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Management of the Solitary Thyroid Nodule

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the investigations used for a solitary thyroid nodule.
2. Explain the importance of thyroid ultrasound and fine-needle aspiration biopsy results.
3. Discuss how thyroid nodules are managed surgically.

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ABSTRACT

Thyroid nodules are common, with up to 8% of the adult population having palpable nodules. With the use of ultrasound, up to 10 times more nodules are likely to be detected. Increasing numbers of nodules are being detected serendipitously because of the rising use of imaging to investigate unrelated conditions. The primary aim in investigating a thyroid nodule is to exclude the possibility of malignancy, which occurs in about 5% of nodules. This begins with a thorough history, including previous exposure to radiation and any family history of thyroid cancer or other endocrine diseases. Clinical examination of the neck should focus on the thyroid nodule and the gland itself, but also the presence of any cervical lymphadenopathy. Biochemical assessment of the thyroid needs to be followed by thyroid ultrasound, which may demonstrate features that are associated with a higher chance of the nodule being malignant. Fine-needle aspiration biopsy is crucial in the investigation of a thyroid nodule. It provides highly accurate cytologic information about the nodule from which a definitive management plan can be formulated. The challenge remains in the management of nodules that fall under the "indeterminate" category. These may be subject to more surgical intervention than is required because histological examination is the only way in which a malignancy can be excluded. Surgery followed by radioactive iodine ablation is the mainstay of treatment for differentiated thyroid cancers, and the majority of patients can expect high cure rates. *The Oncologist* 2008;13:105–112

INTRODUCTION

Thyroid nodules are a common problem. They are found in 4%–8% of adults by palpation and in 13%–67% when ultrasound detection is used. In autopsy studies, they have a prevalence of approximately 50% [1, 2]. The prevalence of thyroid nodules increases with age and women have a

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higher prevalence than men. The natural history of benign nodules is unclear, but most palpable nodules probably reduce in size, with up to 38% disappearing altogether [3, 4]. The concern with thyroid nodules is the possibility of malignancy. Thyroid cancers are rare, accounting for only 1.0% of all cancers in most populations and 0.5% of all cancer deaths [5]. Nonetheless, thyroid cancers occur in approximately 5% of all thyroid nodules independent of their size. With thyroid nodules being so prevalent in the general population, it is important to have a clear strategy of assessing nodules and determining which of these will require surgery or can be managed conservatively.

Clinical Evaluation

As with all assessments, a thorough history and examination is required in patients who present with a thyroid nodule. Most nodules are asymptomatic and are often discovered serendipitously by the patient or their primary medical practitioner when being examined for another problem [6]. With the increasing use of diagnostic imaging, thyroid nodules are not infrequently detected as an incidental finding on ultrasounds and computed tomography (CT) scanning.

History and Examination

Regardless of the way in which thyroid nodules are discovered, a detailed patient history is requisite. Information that needs to be ascertained includes: the presence of symptoms, a change in nodule size, previous head/neck radiation exposure, and a family history of thyroid or endocrine diseases. The patient may report a history of pain, which may follow hemorrhage into a colloid nodule, or a sudden increase in the size of a neck lump, which would raise concern of malignancy. Voice change or hoarseness may also be a progressive symptom associated with an invasive tumor. Symptoms of dysphagia, coughing, choking, and dyspnea should be asked about.

Exposure of the thyroid gland to ionizing radiation is known to contribute to a higher incidence of both benign and malignant thyroid nodules, with malignancy rates in a palpable nodule in a previously irradiated thyroid in the range of 20%–50% [7, 8].

Thyroid carcinomas are classified according to the cell type from which they develop. The majority are nonmedullary thyroid cancers (NMTCs), which arise from the thyroid epithelial cells. These account for approximately 95% of tumors and are divided into four histologic subtypes: papillary (85%), follicular (11%), Hürthle cell (3%), and anaplastic (1%). Of these, 95% are sporadic tumors and the rest are thought to represent a familial origin, that is, familial nonmedullary thyroid cancer (FNMTC).

Medullary thyroid cancers (MTCs) arise from the calcitonin-producing parafollicular cells of the thyroid and account for about 5% of all thyroid malignancies. In 20% they are familial and occur as part of the multiple endocrine neoplasia (MEN) syndromes. It is important to identify these patients, as pheochromocytomas are associated with MEN II and need to be excluded prior to the patient receiving an anesthetic.

FNMTCs are rare. Based on epidemiologic studies and kindred analysis, this group of tumors is believed to result from a genetic inheritance, although environmental influences cannot be excluded. Inheritance is probably autosomal dominant with incomplete penetrance and variable expressivity. The diagnosis of FNMTC is made when thyroid cancer occurs in two or more first-degree relatives [9]. Clinically, FNMTCs can be divided into two groups. The first group includes familial tumor syndromes characterized by a preponderance of nonthyroidal tumors. These cancer syndromes include familial adenosis polyposis (Gardner syndrome), familial hamartoma syndrome (Cowden syndrome), and the Carney complex type 1. In the second group, NMTC predominates [10]. Compared with sporadic NMTC, patients with FNMTC appear to present at an earlier age, have more benign thyroid nodules, have multifocal disease, and have a higher rate of locoregional recurrence [11, 12].

Clinical examination of the thyroid should focus on whether the nodule is solitary or dominant in a multinodular goiter. The characteristics of the nodule, including size, consistency (e.g., soft, firm, woody, or hard), and involvement with adjacent structures, should also be defined. Examination of the cervical lymph nodes, including the central compartment (level VI) and the lateral neck (levels I–V), should also be performed (Fig. 1). Suggestion of involvement of lateral neck lymph nodes will change the extent of preoperative investigation required in these patients.

Investigations

Biochemical Evaluation

Investigation of thyroid nodules should begin with assessment of the functional status of the thyroid. Tests include serum thyroid-stimulating hormone (TSH), free thyroxine, and free tri-iodothyronine. Measurement of TSH is the most useful initial step. With the availability of highly sensitive TSH assays, it is possible to detect subtle thyroid dysfunction with this test alone [13]. If the TSH is abnormal, free thyroid hormones and thyroid antibodies should be the next investigations. Thyroid antibodies such as thyroid peroxidase and antithyroglobulin antibodies are found in most patients with Graves' disease or Hashimoto's thyroiditis.

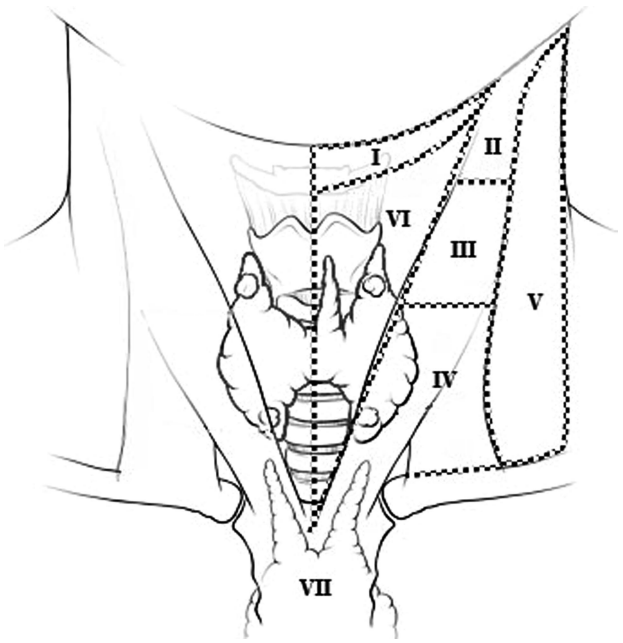

Figure 1. Location of cervical lymph node levels. Level I, submental and submandibular nodes; level II, upper jugular nodes; level III, midjugular nodes; level IV, lower jugular nodes; level V, posterior triangle and supraclavicular nodes; level VI, pretracheal, prelaryngeal, and paratracheal nodes; level VII, nodes within the superior mediastinum.

TSH receptor autoantibodies are detectable in the majority of patients with Graves' disease [14]. Thyroglobulin (Tg) is the major constituent of colloid and precursor of thyroid hormones. Serum Tg can be elevated in most thyroid diseases and is therefore not recommended as a routine initial assessment of thyroid nodules [15].

Calcitonin is produced from the parafollicular cells of the thyroid. Serum levels are usually elevated in patients with MTCs. The calcitonin assay as a screening test is not cost-effective; however, in patients with a history suggestive of MEN, it may aid in the diagnosis of MTC.

Thyroid Scintigraphy

Thyroid scintigraphy has a limited role in the evaluation of a solitary thyroid nodule. It has been relied upon in the past to assist in risk stratification of nodules as being benign or malignant based on their ability to take up isotope. Depending on the pattern of uptake, nodules are classified as hyperfunctioning (hot), hypofunctioning (cold), or normal functioning (warm). Hot nodules are seen in about 5% of scans and are malignant in 5% of cases [16]. Approximately 80%–85% of nodules are cold and 10%–15% of these are malignant [17]. The incidence of malignancy in warm nodules is reported to be 9%. This information on its own is unlikely to change the subsequent management of the nodule and further decision making [18]. Thyroid scintigraphy does have a place in the investigation of a thyroid nodule when serum TSH is suppressed. In this setting, it is useful to determine if the nodule is an autonomously toxic nodule, if it is part of a toxic multinodular goiter or a single nodule in a patient with Grave's disease [18, 19].

Ultrasonography

All patients who present with a thyroid nodule should undergo ultrasound evaluation of the nodule, thyroid gland, and cervical lymph nodes, if indicated. Ultrasound is an inexpensive, readily available, and noninvasive investigation. The superiority of ultrasound examination of the thyroid over clinical examination has been described, with one study showing ultrasonography leading to a change in management of 44% of patients who had been referred for a solitary nodule on physical examination [20]. As has been eloquently described, "The ultrasound machine to the endocrinologist evaluating a thyroid nodule is analogous to the stethoscope of the cardiologist" [21].

An ultrasound examination should focus on the size of the nodule, its composition, the presence of additional nodules, and any sonographic appearance suggestive of malignancy. Patients with multiple thyroid nodules have the same risk for malignancy as those with solitary thyroid nodules [20, 22] or even diffuse goiters [23], and it is recommended that all patients who have a nodular thyroid undergo ultrasound evaluation [15]. Numerous studies have attempted to define which ultrasound characteristics are most predictive of malignancy. To date, no single feature carries a high sensitivity and high positive predictive value for thyroid cancer [24]. However, there are a number of ultrasound qualities that, when they occur in combination, are associated with a higher risk for malignancy [24, 25].

Nodule Size

Nodule size in not predictive of malignancy, and the risk for cancer in a thyroid nodule has been shown to be the same regardless of the size on ultrasound [22, 24, 26]. Previous guidelines had recommended that the decision to perform a fine-needle aspiration biopsy (FNAB) should be based on nodules >10 mm. It has now been demonstrated that cancer in nodules <10 mm is not less frequent, and if this value is used as a cutoff, then a significant proportion of cancers will be missed [22]. The prevalence of extracapsular or metastatic growth was shown to be similar in nodules >10 mm and <10 mm [22, 27]. The lower size limit of a nodule that should be biopsied is currently under debate [24], but nodules <10 mm with associated microcalcifications or a history of neck irradiation should undergo FNAB [13].

Composition

Nodules can be descriptively classified depending on their predominant composition, for example, solid, cystic or mixed, or complex. Papillary thyroid cancer (PTC) is identified in 87% of solid nodules, 7% of mixed composition nodules, and 6% of predominantly cystic nodules [28]. Large cystic or mixed lesions may represent large PTCs that have undergone cystic degeneration. The cystic component is often at the periphery of the nodule, with the solid epithelial portion potentially representing only a small, compressed part of the lesion. It is important to direct the FNAB to this solid component to rule out malignant disease.

Calcification

The presence of any calcification within a nodule increases the likelihood of malignancy. Microcalcifications are defined as multiple, small intranodular punctate hyperechoic spots, with scanty or no posterior acoustic shadowing [13]. They are thought to represent the superimposition of Psammoma bodies upon one another [28]. These lesions are most indicative of PTC and have a specificity of up to 95% [29]. When microcalcifications are seen in a predominantly solid nodule, there is an approximately threefold higher cancer risk, and coarse calcifications are associated with a twofold higher risk, as compared with solid nodules without calcifications [24]. Coarse calcifications are common and can be found in PTCs as well as benign nodules, but their presence in a solitary nodule in a young patient should raise concern for PTC [29].

Solitary Versus Multiple Nodules

The prevalence of thyroid cancer has been shown to be similar in patients with a solitary nodule and patients with multiple nodules [30]. In glands with multiple nodules, the recommendation of the American Thyroid Association (ATA) is to biopsy nodules that are >10 mm and those that have suspicious features [15].

Other Ultrasound Features

Ultrasound with color Doppler evaluates nodule blood flow as a possible predictor of thyroid malignancy. Benign nodules are thought to demonstrate peripheral flow, with malignant lesions showing flow predominantly in the central portion. Results have failed to conclusively support this. Hypoechogenicity and the absence of a halo around the nodule are nonspecific markers of thyroid cancers [28].

A nodule that is shaped more tall than wide (defined as being greater in its anteroposterior dimension than its transverse dimension) has been shown to be suggestive of malignancy [31].

Cervical Lymphadenopathy

Ultrasound is an accurate and sensitive imaging modality for the detection of cervical lymph node metastasis and recurrence [28]. The ultrasound features associated with the highest risk for cancer include a heterogeneous echotexture, calcifications, no hilus, a rounded appearance, cystic changes, and chaotic hypervascularity. These lymph nodes should always be biopsied even in the absence of a malignant-appearing thyroid nodule [13].

Other Imaging Modalities

CT, magnetic resonance imaging (MRI), and positron emission tomography (PET) scanning are not recommended in the routine workup of thyroid nodules. CT is useful in providing additional anatomical information, such as the presence of a retrosternal goiter, compressive symptoms attributable to a posteromedially placed nodule, and the relationship of a goiter to adjacent structures. MRI can do the same, but at a greater cost.

With the advent of the increased use of PET scanning in the staging and surveillance of various malignancies, the phenomenon of the PET-identified thyroid incidentaloma is becoming more prevalent. These PET-detected nodules have been shown, in some studies, to harbor a higher malignancy risk [32–34]. Until more information is collected on the significance of these nodules, it seems prudent to have a low threshold for biopsying these lesions.

FNAB

FNAB is the most crucial step in the evaluation of a thyroid nodule and is the procedure of choice in the workup of thyroid nodules [15, 35]. It is able to provide specific information about the cellular composition of a nodule that directs subsequent management decisions.

FNAB can be performed by palpation or with ultrasound guidance. In our institution, it is performed exclusively with ultrasound guidance. This technique has been shown to decrease false negatives resulting from needle misplacement and reduce the rate of nondiagnostic smears from 15% to 3% [36–39]. The use of FNAB has led to a reduction in the number of patients requiring surgery and increased the diagnostic yield of cancers at thyroidectomy [5, 40, 41].

For FNAB to be regarded as a useful diagnostic tool, it must have a low false-negative rate. The false-negative rate is reported in the literature to be in the range of 1%–11%, with a value $\leq$5% being acceptable [42, 43]. A number of strategies, including aspirating multiple nodule sites, submitting cyst fluid for cytologic examination, and reviewing slides with an experienced cytopathologist [35], have been suggested to minimize false negatives.

Procedure

The technical aspects of FNAB are well described in numerous publications [35, 40, 42–45] and are not repeated here. It is generally well tolerated, with minor complications of local pain and, rarely, a hematoma.

Interpretation

"An accurate diagnosis depends on an adequate and representative sample interpreted correctly in the clinical context" [43]. A diagnostic sample is generally defined as when there are at least two slides that have six or more groups of >10 well-preserved follicular epithelial cells in each group [13, 40]. The four categories that are commonly used to describe FNAB results and their reported incidences are: benign, 70%; indeterminate, 10%; malignant, 5%; and nondiagnostic, 15% [13].

Benign

The majority of aspirates are benign and represent colloid, adenomatous or hyperplastic nodules, simple thyroid cysts, autoimmune thyroiditis, and lymphocytic thyroiditis. Colloid nodules demonstrate abundant colloid with benign follicular cells arranged in sheets, clusters, and spherules [43]. In contrast, hyperplastic nodules have less colloid with more follicular epithelial cells. The cells seen in thyroiditis will depend on the stage of the disease, with lymphoid cells predominating in the early stages and the later showing extensive fibrosis.

Malignant

The most frequent malignant biopsy is that of PTC, with a sensitivity and specificity approaching 100%. The diagnosis is based on the arrangement of the cells and their cellular features. Typically, many neoplastic follicular epithelial cells are seen with or without fibrovascular cores in a papillary configuration. The nuclei are enlarged and show crowding with irregular shapes and pale chromatin [44]. Intranuclear "holes" (pseudoinclusions) and Psammoma bodies are the most important diagnostic features of PTC. The follicular variant of PTC is a source of false-negative diagnosis. This variant has been described as a "pathological paradox" because it does not demonstrate papillae and the diagnosis is made on the nuclear changes seen in the neoplastic cells [46].

MTCs often demonstrate spindle-shaped or plasmacytoid neoplastic cells. Binucleation is common and intranuclear pseudoinclusions may be seen. FNAB may reveal the presence of amyloid, which is associated with MTC. Because these tumors arise from the calcitonin-producing C cells, immunoperoxidase staining for this marker is essentially diagnostic of MTC [40]. A cytological diagnosis of anaplastic thyroid carcinoma can be made when smears show abundant blood, necrotic debris, pleomorphic cells with large irregular nuclei, and the presence of mitotic figures. Metastatic lesions to the thyroid are uncommon and are usually from primary renal, breast, lung, colon, melanoma, and prostate cancers. These are usually diagnostic on FNAB [40].

Indeterminate

This category covers two subgroups. First, "suspicious for malignancy," in which malignancy is suspected but there is not enough information from the smear to make a definitive diagnosis. Second, "follicular neoplasm," when it is not possible to make a diagnosis of a follicular adenoma or carcinoma because this depends on the absence or presence of capsular or lymphovascular invasion, which can only be determined on histology. Approximately 20% of these indeterminate nodules are malignant. Therefore, these lesions should be excised to allow for a definitive diagnosis.

Nondiagnostic

Nondiagnostic smears occur when there are insufficient follicular cells to make a cytological diagnosis. Reaspiration yields satisfactory smears in 50% of cases [13]. An interval of at least 4 weeks should be allowed between repeat FNABs, because inflammation and bleeding from the initial biopsy may limit the ability to adequately interpret the second biopsy. Aspirates of cystic nodules are a source of unsatisfactory specimens and are thought to be a result of sampling error, when only the fluid is examined and the solid component of a cystic lesion is not biopsied. Malignancy rates of the solid component of cystic lesions are thought to approach those of solitary cold nodules [40].

MANAGEMENT

Management of thyroid nodules is based on the combination of history, examination, ultrasound evaluation, and ultimately cytology results.

Benign Nodules

Nodules diagnosed as benign on FNAB, and which are biochemically normal, do not need specific treatment. If the nodule is large and is causing compressive symptoms, then it may require surgery. Toxic nodules require medical management and/or radioactive iodine administration, and occasionally surgery.

Benign nodules require follow-up with annual clinical examinations and repeat ultrasound, because of the small false-negative rate of approximately 5% on FNAB [4]. Most benign nodules grow slowly over time [47], but there is no consensus as to what constitutes significant growth

warranting rebiopsy [24]. One reasonable definition of growth is a 20% increase in nodule diameter with a minimum increase in two or more dimensions ≥2 mm. According to the ATA recommendations, if there is evidence of nodule growth either by palpation or on sonography, ultrasound-guided repeat FNAB should be carried out [15]. Any new features on ultrasound suggestive of malignancy (as described earlier) should also prompt repeat FNAB. If nodule size remains stable, the interval until the next follow-up may be increased [15].

Malignant Nodules

A positive result of malignancy on FNAB almost certainly warrants surgery. Total thyroidectomy for PTC is the preferred treatment option. In one landmark paper with the longest follow-up of patients with PTC [48], mortality and recurrence rates were compared in patients who underwent thyroid lobectomy (ipsilateral total lobectomy with isthmusectomy) versus bilateral resection (including total thyroidectomy and bilateral subtotal or near total thyroidectomy). They were able to demonstrate that, after 20 years, the rates for local recurrence and nodal metastasis were 14% and 19% after thyroid lobectomy and only 2% and 6% after bilateral resection, respectively [48].

Twenty percent to ninety percent of patients diagnosed with PTC have involved cervical lymph nodes at the time of diagnosis. In addition to thyroidectomy, a routine ipsilateral central compartment (level VI) lymph node dissection may be considered. This remains a controversial topic; however, there is some evidence to support its role in reducing the risk for nodal recurrence and improving survival [49–51].

A preoperative ultrasound of the lateral neck (levels II–V) should be performed to determine if there are any pathological nodes present, and if so, these should undergo FNAB. If there is biopsy-proven metastatic disease in the lateral neck, a selective lymph node dissection is required.

Follicular thyroid cancers (FTCs) are classified as minimally or widely invasive. This diagnosis can only be made histogically. Minimally invasive FTC, the more common type, is where there is only slight tumor invasion into or through the capsule with or without vascular invasion. The presence of vascular invasion increases the risk for metastatic disease, and in tumors with this finding, if the patient has had only a thyroid lobectomy, a completion thyroidectomy is warranted [18]. Otherwise, for minimally invasive FTC (of only the capsule), thyroid lobectomy may be adequate. Widely invasive FTC should undergo total thyroidectomy without lymph node dissection because these tumors tend to spread hematogenously, as compared with PTCs, which metastasize through the lymphatics.

Following total thyroidectomy in patients with PTC and FTC, ^{131}I ablation should be undertaken to destroy residual thyroid tissue, decrease the risk for locoregional recurrence, and facilitate long-term surveillance with whole-body iodine scans and stimulated thyroglobulin measurements [52]. This has been shown to have the greatest benefits in patients with tumors >15 mm or those with residual disease after surgery. For patients with low-risk disease (unifocal PTC <10 mm with no extrathyroidal extension or lymph node metastasis), the benefit is more controversial, and the recommendation is to give smaller amounts of ^{131}I [52]. Retrospective studies have demonstrated superior outcomes in patients with high-risk disease with TSH suppression to <0.1 mU/l, with maintenance of TSH at or slightly below the lower limit of normal (0.1–0.5 mU/l) being appropriate for low-risk patients [15].

MTCs should be treated with total thyroidectomy and level VI node dissection. As per PTC, if the lateral neck lymph nodes are positive on FNAB, a level II–V lymphadenectomy should be performed. Because these tumors are not iodine avid, surgery is the mainstay of treatment.

Anaplastic thyroid cancers are aggressive tumors with an extremely poor prognosis. Surgery is rarely possible because of the extent of the local disease. Radiotherapy and chemotherapy are the main modalities of treatment [14].

Indeterminate

Nodules with this cytological diagnosis require surgical excision, usually with thyroid lobectomy. If a "follicular neoplasm" was the preoperative diagnosis, definitive histological confirmation of whether this is an adenoma or a carcinoma (based on the presence or absence of capsular invasion) is necessary. If the nodule is confirmed as a follicular carcinoma on paraffin section, then a completion thyroidectomy is performed if it is the widely invasive type or has vascular invasion. This is usually done in the first or second week following the initial surgery. An FNAB result of "suspicious for malignancy," particularly if it is papillary, allows the use of an intraoperative frozen section diagnosis for decision making [53, 54]. If the pathologist is confident of a diagnosis of papillary carcinoma on frozen section, the patient should proceed to a total thyroidectomy and possibly ipsilateral level VI lymph node dissection. This has the advantage of having a definitive operation performed immediately.

Nondiagnostic

Cysts that recur and nodules that are >4 cm or are repeatedly nondiagnostic on FNAB should be considered for surgical excision. Any nodule that has suspicious features on ultrasound that returns a nondiagnostic FNAB should be strongly considered for excisional biopsy, particularly in

patients with a family history of thyroid malignancies or who have had radiation exposure as a child.

Conclusion

Thyroid nodules are common, and with the increasing use of ultrasound for unrelated problems are detected with greater frequency. The aim of management is to identify which nodules warrant further investigation to exclude the presence of malignancy. Although a thorough history and clinical examination are indispensable, FNAB is essential to decision making and is able to provide highly accurate information that will ultimately determine the management of a nodule.

Author Contributions

Conception/design: Meei J. Yeung, Jonathan W. Serpell
Manuscript writing: Meei J. Yeung, Jonathan W. Serpell
Final approval of manuscript: Meei J. Yeung, Jonathan W. Serpell

References

1 Wang C, Crapo LM. The epidemiology of thyroid disease and implications for screening. Endocrinol Metab Clin North Am 1997;26:189–218.

2 Burguera B, Gharib H. Thyroid incidentalomas. Prevalence, diagnosis, significance, and management. Endocrinol Metab Clin North Am 2000;29: 187–203.

3 Kuma K, Matsuzuka F, Kobayashi A et al. Outcome of long standing solitary thyroid nodules. World J Surg 1992;16:583–587; discussion 587–588.

4 Kuma K, Matsuzuka F, Yokozawa T et al. Fate of untreated benign thyroid nodules: Results of long-term follow-up. World J Surg 1994;18:495–498; discussion 499.

5 Hegedus L. Clinical practice. The thyroid nodule. N Engl J Med 2004;351: 1764–1771.

6 Mitchell J, Parangi S. The thyroid incidentaloma: An increasingly frequent consequence of radiologic imaging. Semin Ultrasound CT MR 2005;26: 37–46.

7 Refetoff S, Harrison J, Karanfilski BT et al. Continuing occurrence of thyroid carcinoma after irradiation to the neck in infancy and childhood. N Engl J Med 1975;292:171–175.

8 Favus MJ, Schneider AB, Stachura ME et al. Thyroid cancer occurring as a late consequence of head-and-neck irradiation. Evaluation of 1056 patients. N Engl J Med 1976;294:1019–1025.

9 Sturgeon C, Clark OH. Familial nonmedullary thyroid cancer. Thyroid 2005;15:588–593.

10 Malchoff CD, Malchoff DM. Familial nonmedullary thyroid carcinoma. Cancer Control 2006;13:106–110.

11 Loh KC. Familial nonmedullary thyroid carcinoma: A meta-review of case series. Thyroid 1997;7:107–113.

12 Uchino S, Noguchi S, Kawamoto H et al. Familial nonmedullary thyroid carcinoma characterized by multifocality and a high recurrence rate in a large study population. World J Surg 2002;26:897–902.

13 Gharib H, Papini E. Thyroid nodules: Clinical importance, assessment, and treatment. Endocrinol Metab Clin North Am 2007;36:707–735, vi.

14 Lennard TWJ. The thyroid gland. In: Garden OJ, Patterson-Brown S (eds). A Companion to Specialist Surgical Practice. Philadelphia: Elsevier, 2006: 43–77.

15 Cooper DS, Doherty GM, Haugen BR et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2006; 16:109–142.

16 Wong CK, Wheeler MH. Thyroid nodules: Rational management. World J Surg 2000;24:934–941.

17 Meier DA, Kaplan MM. Radioiodine uptake and thyroid scintiscanning. Endocrinol Metab Clin North Am 2001;30:291–313, viii.

18 Delbridge L. Solitary thyroid nodule: Current management. ANZ J Surg 2006;76:381–386.

19 Shaha AR. Controversies in the management of thyroid nodule. Laryngoscope 2000;110:183–193.

20 Marqusee E, Benson CB, Frates MC et al. Usefulness of ultrasonography in the management of nodular thyroid disease. Ann Intern Med 2000;133: 696–700.

21 Weiss RE, Lado-Abeal J. Thyroid nodules: Diagnosis and therapy. Curr Opin Oncol 2002;14:46–52.

22 Papini E, Guglielmi R, Bianchini A et al. Risk of malignancy in nonpalpable thyroid nodules: Predictive value of ultrasound and color-Doppler features. J Clin Endocrinol Metab 2002;87:1941–1946.

23 Franklyn JA, Daykin J, Young J et al. Fine needle aspiration cytology in diffuse or multinodular goitre compared with solitary thyroid nodules. BMJ 1993;307:240.

24 Frates MC, Benson CB, Charboneau JW et al. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. Radiology 2005;237:794–800.

25 Nobrega LH, Paiva FJ, Nobrega ML et al. Predicting malignant involvement in a thyroid nodule: Role of ultrasonography. Endocr Pract 2007;13: 219–224.

26 Leenhardt L, Hejblum G, Franc B et al. Indications and limits of ultrasound-guided cytology in the management of nonpalpable thyroid nodules. J Clin Endocrinol Metab 1999;84:24–28.

27 Nam-Goong IS, Kim HY, Gong G et al. Ultrasonography-guided fine-needle aspiration of thyroid incidentaloma: Correlation with pathological findings. Clin Endocrinol (Oxf) 2004;60:21–28.

28 Wang TS, Cheng DW, Udelsman R. Contemporary imaging for thyroid cancer. Surg Oncol Clin N Am 2007;16:431–445.

29 Sosa JA, Udelsman R. Papillary thyroid cancer. Surg Oncol Clin N Am 2006;15:585–601.

30 Frates MC, Benson CB, Doubilet PM et al. Prevalence and distribution of carcinoma in patients with solitary and multiple thyroid nodules on sonography. J Clin Endocrinol Metab 2006;91:3411–3417.

31 Kim EK, Park CS, Chung WY et al. New sonographic criteria for recommending fine-needle aspiration biopsy of nonpalpable solid nodules of the thyroid. AJR Am J Roentgenol 2002;178:687–691.

32 Kang KW, Kim S-K, Kang H-S et al. Prevalence and risk of cancer of focal thyroid incidentaloma identified by 18F-fluorodeoxyglucose positron emission tomography for metastasis evaluation and cancer screening in healthy subjects. J Clin Endocrinol Metab 2003;88:4100–4104.

33 Choi JY, Lee KS, Kim HJ et al. Focal thyroid lesions incidentally identified by integrated 18F-FDG PET/CT: Clinical significance and improved characterization. J Nucl Med 2006;47:609–615.

34 Cohen MS, Arslan N, Dehdashti F et al. Risk of malignancy in thyroid in-

cidentalomas identified by fluorodeoxyglucose-positron emission tomography. Surgery 2001;130:941–946.

35 AACE/AME Task Force on Thyroid Nodules. 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.

36 Deandrea M, Mormile A, Veglio M et al. Fine-needle aspiration biopsy of the thyroid: Comparison between thyroid palpation and ultrasonography. Endocr Pract 2002;8:282–286.

37 Baskin HJ. Ultrasound-guided fine-needle aspiration biopsy of thyroid nodules and multinodular goiters. Endocr Pract 2004;10:242–245.

38 Castro MR, Gharib H. Continuing controversies in the management of thyroid nodules. Ann Intern Med 2005;142:926–931.

39 Morgan JL, Serpell JW, Cheng MSP. Fine-needle aspiration cytology of thyroid nodules: How useful is it? ANZ J Surg 2003;73:480–483.

40 Ogilvie JB, Piatigorsky EJ, Clark OH. Current status of fine needle aspiration for thyroid nodules. Adv Surg 2006;40:223–238.

41 Hadi M, Gharib H, Goellner JR et al. Has fine-needle aspiration biopsy changed thyroid practice? Endocr Pract 1997;3:9–13.

42 Gharib H, Goellner JR. Fine-needle aspiration biopsy of the thyroid: An appraisal. Ann Intern Med 1993;118:282–289.

43 Oertel YC. Fine-needle aspiration of the thyroid: Technique and terminology. Endocrinol Metab Clin North Am 2007;36:737–751, vi–vii.

44 Gharib H, Goellner JR. Fine-needle aspiration biopsy of thyroid nodules. Endocr Pract 1995;1:410–417.

45 Suen KC. Fine-needle aspiration biopsy of the thyroid. CMAJ 2002;167:491–495.

46 Nishiyama R. Pathology of tumors of the thyroid gland. In: Clark O, Duh Q, Kebebew E, eds. Textbook of Endocrine Surgery. Philadelphia: Elsevier, 2005:223–239.

47 Alexander EK, Hurwitz S, Heering JP et al. Natural history of benign solid and cystic thyroid nodules. Ann Intern Med 2003;138:315–318.

48 Hay ID, Grant CS, Bergstralh EJ et al. Unilateral total lobectomy: Is it sufficient surgical treatment for patients with AMES low-risk papillary thyroid carcinoma? Surgery 1998;124:958–964; discussion 964–966.

49 Grodski S, Cornford L, Sywak M et al. Routine level VI lymph node dissection for papillary thyroid cancer: Surgical technique. ANZ J Surg 2007;77:203–208.

50 Sywak M, Cornford L, Roach P et al. Routine ipsilateral level VI lymphadenectomy reduces postoperative thyroglobulin levels in papillary thyroid cancer. Surgery 2006;140:1000–1005; discussion 1005–1007.

51 White ML, Gauger PG, Doherty GM. Central lymph node dissection in differentiated thyroid cancer. World J Surg 2007;31:895–904.

52 Mazzaferri EL. Management of low-risk differentiated thyroid cancer. Endocr Pract 2007;13:498–512.

53 Cheng MS, Morgan JL, Serpell JW. Does frozen section have a role in the intraoperative management of thyroid nodules? ANZ J Surg 2002;72:570–572.

54 Tsan CJ, Serpell JW, Poh YY. The impact of synoptic cytology reporting on fine-needle aspiration cytology of thyroid nodules. ANZ J Surg 2007;77:991–995.