as an initial step (although many advocate fine-needle aspiration biopsy as an initial step, others feel that the subgroup of patients who have a hyperfunctional nodule as evidenced by lab and nuclear studies can be safely observed). The single-most important test is an assay of thyrotropin, or thyroid-stimulating hormone (TSH). This alerts the clinician to one of three states: hyperthyroid, euthyroid, or

hypothyroid. Even if a patient is asymptomatic and has a normal level of thyroxine (as assayed by the free T4 or free thyroxine index), a "normal" level of thyroxine in the face of an abnormal TSH is inappropriate. For example, a T4 level within the laboratory range of normal in the face of an elevated TSH indicates subclinical hypothyroidism, as an elevated TSH ought to produce an elevated T4 level, which under normal conditions would feedback and lower the TSH to an appropriate level.

Other serum tests are not generally ordered will be briefly mentioned. In medullary thyroid carcinoma, many would consider calcitonin levels, as well as regular electrolyte tests. Additionally, the RET proto-oncogene remains the test of choice for MTC. If one suspects Hashimoto's thyroiditis, anti-thyroid antibodies can be assayed. Thyroglobulin is a useful assay in the postoperative care of the thyroid cancer patient, as a rising level likely indicates recurrence.

FNAB

Fine-needle aspiration biopsy (FNAB or FNA) is almost universally accepted now as the single most important test in the evaluation of a thyroid nodule. Initially described in the 1920's, it was reintroduced in 1952 by Söderström which led to its use in Scandinavia and then the rest of Europe.^{2,14} It was not until the 1970's, though, that this technique caught on in America. Previous concerns about seeding of malignancy along the needle track have not been borne out clinically, and lower rate of complications, as well as the ease and simplicity, make it a more attractive option than larger bore needle biopsies. Some have also used this technique for the introduction of a sclerosing agent as a therapeutic option for certain thyroid nodules.

Briefly, although techniques vary, somewhere between a 21 and 27 gauge needle is placed within the lesion. Initially aspiration should be attempted, as a purely fluid-filled cyst may be "cured" by this technique. Next, either with or without suction applied, the needle is passed back and forth over a small range until material is collected in the hub. After withdrawal of the needle, the needle is briefly detached to allow air introduction into the syringe (air introduction before the procedure may weaken the suction), and the collected material expelled onto a slide which is then smeared and fixed for cytology. Very small or very large lesions may introduce sampling error, and the accuracy of FNAB is improved by multiple passes. Excessive blood reduces the ability to interpret the material. Skill and experience of the cytopathologist also play a role in the usefulness of the data.

Campbell and Pillsbury evaluated the results of nine different studies in which 912 patients who received FNAB ultimately underwent surgery. They found a range of false-negatives from 0.5% to 11.8% with a pooled rate of 2.4%. As for false-positives, the range was between 0% and 7.1 % with a pooled rate of 1.2%. this translated to an overall accuracy of over 95%, a result which correlates with other published data.^{2,7}

Results from FNAB can be categorized as benign, malignant, insufficient/inadequate, and indeterminate/suspicious. The latter occurs in certain situations, a common example being that of follicular neoplasm. The differentiation between follicular adenoma and carcinoma is made by evidence of capsular invasion, a finding that has to be made histologically. Largely cystic

aspirations are often hypocellular and result in a "insufficient" diagnosis. Many recommend re-aspiration of these cysts (if they are not gone), and if a second aspiration is inadequate then progressing to surgery.

Imaging -- Nuclear Medicine

The thyroid scan was a mainstay in the evaluation of the thyroid nodule prior to the widespread use of FNAB. The concept is based on the observation in 1939 that malignant thyroid tissue only uptakes a small amount of iodine as compared to normal thyroid tissue.² This property was exploited by administering a radioactive iodine tracer and then using the radiation to image the thyroid gland. Nodules could be classified by their uptake of tracer as "hot", "warm", and "cold". It was thought that cold nodules were more likely to be cancerous. Although true, the sensitivity and specificity of this technique has relegated it to second-tier status behind FNAB.

A brief discussion of the tracers is in order. The two most common tracers are iodine and technetium. These are used to image papillary and follicular carcinoma. Iodine occurs in a number of isotopes, with ¹²⁷I being the common stable form. ¹²⁵I had a role in the past, but is no longer used. The two commonly-used isotopes are ¹²³I and ¹³¹I. ¹²³I is manufactured in a cyclotron and has a half-life of 13.3 hours. Its gamma radiation has optimal imaging characteristics, but it is expensive and difficult to obtain, and it does not have a long shelf life. ¹³¹I, on the other hand, is a product of nuclear fission and has a half-life of 8.1 days. It is cheap and easily obtained. It has both beta and gamma emissions, and this coupled with its longer half-life mean a larger radiation exposure to the patient. Also its gamma emissions make for suboptimal pictures compared to ¹²³I. On the other hand, this isotope is the preferred agent for radioiodine ablation of residual or metastatic thyroid carcinoma.

^{99m}Tc is a product of beta decay of ⁹⁹Molybdenum. The "m" refers to a metastable state that has a relatively long half-life. Thus, the ^{99m}Tc exists at a higher energy state until it undergoes isomeric gamma decay to ⁹⁹Tc. Its half-life is six hours, and it is readily available. Its characteristics are such that images can be obtained shortly after administration. This has made it popular for thyroid clinics in which the patient can go get imaged and return to clinic. The technetium is trapped by the thyroid but not organified (processed into hormone) as iodine is. Thus, a "hot" technetium nodule is not the same as a hyperfunctional thyroid nodule (a distinction of which to be aware when reading the literature). Therefore, any hot nodule on technetium scanning should undergo confirmation by iodine scanning. Occasionally there is a discrepancy, and this is referred to as a discordant nodule. A discordant nodule has a higher cancer risk than a cold nodule, and should be managed with appropriate vigilance.

Other isotopes are sometimes used. Thallium has the advantage that one does not have to be off of thyroid hormone to undergo testing. However, its sensitivity and specificity are suboptimal, and it is expensive. It may have a role in detecting metastasis in non-iodine avid tumors (ones with poor iodine sensitivity) or in patients with a large reservoir of iodine in their body (e.g. after contrasted CT). Additionally, it sometimes will concentrate in medullary carcinoma which can then be imaged. ⁶⁷Gallium is usually used as a non-specific marker for inflammation, but in thyroid scanning it is occasionally used to image anaplastic carcinoma or

lymphoma. ^{99m}Tc -Sestamibi concentrates in the mitochondria and is usually used for cardiac imaging. Hürthle cell neoplasms, which are rich in mitochondria, are poorly imaged with conventional techniques but are imaged well with sestamibi. Other agents are infrequently used, either in special or investigational circumstances.

The utility of thyroid scanning is currently limited. A review of 4457 patients with thyroid nodules who underwent imaging and surgery revealed that the prevalence of cold, warm, and hot nodules was 84, 10, and 5.5% respectively. Of the cold nodules, 16% were malignant. Of the warm nodules, 10% were malignant. Of the hot nodules, 4% were malignant.² This data did not note the thyroid status of the patients. Many authors currently recommend thyroid scans for hyperthyroid patients (by TSH testing) with the belief that the prevalence of cancer in hot nodules is low in these patients who may be safely followed. Also, some authors recommend scanning nodules which are indeterminate by FNAB and following clinically the hot nodules. Whatever the indication, almost all authors recommend further workup for cold or warm nodules. One final clinical note -- a hyperthyroid patient with a nodule (if his or her physician follows hot nodules clinically) should still undergo a scan, as cold nodules may arise against a background of diffuse thyroid hyperfunction.

Imaging -- Ultrasound

Ultrasound has emerged as a diverse modality which has utility in the management of thyroid disease. Perhaps its most widely used role is that of localization for FNAB. This occurs when there is a small nodule that is difficult to reliably sample, or in the case of the non-palpable nodule. The non-palpable nodule by definition has been located through some other technique. Since ultrasound has a lower limit of resolution of 2-3mm, determining the management of incidentally-located non-palpable nodules is controversial, given the high prevalence of nodules. One author recommends ultrasound-guided FNAB for patients with a family history of thyroid cancer, a history of radiation exposure, a nodule greater than 1.0cm, or a nodule with suspicious ultrasonographic features. Absent these, he recommends serial ultrasonography.³⁴ Suspicious ultrasonographic features include presence of a halo, irregular border, presence of cystic components, presence of calcifications, heterogenous echo pattern, or extrathyroidal extension. No findings are definitive but these should be weighed in the whole clinical picture.

Ultrasound may also be used to serially follow a lesion (i.e. after suppression). It is useful for determining cystic versus solid, and in children with hypothyroidism or with a thyroglossal duct cyst it is a good screen for the presence of normal thyroid. Also, pregnant women cannot undergo radioactive imaging, and ultrasound may play a larger role in their management. Although it can aid in the distinction of a solitary nodule from a multinodular goiter, this distinction is somewhat academic as most now feel that the risks of a dominant nodule in a multinodular goiter are the same as the risks of a solitary nodule.

Imaging -- Other

Other modalities have a limited role in thyroid disease. Plain films may incidentally show tracheal deviation. Calcifications on plain films are sometimes associated with thyroid carcinoma, but this is neither sensitive or specific. Computed tomography (CT) and magnetic

resonance imaging (MRI) may play adjunctive roles, especially if there is bulky regional neck metastasis. One should keep in mind that the contrast agent for CT scanning is iodinated and may adversely affect the postoperative ability to treat with ¹³¹I. Non-contrasted CT may be better, if feasible. Positron emission tomography (PET) scanning is not widely available and is still largely investigational.

Thyroid Suppression

Thyroid suppression has been utilized in the past in the management of thyroid nodules. This practice is based on the idea that benign nodules would be TSH-responsive whereas malignant nodules would not. Dropping the TSH with exogenous thyroxine would shrink benign nodules but not malignant ones. Unfortunately, this theory does not translate into reality very well. Five placebo-controlled trials of suppression for benign nodules suggest (although not conclusively) that there is no shrinkage with treatment.¹³ Even if there is, some nodules later shown to be malignant have been shown to shrink with suppression. Additionally, suppression carries with it the risk of increased osteoporosis, although this has not been shown to clinically translate into increased fractures. Although a short trial of suppression may be reasonable in selected cases,^{13,28} many authors do not see a role for suppression in the management of nodular thyroid disease.^{9,14,17} A notable exception is individuals who received childhood irradiation to the head and neck, as suppression has been shown to decrease the incidence of nodules dramatically.¹⁰

Management

Ultimately, then the management of a thyroid nodule should include a history and physical, followed by further testing. Most patients will need an FNAB and a TSH. Benign nodules (by FNA) should be followed and re-aspirated if they do not regress.²⁸ A benign nodule in a hyperthyroid patient may be considered for scan, and if the scan is hot considered for clinical follow-up, otherwise more testing (repeat FNA versus surgery). Inadequate aspirations should be re-aspirated, and if still inadequate should be considered for surgery. Indeterminate aspirations, although scanned by some, are usually considered for surgery in our institution (one problem in making a uniform algorithm being that indeterminate and suspicious are in the same category -- clinical management may depend on discussion with the cytopathologist as to the specific findings). Constant vigilance is key to optimum outcomes, and a thorough understanding of the ideas behind algorithmic approaches permit flexibility when the patient does not fit nicely into the algorithm. For example, one author who writes extensively on this topic recommends serious consideration of surgery for any male over 60, regardless of the FNAB, due to the high pretest probability of malignancy.¹⁸ This recommendation, although itself a generalization, is based not in a "one-size-fits-all" approach to management but based upon a thorough understanding of the scientific basis behind the management of a thyroid nodule that the individual clinician can apply to individual patients for optimum patient care.

Bibliography

- 1) Ashcraft MW, vanHerle AJ. Management of thyroid nodules I: history and physical examination, blood tests, x-ray tests, and ultrasonography. *Head Neck Surg* 1981;3:216-30.
- 2) Ashcraft MW, vanHerle AJ. Management of thyroid nodules II: scanning techniques, thyroid suppressive therapy, and fine needle aspiration. *Head Neck Surg* 1981;3:297-322.
- 3) Asteris GT, DeGroot LJ. Thyroid cancer: relationship to radiation exposure and to pregnancy. *J Reprod Med* 4:209-16, 1976.
- 4) Bates B. *A Guide to Physical Examination and History Taking, 5th Edition*. Lippincott: Philadelphia, 1991.
- 5) Benjamin B, Bingham B, Hawke M, Stammberger H. *A Color Atlas of Otorhinolaryngology*. Lippincott: Philadelphia, 1995.
- 6) Burch HB. Evaluation and management of the solid thyroid nodule. *Endocrinology and Metabolism Clinics of North America*. 24(4): 663-703, 1995 Dec.
- 7) Campbell JP, Pillsbury HC. Management of the thyroid nodule. *Head Neck* 11:414-25, 1989 Sep/Oct.
- 8) Doherty CM, Shindo ML, Rice DH, Montero M, Mestman JH. Management of thyroid nodules during pregnancy. *Laryngoscope* 105:251-5, Mar 1995.
- 9) Dwarakanathan A. Suppressive therapy for thyroid nodules. *Arch Int Med* 158(13)1470-2, 1998.
- 10) Fogelfeld L, Wiviott M, Shore-Freedman E, et al. Recurrence of thyroid nodules after surgical removal in patients irradiated in childhood for benign conditions. *N Engl J Med* 320:835-40, 1989.
- 11) From GLA, Lawson VG. Solitary thyroid nodule: concepts in diagnosis and management. In *Thyroid Disease: Endocrinology, Surgery, Nuclear Medicine, and Radiotherapy*, Falk SA, (ed). Lippincott-Raven: Philadelphia, 1997.
- 12) Hamming JF, Goslings BM, Van Steenis GJ, van Ravenswaay Claasen H, Hermans J, Van de Velde CJH. The value of fine-needle aspiration biopsy in patients with nodular thyroid disease divided into groups of suspicion of malignant neoplasms on clinical grounds. *Arch Intern Med* 150:113-6, 1990.
- 13) Hermus AR, Huysmans DA. Treatment of benign nodular thyroid disease. *N Engl J Med* 338:1438-47, 1998.

- 14) Jones M. management of nodular thyroid disease: the challenge remains identifying which palpable nodules are malignant. *British Medical Journal* 323(7308):293-4, 2001
- 15) Kaplan MM, Hamburger JI. Fine-needle biopsy of the thyroid. In *Thyroid Disease: Endocrinology, Surgery, Nuclear Medicine, and Radiotherapy*, Falk SA, (ed). Lippincott-Raven: Philadelphia, 1997.
- 16) LoPresti JS, Singer PA. Physiology of thyroid hormone synthesis, secretion, and transport. In *Thyroid Disease: Endocrinology, Surgery, Nuclear Medicine, and Radiotherapy*, Falk SA, (ed). Lippincott-Raven: Philadelphia, 1997.
- 17) Mazzaferri EL. Management of a solitary thyroid nodule. *New England Journal of Medicine* 1993; 328(8):553-65.
- 18) Mazzaferri EL. Thyroid cancer in thyroid nodules: finding a needle in a haystack. *Am J Med* 93:359-62; 1992.
- 19) McClellan DR, Francis GL. Thyroid cancer in children, pregnant women, and patients with Graves' disease. *Endocrinology and Metabolism Clinics of North America*. 25(1): 27-48, 1996 Mar.
- 20) Mortenson JD, Woolner LB, Bennett WA. Gross and microscopic findings in clinically normal thyroid glands. *J Clin Endocrinol Metab* 15:1270-80, 1955.
- 21) Muller C, Bailey BJ, Pou AM. Thyroid cancer. In *Dr Quinn's Online Textbook* available at www.utmb.edu/oto, 1998 Oct.
- 22) Netter FH. *The CIBA Collection of Medical Illustrations. Volume 4: Endocrine System and Selected Metabolic Diseases*. PH Forsham (Ed). CIBA: New York, 1965.
- 23) Noyek AM, Finkelstein DM, Witterick IJ, Kirsh JC. Diagnostic imaging of the thyroid gland. In *Thyroid Disease: Endocrinology, Surgery, Nuclear Medicine, and Radiotherapy*, Falk SA, (ed). Lippincott-Raven: Philadelphia, 1997.
- 24) Randolph GW. Management of the Thyroid Nodule. *Slide Lecture Series*. American Academy of Otolaryngology - Head and Neck Surgery Foundation, Inc, 1999.
- 25) Ron E, Kleinerman RA, Schneider AB. Thyroid cancer incidence. *Nature* 360:113, 1992.
- 26) Rosen IB, Walfish PG. Pregnancy as a predisposing factor in thyroid neoplasia. *Arch Surg* 121:1287-90, 1986.
- 27) Sarne D, Schneider AB. External radiation and thyroid neoplasia. *Endocrinology and Metabolism Clinics of North America*. 25(1): 181-95, 1996 Mar.

- 28) Schoem SR, Khan A, Wenig B. *Evaluation and management of the thyroid nodule: a practical approach*. Self-Instruction Package (SIPac). American Academy of Otolaryngology - Head and Neck Surgery Foundation, Inc: Alexandria, 1999.
- 29) Singer PA. Clinical approach to thyroid function testing. In *Thyroid Disease: Endocrinology, Surgery, Nuclear Medicine, and Radiotherapy*, Falk SA, (ed). Lippincott-Raven: Philadelphia, 1997.
- 30) Sobel SH, Bramlet R. Iodine-131 treatment of hyperthyroidism. In *Thyroid Disease: Endocrinology, Surgery, Nuclear Medicine, and Radiotherapy*, Falk SA, (ed). Lippincott-Raven: Philadelphia, 1997.
- 31) Struve CW, Haupt S, Ohlen S. Influence of frequency of previous pregnancies on the prevalence of thyroid nodules in women without clinical evidence of thyroid disease. *Thyroid* 3:7-9, 1993.
- 32) Ureles AL, Freedman ZR. Thyroidology -- reflections on twentieth-century history. In *Thyroid Disease: Endocrinology, Surgery, Nuclear Medicine, and Radiotherapy*, Falk SA, (ed). Lippincott-Raven: Philadelphia, 1997.
- 33) Vander JB, Gaston EA, Dawber TR. The significance of nontoxic thyroid nodules. Final report of a 15-year study on the incidence of thyroid malignancy. *Ann Intern Med* 1968;69:537-40.
- 34) Woeber KA. The year in review: the thyroid. *Ann Int Med* 131(12):959-62, 1999 Dec.
- 35) Wilson GA, O'Mara RE. Uptake tests, thyroid, and whole body imaging with isotopes. In *Thyroid Disease: Endocrinology, Surgery, Nuclear Medicine, and Radiotherapy*, Falk SA, (ed). Lippincott-Raven: Philadelphia, 1997.

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