

Thyroid nodules and cancer management guidelines: comparisons and controversies

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Abstract

Thyroid cancer is an increasingly prevalent malignancy throughout the world. Management guidelines for both thyroid nodules and thyroid cancer have been published and updated by a number of societies internationally. All of these guidelines recognize this increasing incidence, particularly of small papillary thyroid cancers, due in part to improved technology enabling early or even 'over' diagnosis. Recent advances in molecular imaging and molecular methods have been developed to better characterize thyroid nodules, and a number of studies that have clarified risk stratification systems that can be modified over time allow for individualization of diagnosis, initial treatment, and subsequent follow-up strategies. Advances in surgical approaches and new treatments for patients with the most aggressive forms of thyroid cancer have all influenced management guidelines. Despite substantial similarities, there also are important differences between recent guidelines for some of the common clinical scenarios encountered by physicians in clinical practice. In the present manuscript, we will highlight similarities and differences between several of the most recently published guidelines focused on key areas of importance to clinical care and controversy. These are key areas for future research to strengthen the data to support future guideline recommendations.

Key Words

- ▶ thyroid
- ▶ carcinoma

Endocrine-Related Cancer
(2017) **24**, R13–R26

Introduction

Thyroid cancer is one of the most prevalent solid tumor types throughout the world with a rising incidence, particularly in women (Davies & Welch 2014). The range of prognosis for patients with thyroid cancer is highly variable with many small thyroid cancers having very little chance of causing tumor-specific morbidity or mortality to anaplastic thyroid cancer, which is one of the most lethal solid tumor types. To help clinicians practice the most informed and data-driven medical care, a number of societies have established clinical guidelines for thyroid nodules and thyroid cancer. These guidelines

are composed of evidence-based recommendations for particular clinical scenarios after scholarly review and discussion of the data by panels of clinical and research experts from nearly all specialties involved in the care of patients with thyroid cancer. Most guidelines are updated periodically to reflect additional data that influence clinical management over time. However, because these data are continually evolving, any guidelines documented will be slightly outdated at the time of publication. Finally, guidelines in general are meant to reflect the management for the majority of patients with the most common

responses (i.e. what has been studied in a particular study population). It should be recognized therefore that these are not 'rules' to be followed but rather recommendations and reviews of the literature to help guide clinical care of patients. Application of a guideline recommendation to an individual patient requires understanding not only of the guideline recommendation but also the data that support it and how closely a particular patient matches the study population. The details that support a particular recommendation (positive or negative) are features of some, but not all, published guidelines.

In this review, we will discuss several aspects of thyroid nodule and thyroid cancer management that have undergone major changes in recent years and present how different recent guidelines address these topics. These guidelines are those of the American Thyroid Association (ATA) published in 2016 (Haugen *et al.* 2016), the National Comprehensive Cancer Network (NCCN) guidelines most recently updated in 2016 (Haddad *et al.* 2016) and the British Thyroid Association (BTA) guidelines published in 2014 (Perros *et al.* 2014). We also included, when appropriate, guidelines endorsed by the American Association of Clinical Endocrinologists (AACE), American College of Endocrinology and Associazione Medici Endocrinologi focused only on thyroid nodules and the initial surgical management of thyroid nodules and cancer (Gharib *et al.* 2016). Although there are other guidelines available, we tried to limit that to those updated most recently to the completion of this manuscript to keep with more current understanding of the field.

Thyroid nodule: to perform FNA or not to perform FNA?

The incidence of thyroid cancer is rising worldwide; however, mortality attributed to thyroid cancer has been stable or dropping (Davies & Welch 2014) and the greatest increase in incidence is in patients with small (T1) papillary cancers (Hughes *et al.* 2011). The sharp increase in incidence over the past three decades has been associated with the development of widely available sensitive detection methods such as thyroid ultrasound and the increased availability of ultrasound-guided fine-needle aspiration (FNA) (Ezzat *et al.* 1994, Youserm *et al.* 1997, Steele *et al.* 2005, Ahmed *et al.* 2012, Hall *et al.* 2014, Altekruse *et al.* 2015) raising concern for clinical overdiagnosis. Consistent with this concept are data associating the highest thyroid cancer incidence with the density of endocrinologists in a particular region (Udelsman & Zhang 2014). Interesting epidemiological studies also have supported a positive association between thyroid cancer and obesity, similar

to several other solid organ cancers (Han *et al.* 2013). Although overall evidence suggests that the vast majority of the rising incidence is due to the detection of subclinical thyroid cancers, there has also been a smaller concomitant increase in the number of larger tumors diagnosed as well as a progressive rise in the number of thyroid cancer-related deaths reported annually (Ito *et al.* 2013). These data suggest that there may be a smaller but persistent change in thyroid cancer over time, a possibility raised by data demonstrating changes in the frequency of mutations in thyroid cancers diagnosed in the last several decades (Jung *et al.* 2014).

Nonetheless, it is not clear that diagnosis at a very early stage improves the overall outstanding prognosis of patients with thyroid cancer, and there is evidence that monitoring documented small papillary cancers without surgery can be performed safely for prolonged periods of time (Ito *et al.* 2010). There also are defined risks of surgical intervention that can influence quality of life such as recurrent laryngeal nerve injuries, hypoparathyroidism and hypothyroidism as well as the potential financial and psychological impacts of a cancer diagnosis (Ramsey *et al.* 2013). For these reasons, it is critical that the physician determines first if a nodule even requires further evaluation by FNA or if it can be monitored without intervention, striking the balance between avoiding unnecessary intervention on small benign nodules and clinically insignificant thyroid cancer while not missing more aggressive cancers that can occasionally occur.

The four guidelines (ATA (Haugen *et al.* 2016), NCCN (Haddad *et al.* 2016), BTA (Perros *et al.* 2014)

Table 1 Suspicious sonographic characteristics of thyroid nodules that are used in forming patterns of risk stratification.

	ATA (2016)	BTA (2014)	NCCN (2016) ^b	AACE/ AME-AME (2016)
Micro-calcifications	Yes	Yes	Yes	Yes
Taller than wide	Yes	Yes	Yes	Yes
Irregular borders	Yes	Yes	Yes	Yes
Extrathyroidal extension	Yes	Yes	Yes	Yes
Vascularity	No	Yes	ND	Yes ^a
Hypoechoic	Yes	Yes	Yes	Yes
Disrupted rim calcifications	Yes	Yes	ND	Yes
Absence of halo	No	Yes	ND	Yes

^aAlthough intranodular vascularity was used to assess risk of thyroid cancer in thyroid nodules, it was not part of the features that make a nodule high-risk thyroid lesion (Table 2). ^bAdapted with permission from Haddad RI, *et al.*, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Thyroid Carcinoma Version 1.2016. Copyright 2016 National Comprehensive Cancer Network, Inc. Available at NCCN.org. Accessed: November 4, 2016. ND, not discussed.

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Table 2 FNA recommendations based on guidelines according to different cutoff sizes.

Size	ATA (2016) ^a	BTA (2014) ^b	NCCN (2016) ^c	ACE/ACE-AMA (2016) ^d
0.5–1 cm	Personalized approach in the absence of extrathyroidal extension, metastatic cervical nodes or distant metastases	Personalized approach	Not recommended	Personalized approach Recommend FNA for: <ul style="list-style-type: none"> • Sub-capsular or paratracheal lesions • Suspicious nodes or extrathyroidal spread • Positive personal or family history of thyroid cancer, history of head and neck radiation and coexistent suspicious clinical findings High-risk thyroid lesion
1 cm	1. High suspicion pattern 2. Intermediate suspicious pattern ^a	1. Nodule with features that are intermediate, equivocal, suspicious or malignant ^b 2. If extrathyroidal extension or metastatic cervical nodes, cutoff may differ	1. Solid nodule with suspicious sonographic features 2. Cystic/solid nodule with suspicious features if solid component is >1 cm	
1.5 cm	Low suspicion pattern	Further cutoff beyond 1 cm not mentioned	1. Solid nodule without suspicious features 2. Cystic/solid nodule without suspicious features if solid component is >1.5 cm	
2 cm	Very low suspicion pattern	Further cutoff beyond 1 cm not mentioned	Spongiform nodules	1. Intermediate-risk thyroid lesion 2. Low-risk thyroid lesions (>2 cm and increasing in size or associated with high-risk category and before thyroid surgery or minimally invasive ablation therapy)
No biopsy	Benign appearance	Benign appearance	Simple cyst	Excluding the above, biopsy is not recommended

^aATA classifications of suspicious features: *High suspicion* – Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule with one or more of the following features: irregular margins (infiltrative, micro lobulated), micro calcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of ETE. *Intermediate suspicion* – Hypoechoic solid nodule with smooth margins without microcalcifications, ETE, or taller than wide shape. *Low suspicion* – Isoechoic or hyperechoic solid nodule or partially cystic nodule with eccentric solid areas, without microcalcifications, irregular margin or ETE or taller than wide shape. *Very low suspicion* – Spongiform or partially cystic nodules without any of the sonographic features described in low, intermediate or high suspicion patterns. *Benign* – Purely cystic nodules (no solid component). ^bBTA classifications of suspicious features: *Benign appearance* – a-halo, isoechoic/mildly hyperechoic, b-cystic changes \pm ring down sign (colloid), c-micro-cystic/spongiform, d- and e-peripheral eggshell calcification, f-peripheral vascularity. *Intermediate/equivocal* – a-homogenous, hyperechoic (markedly), solid, halo (follicular lesion), b-hypoechoic, equivocal echogenic foci, cystic changes, c-mixed central vascularity. *Suspicious* – a-solid hypoechoic relative to thyroid, b-solid very hypoechoic relative to strap muscle, c-disrupted peripheral calcifications, hypoechoic, d-lobulated nodule. *Malignant* – a-solid, hypoechoic, lobulated irregular outline, microcalcifications, b-solid, hypoechoic, lobulated irregular outline, globular calcifications (? medullary cancer), c-intranodular vascularity, d-shape taller than wide, e-characteristic associated lymphadenopathy. ^cNCCN guidelines classifications of suspicious features: Adapted with permission from Haddad RI, et al., NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Thyroid Carcinoma Version 1.2016. Copyright 2016 National Comprehensive Cancer Network, Inc. Available at NCCN.org. Accessed: November 4, 2016. *Suspicious US features* – Hypoechoic, micro calcifications, infiltrative margins, taller than wide in transverse plane. ^dAAACE/ACE-AME: *High-risk thyroid lesion* – Marked hypoechogenicity, microcalcifications, irregular (speculated) margins, more tall than wide, extracapsular growth, suspicious regional lymph node. *Intermediate-risk thyroid lesion* – Isoechoic nodule with central vascularity, isoechoic nodule with macrocalcifications, isoechoic nodule with indeterminate hyperechoic spots, isoechoic nodule with elevated stiffness on elastography. *Low-risk thyroid lesion* – Thyroid cyst, mostly cystic nodule with reverberating artifacts, isoechoic spongiform nodule.

and AACE/ACE-AME (Gharib *et al.* 2016)) all describe sonographic features of thyroid nodules and then use a constellation of these features to determine the risk of malignancy (Tables 1 and 2). The guidelines then use these features to help determine if FNA should be performed. The use of patterns consisting of more than one sonographic feature carries with it good inter-observer agreement (Russ *et al.* 2013) and compared to individual features, is a better predictor of malignancy (Remonti *et al.* 2015). Overall, there is a general agreement on the sonographic features that make a nodule more suspicious for malignancy. However, it is notable that vascularity, particularly the presence of central vascularity is included in the sonographic nodule features to evaluate in the BTA, NCCN and AACE/ACE-AME guidelines but is not included in the ATA guidelines, which cited a study by Moon and coworkers demonstrating no diagnostic value of intranodular vascularity in predicting malignancy (Moon *et al.* 2010). Only the AACE-ACE-AME guidelines included ultrasound elastography in the evaluation of thyroid nodules. All guidelines recommend a personalized approach regarding nodules smaller than 1 cm that depends on the presence of additional high-risk clinical features such as history of radiation exposure or if it is FDG-avid on PET scan if one has been obtained or was involved in the nodule detection.

Another area of personalized approach is a patient with a family history of thyroid cancer who presents with a thyroid nodule. Although this is discussed as a potential harbinger of more aggressive disease, the data to support this assertion are weak (Naing *et al.* 2009, Mosci & Jagaru 2011, Pinto *et al.* 2014, Wang *et al.* 2015b), creating some controversy regarding this area. It is generally acknowledged that these patients present a more unique situation where a more personalized approach should be implemented.

Although size alone does not predict malignancy, the size criteria are recognized by all three guidelines in that thyroid cancers smaller than 1 cm are unlikely to increase risk of mortality (Jeon *et al.* 2016) or to be associated with distant metastases (Machens *et al.* 2005, Jeon *et al.* 2016) especially when US does not show malignant cervical lymph nodes (Jeon *et al.* 2016). Thus, a more conservative approach is commonly recommended.

Overall, there is consensus between the guidelines on recommending FNA for nodules larger than 1 cm in size that have the following sonographic features: solid, hypoechoic, micro-calcifications, extrathyroidal extension, irregular border and taller than wide dimensions.

Once it has determined that an FNA cytology result would influence clinical management, either by likely 'ruling-out' a malignancy or by identifying a potentially clinically significant thyroid cancer, the test is recommended to be performed under sonographic guidance. A greater emphasis on how comorbidities that might affect 'actionable' results from FNA results likely will be more visible in future guidelines. For example, a patient with non-thyroid life-threatening diseases is not likely to undergo thyroidectomy regardless of FNA results; therefore, FNA would not typically be performed.

The presence and multiplicity of thyroid nodules are more common with aging, and the risk of thyroid cancer in the aging population is lower on a per-nodule basis (Kwong *et al.* 2015). Furthermore, older patients with papillary microcarcinoma who are conservatively observed without surgery are reported to be less likely to progress during follow-up compared to younger patients (Ito *et al.* 2014). Therefore, a more conservative approach also may be more appropriate in this population. However, it should also be emphasized that although thyroid cancer is less likely to be diagnosed when thyroid nodules are found in the elderly, the risk of an aggressive thyroid cancer is higher (Kwong *et al.* 2015) and therefore a conservative approach should be carefully selected in these patients.

Finally, measurement of basal or stimulated serum calcitonin as part of the initial work-up in a patient with a thyroid nodule remains controversial. Because medullary thyroid cancer (MTC) is treated more aggressively surgically than other forms of thyroid cancer, even when small in size, the preoperative diagnosis will influence management. Furthermore, MTC can be difficult to clearly diagnose on FNA cytology (Essig *et al.* 2013). These particular guidelines do not recommend calcitonin measurement routinely in patients with thyroid nodules, although it is recommended by other guidelines documents (Pacini *et al.* 2006). Because MTCs often are interpreted to be follicular neoplasm (FN) or follicular lesions of undetermined significance (FLUS) on cytology, molecular testing may identify some of these nodules preoperatively (see below) or tailoring the measurement of serum or FNA calcitonin to patients with these cytological diagnoses may be considered.

Thyroid nodule: indeterminate FNA cytology results and molecular diagnostics

Over the past several years, a criteria system (Bethesda Classification) has been developed with a goal to improve

the diagnostic consistency of cytology (Cibas *et al.* 2009). However, even with the implementation of the system, data also have highlighted tremendous inter- and even intra-pathologist variability in FNA cytological diagnosis (Cibas *et al.* 2013). This is true particularly for samples that are read as having atypical cells of undetermined significance (AUS), FLUS or FN (Cibas *et al.* 2013). A meta-analysis showed a rate of non-diagnostic results at 12.9% and a rate of indeterminate result based on the Bethesda system (AUS, FLUS, FN, suspicious for FN or suspicious for malignancy (SM)) at 22.4% with a wide range between institutions (Bongiovanni *et al.* 2012). The use of other biomarkers, immunostains and molecular testing has been studied and remains controversial based on both cost and accuracy considerations.

Attempts to further classify these cytologically indeterminate nodules have been actively pursued in recent years and are now part of the lexicon of clinical practice. The molecular diagnostic tests rely either on detecting gene mutations/rearrangements in DNA, expression levels of mRNA and/or expression of miRNAs. Ideally the positive and negative predictive values of a molecular diagnostic test should be at least similar to that of malignant or benign cytology, respectively. This predictive value is affected by the prevalence of thyroid cancer in each of the indeterminate cytology result, which varies between institutions and different cytologists and also is influenced by clinical and radiographic features for individual patients. For example, a lower predicted prevalence of thyroid cancer in a particular patient will reduce the positive predictive value (PPV) of a molecular diagnostic test and increase its negative predictive value (NPV) and a higher prevalence rate will yield a higher PPV and a lower NPV (Ferris *et al.* 2015). Therefore, in nodules where risk of malignancy is high, as in highly suspicious nodules on US or when cytology reading is suspicious for malignancy, the use of these molecular diagnostic tests may not be helpful in further classifying the nodule. On the other hand, cytological readings of AUS/FLUS/SFN/FN in nodules that are indeterminate and not highly suspicious on US are cases where molecular diagnostic tests may be helpful as the usual risk of cancer in these readings is reported to vary from 6 to 48% for AUS/FLUS and 14 to 34% for FN (Ferris *et al.* 2015).

Available molecular diagnostic tests include gene expression using a mRNA transcriptional profile (Alexander *et al.* 2012), a seven-gene panel of somatic point mutations and gene rearrangements (Nikiforov *et al.* 2011), a 60-gene, next-generation sequencing panel (Nikiforov *et al.* 2015), a combination of

a somatic gene panel with miRNA levels (Lodewijk *et al.* 2012, Labourier *et al.* 2015, Wylie *et al.* 2016) and a miRNA-only panel (Peng *et al.* 2014, Stokowy *et al.* 2016). The published studies evaluating the diagnostic utility of these tests have included a prospective blinded study (Alexander *et al.* 2012), prospective non-blinded studies (Nikiforov *et al.* 2011, 2015, Labourier *et al.* 2015) and a large number of retrospective studies. It is difficult to fully compare these results as none have directly compared more than one test on the same samples. For these reasons, and due to the variability in some of the results, the ATA guidelines have focused on the anticipated achievable accuracy in individual patients. Specifically, they have described that an ideal 'rule-in' test would have a PPV for histopathologically proven malignancy similar to a malignant cytological diagnosis (98.6%), and an ideal 'rule-out' test would have a NPV similar to a benign cytological diagnosis (96.3%) (Haugen *et al.* 2016). The NCCN panel has similar recommendations (Haddad *et al.* 2016). Further complicating the interpretation of the prior data is the recent reclassification of encapsulated follicular variants of PTC without vascular or capsular invasion into a new non-malignant category termed non-invasive follicular tumors with papillary features (NIFTP) (Nikiforov *et al.* 2016). This category comprises tumors that previously may have been identified as malignant based on pathology review in the clinical studies. This change in classification may lead to further modifications in the molecular tests and/or re-analysis of previously published data recognizing the challenge that this is a post-operative diagnosis made on surgical pathology. Finally, the availability of only certain molecular tests varies in different countries, a factor that will influence their impact on clinical practice in different locations.

The use of molecular diagnostic tests to classify nodules to predict cancer behavior likely will evolve in the future as molecular markers are developed. For example, the data support that mutations in the promoter of *TERT*, particularly when they co-occur with BRAF V600E are associated with a poor prognosis (Liu & Xing 2014, 2016). The inclusion of these tests on panels in FNA samples may allow studies to determine the potential predictive value of the mutations when applied to thyroid nodule FNA samples. Caution needs to be exercised to apply molecular testing to specific populations, such as patients with papillary microcarcinoma, due to the overwhelmingly outstanding prognosis of nearly all patients with these small tumors despite an ~20% prevalence of BRAF V600E that in large population studies is associated with more aggressive behavior (de Biase *et al.* 2015).

Table 3 Recommendation on indeterminate cytology results.

	ATA (2016)	BTA (2014)	NCCN (2016) ^a	AACE/ACE-AMA (2016)
Suspicious for malignancy	Surgical management similar to that of malignant cytology. Mutational testing considered if would alter surgical plan	Diagnostic hemithyroidectomy	Treat as malignant cytology	Surgery
Follicular neoplasm/suspicion for follicular neoplasm	Surgery or molecular testing depending of clinical risk factors, sonographic pattern and patient preference	Diagnostic hemithyroidectomy	If high risk clinically consider lobectomy or total thyroidectomy. If not, consider diagnostic lobectomy, molecular diagnostics (category 2B) ^b may be employed; if low risk or patient preference, observation may be considered	Surgery in most cases Consider surveillance in a minority of patients Consider molecular testing to reinforce conservative approach
Atypia of undetermined significance	Repeat FNA, molecular testing, observation or surgery depending on clinical risk factors, sonographic pattern and patient preference	Repeat FNA	If high risk clinically consider lobectomy or total thyroidectomy. If not; consider diagnostic lobectomy, molecular diagnostics (category 2B) ^b , repeat FNA or observation may be recommended	Repeat FNA Consider surveillance with reassuring clinical, sonographic and elastography features. Consider molecular testing

^aAdapted with permission from Haddad RI, et al., NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Thyroid Carcinoma Version 1.2016. Copyright 2016 National Comprehensive Cancer Network, Inc. Available at NCCN.org. Accessed: November 4, 2016.

Table 3 summarizes the approach to indeterminate FNA results according to the four guidelines. The four guidelines agree with the surgical approach for suspicious of malignancy cytologies as this portends a higher risk of malignancy and they recommend options of repeating FNA (mainly in AUS/FLUS), surgery or molecular diagnostics taking into consideration clinical and sonographic factors in the other indeterminate categories. BTA and AACE/ACE-AME guidelines specifically recommend a multidisciplinary team in cases where there is an indeterminate cytology. This recommendation emphasizes the importance of direct communications between the different physicians involved in the case of the patient such as endocrinologist, cytologist and surgeon to come up with best plan of care.

Thyroid cancer: surgical questions

As described previously, active surveillance of papillary thyroid microcarcinomas may be an alternative approach to surgery as most of these cancers do not progress and those that do can then be managed surgically in most cases without apparent effect on the overall prognosis (Ito *et al.* 2010, Sugitani *et al.* 2010). It has been suggested that an ideal candidate for observation will be the one with a solitary thyroid nodule with well-defined margins with at least 2 mm

normal thyroid tissue surrounding it without malignant lymph nodes, extrathyroidal extension or suspicious for distant metastases (Brito *et al.* 2016). This ideal patient should also be followed by experts with available high-quality sonogram and with emphasis on compliance for follow-up visits (Brito *et al.* 2016).

Active surveillance is not recommended management for cytologically proven thyroid cancer in the published guidelines unless surgery is high risk (AACE/ACE-AME); however, the 2016 ATA guidelines refer to this option when it is noted that if cancer is smaller than 1 cm and surgery is *chosen* it should be lobectomy unless there are additional features such as extrathyroidal extension or previous history of radiation. More data are likely to emerge on active surveillance of thyroid cancer in additional populations to determine if this is an acceptable option for all patients with small thyroid nodules. This conservative approach may be even more reasonable with patients with major comorbidities and likely is common in clinical practice already. It is also possible that molecular markers may better define populations in whom monitoring is appropriate in the future, including patients with larger nodules.

If surgery is planned, the extent of the procedure is the next clinical decision in patient management addressed by the guidelines. The options include: hemithyroidectomy, bilobar surgery ('total' thyroidectomy) or bilobar surgery

Table 4 Conditions where it is acceptable to consider hemithyroidectomy when FNA biopsy is proven to be malignant by different guidelines.

ATA (2016) ^a	BTA (2014) ^b	NCCN (2016) ^c	AACE/ACE-AME (2016)
No prior radiation	No prior radiation	No prior radiation	Extent of surgery is based on preoperative staging and the clinical setting
No distant metastases	No distant metastases	No distant metastases	
No cervical lymph node metastases	No cervical lymph node metastases	No cervical lymph node metastases	
No ETE	No ETE	No ETE	
T <4 cm	T <4 cm	T <4 cm	
No familial disease	No familial disease		
Unifocal	<45 years Unifocal No angioinvasion		

^aIf surgery is chosen for thyroid microcarcinoma, without extrathyroidal extension and cervical nodal metastases, the initial surgical procedure should be lobectomy unless there are clear indications to remove the contralateral lobe. ^bPersonalized decision making is recommended. Also for micro-PTC, thyroid lobectomy is recommended for unifocal disease without the following identified risk factors: non-incidental tumors, being PET positive, 6–10 mm in size, bilateral or multifocal, poorly differentiated, having extrathyroidal extension and with desmoplastic fibrosis and/or infiltrative growth pattern. ^cAdapted with permission from Haddad RI, *et al.*, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Thyroid Carcinoma Version 1.2016. Copyright 2016 National Comprehensive Cancer Network, Inc. Available at NCCN.org. Accessed: November 4, 2016. In addition to what is listed, if lobectomy is performed, completion thyroidectomy is recommended if there is vascular invasion, macroscopic multifocal disease or positive surgical margins. ETE, extrathyroidal extension.

with neck dissection. Compared to total thyroidectomy, hemithyroidectomy has the advantages of potentially decreasing the surgical risk and the possibility of maintaining a euthyroid state in some patients with normal thyroid function preoperatively. This is balanced against the potential need for reoperation based on the surgical pathology findings. Total thyroidectomy has the advantages of having one surgery from the beginning and enabling easier monitoring of thyroglobulin and neck ultrasounds postoperatively in the event that cancer is diagnosed.

Cost analyses comparing hemithyroidectomy vs total thyroidectomy have shown variable results mostly dependent on rate of complications with total thyroidectomy. For example, Corso and coworkers in Colombia (Corso *et al.* 2014) showed that total thyroidectomy was more cost-effective than hemithyroidectomy; however, when the rates of recurrent laryngeal nerve injury and hypoparathyroidism exceeded 8% and 9%, respectively, hemithyroidectomy became more cost effective. Leiker and coworkers also showed total thyroidectomy to be more cost-effective; however, there was a trend toward more cost-effectiveness with thyroid lobectomy with increasing rates of unilateral (>5%) or bilateral (>2%) RLN injury associated with total thyroidectomy (Leiker *et al.* 2013).

When considering the extent of surgery for a FNA-diagnosed thyroid cancer, all the guidelines recommend total thyroidectomy when the size of the cancer is above 4 cm, local invasion is likely

on the imaging or abnormal nodes are identified preoperatively. In addition, ATA, BTA and NCCN agree that intrathyroidal tumors between 1 and 4 cm represent a 'gray zone' whereby either hemithyroidectomy or total thyroidectomy are appropriate depending on the clinical features and patient and clinician wishes. The AACE/ACE-AME generally states that extent of surgery is based on preoperative staging and the clinical setting. Hemithyroidectomy or no surgery with subsequent active surveillance is the approach to known microcarcinomas as noted previously. Table 4 summarizes the approach of the four guidelines to hemi vs total thyroidectomy. Prophylactic central neck dissection in general is not recommended other than in the case of medullary thyroid cancer and/or in the case of larger tumors with suspected local invasion or tumors with poor differentiation. Long-term monitoring of patients after hemithyroidectomy requires more studies to determine the appropriate follow-up plan in terms of imaging and appropriate cutoff of Tg and also TSH target (see discussion in the 'Dynamic stratification' section below regarding Tg cutoff level in this scenario).

Radioactive iodine: to treat or not to treat?

The guidelines (ATA, BTA and NCCN as the AACE/ACE-AME do not cover thyroid cancer management beyond surgery) agree that patients with low-risk thyroid cancer with no known or likely evidence of residual

disease after surgery should not be treated with I-131, that patients with high-risk thyroid cancer should be treated with I-131, and that selective use should be implemented in patients who are at intermediate risk (Table 5 summarizes the approach of the three guidelines to radioactive iodine treatment). Post-operative thyroglobulin levels and the details of the pathology are factors that classify patients into low- or high-risk categories after surgery. However, the extent of surgery will influence the acceptable thyroglobulin levels and imaging, features that are not fully discussed in the guideline documents. For example, in patients who had less than a total thyroidectomy, a higher thyroglobulin level may be explained by residual benign thyroid tissue. Therefore, before changing the risk category of a patient from low risk to intermediate solely

based on Tg level, it is important to assess for residual thyroid tissue by ultrasound several months after the surgery. Application of one cutoff of Tg across different practices and assays therefore remains challenging. In addition, the optimal strategies for patients with circulating anti-thyroglobulin antibodies have not been fully addressed due to limited data availability.

If a decision is made to treat a patient with RAI, there is agreement that a lower dose of 30 mCi is a reasonable dose for treating individuals with lower risk thyroid cancer. Two randomized, prospective studies (Mallick *et al.* 2012, Schlumberger *et al.* 2012) indicated that 30 or 100 mCi were equally effective in achieving successful ablation in patients with low-risk thyroid cancer with some patients (Mallick *et al.* 2012) also exhibiting intermediate-risk

Table 5 Guidelines for radioactive iodine administration.

RAI	ATA (2016) ^a	BTA (2014)	NCCN (2016) ^b	
Not recommended	ATA low risk and $T \leq 1$ cm N0/Nx M0/Mx	$T \leq 1$ cm unifocal or multifocal PTC or fvPTC or FTC Intrathyroidal No angioinvasion	PTC: Classic PTC <1 cm Intrathyroidal Unifocal or multifocal No detectable anti-Tg Abs Post op (6–12 weeks) unstimulated Tg <1 ng/mL T: 1–4 cm	FTC: $T < 2$ cm Intrathyroidal No vascular invasion Clinical N0 M0 No detectable anti-Tg Abs Post op (6–12 weeks) unstimulated Tg <1 ng/mL T: 2–4 cm
Selective use	ATA low to intermediate risk with T1b-T3 regardless of N status ATA low to intermediate risk with N1a or N1b regardless of T status ^a	T: 1–4 cm Minor ETE Unfavorable cell type Widely invasive Lymph nodes high ratio of positive to negative nodes Extra nodal extension $T > 4$ cm Gross ETE Distant metastases	High-risk histology Lymphatic invasion Cervical node metastases Macroscopic multifocality Post-operative unstimulated Tg <5–10 ng/mL T: >4 cm Gross ETE Post-operative unstimulated Tg >5–10 ng/mL Known or suspected distant metastases	Minor vascular invasion Cervical lymph node metastases Post-operative unstimulated Tg <5–10 ng/mL T: >4 cm Gross ETE Post-operative unstimulated Tg >5–10 ng/mL Extensive vascular invasion Known or suspected distant metastases
Recommended	ATA high risk			

^aThe ATA guidelines use the word 'Not Routine' for ATA low risk T1b-T2 patients and 'Consider' for ATA low-to-intermediate risk with $T > 4$ cm and 'Consider, generally favored' for ATA low-to-intermediate risk with microscopic ETE and/or N1 disease. ^bAdapted with permission from Haddad RI, *et al.*, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Thyroid Carcinoma Version 1.2016. Copyright 2016 National Comprehensive Cancer Network, Inc. Available at NCCN.org. Accessed: November 4, 2016. ETE, extrathyroidal extension.

Table 6 Dynamic assessment after initial treatment.

	Excellent response	Incomplete response	Indeterminate response	Structural recurrence
ATA (2016)	Negative imaging and either suppressed Tg <0.2 ng/mL Stimulated Tg <1 ng/mL	Negative imaging and suppressed Tg ≥1 ng/mL or stimulated Tg ≥10 ng/mL in the absence of anti-Tg antibodies or rising anti-Tg antibody levels	Nonspecific findings on imaging studies faint uptake in thyroid bed on RAI scanning nonstimulated Tg detectable, but <1 ng/mL stimulated Tg detectable, but <10 ng/mL in the absence of anti-Tg antibodies or anti-Tg antibodies stable or declining in the absence of structural or functional disease	Evidence of structural disease
BTA (2014)	All the following: <ul style="list-style-type: none"> Suppressed and stimulated Tg <1 ng/mL Neck US without evidence of disease Cross-sectional and/or nuclear medicine imaging negative (if performed) 	Any of the following <ul style="list-style-type: none"> Suppressed Tg ≥1 ng/mL or stimulated Tg ≥10 ng/mL Rising Tg values 	Any of the following <ul style="list-style-type: none"> Suppressed Tg <1 ng/mL and stimulated Tg ≥1 and <10 ng/mL Neck US with nonspecific changes or stable sub centimeter nodes Cross-sectional and/or nuclear medicine imaging with nonspecific changes, although not completely normal 	Persistent or newly identified possible disease on imaging ^a
NCCN (2016)	Stimulated Tg <2 Negative imaging ^b			Evidence of structural disease

^aThis is mentioned under incomplete response without a specific category of structural disease. ^bIf this is not present, then patient has recurrent/residual disease. Adapted with permission from Haddad RI, *et al.*, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Thyroid Carcinoma Version 1.2016. Copyright 2016 National Comprehensive Cancer Network, Inc. Available at NCCN.org. Accessed: November 4, 2016.

features according to ATA guidelines. However, in patients with high-risk tumors especially when residual disease is highly suspected or known, a higher dose of 100–200 can be used. Dosimetrically calculated doses to limit whole-body retention to 80mCi at 48h and 200cGy exposure to the bone marrow can be considered particularly in patients with renal insufficiency, older patients or in patients with RAI avid macroscopic distant metastases to reduce complications. However, data are not consistent regarding improved efficacy of this treatment approach (Samuel *et al.* 1998, Klubo-Gwiedzinska *et al.* 2011). There is general agreement between guidelines regarding dose ranges for patients with more advanced disease. Given the potential side effects of exceeding a safe RAI dose, the ATA guidelines recommend against empirically administered amounts of 131I exceeding 150mCi in patients over age 70 years as they will often potentially exceed the maximum tolerable tissue dose (Tuttle *et al.* 2006).

In addition to decision-making based on risk of progressive disease, all of the guidelines point to the importance of considering both patient preferences and the potential risks of RAI when determining dose. The dynamic risk stratification strategy that is codified in the guidelines (Table 6) helps better define the goals and

risks of treatment in individual patients. It is also noted that the delay in administration of RAI up to 12 months after thyroid cancer surgery does not appear to influence overall survival (Tsirona *et al.* 2014, Suman *et al.* 2016). This may not be true, however, in the case of patients who have higher risk tumors characterized by extrathyroidal extension or distant metastases (Higashi *et al.* 2011).

Dynamic stratification

Risk stratification after initial treatment aids in determining the status of disease at a given point in time as well as the likelihood structural disease progression over time (Tuttle *et al.* 2010). Although all guidelines agree to this approach in concept, the ATA and BTA, in particular, use similar terms in assessing that response. Nonetheless, there are some differences in defining the response types between those guidelines. For example, the BTA guidelines recommend using a TSH-suppressed and TSH-stimulated thyroglobulin at <1 ng/mL for excellent response, whereas the ATA recommends using suppressed thyroglobulin <0.2 ng/mL or TSH-stimulated thyroglobulin <1 ng/mL. The BTA appears to presume that TSH-stimulated thyroglobulin will be performed on all patients with

Table 7 TSH target after dynamic assessment.

	Excellent response	Indeterminate response	Incomplete response ^a	Structural recurrence
ATA (2016)	0.5–2 U/L (if high risk at presentation, 0.1–0.5 U/L for 5 years)	0.1–0.5 U/L ^b	0.1–0.5 U/L ^b	<0.1 U/L ^c
BTA (2014)	0.3–2 U/L	0.1–0.5 U/L ^e	<0.1 U/L in the absence of contraindications	<0.1 U/L
NCCN (2016) ^f	Free of disease in NCCN guidelines: TSH levels maintained either slightly below or slightly above the lower limit of the reference range ^d	Not clearly stated	Recurrence without structural disease: 0.1–0.5 U/L if low risk	<0.1 U/L

^aNCCN: implied under 'recurrence without structural disease'. ^bModified based on risk factors for adverse outcomes of thyrotoxicosis. With atrial fibrillation TSH target should be 0.5–2 U/L in patients with indeterminate and incomplete response. In patients older than 60 or those who have osteoporosis, TSH target should be 0.5–2 U/L in patients with indeterminate or incomplete responses. In patients with incomplete response who have no risk factors for adverse outcomes from thyrotoxicosis, TSH target <0.1 U/L. ^cTSH target in patients with structural disease who have atrial fibrillation should be 0.1–0.5 U/L. ^dPatients who remain disease free for several years can probably have their TSH levels maintained within the reference range. ^eTSH target 0.1–0.5 for 5–10 years then revisited. ^fAdapted with permission from Haddad RI, *et al.*, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Thyroid Carcinoma Version 1.2016. Copyright 2016 National Comprehensive Cancer Network, Inc. Available at NCCN.org. Accessed: November 4, 2016.

undetectable basal Tg level, on at least one occasion after initial therapies. However, studies since their most recent update demonstrate that undetectable Tg levels on newer and more sensitive Tg assays have a very high negative predictive value, suggesting that TSH-stimulated Tg levels may no longer be necessary in many patients (Giovannella *et al.* 2014). Table 6 describes terms used in assessing response to treatment and the criteria for those different categories of response in the three guidelines. If hemithyroidectomy is to be employed, Tg cutoff points or defining percent changes that should prompt further evaluation need to be developed. Recently, Momesso & Tuttle (2014) reported a cutoff of 30 ng/mL in patients with hemithyroidectomy as a criterion for excellent response to hemithyroidectomy. This potential cut point was validated (Momesso *et al.* 2016) in a study showing a 0% rate of structural recurrence after 100.5 months of follow-up in patients with that cutoff of Tg at <30 ng/mL that indicated excellent response after hemithyroidectomy. However, a larger cohort of patients is needed to validate this proposed Tg cutoff. Studies to assess whether or not Tg is specific enough for monitoring patients with microcarcinoma if they do not undergo surgery are needed; therefore, these data are not included in the guidelines to date.

An important impact of this dynamic stratification of thyroid cancer patients has been the reassessment of the efficacy of long-term TSH suppression therapy. High-risk patients at presentation who are recommended for initial TSH suppression to levels <0.1 U/L are recommended to be treated with less aggressive TSH suppression over time if they have excellent response to treatment. This recommendation for less aggressive long-term TSH suppression is based on

the recognition that long-term TSH suppression can also cause treatment-related morbidity and the minimal data to support a persistent anti-tumor effect. Risks include the well-known higher incidence of atrial fibrillation in patients with suppressed TSH, increased cardiovascular mortality in patients with thyroid cancer (Klein Hesselink *et al.* 2013) and also an increased risk of osteoporosis in postmenopausal woman (Wang *et al.* 2015a). On the other hand, TSH suppression appeared safe in a study in its effect on cognitive function (Moon *et al.* 2014). Additional studies on the impact of exogenous thyrotoxicosis on these patients will be helpful in defining the risk/benefit ratio for patients with persistent thyroid cancer. Table 7 describes the TSH target in patients across different categories of response between the three guidelines.

Cervical nodal metastases: to remove or to observe?

The guidelines agree that low volume residual disease in neck often can be managed with active surveillance. This recommendation is supported by studies showing stability of most cervical nodal disease during conservative observation (Rondeau *et al.* 2011, Robenshtok *et al.* 2012). The guidelines acknowledge the required individualization of therapy for such patients and when treatment is indicated, all recommend surgical removal of regional nodes as the best treatment option, although other choices are discussed for specific populations of patients (see below). The 2016 NCCN guidelines do not comment on active surveillance if locoregional disease is resectable. Table 8 summarizes the approach to active surveillance vs surgery among the three guidelines.

Table 8 Decision on management of cervical nodal metastatic disease.

ATA (2016)	BTA (2014)	NCCN (2016) ^b
Active surveillance for nodes with smallest diameter <8 mm in central neck and <10 mm in lateral neck ^a	Surgery with curative intent is the primary therapy without distant metastases Active surveillance for low volume non-progressive disease	Surgery (preferred) if resectable and/or radioiodine treatment, if radioiodine imaging positive and/or local therapies when available (ethanol ablation, radiofrequency ablation (RFA)) and/or EBRT/IMRT, if radioiodine imaging negative for selected patients not responsive to other therapies

^aFactors such as FDG-PET activity, patient comorbidities and preferences, and surgical risk among others should be considered. ^bAdapted with permission from Haddad RI, *et al.*, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Thyroid Carcinoma Version 1.2016. Copyright 2016 National Comprehensive Cancer Network, Inc. Available at NCCN.org. Accessed: November 4, 2016.

The option of active surveillance on patients with cervical nodal metastases has gained increasing support in the guidelines over time. For example, the ATA guidelines in 2009 (American Thyroid Association Guidelines Taskforce on Thyroid *et al.* 2009) discussed uncertainty regarding the need of surgery in asymptomatic small disease defined as less than 5–8 mm, whereas the 2016 ATA guidelines recommend active surveillance in low-volume locoregional cervical nodes without the need to perform FNA biopsy of suspicious node until the smallest diameter is >0.8 cm in central neck and >1.0 cm in lateral neck.

Although surgery remains the mainstay treatment for recurrent/persistent cervical nodal metastatic disease (Urken *et al.* 2015), ablation of metastatic lymph nodes (Lewis *et al.* 2002, Heilo *et al.* 2011) is another method of controlling cervical disease without surgery. It has been recommended to consider this option in patients with distant metastases where cure will definitely be not possible with surgery for cervical disease and in patients who are poor surgical candidates with growing and possibly symptomatic neck nodes.

Conclusion and reflection

The incidence of thyroid cancer is increasing and survivorship remains excellent, particularly for patients with early stage disease. Over the past several years, data have emerged that have led to greater recognition of the potential side effects of thyroid cancer therapy including surgery and RAI. Taken together, these factors have led to recommendations for a more conservative and individualized approach in nearly all aspects of thyroid nodule and cancer care. In the present review, we discussed some key points in thyroid nodule/cancer diagnosis and management focused on the most common clinical scenarios, and how they were approached by four different guidelines.

All of the newer guidelines documents present an increasing expectation for individualizing diagnosis and treatment approaches. They require physicians to be facile in not only in clinical assessment but also in either performing or providing access to high-precision neck ultrasound, access to high-quality cytology review, and in some cases, access to molecular testing. This evidence-based approach carries important benefits to the patient in terms of avoiding unnecessary treatments and procedures and also allows greater focus on patients most likely to benefit from more aggressive approaches as well.

As noted in the introduction, the guidelines are intended to cover only the most common clinical scenarios and they are intended to help guide, rather than replace, careful clinical decision making. Thus, they are not ‘rules’ for clinical practice but rather are ‘guidelines’ that are intended to summarize and, based on the weight of the evidence, recommend certain approaches to common clinical problems based on the strength of the data. Application of this information to individual patients is more nuanced and requires synthesis of this broad information into the specific clinical scenario for an individual patient that can be influenced by factors such as the availability of local expertise, insurance coverage and patient preferences. One major challenge at present is the multiplicity of guidelines for thyroid nodules and cancer. Although the overall similarity between recommendations of the guidelines is reassuring, there are differences between the documents. In addition to pointing to key knowledge gaps that require further study, such disagreements also can cause an unintended lack of clarity for practicing physicians. As the field continues to evolve over time, combined guidelines summary statements and the use of the same levels of evidence structures by the various groups will ultimately be helpful for maximal impact on clinical practice.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

This research was supported by NIH grant to M D R (P01 CA124570 and P50CA168505).

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Received in final form 9 December 2016

Accepted 13 December 2016

Accepted Preprint published online 13 December 2016