Continuing Controversies in the Management of Thyroid Nodules

M. Regina Castro, MD, and Hossein Gharib, MD

Although thyroid nodules are common, few are malignant and require surgical treatment. A systematic approach to their evaluation is important to avoid unnecessary surgery. Fine-needle aspiration biopsy has resulted in substantial improvements in diagnostic accuracy, cost reductions, and higher malignancy yield at time of surgery. The preferred approach when repeated fine-needle aspiration biopsy fails to yield an adequate specimen remains a challenge. Management of patients with nodules "suspicious for follicular neoplasm" is difficult, since only 15% to 20% of such lesions have been shown to be malignant. Immunohistochemical markers, such as galectin-3 and human bone marrow endothelial cell (HBME-1), have shown promise in preliminary studies. Routine calcitonin measurement in patients with thyroid nodules has been advocated for early detection of medullary thyroid cancer. However, the low frequency of this cancer, coupled with the high cost associated with case detection, has resulted in a lack of general acceptance of this recommendation.

Ann Intern Med. 2005;142:926-931. www.annals.org
For author affiliations, see end of text.

Thyroid nodules are very common, with an estimated prevalence that ranges from 4% by palpation (1) to 67% by ultrasonography (2). Autopsy data from patients with no history of thyroid disease report a prevalence of 50% (3). The Framingham Study estimated the annual incidence, by palpation, at 0.09% (1), which translates into approximately 300 000 new nodules in the United States in 2005. With the use of ultrasonography for evaluating thyroid and nonthyroid neck disease, the incidental finding of unsuspected thyroid nodules has dramatically increased. Thyroid "incidentalomas" have been reported in up to 40% of patients undergoing examination for suspected parathyroid disease (4) and in 13% of patients undergoing carotid ultrasonography (5). Because thyroid nodules are common but only malignant or large symptomatic nodules require surgery, a systematic approach to their evaluation is important to avoid unnecessary surgery.

Nondiagnostic Smears: Role of Ultrasonography-Guided Fine-Needle Aspiration

Fine-needle aspiration (FNA) biopsy of thyroid nodules is an accurate and cost-effective method for distinguishing benign from malignant nodules. Most centers using this procedure have achieved a 35% to 75% reduction in the number of patients requiring surgery, while still doubling or tripling the malignancy yield at thyroidectomy (6–9). Despite its effectiveness and diagnostic accuracy, the "nondiagnostic" smear (approximately 15% of all specimens) remains a management dilemma (10–12). Although criteria to consider a specimen "adequate" vary among institutions (13–15), a commonly accepted definition includes 6 or more groups of 10 to 20 well-preserved follicular epithelial cells per group on at least 2 slides (13). Inadequate sampling has been cited as the most common cause of false-negative biopsy results (16).

Repeated FNA, under ultrasonography guidance, can reduce the rate of nondiagnostic smears from 15% to 3% (11, 12, 17) (**Table 1**). Ultrasonography guidance is particularly valuable in small nodules (<1.5 cm) and is essential for nonpalpable nodules, helping to ensure proper placement of the needle tip for precise sampling (**Figure 1**). In complex or cystic nodules, ultrasonography guidance helps direct the needle tip to the solid component, avoiding areas of central necrosis, which often yield inadequate specimens (18) (**Figure 2**). In patients with multiple nodules, targets for biopsy, besides the dominant nodule, include hypoechoic nodules and those containing microcalcifications, vascular spots, or irregular borders, which are features associated with increased risk for malignancy (19).

"Suspicious" Cytology

The finding of "suspicious" cytology on FNA biopsy of thyroid nodules is a challenging dilemma for the endocrinologist (20–22). This category includes cytologic findings commonly called "follicular neoplasms," which include hyperplastic nodules, follicular adenomas, follicular carcinomas, and follicular variants of papillary carcinoma (23) (**Table 2**). Approximately 10% of all FNA specimens fall into this category (10). The overlapping features in this group make the microscopic distinction difficult, leading most clinicians to recommend surgical excision for a definitive diagnosis. Because only 15% to 20% of these lesions are malignant (21, 24, 25), up to 85% of patients in this subgroup may undergo unnecessary surgery.

Many studies have attempted to determine predictors of malignancy in this subgroup of patients, but results are discordant (26–29). Electron microscopy, flow cytometry, and immunohistochemical and genetic markers have been evaluated to determine whether they improve diagnostic reliability in this subgroup. Although overall results have been generally disappointing, 2 of these markers (human bone marrow endothelial cell [HBME-1] and galectin-3) have shown promise in their ability to predict malignancy

See also:

Web-Only
Conversion of figures and tables into slides

Table 1. **Comparison between Palpation- and Ultrasonography-Guided Fine-Needle Aspiration***

Author, Year (Reference)	Patients (p-FNA/US-FNA), *n (n/n)*	Failure Rate (Nondiagnostic), %		Sensitivity (Specificity), % (%)		Cancer Yield at Time of Surgery, %	
		p-FNA	US-FNA	p-FNA	US-FNA	p-FNA	US-FNA
Carmeci et al., 1998 (11)	497 (370/127)	16	7	89 (69)	100 (100)	40	59
Danese et al., 1998 (12)	9683 (4986/4697)	8.7	3.5	92 (69)	98 (71)	16	19

*p-FNA = palpation-guided fine-needle aspiration biopsy; US-FNA: ultrasonography-guided fine-needle aspiration biopsy.

and their potential for ease-of-use in any laboratory or in academic or community settings (30).

The HBME-1 is a monoclonal antibody developed against the microvillous surface of mesothelial cells and subsequently applied to the diagnosis of malignant thyroid conditions (30). In a study of 463 benign and malignant thyroid tumors, strongly positive staining was seen in most tumor cells of all papillary (145 of 145) and follicular (27 of 27) thyroid carcinomas, and no reactivity or only focal staining was observed in one third of cases of nodular goiter or papillary hyperplasia (31).

Galectin-3, a protein involved in the regulation of cell–cell and cell–matrix interactions, is typically expressed only in malignant transformed thyroid cells (32, 33). This differential expression has allowed the use of this immunohistochemical marker in the evaluation of thyroid tumors. Bartolazzi and colleagues (34) conducted a retrospective analysis of 618 tissue specimens and 165 cell blocks and a prospective analysis of 226 FNA specimens. In the retrospective review of surgical specimens, 94% of 311 malignant cases stained positive for galectin-3. Fewer than 6 of 201 (3%) papillary carcinomas did not express this marker. Thirty-seven of forty (93%) minimally invasive follicular thyroid carcinomas were positive for galectin-3, and this marker was not expressed in any case of nodular hyperplasia or thyroiditis.

Bartolazzi and colleagues' prospective analysis focused on 90 cases with inconclusive conventional cytology, where the addition of galectin-3 allowed the correct identification of all malignant nodules. The sensitivity of galectin-3 for detecting malignancy in that study was 100%, specificity was 98%, positive predictive value was 92%, negative predictive value was 100%, and overall diagnostic accuracy was 99%.

Micronodules and Microcarcinomas

The advent of high-resolution ultrasonography has led to the discovery of small, asymptomatic, and previously unrecognized thyroid nodules. These thyroid incidentalomas, usually smaller than 1.5 cm, are often diagnosed during ultrasonographic evaluation for nonthyroid neck disease, posing a management dilemma for the clinician.

Using ultrasonography, several studies have estimated the prevalence of thyroid nodules in the general population

Figure 1. **Ultrasonography-guided fine-needle aspiration with needle tip accurately placed in the nodule.**

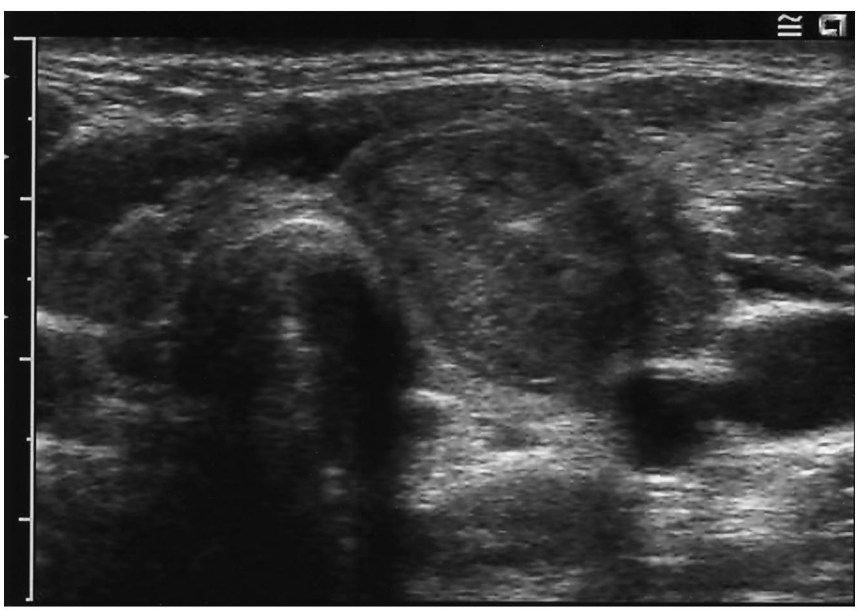

Figure 2. **Cystic lesion.**

The lesion was nondiagnostic on direct fine-needle aspiration and benign by ultrasonography-guided fine-needle aspiration.

as between 19% and 35% (35, 36). Most of these nodules are benign (37). In the absence of features suggestive of malignancy (19), observation has been recommended for incidentalomas smaller than 1 cm and ultrasonography-guided FNA has been recommended for larger nodules or those with suspicious ultrasonographic appearance.

Papillary microcarcinomas are being increasingly diagnosed at earlier stages because of the widespread use of high-resolution ultrasonography, resulting in reduced metastatic lesions and improved 5-year survival (96%) (38). An autopsy study from Finland found a prevalence of occult papillary thyroid cancer of 36% (39). The prevalence of clinically apparent thyroid cancer is only 0.1% in adults between 50 and 70 years of age (40), and thyroid cancer accounts for only 0.3% of cancer deaths in the United States annually (41). Hence, most types of subclinical cancer will never become apparent. A study of 162 patients who elected close follow-up without surgical intervention for FNA-proven papillary microcarcinoma showed that more than 70% of these tumors did not change in size over a median follow-up of up to 5 years (42). A retrospective study from Japan demonstrated nodal metastatic lesions in up to 60% of patients without palpable cervical adenopathy who underwent thyroidectomy with prophylactic node dissection for papillary microcarcinoma (43).

Is total or near-total thyroidectomy warranted in this group of patients, or would lobectomy be sufficient? Lobectomy may preserve thyroid function and results in lower incidence of hypoparathyroidism and recurrent laryngeal nerve injury. However, Farkas and colleagues (44) showed that approximately 50% of patients will require L-thyroxine replacement after lobectomy and, ultimately, most will need this therapy. The rate of permanent hypoparathyroidism and laryngeal nerve injury is very low in the hands of experienced surgeons. Papillary carcinoma is frequently multifocal, with a high incidence of local metastatic lesions at diagnosis (42, 43, 45–47). Therefore, total or near-total thyroidectomy is often recommended (45, 47, 48). Several studies have shown higher recurrence in patients treated with lobectomy compared with those treated with total thyroidectomy (45, 49). Other studies argue that such aggressive surgery is not warranted (42, 50). Whether completion thyroidectomy should be performed for microcarcinomas found incidentally after lobectomy for suspected benign disease remains controversial (50–52).

Routine Calcitonin Measurement

Medullary thyroid carcinoma represents approximately 5% of all malignant thyroid nodules. Most (75%) are sporadic, with the remainder occurring as part of either familial medullary thyroid cancer or multiple endocrine neoplasia type 2 (MEN-2) syndromes. When medullary thyroid cancer presents as nodular disease, it has usually metastasized to cervical nodes or distant sites; early diagnosis and total thyroidectomy offer the best chance for cure (53). In 1994, Pacini and colleagues (54) recommended routine calcitonin measurement in patients with thyroid nodules to screen for medullary thyroid cancer. Since then, several authors have supported (55–60) or refuted (61) this. Studies have estimated that 0.4% to 1.37% of patients presenting with thyroid nodules have medullary thyroid cancer (54–56, 60, 62). Most authors agree that medullary thyroid cancer should be strongly suspected if basal serum calcitonin levels are markedly elevated (>28.57 pmol/L) and that surgery will probably be necessary (58, 63, 64). Mild or moderate elevations in basal serum calcitonin levels of 2.85 to 28.57 pmol/L are considered a "gray zone" (61); among several series, values in this range were predictive of medullary thyroid cancer in only 13% of cases (61, 64). No absolute threshold value for basal calcitonin discriminates between benign and malignant disease.

Table 2. **Suspicious Fine-Needle Aspiration Results in 2175 Smears with 73% Tissue Examination (1980–2001) at the Mayo Clinic***

Cytology†	Histology, *n*	Malignant Tumors, *n (%)*
Follicular neoplasm	561	83 (15)
Hürthle cell neoplasm	548	77 (14)
Papillary carcinoma	489	318 (65)
Total	1598	478 (29)

* Data from Sebo T and Gharib H (unpublished data).
† Labeled by cytopathologist as "suspicious for" follicular neoplasm, Hürthle cell neoplasm, or papillary thyroid carcinoma.

In 1997, Vierhapper and colleagues (57) estimated the cost of detecting a new case of C-cell hyperplasia or medullary thyroid cancer at approximately $3000 (or $6000 if only malignant cases were considered). Serum calcitonin measurement cost $35 at their institution. The average cost of this assay in the United States is $100 (59). Given an estimated prevalence of medullary thyroid cancer of approximately 0.5% (54–56, 60), the cost of screening per case detected would approach $20 000. Since many cases in the gray zone will require additional testing with pentagastrin stimulation (no longer available in the United States) or the short calcium infusion test (which at our institution costs approximately $280), the costs of routine screening would increase dramatically.

Treatment of Benign Thyroid Nodules

Because thyroid-stimulating hormone (TSH) has been regarded as a growth factor for thyroid epithelial cells (65, 66), treatment with L-thyroxine in doses sufficient to suppress TSH has been used for years to prevent or reduce growth of thyroid nodules. However, its effectiveness remains controversial.

Several studies have reported that suppressive L-thyroxine therapy results in statistically significant reduction in nodule volume (67–72). Other studies do not support this finding (73, 74). These discrepancies are due to several factors, including lack of control groups or randomization in some studies, the heterogeneous group of patients evaluated (single nodule vs. multinodular goiter), variable treatment doses and duration of therapy, different definitions of response to treatment, level of TSH suppression, and method used to assess nodule volume. Several meta-analyses evaluating the effectiveness of such therapy have yielded conflicting results (71, 75, 76), although most observe at least a trend toward reduction in nodule volume.

Conclusions and Recommendations

Thyroid nodules are usually benign. Only malignant or large symptomatic nodules require surgical excision. Fine-needle aspiration biopsy, guided by ultrasonography when possible, results in substantial reduction of unnecessary surgery. When FNA results are inconclusive, clinical judgment must be used. In patients with multinodular goiter, selecting the target for biopsy may be challenging. Nodules with ultrasonographic features associated with increased risk for malignancy (19) should be considered, and we recommend periodic follow-up with ultrasonography. Nodules that demonstrate substantial growth should be considered for repeated biopsy. Despite its utility in thyroid nodule management, ultrasonography has added another level of complexity by revealing incidental, nonpalpable nodules, which pose another clinical dilemma.

The effectiveness of L-thyroxine suppressive therapy in reducing nodule volume remains controversial. Because such therapy has been associated with adverse cardiovascular (77) and skeletal effects (78, 79), we advise a careful risk–benefit assessment before recommending this treatment.

From the Mayo Clinic College of Medicine, Rochester, Minnesota.

Potential Financial Conflicts of Interest: None disclosed.

Requests for Single Reprints: M. Regina Castro, MD, Mayo Clinic, 200 First Street SW, Rochester, MN 55902; e-mail, castro.regina@mayo.edu.

Current author addresses are available at www.annals.org.

References

1. **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. 1968;69:537-40. [PMID: 5673172]
2. **Ezzat S, Sarti DA, Cain DR, Braunstein GD.** Thyroid incidentalomas. Prevalence by palpation and ultrasonography. Arch Intern Med. 1994;154:1838-40. [PMID: 8053752]
3. **Mortensen JD, Woolner LB, Bennett WA.** Gross and microscopic findings in clinically normal thyroid glands. J Clin Endocrinol Metab. 1955;15:1270-80. [PMID: 13263417]
4. **Reading CC, Charboneau JW, James EM, Karsell PR, Purnell DC, Grant CS, et al.** High-resolution parathyroid sonography. AJR Am J Roentgenol. 1982; 139:539-46. [PMID: 6981321]
5. **Carroll BA.** Asymptomatic thyroid nodules: incidental sonographic detection. AJR Am J Roentgenol. 1982;138:499-501. [PMID: 6978000]
6. **Werk EE Jr, Vernon BM, Gonzalez JJ, Ungaro PC, McCoy RC.** Cancer in thyroid nodules. A community hospital survey. Arch Intern Med. 1984;144: 474-6. [PMID: 6703815]
7. **Pepper GM, Zwickler D, Rosen Y.** Fine-needle aspiration biopsy of the thyroid nodule. Results of a start-up project in a general teaching hospital setting. Arch Intern Med. 1989;149:594-6. [PMID: 2919935]
8. **Asp AA, Georgitis W, Waldron EJ, Sims JE, Kidd GS 2nd.** Fine needle aspiration of the thyroid. Use in an average health care facility. Am J Med. 1987;83:489-93. [PMID: 3661585]
9. **Hamburger JI.** Consistency of sequential needle biopsy findings for thyroid nodules. Management implications. Arch Intern Med. 1987;147:97-9. [PMID: 3800535]
10. **Gharib H, Goellner JR.** Fine-needle aspiration biopsy of the thyroid: an appraisal. Ann Intern Med. 1993;118:282-9. [PMID: 8420446]
11. **Carmeci C, Jeffrey RB, McDougall IR, Nowels KW, Weigel RJ.** Ultrasound-guided fine-needle aspiration biopsy of thyroid masses. Thyroid. 1998;8: 283-9. [PMID: 9588492]
12. **Danese D, Sciacchitano S, Farsetti A, Andreoli M, Pontecorvi A.** Diagnostic accuracy of conventional versus sonography-guided fine-needle aspiration biopsy of thyroid nodules. Thyroid. 1998;8:15-21. [PMID: 9492148]
13. **Goellner JR, Gharib H, Grant CS, Johnson DA.** Fine needle aspiration cytology of the thyroid, 1980 to 1986. Acta Cytol. 1987;31:587-90. [PMID: 3673463]
14. **Hamburger JI, Husain M.** Semiquantitative criteria for fine-needle biopsy diagnosis: reduced false-negative diagnoses. Diagn Cytopathol. 1988;4:14-7. [PMID: 3378485]
15. **MacDonald L, Yazdi HM.** Nondiagnostic fine needle aspiration biopsy of the thyroid gland: a diagnostic dilemma. Acta Cytol. 1996;40:423-8. [PMID: 8669173]
16. **Hamburger JI, Husain M, Nishiyama R, Nunez C, Solomon D.** Increasing the accuracy of fine-needle biopsy for thyroid nodules. Arch Pathol Lab Med. 1989;113:1035-41. [PMID: 2774855]
17. **Takashima S, Fukuda H, Kobayashi T.** Thyroid nodules: clinical effect of ultrasound-guided fine-needle aspiration biopsy. J Clin Ultrasound. 1994; 22:535-42. [PMID: 7806661]
18. **Baskin HJ.** Ultrasound-guided fine-needle aspiration biopsy of thyroid nodules and multinodular goiters. Endocr Pract. 2004;10:242-5. [PMID: 15310533]

19. **Papini E, Guglielmi R, Bianchini A, Crescenzi A, Taccogna S, Nardi F, et al.** Risk of malignancy in nonpalpable thyroid nodules: predictive value of ultrasound and color-Doppler features. J Clin Endocrinol Metab. 2002;87:1941-6. [PMID: 11994321]
20. **Hamburger JI, Hamburger SW.** Fine needle biopsy of thyroid nodules: avoiding the pitfalls. N Y State J Med. 1986;86:241-9. [PMID: 3520410]
21. **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. 1984;101:25-8. [PMID: 6547282]
22. **Ridgway EC.** Clinical review 30: clinician's evaluation of a solitary thyroid nodule. J Clin Endocrinol Metab. 1992;74:231-5. [PMID: 1730801]
23. **Greaves TS, Olvera M, Florentine BD, Raza AS, Cobb CJ, Tsao-Wei DD, et al.** Follicular lesions of thyroid: a 5-year fine-needle aspiration experience. Cancer. 2000;90:335-41. [PMID: 11156516]
24. **Mazzaferri EL.** Management of a solitary thyroid nodule. N Engl J Med. 1993;328:553-9. [PMID: 8426623]
25. **Burch HB.** Evaluation and management of the solid thyroid nodule. Endocrinol Metab Clin North Am. 1995;24:663-710. [PMID: 8608777]
26. **Tuttle RM, Lemar H, Burch HB.** Clinical features associated with an increased risk of thyroid malignancy in patients with follicular neoplasia by fine-needle aspiration. Thyroid. 1998;8:377-83. [PMID: 9623727]
27. **Raber W, Kaserer K, Niederle B, Vierhapper H.** Risk factors for malignancy of thyroid nodules initially identified as follicular neoplasia by fine-needle aspiration: results of a prospective study of one hundred twenty patients. Thyroid. 2000;10:709-12. [PMID: 11014317]
28. **Schlinkert RT, van Heerden JA, Goellner JR, Gharib H, Smith SL, Rosales RF, et al.** Factors that predict malignant thyroid lesions when fine-needle aspiration is "suspicious for follicular neoplasm". Mayo Clin Proc. 1997;72:913-6. [PMID: 9379692]
29. **Cersosimo E, Gharib H, Suman VJ, Goellner JR.** "Suspicious" thyroid cytologic findings: outcome in patients without immediate surgical treatment. Mayo Clin Proc. 1993;68:343-8. [PMID: 8455392]
30. **Raphael SJ.** The meanings of markers: ancillary techniques in diagnosis of thyroid neoplasia. Endocr Pathol. 2002;13:301-11. [PMID: 12665648]
31. **Miettinen M, Kärkkäinen P.** Differential reactivity of HBME-1 and CD15 antibodies in benign and malignant thyroid tumours. Preferential reactivity with malignant tumours. Virchows Arch. 1996;429:213-9. [PMID: 8972756]
32. **Xu XC, el-Naggar AK, Lotan R.** Differential expression of galectin-1 and galectin-3 in thyroid tumors. Potential diagnostic implications. Am J Pathol. 1995;147:815-22. [PMID: 7677193]
33. **Gasbarri A, Martegani MP, Del Prete F, Lucante T, Natali PG, Bartolazzi A.** Galectin-3 and CD44v6 isoforms in the preoperative evaluation of thyroid nodules. J Clin Oncol. 1999;17:3494-502. [PMID: 10550147]
34. **Bartolazzi A, Gasbarri A, Papotti M, Bussolati G, Lucante T, Khan A, et al.** Application of an immunodiagnostic method for improving preoperative diagnosis of nodular thyroid lesions. Lancet. 2001;357:1644-50. [PMID: 11425367]
35. **Woestyn J, Afschrift M, Schelstraete K, Vermeulen A.** Demonstration of nodules in the normal thyroid by echography. Br J Radiol. 1985;58:1179-82. [PMID: 3916164]
36. **Bruneton JN, Balu-Maestro C, Marcy PY, Melia P, Mourou MY.** Very high frequency (13 MHz) ultrasonographic examination of the normal neck: detection of normal lymph nodes and thyroid nodules. J Ultrasound Med. 1994; 13:87-90. [PMID: 7932966]
37. **Tan GH, Gharib H.** Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. Ann Intern Med. 1997;126:226-31. [PMID: 9027275]
38. **Chow SM, Law SC, Au SK, Mang O, Yau S, Yuen KT, Lau WH.** Changes in clinical presentation, management and outcome in 1348 patients with differentiated thyroid carcinoma: experience in a single institute in Hong Kong, 1960-2000. Clin Oncol (R Coll Radiol). 2003;15:329-36. [PMID: 14524486]
39. **Harach HR, Franssila KO, Wasenius VM.** Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. Cancer. 1985;56:531-8. [PMID: 2408737]
40. **Feldman AR, Kessler L, Myers MH, Naughton MD.** The prevalence of cancer. Estimates based on the Connecticut Tumor Registry. N Engl J Med. 1986;315:1394-7. [PMID: 3773965]
41. **Jemal A, Tiwari RC, Murray T, Ghafoor A, Samuels A, Ward E, et al.** Cancer statistics, 2004. CA Cancer J Clin. 2004;54:8-29. [PMID: 14974761]
42. **Ito Y, Uruno T, Nakano K, Takamura Y, Miya A, Kobayashi K, et al.** An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. Thyroid. 2003;13:381-7. [PMID: 12804106]
43. **Wada N, Duh QY, Sugino K, Iwasaki H, Kameyama K, Mimura T, et al.** Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. Ann Surg. 2003;237:399-407. [PMID: 12616125]
44. **Farkas EA, King TA, Bolton JS, Fuhrman GM.** A comparison of total thyroidectomy and lobectomy in the treatment of dominant thyroid nodules. Am Surg. 2002;68:678-82; discussion 682-3. [PMID: 12206601]
45. **Baudin E, Travagli JP, Ropers J, Mancusi F, Bruno-Bossio G, Caillou B, et al.** Microcarcinoma of the thyroid gland: the Gustave-Roussy Institute experience. Cancer. 1998;83:553-9. [PMID: 9690549]
46. **Chow SM, Law SC, Chan JK, Au SK, Yau S, Lau WH.** Papillary microcarcinoma of the thyroid—prognostic significance of lymph node metastasis and multifocality. Cancer. 2003;98:31-40. [PMID: 12833452]
47. **Pellegriti G, Scollo C, Lumera G, Regalbuto C, Vigneri R, Belfiore A.** Clinical behavior and outcome of papillary thyroid cancers smaller than 1.5 cm in diameter: study of 299 cases. J Clin Endocrinol Metab. 2004;89:3713-20. [PMID: 15292295]
48. **Hay ID, Grant CS, van Heerden JA, Goellner JR, Ebersold JR, Bergstralh EJ.** Papillary thyroid microcarcinoma: a study of 535 cases observed in a 50-year period. Surgery. 1992;112:1139-46; discussion 1146-7. [PMID: 1455316]
49. **Hay ID, McConahey WM, Goellner JR.** Managing patients with papillary thyroid carcinoma: insights gained from the Mayo Clinic's experience of treating 2,512 consecutive patients during 1940 through 2000. Trans Am Clin Climatol Assoc. 2002;113:241-60. [PMID: 12053713]
50. **Noguchi S, Yamashita H, Murakami N, Nakayama I, Toda M, Kawamoto H.** Small carcinomas of the thyroid. A long-term follow-up of 867 patients. Arch Surg. 1996;131:187-91. [PMID: 8611077]
51. **Kim ES, Kim TY, Koh JM, Kim YI, Hong SJ, Kim WB, et al.** Completion thyroidectomy in patients with thyroid cancer who initially underwent unilateral operation. Clin Endocrinol (Oxf). 2004;61:145-8. [PMID: 15212657]
52. **Giles Y, Boztepe H, Terzioglu T, Tezelman S.** The advantage of total thyroidectomy to avoid reoperation for incidental thyroid cancer in multinodular goiter. Arch Surg. 2004;139:179-82. [PMID: 14769577]
53. **Wells SA Jr, Baylin SB, Leight GS, Dale JK, Dilley WG, Farndon JR.** The importance of early diagnosis in patients with hereditary medullary thyroid carcinoma. Ann Surg. 1982;195:595-9. [PMID: 7073356]
54. **Pacini F, Fontanelli M, Fugazzola L, Elisei R, Romei C, Di Coscio G, et al.** Routine measurement of serum calcitonin in nodular thyroid diseases allows the preoperative diagnosis of unsuspected sporadic medullary thyroid carcinoma. J Clin Endocrinol Metab. 1994;78:826-9. [PMID: 8157706]
55. **Hahm JR, Lee MS, Min YK, Lee MK, Kim KW, Nam SJ, et al.** Routine measurement of serum calcitonin is useful for early detection of medullary thyroid carcinoma in patients with nodular thyroid diseases. Thyroid. 2001;11:73-80. [PMID: 11272100]
56. **Rieu M, Lame MC, Richard A, Lissak B, Sambort B, Vuong-Ngoc P, et al.** Prevalence of sporadic medullary thyroid carcinoma: the importance of routine measurement of serum calcitonin in the diagnostic evaluation of thyroid nodules. Clin Endocrinol (Oxf). 1995;42:453-60. [PMID: 7621562]
57. **Vierhapper H, Raber W, Bieglmayer C, Kaserer K, Weinhäusl A, Niederle B.** Routine measurement of plasma calcitonin in nodular thyroid diseases. J Clin Endocrinol Metab. 1997;82:1589-93. [PMID: 9141554]
58. **Ozgen AG, Hamulu F, Bayraktar F, Yilmaz C, Tüzün M, Yetkin E, et al.** Evaluation of routine basal serum calcitonin measurement for early diagnosis of medullary thyroid carcinoma in seven hundred seventy-three patients with nodular goiter. Thyroid. 1999;9:579-82. [PMID: 10411120]
59. **Sheppard MC.** Should serum calcitonin be measured routinely in all patients with nodular thyroid disease? Clin Endocrinol (Oxf). 1995;42:451-2. [PMID: 7621561]
60. **Elisei R, Bottici V, Luchetti F, Di Coscio G, Romei C, Grasso L, et al.** Impact of routine measurement of serum calcitonin on the diagnosis and outcome of medullary thyroid cancer: experience in 10,864 patients with nodular thyroid disorders. J Clin Endocrinol Metab. 2004;89:163-8. [PMID: 14715844]
61. **Hodak SP, Burman KD.** The calcitonin conundrum—is it time for routine measurement of serum calcitonin in patients with thyroid nodules? [Editorial] J Clin Endocrinol Metab. 2004;89:511-4. [PMID: 14764754]
62. **Niccoli P, Wion-Barbot N, Caron P, Henry JF, de Micco C, Saint Andre JP, et al.** Interest of routine measurement of serum calcitonin: study in a large series of thyroidectomized patients. The French Medullary Study Group. J Clin Endocrinol Metab. 1997;82:338-41. [PMID: 9024213]

63. **Scheuba C, Kaserer K, Weinhäusl A, Pandev R, Kaider A, Passler C, et al.** Is medullary thyroid cancer predictable? A prospective study of 86 patients with abnormal pentagastrin tests. Surgery. 1999;126:1089-95; discussion 1096. [PMID: 10598192]

64. **Karanikas G, Moameni A, Poetzi C, Zettinig G, Kaserer K, Bieglmayer C, et al.** Frequency and relevance of elevated calcitonin levels in patients with neoplastic and nonneoplastic thyroid disease and in healthy subjects. J Clin Endocrinol Metab. 2004;89:515-9. [PMID: 14764755]

65. **Milazzo G, La Rosa GL, Catalfamo R, Vigneri R, Belfiore A.** Effect of TSH in human thyroid cells: evidence for both mitogenic and antimitogenic effects. J Cell Biochem. 1992;49:231-8. [PMID: 1322918]

66. **Maenhaut C, Lefort A, Libert F, Parmentier M, Raspé E, Roger P, et al.** Function, proliferation and differentiation of the dog and human thyrocyte. Horm Metab Res Suppl. 1990;23:51-61. [PMID: 2210634]

67. **Shimaoka K, Sokal JE.** Suppressive therapy of nontoxic goiter. Am J Med. 1974;57:576-83. [PMID: 4432862]

68. **Celani MF, Mariani M, Mariani G.** On the usefulness of levothyroxine suppressive therapy in the medical treatment of benign solitary, solid or predominantly solid, thyroid nodules. Acta Endocrinol (Copenh). 1990;123:603-8. [PMID: 2284885]

69. **Lima N, Knobel M, Cavaliere H, Sztejnsznajd C, Tomimori E, Medeiros-Neto G.** Levothyroxine suppressive therapy is partially effective in treating patients with benign, solid thyroid nodules and multinodular goiters. Thyroid. 1997;7:691-7. [PMID: 9349571]

70. **La Rosa GL, Lupo L, Giuffrida D, Gullo D, Vigneri R, Belfiore A.** Levothyroxine and potassium iodide are both effective in treating benign solitary solid cold nodules of the thyroid. Ann Intern Med. 1995;122:1-8. [PMID: 7985890]

71. **Zelmanovitz F, Genro S, Gross JL.** Suppressive therapy with levothyroxine for solitary thyroid nodules: a double-blind controlled clinical study and cumulative meta-analyses. J Clin Endocrinol Metab. 1998;83:3881-5. [PMID: 9814462]

72. **Wémeau JL, Caron P, Schvartz C, Schlienger JL, Orgiazzi J, Cousty C, et al.** Effects of thyroid-stimulating hormone suppression with levothyroxine in reducing the volume of solitary thyroid nodules and improving extranodular nonpalpable changes: a randomized, double-blind, placebo-controlled trial by the French Thyroid Research Group. J Clin Endocrinol Metab. 2002;87:4928-34. [PMID: 12414852]

73. **Gharib H, James EM, Charboneau JW, Naessens JM, Offord KP, Gorman CA.** Suppressive therapy with levothyroxine for solitary thyroid nodules. A double-blind controlled clinical study. N Engl J Med. 1987;317:70-5. [PMID: 3295553]

74. **Larijani B, Pajouhi M, Bastanhagh MH, Sadjadi A, Sedighi N, Eshraghian MR.** Evaluation of suppressive therapy for cold thyroid nodules with levothyroxine: double-blind placebo-controlled clinical trial. Endocr Pract. 1999;5:251-6. [PMID: 15251662]

75. **Csako G, Byrd D, Wesley RA, Sarlis NJ, Skarulis MC, Nieman LK, et al.** Assessing the effects of thyroid suppression on benign solitary thyroid nodules. A model for using quantitative research synthesis. Medicine (Baltimore). 2000;79:9-26. [PMID: 10670406]

76. **Castro MR, Caraballo PJ, Morris JC.** Effectiveness of thyroid hormone suppressive therapy in benign solitary thyroid nodules: a meta-analysis. J Clin Endocrinol Metab. 2002;87:4154-9. [PMID: 12213864]

77. **Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, et al.** Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med. 1994;331:1249-52. [PMID: 7935681]

78. **Franklyn JA, Betteridge J, Daykin J, Holder R, Oates GD, Parle JV, et al.** Long-term thyroxine treatment and bone mineral density. Lancet. 1992;340:9-13. [PMID: 1351654]

79. **Faber J, Galløe AM.** Changes in bone mass during prolonged subclinical hyperthyroidism due to L-thyroxine treatment: a meta-analysis. Eur J Endocrinol. 1994;130:350-6. [PMID: 8162163]

Current Author Addresses: Drs. Castro and Gharib: Mayo Clinic, 200 First Street SW, Rochester, MN 55902.