AJUM November 2010; 13 (4): 33–36

REVIEW

Thyroid nodules and evaluation of thyroid cancer risk

Jeremy Hoang

Westmead Hospital, Westmead, New South Wales 2145, Australia.
Correspondence to author via ASUM. Email authors@asum.com.au

Table 1: Ultrasound findings associated with an increased risk of thyroid cancer.

Composition
Solid or predominantly solid (vs. cystic, predominantly cystic or mixed)
Echogenicity
Hypoechoic (vs. hyperechoic or isoechoic)
Shape and margin
Taller than wide on transverse view
Irregular margin (vs. well defined margin)
Internal characteristics
Calcifications
• Microcalcifications
• Coarse calcifications
• Disrupted peripheral or 'eggshell' calcifications
Increased central vascularity by colour-Doppler
Cervical lymphadenopathy

General aspects

Palpable thyroid nodules occur in about 6% of women and 2% of men with higher prevalence in the elderly and in iodine-deficient areas[1]. However, the great majority of thyroid nodules are impalpable and asymptomatic with an estimated prevalence of 20–76% in the general population[1]. These small nodules are increasingly detected by neck ultrasound and parallel the rising incidence of small differentiated thyroid cancer over the last two decades[1,2].

The most common causes of thyroid nodules are colloid nodules, Hashimoto's and subacute thyroiditis, cysts, follicular adenomas and thyroid cancer[3]. The presenting clinical problems include hyperthyroidism, pain (often due to haemorrhage into a cyst) and compressive symptoms (due to a multinodular goitre). However, the clinical priority in the initial management of a thyroid nodule is to evaluate its thyroid cancer risk to guide decision regarding thyroidectomy[1,2]. Thyroid cancer occurs in 5–15% of nodules[2]. Approximately 90% of all thyroid cancers are differentiated thyroid cancer, 85% of which are papillary cancer[2].

The evaluation of thyroid cancer risk considers the clinical picture, thyroid function, ultrasound characteristics of the nodule and, depending on the ultrasound appearance, fine-needle aspiration biopsy (FNAB).

Clinical risk factors and thyroid function

A number of clinical findings indicate an increased risk of thyroid cancer. These include a hard nodule, evidence of local invasion such as fixation to adjacent structures or vocal cord palsy, cervical lymphadenopathy or rapid nodule growth[3]. Other important clinical risk factors include a prior hemithyroidectomy with discovery of thyroid cancer, history of thyroid cancer or thyroid cancer syndrome in first degree relatives (e.g. multiple endocrine neoplasia type 2 or MEN2) and a history of head and neck or whole body irradiation[2]. Incidental focal thyroid uptake on flurodeoxyglucose positron emission tomography (FDG PET) imaging is associated with about 33% risk of thyroid cancer which may be more aggressive[2,4].

A serum thyroid stimulating hormone test (TSH) should be performed routinely. If the serum TSH is low, a radionuclide thyroid scan (using either Technetium-99m pertechnetate or radioiodine) is useful in assessing if the nodule is autonomous. This finding is important as autonomous nodules are almost never malignant and FNAB is generally not required. On the other hand, a higher serum TSH is associated with an increased risk of cancer in a thyroid nodule[5,6]. While the cost-effectiveness of routine serum calcitonin measurement is debatable given the low incidence of medullary thyroid cancer, serum calcitonin level should be measured if there is a family history of medullary cancer or MEN2[2,3].

Thyroid ultrasound

A thyroid ultrasound should be performed for any thyroid nodule detected on palpation or other imaging. It confirms and characterises the index nodule and other clinically important nodules if present, selects the most appropriate nodules for FNAB, assesses the presence of abnormal cervical lymph nodes and helps guide the surgical approach[7]. Although no single or combined ultrasound findings are diagnostic of malignancy, a number of features are associated with an increased risk of thyroid cancer[2, 8–15] (Table 1).

The predictive value of these ultrasound characteristics is highly variable across the literature[13]. Microcalcifications and abnormal cervical lymph nodes probably have the highest predictive values for thyroid cancer (up to 94% and 100% respectively), although their sensitivity is generally low (26% and 5% respectively)[2,12–15]. Microcalcifications seen as punctate echogenicities are due to calcified psammoma bodies typical of papillary thyroid cancer[12]. They can be difficult to distinguish from colloid but the presence of comet-tail artifacts associated with colloid crystals may be helpful[2,13]. The association of macrocalcifications with thyroid cancer is less consistent[8,11,12,15]. However, recent data suggest that coarse calcifications and disrupted peripheral or "eggshell" calcifications are also markers of increased cancer risk[4,11,12].

Certain combinations of ultrasound findings are highly predictive of thyroid cancer. For example, a solid solitary nodule with microcalcifications may harbour cancer in up to 50% of cases[8]. It should be noted that while these ultrasound characteristics are typical of papillary cancer (PTC), they

Table 2: Ultrasound (US) and clinical features of thyroid nodules and recommendations for FNAB.

Nodule US or clinical features	Recommended nodule threshold size for FNAB	Strength of recommendation
High-risk history[a]		
Nodule WITH suspicious US features[b]	> 0.5 cm	Good evidence
Nodule WITHOUT suspicious US features[b]	> 0.5 cm	Insufficient evidence
Abnormal cervical lymph nodes	All[c]	Good evidence
Microcalcifications present in nodule	≥ 1 cm	Fair evidence
Solid nodule		
AND hypoechoic	> 1 cm	Fair evidence
AND iso- or hyperechoic	≥ 1–1.5 cm	Expert opinion
Mixed cystic-solid nodule		
WITH any suspicious US features[b]	≥ 1.5–2.0 cm	Fair evidence
WITHOUT suspicious US features	≥ 2.0 cm	Expert opinion
Spongiform nodule	≥ 2.0 cm[d]	Expert opinion
Purely cystic nodule	FNAB not indicated[e]	Fair evidence

Adapted with permission from the Revised ATA Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer[2]; a High-risk history: see text 'Clinical risk factors and thyroid function'; b Suspicious features: microcalcifications; hypoechoic; increased nodular vascularity; infiltrative margins; taller than wide on transverse view; c FNA cytology may be obtained from the abnormal lymph node in lieu of the thyroid nodule; d US monitoring without biopsy may be an acceptable alternative; e Unless indicated as therapeutic modality.

are less commonly found in follicular cancer (FTC) which tend to be iso- to hyperechoic, flat in orientation and lack microcalcifications[10]. Similarly, follicular variant papillary thyroid cancer tends to exhibit more benign ultrasound features[16].

Nodule size is not predictive of malignancy either in a solitary nodule or multinodular thyroid[8,9,13]. One study showed that in patients with multiple nodules and thyroid cancer, if only the largest nodule was selected for biopsy, nearly 50% of cancer would be missed[8]. However, tumour size predicts outcome. The available evidence suggests that the risk of extrathyroidal extension and metastasis increases when tumour size exceeds 0.5 cm for PTC and 2 cm for FTC[17–19].

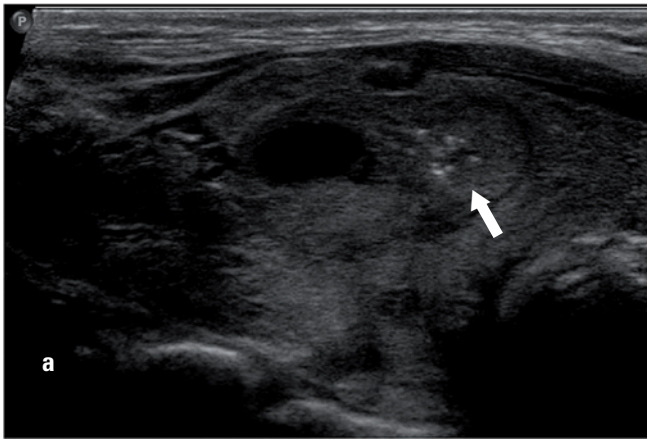
The more cystic a nodule, the more likely it is to be benign[8]. The cancer risk of a predominantly cystic non-solitary nodule without calcifications is less than 2% and completely cystic nodules are rarely malignant[8]. The "spongiform" colloid nodule containing aggregated multiple microcystic components (involving more than 50% of nodule volume) is also unlikely to be malignant[2,12].

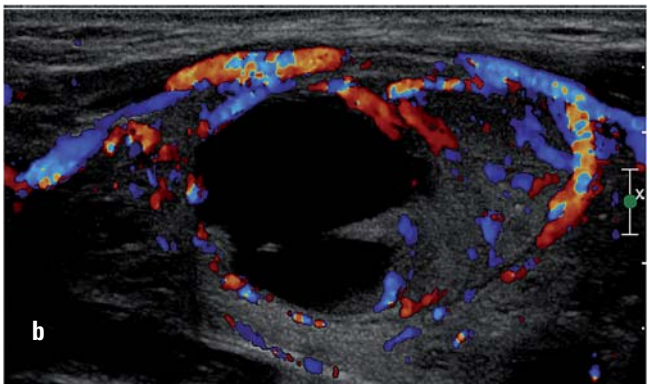
Guidelines for recommending fine-needle aspiration biopsy

FNAB is the most accurate and cost-effective method in selecting patients with thyroid nodules for surgery[2]. In performing the FNAB procedure, ultrasound guidance has been shown to reduce the rates of nondiagnostic and false-negative results[21] and is recommended for the nonpalpable, predominantly cystic (> 25–50% cystic) or posteriorly located nodules, or when repeating FNAB following an initial nondiagnostic result[2].

A number of guidelines are available to assist the clinician in selecting thyroid nodules for FNAB[1,2,13]. A decision analysis study suggests that criteria for FNAB based on nodule size and high-risk ultrasound findings such as microcalcifications result in better outcomes than selection based on nodule size alone in weighing the risk of missing cancer diagnosis against having surgery for benign nodules[20]. The 2009 *Revised American Thyroid Association (ATA) Guidelines* have moved away from recommending routine biopsy for all nodules ≥ 1 cm and now include specific ultrasound characteristics that may be used to determine the nodule size cut-off for FNAB (Table 2). Importantly, the ATA Guidelines recognise that nodules < 1 cm rarely harbour clinically significant cancer and do not routinely require evaluation because of the low cost benefit ratio. However some small nodules, especially those > 0.5 cm, may be considered for FNAB if they are associated with abnormal lymph nodes on palpation or imaging at presentation, 'high risk' history, focal avidity on PET scanning or suspicious ultrasound features[2,18]. Guidelines from the American Association of Clinical Endocrinologists and Society of Radiologists in Ultrasound similarly use suspicious ultrasound findings to recommend FNAB although their size criteria differ from the ATA Guidelines[1,2,13].

The multinodular thyroid carries the same overall cancer risk as a solitary nodule[8]. However, the cancer risk of each non-solitary nodule is lower than that of a solitary nodule and diminishes with increasing number of nodules in the thyroid gland[8]. If there are two or more thyroid nodules > 1 cm, suspicious ultrasound characteristics should be considered preferentially to size in selecting nodules for FNAB[2]. A low or low-normal TSH suggests autonomous function in one or more nodules and a thyroid scan is useful in identifying the iso- or hypofunctioning nodules for which FNAB may be considered based preferentially on suspicious ultrasound findings[2].





Figs. 1a & 1b: 53-year-old patient with a complex 3.1 cm thyroid nodule showing micro-calcification (arrow, image a) and increased vascularity (image b). Histopathology confirmed papillary thyroid cancer.

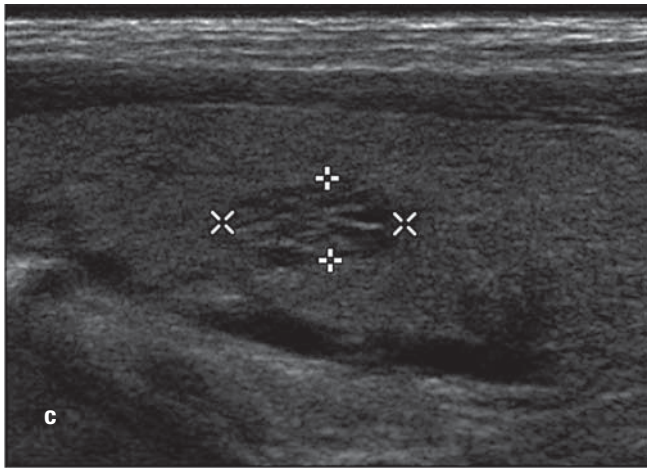


Fig. 1c: 87-year-old patient with a benign 1.2 cm spongiform thyroid nodule (marked).

The ATA Guidelines recommend that thyroid nodules be followed with a repeat ultrasound 6–18 months after an initial benign cytology. False-negative results of up to 2% may occur with ultrasound-guided FNAB[22]. This may be higher for nodules with suspicious ultrasound features[22]. Benign cytology on both initial and repeat FNAB has a predictive value for benignity approaching 100%[22]. Nodules > 1 cm, which are not biopsied, should also be observed with serial ultrasound studies[2]. Nodule growth detected by palpation or ultrasound is not specific for malignancy because benign nodules may also increase in size but it should be further evaluated with FNAB[2]. A 20% increase with a minimal increase of 2 mm in at least two nodule dimensions in solid nodules or the solid component of mixed nodules has been suggested as an appropriate cut-off to warrant biopsy[2]. If there is no significant change in nodule size or appearance, further clinical or ultrasound examinations may be performed at increased intervals, e.g. every 3–5 years[2].

Thyroid ultrasound report

There is currently no standardised format for reporting the results of thyroid ultrasound. Tailored to the commonly referred guidelines, an informative ultrasound report should describe all thyroid nodules ≥ 1 cm with reference to location, size, any suspicious characteristics (Table 1) and any interval change in follow-up studies[1,2,13]. Nodules < 1 cm with suspicious ultrasound features should also be noted and if present, ultrasound assessment and report of lymph nodes in lateral and central neck compartments should be performed[2].

There are recent efforts to stratify thyroid nodules in categories of probability of malignancy based on the estimated risks of various ultrasound characteristics[15,23]. Such a reporting system may facilitate communication of thyroid cancer risk particularly when multiple nodules are present and provide clearer guidelines for using FNAB. However their application awaits prospective studies with long-term clinical outcomes.

Conclusions

The assessment of cancer risk in a thyroid nodule permits a cost-effective risk adapted approach in selecting patients ultimately either for surgery or observation. This assessment begins with a review of the clinical and ultrasound risk factors and measurement of the serum TSH. If the serum TSH is subnormal, a thyroid scan should be performed. FNAB provides the most accurate assessment of the malignancy risk but should be considered for nodules based on both their ultrasound characteristics and size and not their size alone. Nodules < 1 cm do not routinely require FNAB unless there are cervical lymphadenopathy or other findings associated with cancer risk.

Acknowledgement

The author is grateful to Dr Simon Gruenewald and Dr Socrates Angelides for contributing the ultrasound images displayed in this review.

References

1 American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. *Endocr Pract* 2006; 12: 63–102.

2 Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, *et al*. Revised American Thyroid Association Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009; 19 (11): 1167–214.

3 Hegedus L. The thyroid nodule. *N Engl J Med* 2004; 351: 1764–71.

4 Kang KW, Kim SK, Kang HS, Lee ES, Sim JS, Lee IG, *et al*. Prevalence and risk of cancer of focal thyroid incidentaloma identified by ^{18}F-fluorodexyglucose positron emission tomography for metastatis evaluation and cancer screening in healthy subjects. *J Clin Endocrinol Metab* 2003; 88 (9): 4100–4.

5 Boelaert K, Horacek J, Holder RL, Watkinson JC, Sheppard MC, Franklyn JA. Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. *J Clin Endocrinol Metab* 2006; 91 (11): 4253–5.

6 Haymart MR, Repplinger DJ, Leverson GE, Elson DF, Sippel RS,

Jaume JC, Chen H. Higher serum thyroid stimulating hormone level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage. *J Clin Endocrinol Metab* 2008; 93 (3): 809–14.

7 Wartofsky L. Highlights of the Amercian Thyroid Association guidelines for patients with thyroid nodules or differentiated thyroid carcinoma: the 2009 revision. *Thyroid* 2009; 19 (11): 1139–43.

8 Frates MC, Benson CB, Doubilet PM, Kunreuther E, Contreras M, *et al*. Prevalence and distribution of carcinoma in patients with solitary and multiple thyroid nodules on sonography. *J Clin Endocrinol Metab* 2006; 91 (9): 3411–17.

9 Papini E, Guglielmi R, Bianchini A. Risk of malignancy in nonpalpable thyroid nodules: predictive value of ultrasound and color-Doppler features. *J Clin Endocrinol Metab* 2002; 87 (5): 1941–6.

10 Jeh S, Jung SL, Kim BS, Lee YS. Evaluating the degree of conformity of papillary carcinoma and follicular carcinoma to the reported ultrasonographic findings of malignant thyroid tumor. *Korean J Radiol* 2007: 192–7.

11 Kim BM, Kim MJ, Kim EK, Kwak JY, Hong SW, Son EJ, Kim KH. Sonographic differentiation of thyroid nodules with eggshell calcifications. *J Ultrasound Med* 2008; 27: 1425–30.

12 Moon WJ, Jung SL, Lee JH, Na DG, Baek JH, Lee YH, *et al*. Benign and malignant thyroid nodules: US differentiation – multicenter retrospective study. *Radiology* 2008; 247: 762–70.

13 Frates MC, Benson CB, Charboneau 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.

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

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

16 Kim DS, Kim JH, Na DG, Park SH, Kim E, Chang KH. Sonographic features of follicular variant papillary thyroid carcinomas in comparison with conventional papillary thyroid carcinomas. *J Ultrasound Med* 2009; 28 (12): 1685–92.

17 Mazzaferri EL. Managing small thyroid cancers. *JAMA* 2006; 295 (18): 2179–82.

18 Noguchi S, Yamashita H, Uchino S, Watanabe S. Papillary microcarcinoma. *World J Surg* 2008; 32: 747–53.

19 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 (4): 381–7.

20 McCartney CR, Stukenborg GJ. Decision analysis of discordant thyroid nodule biopsy guideline criteria. *J Clin Endocrinol Metab* 2008; 93: 3037–44.

21 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 (1): 15–21.

22 Kwak JY, Koo H, Youk JH, Kim MJ, Moon HJ, Son EJ, Kim EK. Value of US correlation of a thyroid nodule with initially benign cytologic results. *Radiology* 2010; 254 (1): 292–300.

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