Thyroid nodules are common, occurring in almost two-thirds of some populations; among these only about 7% are malignant (1). The most important question with any new discovered thyroid nodule is, "is this malignant?" The main arbiter of malignancy or benignity remains fine needle aspiration. Given the resources involved, doing a fine needle aspiration cytology (FNAC) in every discovered nodule would be prohibitive to impossible. The clinician must decide which nodule to investigate and which to watch in the hope that this will never turn out to be malignant. FNACs are used basically to decide which nodule to operate upon (or more importantly which to not operate upon) and clinical and imaging features are used to decide which nodule to investigate by FNAC and which to leave alone. This paper describes the various imaging options for looking at thyroid nodules and briefly discusses the advantages and disadvantages with each.

Clinical

Features that raise suspicion include a nodule in males, one that is solitary, growing, hard, fixed and associated with hoarseness (2). While the presence of these features is likely to be of concern for a thyroid cancer, only very few patients of thyroid malignancy present in this classical manner. Several studies have shown women to outnumber men in a thyroid cancer population, cancers in Multinodular Goiters (MNG) to be far more common than in solitary nodules (3-5) and small impalpable nodules as likely to be malignant as larger more obvious ones (6). This means additional information is needed if some patients are to be stratified into a "low-risk, observe-only" group. Various imaging modalities are available that allow, with varying degrees of success and accuracy, the classification of nodules in to benign and malignant groups.

Nuclear Medicine

Thyroid imaging with radioactive iodine and Technetium ($^{99m}$Tc) was the monopoly of nuclear medicine for over a quarter of a century with hot nodules interpreted to be benign and cold possibly malignant, Figure 1. As more specific imaging developed, the utility of Iodine and Technetium scanning declined so that it is no longer a preferred investigation when a thyroid nodule is first diagnosed. Radionuclide thyroid scans do not differentiate benign from malignant (7), do not alter therapy and do not come cheap (8). Hot nodules have a reported incidence of malignancy (9, 10). The only situation where a hot nodule can be placed in a low risk category is when there is suppressed Thyroid Stimulating Hormone (TSH) level (11). Other nuclear medicine were developed to lend
specificity to the images, these include Thallium, sestamibi, tetrofosmin etc but although useful in niche situations, did not demonstrate sufficient sensitivity and specificity (12, 13) to find acceptance in routine initial imaging of a thyroid nodule.

**Positron Emission Tomography (PET)**

The practice of oncology has changed with the introduction of PET scanning, and PET is used in the initial diagnosis, staging, follow-up, re-staging and prognostic assessment in many cancers. Well differentiated thyroid cancers (WDTC) unfortunately do not lend themselves to an initial PET assessment due to wide variability of results (14) (Figure 2, 3). There is however an indispensable place for PET imaging in treated Thyroglobulin (TG) positive Whole-body Iodine Scan Negative cases (15).

**Computerized Tomography and Magnetic Resonance Imaging**

The level of anatomical detail in computerized
Tomography (CT) and MR have made these the investigation of choice for most macroscopic pathological processes Figure 4 and there is a high number of thyroid incidentaloma discovery on CT/MR of the neck done for other indications. Despite the resolution that is achievable, initial thyroid nodule imaging with CT/MRI has mixed reviews with some suggesting that all such nodules be assessed by ultrasound (16) while others find these modalities useful in giving added specificity and confidence in stratifying patients who can avoid FNAC without missing significant disease (17).

**Ultrasound**

A consensus that has emerged over the last few years is that ultrasound currently offers the most valuable tool in the early assessment of thyroid cancer (18). The advantages of ultrasound examination of thyroid include:

- The ability to identify non-palpable nodules
- Accurately measure nodule and detect any interval change in size
- Differentiate thyroid from non-thyroid nodules (lymph nodes, thyroglossal cyst, cystic hygroma, vascular malformations etc) (19, 20)
- Identify cervical lymphadenopathy and characterize enlarged nodes into benign and malignant (21)
- Stratify thyroid nodules according to probability of malignancy (22-24)
- In MNG select nodules for FNAC
- Evaluate residual thyroid tissue after surgery
- Evaluate diffuse thyroid changes (25)
- Guide needle tip placement for FNAC

Given the ubiquity of thyroid nodules, it would be impossible to biopsy all nodules for selection for surgery and ultrasound criteria have been used to try and divide nodules into those that are suspicious or look malignant and those in whom biopsy can be deferred (Figure 5, 6). All ultrasound modalities including gray-scale, Doppler, elastography as well as contrast have been used to differentiate benign from malignant nodules. Gray scale and Doppler characteristics have been well defined that help in categorization of the nodules.

Several benign and malignant ultrasound gray scale and Doppler features have emerged over the last few years (22, 26) (Table 1). These can be used in different ways to assign probabilities and a method based on the Breast Imaging Reporting and Data System (BIRADS) system, called Thyroid

| Ultrasound features associated with Benign or Malignant Probability of Thyroid Nodules |
|----------------------------------|----------------------------------|
| Uniform Halo | Microcalcification |
| Predominantly Cystic | Extension beyond thyroid |
| Avascular | Metastatic nodes |
| Reverberating echogenicities | Taller than Wide |
| | Hypoechoic |
| | Irregular Margin |
| | Solid |
| | Increased Central Vascularity |

| Ultrasound features of different classes of TIRADS system (24) |
|----------------------------------|----------------------------------|
| Group | Significance, (% probability of malignancy) | US Pattern | Comment |
| TIRADS 1 | Normal |
| TIRADS 2 | Benign (0%) | Colloid 1 | Anechoic, avascular, echogenic spots |
| | | Colloid 2 | Nonencapsulated, mixed, non expansile, hyperechogenic spots, vascularized, spongiform |
| TIRADS 3 | Probably benign (<5%) | Colloid 3 | Non-encapsulated, solid/cystic, iso/hyperechogenic, expansile, vasculatized, hypoechoic spots |
| | Hashimoto pseudonodule | Hyper/iso/hypoechogenic, partially encapsulated, peripheral vascularity in background of Hashimotos thyroiditis |
| TIRADS 4 | 4A, Suspicious (5-10%) | Simple neoplastic | Solid or heterogeneous nodule with thin capsule |
| | De Quervain pattern | Hypoechoic ill defined lesion, without calcification |
| | 4B, Suspicious (10-80%) | Suspicious neoplastic | Hyper/iso/hypoechoic, hypervascularized, thick capsule, calcification |
| TIRADS 5 | Probably Malignant (>80%) | Malignant B | Iso/hypoechoic, nonencapsulated, multiple peripheral calcifications and increased vascularity |
| | Malignant C | Malignant A, without calcification |
| TIRADS 6 | Biopsy Proven |
Imaging Reporting and Data System (TIRADS) was described in 2009 (24, 27) (Table 2).

There are several methods of characterization of ultrasound features. The original TIRADS papers (24, 27) describe an extensive spectrum of benign and malignant features. Despite their comprehensiveness, or perhaps because of it, the original TIRADS schemes are difficult to apply and have a very long learning curve. The description of nodules is complex and in real-life one is often unsure which category to put a particular nodule in.

There has been extensive work on determining the statistical significance of each ultrasound feature in predicting malignancy (7, 11, 22, 23). Using the established features of malignancy, simplified, easier to use methods of thyroid nodule classifications have been proposed (22, 23). These schemes assign probability of malignancy depending upon how many suspicious features are present in a nodule. Some schemes assign weighting factors to pre-existing high risk conditions (Table 3). Most malignant nodules are seen to have at least two suspicious features, but nodules with even one suspicious feature are a candidate for biopsy (22).

Sensitivities and specificity for the various schemes have been worked out (28). Sensitivity ranges from 60% to nearly 94% (Table 4).

The later schemes, especially of Kwak, are simple enough to be practically implementable by even less experienced radiologists (29, 30).

A recently published retrospective study with 8806 patients (31) used only three ultrasound characteristics, microcalcifications, size >2 cm and an entirely solid composition. By using two characteristics, the authors claim that 90% biopsies would be avoided with a residual thyroid cancer rate of 5 per 1000 with sensitivity of 0.52 and false positive rate of 0.07. The same issue of the journal carries a cautionary comment (32) on implementing this rather simplistic approach and recommends biopsy for the nodules larger

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**Figure 3.** Spectrum of metabolic activity in benign thyroid nodular disease on PET. A: Right lobe benign follicular adenoma showing increased glucose metabolism on PET with an SUV$_{max}$ 10.5. B: Right lobe follicular adenoma showing very subtle, low metabolic activity with an SUV$_{max}$ of 3.1.

(Image A, Courtesy Prof Henry Bom, Hwasun Korea. Image B, Courtesy Prof. Dr. Jun Hatazawa, MD, PhD Osaka University Graduate School of Medicine)

**Figure 4.** CT scans of thyroid nodular disease. A, B, Papillary carcinoma showing a hyperattenuating mass in the left lobe of the thyroid and a complex mass with calcification in the left lobe of the thyroid. (Image courtesy Prof. Dr. Jun Hatazawa, Osaka University Graduate School of Medicine) C, benign adenoma seen as a complex mass deep within the left lobe of thyroid (Image courtesy Prof. Dr. Henry Bom, Hwasun, Korea)
than 1 to 1.5 cm, solid and hypoechoic with microcalcifications.

Work has been done on trying to identify, with certainty, benign nodules on ultrasound (33-35) and criteria for benign nodules are emerging too. Tay SY et al. (33) concluded that the nodules with well-defined margins, no calcification, normal vascularity and negative lymphadenopathy should allow follow up. Vinyak S. et al. (34) described that the nodules with regular margins, having homogenous texture, normal vascularity and no calcification need follow up without FNAC. Brito et al. (35) reported that pure cystic or spongiform nodules do not need FNAC and require follow up.

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**Table 3. American Thyroid Association Criteria for biopsy of a Thyroid Nodule (11)**

| US feature | Threshold |
|------------|-----------|
| High risk history of Thyroid Cancer in first degree relatives, history of childhood radiation to neck, previous cancer in contralateral lobe, FDG avidity | Solid, suspicious features: Microcalcification, hypoechoic, irregular, taller than wide on transverse view | ≥5 mm |
| | No suspicious features | 0.5-1.5 cm |
| | Abnormal nodes | All |
| | Microcalcification | All |
| Solid Nodule | Hypoechoic | >1 cm |
| | Hyperechoic | >1.5 cm |
| Mixed solid-cystic | With suspicious features | 1.5-2.0 cm |
| | Without suspicious features | > 2.0 cm |
| Spongiform | Not indicated but FNAC node if present |
| Purely cystic | Not indicated |

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**Figure 5.** Spectrum of findings in benign thyroid nodules. A, B; colloid cysts, the Echogenic specs in both purely cystic lesions are colloid crystals. C, D; microcystic or spongiform nodules, these are benign colloid nodules. E, F; hemorrhagic cysts showing a reticular appearance in E, and retracted clot in F

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**Discussion**

The management of thyroid nodules has become increasingly complex. In almost all other cases of focal disease, the aim of early detection is to identify cases that might be malignant, so that an appropriate intervention can be planned. Managing cases of early thyroid cancer is not so straightforward. Most patients of thyroid cancer will die with thyroid cancer but not of thyroid cancer (32). Tools for early diagnosis, especially ultrasound, are picking up smaller and smaller thyroid cancers, resulting in an epidemic of sorts of thyroid cancers (36, 37). The number of new cases of thyroid cancer have tripled in recent years.
from 4.8 per 100,000 in 1972 to 14.7 per 100,000 in 2011, cancer mortality has remained stable at about 0.5 per 100,000 during this period (38). Some autopsy series have picked up undetected thyroid cancers in up to a third of all cases (39). Very small papillary thyroid carcinomas are already being classified into microcarcinomas and even smaller latent microcarcinomas that are less than 1-3 mm across (40). With the strides that ultrasound resolution is making it is already possible to identify and characterize thyroid nodules that are 2-3 mm in size. This barrier is likely to be temporary and soon we should expect millimeter resolution for ultrasound detection thresholds.

This raises two important questions in patients with palpable or impalpable thyroid nodules; is this likely to be malignant? And, if malignant, does this warrant aggressive treatment? There are no easy answers to these questions, especially the second, but due to resource constraints some stratification strategy that will obviate biopsy as a first step is needed.

The whole discussion of thyroid imaging boils down to establishing thresholds at which to decide if biopsy needs to be done or not. The

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### Table 4. Performance of various classification schemes for thyroid nodules. From ref (28)

| Study                          | Diagnostic Criteria                               | Sensitivity % | Specificity % | Ppv  | Npv  | Accuracy |
|-------------------------------|--------------------------------------------------|---------------|---------------|------|------|----------|
| TIRADS (Kwak et al. (22))     | Benign: TIRADS 2, 3, 4a                           | 60.2          | 85            | 75.5 | 73.6 | 74.2     |
|                               | Malignant: TIRADS 4b, 4c, 5                      |               |               |      |      |          |
| TIRADS (Horvath (24))         | Benign: TIRADS 1, 2, 3                           | 88            | 49            | 49   | 88   | 94       |
|                               | Non-benign: TIRADS 4, 5                          |               |               |      |      |          |
| Diagnostic categories (Kim (43)) | Sonographic characteristics: Microcalcification, Irregular or lobulated margins, marked hypoechogeticity and more tall than wide | 93.8          | 66            | 56.1 | 95.9 | 74.8     |

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**Figure 6.** Spectrum of findings in malignant thyroid nodules (all cases of papillary carcinoma). A, small isthmic mass with an irregular contour, marked hypoechogeticity and microcalcifications. B, marked hypoechogeticity, pointed margins in the upper pole of the right lobe. C, complex mixed cystic and solid mass with contour irregularity laterally and microcalcifications. D, uniformly solid, markedly hypoechoic taller than wide mass with a few internal microcalcifications. (Image A courtesy Dr. Ravi Kadasne, UAE. Images B-D courtesy Shlomo Gobi, Jerusalem.)
American Thyroid Association has laid down very detailed criteria of biopsy thresholds (11). These criteria are dynamic, and take into account not only the imaging characteristics of the thyroid nodules but also the clinical and individual context of the patient so that the thresholds are lower for a patient with a high risk background (Table 3). There are other biopsy criteria too, each having advantages and trade-offs (41).

Many groups have demonstrated sufficient confidence in their ultrasound findings to use the FNAC results only to confirm their initial ultrasound impression. In cases of discordant FNACs (malignant ultrasound features, benign FNAC results), they suggest a second FNAC reading (42).

Ultrasound imaging has been used, though with less-than-perfect sensitivity, for identifying patients who do not need an FNACC but more work is needed to ensure that the patients who are not biopsied do not develop cancer at a later stage. The development of new applications and new methods of extracting information from ultrasound data like elastography and contrast will bring in more sensitivity and specificity to the ultrasound data like elastography and contrast will bring in more sensitivity and specificity to the diagnostic process. At present we can confidently state that ultrasound imaging offers a powerful tool to help in making management decisions in thyroid nodular disease.

References

1. Welker MJ, Orlov D. Thyroid nodules. Am Fam Physician. 2003;67(3):559-66.
2. 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(5):377-83.
3. Zuberi LM, Yawar A, Islam N, Jābbar A. Clinical presentation of thyroid cancer patients in Pakistan-AKUH experience. IPMA The Journal of the Pakistan Medical Association. 2004;54(10):526-8.
4. McCall A, Jarosz H, Lawrence AM, Paloyan E. The incidence of thyroid carcinoma in solitary cold nodules and in multinodular goiters. Surgery. 1986;100(6):1120-32.
5. Sachmecchi I, Miller E, Varatharajah R, Chernys A, Carroll Z, Kassin E, et al. Thyroid carcinoma in single cold nodules and in cold nodules of multinodular goiters. Endocr Pract. 2000; 6(1):5-7.
6. 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(5):1941-6.
7. Hoang J, Lee WK, Lee M, Johnson D, Farrell S. US Features of thyroid malignancy: pearls and pitfalls. Radiographics. 2007;27(3):847-60.
8. Mancuso AA. Oh $#%# Another pesky incidental thyroid nodule! AJNR Am J Neuroradiol. 2005;26(10):2444-5.
9. Daumerie C, Ayoubi S, Rahier J, Buyschaert M, Squifflet JP. Prevalence of thyroid cancer in hot nodules. Ann Chir. 1998;52(5):444-8.
10. Mirfakhraee S, Mathews D, Peng L, Woodruff S, Zigan JM. A solitary hyperfunctioning thyroid nodule harboring thyroid carcinoma: review of the literature. Thyroid Res. 2013;6(1):7.
11. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mendel SJ, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer: Thyroid. 2009;19(11):1672-214.
12. Sathkeghe MM, Mageza RB, Muthuphei MN, Modiba MC, Clauss RC. Evaluation of thyroid nodules with technetium-99m MIBI and technetium-99m pertechnetate. Head Neck. 2001;23(4):305-10.
13. Nakahara H, Noguchi S, Murakami N, Hoshi H, Jinouchi S, Nagamachi S, et al. Technetium-99m-sestamibi scintigraphy compared with thallium-201 in evaluation of thyroid tumors. J Nucl Med. 1996;37(6):901-4.
14. Bertagna F, Treglia G, Piccardo A, Giubbini R. Diagnostic and clinical significance of F-18-FDG-PET/CT thyroid incidentalomas. J Clin Endocrinol Metab. 2012;97(11):3866-75.
15. Mosci C, Iagaru A. PET/CT imaging of thyroid cancer. Clin Nucl Med. 2011;36(12):e185-0.
16. Hoang JK, Raduzao P, Yousem DM, Eastwood JD. What to do with incidental thyroid nodules on imaging? An approach for the radiologist. Semin Ultrasound CT MR. 2012;33(2):150-7.
17. Hobbs HA, Bahl M, Nelson RC, Kranz PG, Esdamado RM, Wnuk NM, et al. Journal Club: incidental thyroid nodules detected at imaging: can diagnostic workup be reduced by use of the Society of Radiologists in Ultrasound recommendations and the three-tiered system? AJR Am J Roentgenol. 2014;202(1):18-24.
18. Chaudhary V, Bano S. Thyroid ultrasound. Indian J Endocrinol Metab. 2013;17(2):219-27.
19. Kotecha S, Bhatia P, Rout PG. Diagnostic ultrasound in the head and neck region. Dent Update. 2008; 35(8):529-30, 33-4.
20. Koischwitz D, Gritzmann N. Ultrasound of the neck. Radiographics. 2007;27(3):847-60.
US features of nodules: a step in establishing better stratification of cancer risk. Radiology. 2011; 260(3): 892-9.

23. Russ G, Bigorgne C, Royer B, Rouxel A, Bienvenu-Perrard M. The Thyroid Imaging Reporting and Data System (TIRADS) for ultrasound of the thyroid. J Radiol. 2011;92(7-8):101-13.

24. Horvath E, Majlis S, Rossi R, Franco C, Niedmann JP, Castro A, et al. An ultrasonogram reporting system for thyroid nodules stratifying cancer risk for clinical management. J Clin Endocrinol Metab. 2009; 94(5): 1748-51.

25. Kim DW, Jung SJ, Ha TK, Park HK, Kang T. Comparative Study of Ultrasound and Computed Tomography for Incidentally Detecting Diffuse Thyroid Disease. Ultrasound Med Biol. 2014.

26. Frates MC, Benson CB, Charbonneau JW, Cibas ES, Clark OH, Coleman BG, et al. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. Radiology. 2005;237(3):794-800.

27. Park JY, Lee HJ, Jang HW, Kim HK, Yi JH, Lee W, et al. A proposal for a thyroid imaging reporting and data system for ultrasound features of thyroid carcinoma. Thyroid. 2009; 19(11):1257-64.

28. Anuradha C, Abhishek K, Pushpa B, Deepak A, MJ P. Positive predictive value and inter-observer agreement of TIRADS for ultrasound features of thyroid nodules. ECR 20142014.

29. Ko SY, Lee HS, Kim EK, Kwak JY. Application of the Thyroid Imaging Reporting and Data System in thyroid ultrasonography interpretation by less experienced physicians. Ultrasoundography. 2014; 33(1): 49-57.

30. Ko SY, Lee HS, Kim EK, Kwak JY. Application of the Thyroid Imaging Reporting and Data System in thyroid ultrasonography interpretation by less experienced physicians. Ultrasoundography. 2013; 33(1): 49-57.

31. Smith-Bindman R, Lebda P, Feldstein VA, Sellami D, Goldstein RB, Brasic N, et al. Risk of thyroid cancer based on thyroid ultrasound imaging characteristics: results of a population-based study. JAMA Intern Med. 2013; 173(19):1788-96.

32. Alexander EK, Cooper D. The importance, and important limitations, of ultrasound imaging for evaluating thyroid nodules. JAMA Intern Med. 2013; 173(19): 1796-7.

33. Tay SY, Chen CY, Chan WP. Sonographic criteria predictive of benign thyroid nodules useful in avoiding unnecessary ultrasound-guided fine needle aspiration. J Formos Med Assoc. 2014; pii: S0929-6646(14)00109-0.

34. Vinayak S, Sande JA. Avoiding unnecessary fine-needle aspiration cytology by accurately predicting the benign nature of thyroid nodules using ultrasound. J Clin Imaging Sci. 2012;2:23.

35. Brito JP, Gionfriddo MR, Al Nofal A, Boehmer KR, Leppin AL, Reading C, et al. The accuracy of thyroid nodule ultrasound to predict thyroid cancer: systematic review and meta-analysis. J Clin Endocrinol Metab. 2014;99(4):1253-63.

36. Kim JY, Kim SY, Yang KR. Ultrasonographic criteria for fine needle aspiration of nonpalpable thyroid nodules 1-2 cm in diameter. Eur J Radiol. 2013;82:321-6.

37. McCarthy M. US thyroid cancer rates are epidemic of diagnosis not disease, study says. BMJ. 2014; 348: g1743.

38. Howlader N, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, et al. SEER Cancer Statistics Review. 2013; 1975-2011.

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(3):531-8.

40. Lee YS, Lim HS, Chang HS, Park CS. Papillary thyroid microcarcinomas are different from latent papillary thyroid carcinomas at autopsy. J Korean Med Sci. 2014;29(5):676-9.

41. Ahn SS, Kim EK, Kang DR, Lim SK, Kwak JY, Kim MJ. Biopsy of thyroid nodules: comparison of three sets of guidelines. AJR Am J Roentgenol. 2010;194:31-7.

42. Moon HJ, Kim EK, Kwak JY. Malignancy risk stratification in thyroid nodules with benign results on cytology: combination of thyroid imaging reporting and data system and Bethesda system. Ann Surg Oncol. 2014;21(6):1898-903.

43. Kim EK, Park CS, Chung WY, Oh KK, Kim DJ, Lee JT, et al. New sonographic criteria for recommending fine-needle aspiration biopsy of nonpalpable solid nodules of the thyroid. AJR Am J Roentgenol. 2002;178(3):687-91.