Approach to the Patient with a Cytologically Indeterminate Thyroid Nodule

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Background: Fine-needle aspiration remains the primary diagnostic intervention for the evaluation of most thyroid nodules larger than 1–1.5 cm. Although most aspirates provide diagnostic cytology, approximately 15–25% will be classified indeterminate (often referred to as follicular neoplasm, suspicious for carcinoma, or atypical). In such cases, abnormal cellular findings preclude interpretation of benignity, although only a minority will prove cancerous upon final histopathology. Nonetheless, patients with indeterminate aspirates are commonly referred for consideration of hemi- or near-total thyroidectomy. Recently, improved understanding and novel investigation of clinical, radiological, cytological, and molecular factors has allowed improved stratification of cancer risk.

Conclusion: Although surgery continues to be commonly recommended, strategies for such patients should increasingly seek to define treatment based on the estimation of an individual's thyroid cancer risk in comparison with associated operative risk and morbidity. In doing so, the rate of unnecessary surgical procedures and associated complications can be reduced. **(*J Clin Endocrinol Metab* 93: 4175–4182, 2008)**

A 75 yr-old male is found to have a 2-cm, incidentally discovered thyroid nodule while undergoing computed tomography scanning. He is asymptomatic and reports no prior thyroid illness. The patient confirms no evidence of childhood exposure to ionizing radiation or family history of thyroid carcinoma. Assessment of serum TSH concentration reveals a value of 3.8 mIU/liter (normal 0.5–5.0 mIU/liter). The patient undergoes ultrasound evaluation of the thyroid, and a 2.1-cm hypoechoic, solid nodule is identified. No abnormal lymphadenopathy is detected. The patient is recommended for ultrasound-guided fine-needle aspiration (FNA) of the nodule, which occurs without complication. The cytology results demonstrate numerous follicular cells, some with mild nuclear crowding and pallor. The final cytological report reads, "Indeterminate cytology; Classification of benign or malignant process cannot be conclusively made." Given this uncertainty, the cytology sample is sent for a second expert opinion. The secondary interpretation of the same FNA specimen is reported as suspicious for papillary cancer. The patient is referred for management recommendations.

Background

Thyroid nodular disease is increasing in incidence. The cause appears multifactorial, largely influenced by an aging population as well as increased use of cross-sectional imaging of the head, neck, and chest (1). Most thyroid nodules are completely asymptomatic and likely to never cause harm. However, approximately 10–15% of thyroid nodules prove cancerous. For such patients, early detection of malignancy followed by treatment is associated with an excellent outcome in the majority of cases. Thus, the desire to diagnose and address any potential harmful malignancy has lead to the widespread recommendation that all nodules larger than 1–1.5 cm be evaluated (2, 3).

Initial evaluation of a patient with a thyroid nodule includes measurement of serum TSH. If TSH is suppressed, this may signal a toxic adenoma, which should be confirmed by thyroid scintigraphy. Such nodules are almost universally benign, and management is primarily directed at hormone control. However, 90–95% of patients will have normal or elevated TSH concentrations. For such patients, FNA (usually with ultrasound guidance) is the next step. Aspirate cytology is processed either as a

Abbreviation: FNA, Fine-needle aspiration.

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smear directly onto a glass slide or via thin-layer preparation. Both methods are used, although increasingly thin-layer preparation is employed. Regardless of method, numerous large-scale experiences with thyroid nodule FNA have been published and confirm common findings (4, 5). Approximately 60–70% of aspirates prove cytologically benign, 5% of aspirates are positive for papillary carcinoma, and 5–15% of aspirates are persistently nondiagnostic. The remaining 15–25% of aspirates are indeterminate.

Indeterminate cytology arises from the imperfection inherent in cytology analysis. Numerous benign processes can cause modest cellular or nuclear changes that are minimal, yet may be indistinguishable from findings of papillary carcinoma. Furthermore, follicular carcinoma is defined by a tumor's ability to penetrate capsular or vascular structures. Such a property is not visible on aspiration cytology, because tissue architecture has been disrupted. In these cases, surrogate markers such as microfollicles signal a possibility of cancer. Together, indeterminate FNA cytology encompasses a cohort of microscopic findings that suggest concern for thyroid malignancy, yet are inconclusive. Unfortunately, consensus terminology for classifying indeterminate FNA cytology specimens has also been lacking (6). Descriptions range from indeterminate, to atypical cellularity, to suspicious for a follicular neoplasm, or suggestive of malignancy, often all conferring similar malignancy risk (Table 1). Recently, some centers have favored a stratified system that better depicts cancer risk (4, 7).

Regardless, the patient and physician face considerable anxiety when indeterminate cytology is obtained. Thyroid scintigraphy can be used to evaluate nodule function, which may change management if the nodule is autonomous. The utility of this approach is modest, because most nodules discovered in patients with normal TSH concentrations are nonfunctional or cold. However, recent data suggest low-normal TSH concentrations may predict benign disease. Although not yet currently recommended pending confirmatory data, this may suggest that thyroid scintigraphy is best targeted toward subgroups of affected patients with TSH values in the lower portion of the normal range.

TABLE 1. Classification of indeterminate FNA cytology

Current (does not differentiate cancer risk)	Proposed (conveys hierarchical cancer risk)
Indeterminate cytology	
Atypical cellular features	Suspicious for papillary carcinoma
Suggestive of a follicular neoplasm	Follicular neoplasm (microfollicular pattern)
Suggestive of a Hurthle cell neoplasm	Atypical cells of an undetermined significance
Suspicious for malignancy	
Microfollicular predominance	
Abnormal cellularity	
Mixed microfollicular and macrofollicular pattern	
Features of papillary carcinoma suspected	
Inconclusive cytology	
Abnormal follicular pattern	

The *left* column lists commonly used terminology. The *right* column lists a proposed schema (6, 7) that limits strict terminology to cellular findings that convey hierarchical cancer risk.

In most cases, the possibility of thyroid malignancy combined with the inability to prove benignity without histopathological analysis, usually leads to a recommendation for partial or near-total surgical thyroidectomy. Although generally a very safe procedure, thyroidectomy does carry small but consistent risk of surgical complications. National data suggest an approximate 1–2% combined rate of complications, primarily including parathyroid or recurrent laryngeal nerve damage (4, 8). Postoperative morbidity and recovery exert other time and financial pressures that also must be accounted for.

Approximately 25–50% of cytologically indeterminate nodules prove to be cancerous upon final histopathological analysis. The remaining nodules are benign. Herein lay the challenge and difficulty in managing thyroid nodules with indeterminate cytology. Should all such patients undergo thyroidectomy to prevent potential harm from thyroid cancer, especially when there exists a small but real risk of operative morbidity? Others will also argue that malignancy, even if not surgically resected, may not shorten patient longevity (1).

Diagnostic and Therapeutic Strategies

The above question is difficult to answer, and often a strict yes or no response is impossible. In formulating consensus statements for the management of patients with thyroid nodules, both the American Thyroid Association and the European Thyroid Association have broadly recommended partial or near-total thyroidectomy for patients with indeterminate nodule cytology (2, 3). These recommendations seem logical given a lack of available data confirming any superior approach in the setting of possible carcinoma. Yet no investigations have confirmed survival or morbidity benefits from such a recommendation.

In the last decade, investigators have increasingly studied the potential for clinical, radiological, and molecular markers to predict nodule benignity or cancer. It is almost certain that no single factor will prove perfectly predictive. However, increasing use of multivariate assessment demonstrates the benefits of an approach using several risk factors in conjunction with cytology findings. Early investigations using this approach first investigated subpopulations of patients with small nodules, seeking to define whether clinical factors might allow some nodules to be followed conservatively (9, 10). More recently, large datasets have allowed multivariate assessment on a broader scale, incorporating clinical, radiological, and molecular variables (11, 12). Together, it has become clear that advancing technology and expanded multivariate analysis is allowing physicians to more clearly stratify cancer risk among patients with indeterminate cytology. From this, more specific recommendations can be applied to discrete patient cohorts based on their cancer risk. Thus, the standard surgical recommendation for a patient with an indeterminate thyroid nodule is being rapidly replaced by a process that seeks to better identify cohorts with higher cancer risk while limiting unnecessary surgery for those with presumed benign

disease Below describes the clinical, radiological, and molecular variables that have been investigated, ending with studies seeking to create a unified, multivariate model.

Clinical factors that modify thyroid cancer risk

Clinical variables have long been investigated with regard to their ability to predict risk that a thyroid nodule may be cancerous (13). Traditionally, high-risk historical or examination findings such as new-onset hoarseness of voice, fixation of the nodule to surrounding neck structures, known medullary carcinoma in a first-degree relative, or childhood exposure to ionizing radiation were most predictive of malignancy. Although useful, it is also apparent that such findings are only rarely identified. Therefore, although still important, more recent research has focused on whether clinical variables such as patient age, sex, and thyroid nodule size predict thyroid cancer.

Patient age at the time of nodule identification appears to modify thyroid cancer risk. In particular, young age (variably defined as age <18–25 yr) increases the relative risk a nodule is cancerous by approximately 1.5- to 2-fold (13–17). Unfortunately all such data are retrospective, and selection bias is difficult to fully exclude. Nonetheless, the general consistency of findings from numerous independent sources supports its validity while awaiting more definitive prospective epidemiological investigations. In contrast, the impact of older age (variably defined as age >60–70 yr) on cancer risk remains uncertain. Traditionally, it was believed that older age was also associated with an approximate 1.5- to 2-fold increased risk of cancer. However, more recent data are contradictory (16–18). Thus, at present, the effects of older age on cancer risk remains uncertain, and it seems prudent to assume only young age (<25 yr) be used as a clinical risk factor presently.

Patient sex also predicts thyroid cancer risk (12, 16, 17). Male patients with thyroid nodules consistently demonstrate a 1.5- to 2-fold increased risk of carcinoma compared with female patients. The reason for this remains uncertain, although this finding appears independent of patient age. In contrast, thyroid nodule size surprisingly does not influence cancer risk. Numerous large analyses have confirmed similar mean diameters in benign *vs.* cancerous nodules (19, 20). Others have investigated malignancy rate based upon quintiles describing nodule size (12). Findings consistently suggest no influence of nodule size on cancer risk. In summary, available data suggest that clinical variables do influence the risk that a thyroid nodule larger than 1 cm is cancerous. Specifically, rare but important historical or examination findings as well as young age and male sex increase cancer risk and thus are useful when defining the approach to a patient with indeterminate FNA cytology.

Sonographic factors that modify thyroid cancer risk

Ultrasound is recommended as part of the initial evaluation for any patients with a known or suspected thyroid nodule (2, 3). It is also increasingly used to guide FNA, because data confirm the ability of ultrasound guidance to reduce false-negative and nondiagnostic (insufficient) aspirates. Early experience with thyroid nodule sonography demonstrated that individual nodules exhibit different sonographic characteristics. Over the last 15 yr, numerous investigators have sought to associate these characteristics with either benign or malignant disease. Although interobserver variability can be high, the consistency of reported findings suggests microcalcifications, irregular nodule margins, parenchymal hypoechogenicity, increased nodule vascularity, and abnormal neck lymphadenopathy are each associated with higher malignancy risk (9, 10, 12, 20, 21–23).

Each of these solitary variables confers an approximate 1.5- to 3-fold increased risk of cancer, although when two or more variables are present in combination, the risk of cancer appears substantially higher (9, 10, 20). In contrast, increased cystic fluid content in a nodule (generally >50%) is associated with lower cancer risk (12). Purely cystic nodules (>99% cystic) appear to have a risk of malignancy of less than 1%. Finally, multinodularity (two or more nodules each >1 cm) is not protective of malignancy (12). Findings confirm the risk of cancer per patient is equal whether one or more nodules larger than 1 cm are present.

Recently, other imaging techniques have been investigated for their ability to predict thyroid cancer. Ultrasound-elastography, a technique employed to estimate tissue stiffness by measuring the degree of tissue's deformation in response to external force, appears able to accurately predict malignancy in many solid nodules (25–27). Although encouraging, its widespread applicability to all thyroid nodules is limited because of its inability to predict malignancy in partially or completely cystic nodules as well as the difficulty in applying this technique to multinodular glands. Similarly, findings from positron emission tomography generally suggest that the relative avidity of thyroid nodules for [^{18}F]deoxyglucose (expressed as the maximum standard uptake value) is associated with an increased risk of thyroid cancer (28, 29). One study suggests an standard uptake value of more than 5.0 conveys an almost 5-fold increased risk in nodules with indeterminate cytology (28). Positron emission tomography scans of thyroid nodules are not routinely warranted, however, given potential exposure to ionizing radiation as well as the substantial cost for testing.

In summary, certain nodule characteristics detected during radiological imaging are also predictive of thyroid cancer risk, especially when present in combination. Ultrasound characteristics are often available in the evaluation of any patient with nodular disease and thus are likely to have the greatest near-term impact on patient care. The application of these findings to newly diagnosed thyroid nodules (Fig. 1) as well as those with indeterminate FNA cytology (Fig. 2) has also been explored. Similar to clinical variables, however, none (with the exception of purely cystic parenchyma) are perfectly predictive.

Molecular factors that modify cancer risk

The ability of identify molecular markers that predict cancer holds great promise for improving the care of patients with indeterminate thyroid aspirates. These markers broadly include serum proteins such as TSH as well as cellular protein DNA and RNA findings isolated from aspirate samples themselves. Thus far, such markers have proven most useful for detecting malignant disease. In contrast, virtually no markers have been identified that signal a high negative predictive value.

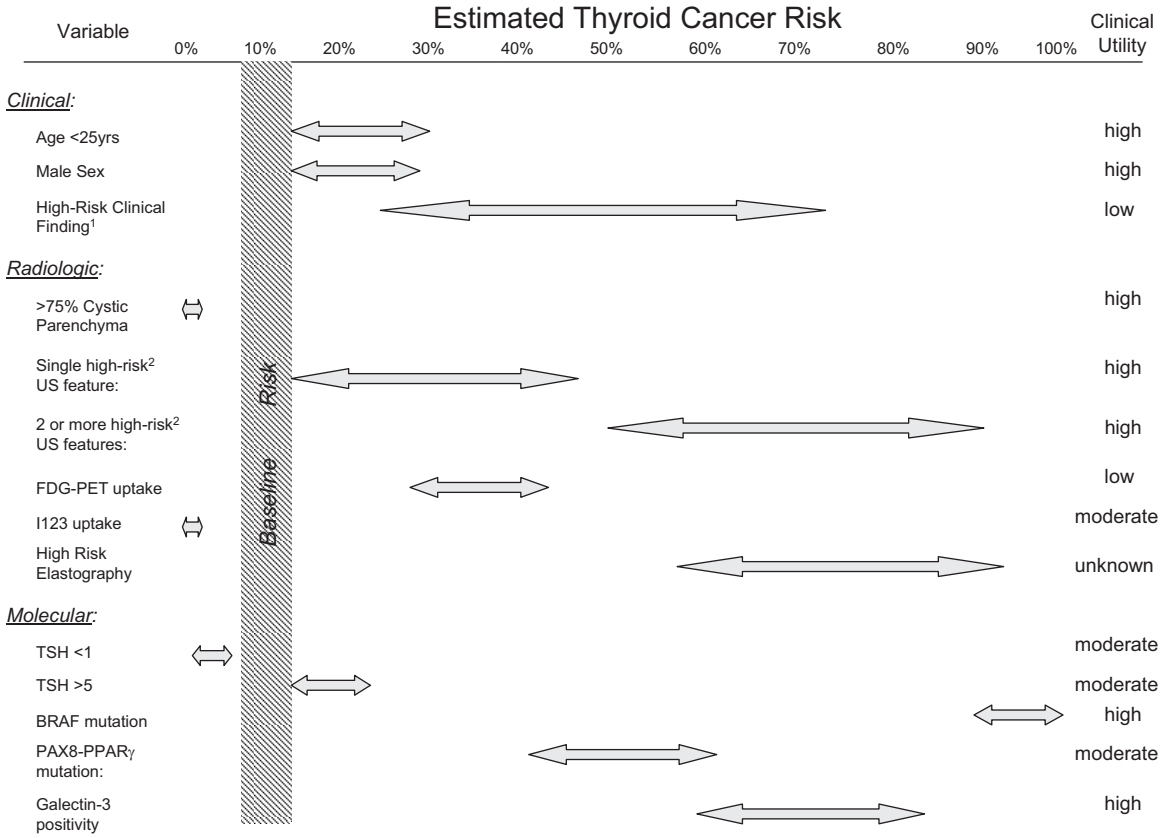

FIG. 1. Modification of cancer risk in thyroid nodules larger than 1 cm in diameter based on the presence or absence of clinical, radiological, or molecular variables. Based on epidemiological data, a baseline 8–15% cancer risk is assumed and shown in the *shaded* section. The clinical utility of each variable in clinical practice is estimated to the *right*, as influenced by the cost, risk, and prevalence of the finding. 1) High-risk clinical findings include exposure to ionizing radiation before age 16 yr, fixation of the nodule to surrounding neck structures, new-onset persistent hoarseness of voice, and known medullary thyroid carcinoma in a first-degree relative. 2) High-risk ultrasound findings include the presence of microcalcifications, hypoechoic parenchyma, irregular nodule borders, hypervascularity (assessed by Doppler), and abnormal lymphadenopathy.

Two groups have investigated serum TSH concentrations in patients with thyroid nodules, both confirming that higher concentrations are associated with higher risk of malignancy (16, 30). In general, TSH concentrations above the mean normal range are associated with a 2- to 3-fold increased risk that a nodule is cancerous. Prospective validation of these findings, however, is not available.

Molecular assessment of cellular DNA mutations or protein expression commonly discovered in cancerous nodules is likely to become a mainstay of FNA cytology assessment into the future. Among many suggested markers, the protein galectin-3 appears highly promising. Cytology samples that stain positive for galectin-3 are far more likely to prove cancerous on final histopathological analysis compared with those that do not. A recent study of over 450 patients with indeterminate FNA cytology confirmed that galectin-3 positivity conveyed a 5-fold increased cancer risk (31). Although not a universal marker of malignancy, such a high association with cancer suggests this marker may hold great promise.

Similarly, BRAF point mutations at residue 599 (V599E) and 600 (K600E) have been strongly associated with papillary thyroid carcinoma (32, 33). Such mutations are present in approximately 45–50% of papillary carcinomas, and diagnostic mutational analysis can be effectively performed on most indeterminate FNA aspirates. When detected, the positive predictive value is very high. Therefore, although this marker has only a modest negative predictive value, its presence in material from indeterminate cytology aspirates increases papillary carcinoma risk 7- to 9-fold above baseline. Recently, combined analysis of galectin-3 and BRAF mutation status was performed on indeterminate FNA aspirate samples, demonstrating a substantial increase in the ability to preoperatively define benign from malignant nodules (34). A separate although less sensitive molecular marker of thyroid cancer involves detection of a novel translocation t (2;3)(q13;p25), leading to the formation of a chimeric PAX8-PPARγ1 oncogene. When detected, this translocation predicts a nearly 3-fold increased risk that a nodule is cancerous (usually follicular carcinoma) in comparison with standard baseline risk (35–36). Finally, detection of the RET/PTC gene rearrangement has also proven predictive of thyroid cancer (37). Importantly, serum TSH, galectin-3, BRAF, PAX8-PPARγ1, and RET/PTC mutations all appears to be mostly independent risk factors. Thus, combined analysis of multiple markers is likely to hold the greatest clinical utility.

Most recently, investigators have studied the potential of separate molecular markers including the presence of trisomy 17 in FNA aspirates (38) as well as distinct profiles of aspirate microRNA (39). Each has demonstrated initial promise, although formal testing to define their full utility in clinical practice remains ahead. To conclude, the presence or absence of molecular mark-

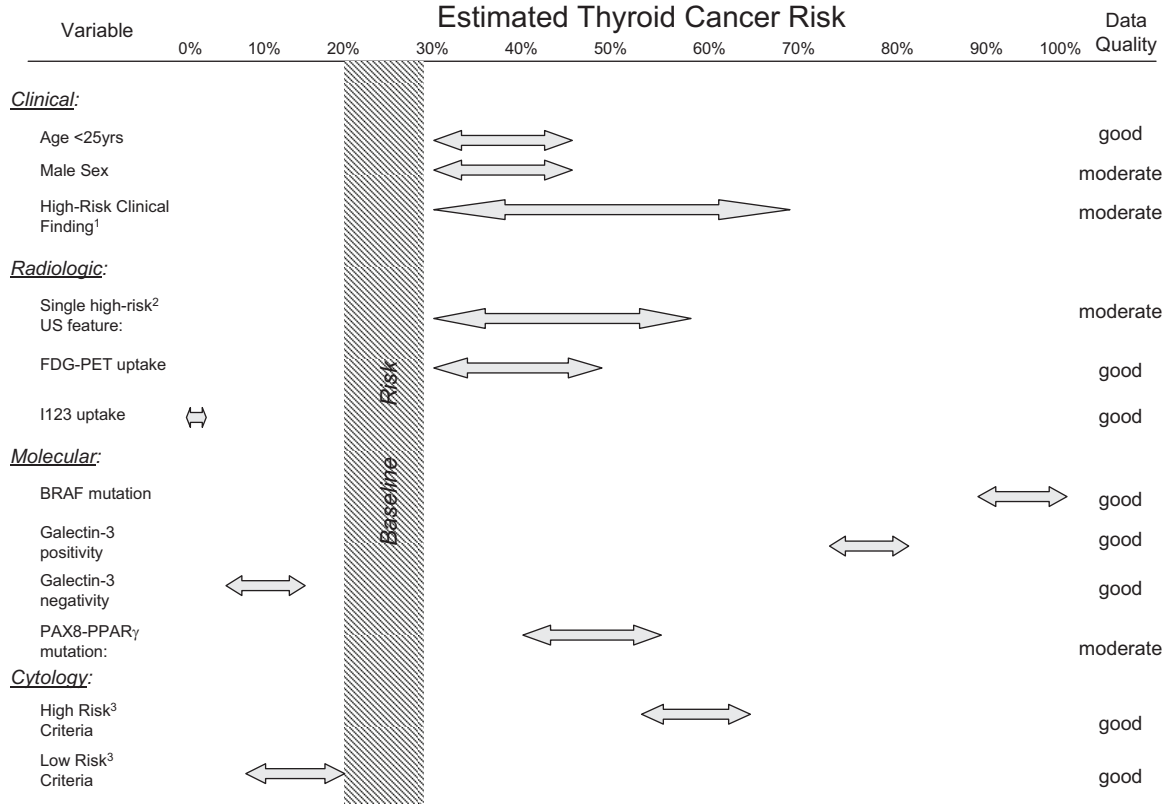

FIG. 2. Modification of cancer risk in thyroid nodules larger than 1 cm in diameter with indeterminate FNA cytology based on the presence or absence of clinical, radiological, or molecular variables. Based on epidemiological data, a baseline 20–30% cancer risk is assumed and shown in the *shaded* section. Data quality of each variable specific to nodules with indeterminate FNA cytology is estimated to the *right*. 1) High-risk clinical findings include exposure to ionizing radiation before age 16 yr, fixation of the nodule to surrounding neck structures, new-onset persistent hoarseness of voice, and known medullary thyroid carcinoma in a first-degree relative. 2) High-risk ultrasound findings include the presence of microcalcifications, hypoechoic parenchyma, irregular nodule borders, hypervascularity (assessed by Doppler), and abnormal lymphadenopathy. 3) High-risk cytology criteria include the presence of some, but not all, of the features of papillary carcinoma, including crowded cells, enlarged nuclei with pale, powdery chromatin, nuclear grooves, nuclear pseudo-inclusions, distinct nucleoli, papillary structures, and psammoma bodies as defined in Refs. 6 and 7. Low-risk cytology criteria excludes the presence of microfollicles and refers to the presence of rare and/or mildly abnormal cells, not definitively benign or suspicious for malignancy as defined in Ref. 6.

ers, either in the serum or in FNA aspirate material, is increasingly demonstrating ability to provide additive risk assessment for thyroid nodules. Data confirm the influence of these markers upon the cancer risk in newly discovered thyroid nodules (Fig. 1) as well as those with indeterminate FNA cytology (Fig. 2).

Subclassification of indeterminate cytology

Traditionally, FNA cytology specimens have been classified into three broad diagnostic categories – benign, malignant, or indeterminate. Growing consensus, however, suggests that the indeterminate category remains too broad, and improved risk assessment can be performed via subclassification (6). Many high volume FNA centers have separately classified cytology demonstrating predominantly microfollicles from those with nuclear characteristics suspicious for, but not diagnostic of, papillary carcinoma (4, 7). The former aspirates are often classified as suggestive of a follicular neoplasm, whereas the latter is suspicious for papillary carcinoma. The utility of this modest change surrounds the change in cancer risk associated with each category, which increases from 20–30% in aspirates suggestive of a follicular neoplasm to 40–60% in aspirates suspicious for papillary carcinoma. More recently, some centers have also formulated a separate subcategory of indeterminate aspirates termed atypical of an undetermined significance. Such aspirates often exhibit rare atypical features, but the predominance of evidence suggests benignity. Some recommend repeat FNA of these nodules, demonstrating that approximately 50% will prove benign on repeat FNA (4), although surgical validation of these findings is not available. Of those persistently atypical of an undetermined significance, only 20–25% prove cancerous after surgical removal. Together, these above data support the utility of a more complex subcategorization of indeterminate cytology (Table 1). Pathologists and cytologists increasingly acknowledge that cancer risk lies on a continuum that can be more precisely defined.

Multivariate, unifying approaches to risk assessment

Despite the advances described above, it remains clear that no single risk factor is likely to prove perfectly predictive of benign and malignant disease. However, many of the variables currently investigated appear mutually independent. Thus, the ability to assess risk in a multivariate fashion has long been sought and is increasingly proving beneficial. For example, several studies have combined clinical, sonographic, and cytological assessment to identify patients at risk of cancer (11–12, 24, 40–41). Nearly all combined analyses demonstrate significant improvement in

predictive power. However, the lack of prospective, multi-institutional investigations has hampered widespread applicability of these models into clinical practice. Furthermore, published multivariate analyses often use different combinations of sonographic, clinical, and molecular variables, making direct comparisons of superiority (or inferiority) impossible. Nonetheless, these investigations represent the beginnings of a process that appears to hold great promise for transforming the clinical care of patients with indeterminate nodule aspirates. The clinical benefit of such models is already evidenced in the fields of cardiovascular or oncological illness.

Controversies and Uncertainties

Despite the potential conveyed by the data above, many controversies and uncertainties have prevented widespread change in clinical recommendations for patients with indeterminate cytology. Almost all investigations to date represent single institution experiences. Concern of high interobserver variability in sonographic and molecular analysis has precluded detailed assessment of an individual's cancer risk outside of a specific healthcare institution. Multi-institutional studies investigating sonographic variables are underway, although even these will fail to incorporate molecular assessment. Ultimately, a large prospective assessment of all variables in combination holds the greatest promise for finding translatable answers. Thereafter, a separate discussion must ensue that questions at what level of risk (or benefit) we can achieve consensus to recommend nonsurgical management of an indeterminate nodule. Or *vice versa*?

Separately, pathologists and cytologists must seek to unify the classification system for indeterminate cytology (6). Data confirm the ability to subclassify indeterminate thyroid nodule aspirates, which can prove highly valuable to endocrinologists and surgeons alike. The benefits of adopting standard terminology (linked to clearly defined and unambiguous cytology findings) can be witnessed from similar consensus achieved for the evaluation of cervical Papanicolaou smears. Currently, no such consensus exists for thyroid FNA cytology interpretation. This is particularly harmful given the multidisciplinary care of these patients. At present, physicians must learn what is meant by their institution's unique terminology (Table 1). This lack of standardization increases interobserver variability, even within a single healthcare institution.

Others have questioned whether FNA should be repeated after an indeterminate aspirate. Some argue that a larger sample provides better analysis of the true cellular process, whereas others suggest that a benign reading on secondary aspiration may provide false assurance of benignity despite cancer that was simply not sampled effectively on the second FNA. Answers to this debate remain unclear, although at present, several centers are recommending repeat FNA only on those nodules with low-risk indeterminate cytology (often labeled atypical cells of undetermined significance).

Finally, should nodules with indeterminate cytology undergo hemi- or near-total thyroidectomy? At present, many centers favor hemi-thyroidectomy for all indeterminate lesions, given the probability for benign disease and the possibility that exogenous levothyroxine will not be required if half the normal thyroid remains. Hemi-thyroidectomy is also associated with much lower risk of parathyroid complications. However, if cancerous, routine recommendation for completion thyroidectomy is made. Better preoperative assessment of cancer risk appears to hold great promise for modifying these recommendations and assisting with these decisions. Importantly, diagnostic and therapeutic decisions must be based on numerous factors inclusive of both cancer risk as well as patient preference and overall risk/benefit analysis. Many centers are increasingly favoring near-total thyroidectomy for nodules with cytology suspicious for papillary carcinoma, whereas hemi-thyroidectomy is favored for those demonstrating findings consistent with a follicular neoplasm or with low-risk atypical features of an undetermined significance.

Returning to the Patient

Thyroid ultrasound confirmed the thyroid nodule was hypoechoic and with approximately 25% cystic fluid, although no calcifications or irregular borders were present. These findings, combined with the patient's gender and TSH concentration, suggested an approximate 2-fold increase in cancer risk from baseline. As noted, aspiration cytology demonstrated cells suspicious for papillary carcinoma, a category that carried a 60% risk of malignancy at the patient's healthcare institution. Together, the patient was advised that his risk of thyroid carcinoma appeared between 50 and 75%, and near-total thyroidectomy was recommended. The procedure was performed without complication.

Histopathological analysis confirmed a 2.5-cm follicular variant of papillary carcinoma, without lymph node metastasis. The patient is fully recovered and has resumed normal activities.

Conclusion

Thyroid nodular disease is increasingly common. Initial assessment of biochemically euthyroid patients is based primarily on FNA, because this allows highly accurate determination of benign or malignant disease in most cases. However, nodule cytology remains indeterminate in nearly 15–25% of cases, raising suspicion of carcinoma. Although surgery is recommended in most of these cases, investigations are increasingly confirming the ability of clinical, sonographic, and molecular variables to predict final histopathological findings with greater accuracy. In the future, prospective, multi-institutional, multivariate studies will increasingly provide data with wider clinical applicability. As this happens, the ability to individualize treatment recommendations will improve the care for affected patients.

Acknowledgments

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