Review Article ISSN (O):2395-2822; ISSN (P):2395-2814

Diagnostic Approach to Thyroid Nodules.

Hena A. Ansari[1], Shaista M Vasenwala[2], Noora Saeed[3], Kafil Akhtar[4], Suhailur Rehman[3]

[1]Assistant Professor, Department of Pathology, Jawaharlal Nehru Medical College, AMU, Aligarh, U.P, India.
[2]Professor, Department of Pathology, Jawaharlal Nehru Medical College, AMU, Aligarh, U.P, India.
[3]Senior Resident, Department of Pathology, Jawaharlal Nehru Medical College, AMU, Aligarh, U.P, India.
[4]Associate Professor, Department of Pathology, Jawaharlal Nehru Medical College, AMU, Aligarh, U.P, India.

Received: October 2016
Accepted: October 2016

ABSTRACT

Derangement of thyroid function is a common clinical problem, with variable clinical presentations ranging from subtle, incidentally discovered disorders to overt disease, with frank disturbances of hormone levels and visible thyroid enlargement. In addition, there are the autoimmune thyroid disorders, and the neoplastic enlargements which result in palpable nodules. A large amount of new information has become available in recent times. They provide a comprehensive approach to diagnosis of thyroid nodules, ranging from initial evaluation, clinical and ultrasound criteria for fine-needle aspiration biopsy, interpretation of fine-needle aspiration biopsy results, and their management. Recommendations regarding the initial management of thyroid cancer include those relating to optimal surgical management, radioiodine remnant ablation, and suppression therapy using levothyroxine. Recommendations related to long-term management of differentiated thyroid cancer include those related to surveillance for recurrent disease using ultrasound and serum thyroglobulin as well as those related to management of recurrent and metastatic disease. We went through the published literature available electronically and assessed the various studies and their results. The results were reviewed carefully and interpreted in order to analyse the approach to diagnosis of thyroid swellings, especially in the Indian context. Although a detailed review is outside the scope of this paper, we will attempt to discuss some of these guidelines, especially in light of the scenario in our region.

Keywords: Thyroid nodule, management, FNAC, Clinical guidelines.

INTRODUCTION

Derangement of thyroid function is a common clinical problem, with variable clinical presentations ranging from subtle, incidentally discovered disorders to overt disease, with frank disturbances of hormone levels and visible thyroid enlargement. The clinical presentation may vary from a hypofunctional thyroid (hypothyroidism) to over secretion of thyroid hormones. In addition, there are the autoimmune thyroid disorders, and the neoplastic enlargements which result in palpable nodules. A discrete thyroid nodule maybe the initial presentation in both benign as well as malignant neoplasms. The prevalence of clinically inapparent thyroid nodules (on ultrasonography, USG) ranges from 20% to 76% in the general population.[1] Moreover, 20% to 48% of patients with palpable thyroid nodules are found to have additional nodules on USG.[2] In India, the incidence of clinically palpable nodules in adults is around 12.2%.[3]

Name & Address of Corresponding Author
Suhailur Rehman
Senior Resident, Department of Pathology,
Jawaharlal Nehru Medical College,
AMU, Aligarh, U.P, India.

A large amount of new information has become available in recent times. They provide a comprehensive approach to diagnosis of thyroid nodules, ranging from initial evaluation, clinical and ultrasound criteria for fine-needle aspiration biopsy, interpretation of fine-needle aspiration biopsy results, and their management. The American Association of Clinical Endocrinologists (AACE) have provided a well defined system of approach to thyroid nodules.4 These cover recommendations related to the initial diagnosis, categorization and management. We went through the published literature available electronically and assessed the various studies and their results. The results were reviewed carefully and interpreted in order to analyse the approach to diagnosis of thyroid swellings, especially in the Indian context. Although a detailed review is outside the scope of this paper, we will attempt to discuss some of these guidelines, especially in light of the scenario in our region.

MAGNITUDE OF THE PROBLEM

The estimated prevalence of thyroid disease in the Indian population is variable. The most common presentation in india is hypothyroidism. This is primarily attributable to iodine deficiency. In recent

times, autoimmunity has increasingly been recognized as a major cause of thyroid enlargement and hypofunction. Around 16.7% of adults in India have anti- thyroid peroxidase (anti- TPO) antibodies and 12% have anti- thyroglobulin (anti-Tg) antibodies.[3] In a study on schoolgirls, it was estimated that colloid goitre was the commonest cause, followed by thyroiditis.[5] Another study in Delhi showed the incidence of clinically palpable nodules to be around 1.6% with the figures rising to 4.6% and 5.6% in males and females, respectively, after USG. Subclinical hypothyroidism was frequent and anti-TPO antibody levels were raised in 13.3% of subjects.[6]

Thyroid cancer is another major problem, especially in the background of autoimmune thyroiditis which is known to be associated with thyroid neoplasms. The age- adjusted incidence rates are 1 and 1.8 for males and females respectively. Papillary cancer is reported to be the commonest histological type.[7] This is again a matter of concern since papillary cancer is linked to autommune thyroiditis and hence, early recognition of autoimmune thyroid dysfunction is essential and potentially a preventive measure for cancer. In a study by Ahn D et al, out of 269 patients with papillary thyroid cancer, 21.6% (58/269) had concurrent hashimoto's thyrodidtis.[8]

THYROID DISEASE AND DIABETES

India is facing an epidemic of diabetes mellitus with an estimate of 62.4 million people with diabetes and 77.2 million people with prediabetes according to Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study.[9]

The prevalence of thyroid dysfunction is higher among diabetic patients, especially females with type 1 diabetes mellitus.[10] Autoimmune thyroiditis is significantly associated with type 1 diabetes.[11] Post-partum thyroiditis is also more common in diabetic females.[12] From the point of view of management, the clinician needs to be aware of the effect of altered metabolic rates on glucose levels and lipid profile, as there is evidence of disturbances in glycemic control and increased risk of cardiovascular events in these patients.[13]

Metabolic syndromes are also associated with thyroid disorders, especially in hypothyroidism.[14] Both thyroid disorders and diabetes (individually) predispose to increased risk of cardiovascular events. It is our view that all patients with thyroid dysfunction, especially hypothyroidism, should be monitored for derangements of glucose and lipid levels. In addition, anti TPO antibody testing should be done along with TSH in diabetic patients, especially females, including expectant mothers. A careful regulation of TSH can help in good glycemic and lipid control also.

Hormonal evaluation

The AACE guidelines recommend that the initial step should be estimation of serum Thyroid stimulating hormone (TSH) levels. This is followed by an antibody assay.

Anti -TPO (Thyroperoxidase) if TSH levels are high, or free thyroxin and tri-iodothyronine levels if TSH is low. Anti-thyroglobulin (Tg) levels should be assessed only if anti- TPO levels are low and there is clinical indication of chronic lymphocytic thyroiditis. Thyroid receptor antibodies (TrAb) are tested for if TSH levels are low.[4]

The 2011 consensus statement by the Endocrine Society of India also15 recommends the estimation of serum TSH, along with USG and aspiration biopsy, for the evaluation of thyroid swellings. Antibody estimation is to be recommended if there is clinical suspicion of autoimmune disease.[15]

The general approach is to subject all palpable nodules to aspiration biopsy.

Given the high prevalence of subclinical thyroid disorders, especially hypothyroidism and autoimmune disease, we feel that it is prudent to screen all patients with a thyroid nodule for antibodies, apart from imaging and FNAB, as required. This will have two fold benefit - firstly the detection and appropriate treatment of autoimmune thyroid disease, and secondly, screening or followup for malignant change in those patients who have significantly raised antibody levels. However, as we will discuss later, cytological examination should not be relied upon solely. Moreover, the pathologist receives supportive evidence if thyroid function tests are done initially or alongside.

Ultrasonography

The AACE recommends the use of USG in all patients at risk of malignancy, and all patients with multinodular goitre or palpable thyroids or suspicious lymphadenopathy. It is not recommended as a screening test in the general population.4 Certainly, USG has high specificity in diagnosis of thyroid nodules (upto 95% for microcalcifications and upto 91.8% for irregular margins). Findings suspicious of malignancy are a taller-than-wide shape, a spiculated margin, marked hypoechogenicity and microcalcification. The US findings for benign nodules include isoechogenicity and a spongiform appearance. USG evaluation can provide excellent insight into the nature of the nodule and the area which is most suited for cytological evaluation. It is also possible to detect other inapparent nodules.[4] The recommendations are similar to the consensus statement on USG evaluation by the Endocrine society of India.[15] An important factor to be considered here is that in rural areas of developing countries, there are patients who may not undergo USG evaluation due to financial constraints or lack of access. Therefore, the clinician may have to decide which patient will require this

test, and if needed, this may be done after assessing the pathological report as an initial investigation.

Aspiration biopsy

Thyroid FNA has been shown to have good specificity and sensitivity (92 and 83%) respectively in diagnosis of nodular thyroid swellings. The false negative rate varies from 1 to 7% while the incidence of false positive report is upto 7.7%.[16,17] This can be minimized with USG guidance. USG is an excellent modality for selecting specific areas for aspiration.

The 2016 recommendations of AACE regarding the criteria for selection of nodules for FNA are that all nodules larger than 10mm with a high – risk category on USG should undergo cytological evaluation. Nodules 5 - 10mm with suspicious features, nodules in patients with a correlative family history of thyroid cancer, or presence of lymphnodes or extrathyroidal spread should undergo FNA. Nodules which are 'hot' on scintigraphy are excluded.[4]

The Endocrine society of India consensus statement recommends that all palpable nodules, especially those larger than 1cm in size, should be aspirated. In addition, it is recommended that palpation guided FNA must not be practiced in nonpalpable lesions, lesions with more than 25% cystic areas, nodules with previously inconclusive FNA report and in suspicious nodules.[15]

These guidelines are comprehensive and provide a framework within which decisions are to be made, with efficiency and reproducibility. It is necessary to state here that palpation - guided FNA still remains the mainstay of cytological examination in developing regions. It appears that the simple rule to follow would be that all palpable nodules are to be investigated with FNA, especially those with size large than 1cm, or in patients with a relevant clinical history or examination finding.

Role of Molecular Testing

FNA cytology accurately diagnoses a benign or malignant lesion in the majority of cases; however, approximatyely 10-40%of all FNA samples are diagnosed as indeterminate for malignancy, often prompting diagnostic hemithyroidectomy.[18-22] This is because cytological features of thyroid lesions with a follicular growth pattern are frequently not sufficiently clear to distinguish between benign and malignant lesions. Currently among surgically removed thyroid nodules only 8 to 56% are found to be malignant.[22-24] Such a high volume of unnecessary thyroid surgeries results in additional morbidity and higher health care costs.[25,26] Moreover, patients with malignant tumors and indeterminate FNA cytology typically undergo a limited surgery, i.e. thyroid lobectomy. After the diagnosis of malignancy is established by pathological examination of the removed nodule, these patients require a second operation to complete the thyroidectomy, which is associated with additional costs and morbidity. In addition, 1–3% of nodules diagnosed as benign on FNA cytology are later found to be malignant on follow-up (false-negative FNA), and the delay in treatment places patients at risk for progression of disease during the interval before definitive diagnosis.[19,24] Additional methods to improve the sensitivity and specificity of FNA cytological diagnosis are highly desirable and could have a significant impact on clinical care. Recent advances in molecular genetics of thyroid cancer can be applied to developing new diagnostic markers for FNA samples.[27,28] Papillary carcinoma, the most common thyroid malignancy, frequently carries BRAF, RET/PTC, or RAS mutations.

These mutually exclusive somatic mutations are found in more than 70% of papillary carcinomas, and some of them are associated with more aggressive tumor behavior.[29,30-31] Follicular carcinomas, the second most common type of thyroid cancer, harbor either RAS or PAX8/PPAR mutations, which are identified in approximately 80% of these tumors.[32] Several studies have demonstrated the feasibility of detecting BRAF, RET/PTC, or RAS mutations in thyroid FNA samples and have shown that this may improve the cytological FNA diagnosis.[33-38]

For both the clinician and the pathologist, the problematic categories are those of nondiagnostic aspirates, those with atypia of undetermined significance and suspicious lesions. In general, these nodules would ideally have to be reaspirated. USG guidance is preferable in such cases.

For example, a very common problem is that only cystic fluid is aspirated without anycells. Such a sample would be considered inadequate and nondiagnostic. However, USG correlation can solve the problem and avoid unnecessary reaspiration. Similarly, atypia can be as a result of artefactual changes, degenerative changes, inflammation, or a feature of a hyperfunctioning thyroid, or secondary to radioablation. So a careful clinical correlation is necessary to avoid misinterpretation. Another potential pitfall is the presence of hypercellular cell groups and scant colloid in a hyperfunctional thyroid. This can lead to a suspicion of neoplasia, especially papillary cancer. Clinical history, thyroid profile or USG findings can solve the problem here and avoid unnecessary reaspiration.

CONCLUSION

Based on the review of current literature regarding thyroid disease and diabetes mellitus especially in India, we would like to suggest a few general guidelines.

- Diabetic patients should be screened for thyroid dysfunction at the outset as both hypothyroidism (sub-clinical and overt) and

metabolic syndromes are recognized risk factors for atherosclerotic cardiovascular disease.

- All patients with a thyroid nodule and hypothyroidism should be evaluated for anti-TPO and not only TSH levels at the start which will help in both detection and treatment of autoimmune thyroid disease, as well as during followup for malignant change in those patients who have significantly raised antibody levels.
- In developing regions, palpation guided FNA still remains the mainstay of cytological examination.
- USG should be used in conjunction with FNA where ever possible.

REFERENCES

1. Ross DM. Diagnostic approach to and treatment of thyroid nodules.I. In: Rose BD, ed. Wellesley(MA): UpToDate; 2005. http://www.uptodate.com/contents/diagnostic-approach-to-and-treatment-of-thyroid-nodules
2. Tan GH, Gharib H. Thyroid incidentalomas: Management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. Ann Intern Med. 1997;126:226-231
3. Usha Menon V, Sundaram KR, Unnikrishnan AG, Jayakumar RV, Nair V, Kumar H. High prevalence of undetected thyroid disorders in an iodine sufficient adult south Indian population. J Indian Med Assoc. 2009;107:72–7.
4. Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedus L, Paschke R, Valcavi R, Vitti P. American association of clinical endocrinologists, American college of endocrinology, and Associazione medici endocrinology medical guidelines for clinical practice for the diagnosis and management of thyroid nodules 2016 update appendix. Endocrine Practice 2016; 22:1
5. Marwaha RK, Tandon N, Karak AK, Gupta N, Verma K, Kochupillai N. Hashimoto's thyroiditis: countrywide screening of goitrous healthy young girls in postiodization phase in India. J Clin Endocrinol Metab 2000;85:3798-802.
6. Marwaha RK, Tandon N, Ganie MA, Kanwar R, Sastry A, Garg MK, et al. Status of thyroid function in Indian adults: two decades after universal salt iodization. J Assoc Physicians India. 2012;60:32-6
7. Gangadharan P, Nair MK, Pradeep VM. Thyroid Cancer in Kerala. In: Shah AH, Samuel AM, Rao RS, editors. Thyroid Cancer- An Indian Perspective. Mumbai: Quest Publications; 1999. p. 17-32.
8. Ahn D, Heo SJ, Park JH, Kim JH, Sohn JH, Park JY, Park SK, Park J. Clinical relationship between Hashimoto's thyroiditis and papillary thyroid cancer. Acta Oncol. 2011 Nov;50:1228-34.
9. Anjana RM, Pradeepa R, Deepa M, Datta M, Sudha V, Unnikrishnan R, et al. ICMR–INDIAB Collaborative Study Group. Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: phase I results of the Indian Council of Medical Research-INdia DIABetes (ICMR-INDIAB) study. Diabetologia. 2011; 54:3022-7.
10. Perros P, McCrimmon RJ, Shaw G, and Frier BM. Frequency of thyroid dysfunction in diabetic patients: value of annual screening. Diabetic Medicine 1995; 12: 622-27.
11. Radetti G, Paganini C, Gentill L, Bernasconi S, Betterle C, Borkenstein M et al. Frequency of Hashimoto's thyroiditis in children with type 1 diabetes mellitus. Acta Diabetologica 1995; 32: 121-24.
12. Triggiani V, Ciampolillo A, Guastamacchia E, Licchelli B, Fanelli M, Resta F et al. Prospective study of post-partum thyroid immune dysfunctions in type 1 diabetic women and in a healthy control group living in a mild iodine deficient area. Immunopharmacol Immunotoxicol. 2004; 26: 215-24.
13. Roos A, Bakker SJ, Links TP, Gans RO, Wolffenbuttel BH. Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. J Clin Endocrinol Metab. 2007; 92:491-6.
14. Ogbera AO, Kuku S, Dada O. The metabolic syndrome in thyroid disease: A report from Nigeria. Indian J Endocrinol Metab. 2012; 16: 417-22.
15. Unnikrishnan A G, Kalra S, Baruah M, Nair G, Nair V, Bantwal G, Sahay RK. Endocrine Society of India management guidelines for patients with thyroid nodules: A position statement. Indian J Endocr Metab 2011;15:2-8
16. Wu HH, Jones JN, Osman J. Fine-needle aspiration cytology of the thyroid: Ten years experience in a community teaching hospital. Diagn Cytopathol. 2006;34:93-96.
17. Caruso D, Mazzaferri EL. Fine needle aspiration biopsy in the management of thyroid nodules. Endocrinologist. 1991;1:194-202.
18. Gharib H. Changing trends in thyroid practice: understanding nodular thyroid disease. Endocr Pract 2004;10:31–39.
19. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Sherman SI, Tuttle RM. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2006;16:109 –142
20. Greaves TS, Olvera M, Florentine BD, Raza AS, Cobb CJ, Tsao-Wei DD, Groshen S, Singer P, Lopresti J, Martin SE . Follicular lesions of thyroid: a 5-year fine-needle aspiration experience. Cancer 2000; 90:335–341
21. Sclabas GM, Staerkel GA, Shapiro SE, Fornage BD, Sherman SI, VassillopoulouSellin R, Lee JE, Evans DB . Fine-needle aspiration of the thyroid and correlation with histopathology in a contemporary series of 240 patients. Am J Surg 2003;186:702–709.
22. Yassa L, Cibas ES, Benson CB, Frates MC, Doubilet PM, Gawande AA, Moore Jr FD, Kim BW, Nose´ V, Marqusee E, Larsen PR, Alexander EK. Longterm assessment of a multidisciplinary approach to thyroid nodule diagnostic evaluation. Cancer 2007; 111:508 –516.
23. Mazzaferri EL. Management of a solitary thyroid nodule. N Engl J Med 1993;328:553–559.
24. Baloch ZW, Fleisher S, LiVolsi VA, Gupta PK. Diagnosis of "follicular neoplasm": a gray zone in thyroid fine-needle aspiration cytology. Diagn Cytopathol 2002; 26:41– 44.
25. Callcut RA, Selvaggi SM, Mack E, Ozgul O, Warner T, Chen H . The utility of frozen section evaluation for follicular thyroid lesions. Ann Surg Oncol 2004;11:94 –98.
26. Robertson ML, Steward DL, Gluckman JL, Welge J . Continuous laryngeal nerve integrity monitoring during thyroidectomy: does it reduce risk of injury? Otolaryngol Head Neck Surg 2004;131:596 – 600.
27. Kondo T, Ezzat S, Asa SL. Pathogenetic mechanisms in thyroid follicularcell neoplasia. Nat Rev Cancer2006; 6:292–306
28. Fagin JA. Genetics of papillary thyroid cancer initiation: implications for therapy. Trans Am Clin Climatol Assoc 2005;116:259 –269; discussion 269 – 271.
29. Adeniran AJ, Zhu Z, Gandhi M, Steward DL, Fidler JP, Giordano TJ, Biddinger PW, Nikiforov YE . Correlation between genetic alterations and microscopic features, clinical manifestations, and prognostic characteristics of thyroid papillary carcinomas. Am J Surg Pathol 2006;30:216 –222.
30. Kimura ET, Nikiforova MN, Zhu Z, Knauf JA, Nikiforov YE, Fagin JA . High prevalence of BRAF mutations in thyroid cancer: genetic evidence for constitutive activation of the RET/PTC-RAS-BRAF signaling pathway in papillary thyroid carcinoma. Cancer Res 2003;63:1454 –1457.
31. Xing M . BRAF mutation in papillary thyroid cancer: pathogenic role, molecular bases, and clinical implications. Endocr Rev 2007;28:742–762.

32. Nikiforova MN, Lynch RA, Biddinger PW, Alexander EK, Dorn 2nd GW, Tallini G, Kroll TG, Nikiforov YE . RAS point mutations and PAX8- PPAR rearrangement in thyroid tumors: evidence for distinct molecular pathways in thyroid follicular carcinoma. J Clin Endocrinol Metab 2003;88:2318 – 2326.
33. Pizzolanti G, Russo L, Richiusa P, Bronte V, Nuara RB, Rodolico V, Amato MC, Smeraldi L, Sisto PS, Nucera M, Bommarito A, Citarrella R, Lo Coco R, Cabibi D, Lo Coco A, Frasca F, Gulotta G, Latteri MA, Modica G, Galluzzo A, Giordano C . Fine-needle aspiration molecular analysis for the diagnosis of papillary thyroid carcinoma through BRAF V600E mutation and RET/PTC rearrangement. Thyroid 2007;17:1109 –1115.
34. Sapio MR, Guerra A, Posca D, Limone PP, Deandrea M, Motta M, Troncone G, Caleo A, Vallefuoco P, Rossi G, Fenzi G, Vitale M . Combined analysis of galectin-3 and BRAFV600E improves the accuracy of fine-needle aspiration biopsy with cytological findings suspicious for papillary thyroid carcinoma. Endocr Relat Cancer 2007;14:1089 –1097.
35. Xing M, Tufano RP, Tufaro AP, Basaria S, Ewertz M, Rosenbaum E, Byrne PJ, Wang J, Sidransky D, Ladenson PW . Detection of BRAF mutation on fine needle aspiration biopsy specimens: a new diagnostic tool for papillary thyroid cancer. J Clin Endocrinol Metab 2004;89:2867–2872.
36. Salvatore G, Giannini R, Faviana P, Caleo A, Migliaccio I, Fagin JA, Nikiforov YE, Troncone G, Palombini L, Basolo F, Santoro M . Analysis of BRAF point mutation and RET/PTC rearrangement refines the fine-needle aspiration diagnosis of papillary thyroid carcinoma. J Clin Endocrinol Metab 2004;89:5175– 5180.
37. Cheung CC, Carydis B, Ezzat S, Bedard YC, Asa SL . Analysis of ret/PTC gene rearrangements refines the fine needle aspiration diagnosis of thyroid cancer. J Clin Endocrinol Metab 2001;86:2187–2190.
38. Sciacchitano S, Paliotta DS, Nardi F, Sacchi A, Andreoli M, Pontecorvi A . PCR amplification and analysis of ras oncogenes from thyroid cytologic smears. Diagn Mol Pathol 1994;3:114 –121.

How to cite this article: Ansari HA, Vasenwala SM, Saeed N, Akhtar K, Rehman SU. Diagnostic Approach to Thyroid Nodules. Ann. Int. Med. Den. Res. 2016; 2(6):PT01-PT05.

Source of Support: Nil, **Conflict of Interest:** None declared