Ontario Health
Cancer Care Ontario

Guideline Endorsement 5-13 REQUIRES UPDATING

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Cancer Care Ontario Thyroid Cancer Guideline: An Endorsement of the 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

J. Yoo, C. Agbassi, H. Lochnan, D. Morrison, A. M. Sawka, J. Brierley, and the Head and Neck Disease Site Group Thyroid Cancer Subcommittee

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This publication is an endorsement of the 2015 American Thyroid Association (ATA) Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. The original publication is available at http://www.thyroid.org/professionals/ata-professional-guidelines/

June 2023 Update
The endorsed recommendations from the 2015 ATA Management Guidelines in this document remain valid for use in Ontario for all aspects of care for thyroid cancer, except for ultrasound (US) reporting of thyroid nodular disease. For US reporting OH-CCO endorses the American College of Radiology Thyroid Imaging Reporting and Data System (ACR-TIRADS) as the gold standard for US reporting of thyroid nodular disease in Ontario. This decision affected recommendations #8, #23 and #24 that referenced US reporting of nodule sizes and pattern.

An assessment conducted in November 2025 indicated that Guideline 5-13 REQUIRES UPDATING. It is still appropriate for this document to be available while this process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 5-13 is comprised of 2 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/74246

Section 1: Recommendations Summary
Section 2: Methods and Review Overview

For information about this document, please contact Dr. John Yoo through the PEBC via: Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at: Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

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Guideline 5-13: Section 1

Cancer Care Ontario Thyroid Cancer Guideline: An Endorsement of the 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

GUIDELINE OBJECTIVES

The objectives of this guideline are to provide clinical practice recommendations for the management of thyroid nodules and differentiated thyroid cancers. Our recommendations are based on the 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer [1] (the 2015 ATA Guidelines).

TARGET POPULATION

Adults with thyroid nodules and differentiated thyroid cancers.

INTENDED USERS

Healthcare providers involved in the management of thyroid diseases.

RECOMMENDATIONS

The recommendations of the 2015 ATA Guidelines were endorsed with adaptations by the Cancer Care Ontario (CCO) Thyroid Cancer Working Group (WG). The adaptations and accompanying qualifying statements for selected recommendations were made for the purposes of clarification and to reflect the Ontario context.

The endorsed ATA recommendations are presented in the table below. Recommendations that have been adapted and/or modified are indicated by grey highlighting and italicized text.

BACKGROUND AND JUSTIFICATION FOR GUIDELINE

In 2015, it was estimated that over 6000 Canadians will receive a new diagnosis of thyroid cancer [2]. Furthermore, the incidence of thyroid cancer is the most rapidly increasing rate among all major cancers not only in Canada but worldwide [2-5]. Part of the rise may be due to the detection and investigation of thyroid nodules discovered incidentally by the increasing frequency of imaging studies such as ultrasounds [6].

The presence of thyroid nodules is common, and occurs in up to 35% of the population [7]. The vast majority of thyroid nodules are benign, with less than 5% of nodules larger than 1 cm representing thyroid cancers. Based on various clinical parameters and imaging characteristics, a thyroid nodule may require further evaluation in order to determine the presence of malignancy.

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer and accounts for 70% of new diagnoses. Follicular thyroid carcinomas are the second most

common type at approximately 20% frequency [8]. Other types include medullary and anaplastic thyroid cancers while lymphomas, sarcomas, and squamous cell carcinomas may also affect the thyroid gland.

Differentiated thyroid cancers (DTC) consist of papillary and follicular thyroid carcinomas. The management of DTC may include surgery, radioactive iodine (RAI) therapy, hormonal therapy, external beam radiation therapy (EBRT), and systemic treatment. Thyroid surgery in particular is an important aspect of care in this disease. For the purposes of this document, total thyroidectomy is synonymous with bilateral thyroidectomy, and unilateral thyroidectomy includes lobectomy or hemithyroidectomy.

Considerable variation exists across healthcare centres in Ontario in regard to the evaluation of thyroid nodules and the management of thyroid cancers. The 2015 ATA Guidelines – a series of 101 specific recommendations addressing thyroid nodules, DTC early management and DTC long-term management and advanced cancer management - were evaluated and considered for the Ontario context.

Using the formal guideline endorsement process of the Program in Evidence-Based Care (PEBC), the Head and Neck Disease Site Group (DSG) Thyroid Cancer Subcommittee endorsed and adapted the ATA Guidelines. Table 1-1 presents the recommendations that resulted from these deliberations. Unless otherwise stated, the group endorses the ATA guideline recommendations as stated.

Table 1-1: CCO Guideline Recommendations. Endorsement and adapation of ATA Guideline Recommendations [1]
NOTE: Recommendations that have been adapted or modified by the Head and Neck DSG Thyroid Cancer Subcommittee are highlighted in grey, and adaptations are in Italic font. Justification/explanation for the modficiations can be found in the footnotes.

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
[A1]		**THYROID NODULE GUIDELINES**	
[A2]		**What is the role of thyroid cancer screening in people with familial follicular cell-derived differentiated thyroid cancer?**	
	1	Screening people with familial follicular cell–derived DTC may lead to an earlier diagnosis of thyroid cancer, but the panel cannot recommend for or against ultrasound (US) screening since there is no evidence that this would lead to reduced morbidity or mortality	No recommendation, Insufficient evidence
[A3]		**What is the appropriate laboratory and imaging evaluation for patients with clinically or incidentally discovered thyroid nodules?**	
[A4]		**Serum thyroid stimulating hormone (TSH) measurement**	
	2A	Serum thyrotropin (TSH) should be measured during the initial evaluation of a patient with a thyroid nodule.	Strong recommendation, Moderate-quality evidence
	2B	If the serum TSH is subnormal, a radionuclide (preferably ^{123}I) thyroid scan should be performed.	Strong recommendation, Moderate-quality evidence
	2C	If the serum TSH is normal or elevated, a radionuclide scan should not be performed as the initial imaging evaluation	Strong recommendation, Moderate-quality evidence
[A5]		**Serum thyroglobulin (Tg) measurement**	

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	3	Routine measurement of serum Tg for initial evaluation of thyroid nodules is not recommended.	Strong recommendation, Moderate-quality evidence
[A6]		**Serum calcitonin measurement**	
	4	The panel cannot recommend either for or against routine measurement of serum calcitonin in patients with thyroid nodules. ***Qualifying Statement:*** *The current standard of care in Ontario is not to measure calcitonin in the routine evaluation of thyroid nodules.*[1]	No recommendation, Insufficient evidence
[A7]		**^{18}Fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) scan**	
	5A	Focal ^{18}FDG-PET uptake within a sonographically confirmed thyroid nodule conveys an increased risk of thyroid cancer, and fine-needle aspiration (FNA) is recommended for those nodules ≥1 cm.	Strong recommendation, Moderate-quality evidence
	5B	Diffuse ^{18}FDG-PET uptake, in conjunction with sonographic and clinical evidence of chronic lymphocytic thyroiditis, does not require further imaging or FNA	Strong recommendation, Moderate-quality evidence
[A8]		**Thyroid sonography**	
	6	Thyroid sonography with survey of the cervical lymph nodes should be performed in all patients with known or suspected thyroid nodules.	Strong recommendation, High-quality evidence
[A9]		**Ultrasound (US) for fine-needle aspiration (FNA) decision-making**	
	7	FNA is the procedure of choice in the evaluation of thyroid nodules, when clinically indicated.	Strong recommendation, High-quality evidence

[1] *There is insufficient evidence to recommend its routine use*

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
[A10]		**Recommendations for diagnostic FNA of a thyroid nodule based on sonographic pattern.** ***May 2023 Update*** ***Due to the CCO-OH adoption of ACR-TIRADS as the gold standard for (US) reporting of thyroid nodular disease in Ontario, recommendation #8 is to be used with caution (or to be used with reference to ACR-TIRADS guidelines). See*** APPENDIX 3: ACR TIRADS map ***ACR-TIRADS map.***	
	8A	Thyroid nodule diagnostic FNA is recommended for nodules ≥1 cm in greatest dimension with high-suspicion sonographic pattern.	Strong recommendation, Moderate-quality evidence
	8B	Thyroid nodule diagnostic FNA is recommended for nodules ≥1 cm in greatest dimension with intermediate-suspicion sonographic pattern	Strong recommendation, Low-quality evidence
	8C	Thyroid nodule diagnostic FNA is recommended for nodules ≥1.5 cm in greatest dimension with low suspicion sonographic pattern	Weak recommendation, Low-quality evidence
	8D	Thyroid nodule diagnostic FNA may be considered for nodules ≥2 cm in greatest dimension with very low-suspicion sonographic pattern (e.g., spongiform). Observation without FNA is also a reasonable option. ***Qualifying statements***[2] • *The ATA recommendation #8A is appropriate in order to reduce the overtreatment of potentially clinically insignificant papillary microcarcinomas.* • *However, the presence of symptoms, lymphadenopathy, radiation, or a history of familial thyroid cancer or known genetic syndromes may influence risk, with implications on decision-making.* • *In the absence of suspicious US findings, higher size criteria may be considered.*	Weak recommendation, Moderate-quality evidence

[2] *To reduce the biopsy of potentially insignificant cancers*

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	8E	Thyroid nodule diagnostic FNA is not required for nodules that do not meet the above criteria.	Strong recommendation, Moderate-quality evidence
	8F	Thyroid nodule diagnostic FNA is not required for nodules that are purely cystic.	Strong recommendation, Moderate-quality evidence
[A11]		**What is the role of FNA, cytology interpretation, and molecular testing in patients with thyroid nodules?**	
	9	Thyroid nodule FNA cytology should be reported using diagnostic groups outlined in the Bethesda System for Reporting Thyroid Cytopathology.	Strong recommendation, Moderate-quality evidence
[A12]		**Nondiagnostic cytology**	
	10A	For a nodule with an initial nondiagnostic cytology result, FNA should be repeated with US guidance and, if available, on-site cytologic evaluation	Strong recommendation, Moderate-quality evidence
	10B	Repeatedly nondiagnostic nodules without a high suspicion sonographic pattern require close observation or surgical excision for histopathologic diagnosis	Weak recommendation, Low-quality evidence)
	10C	Surgery should be considered for histopathologic diagnosis if the cytologically nondiagnostic nodule has a high-suspicion sonographic pattern, growth of the nodule (>20% in two dimensions) is detected during US surveillance, or clinical risk factors for malignancy are present	Weak recommendation, Low-quality evidence)
[A13]		**Benign cytology**	
	11	If the nodule is benign on cytology, further immediate diagnostic studies or treatment are not required	Strong recommendation, Moderate-quality evidence
[A14]		**Malignant cytology**	

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	12	If a cytology result is diagnostic for primary thyroid malignancy, surgery is generally recommended.	Strong recommendation, Moderate-quality evidence
[A15]		**Indeterminate cytology (atypia of undetermined significance/follicular lesion of undetermined significance [AUS/FLUS], follicular neoplasm [FN], suspicious for malignancy [SUSP])**	
[A16]		**What are the principles of the molecular testing of FNA samples?**	
	13	If molecular testing is being considered, patients should be counseled regarding the potential benefits and limitations of testing and about the possible uncertainties in the therapeutic and long-term clinical implications of results.	(Strong recommendation, Low-quality evidence
	14	If intended for clinical use, molecular testing should be performed in Clinical Laboratory Improvement Amendments/ College of American Pathologists (CLIA/CAP)-certified molecular laboratories, or the international equivalent, because reported quality assurance practices may be superior compared with other settings. ***Qualifying Statement:*** *While not currently routinely available, if molecular testing is performed in Ontario it should be in accredited laboratories*	Strong recommendation, Low-quality evidence
[A17]		**AUS/FLUS cytology**	
	15A	For nodules with AUS/FLUS cytology, after consideration of worrisome clinical and sonographic features, investigations such as repeat FNA or molecular testing may be used to supplement malignancy risk assessment in lieu of proceeding directly with a strategy of either surveillance or diagnostic surgery. Informed patient preference and feasibility should be considered in clinical decision-making.	Weak recommendation, Moderate-quality evidence

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	15B	If repeat FNA cytology, molecular testing, or both are not performed or inconclusive, either surveillance or diagnostic surgical excision may be performed for an AUS/ FLUS thyroid nodule, depending on clinical risk factors, sonographic pattern, and patient preference. ***Additional Recommendation Statement:*** *In thyroid nodules with a cytological diagnosis of Bethesda 3 (AUS/FLUS) or one of its subcategories, knowledge of local malignancy rates - in addition to clinical risk factors, sonographic pattern and patient preference - should influence decisions about repeat FNA, surveillance, or diagnostic surgical excision.* ***Qualifying Statement:*** *The risk of malignancy in the Bethesda 3 (AUS/FLUS) category and its subcategories is imprecise and varies widely. Local malignancy rates should be considered in decision-making.*	Strong recommendation, Low-quality evidence
[A18]		**FN/suspicious for follicular neoplasm (SFN) cytology**	

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	16A	Diagnostic surgical excision is the long-established standard of care for the management of FN/SFN cytology nodules. However, after consideration of clinical and sonographic features, molecular testing may be used to supplement malignancy risk assessment data in lieu of proceeding directly with surgery. Informed patient preference and feasibility should be considered in clinical decision-making. ***Additional Recommendation Statement:*** *In selected cases, a second pathologic opinion may be useful.* ***Qualifying Statement*** • *There is a broad degree of subjectivity in clinical judgement regarding urgency and careful follow-up in this recommendation, regarding the management, and utilization of diagnostic studies.* • *The risk of choosing observation is low if there are no suspicious US features, clinical risk factors, stable nodule size, and nodule size <2 cm.* • *If surgery is being considered, surgical excision generally implies a unilateral thyroidectomy (see Recommendation #19).*	Weak recommendation, Moderate-quality evidence
	16B	If molecular testing is either not performed or inconclusive, surgical excision may be considered for removal and definitive diagnosis of an FN/SFN thyroid nodule[3]	Strong recommendation, Low-quality evidence
[A19]		**SUSP cytology**	
	17A	If the cytology is reported as suspicious for papillary carcinoma (SUSP), surgical management should be similar to that of malignant cytology, depending on clinical risk factors, sonographic features, patient preference, and possibly results of mutational testing (if performed).	Strong recommendation, Low-quality evidence)

[3] *The province does not fund molecular testing. Health care providers should also understand the limitations of molecular testing in thyroid nodules.*

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	17B	After consideration of clinical and sonographic features, mutational testing for BRAF or the seven-gene mutation marker panel (BRAF, RAS, RET/PTC, PAX8/ PPARc) may be considered in nodules with SUSP cytology if such data would be expected to alter surgical decisionmaking. ***Qualifying Statements:*** • *Mutation testing has limited usefulness to alter surgical decision-making.* • *There are no long-term outcomes that support the benefit of mutation testing in this context.*	Weak recommendation, Moderate-quality evidence
[A20]		**What is the utility of ^{18}FDG-PET scanning to predict malignant or benign disease when FNA cytology is indeterminate (AUS/FLUS, FN, SUSP)?**	
	18	^{18}FDG-PET imaging is not routinely recommended for the evaluation of thyroid nodules with indeterminate cytology.	Weak recommendation, Moderate-quality evidence
[A21]		**What is the appropriate operation for cytologically indeterminate thyroid nodules?**	
	19	When surgery is considered for patients with a solitary, cytologically indeterminate nodule, thyroid lobectomy is the recommended initial surgical approach. This approach may be modified based on clinical or sonographic characteristics, patient preference, and/or molecular testing when performed (see Recommendations 13–16) ***Qualifying Statements:*** *Total thyroidectomy should be the exception but may be indicated for other clinical reasons.*	Strong recommendation, Moderate-quality evidence

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	20A	Because of increased risk for malignancy, total thyroidectomy may be preferred in patients with indeterminate nodules that are cytologically suspicious for malignancy, positive for known mutations specific for carcinoma, sonographically suspicious, or large (>4 cm), or in patients with familial thyroid carcinoma or history of radiation exposure, if completion thyroidectomy would be recommended based on the indeterminate nodule being malignant following lobectomy ***Qualifying Statements:*** *Total thyroidectomy should be the exception but may be indicated for other clinical reasons.*	Strong recommendation, Moderate-quality evidence
	20B	Patients with indeterminate nodules who have bilateral nodular disease, those with significant medical comorbidities, or those who prefer to undergo bilateral thyroidectomy to avoid the possibility of requiring a future surgery on the contralateral lobe, may undergo total or near-total thyroidectomy, assuming completion thyroidectomy would be recommended if the indeterminate nodule proved malignant following lobectomy. ***Qualifying Statements:*** *Total thyroidectomy should be the exception but may be indicated for other clinical reasons.*	Weak recommendation, Low-quality evidence
[A22]		**How should multinodular thyroid glands (i.e., two or more clinically relevant nodules) be evaluated for malignancy?**	
	21A	Patients with multiple thyroid nodules ≥1 cm should be evaluated in the same fashion as patients with a solitary nodule ≥1 cm, except that each nodule that is >1 cm carries an independent risk of malignancy and therefore multiple nodules may require FNA.	Strong recommendation, Moderate-quality evidence
	21B	When multiple nodules ≥1 cm are present, FNA should be performed preferentially based upon nodule sonographic pattern and respective size cutoff	Strong recommendation, Moderate-quality evidence

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	21C	If none of the nodules has a high or moderate-suspicion sonographic pattern, and multiple sonographically similar very low or low-suspicion pattern nodules coalesce with no intervening normal parenchyma, the likelihood of malignancy is low and it is reasonable to aspirate the largest nodules (≥2 cm) or continue surveillance without FNA.	Weak recommendation, Low-quality evidence
	22	A low or low-normal serum TSH concentration in patients with multiple nodules may suggest that some nodule(s) may be autonomous. In such cases, a radionuclide (preferably ^{123}I) thyroid scan should be considered and directly compared to the US images to determine functionality of each nodule ≥1 cm. FNA should then be considered only for those isofunctioning or nonfunctioning nodules, among which those with high-suspicion sonographic pattern should be aspirated preferentially.	Weak recommendation, Low-quality evidence
[A23]		**What are the best methods for long-term follow-up of patients with thyroid nodules?**	
[A24]		**Recommendations for initial follow-up of nodules with benign FNA cytology** ***May 2023 Update*** ***Due to the CCO-OH adoption of ACR-TIRADS as the gold standard for (US) reporting of thyroid nodular disease in Ontario, recommendation #8 is to be used with caution (or to be used with reference to ACR-TIRADS guidelines). See*** **APPENDIX 3:** ACR TIRADS map ***for ACR-TIRADS map.***	
	23A	Given the low false-negative rate of US-guided FNA cytology and the higher yield of missed malignancies based upon nodule sonographic pattern rather than growth, the follow-up of thyroid nodules with benign cytology diagnoses should be determined by risk stratification based upon US pattern. Nodules with high-suspicion US pattern: repeat US and US-guided FNA within 12 months.	Strong recommendation, Moderate-quality evidence

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	23B	Nodules with low to intermediate-**suspicion** US pattern: repeat US at 12–24 months. If sonographic evidence of growth (20% increase in at least two nodule dimensions with a minimal increase of 2 mm or more than a 50% change in volume) or development of new suspicious sonographic features, the FNA could be repeated or observation continued with repeat US, with repeat FNA in case of continued growth.	Weak recommendation, Low-quality evidence
	23C	Nodules with very low-suspicion US pattern (including spongiform nodules): the utility of surveillance US and assessment of nodule growth as an indicator for repeat FNA to detect a missed malignancy is limited. If US is repeated, it should be done at ≥24 months.	Weak recommendation, Low-quality evidence
[A25]		**Recommendation for follow-up of nodules with two benign FNA cytology results**	
	23D	If a nodule has undergone repeat US-guided FNA with a second benign cytology result, US surveillance for this nodule for continued risk of malignancy is no longer indicated.	Strong recommendation, Moderate-quality evidence
[A26]		**Follow-up for nodules that do not meet FNA criteria.** ***May 2023 Update*** ***Due to the CCO-OH adoption of ACR-TIRADS as the gold standard for (US) reporting of thyroid nodular disease in Ontario, recommendation #8 is to be used with caution (or to be used with reference to ACR-TIRADS guidelines). See*** **APPENDIX 3:** ACR TIRADS map ***for ACR-TIRADS map.***	
	24	Nodules may be detected on US that do not meet criteria for FNA at initial imaging (Recommendation 8). The strategy for sonographic follow-up of these nodules should be based upon the nodule's sonographic pattern	Not applicable
	24A	Nodules with high suspicion US pattern: repeat US in 6–12 months.	Weak recommendation, Low-quality evidence
	24B	Nodules with low to intermediate-suspicion US pattern: consider repeat US at 12–24 months.	Weak recommendation, Low-quality evidence

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	24C	Nodules >1 cm with very low-suspicion US pattern (including spongiform nodules) and pure cyst: the utility and time interval of surveillance US for risk of malignancy is not known. If US is repeated, it should be at ≥24 months.	No recommendation, Insufficient evidence
	24D	Nodules ≤1 cm with very low-suspicion US pattern (including spongiform nodules) and pure cysts do not require routine sonographic follow-up.	Weak recommendation, Low-quality evidence
[A27]		**What is the role of medical or surgical therapy for benign thyroid nodules?**	
	25	Routine TSH suppression therapy for benign thyroid nodules in iodine-sufficient populations is not recommended. Though modest responses to therapy can be detected, the potential harm outweighs benefit for most patients.	Strong recommendation, High-quality evidence
	26	Individual patients with benign, solid, or mostly solid nodules should have adequate iodine intake. If inadequate dietary intake is found or suspected, a daily supplement (containing 150 µg iodine) is recommended.	Strong recommendation, Moderate-quality evidence
	27A	Surgery may be considered for growing nodules that are benign after repeat FNA if they are large (>4 cm), causing compressive or structural symptoms, or based upon clinical concern. ***Qualifying Statements:*** *Unless symptomatic or concerned, patients can be followed if two FNA biopsies are benign.*	Weak recommendation, Low-quality evidence
	27B	Patients with growing nodules that are benign after FNA should be regularly monitored. Most asymptomatic nodules demonstrating modest growth should be followed without intervention. ***Qualifying Statements:*** *After two benign FNA biopsies, routine US follow- up of the index nodule is not indicated.*	Strong recommendation, Low-quality evidence
	28	Recurrent cystic thyroid nodules with benign cytology should be considered for surgical removal or percutaneous ethanol injection based on compressive symptoms and cosmetic concerns. Asymptomatic cystic nodules may be followed conservatively	Weak recommendation, Low-quality evidence

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	29	There are no data to guide recommendations on the use of thyroid hormone therapy in patients with growing nodules that are benign on cytology. ***Additional Recommendation Statement:*** *This recommendation is directly related to Recommendation # 25. Suppressive doses of levothyroxine (LT4) is not recommended.* ***Qualifying Statements:*** *The risk of harm due to thyroid hormone excess may outweigh unproven benefit of minimal reduction in growth*[4] .	No recommendation, Insufficient evidence
[A28]		**How should thyroid nodules in pregnant women be managed?**	
[A29]		**FNA for thyroid nodules discovered during pregnancy**	
	30A	FNA of clinically relevant thyroid nodules (refer to section [A10]) should be performed in euthyroid and hypothyroid pregnant women.	Strong recommendation, Moderate-quality evidence
	30B	For women with suppressed serum TSH levels that persist beyond 16 weeks gestation, FNA may be deferred until after pregnancy and cessation of lactation. At that time, a radionuclide scan can be performed to evaluate nodule function if the serum TSH remains suppressed	Strong recommendation, Moderate-quality evidence
[A30]		**Approaches to pregnant patients with malignant or indeterminate cytology**	
	31	PTC discovered by cytology in early pregnancy should be monitored sonographically. If it grows substantially (as defined in section [A24]) before 24–26 weeks gestation, or if US reveals cervical lymph nodes that are suspicious for metastatic disease, surgery should be considered during pregnancy. However, if the disease remains stable by midgestation, or if it is diagnosed in the second half of pregnancy, surgery may be deferred until after delivery	Weak recommendation, Low-quality evidence
[B1]		**DIFFERENTIATED THYROID CANCER: INITIAL MANAGEMENT GUIDELINES**	

[4] *Routine use of suppressive therapy is not indicated. See Rec #25*

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
[B2]		**Goals of initial therapy of DTC**	
[B3]		**What is the role of preoperative staging with diagnostic imaging and laboratory tests?**	
[B4]		**Neck imaging – US**	
	32A	Preoperative neck US for cervical (central and especially lateral neck compartments) lymph nodes is recommended for all patients undergoing thyroidectomy for malignant or suspicious for malignancy cytologic or molecular findings	Strong recommendation, Moderate-quality evidence
	32B	US-guided FNA of sonographically suspicious lymph nodes ≥ 8–10 mm in the smallest diameter should be performed to confirm malignancy if this would change management.	Strong recommendation, Moderate-quality evidence
	32C	The addition of FNA-Tg washout in the evaluation of suspicious cervical lymph nodes is appropriate in select patients, but interpretation may be difficult in patients with an intact thyroid gland. ***Qualifying Statements**: This test may not be available in many institutions in Ontario and quality standards are not clear.*	Weak recommendation, Low-quality evidence
[B5]		**Neck imaging - computed tomography (CT)/magnetic resonance imaging (MRI)/PET**	
	33A	Preoperative use of cross-sectional imaging studies (CT, MRI) with intravenous (IV) contrast is recommended as an adjunct to US for patients with clinical suspicion for advanced disease, including invasive primary tumour, or clinically apparent multiple or bulky lymph node involvement	Strong recommendation, Low-quality evidence
	33B	Routine preoperative ^{18}FDG-PET scanning is not recommended.	Strong recommendation, Low-quality evidence
[B6]		**Measurement of serum Tg and Tg antibodies**	

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	34	Routine preoperative measurement of serum Tg or anti-Tg antibodies is not recommended.	Strong recommendation, Low-quality evidence
[B7]		**Operative approach for a biopsy diagnostic for follicular cell-derived malignancy**	
	35A	For patients with thyroid cancer >4 cm, or with gross extrathyroidal extension (clinical T4), or clinically apparent metastatic disease to nodes (clinical N1) or distant sites (clinical M1), the initial surgical procedure should include a near-total or total thyroidectomy and gross removal of all primary tumor unless there are contraindications to this procedure.	Strong recommendation, Moderate-quality evidence
	35B	For patients with thyroid cancer >1 cm and <4 cm without extrathyroidal extension, and without clinical evidence of any lymph node metastases (cN0), the initial surgical procedure can be either a bilateral procedure (neartotal or total thyroidectomy) or a unilateral procedure (lobectomy). Thyroid lobectomy alone may be sufficient initial treatment for low-risk papillary and follicular carcinomas; however, the treatment team may choose total thyroidectomy to enable RAI therapy or to enhance followup based upon disease features and/or patient preferences. ***Qualifying Statements[5]:*** • *Based on disease mortality, there is no evidence that total thyroidectomy is better than unilateral thyroidectomy* • *There is strong evidence that total thyroidectomy has increased surgical morbidity as compared with unilateral thyroidectomy.*	Strong recommendation, Moderate-quality evidence

[5] *Generally favour unilateral operation*

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	35C	If surgery is chosen for patients with thyroid cancer <1 cm without extrathyroidal extension and cN0, the initial surgical procedure should be a thyroid lobectomy unless there are clear indications to remove the contralateral lobe.Thyroid lobectomy alone is sufficient treatment for small, unifocal, intrathyroidal carcinomas in the absence of prior head and neck radiation, familial thyroid carcinoma, or clinically detectable cervical nodal metastases.	Strong recommendation, Moderate-quality evidence
[B8]		**Lymph node dissection**	
	36A	Therapeutic central-compartment (level VI) neck dissection for patients with clinically involved central nodes should accompany total thyroidectomy to provide clearance of disease from the central neck.	Strong recommendation, Moderate-quality evidence
	36B	Prophylactic central-compartment neck dissection (ipsilateral or bilateral) should be considered in patients with papillary thyroid carcinoma with clinically uninvolved central neck lymph nodes (cN0) who have advanced primary tumors (T3 or T4) or clinically involved lateral neck nodes (cN1b), or if the information will be used to plan further steps in therapy.	Weak recommendation, Low-quality evidence
	36C	Thyroidectomy without prophylactic central neck dissection is appropriate for small (T1 or T2), noninvasive, clinically node-negative PTC (cN0) and for most follicular cancers.	Strong recommendation, Moderate-quality evidence
	37	Therapeutic lateral neck compartmental lymph node dissection should be performed for patients with biopsy-proven metastatic lateral cervical lymphadenopathy.	Strong recommendation, Moderate-quality evidence
[B9]		**Completion thyroidectomy**	
	38A	Completion thyroidectomy should be offered to patients for whom a bilateral thyroidectomy would have been recommended had the diagnosis been available before the initial surgery. Therapeutic central neck lymph node dissection should be included if the lymph nodes are clinically involved. Thyroid lobectomy alone may be sufficient treatment for low-risk papillary and follicular carcinomas	Strong recommendation, Moderate-quality evidence

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	38B	RAI ablation in lieu of completion thyroidectomy is not recommended routinely; however, it may be used to ablate the remnant lobe in selected cases.	Weak recommendation, Low-quality evidence
[B10]		**What is the appropriate perioperative approach to voice and parathyroid issues?**	
[B11]		**Preoperative care communication**	
	39	Prior to surgery, the surgeon should communicate with the patient regarding surgical risks, including nerve and parathyroid injury, through the informed consent process and communicate with associated physicians, including anesthesia personnel, regarding important findings elicited during the preoperative work-up.	Strong recommendation, Moderate-quality evidence
[B12]		**Preoperative voice assessment**	
	40	All patients undergoing thyroid surgery should have preoperative voice assessment as part of their preoperative physical examination. This should include the patient's description of vocal changes, as well as the physician's assessment of voice.	Strong recommendation, Moderate-quality evidence
	41A	Preoperative laryngeal exam should be performed in all patients with preoperative voice abnormalities	Strong recommendation, Moderate-quality evidence
	41B	Preoperative laryngeal exam should be performed in all patients with history of cervical or upper chest surgery, which places the recurrent laryngeal nerve (RLN) or vagus nerve at risk	Strong recommendation, Moderate-quality evidence
	41C	Preoperative laryngeal exam should be performed in all patients with known thyroid cancer with posterior extrathyroidal extension or extensive central nodal metastases.	Strong recommendation, Low-quality evidence
[B13]		**Intraoperative voice and parathyroid management**	

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	42A	Visual identification of the RLN during dissection is required in all cases. Steps should also be taken to preserve the external branch of the superior laryngeal nerve (EBSLN) during dissection of the superior pole of the thyroid gland.	Strong recommendation, Moderate-quality evidence
	42B	Intraoperative neural stimulation (with or without monitoring) may be considered to facilitate nerve identification and confirm neural function.	Weak recommendation, Low-quality evidence
	43	The parathyroid glands and their blood supply should be preserved during thyroid surgery	Strong recommendation, Moderate-quality evidence
[B14]		**Post-operative voice care**	
	44	Patients should have their voice assessed in the postoperative period. Formal laryngeal exam should be performed if the voice is abnormal	Strong recommendation, Moderate-quality evidence
	45	Important intraoperative findings and details of postoperative care should be communicated by the surgeon to the patient and other physicians who are important in the patient's postoperative care.	Strong recommendation, Low-quality evidence
[B15]		**What are the basic principles of histopathologic evaluation of thyroidectomy samples?**	
	46A	In addition to the basic tumour features required for American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) thyroid cancer staging including status of resection margins, pathology reports should contain additional information helpful for risk assessment, such as the presence of vascular invasion and the number of invaded vessels, number of lymph nodes examined and involved with tumour, size of the largest metastatic focus to the lymph node, and presence or absence of extranodal extension of the metastatic tumour.	Strong recommendation, Moderate-quality evidence

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	46B	Histopathologic variants of thyroid carcinoma associated with more unfavourable outcomes (e.g., tall cell, columnar cell, and hobnail variants of PTC; widely invasive FTC; poorly differentiated carcinoma) or more favourable outcomes (e.g., encapsulated follicular variant of PTC without invasion, minimally invasive FTC) should be identified during histopathologic examination and reported. ***Qualifying Statements:*** *The percentage or extent of involvement by unfavourable histopathologic variants included in the pathologic report may be of value in management*	Strong recommendation, Low-quality evidence
	46C	Histopathologic variants associated with familial syndromes (cribriform-morular variant of papillary carcinoma often associated with familial adenomatous polyposis (FAP), follicular or papillary carcinoma associated with PTEN-hamartoma tumor syndrome) should be identified during histopathologic examination and reported.	Weak recommendation, Low-quality evidence
[B16]		**What is the role of post-operative staging systems and risk stratification in the management of DTC?**	
[B17]		**Post-operative staging**	
	47	AJCC/UICC staging is recommended for all patients with DTC, based on its utility in predicting disease mortality, and its requirement for cancer registries.	Strong recommendation, Moderate-quality evidence
[B18]		**American Joint Committee on Cancer/Union for International Cancer Control TNM staging**	
[B19]		**What initial stratification system should be used to estimate the risk of persistent/recurrent disease?**	
	48A	The 2009 ATA Initial Risk Stratification System is recommended for DTC patients treated with thyroidectomy, based on its utility in predicting risk of disease recurrence and/or persistence.	Strong recommendation, Moderate-quality evidence

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	48B	Additional prognostic variables (such as the extent of lymph node involvement, mutational status, and/or the degree of vascular invasion in FTC), not included in the 2009 ATA Initial Risk Stratification system may be used to further refine risk stratification for DTC as described in the following text (and in Fig. 4) in the Modified Initial Risk Stratification system. However, the incremental benefit of adding these specific prognostic variables to the 2009 Initial Risk Stratification system has not been established.	Weak recommendation, Low-quality evidence
	48C	While not routinely recommended for initial postoperative risk stratification in DTC, the mutational status of *BRAF*, and potentially other mutations such as *TERT*, have the potential to refine risk estimates when interpreted in the context of other clinico-pathologic risk factors.	Weak recommendation, Moderate-quality evidence
[B20]		**Potential impact of specific clinico-pathologic features on the risk estimates in PTC**	
[B21]		**Potential impact of *BRAF*^{V600E} and other mutations on risk estimates in PTC**	
[B22]		**Potential impact of post-operative serum Tg on risk estimates**	
[B23]		**Proposed modifications to the 2009 ATA initial risk stratification system**	
[B24]		**Risk of recurrence as a continuum of risk**	
[B25]		**How should initial risk estimates be modified over time?**	
	49	Initial recurrence risk estimates should be continually modified during follow-up, because the risk of recurrence and disease-specific mortality can change over time as a function of the clinical course of the disease and the response to therapy.	Strong recommendation, Low-quality evidence
[B26]		**Proposed terminology to classify response to therapy and clinical implications**	

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
[B27]		**Excellent response: no clinical, biochemical, or structural evidence of disease after initial therapy (remission, no evidence of disease)**	
[B28]		**Biochemical incomplete response: abnormal Tg values in the absence of localizable disease**	
[B29]		**Structural incomplete response: persistent or newly identified loco-regional or distant metastases**	
[B30]		**Indeterminate response: biochemical or structural findings that cannot be classified as either benign or malignant (acceptable response)**	
[B31]		**Using risk stratification to guide disease surveillance and therapeutic management decisions**	
[B32]		**Should post-operative disease status be considered in decision-making for RAI therapy for patients with DTC?**	
	50A	Postoperative disease status (i.e., the presence or absence of persistent disease) should be considered in deciding whether additional treatment (e.g., RAI, surgery, or other treatment) may be needed.	Strong recommendation, Low-quality evidence
	50B	Postoperative serum Tg (on thyroid hormone therapy or after TSH stimulation) can help in assessing the persistence of disease or thyroid remnant and predicting potential future disease recurrence. The Tg should reach its nadir by 3–4 weeks postoperatively in most patients.	Strong recommendation, Moderate-quality evidence
	50C	The optimal cutoff value for postoperative serum Tg or state in which it is measured (on thyroid hormone therapy or after TSH stimulation) to guide decision-making regarding RAI administration is not known.	No recommendation, Insufficient evidence

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	50D	Postoperative diagnostic RAI whole-body scans (WBSs) may be useful when the extent of the thyroid remnant or residual disease cannot be accurately ascertained from the surgical report or neck ultrasonography, and when the results may alter the decision to treat or the activity of RAI that is to be administered. Identification and localization of uptake foci may be enhanced by concomitant single photon emission computed tomography–computed tomography (SPECT/CT). When performed, pretherapy diagnostic scans should utilize ^{123}I (1.5–3 mCi) or a low activity of ^{131}I (1–3 mCi), with the therapeutic activity optimally administered within 72 hours of the diagnostic activity.	Weak recommendation, Low-quality evidence
[B33]		**Utility of post-operative serum Tg in clinical decision-making**	
[B34]		**Potential role of post-operative US in conjunction with post-operative serum Tg in clinical decision-making**	
[B35]		**Role of post-operative radioisotope diagnostic scanning in clinical decision-making**	
[B36]		**What is the role of RAI (including remnant ablation, adjuvant therapy, or therapy of persistent disease) after thyroidectomy, in the primary management of DTC?**	
	51A	RAI remnant ablation is not routinely recommended after thyroidectomy for ATA low-risk DTC patients. Consideration of specific features of the individual patient that could modulate recurrence risk, disease follow-up implications, and patient preferences are relevant to RAI decision-making.	Weak recommendation, Low-quality evidence
	51B	RAI remnant ablation is not routinely recommended after lobectomy or total thyroidectomy for patients with unifocal papillary microcarcinoma, in the absence of other adverse features.	Strong recommendation, Moderate-quality evidence
	51C	RAI remnant ablation is not routinely recommended after thyroidectomy for patients with multifocal papillary microcarcinoma in absence of other adverse features. Consideration of specific features of the individual patient that could modulate recurrence risk, disease follow-up implications, and patient preferences are relevant to RAI decision-making.	Weak recommendation, Low-quality evidence

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	51D	RAI adjuvant therapy should be considered after total thyroidectomy in ATA intermediate-risk level DTC patients.	Weak recommendation, Low-quality evidence
	51E	RAI adjuvant therapy is routinely recommended after total thyroidectomy for ATA high-risk DTC patients	Strong recommendation, Moderate-quality evidence
[B37]		**What is the role of molecular marker status in therapeutic RAI decision-making?**	
	52	The role of molecular testing in guiding postoperative RAI use has yet to be established; therefore, no molecular testing to guide postoperative RAI use can be recommended at this time.	No recommendation, Insufficient evidence
[B38]		**How long does thyroid hormone need to be withdrawn in preparation for RAI remnant ablation/treatment or diagnostic scanning?**	
	53A	If thyroid hormone withdrawal is planned prior to RAI therapy or diagnostic testing, LT4 should be withdrawn for three to four weeks. Liothyronine (LT3) may be substituted for LT4 in the initial weeks if LT4 is withdrawn for four or more weeks, and in such circumstances, LT3 should be withdrawn for at least two weeks. Serum TSH should be measured prior to radioisotope administration to evaluate the degree of TSH elevation.	Strong recommendation, Moderate-quality evidence
	53B	A goal TSH of >30 mIU/L has been generally adopted in preparation for RAI therapy or diagnostic testing, but there is uncertainty relating to the optimum TSH level associated with improvement in long-term outcomes.	Weak recommendation, Low-quality evidence
[B39]		**Can recombinant human (rh) TSH (Thyrogen™) be used as an alternative to thyroxine withdrawal for remnant ablation or adjuvant therapy in patients who have undergone near-total or total thyroidectomy?**	

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	54A	In patients with ATA low-risk and ATA intermediaterisk DTC without extensive lymph node involvement (i.e., T1–T3, N0/Nx/N1a, M0), in whom RAI remnant ablation or adjuvant therapy is planned, preparation with rhTSH stimulation is an acceptable alternative to thyroid hormone withdrawal for achieving remnant ablation, based on evidence of superior short-term quality of life, noninferiority of remnant ablation efficacy, and multiple consistent observations suggesting no significant difference in long-term outcomes	Strong recommendation, Moderate-quality evidence
	54B	In patients with ATA intermediate-risk DTC who have extensive lymph node disease (multiple clinically involved lymph node) in the absence of distant metastases, preparation with rhTSH stimulation may be considered as an alternative to thyroid hormone withdrawal prior to adjuvant RAI treatment	Weak recommendation, Low-quality evidence
	54C	In patients with ATA high-risk DTC with attendant higher risks of disease-related mortality and morbidity, more controlled data from long-term outcome studies are needed before rhTSH preparation for RAI adjuvant treatment can be recommended.	No recommendation, Insufficient evidence
	54D	In patients with DTC of any risk level with signifi- cant comorbidity that may preclude thyroid hormone withdrawal prior to iodine RAI administration, rhTSH preparation should be considered. Significant comorbidity may include (a) a significant medical or psychiatric condition that could be acutely exacerbated with hypothyroidism, leading to a serious adverse event, or (b) inability to mount an adequate endogenous TSH response with thyroid hormone withdrawal.	Strong recommendation, Low-quality evidence
	55A	If RAI remnant ablation is performed after total thyroidectomy for ATA low-risk thyroid cancer or intermediate-risk disease with lower risk features (i.e., low- volume central neck nodal metastases with no other known gross residual disease or any other adverse features), a low administered activity of approximately of 30 mCi is generally favoured over higher administered activities.	Strong recommendation, High-quality evidence

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	55B	Higher administered activities may need to be considered for patients receiving less than a total or near-total thyroidectomy in which a larger remnant is suspected or in which adjuvant therapy is intended.	Weak recommendation, Low-quality evidence
[B40]		**What activity of ^{131}I should be used for remnant ablation or adjuvant therapy?**	
	56	When RAI is intended for initial adjuvant therapy to treat suspected microscopic residual disease, administered activities above those used for remnant ablation up to 150 mCi are generally recommended (in absence of known distant metastases). It is uncertain whether routine use of higher administered activities (>150 mCi) in this setting will reduce structural disease recurrence for T3 and N1 disease.	Weak recommendation, Low-quality evidence
[B41]		**Is a low-iodine diet necessary before remnant ablation?**	
	57	A low iodine diet for approximately one to two weeks should be considered for patients undergoing RAI remnant ablation or treatment.	Weak recommendation, Low-quality evidence
[B42]		**Should a post-therapy scan be performed following remnant ablation or adjuvant therapy?**	
	58	A posttherapy WBS (with or without SPECT/CT) is recommended after RAI remnant ablation or treatment, to inform disease staging and document the RAI avidity of any structural disease.	Strong recommendation, Low-quality evidence
[B43]		**Early management of DTC after initial therapy**	
[B44]		**What is the appropriate degree of initial TSH suppression?**	
	59A	For high-risk thyroid cancer patients, initial TSH suppression to below 0.1 mU/L is recommended	Strong recommendation, Moderate-quality evidence
	59B	For intermediate-risk thyroid cancer patients, initial TSH suppression to 0.1– 0.5 mU/L is recommended.	Weak recommendation, Low-quality evidence

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	59C	For low-risk patients who have undergone remnant ablation and have undetectable serum Tg levels, TSH may be maintained at the lower end of the reference range (0.5– 2 mU/L) while continuing surveillance for recurrence. Similar recommendations hold for low-risk patients who have not undergone remnant ablation and have undetectable serum Tg levels.	Weak recommendation, Low-quality evidence
	59D	For low-risk patients who have undergone remnant ablation and have low-level serum Tg levels, TSH may be maintained at or slightly below the lower limit of normal (0.1–0.5 mU/L) while surveillance for recurrence is continued. Similar recommendations hold for low-risk patients who have not undergone remnant ablation, although serum Tg levels may be measurably higher and continued surveillance for recurrence applies.	Weak recommendation, Low-quality evidence
	59E	For low-risk patients who have undergone lobectomy, TSH may be maintained in the mid to lower reference range (0.5–2 mU/L) while surveillance for recurrence is continued. Thyroid hormone therapy may not be needed if patients can maintain their serum TSH in this target range.	Weak recommendation, Low-quality evidence
[B45]		**Is there a role for adjunctive external beam irradiation or chemotherapy?**	
[B46]		**External beam irradiation**	
	60	There is no role for routine adjuvant EBRT to the neck in patients with DTC after initial complete surgical removal of the tumour.	Strong recommendation, Low-quality evidence
[B47]		**Systemic adjuvant therapy**	
	61	There is no role for routine systemic adjuvant therapy in patients with DTC (beyond RAI and/or TSH suppressive therapy using LT4).	Strong recommendation, Low-quality evidence
[C1]		**DTC: LONG-TERM MANAGEMENT AND ADVANCED CANCER MANAGEMENT GUIDELINES**	
[C2]		**What are the appropriate features of long-term management?**	

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
[C3]		**What are the criteria for absence of persistent tumour (excellent response)?**	
[C4]		**What are the appropriate methods for following patients after initial therapy?**	
[C5]		**What is the role of serum Tg measurement in the follow-up of DTC?**	
	62A	Serum Tg should be measured by an assay that is calibrated against the CRM457 standard. Tg antibodies should be quantitatively assessed with every measurement of serum Tg. Ideally, serum Tg and anti-Tg antibodies should be assessed longitudinally in the same laboratory and using the same assay for a given patient	Strong recommendation, High-quality evidence
	62B	During initial follow-up, serum Tg on thyroxine therapy should be measured every 6–12 months. More frequent Tg measurements may be appropriate for ATA high-risk patients	Strong recommendation, Moderate-quality evidence
	62C	In ATA low- and intermediate-risk patients that achieve an excellent response to therapy, the utility of subsequent Tg testing is not established. The time interval between serum Tg measurements can be lengthened to at least 12–24 months	Weak recommendation, Low-quality evidence
	62D	Serum TSH should be measured at least every 12 months in all patients on thyroid hormone therapy	Strong recommendation, Low-quality evidence
	62E	ATA high-risk patients (regardless of response to therapy) and all patients with biochemical incomplete, structural incomplete, or indeterminate response should continue to have Tg measured at least every 6–12 months for several years	Weak recommendation, Low-quality evidence
	63A	In ATA low-risk and intermediate-risk patients who have had remnant ablation or adjuvant therapy and negative cervical US, serum Tg should be measured at 6–18 months on thyroxine therapy with a sensitive Tg assay	Strong recommendation, Moderate-quality evidence

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	63B	Repeat TSH-stimulated Tg testing is not recommended for low- and intermediate-risk patients with an excellent response to therapy ***Qualifying Statements:*** *In Ontario, a sensitive Tg should be measured using a sensitive assay*[6]	Weak recommendation, Low-quality evidence
	63C	Subsequent TSH-stimulated Tg testing may be considered in patients with an indeterminate, biochemical incomplete, or structural incomplete response following either additional therapies or a spontaneous decline in Tg values on thyroid hormone therapy over time in order to reassess response to therapy.	Weak recommendation, Low-quality evidence
[C6]		**Serum Tg measurement and clinical utility**	
[C7]		**Anti-Tg antibodies**	
[C8]		**What is the role of serum Tg measurement in patients who have not undergone radioiodine remnant ablation?**	
	64	Periodic serum Tg measurements on thyroid hormone therapy should be considered during follow-up of patients with DTC who have undergone less than total thyroidectomy and in patients who have had a total thyroidectomy but not RAI ablation. While specific cutoff levels of Tg that optimally distinguish normal residual thyroid tissue from persistent thyroid cancer are unknown, rising Tg values over time are suspicious for growing thyroid tissue or cancer	Strong recommendation, Low-quality evidence
[C9]		**What is the role of US and other imaging techniques (RAI SPECT-CT, CT, MRI, PET-CT) during follow-up?**	
[C10]		**Cervical US**	

[6] *Sensitive Tg assay should be made available*

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	65A	Following surgery, cervical US to evaluate the thyroid bed and central and lateral cervical nodal compartments should be performed at 6–12 months and then periodically, depending on the patient's risk for recurrent disease and Tg status.	Strong recommendation, Moderate-quality evidence
	65B	If a positive result would change management, ultrasonographically suspicious lymph nodes ≥8–10 mm (see Recommendation 71) in the smallest diameter should be biopsied for cytology with Tg measurement in the needle washout fluid	Strong recommendation, Low-quality evidence
	65C	Suspicious lymph nodes less than 8–10 mm in smallest diameter may be followed without biopsy with consideration for FNA or intervention if there is growth or if the node threatens vital structures.	Weak recommendation, Low-quality evidence
	65D	Low-risk patients who have had remnant ablation, negative cervical US, and a low serum Tg on thyroid hormone therapy in a sensitive assay	Weak recommendation, Low-quality evidence
[C11]		**Diagnostic whole-body RAI scans**	
	66	After the first posttreatment WBS performed following RAI remnant ablation or adjuvant therapy, low-risk and intermediate-risk patients (lower risk features) with an undetectable Tg on thyroid hormone with negative antiTg antibodies and a negative US (excellent response to therapy) do not require routine diagnostic WBS during follow-up	Strong recommendation, Moderate-quality evidence
	67A	Diagnostic WBS, either following thyroid hormone withdrawal or rhTSH, 6–12 months after adjuvant RAI therapy can be useful in the follow-up of patients with high or intermediate risk (higher risk features) of persistent disease (see risk stratification system, section [B19]) and should be done with ^{123}I or low activity ^{131}I	Strong recommendation, Low-quality evidence
	67B	SPECT/CT RAI imaging is preferred over planar imaging in patients with uptake on planar imaging to better anatomically localize the RAI uptake and distinguish between likely tumors and nonspecific uptake	Weak recommendation, Moderate-quality evidence

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
[C12]		**^{18}FDG-PET scanning**	
	68A	^{18}FDG-PET scanning should be considered in highrisk DTC patients with elevated serum Tg (generally >10 ng/mL) with negative RAI imaging	Strong recommendation, Moderate-quality evidence
	68B	^{18}FDG-PET scanning may also be considered as: (i) a part of initial staging in poorly differentiated thyroid cancers and invasive Hürthle cell carcinomas, especially those with other evidence of disease on imaging or because of elevated serum Tg levels; (ii) a prognostic tool in patients with metastatic disease to identify lesions and patients at highest risk for rapid disease progression and disease-specific mortality; and (iii) an evaluation of post-treatment response following systemic or local therapy of metastatic or locally invasive disease. ***Qualifying Statement**: In Ontario, PET scanning may not be funded for these indications.*[7]	Weak recommendation, Low-quality evidence
[C13]		**CT and MRI imaging**	
	69A	Cross-sectional imaging of the neck and upper chest (CT, MRI) with IV contrast should be considered (i) in the setting of bulky and widely distributed recurrent nodal disease where US may not completely delineate disease, (ii) in the assessment of possible invasive recurrent disease where potential aerodigestive tract invasion requires complete assessment, or (iii) when neck US is felt to be inadequately visualizing possible neck nodal disease (high Tg, negative neck US).	Strong recommendation, Moderate-quality evidence
	69B	CT imaging of the chest without IV contrast (imaging pulmonary parenchyma) or with IV contrast (to include the mediastinum) should be considered in high risk DTC patients with elevated serum Tg (generally >10 ng/ mL) or rising Tg antibodies with or without negative RAI imaging.	Strong recommendation, Moderate-quality evidence

[7] *The WG agreed with ATA recommendation. However the use of PET scan for these indications may not be supported in Ontario.*

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	69C	Imaging of other organs including MRI brain, MR skeletal survey, and/or CT or MRI of the abdomen should be considered in high-risk DTC patients with elevated serum Tg (generally >10 ng/mL) and negative neck and chest imaging who have symptoms referable to those organs or who are being prepared for TSH-stimulated RAI therapy (withdrawal or rhTSH) and may be at risk for complications of tumor swelling	Strong recommendation, Low-quality evidence
[C14]		**Using ongoing risk stratification (response to therapy) to guide disease long-term surveillance and therapeutic management decisions**	
[C15]		**What is the role of TSH suppression during thyroid hormone therapy in the long-term follow-up of DTC?**	
	70A	In patients with a structural incomplete response to therapy, the serum TSH should be maintained below 0.1 mU/L indefinitely in the absence of specific contraindications.	Strong recommendation, Moderate-quality evidence
	70B	In patients with a biochemical incomplete response to therapy, the serum TSH should be maintained between 0.1 and 0.5 mU/L, taking into account the initial ATA risk classification, Tg level, Tg trend over time, and risk of TSH suppression.	Weak recommendation, Low-quality evidence
	70C	In patients who presented with high-risk disease but have an excellent (clinically and biochemically free of disease) or indeterminate response to therapy, consideration should be given to maintaining thyroid hormone therapy to achieve serum TSH levels of 0.1–0.5 mU/L for up to five years after which the degree of TSH suppression can by reduced with continued surveillance for recurrence.	Weak recommendation, Low-quality evidence
	70D	In patients with an excellent (clinically and biochemically free of disease) or indeterminate response to therapy, especially those at low risk for recurrence, the serum TSH may be kept within the low reference range (0.5–2 mU/L).	Strong recommendation, Moderate-quality evidence

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	70E	In patients who have not undergone remnant ablation or adjuvant therapy who demonstrate an excellent or indeterminate response to therapy with a normal neck US, and low or undetectable suppressed serum Tg, and Tg or anti-Tg antibodies that are not rising, the serum TSH can be allowed to rise to the low reference range (0.5–2 mU/L)	Weak recommendation, Low-quality evidence
[C16]		**What is the most appropriate management of DTC patients with metastatic disease?**	
[C17]		**What is the optimal directed approach to patients with suspected structural neck recurrence?**	
	71	Therapeutic compartmental central and/or lateral neck dissection in a previously operated compartment, sparing uninvolved vital structures, should be performed for patients with biopsy-proven persistent or recurrent disease for central neck nodes ≥8 mm and lateral neck nodes ≥10 mm in the smallest dimension that can be localized on anatomic imaging	Strong recommendation, Moderate-quality evidence
[C18]		**Nodal size threshold**	
[C19]		**Extent of nodal surgery**	
[C20]		**Ethanol injection**	
[C21]		**Radiofrequency or laser ablation**	
[C22]		**Other therapeutic options**	
[C23]		**What is the surgical management of aerodigestive invasion?**	
	72	When technically feasible, surgery for aerodigestive invasive disease is recommended in combination with RAI and/or EBRT.	Strong recommendation, Moderate-quality evidence
[C24]		**How should RAI therapy be considered for loco-regional or distant metastatic disease?**	

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
[C25]		**Administered activity of ^{131}I for loco-regional or metastatic disease**	
	73A	Although there are theoretical advantages to dosimetric approaches to the treatment of loco-regional or metastatic disease, no recommendation can be made about the superiority of one method of RAI administration over another (empiric high activity versus blood and/or body dosimetry versus lesional dosimetry).	No recommendation, Insufficient evidence
	73B	Empirically administered amounts of ^{131}I exceeding 150 mCi that often potentially exceed the maximum tolerable tissue dose should be avoided in patients over age 70 years	Strong recommendation, Moderate-quality evidence
[C26]		**Use of rhTSH (Thyrogen™) to prepare patients for 131I therapy for loco-regional or metastatic disease**	
	74	There are currently insufficient outcome data to recommend rhTSH-mediated therapy for all patients with distant metastatic disease being treated with ^{131}I.	No recommendation, Insufficient evidence
	75	Recombinant human TSH–mediated therapy may be indicated in selected patients with underlying comorbidities making iatrogenic hypothyroidism potentially risky, in patients with pituitary disease whose serum TSH cannot be raised, or in patients in whom a delay in therapy might be deleterious. Such patients should be given the same or higher activity that would have been given had they been prepared with hypothyroidism or a dosimetrically determined activity.	Strong recommendation, Low-quality evidence
[C27]		**Use of lithium in ^{131}I therapy**	
	76	Since there are no outcome data that demonstrate a better outcome of patients treated with lithium as an adjunct to ^{131}I therapy, the data are insufficient to recommend lithium therapy	No recommendation, Insufficient evidence
[C28]		**How should distant metastatic disease to various organs be treated?**	
[C29]		**Treatment of pulmonary metastases**	

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	77A	Pulmonary micrometastases should be treated with RAI therapy and RAI therapy should be repeated every 6– 12 months as long as disease continues to concentrate RAI and respond clinically because the highest rates of complete remission are reported in these subgroups. ***Qualifying Statement:*** *There is strong evidence that these patients should be treated with RAI but the optimal interval between treatment is uncertain*[8].	Strong recommendation, Moderate-quality evidence
	77B	The selection of RAI activity to administer for pulmonary micrometastases can be empiric (100–200 mCi, or 100–150 mCi for patients ≥70 years old) or estimated by dosimetry to limit whole-body retention to 80 mCi at 48 hours and 200 cGy to the bone marrow.	Strong recommendation, Moderate-quality evidence
	78	Radioiodine-avid macronodular metastases may be treated with RAI and treatment may be repeated when objective benefit is demonstrated (decrease in the size of the lesions, decreasing Tg), but complete remission is not common and survival remains poor. The selection of RAI activity to administer can be made empirically (100–200 mCi) or by lesional dosimetry or whole-body dosimetry if available in order to limit whole-body retention to 80 mCi at 48 hours and 200 cGy to the bone marrow.	Weak recommendation, Low-quality evidence
[C30]		**RAI treatment of bone metastases**	
	79A	RAI therapy of iodine-avid bone metastases has been associated with improved survival and should be employed, although RAI is rarely curative.	Strong recommendation, Moderate-quality evidence
	79B	The RAI activity administered can be given empirically (100–200 mCi) or determined by dosimetry	Weak recommendation, Low-quality evidence
[C31]		**When should empiric RAI therapy be considered for Tg-positive, RAI diagnostic scan-negative patients?**	

[8] *Pulmonary micrometastases should be treated with RAI therapy, and repeated treatment should be individualized.*

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	80	In the absence of structurally evident disease, patients with stimulated serum Tg <10 ng/mL with thyroid hormone withdrawal or <5 ng/mL with rhTSH (indeterminate response) can be followed without empiric RAI therapy on continued thyroid hormone therapy alone, reserving additional therapies for those with rising serum Tg levels over time or other evidence of structural disease progression	Weak recommendation, Low-quality evidence
	81	Empiric (100–200 mCi) or dosimetrically determined RAI therapy may be considered in patients with more signifi- cantly elevated serum Tg levels (see Recommendation 80), rapidly rising serum Tg levels, or rising anti-Tg antibody levels, in whom imaging (anatomic neck/chest imaging and/ or ^{18}FDG-PET/CT) has failed to reveal a tumor source that is amenable to directed therapy. The risk of high cumulative administered activities of RAI must be balanced against uncertain long-term benefits. If empiric RAI therapy is given and the posttherapy scan is negative, the patient should be considered to have RAI-refractory disease and no further RAI therapy should be administered.	Weak recommendation, Low-quality evidence
	82	If persistent nonresectable disease is localized after an empiric dose of RAI, and there is objective evidence of significant tumour reduction, then consideration can be made for RAI therapy to be repeated until the tumour has been eradicated or the tumour no longer responds to treatment. The risk of repeated therapeutic doses of RAI must be balanced against uncertain long-term benefits.	Weak recommendation, Low-quality evidence
[C32]		**What is the management of complications of RAI therapy?**	
	83	The evidence is insufficient to recommend for or against the routine use of measures to prevent salivary gland damage after RAI therapy.	No recommendation, Insufficient evidence
	84	Patients with xerostomia are at increased risk of dental caries and should discuss preventive strategies with their dental/oral health professional.	Weak recommendation, Low-quality evidence
	85	Surgical correction should be considered for nasolacrimal outflow obstruction, which often presents as excessive tearing (epiphora) but also predisposes to infection.	Strong recommendation, Low-quality evidence

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
[C33]		**How should patients who have received radioiodine therapy be monitored for risk of secondary malignancies?**	
	86	Although patients should be counseled on the risks of second primary malignancy with RAI treatment for DTC, the absolute increase in risk of developing a second primary malignancy attributable to RAI treatment is considered small and does not warrant specific screening to any extent greater than age-appropriate general population health screening.	Weak recommendation, Low-quality evidence
[C34]		**What other testing should patients receiving RAI therapy undergo?**	
	87	Patients receiving therapeutic doses of RAI should have baseline complete blood count and assessment of renal function.	Weak recommendation, Low-quality evidence
[C35]		**How should patients be counselled about radioiodine therapy and pregnancy, nursing, and gonadal function?**	
	88	Women of childbearing age receiving RAI therapy should have a negative screening evaluation for pregnancy prior to RAI administration and avoid pregnancy for 6–12 months after receiving RAI.	Strong recommendation, Low-quality evidence
	89	Radioactive iodine should not be given to nursing women. Depending on the clinical situation, RAI therapy could be deferred until lactating women have stopped breastfeeding or pumping for at least three months. A diagnostic ^{123}I or low-dose ^{131}I scan should be considered in recently lactating women to detect breast uptake that may warrant deferral of therapy	Strong recommendation, Moderate-quality evidence
	90	Men receiving cumulative RAI activities ≥400 mCi should be counseled on potential risks of infertility.	Weak recommendation, Low-quality evidence
[C36]		**How is RAI-refractory DTC classified?**	

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	91	Radioiodine-refractory structurally evident DTC is classified in patients with appropriate TSH stimulation and iodine preparation in four basic ways: (i) the malignant/ metastatic tissue does not ever concentrate RAI (no uptake outside the thyroid bed at the first therapeutic WBS); (ii) the tumour tissue loses the ability to concentrate RAI after previous evidence of RAI-avid disease (in the absence of stable iodine contamination); (iii) RAI is concentrated in some lesions but not in others; and (iv) metastatic disease progresses despite significant concentration of RAI. When a patient with DTC is classified as refractory to RAI, there is no indication for further RAI treatment.	Weak recommendation, Low-quality evidence
[C37]		**Which patients with metastatic thyroid cancer can be followed without additional therapy?**	
	92A	Patients with ^{131}I-refractory metastatic DTC that is asymptomatic, stable, or minimally progressive who are not likely to develop rapidly progressive, clinically significant complications and do not have indications for directed therapy can be monitored on TSH-suppressive thyroid hormone therapy with serial radiographic imaging every 3–12 months.	Weak recommendation, Moderate-quality evidence
	92B	*BRAF* or other mutational testing is not routinely recommended for prognostic purposes in patients with RAIrefractory, progressive, locally advanced, or metastatic DTC.	Weak recommendation, Moderate-quality evidence
[C38]		**What is the role for directed therapy in advanced thyroid cancer?**	
	93A	Both stereotactic radiation and thermal ablation (radiofrequency ablation and cryoablation) show a high efficacy in treating individual distant metastases with relatively few side effects and may be considered as valid alternatives to surgery	Weak recommendation, Moderate-quality evidence
	93B	Stereotactic radiation or thermal ablation should be considered prior to initiation of systemic treatment when the individual distant metastases are symptomatic or at high risk of local complications.	Strong recommendation, Moderate-quality evidence
[C39]		**Treatment of brain metastases**	

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
	94	While surgical resection and stereotactic EBRT are the mainstays of therapy for central nervous system (CNS) metastases, RAI can be considered if CNS metastases concentrate RAI. If RAI is being considered, stereotactic EBRT and concomitant glucocorticoid therapy are recommended prior to RAI therapy to minimize the effects of a potential TSH-induced increase in tumour size and RAI-induced inflammatory response.	Weak recommendation, Low-quality evidence
[C40]		**Who should be considered for clinical trials?**	
	95	Patients should be considered for referral to participate in prospective therapeutic clinical trials based upon specific eligibility requirements for given studies and the likelihood that the patient may or may not benefit from study participation. Clinicians considering referral of patients for trials should review available treatment options and eligibility criteria, preferably through discussions with trial centre personnel and review of trial materials at the website www.clinicaltrials.org.	Strong recommendation, Moderate-quality evidence
[C41]		**What is the role of systemic therapy (kinase inhibitors, other selective therapies, conventional chemotherapy, b-isphosphonates, denosumab) in treating metastatic DTC?**	
[C42]		**Kinase inhibitors**	
	96A	Kinase inhibitor therapy should be considered in RAI refractory DTC patients with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease not otherwise amenable to local control using other approaches. Kinase inhibitors that are FDA approved for differentiated thyroid carcinoma or other available kinase inhibitors (preferably within the context of therapeutic clinical trials) can be considered since the impact of these agents on	Weak recommendation, Moderate-quality evidence
	96B	Patients who are candidates for kinase inhibitor therapy should be thoroughly counseled on the potential risks and benefits of this therapy as well as alternative therapeutic approaches including best supportive care. Appropriate informed consent should be obtained and documented in the medical record prior to initiation of any therapy, regardless of whether the patient is being treated in the context of a clinical trial.	Strong recommendation, Low-quality evidence

ATA Ref #	Rec #	Topic, Question and Recommendation Statement	Recommendation strength/, Evidence quality
[C43]		**Patients who fail first-line kinase inhibitor therapy**	
	97	Patients who have disease progression while on initial kinase inhibitor therapy without prohibitive adverse effects should be considered for second-line kinase inhibitor therapy. Ideally, such therapy should be undertaken within the context of therapeutic clinical trials.	Weak recommendation, Low-quality evidence
[C44]		**Management of toxicities from kinase inhibitor therapy**	
	98	Proactive monitoring and timely intervention in response to emergent toxicities are critical components of management in patients receiving kinase inhibitor therapy	Strong recommendation, High-quality evidence
[C45]		**Other novel agents**	
	99	Agents without established efficacy in DTC should be used primarily within the context of therapeutic clinical trials.	Strong recommendation, High-quality evidence
[C46]		**Cytotoxic chemotherapy**	
	100	Cytotoxic chemotherapy can be considered in RAI refractory DTC patients with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease not otherwise amenable to control through other approaches, including kinase inhibitors. Too few data exist to recommend specific cytotoxic regimens, and use within the context of a therapeutic clinical trial is preferred.	Weak recommendation, Low-quality evidence
[C47]		**Bone-directed agents**	
	101	Bisphosphonate or denosumab therapy should be considered in patients with diffuse and/or symptomatic bone metastases from RAI-refractory DTC, either alone or concomitantly with other systemic therapies. Adequate renal function (bisphosphonates) and calcium level (bisphosphonates and denosumab) should be documented prior to each dose, and dental evaluation should take place before initial use.	Strong recommendation, Moderate-quality evidence

Note: It was a general recommendation by the WG that for selected cases where cytopathology and pathology are important aspects of determining care, a second opinion may be of value.

ADDENDUM

The Working Group has been made aware of the ATA Guidelines on the Management of Thyroid Nodules and Differentiated Thyroid Cancer Task Force position paper on renaming the Encapsulated Follicular Variant Papillary Thyroid Carcinoma (eFVPTC) without Invasion to Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP) [9]. The following recommendation statement was made by the task force and the Head and Neck DSG Thyroid Cancer Subcommittee endorsed it.

ATA Task Force Recommendation Statement

The histopathologic nomenclature for eFVPTC without invasion may be reclassified as NIFTP, given the excellent prognosis of this neoplastic variant. Prospective studies are needed to validate the observed patient outcomes (and test performance in predicting thyroid cancer outcomes), as well as implications on patients' psychosocial health and economics. (Weak recommendation, moderate-quality evidence)

DISCUSSION

The 2015 ATA Management Guidelines for Adult Patients with Thyroid Nodules and DTC [1] consist of 101 recommendation statements addressing topics including screening, initial evaluation, initial management, surveillance, and management of recurrent disease. The clinical questions used to frame the guidelines were based on the questions from prior versions as well as the contributions of the stakeholders and task force members. Although a formal systematic review was not conducted in the development of the ATA guideline, the WG believes that the document is appropriately comprehensive and reflects present practice standards.

The CCO endorsement process was solely based on the recommendations from the 2015 ATA document and thereby may seem less than up-to-date. One example is the new histopathological entity non-invasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP). The 2015 ATA Guidelines predate this new entity and therefore the present document did not address this subject specifically. A subsequent supplement from the ATA may be forthcoming. It is recommended that clinicians involved in the care of patients with thyroid nodules and cancer familiarize themselves with this new classification. In particular that some FNA biopsies suspicious or diagnostic of PTC may ultimately be defined as NIFTP after surgical excision. This may be a consideration when recommending extent of surgery in selected patients.

After reviewing the evidence and the recommendations of the ATA, the WG acknowledged that controversies persist. Adaptations and qualifying statements to the existing ATA recommendations were included in order to provide clarity and to help Ontario practitioners.

Cancer Care Ontario Thyroid Cancer Guideline: An Endorsement of the 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: Methods and Review Overview

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control. All work produced by the PEBC and any associated programs is editorially independent from the OMHLTC.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [10,11]. This process includes a systematic review, interpretation of the evidence, and draft recommendations by the members of the WG, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [12] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Existing Guidelines

A search for existing guidelines is generally undertaken to identify existing guidelines for adaptation or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions. For this project, the following sources were searched for existing guidelines in thyroid cancer:

- Practice guideline databases: Standards and Guidelines Evidence Directory of Cancer Guidelines (SAGE), Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse, and the Canadian Medical Association Infobase.
- The websites of guideline developers such as the National Institute for Health and Clinical Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), New Zealand Guidelines Group (NZGG), and National Health and Medical Research Council- Australia(NHMRC) were also searched.

Guidelines that were considered relevant were evaluated for quality using the AGREE II instrument[12]. The AGREE II score for the ATA guideline is 65%. The details of the assessment can be found in Appendix 2.

ACKNOWLEDGEMENTS

The Head and Neck Cancer DSG thyroid subcommittee and the WG would like to thank the following individuals for their assistance in developing this report:

- Melissa Brouwers, Sheila McNair, Hans Messersmith, and CCO thyroid disease pathway management (DPM) expert panel for providing feedback on draft versions.
- Sara Miller for copy editing.

INTERNAL REVIEW

The draft endorsement document was evaluated and approved by the Head and Neck DSG Thyroid Cancer Subcommittee members and CCO thyroid DPM panel members (see Appendix 1) that provided PEBC with their conflict of interest declaration (see the PEBC Conflict of Interest (COI) Policy). One member of the PEBC Report Approval Panel (RAP) also reviewed the document and recommended that instead of an outline of questions and topic areas covered in the ATA guideline, a complete list of the 101 recommendations be presented.

Expert Panel Review and Approval

In October 2016, 23 of the 26 panel members (excluding the WG) cast votes for a 89% response rate. Of those that cast votes, 22 (95%) approved the document. The main comments from the Expert Panel and the WG's responses are summarized in Table 2-1.

Table 2-1: Expert Panel Feedback and WG Response

Comments	Responses
Although there is a comment about the impact of NIFTP in the document, there is literature accumulating about the impact for FNA biopsy terminology and risk of malignancy and the document should address this more robustly	The goal of the document is to endorse the ATA guidelines as written. Addressing new entities such as NIFTP is outside the scope.
My only comment would be in section B15, encapsulated follicular variant of PTC without invasion could be followed by NIFTP ("noninvasive follicular thyroid neoplasm with papillary-like nuclear features"), as many of the "encapsulated follicular variant of PTC without invasion" will be replaced with the new designation of NIFTP.	

[A10] Recommendation #8 C & D regarding nodules >1.5cm or >2cm. If these recommendations are left the way they are now, every nodule over 1cm will be sampled. There is no way a biopsy will ever be refused. ATA risk scores for low suspicion is 5% to10% and very low suspicion <3%. For a disease with a very low disease-specific mortality, sampling these nodules should NOT be recommended. I think the best compromise would be to allow low-suspicion nodules to be sampled ONLY if >2cm. Spongiform nodules should not be biopsied unless they grow markedly in size to over 4cm.	The WG is in agreement but cannot extrapolate beyond the ATA Guidelines.

EXTERNAL REVIEW

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. Professionals in the PEBC database with an interest in thyroid cancer, head and neck cancer, FNA, biopsy, and guideline evaluation (AGREE II), were contacted by email to inform them of the survey. Experts suggested by the CCO thyroid cancer disease pathway panel members were also contacted. Ninety-eight professionals who practice in Ontario (97%), other provinces (2%), and outside Canada (1%) were contacted. Twenty-four (25%) responses were received. Six stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback from 18 people are summarized in Table 2-1. The main comments from the consultation and the WG responses are summarized in Table 2-3.

Table 2-2. Responses to four items on the professional consultation survey

	Number 18 (98)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0	0	1	6	11
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	0	0	2	2	14
3. I would recommend this guideline for use in practice.	0	0	0	4	14
4. What are the barriers or enablers to the implementation of this guideline report?	Although the guideline is very long and may need a shorter format of key messages before dissemination to all providers in Ontario, there should be great receptivity to these guidelines.				

	Clinicians and diagnosticians are looking for guidance and leadership in the management of thyroid nodules because of the great interest and concern about overdiagnosis and overtreatment of thyroid nodules especially in the pathology community. Many physicians are still sticking to unnecessary full TSH suppression when not needed. This should perhaps be highlighted in some memo as a key feature to these new guidelines. A potential barrier would be physician awareness of this guidelines' existence. Proper and adequate dissemination is required. Reaching the target audience through education will be helpful - CCO would need to have a physician information campaign to make stakeholders aware of this existence. Potentially emailing physicians and maybe providing mailed copies of the completed guidelines (or shortened card of highlights of the guidelines) for use in clinics. Some other barriers include: • Availability of molecular testing and its reliability may be a barrier as a screening test. • The recommendation of molecular testing may not be appropriate for all centres. • Access to PET scans. • Potentially continued overuse of US in thyroid cancer screening • Convincing some surgeons to operate more conservatively. For example, lobectomy instead of total thyroidectomy for indeterminate and low risk lesions • There is insufficient or low-quality evidence for many of the recommendations which may never be feasible to obtain - this may result in uncertainties or discrepancies in certain practices. • The guideline is very long and will need a shorter format of key messages before dissemination to all providers in Ontario.

Table 2-3. Modifications/Actions taken/Responses regarding main written comments from professional consultation.

Comments	Responses

1. Many comments addressed a desire for more specific guidance in areas not within the scope of the ATA guidelines. 2. In Recommendation #14 – The statement 'molecular testing of FNA specimen is done in Ontario labs' does not seem to be accurate.	1. The goal of the document is to endorse the ATA guidelines as written. Addressing new entities is outside the scope. 2. Qualifying statement has been modified.

Reference

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2. **Canadian Cancer Society's Advisory Committee on Cancer Statistics. (2015). Canadian Cancer Statistics 2015. Toronto, ON: Canadian Cancer Society.**
3. **Ukrainski MB, Pribitkin EA, Miller JL. Increasing Incidence of Thyroid Nodules and Thyroid Cancer: Does Increased Detection of a Subclinical Reservoir Justify the Associated Anxiety and Treatment? Clinical Therapeutics. 2016;38(4):976-85.**
4. **Davies L, Welch H. CUrrent thyroid cancer trends in the united states. JAMA Otolaryngology–Head & Neck Surgery. 2014;140(4):317-22.**
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9. **Haugen BR, Sawka AM, Alexander EK, Bible KC, Caturegli P, Doherty G, et al. The ATA Guidelines on Management of Thyroid Nodules and Differentiated Thyroid Cancer Task Force Review and Recommendation on the Proposed Renaming of eFVPTC without Invasion to NIFTP. Thyroid. 2017.**
10. **Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A ea. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. . J Clin Oncol 1995;13:502-12.**
11. **Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI ea. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31.**
12. **Brouwers M, Kho ME, Browman GP, Burgers JS, Cluzeau F, G F. AGREE II: Advancing guideline development, reporting and evaluation in healthcare. CMAJ: Canadian Medical Association Journal. 2010**

Appendix 1: Members of the Working Group, Expert Panel, Report Approval Panel and target reviewers and their COI declarations (see the PEBC Conflict of Interest (COI) Policy)

Name	Affiliation	COI Declared
Working Group		
John Yoo	London Health Sciences Centre	Yes[1]
Chika Agbassi	Department of Oncology, McMaster University	No
Deric Morrison	St Joseph's Health Care London	No
Heather Lochnan	Faculty of Medicine, University of Ottawa	No
Anna Sawka	Toronto General Research Institute	Yes[2]
Jim Brierley	Head and Neck Surgery, University of Toronto	No
CCO Head & Neck – Thyroid Subcommittee and DPM Expert Panel		
Eric Winquist – Co chair	London Health Sciences Centre	No
Michael Gupta	St. Joseph's Healthcare, Hamilton	No
David Goldstein	University Health Network, Toronto	Yes[3]
Ozgur Mete	University Health Network, Toronto	No
Shereen Ezzat	Princess Margaret Hospital, Toronto	No
Chris Marriott	Hamilton Health Sciences	No
Jim Gibson	St. Joseph's Healthcare, Hamilton	No
Michele Weir	Schulich School of Medicine & Dentistry	No
Bibianna Maria Purgina	Faculty of Medicine, University of Ottawa	No
Eugene Leung	Department of Medicine, University of Ottawa	No
Kevin Higgins	Sunnybrook Health Sciences Centre	No
Andrew Boright	University of Toronto	No
Andrew Pearce	Northeast Regional Cancer Program	No
Hugh Langley	South East Regional Cancer Program	No
James (Ted) Young	Head and Neck Surgery, McMaster University	No
James Gibson	Department of Medicine, McMaster University	No
Jeremy Freeman	Head and Neck Surgery, University of Toronto	Yes[4]
Jim Wright	Department of Oncology, McMaster University	No
John Kim	Princess Margaret Cancer Centre, Toronto	No
Joshua Lakoff	Department of Medicine, Queen's University	No
Karen Devon	Women's College Hospital, University of Toronto	Yes[5]
Lisa Thain	Faculty of Medicine, University of Toronto	No
Lorne Rotstein	Division of General Surgery, Toronto General Hospital	No
Michael Chang	Head and Neck Surgery, University of Toronto	No
Michael Odell	The Ottawa Hospital Regional Cancer Centre	No
Praveen Bansal	Mississauga Halton Central West Regional Cancer Program	No
Robert Josse	St. Michael's Hospital, Toronto	No
Sangeet Ghai	Princess Margaret Cancer Centre, Toronto	Yes[6]
Claudette Chase		No
Report Approval Panel		
Melissa Brouwers	Department of Oncology, McMaster University	No

[1] Board of directors of a public company named critical outcomes technologies and the scientific adviser of a cancer diagnostic company
[2] Co-authored the ATA guideline
[3]Received a CCSRI (Academic Funding Plan) innovation grant
[4] Consultant for Eisai, Johnson and Johnson, Genzyme
[5] Consultant for Johnson and Johnson
[6]Have set up thyroid biopsy specialists program at UHN-MSH-WCH

Appendix 2: AGREE II Score Sheet

Domain	Item	AGREE II Rating		
		Appraiser 1	Appraiser 2	Appraiser 3
Scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described.	7	6	7
	2. The health question(s) covered by the guideline is (are) specifically described.	6	7	7
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	7	7	7
Stakeholder involvement	4. The guideline development group includes individuals from all the relevant professional groups.	7	5	4
	5. The views and preferences of the target population (patients, public, etc.) have been sought.	7	4	1
	6. The target users of the guideline are clearly defined.	7	6	7
Rigor of development	7. Systematic methods were used to search for evidence.	2	4	2
	8. The criteria for selecting the evidence are clearly described.	1	4	1
	9. The strengths and limitations of the body of evidence are clearly described.	5	5	6
	10. The methods for formulating the recommendations are clearly described.	7	4	3
	11. The health benefits, side effects and risks have been considered in formulating the recommendations.	7	5	5
	12. There is an explicit link between the recommendations and the supporting evidence.	6	6	5
	13. The guideline has been externally reviewed by experts prior to its publication.	7	5	6
	14. A procedure for updating the guideline is provided.	1	5	1
Clarity of presentation	15. The recommendations are specific and unambiguous.	6	5	6
	16. The different options for management of the condition or health issue are clearly presented.	6	5	7
	17. Key recommendations are easily identifiable.	3	6	7
Applicability	18. The guideline describes facilitators and barriers to its application.	6	4	3
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	5	2	5

Domain	Item	AGREE II Rating		
		Appraiser 1	Appraiser 2	Appraiser 3
	20. The potential resource implications of applying the recommendations have been considered.	3	2	2
	21. The guideline presents monitoring and/ or auditing criteria.	1	2	2
Editorial independence	22. The views of the funding body have not influenced the content of the guideline.	7	6	7
	23. Competing interests of guideline development group members have been recorded and addressed.	7	5	7
Overall Guideline Assessment	1. Rate the overall quality of this guideline.	**5**	**6**	**5**
Overall Guideline Assessment	2. I would recommend this guideline for use.	*Yes, with modifications*	*Yes*	*Yes*

$$\frac{\text{(Obtained score – Minimum possible score)}}{\text{(Maximum possible score – Minimum possible score)}}$$

(339-69) / (483-69) = 0.652 X 100 = 65%

APPENDIX 3: ACR TIRADS map