The Philippine Interim Clinical Practice Guidelines for the Diagnosis and Management of Well-Differentiated Thyroid Cancer 2021

Commissioned by the Department of Health
to Jose R. Reyes Memorial Medical Center

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TABLE OF CONTENTS

DISCLAIMER

This clinical practice guideline on thyroid cancer was developed following the ADAPTE process of searching, appraising, and adapting recommendations from the most recent local and international guidelines.

Relevant clinical and health economic issues about thyroid cancer diagnosis and management that were often encountered in the local setting were considered in planning the scope of the guideline. Although the recommendations contained herein are intended to aid in decision-making for clinicians, patients, policymakers, and other stakeholders based on available evidence, the technical working group should not be held liable for the eventual outcome of patients to whom the recommendations were applied. It is the responsibility of each attending physician or clinician to follow his best clinical judgement when applying these recommendations to his patient.

Although this clinical practice guideline development project was commissioned by the Department of Health to Jose R. Reyes Memorial Medical Center, it is still subject to evaluation and approval by the National Guideline Clearinghouse before it can be endorsed by the Department of Health.

LIST OF ABBREVIATIONS

AACE	American Association of Clinical Endocrinologists
AAES	American Association of Endocrine Surgeons
ACE	American College of Endocrinology
AfHNS	African Head and Neck Society
AHNS	American Head and Neck Society
AJCC/UICC	American Joint Committee/Union for International Cancer Control
AME	Associazione Medici Endocrinologi
AGREE	Appraisal of Guidelines Research & Evaluation
ATA	American Thyroid Association
ATC	anaplastic thyroid cancer
AUS	atypia of undetermined significance
CP	consensus panel
CPG	clinical practice guideline
CRT	chemoradiation
CT	computed tomography
DOH	Department of Health
DTC	differentiated thyroid cancer
EBRT	external beam radiation therapy
FLUS	follicular lesion of undetermined significance
FNAB	fine-needle aspiration biopsy
FNAC	fine-needle aspiration cytology
HFSRT	hypofractionated stereotactic radiotherapy
ICER	incremental cost-effectiveness ratio
KTA	Korean Thyroid Association
LNM	lymph node metastases
LT4	levothyroxine
MRI	magnetic resonance imagine
NGC	National Guideline Clearinghouse
NICCA	National Integrated Cancer Control Act
PET/CT	positron emission tomography/computed tomography
PTC	papillary thyroid cancer
QALY	quality-adjusted life year
RAI	radioactive iodine, radioiodine
RAIA	radioactive iodine ablation
rhTSH	recombinant human thyroid-stimulating hormone
RR-DTC	radioiodine-refractory differentiated thyroid cancer
RT	radiotherapy, radiation therapy
SC	steering committee
SFN	suspicious for a follicular neoplasm
SRS	stereotactic radiosurgery
SRT	stereotactic radiotherapy

TBSRTC	The Bethesda System for Reporting Thyroid Cytopathology
Tg	thyroglobulin
TgAb	anti-thyroglobulin
THST	thyroid hormone suppression therapy
TLUS	transcutaneous laryngeal ultrasound
TMB	tumor mutational burden
TNM	Tumor Node Metastasis
TSH	thyroid-stimulating hormone
TWG	technical working group
US	ultrasound or ultrasonography
USPSTF	United States Preventive Services Task Force
WBRT	whole brain radiotherapy
WDTC	well-differentiated thyroid cancer

DEFINITION OF TERMS

Completion thyroidectomy
the surgical removal of the remnant thyroid tissue following procedures less than total or near-total thyroidectomy

Extrathyroidal extension
tumor extension into the adjacent tissues

Minimal extrathyroidal extension
invasion into immediate perithyroidal soft tissues or sternothyroid muscle typically detected only microscopically (T3 tumors)

Papillary thyroid microcarcinoma
defined as a tumor 1 cm or less in size

Prophylactic/elective neck dissection
implies nodal metastasis is not detected clinically or by imaging (clinically N0)

Therapeutic neck dissection
implies that nodal metastasis is apparent clinically (preoperatively or intraoperatively) or by imaging (clinically N1a)

LIST OF TABLES, FIGURES, AND BOXES

SUMMARY OF RECOMMENDATIONS

Screening

	Question		Recommendation	Certainty of evidence	Strength of recommendation
1.1	Among asymptomatic apparently healthy adults, should screening for thyroid cancer be done?		We do not recommend screening asymptomatic apparently healthy adults for thyroid cancer.	Moderate	Strong
1.2	Who should be screened for thyroid cancer?		We recommend screening for thyroid cancer in individuals at high risk, defined as having any one of the following: • a history of significant exposure to ionizing radiation to the head and neck area, especially in childhood; • inherited genetic syndromes associated with thyroid cancer (e.g., familial adenomatous polyposis); or • one or more first-degree relatives with a history of thyroid cancer.	Moderate	Strong
1.3	Among individuals at high risk, how should screening for thyroid cancer be done?	a	We recommend systematic neck palpation and neck US in individuals at high risk to screen for thyroid cancer.	Low	Strong
		b	In low-resource settings, we recommend systematic neck palpation at each outpatient visit to screen for thyroid cancer.	Moderate	Strong

Diagnosis and preoperative evaluation

	Question		Recommendation	Certainty of evidence	Strength of recommendation
2.1	What are the clinical data which support an impression of thyroid malignancy?	a	Clinical features suggestive of increased risk for thyroid malignancy include: • age <14 years old or >70 years old; • male sex; • family history of thyroid cancer; • previous head or neck irradiation; • rapid neck mass growth; • recent onset hoarseness, dysphagia or dyspnea.	Low to Moderate	Strong
		b	Physical examination findings suggestive of higher risk for thyroid malignancy include: • firm or hard thyroid nodule consistency; • fixed nodule; • cervical adenopathy.	Low to Moderate	Strong
2.2	Among patients suspected to have malignant thyroid nodules, what are the essential diagnostic and preoperative work-up that should be requested?	a	We recommend serum TSH ± T4 (free or total) measurement in the initial evaluation of patients suspected to have malignant thyroid nodules.	Moderate to High	Strong
		b	If the serum TSH is subnormal, we recommend a radionuclide thyroid scan to determine whether the nodule is hyperfunctioning or not.	Moderate	Strong
		c	We recommend a diagnostic neck US for all patients with thyroid nodule.	High	Strong
		d	We recommend that US evaluation of the neck must include assessment of the status of the cervical lymph nodes whenever a thyroid nodule is detected.	High	Strong
2.3	What are the indications for doing thyroid biopsy?	a	We recommend that FNAB should be performed on all nodules suspected of being malignant based on clinical or US findings.	High	Strong

Diagnosis and preoperative evaluation

	Question		Recommendation	Certainty of evidence	Strength of recommendation
		b	For thyroid glands with multiple nodules, we recommend that each nodule be evaluated separately and the decision to perform a FNAB be individualized.	Moderate	Strong
		c	We do not recommend FNAB for nodules that are purely cystic and hyperfunctioning on thyroid scintigraphy.	Low	Strong
		d	We recommend FNAB for cervical lymph nodes with suspicious clinical and US findings	Moderate	Moderate
2.4	When should US-guided FNAB be done?		We recommend US-guided FNAB in the following: • multi nodular goiter; • complex nodules with more than 25% cystic component; • posteriorly located nodules; • nodules greater than 1 cm with indeterminate us findings; • nodules less than 1 cm with indeterminate us findings which increased in size after 6 months; • subcapsular or paratracheal lesions; • if initial FNAB result is inadequate.	Moderate	Strong
2.5	How should the FNAB/FNAC/ABC* result be reported?		We recommend reporting of the thyroid cytopathology using the TBSRTC for FNAB* cytodiagnosis.	High	Strong
2.6	Among patients who underwent FNAC of a thyroid nodule, when is molecular testing warranted and most helpful in diagnostic and therapeutic applications?		We can consider molecular testing, for indeterminate FNAB diagnosis, in particular, Bethesda Category III and IV to further stratify thyroid lesions into molecular/behavioral subsets of lesions.	Moderate	Strong
2.7	Among patients suspected to have DTC, what are the indications for	a	We do not recommend the routine use of CT scan, MRI, thyroid scintigraphy and PET/CT.	High	Strong

Diagnosis and preoperative evaluation

	Question		Recommendation	Certainty of evidence	Strength of recommendation
	additional diagnostic imaging?	b	Use of CT scan and/or MRI with intravenous contrast may be considered in clinically advanced cases like bulky and fixed tumors.	Moderate	Strong
2.8	Among patients suspected to have thyroid cancer, what are the indications for evaluating vocal cord function preoperatively?		We recommend visualization of vocal folds for the following patients with: • notable voice changes based on physical examination; • pre-existing laryngeal disorder; • prior neck, mediastinal, cardiac or upper thoracic surgery; • known thyroid cancer with extrathyroidal extension; • large substernal goiter; • extensive central nodal metastasis; • history of long-standing hoarseness which resolves spontaneously.	Low to Moderate	Strong

Surgical management

	Question		Recommendation	Certainty of evidence	Strength of recommendation
3.1	What is the appropriate operation for patients with proven malignant thyroid nodules (Category V to VI)?	a	We recommend total thyroidectomy for all Category V and VI unifocal nodules measuring >1 cm.	Moderate	Strong
		b	We recommend total thyroidectomy for Category V and VI nodules with clinical or radiographic evidence of the following regardless of the size: • bilateral thyroid disease; • extrathyroidal invasion; • LNM; • distant metastases.	Moderate	Strong
3.2	What is the appropriate operation for patients with thyroid nodules cytologically suspicious for FN (Category IV)?		We recommend lobectomy with isthmusectomy as the initial and minimum surgery for solitary category IV nodule.	Low to Moderate	Strong
3.3	What is the appropriate neck dissection for patients diagnosed with thyroid malignancy with gross metastatic nodal disease?	a	We recommend therapeutic neck dissection for patients with gross metastatic nodal disease.	High	Strong
		b	We recommend therapeutic central neck dissection (Level VI) if there are LNM in the central compartment.	High	Strong
		c	We recommend therapeutic central (Level VI) and posterolateral neck dissection (Level II–V) if there are LNM in the ipsilateral lateral compartment.	High	Strong
3.4	What is the role of surgery for patients presenting with distant metastasis of DTC?	a	We recommend total thyroidectomy ± neck dissection for patients with DTC even with distant metastasis.	Moderate	Strong
		b	We recommend surgical excision for resectable metastatic disease without adverse functional outcome in selected patients.	Moderate	Strong
3.5	How should we manage perioperative complications after thyroidectomy?	a	We recommend at least an overnight observation for patients at high risk for postoperative hematoma, when clinically appropriate.	Moderate	Strong

Surgical management

Question		Recommendation	Certainty of evidence	Strength of recommendation
	b	We recommend oral calcium as first line therapy for post-operative hypocalcemia. If hypocalcemia is persistent or refractory, calcitriol may be added. If hypocalcemia is severe, persistent or refractory, intravenous calcium should be used.	Low	Strong
	c	For patients at high risk for hypocalcemia, determination of ionized calcium or serum calcium and albumin should be requested post-operatively.	Low	Strong
	d	We recommend preoperative assessment and supplementation of calcium and 25 hydroxy vitamin D when appropriate, such as in patients post Roux-en-Y gastric bypass, those with Graves' disease, and other conditions known to be at risk for postoperative hypocalcemia.	Moderate	Strong
	e	We recommend formal laryngeal evaluation for patients with dyspnea and/or stridor, aspiration, dysphagia, and hoarseness.	Low	Strong
3.6 What is the role of surgery for pregnant patients with thyroid nodules?		We recommend to defer surgery until after delivery for patients with nodules that remain stable clinically and on USG, or if it is diagnosed beyond 24–26 weeks of gestation or the second half of pregnancy.	Low	Moderate
3.7 What is the role of frozen section in the management of thyroid nodules suspicious for malignancy?		Frozen section is not routinely used, but may be considered in the following: • confirmation of extrathyroidal extension; • confirmation of PTC if the diagnosis will alter the extent of the surgical plan; • confirmation of the nature of equivocal structure (e.g., parathyroid glands, lymph nodes).	Moderate	Strong

Surgical management

	Question	Recommendation	Certainty of evidence	Strength of recommendation
3.8	What are the indications for completion thyroidectomy?	We recommend completion thyroidectomy in any of the following: • unanticipated malignancy with a tumor diameter >1 cm; • confirmed contralateral malignancy; • confirmed nodal metastasis; • aggressive histologic type.	Moderate	Moderate

Postoperative management

	Question		Recommendation	Certainty of evidence	Strength of recommendation
4.1	What is the role of postoperative staging systems in the management of DTC?		We recommend the use of the AJCC/UICC staging for all patients with DTC to standardize encoding in cancer registry and for its utility in predicting disease mortality.	Moderate	Moderate
4.2	What is the role of initial risk stratification in the management of DTC?		We recommend the use of the 2015 ATA risk stratification system for patients with DTC to serve as a guide for further treatment and for surveillance.	Moderate	Moderate
4.3	Should postoperative disease status be considered in decision-making for RAI therapy for patients with DTC?	a	We recommend that postoperative disease status (i.e., the presence or absence of residual disease) should be considered in deciding whether additional treatment (e.g., RAI, surgery, or other treatment) may be needed.	Low	Strong
		b	Postoperative serum Tg, ideally 3–4 weeks postoperatively, can help in assessing the persistence of disease or thyroid remnant and predicting potential future disease recurrence.	Moderate	Strong
4.4.1	What is the role of RAI (including remnant ablation, adjuvant therapy, or therapy for persistent disease) after thyroidectomy in the primary management of DTC?	a	We recommend routine RAI adjuvant therapy after total thyroidectomy for ATA high risk DTC patients.	Moderate	Strong
		b	We recommend RAI adjuvant therapy after total thyroidectomy in ATA intermediate-risk level DTC patients.	Low	Strong
		c	We do not recommend routine RAI remnant ablation after thyroidectomy for ATA low-risk DTC patients.	Low	Strong
		d	We do not recommend routine RAI remnant ablation after lobectomy or total thyroidectomy for patients with unifocal papillary microcarcinoma, in the absence of other adverse features.	Moderate	Strong

Postoperative management

	Question		Recommendation	Certainty of evidence	Strength of recommendation
		e	We do not recommend routine RAI remnant ablation after thyroidectomy for patients with multifocal papillary microcarcinoma, in absence of other adverse features.	Low	Moderate
4.4.2	How should post-thyroidectomy patients be prepared for RAI remnant ablation/treatment or diagnostic scanning?		We recommend that RAI should be given after TSH stimulation, ideally, until serum TSH levels reach at least 30 mIU/ml or alternatively, rhTSH can be given.	Moderate	Strong
4.4.3	Should a posttherapy scan be performed following remnant ablation or adjuvant therapy?		We recommend that RAI administration must be followed by WBS to stage the disease and document the ^{131}I avidity of any structural lesion.	High	Strong
4.5	Among patients with DTC post-surgery, what is the role of thyroid hormone suppression?	a	We recommend initial TSH suppression to <0.1 mU/L for high-risk DTC patients.	Moderate	Strong
		b	We suggest initial TSH suppression to 0.1–0.5 mU/L for intermediate-risk DTC patients.	Low	Strong
		c	We suggest that TSH may be maintained at the lower end of the reference range (0.5–2 mU/L) for low-risk DTC patients who have undergone remnant ablation and have undetectable serum Tg levels while continuing surveillance for recurrence.	Low	Strong
		d	We suggest that TSH may be maintained at or slightly below the lower limit of normal (0.1–0.5 mU/L) for low-risk DTC patients who have undergone remnant ablation and have low-level serum Tg levels while continuing surveillance for recurrence.	Low	Strong

Postoperative management

	Question		Recommendation	Certainty of evidence	Strength of recommendation
		e	We suggest that TSH may be maintained in the mid to lower reference range (0.5–2 mU/L) for low-risk DTC patients who have undergone lobectomy while continuing surveillance for recurrence. Thyroid hormone therapy may not be needed if patients can maintain their serum TSH in this target range.	Low	Strong
4.6.1	Among patients with DTC post-surgery, is there a role for adjuvant EBRT?	a	We do not recommend routine adjuvant EBRT to the neck in patients with DTC after initial complete surgical removal of the tumor.	Low	Strong
		b	We suggest that EBRT may however be very selectively considered within the context of a multidisciplinary team for DTC patients with high-risk features such as, but not limited to, the following: • surgically unresectable gross residual disease; • inadequate RAI uptake; • extranodal extension or involvement of soft tissues; • tumors threatening vital structures; • rapid progression; • locally advanced disease; • older age with extrathyroidal extension; • tumors undergoing multiples and frequent serial reoperations for locoregionally recurrent disease.	Low	Strong
4.6.2	Among patients with ATC diagnosed postoperatively, what is the role of EBRT?	a	We recommend post-operative EBRT with systemic therapy for resectable, non-metastatic, good performance status patients desirous of aggressive treatment.	Low	Strong

Postoperative management

	Question		Recommendation	Certainty of evidence	Strength of recommendation
		b	We recommend EBRT with systemic therapy for unresectable, nonmetastatic, good performance status patients desirous of aggressive treatment. Surgery can be reconsidered after neoadjuvant therapy depending on response.	Low	Strong
4.7.1	Among patients with DTC post-surgery, is there a role for chemotherapy in the adjuvant setting		We do not recommend the use of chemotherapy in patients with DTC (beyond RAI and/or TSH suppressive therapy) in the adjuvant setting.	Very low	Strong
4.7.2	Among patients with ATC diagnosed postoperatively, is there a role for chemotherapy in the adjuvant setting?		We recommend the use of cytotoxic chemotherapy with or without RT in patients with ATC when clinically appropriate in the adjuvant setting.	Low	Strong
4.8.1	Among patients with DTC post-surgery, what is the role of targeted therapy and immunotherapy in the adjuvant setting?		We do not recommend the use of targeted treatment such as kinase inhibitors and immunotherapy in the adjuvant setting.	Low	Strong
4.8.2	Among patients with ATC, what is the role of targeted therapy and immunotherapy in the adjuvant setting?		We can consider the use of targeted agents in the presence of druggable mutations and genetic aberrations in the adjuvant setting, if accessible.	Low	Strong

Surveillance

	Question		Recommendation	Certainty of evidence	Strength of recommendation
5.1	Which criteria should be utilized to classify response to therapy of a patient with DTC?		We recommend to utilize the response to treatment categories based on the modified ATA dynamic or ongoing risk stratification system. Response to treatment is classified as any of the following: excellent, biochemical incomplete, structural incomplete or indeterminate response.	Moderate	Strong
5.2	How should a patient's response to therapy in the first year of treatment be followed up?	a	We recommend that the initial dynamic risk stratification should be determined within 6 months after treatment.	Moderate	Strong
		b	We recommend using Tg and TgAb assays that are calibrated with a reference standard.	High	Strong
		c	We recommend that serum Tg and TgAb levels be checked every 3–6 months in the first year after treatment.	Moderate	Strong
		d	We recommend measurement of unstimulated or stimulated Tg and TgAb for patients who have undergone total thyroidectomy and radioactive remnant ablation therapy.	Moderate	Strong
		e	We recommend measurement of unstimulated Tg and TgAb for patients who have undergone total thyroidectomy but do not require radioactive remnant ablation, and who are at low risk of recurrence.	Moderate	Strong
		f	We do not recommend routine measurement of serum Tg and TgAb for patients who have not undergone total thyroidectomy and with low risk of recurrence.	Moderate	Strong
		g	We recommend that neck US should be performed at a 6- to 12-month interval depending on risk assessment.	Moderate	Strong

Surveillance

	Question		Recommendation	Certainty of evidence	Strength of recommendation
5.3	How should a patient's response to therapy after the first year of treatment be followed up?	a	We recommend increasing the time interval between repeat measurements of unstimulated Tg and TgAb for patients who achieve excellent response.	Moderate	Strong
		b	We recommend measuring stimulated or unstimulated Tg at least every 6–12 months for high-risk and all patients with biochemical incomplete, structural incomplete or indeterminate response.	Low	Strong
		c	We do not recommend using stimulated Tg and TgAb in the follow up of these subsets of patients: those with excellent response, and those with incomplete structural response.	Low	Strong
		d	We recommend increasing the time interval between repeat neck US for patients who achieve excellent response.	Moderate	Strong
5.4	What are the roles of radiologic and nuclear imaging studies in the follow-up of DTC?	a	We recommend periodic neck US depending on the patient's risk for recurrent disease and Tg status.	Moderate	Strong
		b	We recommend US-guided FNAB for ultrasonographically suspicious lymph nodes $\geq$10 mm in widest dimension.	Moderate	Strong
		c	We do not recommend routine diagnostic WBS using low-dose ^{131}I in low-risk patients who have negative serum Tg, TgAb, and neck US during follow-up. WBS may be considered if persistent disease is suspected, despite a negative finding in the other tests.	Low	Strong
		d	We recommend FDG-PET scanning in high-risk DTC patients with elevated serum Tg and with negative RAI imaging.	Moderate	Strong

Surveillance

Question		Recommendation	Certainty of evidence	Strength of recommendation
	e	We recommend neck and/or chest CT or MRI in the following settings: • bulky and recurrent nodal disease where US may not completely delineate disease; • possible invasive recurrent disease involving aerodigestive tract; • inadequacy of neck US in visualizing nodal disease (high Tg, negative neck US); and • possible involvement of lung parenchyma and/or mediastinum.	Moderate	Strong
	f	We recommend imaging of other organs including brain MRI, skeletal MRI, and/or CT or MRI of the abdomen in high-risk DTC patients with elevated serum Tg and negative neck and chest imaging who have symptoms referable to those organs.	Moderate	Strong

Palliative care

	Question		Recommendation	Certainty of evidence	Strength of recommendation
6.1	What services/interventions can be provided for palliation?		We recommend consult with a multidisciplinary team that includes a pain medicine/ palliative care practitioner to address the needs of a thyroid cancer patient in the advanced stage of the disease.	Moderate	Strong
6.2	How do we treat advanced RAI refractory thyroid cancer?	a	We do not recommend further RAI when a patient with DTC is classified as refractory to RAI.	Low	Strong
		b	We recommend kinase inhibitors or immunotherapy for patients with RR-DTC.	High	Strong
		c	We recommend multidisciplinary discussion and enrollment in clinical trials for patients with RR-DTC.	Low	Strong
6.3	What is the role of RT in the palliative setting?		We recommend EBRT to patients who develop metastasis that can cause symptoms that affect function and quality of life.	Moderate	Strong
6.3.1	What is the role of RT in spinal cord compression due to bone metastasis?		We recommend EBRT to patients who develop spinal cord compression secondary to bone metastasis.	Moderate	Strong
6.3.2	What is the role of RT in bleeding tumor?		We can consider palliative RT to patients with bleeding tumors not amenable to surgery or other treatments.	Moderate	Strong
6.3.3	What is the role of RT in brain metastasis?		We recommend EBRT to patients who develop brain metastasis.	Moderate	Strong
6.4.1	What is the role of systemic therapy in lung/visceral metastases?	a	In high-resource settings, we recommend the use of kinase inhibitors or immunotherapy for RR- DTC patients with lung and/or other visceral metastases not otherwise amenable to local therapies.	High	Strong

Palliative care

	Question		Recommendation	Certainty of evidence	Strength of recommendation
		b	In low-resource settings, we can consider the use of cytotoxic chemotherapy in RR-DTC patients with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease when kinase inhibitors or immunotherapy are not available.	Low	Strong
6.4.2	What is the role of systemic therapy in brain metastases?	a	In high-resource settings, we may consider the use of kinase inhibitors or immunotherapy for brain metastases in RR-DTC patients not otherwise amenable to local therapies.	Low	Strong
		b	In low-resource settings, we do not recommend the use cytotoxic chemotherapy for brain metastases.	Low	Strong
6.4.3	What is the role of systemic therapy in bone metastases?	a	In high-resource settings, we recommend the use of denosumab in RR-DTC patients with diffuse and/or symptomatic bone metastases, either alone or concomitantly with other therapies.	Moderate	Strong
		b	In low-resource settings, we recommend the use of bisphosphonates in RR-DTC patients with diffuse and/or symptomatic bone metastases, either alone or concomitantly with other therapies**.**	Moderate	Strong
6.5	What is the role of systemic therapy in the palliative setting in ATC?		We recommend chemotherapy, targeted therapy or immunotherapy used alone or sequentially, when clinically appropriate.	Moderate	Strong
6.6	How should pain be managed among patients with thyroid cancer	a	We recommend the use of the WHO 3-Step Ladder Approach to pain management across stages of thyroid cancer.	Moderate	Strong

Palliative care

Question		Recommendation	Certainty of evidence	Strength of recommendation
	b	We recommend a non-opioid analgesic combined with adjuvant drugs for thyroid cancer patients with mild cancer-related pain.	Moderate	Strong
	c	For patients with moderate to severe pain, we recommend a trial of a strong opioid.	Moderate	Moderate
	d	For cancer-related pain that is non-responsive to conventional analgesic drugs, we recommend a multimodal approach to include any of the following pain management strategies: interventional pain procedures such as epidural plexus block, rehabilitation and complementary/ integrative therapies.	Moderate	Strong
	e	We recommend pain management using alternative routes when the conventional routes (oral and intravenous) are not tolerated or possible. These include subcutaneous administration, transdermal opioid delivery system, morphine elixir by gastrostomy or jejunostomy tube, or sublingual route (when indicated).	Low	Strong
	f	We recommend the use of non-pharmacologic modalities such as (but not limited to) cognitive behavioral therapy, support groups, and acupuncture as part of the holistic approach to a patient with cancer-related pain**.**	Low	Strong

CHAPTER 1. INTRODUCTION

Background

Republic Act 11215 or the National Integrated Cancer Control Act (NICCA) was signed into law on February 2019, and it introduced positive reforms in cancer management in the country. This law seeks to "prevent cancer, improve cancer survivorship and make cancer care and treatment equitable and available to all Filipinos,"[1] and is implemented through the National Integrated Cancer Control Program (NICCP). The NICCP serves as the framework for all government cancer-related activities, while the National Integrated Cancer Control Council functions as the policy-making, planning, and coordinating body on cancer control. Among the many roles of the Council is the development, update, and promotion of evidence-based treatment standards and guidelines for cancer of all ages and stages.

Thyroid cancer is considered the most common endocrine cancer in the Philippines.[2] Recent data show that thyroid cancer is the 9th most common cancer in the world for both sexes, with an incidence of 586,202 cases in 2020 alone.[3] In the Philippines, thyroid cancer is the 7th most common cancer with a 5-year prevalence of 19,260 cases, and it ranks 21st in terms of mortality as of 2020.[4] Thyroid cancer affects more women of reproductive age than other population groups. There are several local and international guidelines available; however, the recommendations stated in these guidelines may not be applicable in the local setting due to cost or availability.

Considering the burden of thyroid cancer in the Philippines, the Department of Health (DOH) called for the development of a national guideline on thyroid cancer that could address the needs of patients afflicted with this malignancy and aid the physician in his/her clinical decision-making for these patients. Dr. Jose R. Reyes Memorial Medical Center (JRRMMC), under the leadership of Medical Center Chief II, Dr. Emmanuel F. Montaña, Jr., embarked on the development of the clinical practice guideline (CPG) following the DOH-PHIC Manual for Clinical Practice Guideline Development (see Appendix 1).[5]

This guideline, if approved by the National Guideline Clearinghouse (NGC), may be used to help align the implementation of NICCA with the Universal Health Coverage law. The guideline could also be used as basis for benefit packages offered by the Philippine Health Insurance Corporation, which will include primary care screening, detection, diagnosis, treatment assistance, supportive care, survivorship follow-up care, rehabilitation, and palliative care for all types and stages of cancer across all age groups.

Objectives and scope

This CPG aims to present recommendations on the screening, diagnosis, surgical management, postoperative management, surveillance, and palliative care of adult patients (18 years old and above) with clinical manifestations suspicious for or already diagnosed with well-differentiated thyroid cancer (WDTC) (both papillary and follicular). It

also presents recommendations on the postoperative management and palliative care of thyroid cancers with pathologic findings of poor differentiation or anaplasia (ATC).

The recommendations contained herein are intended to aid in the decision-making of the following stakeholders: general practitioners, internists, endocrinologists, surgeons, nuclear medicine specialists, radiation oncologists, medical oncologists, radiologists, pain medicine and palliative care specialists, family physicians, and pathologists; patients; hospital administrators; policy makers; and other stakeholders including PHIC.

The evidence used in developing this CPG were based on existing local and international CPGs from 2012 to the present. Recent evidence that came out during the drafting of the guideline were also included.

CHAPTER 2. GUIDELINE DEVELOPMENT METHODS

Guideline preparation

A steering committee (SC) was formed, composed of specialists from JRRMMC and from various medical societies who are involved in the management of thyroid cancer such as the Philippine College of Surgeons, Philippine Society of General Surgeons, Philippine Society of Otolaryngology-Head and Neck Surgery, Philippine Academy for Head and Neck Surgery, Inc., Philippine Society of Endocrinology Diabetes and Metabolism, Philippine Thyroid Association, Philippine Society of Nuclear Medicine, and Philippine Radiation Oncology Society (see Chapter 7). The SC was responsible for determining the scope and the target users of the CPG, developing clinical questions, deciding on the process of CPG development to be pursued, and drafting the recommendation statements. These were done in coordination with the lead CPG developer.

The consensus panel (CP) consisted of representatives from different specialties involved in the management of thyroid cancer; a representative from DOH to provide the public health point of view; and a lay person and a thyroid cancer survivor to provide a patient's perspective (see Chapter 7). These professionals came from different parts of the Philippines, in a variety of practice settings. The panel reviewed the evidence summaries and voted on recommendations during the *en banc* sessions. Members of the CP were recommended by their respective organizations based on their expertise, training, and experience in the management of thyroid cancer.

The technical working group (TWG) was composed of physicians from different specialties of medicine involved in the management of thyroid cancer (see Chapter 7). These professionals have varied backgrounds (including government, private and academic institutions) and practice in different parts of the Philippines (including the National Capital Region, Northern Luzon, Central Luzon, Southern Luzon, Bicol, and Visayas). Members of the TWG were recommended by their respective organizations based on their expertise, training and experience in the preparation of CPGs. They were responsible for reviewing existing CPGs and drafting recommendations based on the gathered evidence.

Professor Leonila F. Dans, a clinical epidemiologist from the Department of Clinical Epidemiology of the University of the Philippines Manila, was invited to an orientation workshop to discuss the ADAPTE process of CPG development as part of the preparation for evidence synthesis.

Declaration and management of conflicts of interest

All individuals involved in the development of the CPG were required to disclose potential conflicts of interest that have existed in the past 12 months (Appendix 2). None of the members of the TWG nor the CP have primary conflicts of interest. Those with secondary

conflicts of interest (i.e., authorship in reviews and sponsorships from pharmaceutical companies) declared their conflict of interest during the CP meetings.

Evidence synthesis

The TWG agreed that the CPG would cover aspects of management of the more frequently encountered WDTC (papillary, follicular and mixed papillary-follicular) from screening to diagnosis and preoperative evaluation, surgical management, postoperative management, surveillance, and pain and palliative management. Clinical questions on the postoperative management and palliative management for ATC were also included to consider clinical situations wherein, after surgical management for what was diagnosed as WDTC, the histopathology would turn out to be poorly differentiated thyroid cancer or ATC. With these considerations in mind, the TWG formulated the clinical questions that were used to guide the literature search (Table 1). Relevant questions or issues were likewise listed under each subcategory.

Table 1. General guide questions in PICO format

Category	Question(s)
Screening	Among individuals at risk for thyroid cancer, which screening tools (physical exam and/or ultrasound) are accurate in detecting cancer?
Diagnosis and preoperative evaluation	Among individuals with thyroid nodules suspected to be cancer, which diagnostic tests are accurate? Among patients diagnosed with well-differentiated thyroid cancer, what preoperative diagnostic tests are necessary?
Surgical management	Among patients diagnosed to have well-differentiated thyroid cancer, which surgical procedure is appropriate?
Postoperative management and follow-up	Among patients who underwent thyroidectomy for well-differentiated thyroid cancer, is radioactive iodine ablation effective? Among patients with well-differentiated thyroid cancer who underwent thyroidectomy and radioactive iodine ablation, how should follow-up be done to improve outcomes? Among patients with well-differentiated thyroid cancer who underwent thyroidectomy and/or radioactive iodine ablation, is systemic therapy necessary? Among patients with well-differentiated thyroid cancer who underwent thyroidectomy and/or radioactive iodine ablation, is radiation therapy necessary?
Surveillance	Among patients with well-differentiated thyroid cancer who underwent thyroid surgery with or without radioactive iodine ablation therapy, how should their response to therapy be assessed and classified? Among patients with well-differentiated thyroid cancer who underwent thyroid surgery with or without radioactive iodine ablation therapy, what biochemical tests and imaging studies are necessary during follow-up?
Palliative care	Among patients with recurrent, advanced, and/or radioactive iodine-refractory thyroid cancer, can systemic therapy improve survival and quality of life? Among patients with recurrent, advanced, and/or radioactive iodine-refractory thyroid cancer, can radiation therapy improve survival and quality of life? Among patients with recurrent, advanced, and/or radioactive iodine-refractory thyroid cancer, which pain and palliative care management regimen can improve quality of life?

Search and retrieval of guidelines

At least three members of the TWG performed a systematic search for existing thyroid cancer CPGs in MEDLINE, Google Scholar, and HERDIN Plus. These guidelines were initially assessed using the criteria in Table 2.

Table 2. Inclusion and exclusion criteria for selecting a thyroid cancer clinical practice guideline

Inclusion criteria	Exclusion criteria
• About adults with WDTC and ATC[a] • Published in text or online • Written in English or with English translations • Published in the last 10 years (2012 onwards)[b] • Must include a report on systematic literature searches and explicit links between individual recommendations and their supporting evidence	• Older versions of the guideline • Guidelines about medullary thyroid cancer • Guidelines involving pediatric patients • Guidelines involving pregnant patients

[a] Only recommendations for postoperative management and palliative care were considered for anaplastic thyroid cancer
[b] If the guideline had an update, the update was retrieved and reviewed

A total of 424 articles were retrieved from the three databases, and the search terms used for each database were summarized in Table 3. Two hundred and thirty articles were retrieved from MEDLINE; of these 230 articles, 20 remained after reviewing their titles and abstracts. Only eight articles remained after review of the full-text documents. For Google Scholar, one hundred and ninety articles were retrieved. Thirty-one of these remained after reviewing their titles and abstracts, and seven articles remained after reviewing the full-text documents. Lastly, only four articles were retrieved from HERDIN Plus. Two articles remained after review of title and abstracts, and of their corresponding full-text versions. Search results were eventually merged to eliminate duplicate publications. Subsequently, only nine guidelines were left.

Table 3. Keywords used to retrieve guidelines from MEDLINE, Google Scholar, and HERDIN Plus

Database	Keywords
MEDLINE	“thyroid carcinoma”, “thyroid neoplasm”, “thyroid malignancy”, “thyroid tumor”, “thyroid nodule”, “thyroid neoplasm”, “practice guidelines”
Google Scholar	“thyroid cancer”, “thyroid neoplasm”, “thyroid mass”, “thyroid nodule”, “practice guidelines”
HERDIN Plus	“thyroid cancer”, “guidelines”

Assessment of guidelines using the AGREE-II tool for critical appraisal

The Appraisal of Guidelines Research & Evaluation-II (AGREE-II) instrument provided a framework for assessing the quality of CPGs. The checklist consisted of 23 items that were used to assess the methods used for developing the guideline and the quality of the reporting. Each guideline was assessed by at least two members of the technical review committee (a subgroup of the TWG). After evaluation of each item in the tool, an overall

assessment was made. Based on the final AGREE assessment and as agreed upon by the appraisers, the final list of guidelines are as follows (Box 1). The level of evidence was classified using the GRADE system (Table 4).

Box 1. List of clinical practice guidelines assessed using the AGREE-II tool

- 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer
- African Head and Neck Society clinical practice guidelines for thyroid nodules and cancer in developing countries and limited resource settings
- American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules – 2016 update
- Screening for thyroid cancer us preventive services task force recommendation statement
- The American Association of Endocrine Surgeons guidelines for the definitive surgical management of thyroid disease in adults
- The revised clinical practice guidelines on the management of thyroid tumors by the Japan Associations of Endocrine Surgeons: Core questions and recommendations for treatments of thyroid cancer
- Thyroid cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up
- University of the Philippines – Philippine General Hospital revised clinical practice guidelines for the management of well-differentiated thyroid carcinoma of follicular cell origin
- Update on certain aspects of the evidence-based clinical practice guidelines on thyroid nodules (focused on the diagnosis and management of well-differentiated thyroid cancer)

Table 4. Quality of evidence across outcomes

Quality	Definition	Implications
High	The group is very confident that the true effect lies close to that of the estimate of the effect	Further research is very unlikely to change confidence in the estimate of effect
Moderate	The group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect	Further research is very likely to have an important impact on confidence in the estimate of effect and is unlikely to change the estimate
Very low	The group has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	Any estimate of effect is very uncertain

Adapted from DOH-PHIC[5] (modified from GRADE)

Formulation of recommendation statements

The SC and the TWG drafted recommendations answering the clinical questions based on the evidence collected from the CPGs. When no evidence was found to answer a clinical question, a consensus statement was prepared. Local publications were used as evidence even though they were not obtained through the initial literature searches.

Consensus panel meeting process

The evidence base and the draft recommendations were sent to the CP members a week prior the *en banc* meetings.

CP meetings were held virtually and were conducted in four sessions (August 28, September 18, September 20, and September 27, 2021). The manner of conducting the *en banc* meeting, voting process, and consensus development process were first discussed and agreed upon. Recommendation statements were presented and panelists were given the opportunity to voice their opinions or concerns about the recommendation. Panelists then voted on the recommendations, and consensus was reached when there was 75% agreement from the CP for both the direction and strength of the recommendations (Box 2). Voting was repeated for a maximum of three times until consensus was reached.

Box 2. Basis for strength of recommendations

Vote >75 of Consensus panel	Strong recommendation
Vote >50 but <75	Moderate recommendation
Vote < 50	Weak recommendation

To facilitate the review of recommendations and voting in the succeeding CP meetings, the draft of recommendations was sent to the CP members through a Google form where they could comment and vote on the recommendations. The Delphi method was employed, and voting was repeated until consensus was reached.

External review process

The guideline underwent a series of external reviews by the NGC and later on, by its quality review panel. An initial appraisal was performed by the CPG subunit of the Disease Prevention and Control Bureau – Evidence Generation and Management Division based on the AGREE-II instrument. The recommendations of the guideline may be publicly disseminated to target users upon passing this initial review. The guideline would be considered as a DOH-endorsed national practice guideline on thyroid cancer if it achieves a minimum rating of 75% for all domains in the AGREE-II from the formal appraisal of the quality review panel.

The manuscript was also sent to a panel of external reviewers who were not part of the TWG or the CP. The panel included content and methods experts representing both specialty and non-specialty organizations involved in thyroid cancer management. Experts coming from different areas and types of practice were selected in order to obtain feedback on the applicability and feasibility of the recommendations in different areas in the country and in different healthcare settings.

The overall evaluation by the external reviews showed that the guideline was considered to be of high quality and that it was also recommended for use. See Chapter 7 for the composition of the external review panel, and Appendix 3 for a summary of the assessments.

CHAPTER 3. EVIDENCE AND FINAL RECOMMENDATIONS

Screening

1.1 Among asymptomatic apparently healthy adults, should screening for thyroid cancer be done?

We do not recommend screening asymptomatic apparently healthy adults for thyroid cancer.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

For screening to be effective, there should be a substantial proportion of undiagnosed disease in the target population, which may not be assured if the prevalence of disease is low. This may be the case for the Philippines where only 3.9% of non-pregnant and non-lactating Filipino adults aged 20 years and older had nodular goiter, based on a national survey conducted in 2008.[6] The evidence assessed showed that the prevalence of thyroid cancer was low relative to the prevalence of cancers of other sites.[7]

According to recent guidelines on thyroid cancer by the United States Preventive Services Task Force (USPSTF), there was insufficient evidence to estimate the accuracy of neck palpation or ultrasound (US) as screening tests for thyroid cancer in asymptomatic persons.[7]

Direct evidence was also lacking to determine if there were significant benefits in screening asymptomatic individuals. Aside from low prevalence, other evidence on the small benefit of screening showed that outcomes were similar between patients treated for the disease and patients with common tumor types who were only monitored. Data from observational studies also showed a lack of difference in trends of deaths due to thyroid cancer after a population-based screening program was introduced.

There was also inadequate direct evidence to determine if there were significant harms associated with screening asymptomatic individuals. Overall harm was judged to be moderate, due to findings of serious adverse events related to treatment of thyroid cancer, as well as the likelihood of overdiagnosis and overtreatment, which could result from screening.[7] Given these considerations, the USPSTF was moderately certain that the harms of screening for thyroid cancer in asymptomatic individuals outweighed the potential benefits.

1.2 Who should be screened for thyroid cancer?

We recommend screening for thyroid cancer in individuals at high risk, defined as having any one of the following:

- a history of significant exposure to ionizing radiation to the head and neck area, especially in childhood;
- inherited genetic syndromes associated with thyroid cancer (e.g., familial adenomatous polyposis); or
- one or more first-degree relatives with a history of thyroid cancer.

Strength of recommendation: Strong

Certainty of evidence: Moderate

Although the USPSTF recommended against screening in the general asymptomatic adult population, the recommendation does not apply to those at high risk for thyroid cancer.[7] These individuals include those with (a) a history of radiation exposure to the head and neck as a child, (b) exposure to radioactive fallout, (c) family history of thyroid cancer in a first-degree relative, and (d) certain genetic conditions, such as familial adenomatous polyposis, which are highly associated with papillary thyroid cancer (PTC).[7]

1.3 Among individuals at high risk, how should screening for thyroid cancer be done?

a We recommend systematic neck palpation and neck US in individuals at high risk to screen for thyroid cancer.

Strength of recommendation: Strong

Certainty of evidence: Low

b In low-resource settings, we recommend systematic neck palpation at each outpatient visit to screen for thyroid cancer.

Strength of recommendation: Strong

Certainty of evidence: Moderate

Neck palpation and US could be used as screening tools for thyroid cancer. While neck US has a high degree of accuracy in detecting thyroid nodules (sensitivity 95–100%, specificity 95–100%),[8] current evidence does not support the implementation of an US-based screening program in high-risk populations.

The overall prevalence of thyroid cancer and the aggressiveness of differentiated thyroid cancer (DTC) are low, meaning that only a small proportion of patients will present at

advanced stages. Furthermore, the true benefits of early detection have not been demonstrated. US screening was only found to be associated with increased detection of one tumor histology, based on the 2010 Korea Community Health Survey.[9] This method could also detect a large number of benign nodules, which could lead to a substantial number of unnecessary fine-needle aspirations (FNAB) and surgeries with associated risks and harms.[8] Although not found to be associated with mortality,[9] such screening would result in harms that outweighed any potential benefits.

Neck palpation (sensitivity 17–43%, specificity 96–100%) might represent a balanced compromise between potentially overly sensitive neck US and no screening at all, despite poor diagnostic performance.[8]

Diagnosis

2.1 What are the clinical data which support an impression of thyroid malignancy?

a Clinical features suggestive of increased risk for thyroid malignancy include:
- Age <14 years old or >70 years old
- Male sex
- Family history of thyroid cancer
- Previous head or neck irradiation
- Rapid neck mass growth
- Recent onset hoarseness, dysphagia or dyspnea

Strength of recommendation:	Certainty of evidence:
Strong	Low to Moderate

b Physical examination findings suggestive of higher risk for thyroid malignancy include:
- Firm or hard thyroid nodule consistency
- Fixed nodule
- Cervical adenopathy

Strength of recommendation:	Certainty of evidence:
Strong	Low to Moderate

The American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi (AACE/ACE/AME) 2016, the American Association of Endocrine Surgeons (AAES), the American Thyroid Association (ATA) 2015, and the African Head and Neck Society (AfHNS) 2020 guidelines listed clinical features suggestive of higher risk for thyroid malignancy.[10–13]

Malignancy rate is higher among younger patients compared to adult patients.[14] In contrast, the risk of thyroid cancer is slightly higher in older persons and in males.[15,16] In a meta-analysis of 41 studies,[17] clinical features found to be significantly associated with thyroid cancer were male sex (OR 1.22; 95% CI 1.01–1.47), family history of thyroid cancer (for nodule size ≥4 cm: OR 1.63; 95% CI 1.04–2.55; for a single nodule: OR 1.43 95% CI 1.09–1.88), and prior head or neck irradiation (OR 1.29; 95% CI 1.02–1.64). This meta-analysis did not show any statistically significant difference in the rate of malignancy for those aged less than 18 years (OR 1.33; 95% CI 0.70–2.50), and those aged older than 65 years (OR 1.15; 95% CI 0.70–1.89).

Progressive nodule growth (during weeks or months) may suggest malignancy. The sudden appearance of a lump in the thyroid region associated with pain is commonly due to hemorrhage in a cystic nodule. However, in patients with progressive and painful enlargement of a thyroid nodule, ATC, rare forms of chronic thyroiditis (e.g., Riedel disease), and primary lymphoma of the thyroid should be considered.[18,19]

In a retrospective review among adult patients who underwent thyroid surgery at a tertiary center in the Philippines, male sex (OR 2.4), a rapidly enlarging thyroid nodule (OR 2.6), the presence of a hard (OR 103.7), firm (OR 12.8) or fixed nodule (OR 5.0), and the presence of cervical lymphadenopathies (OR 4.4) were found to increase the likelihood of thyroid malignancy.[20]

2.2 Among patients suspected to have malignant thyroid nodules, what are the essential diagnostic and preoperative work-up that should be requested?

a We recommend serum TSH ± T4 (free or total) measurement in the initial evaluation of patients suspected to have malignant thyroid nodules.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate to High

b If the serum TSH is subnormal, we recommend a radionuclide thyroid scan to determine whether the nodule is hyperfunctioning or not.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

c We recommend a diagnostic neck US for all patients with thyroid nodule.

Strength of recommendation:	Certainty of evidence:
Strong	High

d We recommend that US evaluation of the neck must include assessment of the status of the cervical lymph nodes whenever a thyroid nodule is detected.

Strength of recommendation:	Certainty of evidence:
Strong	High

Serum thyroid-stimulating hormone (TSH) should be obtained upon discovery of a thyroid nodule greater than 1 cm in diameter. For subnormal serum TSH, a radionuclide thyroid scan should be obtained to determine whether the nodule is hyperfunctioning (“hot,’’ i.e.,

tracer uptake is greater than the surrounding normal thyroid), isofunctioning (‘‘warm,’’ i.e., tracer uptake is equal to the surrounding thyroid), or nonfunctioning (‘‘cold,’’ i.e., has uptake less than the surrounding thyroid tissue).[18] The prevalence of malignancy is low in hyperfunctioning nodules; hence, if a hyperfunctioning nodule is found, no cytologic evaluation is necessary unless suspicious clinical findings are present.[18,21–24] A warm nodule has the same risk of malignancy as cold nodules; therefore, both cold and warm nodules necessitate FNAB.[25]

Multinodular goiters may harbor both hyperfunctioning and nonfunctioning (potentially malignant) lesions.[25] Nodules appearing in patients with Graves' disease or Hashimoto thyroiditis should be managed similar to nodules in any other patient.[26]

Thyroid sonography with assessment of the cervical lymph nodes in all patients having clinically suspected or known thyroid nodule was strongly recommended by ATA 2015, the AACE/ACE/AME 2016, the Korean Thyroid Association (KTA) 2016 and the AAES 2020 based on high quality evidence.[10–12,27] The assessment of thyroid nodule(s) and cervical lymph nodes using neck US can inform risk stratification and in deciding whether FNAB is indicated.

A thyroid nodule should be assessed in terms of its size, location, presence of suspicious features, and presence of lymph node spread in the central and lateral compartments of the neck. Sonographic features highly suspicious for thyroid cancer have been shown in many studies to include microcalcifications, hypoechogenicity, irregular margins, and a taller-than-wide shape measured on transverse view.[28–37] Although there are available scoring systems for thyroid nodules such as the TIRADS scoring system, clinicians are not yet familiar with these and it does not always capture the degree of the thyroid problem. The radiologist in the CP believed that the description of the nodule and the lymph node sonographic characteristics could be better understood by the clinician (Figure 1).

The central and lateral compartment should be routinely evaluated for the presence of lymph nodes whenever a thyroid nodule is detected. In up to 70% of cases, PTC can metastasize into these areas either at presentation or during surveillance.[38] US features of lymph nodes suspicious for malignant involvement include loss of fatty hilum;[39] microcalcifications; cystic, peripheral vascularity; hyperechogenecity; and round shape.[40] The sensitivity of US in detecting abnormal lymph nodes varies between 25–60% in the central neck and between 70–95% in the lateral neck.[41,42]

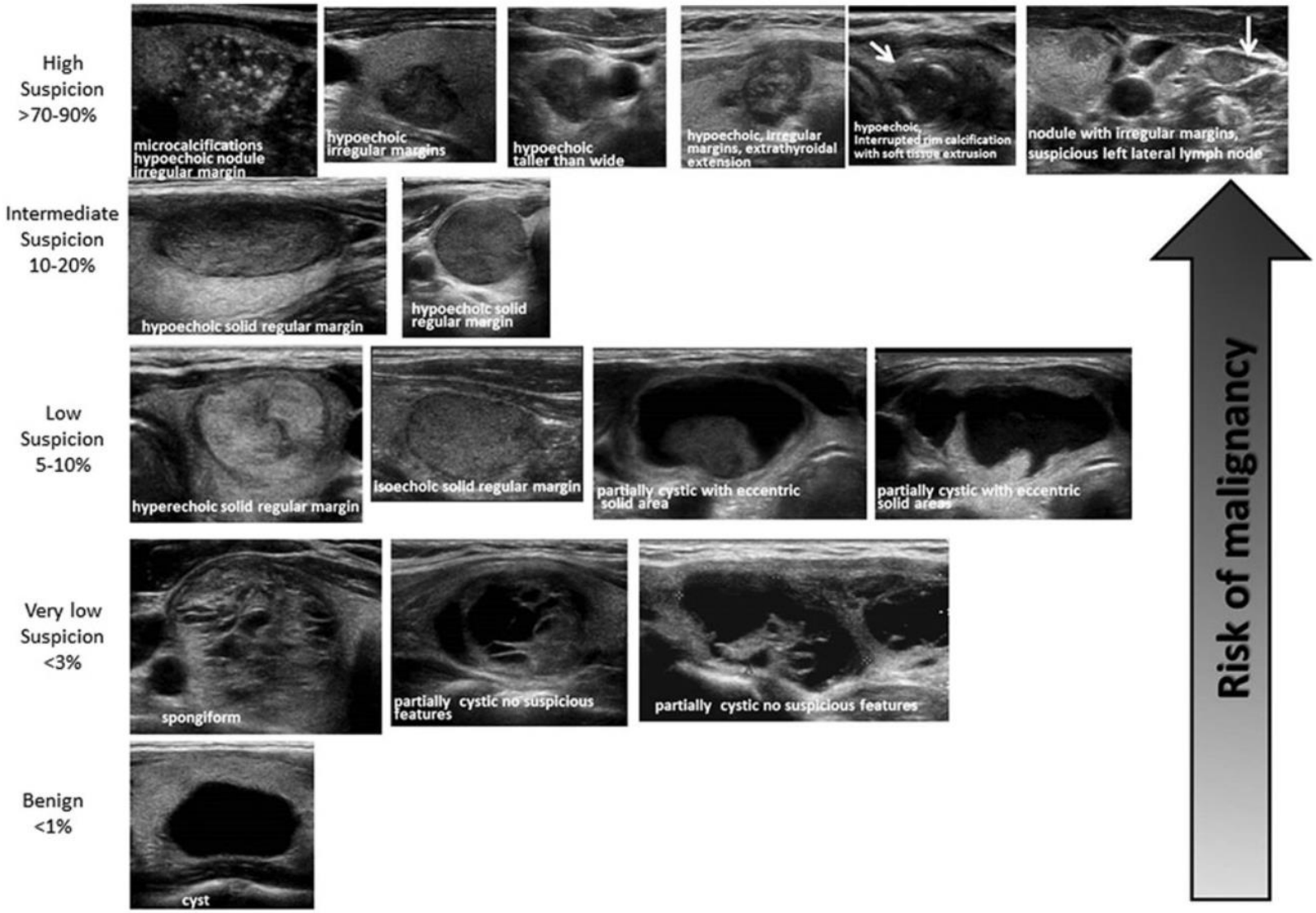

Figure 1. ATA nodule sonographic patterns and risk of malignancy. From Haugen et al[12]

2.3 What are the indications for doing thyroid biopsy?

a We recommend that FNAB should be performed on all nodules suspected of being malignant based on clinical or US findings.

Strength of recommendation:	Certainty of evidence:
Strong	High

b For thyroid glands with multiple nodules, we recommend that each nodule be evaluated separately and the decision to perform a FNAB be individualized.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

c We do not recommend FNB for nodules that are purely cystic or hyperfunctioning on thyroid scintigraphy.

Strength of recommendation:	Certainty of evidence:
Strong	Low

d We recommend FNAB for cervical lymph nodes with suspicious clinical and US findings.

Strength of recommendation:	Certainty of evidence:
Moderate	Moderate

FNAB is the diagnostic procedure of choice in confirming thyroid malignancy due to its accuracy and cost-effectiveness.[11,12,43] Use of FNAB was said to decrease the number of individuals undergoing thyroidectomy. Evidence showed that even with as the rate of FNAB doubled in a 5-year span, the increase in the rate of thyroidectomy was slower.[11] In areas where FNAB could not be adequately performed, clinical and US findings may be used to stratify risk wherein those classified as high-risk were advised to undergo surgery.[13] Results of this evaluation should guide the management for these patients.

Some guidelines provided specific considerations regarding the performance of FNAB based on sonographic patterns, such as US risk stratification and of nodule size.[10,12] These guidelines agree that FNAB should be performed on lesions with high suspicion of malignancy based on US, and for lesions greater than 1 cm (Table 5).

For nodules of low to intermediate risk, the recommendations presented by the AACE/ACE/AME 2016 had strong recommendations with high-quality evidence. The guideline set that FNAB may be performed for nodules of intermediate risk if they are greater than 2 cm, while FNAB could be performed among nodules of low risk if they measured 2 cm.[10] Other qualifiers included increase in size, nodules associated with a risk based on history, and if surgery or minimally invasive ablation theory was

contemplated. While the ATA 2015 recommendations were prescribed as low-quality evidence by their respective authors, the guideline indicated that FNAB may be done among intermediate-risk nodules with a cutoff size of greater than 1 cm, and in low-risk nodules with a cutoff size of 1.5 cm.[12] The ATA 2015 further recommended that FNAB with observation among very low-risk nodules greater than 2 cm was a reasonable option, although their recommendation was weak with moderate-quality evidence.

Table 5. Sonographic patterns, estimated risk of malignancy, and fine-needle aspiration guidance for thyroid nodules[a]

Sonographic pattern	US features	Estimated risk of malignancy, %	FNAB size cutoff (largest dimension)
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule ***with*** one or more of the following features: irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of ETE	>70–90[b]	Recommend FNAB at ≥1 cm
Intermediate suspicion	Hypoechoic solid nodule with smooth margins ***without*** microcalcifications, ETE, or taller than wide shape	10–20	Recommend FNAB at ≥1 cm
Low suspicion	Isoechoic or hypoerechoic solid nodule, or partially cystic nodule with eccentric solid areas, ***without*** microcalcification, irregular margin or ETE, or taller than wide shape	5–10	Recommend FNAB at ≥1.5 cm
Very low suspicion	Spongiform or partially cystic nodules ***without*** any of the sonographic features described in low, intermediate, or high suspicion patterns	<3	Recommend FNAB at ≥2 cm Observation w/o FNA is an option
Benign	Purely cystic nodules (no solid component)	<1	No biopsy[c]

From Haugen et al.[12]
ETE *extrathyroidal extension*
[a] US-guided FNAB is recommended for cervical lymph nodes that are sonographically suspicious for thyroid cancer; [b] The estimate is derived from high volume centers, the overall risk of malignancy may be lower given the interobserver variability in sonography; [c] Aspiration of the cyst may be considered for symptomatic or cosmetic drainage

The ATA 2015 and the AACE/ACE/AME 2016 guidelines recommend applying the same criteria in selecting which nodule to biopsy in multinodular thyroid glands. These were strongly recommended and supported by moderate-quality evidence. Patients presenting with multiple thyroid nodules should be evaluated in the same manner as those presenting with a single nodule.[10,12] Evaluation of each nodule should be made independent of the others, and the recommendation on whether to biopsy or not should be based on the clinical and US findings of each particular nodule. The members of the CP emphasized the need to choose the most suspicious nodule for sampling.

The ATA 2015 does not recommend performing a biopsy on a nodule that is purely cystic on US because of the low incidence of malignancy.[12] This was a strong recommendation based on moderate-quality evidence. In the AACE/ACE/AME 2016, they do not

recommend FNAB on hyperfunctioning nodules on thyroid scintigraphy to avoid triggering a thyroid storm.[10] This recommendation was based on moderate-quality of evidence.

The evidence regarding partially cystic nodules that was gathered by the authors of both guidelines were not as robust. Evidence cited by the ATA 2015 mainly came from a study that performed a univariate rather than a multivariate analysis of factors associated with malignancy. They identified certain features that were associated with malignancy such as solid components that were located eccentrically along the cyst wall; having more than 50% solid component; the presence of microcalcifications; irregular margins; and an increase in the vascularity of the solid component.[12] In contrast, the AACE/ACE/AME 2016 recommended biopsy of the solid component of nodules described as complex or partially cystic. If a doppler US is available, they recommend sampling the vascular areas in the solid component.[10] However, this recommendation was supported by low-quality evidence.

The AAES 2020 and the AACE/ACE/AME 2016 recommended performing biopsy on any cervical lymph node with suspicious findings on physical examination and US evaluation.[10,11] Both guidelines had strong recommendations, although the quality of evidence differed. The AAES 2020 used low-quality evidence, while the AACE/ACE/AME 2016 recommendation was based on strong evidence.

The CP had different opinions on the recommendation, with some surgeons indicating that their decision on the management of the cervical lymph nodes would be made on a clinical basis. Questions arose on the utility of performing the procedure, such as if a negative result will prevent neck dissection. Further evaluation, such as the use of a color flow or doppler, has been suggested. The panel agreed that biopsy of suspicious nodes should be performed pre-operatively during the time the primary tumor was sampled.

2.4 When should ultrasound-guided fine-needle aspiration biopsy be done?

We recommend US-guided FNAB in the following:

- Multi nodular goiter
- Complex nodules with more than 25% cystic component
- Posteriorly located nodules
- Nodules >1 cm with indeterminate US findings
- Nodules <1 cm with indeterminate US findings, which increased in size after 6 months
- Subcapsular or paratracheal lesions
- If initial FNAB result is inadequate

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

The ATA 2015, the AAES 2020, and the Philippine College of Surgeons (PCS) 2013 listed down several indications for the use of US-guided FNAB all of which were strongly recommended. Evidence used by the ATA 2015 and AAES 2020 were classified as strong, while the local guideline by the PCS had evidence that was of moderate quality. All guidelines agreed that FNAB yield and adequacy is enhanced by US guidance.[11,12,44] Evidence showed that this strategy makes the procedure safer, more reliable and more accurate.[11] Both the ATA 2015 and AAES 2020 guidelines stated that utilizing this technique lowered the rates of both non-diagnostic and false-negative reports.[11,12] Both guidelines also stated that, for clinically palpable nodules, free hand or US-guided FNAB can be done.

The CP also recommended an additional indication for performing US-guided FNAB, which was that a significant increase in the size of a nodule of 50% or more in a 6-month period should be sampled.

2.5 How should the fine-needle aspiration biopsy/fine-needle aspiration cytology/aspiration biopsy cytology* result be reported?

We recommend reporting of thyroid cytopathology using the TBSRTC for FNAB* cytodiagnosis.

Strength of recommendation:	Certainty of evidence:
Strong	High

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) established a standardized reporting system with a limited number of diagnostic categories for thyroid FNAB specimens (Table 6).[45–47] This system of reporting should be adapted to establish a standardized, category-based reporting system for thyroid FNAB specimens. Using TBSRTC, cytopathologists can communicate their interpretations to the referring physician in terms that are succinct, unambiguous, and clinically useful. As a function of their risk associations, each category is linked to updated, evidence-based clinical management recommendations that should be stated alongside the diagnosis on the report.

The 2017 revision reaffirms that every thyroid FNAB report should begin with one of six diagnostic categories,[46] the names of which remain unchanged since they were first introduced. There is a choice of two different names for some of the categories. A laboratory should choose the one it prefers and use it exclusively for that category. Synonymous terms (e.g., AUS and FLUS) should not be used to denote two distinct interpretations. Each category has an implied cancer risk that ranges from 0–3% for the "benign" category to virtually 100% for the "malignant" category. In the 2017 revision, the malignancy risks were updated based on new data. Recommendation of treatment and options are provided per category.

Table 6. The risk stratification for categories of the Bethesda system for reporting thyroid cytopathology

Diagnostic category	Description	Risk of malignancy (%)
I	Non-diagnostic/unsatisfactory	1–4
II	Benign	0–3
III	Atypia or follicular lesion of undetermined significance (AUS/FLUS)	5–15
IV	Follicular neoplasm or suspicious for follicular neoplasm (FN/SFN)	15–30
V	Suspicious for malignancy	60–75
VI	Malignant	97–99

Adapted from Cibas ES & Ali SZ[46]

2.6 Among patients who underwent fine needle aspiration cytology of a thyroid nodule, when is molecular testing warranted and most helpful in diagnostic and therapeutic applications?

We can consider molecular testing, for indeterminate FNAB diagnosis, in particular, Bethesda Category III and IV to further stratify thyroid lesions into molecular/behavioral subsets of lesions.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

There are many factors that can lead to a diagnosis of an indeterminate thyroid nodule, based on TBSRTC, classified as Bethesda III (AUS/FLUS) or IV (FN/SFN). These factors include the following such as size, nature, and consistency of the thyroid lesion, operator's technique and experience, age of the patient, and anatomic accessibility. Although molecular testing may further stratify the risk of these lesions to aid in clinical decision-making (e.g., close follow-up vs. repeat FNAB vs. surgical lobectomy vs. thyroidectomy), the CP expressed their concern that a fine-needle specimen may not be the ideal one. There is no significant evidence yet on the use of FNAB for molecular testing. Nevertheless, more studies will demonstrate the usefulness of molecular test in indeterminate FNAB.

PTC most commonly contains the following genetic alterations: *RET* (13–43%), *BRAF* mutation (29–69%), *NTRK1* rearrangement (5–13%), *Ras* mutation (0–21%).[48] In follicular thyroid cancer (FTC), the most common genetic alterations found are *Ras* mutation (40–53%) and *PPARG* rearrangement (25–63%).[48] About 25% of cases lack the common driver mutations.[49] Non-invasive FTC with papillary-like nuclear features and invasive encapsulated follicular variant of PTC possess molecular profiles similar to follicular adenomas or carcinomas, such as higher rates of *Ras* than *BRAF* mutations.[50] Conversely, the infiltrative follicular variant of PTC has a molecular profile more similar to that of classic PTC (i.e., higher rates of *BRAF* than *Ras* mutations). The molecular profiles of encapsulated and of infiltrative follicular variant parallel their biological behavior.

Hence, FNAB-indeterminate diagnoses may suggest the need for molecular testing to further prognosticate thyroid lesions into these molecular/behavioral subsets of lesions.

2.7 Among patients suspected to have differentiated thyroid cancer, what are the indications for additional diagnostic imaging?

a We do not recommend the routine use of CT scan, MRI, thyroid scintigraphy and PET/CT.

Strength of recommendation:	Certainty of evidence:
Strong	High

b Use of CT scan and/or MRI with intravenous contrast may be considered in clinically advanced cases like bulky and fixed tumors.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

The AACE/ACE/AME 2016 and ATA 2015 guidelines do not recommend the routine use of contrast-enhanced CT scan and/or MRI for evaluation of all patients suspected with thyroid malignancy. However, the guidelines acknowledge that these imaging tests may be used in more advanced cases to better assess the size of the mass, degree of airway compression, possible substernal extension, presence of nodal involvement, and extent of local or distant metastases after initial physical examination and neck US.[10,12]

According to the AACE/ACE/AME 2016 guideline, thyroid scintigraphy using Tc-99m sodium pertechnetate is indicated if serum TSH is low to exclude hyperfunctioning thyroid nodule(s) and to rule out ectopic thyroid tissue. Thyroid scintigraphy using ^{131}I sodium iodide is useful to evaluate suspected retrosternal goiter. Pre-operative whole-body scintigraphy using ^{131}I sodium iodide is not recommended since the radiotracer will only concentrate in the normal thyroid tissue and preclude visualization of the suspected malignant mass and the possible sites of local or distant metastasis.[10]

Based on the ATA 2015 guidelines, PET/CT using FDG is not recommended as the initial diagnostic imaging for patients with thyroid nodule or mass. For those patients with incidental findings of FDG-avid or hypermetabolic foci in the thyroid gland, sonographic correlation is recommended to assess the need for FNAB.[12]

2.8 Among patients suspected to have thyroid cancer, what are the indications for evaluating vocal cord function preoperatively?

We recommend visualization of vocal folds for the following patients with:

- Notable voice changes based on physical examination;
- Pre-existing laryngeal disorder;
- Prior neck, mediastinal, cardiac or upper thoracic surgery;
- Known thyroid cancer with extrathyroidal extension;
- Large substernal goiter;
- Extensive central nodal metastasis; and/or
- History of long-standing hoarseness which resolves spontaneously.

Strength of recommendation:	Certainty of evidence:
Strong	Low to Moderate

AAES 2020 and the ATA 2015 enumerated indications for evaluating vocal fold function preoperatively with low to moderate qualities of evidences.[11,12]

According to the AAES 2020, visualization of the vocal folds before thyroidectomy is recommended for patients who were determined to be at risk: those with notable voice changes; with known vocal fold dysfunction; with prior neck, mediastinal, cardiac or upper thoracic surgery; with apparent invasive malignancy; with large substernal goiter; or with extensive lymph node metastasis. Opinions of medical societies differed in terms of the frequency of this procedure as some proposed that this be routinely done while others recommended for this to be performed selectively.[11]

Vocal cord paresis or paralysis at preoperative laryngoscopy has incidence rates that could range from 0–3.5% among patients where thyroid disease is benign, and could reach up to 8% for patients with more advanced cancer.[12] Vocal cord paralysis on preoperative examination is strongly suggestive of local metastasis. Extrathyroidal extension could be found in about 10–15% of thyroid cancers, with the following structures being most commonly involved: strap muscle (53%), the RLN (47%), trachea (30%), esophagus (21%), and larynx (12%).

According to the ATA 2015, a patient with a normal voice should still be examined if they fit the following criteria: having a past thyroid or parathyroid surgery, carotid endartectomy, cervical esophagectomy, an anterior approach to the cervical spine, or other procedures that put the RLN or the vagus nerve at risk, or a history of external beam radiation (EBRT) to the neck. Factors such as variation in paralytic cord position, degree of partial nerve function, and contralateral cord function/compensation could mean that symptoms may be absent in those with poor vocal cord function. Among asymptomatic patients, evidence

showed that vocal cord paralysis could present in up to a third of these patients after surgery.[12] Hence, it may then be necessary to perform other examinations aside from voice assessment to identify these patients.[51]

Anatomic assessment of vocal fold function can be performed in the office by indirect mirror examination, by transcutaneous laryngeal ultrasound (TLUS), or by indirect flexible laryngoscopy and videolaryngostroboscopy.[11] The last method should be performed if the indirect mirror exam and TLUS fail to provide sufficient visualization of the vocal folds.

Treatment

3.1 What is the appropriate operation for patients with proven malignant thyroid nodules (Category V and VI)?

a We recommend total thyroidectomy for all Category V and VI unifocal nodules measuring >1 cm.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

b We recommend total thyroidectomy for Category V and VI nodules with clinical or radiographic evidence of the following regardless of the size:

- bilateral thyroid disease
- extrathyroidal invasion
- lymph node metastases
- distant metastases

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

The basic goals of initial therapy for patients with DTC are the improvement of overall survival and disease-specific survival; risk reduction for persistent/recurrent disease and associated morbidity; and accurate disease staging and risk stratification while minimizing treatment-related morbidity and unnecessary therapy. The specific goals of initial therapy include the following:

a. To remove the primary tumor, disease that has extended beyond the thyroid capsule, and clinically significant lymph node metastases (LNM).
b. To minimize the risk of disease recurrence and metastatic spread. Adequate surgery is the most important treatment variable influencing prognosis.
c. To facilitate postoperative treatment with radioiodine (RAI), where appropriate.
d. To permit accurate staging and risk stratification of the disease.
e. To permit accurate long-term surveillance for disease recurrence.
f. To minimize treatment-related morbidity.

Recommendations in literature state that nodules should be at least 4 cm in size to be considered for total thyroidectomy of Category V and VI nodules.[11–13] However, we consider that Filipinos are at higher risk of aggressive disease and recurrence, needing treatment for DTC that would be equally as aggressive. Local data suggest that a lower cutoff of 2 cm for total thyroidectomy is sufficient.[52] In a local study by Jauculan et al., the recurrence rate among persons with low-risk PTC (n=145) who underwent total/near total thyroidectomy was 35.17%.[53] The significant predictors for recurrence in this study were

found to be a tumor diameter ≥2 cm (OR 9.17; 95% CI 1.62–51.88; *p*=0.012) and a family history of PTC (OR 67.27; 95% CI 2.03–2,228.96; *p*=0.018), while RAI therapy and low initial titers of Tg and TgAb were shown to be significant protective factors against disease recurrence among the low-risk patients.[53]

Leaving more than 1 gram of tissue with the posterior capsule on the uninvolved side is also inappropriate for possible thyroid cancer. Lastly, we also consider that the completeness of surgical resection is a very important determinant of outcome. For a clear definition of thyroid operations, please see the nomenclature of thyroid operations (Table 7).

Table 7. Thyroidectomy nomenclature

Name of procedure	Extent of resection
Lobectomy	One entire thyroid lobe without isthmus
Lobectomy and isthmusectomy	One entire thyroid lobe with isthmus and pyramidal lobe
Isthmusectomy	Isolated isthmus resection
Subtotal thyroidectomy	Preservation of small posterior remnant(s) of the contralateral or bilateral lobe(s) (Rarely recommended today)
Near-total thyroidectomy	Resection of all but a very small posterior remnant, i.e., at the ligament of Berry
Total thyroidectomy	All visible thyroid tissue
Completion thyroidectomy	Reoperative resection of any remaining thyroid tissue

From Patel et al.[11]

3.2 What is the appropriate operation for patients with thyroid nodules cytologically suspicious for follicular neoplasm (Category IV)?

We recommend lobectomy with isthmusectomy as the initial and minimum surgery for solitary Category IV nodules.

Strength of recommendation: Strong

Certainty of evidence: Low to Moderate

According to the Bethesda System, Category IV is an intermediate risk category with an estimated 15–30% risk of malignancy. The primary goal of thyroid surgery for a thyroid nodule that is cytologically indeterminate (i.e., AUS/FLUS or FN/SFN) is to establish a histological diagnosis and definitive removal, while reducing the risks associated with remedial surgery in the previously operated field if the nodule proves to be malignant.[11,12]

The extent of surgery may be modified or converted to total thyroidectomy based on aggressive sonographic characteristics, high clinical risks for malignancies, a nodule size greater than 4 cm, patient preference, and/or molecular testing, if performed.

3.3 What is the appropriate neck dissection for patients diagnosed with thyroid malignancy with gross metastatic nodal disease?

a We recommend therapeutic neck dissection for patients with gross metastatic nodal disease.

Strength of recommendation:	Certainty of evidence:
Strong	High

b We recommend therapeutic central neck dissection (Level VI) if there are lymph node metastases in the central compartment.

Strength of recommendation:	Certainty of evidence:
Strong	High

c We recommend therapeutic central (Level VI) and posterolateral neck dissection (Level II–V) if there are lymph node metastases in the ipsilateral lateral compartment.

Strength of recommendation:	Certainty of evidence:
Strong	High

PTC is known to spread to regional lymph nodes. Although LNM in PTC have been reported in some literature to have no clinically important effect on outcome among low-risk patients, a study of the SEER database found that LNM, age greater older than 45 years, distant metastasis, and large tumor size significantly predicted poor overall survival outcome in a multivariate analysis.[11,12,43,54–56] In a retrospective cohort study among WDTC patients (n=723) at a government-university hospital, LNM at presentation was a strong predictor of recurrence for PTC (OR 4; 95% CI 2.99–5.34; p<0.001).[57]

The role of therapeutic lymph node dissection for treatment of thyroid cancer nodal metastases is well-accepted for the clinically positive or cN1 disease, but the value of routine prophylactic Level VI (central) neck dissection and lateral neck dissection for cN0 disease remains unclear.[11,12,43,54–56] There are limited data to prove that prophylactic dissection of microscopic PTC LNM improves disease-specific outcomes.[12,58]

To have a clear understanding of the different classifications of neck dissection, one must familiarize with the nodal basins and their anatomic boundaries. Table 8 shows the anatomic boundaries of cervical nodal basins and the likelihood of lymph node metastasis.[11] Figure 2 shows the cervical levels and sublevels relevant to neck dissection, and Figure 3 shows the central neck compartment and lymph node basins relevant to central neck dissection

Table 8. Anatomic boundaries of cervical node levels and likelihood of lymph node metastases

Level	Anatomic Boundaries	Likelihood of LNM
I	S: body of the mandible P: stylohyoid muscle A: anterior belly of the contralateral digastric muscle I: hyoid Triangular boundaries comprising anterior bellies of digastric muscles and hyoid separates Ia and Ib	5–9% [na]
II	S: skull base P: posterior SCM A: stylohyoid muscle I: hyoid CN XI separates IIa and IIb IIa nodes lie anterior to IJV	IIa: 53% [47–60%] IIb: 16% [8–27%]
III	S: hyoid P: posterior SCM A: sternohyoid muscle I: horizontal plane defined by the cricoid cartilage	71% [67–74%]
IV	S: inferior border of the cricoid cartilage P: posterior SCM A: sternohyoid muscle I: clavicle	66% [61–71%]
V	S: convergence of SCM and trapezius P: anterior border of trapezius A: posterior SCM I: clavicle Inferior border of cricoid separates Va and Vb	Va: 8% [3–20%] Vb: 22% [8–48%]
VI	S: hyoid superiorly P: deep layer of the cervical fascia A: anterior layer of the cervical fascia I: sternal notch	40–60% [na]
VII	S: sternal notch P: deep layer cervical fascia A: sternum I: innominate on right and equivalent plane on the left	

From Patel et al.[11]
A *anterior*, CN XI *spinal accessory nerve*, I *inferior*, IJV *internal jugular vein*, na *not available*, P *posterior*, S *superior*, SCM *sternocleidomastoid muscle*

Central neck dissection should include the prelaryngeal, pretracheal, and at least one paratracheal lymph node basin. “Berry picking“ or “plucking” (which refers to the removal only of the clinically involved node) is not acceptable and is not synonymous with selective “compartment-oriented” dissection. When doing central neck dissection, one should indicate whether a unilateral or bilateral paratracheal neck dissection was performed. The dissection may be extended to include comprehensive removal of additional nodal basins such as the retropharyngeal, retroesophageal, paralaryngopharyngeal (superior vascular pedicle), and/or the superior mediastinal (inferior to innominate artery). These additional nodal basins that were included should be mentioned in the procedure.

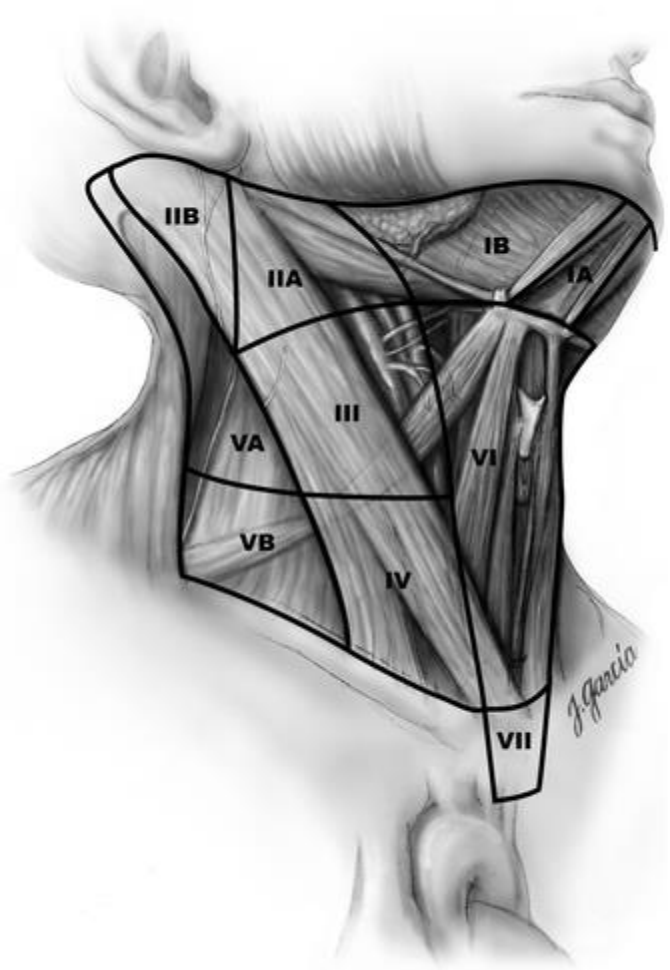

Figure 2. Levels of the neck and sublevels relevant to neck dissection, including upper mediastinum.[59] Reprinted with permission from Mary Ann Liebert, Inc.

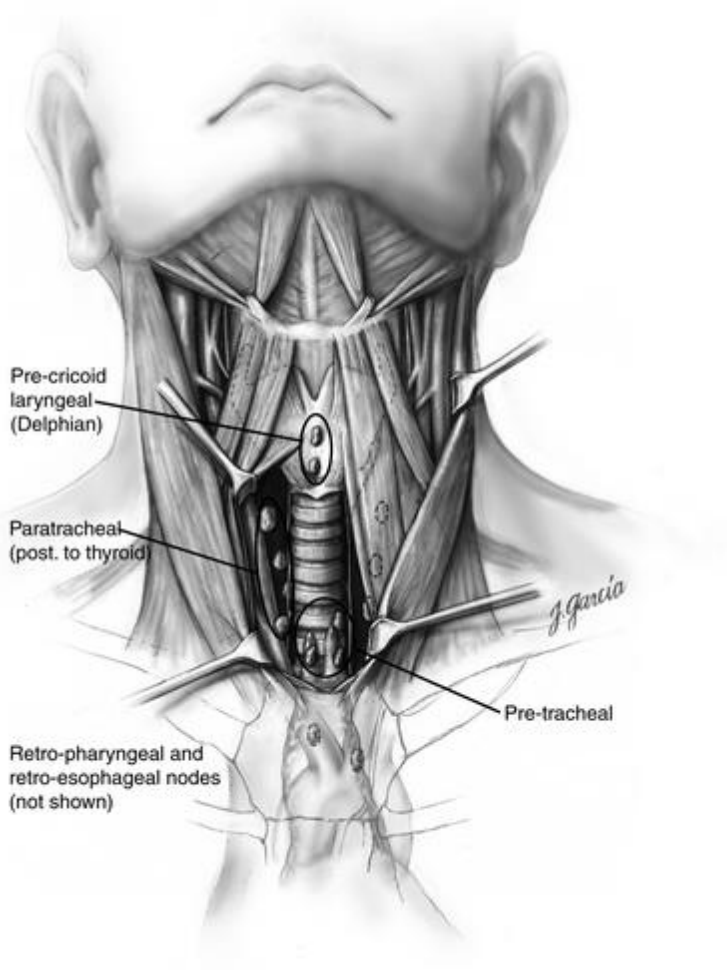

Figure 3. Detailed anterior view of the central neck compartment indicating location of lymph node basins relevant to central neck dissection.[59] Reprinted with permission from Mary Ann Liebert, Inc.

The lateral compartment has five nodal levels: Level I (the submandibular and submental triangles), Level II (the upper), Level III (middle), Level IV (lower jugular), and Level V (posterior triangle). A radical neck dissection involves removal of all lymph nodes from levels I to V, together with resection of the following non-lymphatic structures: the internal jugular vein, the spinal accessory nerve, and the sternocleidomastoid. Radical neck dissection is rarely indicated for thyroid cancer due to the morbidity of the procedure, and infrequent involvement of Level I nodes. A modified radical neck dissection entails removal of Level I–V lymph node groups with preservation of the internal jugular nerve, the spinal accessory nerve, and/or the sternocleidomastoid. A compartment-oriented selective neck dissection involves removal of less than all five lymph node basins with preservation of the internal jugular nerve, spinal accessory nerve, and sternocleidomastoid, and it is the most commonly applied type of therapeutic lymph node resection for thyroid cancer.[60] It should be reported to indicate the laterality and nodal levels removed.

In selective neck dissection for PTC, Levels IIa, III, IV, and Vb are included (Table 8). To avoid injury to the spinal accessory nerve, Level IIb is dissected only if there is radiographic evidence of LNM, or if Level IIa is positive. Level Va is dissected only when there is clinically or radiographically detected LNM. Thyroid cancer LNM in Level I is rare (<10%), and recurrence is also rare (<1%) if not dissected at initial selective neck dissection.[61] Prophylactic lateral node dissection has not been shown to improve PTC survival or recurrence rates; thus, selective neck dissection is typically performed only for clinically evident disease. Clearance of Levels II–V is associated with a lower risk of recurrence. [60]

3.4 What is the role of surgery for patients presenting with distant metastasis of well-differentiated thyroid cancer?

a We recommend total thyroidectomy ± neck dissection for patients with DTC even with distant metastasis.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

b We recommend surgical excision for resectable metastatic disease without adverse functional outcome in selected patients.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

Metastases may be discovered at the time of initial disease staging or may be identified during longitudinal follow-up. If metastases are found following initial therapy, some patients may experience a reduction in tumor burden with additional treatments that may offer a survival or palliative benefit. The preferred hierarchy of treatment for metastatic

disease still starts with surgical excision of locoregional disease in potentially curable patients before other systemic and/or adjuvant treatment modalities.[12] Since most metastatic WDTC are considered as oligometastasis, the purpose of local treatment remains to be curative. Individualized course or decision may be applied based on functional performance status and life expectancy.

3.5 How should we manage perioperative complications after thyroidectomy?

a We recommend at least an overnight observation for patients at high risk for postoperative hematoma, when clinically appropriate.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

b We recommend oral calcium as first-line therapy for postoperative hypocalcemia. If hypocalcemia is persistent or refractory, calcitriol may be added. If hypocalcemia is severe, persistent or refractory, intravenous calcium should be used.

Strength of recommendation:	Certainty of evidence:
Strong	Low

c For patients at high risk for hypocalcemia, determination of ionized calcium or serum calcium and albumin should be requested post-operatively.

Strength of recommendation:	Certainty of evidence:
Strong	Low

d We recommend preoperative assessment and supplementation of calcium and 25 hydroxy vitamin D when appropriate, such as in patients post Roux-en-Y gastric bypass, those with Graves' disease, and other conditions known to be at risk for postoperative hypocalcemia.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

e We recommend formal laryngeal evaluation for patients with dyspnea and/or stridor, aspiration, dysphagia, and hoarseness.

Strength of recommendation:	Certainty of evidence:
Strong	Low

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. Although outpatient thyroid surgery has been proven to

be safe, patients undergoing a total thyroidectomy have a higher complication rate than those who undergo partial thyroid surgery. Complications include hypocalcemia, vocal cord paralysis, and hematoma formation.[12]

Voice assessment should be based on the patient's subjective report and the physician's objective assessment of voice. This assessment can be performed at 2 weeks to 2 months after surgery, except in the presence of absolute functional limitations (e.g., dysphagia, aspiration, dyspnea, etc.). Early detection of vocal cord motion abnormalities after thyroidectomy is important for facilitating prompt intervention (typically through early injection vocal cord medialization), which is associated with better long-term outcome, including a lower rate of formal open thyroplasty repair.[11,12,62–64]

3.6 What is the role of surgery for pregnant patients with thyroid nodules?

We recommend to defer surgery until after delivery for patients with nodules that remain stable clinically and on USG, or if it is diagnosed beyond 24–26 weeks of gestation or the second half of pregnancy.

Strength of recommendation:	Certainty of evidence:
Moderate	Low

It is currently unknown if the likelihood of malignancy is higher for thyroid nodules discovered in pregnant women than in nonpregnant women as current evidence has not explicitly demonstrated this phenomenon.[12] The recommendation by the ATA 2015 on evaluating clinically relevant nodules is the same for pregnant and non-pregnant patients, however a radionuclide scan is contraindicated for the former.[12] In patients found to have DTC via FNAB during pregnancy, there is no significant difference in outcomes if surgery is delayed until after delivery. However, undergoing surgery during pregnancy carries the risk of adverse events and increased cost.

Patients in the early stages of pregnancy who were found to have PTC by cytology should be monitored sonographically. Surgery among these patients is usually delayed to minimize risk from surgery after the second trimester. However, surgical intervention may be necessary for progressively enlarging biopsy-proven Category V and VI nodules and/or biopsy-proven LNM in pregnant patients before 24–26 weeks of gestation, or if there are other risks.[12]

3.7 What is the role of frozen section in the management of thyroid nodules suspicious for malignancy?

Frozen section is not routinely used, but may be considered in the following:

- Confirmation of extrathyroidal extension
- Confirmation of PTC if the diagnosis will alter the extent of the surgical plan
- Confirmation of the nature of equivocal structure (e.g., parathyroid glands, lymph nodes)

Strength of recommendation: Strong

Certainty of evidence: Moderate

Intraoperative evaluation could be performed during a lobectomy to determine whether completion thyroidectomy would be recommended. A frozen section could be used for this purpose and would provide the most utility for a diagnosis of classic PTC, but not for the follicular variant of PTC and in FTC.[11,12] The patient should be informed of the advantages and disadvantages of these procedures (i.e., having a thyroidectomy from the start versus thyroid lobectomy with isthmusectomy that may proceed to thyroidectomy) that must be considered.

3.8 What are the indications for completion thyroidectomy?

We recommend completion thyroidectomy in any of the following:

- Unanticipated malignancy with a tumor diameter >1 cm
- Confirmed contralateral malignancy
- Confirmed nodal metastasis
- Aggressive histologic type

Strength of recommendation: Moderate

Certainty of evidence: Moderate

Completion thyroidectomy in general, should be offered to patients for whom a total thyroidectomy would have been recommended had the diagnosis been available before the initial surgery.[11,12,43,55]

Post-operative management

4.1 What is the role of postoperative staging systems in the management of well-differentiated thyroid cancer?

We recommend the use of the AJCC/UICC staging for all patients with DTC to standardize encoding in the cancer registry and for its utility in predicting disease mortality.

Strength of recommendation: Moderate

Certainty of evidence: Moderate

No staging system has demonstrated significant superiority to the others, but a number of guidelines have recommended the use of the most recent American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) TNM staging system (Table 9).[12,43,52,55] Evidence from multiple studies have shown that the AJCC/UICC system had the highest proportion of variance explained relative to other staging systems, and was consistently able to better predict mortality among various patient cohorts.[12] The system has also been validated in clinical practice through prospective and retrospective studies. However, similar to other staging systems for the prediction of mortality, the AJCC/UICC system was only able to account for a small proportion of eventual deaths due to thyroid cancer.

Table 9. AJCC TNM staging, 8th edition

Stage	T	N	M
	Age <55 years		
I	Any tumor size	Any lymph node status	Absence of distant metastases (M0)
II	Any tumor size	Any lymph node status	Presence of distant metastases (M1)
	Age ≥55 years		
I	Tumor of ≤4 cm limited to the thyroid (T2)	Absence of LNM (Nx/N0)	Absence of distant metastases (M0)
II	Tumor of any size with lymph node metastases (N1) *or* with gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyroidhyoid, omohyoid) with/without LNM (T3b)		Absence of distant metastases (M0)
III	Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve (T4a)	Any lymph node status	Absence of distant metastases (M0)
IVa	Gross extrathyroidal extension invading prevertebral fascia or encasing the carotid artery or mediastinal vessels (T4b)	Any lymph node status	Absence of distant metastases (M0)
IVb	Any tumor size	Any lymph node status	Presence of distant metastases (M1)

From Lamartina et al.[65]

4.2 What is the role of initial risk stratification in the management of well-differentiated thyroid cancer?

We recommend the use of the 2015 ATA risk stratification system for patients with DTC to serve as a guide for further treatment and for surveillance.

Strength of recommendation: Moderate

Certainty of evidence: Moderate

On stratifying risk of recurrent disease, some guidelines recommended the use of the 2015 ATA risk stratification system (Table 10).[12,43] Risk stratification could contribute in decision-making regarding further management, especially in those who were determined to be at high risk.

Table 10. 2015 ATA risk stratification system

ATA low risk	• PTC (with all of the following):
	  ○ No local or distant metastases;
	  ○ All macroscopic tumor has been resected
	  ○ No tumor invasion of loco-regional tissues or structures
	  ○ The tumor does not have aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma)
	  ○ If ^{131}I is given, there are no RAI-avid metastatic foci outside the thyroid bed on the first posttreatment whole-body RAI scan
	  ○ No vascular invasion
	  ○ Clinical N0 or ≤5 pathologic N1 micrometastases (<0.2 cm in largest dimension)
	• Intrathyroidal, encapsulated follicular variant of PTC
	• Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion
	• Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including *BRAF^{V600E}* mutated (if known)

ATA intermediate risk	• Microscopic invasion of tumor into the perithyroidal soft tissues • RAI-avid metastatic foci in the neck on the first posttreatment whole-body RAI scan • Aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) • PTC with vascular invasion • Clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension • Multifocal papillary microcarcinoma with ETE and *BRAF^{V600E}* mutated (if known)
ATA high risk	• Macroscopic invasion of tumor into the perithyroidal soft tissues (gross ETE) • Incomplete tumor resection • Distant metastases • Postoperative serum thyroglobulin suggestive of distant metastases • Pathologic N1 with any metastatic lymph node ≥3 cm in largest dimension • Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion)

From Haugen et al.[12]

Some studies show that recurrence in Filipinos is higher than in other population groups; therefore, it is recommended that a risk stratification system be developed specifically for the Filipino people, especially on the management of patients considered to be of low risk according to the ATA 2015 guidelines. In a Canadian study on thyroid cancer outcomes

among Filipino patients, the odds of recurrence in Filipinos was 6.99 (95% CI 2.31–21.07; p<0.001) times higher compared to non-Filipinos.[66] No local study is available for reference; hence, further observational study is recommended.

4.3 Should postoperative disease status be considered in decision-making for radioiodine therapy for patients with well-differentiated thyroid cancer?

a We recommend that postoperative disease status (i.e., the presence or absence of residual disease) should be considered in deciding whether additional treatment (e.g., RAI, surgery, or other treatment) may be needed.

Strength of recommendation:	Certainty of evidence:
Strong	Low

b Postoperative serum Tg, ideally 3-4 weeks postoperatively, can help in assessing the persistence of disease or thyroid remnant and predicting potential future disease recurrence.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

Postoperative status is considered in determining subsequent management. Status could be evaluated through serum thyroglobulin (Tg), neck US, and RAI scanning.

Determination of serum Tg and anti-thyroglobulin (TgAb) can help in the assessment of persistent disease and the prediction of future disease recurrence. Advice from the ATA 2015 suggests that the measurement of Tg and of TgAb be done in pairs.[12] A retrospective study found that the measurement of Tg is unreliable when TgAb is present as the latter may interfere in the detection of significant residual/recurrent tumors.[67] This should be done 3–4 weeks postoperatively, which is when postoperative Tg is at its lowest for nearly all patients.[12] TgAb should be measured at least once to be used in ascertaining the reliability of the measured serum Tg.[52]

Routine postoperative diagnostic whole-body scan (WBS) with ^{131}I is not recommended as problems with detection sensitivity and post-imaging stunning may arise.[52] However, these may be prevented by the use of low-activity ^{131}I (about 1–3 mCi) or alternative isotopes such as ^{123}I.[12] It is recommended that reporting of outcomes is standardized so future studies on long-term outcomes can be done.

4.4.1 What is the role of radioiodine (including remnant ablation, adjuvant therapy, or therapy for persistent disease) after thyroidectomy in the primary management of well-differentiated thyroid cancer?

a We recommend routine RAI adjuvant therapy after total thyroidectomy for ATA high risk DTC patients.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

b We recommend RAI adjuvant therapy after total thyroidectomy in ATA intermediate-risk level DTC patients.

Strength of recommendation:	Certainty of evidence:
Strong	Low

c We do not recommend routine RAI remnant ablation after thyroidectomy for ATA low-risk DTC patients.

Strength of recommendation:	Certainty of evidence:
Strong	Low

d We do not recommend routine RAI remnant ablation after lobectomy or total thyroidectomy for patients with unifocal papillary microcarcinoma, in the absence of other adverse features.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

e We do not recommend routine RAI remnant ablation after thyroidectomy for patients with multifocal papillary microcarcinoma, in absence of other adverse features.

Strength of recommendation:	Certainty of evidence:
Moderate	Low

Evidence from observational studies show that Filipinos have a higher likelihood of negative outcomes such as disease recurrence and mortality compared with non-Filipinos.[66,68] A local study by Espiritu et al. observed an increasing trend in the incidence of *BRAF* V600E mutation among patients with PTC, which is associated with a more aggressive type of PTC.[69] The local incidence rate of *BRAF* V600E mutation is parallel with other countries such as South Korea, China, Poland, and the United States.

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. Patients without nodal extension, perithyroidal extension, or distant metastasis may be given an ^{131}I activity of 30–100 mCi (or 1,110–3,700 MBq). In patients with nodal metastasis or distant metastasis on their RAI therapy, an activity of 150 mCi (5,550 MBq) will be delivered. An activity of 200 mCi (7,300 MBq) will be used in succeeding RAI ablation (RAIA) among patients with distant metastases, except if diffuse lung metastases are present as the recommended activity would then be 150 mCi (5,550 MBq).[52]

The ATA 2015 recommends temporary high-dose therapy with corticosteroids when metastases are present in order to minimize the risk of acute tumor swelling and compromised function.[12] Evidence has shown that radiotherapy (RT) and chemotherapy could increase the risk for secondary primary malignancy.[70] In a meta-analysis of two multi-centric studies, patients who underwent RAI therapy had a 1.19 times greater risk of developing secondary primary malignancy compared to patients who did not undergo RAI therapy. Thyroid cancer survivors treated with RAI also had a higher risk for leukemia.[71]

4.4.2 How should post-thyroidectomy patients be prepared for radioiodine remnant ablation/treatment or diagnostic scanning?

We recommend that RAI should be given after TSH stimulation, ideally, until serum TSH levels reach at least 30 mIU/ml or alternatively, rhTSH can be given.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

Prior to RAIA, TSH stimulation must be done until serum TSH levels reach a minimum of 30 µIU/ml.[12,43,52] TSH stimulation could be facilitated through prescription of a low iodine diet, withdrawal of levothyroxine (LT4), or through administration of recombinant human TSH (rhTSH). LT4 may be withdrawn for 4–5 weeks, and is recommended especially for patients with distant metastases. rhTSH could be administered as a daily injection of 0.9 mg of rhTSH for two days, immediately followed by RAI on the third day. Additionally, use of rhTSH has shown positive effects short-term effects on quality of life.[72] The consensus panel member suggested a cheaper alternative to rhTSH is T3 (Tertoxine or Cytomel) given 2 weeks before therapy, thus shortening the period of hypothyroidism.

4.4.3 Should a posttherapy scan be performed following remnant ablation or adjuvant therapy?

We recommend that RAI administration must be followed by WBS to stage the disease and document the ^{131}I avidity of any structural lesion.

Strength of recommendation:	Certainty of evidence:
Strong	High

All patients who had RAIA should have a post-therapy WBS with ^{131}I within 3–7 days of RAIA.[52] Routine diagnostic WBS is not required during follow-up among patients with negative stimulated Tg levels, TgAb levels and cervical US.

4.5 Among patients with differentiated thyroid cancer post-surgery, what is the role of thyroid hormone suppression?

a We recommend initial TSH suppression to below 0.1 mU/L for high-risk DTC patients.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

b We suggest initial TSH suppression to 0.1–0.5 mU/L for intermediate-risk DTC patients.

Strength of recommendation:	Certainty of evidence:
Strong	Low

c We suggest that TSH may be maintained at the lower end of the reference range (0.5–2 mU/L) for low-risk DTC patients who have undergone remnant ablation and have undetectable serum thyroglobulin levels while continuing surveillance for recurrence.

Strength of recommendation:	Certainty of evidence:
Strong	Low

d We suggest that TSH may be maintained at or slightly below the lower limit of normal (0.1–0.5 mU/L) for low-risk DTC patients who have undergone remnant ablation and have low-level serum thyroglobulin levels while continuing surveillance for recurrence.

Strength of recommendation: Strong | Certainty of evidence: Low

e We suggest that TSH may be maintained in the mid to lower reference range (0.5–2 mU/L) for low-risk DTC patients who have undergone lobectomy while continuing surveillance for recurrence. Thyroid hormone therapy may not be needed if patients can maintain their serum TSH in this target range.

Strength of recommendation: Moderate | Certainty of evidence: Low

Thyroid hormone suppression therapy (THST) has been used to improve health outcomes in the management of DTC. In a systematic review of 10 observational studies (n=4,174) with follow-up that ranged from 4.5–19.5 years, there was decreased risk of any of the following outcomes for those who received THST: disease progression, recurrence, or death (RR 0.73; 95% CI 0.60–0.88).[73]

The ATA 2015 and the Japan Associations of Endocrine Surgeons (JAES) 2020 both recommend TSH suppression for high-risk patients, with the ATA 2015 recommending that the cutoff for initial TSH suppression be below 0.1 mU/L. Both guidelines also recommended TSH suppression for intermediate-risk patients.[12,55] The ATA 2015 recommended initial TSH suppression to 0.1–0.5 mU/L. Consequently, the JAES 2020 recommended that the TSH suppression therapy indication be determined from the intra-operative and pathological evaluations.

Observational studies provided evidence of improved long-term outcomes from TSH suppression to <0.1 mU/L, such as longer relapse-free survival with consistent TSH suppression (≤0.05 mU/L),[74] and decreased likelihood of disease progression compared to patients with lesser degree of TSH suppression (p=0.03).[75] Overall survival was better in high-risk patients with a mean TSH score of 1.0–1.99 compared to those with higher mean scores (p=0.011).[76] This also extends to NTCTCSG Stage II classification where those with a mean TSH score of 1.0–2.99 had better overall survival compared to patients with a mean TSH score of 3.0–4.0 (p<0.0001). However, TSH suppression at undetectable levels did not provide incremental benefit. Disease-specific survival was also improved in high-risk patients with greater TSH suppression compared to those with lesser TSH suppression (p=0.024). The benefits were not evident in low-risk patients.

The ATA 2015 guideline recommends TSH suppression in low-risk patients, and cut-offs are based on serum Tg levels and the type of surgery done. Similar recommendations are offered to low-risk patients regardless of whether or not they had residual ablation.

Continuous monitoring for recurrence is essential because serum Tg may have increased since the previous measurement. The cut-offs were as follows:

a. 0.5–2.0 mU/L (lower end of the reference range) for patients with undetectable Tg levels regardless of remnant ablation, and for patients who have undergone lobectomy. TSH suppression may not be needed if TSH may be maintained at this range
b. 0.1–0.5 mU/L (slightly below the lower limit of normal) for those with low level serum Tg regardless of remnant ablation

The JAES 2020 did not recommend TSH suppression based on data from a single-center randomized controlled trial involving patients with PTC (n=441). The study found that patients with normal TSH (3.19 ± 1.74 mU/L) and those on LT4 suppression medication to a goal of <0.01 uU/ml (TSH 0.07 ± 0.13 mU/L) had similar 5-year disease-free survival rates (89% vs. 91%, *p*=0.39).[77] Majority of the participants had undergone less than total thyroidectomy and dissection of the central lymph node compartment. The study excluded patients with distant metastasis and those with microcarcinoma defined as ≤1 cm. The study concluded that thyroid-conserving surgery without TSH suppression should be considered for patients with low-risk PTC to avoid potential adverse effects of TSH suppression.

In an observational study among patients with DTC (n=366, median follow up 8.5 years), treatment with near-total thyroidectomy was followed by RAIA with 2,800 MBq ^{131}I.[78] The TSH threshold of 2 mU/L was shown to be the most effective in distinguishing between recurrence-free survival and thyroid carcinoma-related mortality or cancer relapse. The study concluded that in treated low-risk individuals, a low normal range should be targeted, whereas TSH levels should be suppressed in noncured or high-risk patients.

In the analysis of registry (n=4,941, median follow-up up 6 years) of DTC, TSH score 2.0–2.9 (subnormal) was related with lower risk of recurrence and mortality compared to TSH score 3.0–4.0 (normal elevated).[79] At different stages of thyroid cancer, there was an improvement in overall survival (RR stages I-IV: 0.13, 0.09, 0.13, 0.33) and disease-free survival (RR stages I-III: 0.52, 0.40, 0.18).

The known effects of subclinical thyrotoxicosis, a consequence of TSH suppression, could include worsening angina, increased the risk of atrial fibrillation for elderly patients and increased risk of postmenopausal women's osteoporosis.[80] Thus, the ATA 2015 suggested relaxing TSH targets may be considered for those with tachycardia, osteopenia, age older than 60, osteoporosis and atrial fibrillation [12].

There is paucity of data to guide the recommendation of TSH suppression among those who had undergone lobectomy. Studies investigating the extent of surgery comparing lobectomy to total thyroidectomy did not analyze TSH suppression therapy[81,82] or even excluded.[83] In a retrospective study of patients with DTC who underwent lobectomy

(n=466) comparing those with and without TSH suppression (less than 2 mIU/L), no significant difference was noted on disease-free survival regardless of TSH levels (p=0.63).[84]

4.6.1 Among patients with differentiated thyroid cancer post-surgery, is there a role for adjunctive external beam radiation therapy?

a We do not recommend routine adjuvant EBRT to the neck in patients with DTC after initial complete surgical removal of the tumor.

Strength of recommendation:	Certainty of evidence:
Strong	Low

b We suggest that EBRT may however be very selectively considered within the context of a multidisciplinary team for DTC patients with high-risk features such as, but not limited to, the following:

- Surgically unresectable gross residual disease
- Inadequate RAI uptake
- Extranodal extension or involvement of soft tissues
- Tumors threatening vital structures
- Rapid progression
- Locally advanced disease
- Older age with extrathyroidal extension
- Tumors undergoing multiples and frequent serial reoperations for locoregionally recurrent disease

Strength of recommendation:	Certainty of evidence:
Strong	Low

The use of adjuvant EBRT for DTC is controversial with lack of prospective data and conflicting reports on its benefit after surgical resection. Therefore, its routine use is not recommended for patients after complete surgical removal of the tumor. In some guidelines, EBRT was very selectively considered in patients with high-risk features such as, but not limited to:

- surgically unresectable gross residual disease[12,54,55,85]
- inadequate RAI uptake[12,54,85]
- extranodal extension or involvement of soft tissues[12,85]
- tumors threatening vital structures[11,85]
- rapid progression[85]
- locally advanced disease[12,54]
- older patients with extensive extrathyroidal extension[12,54]

- tumors undergoing multiple and frequent serial reoperations for locoregionally recurrent disease[12]

Two guidelines mentioned that EBRT should be considered for patients above age 60 with extensive thyroidal extension.[12,54] However, the American Head and Neck Society (AHNS) Statement recommended the consideration of EBRT only for select high-risk patients older than age 45, partially due to concern for the risks of late toxicities or secondary malignancies in younger age groups.[86] The AHNS 2016 also recommended consideration of EBRT for extracapsular extension in patients with unfavorable histology and RAI-refractory disease.

The decision to apply adjuvant RT to the high-risk cases should be done on an individualized patient basis within the context of a multidisciplinary team, with consideration of all other available treatment modalities compared with the possible benefits and toxicities of EBRT.

4.6.2 Among patients with anaplastic thyroid cancer diagnosed postoperatively, what is the role of external beam radiation therapy?

a We recommend post-operative EBRT with systemic therapy for resectable, non-metastatic, good performance status patients desirous of aggressive treatment.

Strength of recommendation: Strong | Certainty of evidence: Low

b We recommend EBRT with systemic therapy for unresectable, nonmetastatic, good performance status patients desirous of aggressive treatment. Surgery can be reconsidered after neoadjuvant therapy depending on response.

Strength of recommendation: Strong | Certainty of evidence: Low

The ATA 2021 and NCCN guidelines recommend post-operative EBRT with systemic therapy for resectable, non-metastatic, good performance status patients desirous of aggressive treatment.[85,87] EBRT can improve local control and increase short term-survival in IVA/IVB ATC patients who are able to undergo complete (R0) or near-complete (R1) surgical resection followed by radiation therapy. The ATA 2021 in particular recommends that adjuvant radiation therapy should begin no later than 6 weeks after surgery.[87] Even for patients with unresectable or gross residual (R2) regionally confined

disease, radiation therapy and/or systemic therapy has been recommended to increase local control for symptom prevention or palliation (e.g., to prevent asphyxiation). Intensity modulated radiation therapy as an available EBRT technique is recommended by the ATA 2021 in both the post-operative and unresectable settings to decrease the dose to surrounding normal structures and to reduce possible treatment-related toxicity.[87] The decision however to undergo aggressive bi- or tri-modality therapy must be weighed with the patient's goals of care, medical and psychosocial fitness for therapy, availability of social support, and expected impacts on quality of life.

4.7.1 Among patients with differentiated thyroid cancer post-surgery, is there a role for chemotherapy in the adjuvant setting?

We do not recommend the use of chemotherapy in patients with DTC (beyond RAI and/or TSH suppressive therapy) in the adjuvant setting.

Strength of recommendation:	Certainty of evidence:
Strong	Very low

There are no clinical trial data to indicate that any adjuvant therapy beyond RAI and/or TSH suppressive therapy using LT4 provides net benefit to patients with DTC.[12,43,52,85] The prognosis of these patients in complete remission is very good, especially if they are without any indication of active systemic disease. As toxicities, and even the risk of death, from use of kinase inhibitor therapies are appreciable, these risks have strong potential to exceed expected therapeutic benefit in the adjuvant context in most patients with DTC.

4.7.2 Among patients with anaplastic thyroid cancer diagnosed postoperatively, is there a role for chemotherapy in the adjuvant setting?

We recommend the use of cytotoxic chemotherapy with or without RT in patients with ATC when clinically appropriate in the adjuvant setting.

Strength of recommendation:	Certainty of evidence:
Strong	Low

For patients who present with resectable tumors, we suggest complete resection followed by combined chemotherapy and RT.[12,43,85,87] There are very little data about the optimal chemotherapy to be used with RT for ATC. The majority of the data includes either anthracyclines, taxanes, or even the combination of both.

In one study, 37 patients were treated with weekly doxorubicin (10 mg/m^2) with hyperfractionated RT (given 3 days per week) for a median total dose of 5760 cGy. Median survival was 6 months with 28% alive after 1 year. The median locoregional, progression-free survival (PFS) was 10.1 months. Older patients (≥70 years) had worse outcomes than younger patients, with 60% dying in the first 3 months. Another study evaluated a more intensive regimen combining surgery (if possible) with cisplatin (120 mg/m^2) and doxorubicin (60 mg/m^2), both before and after hyperfractionated RT. For 30 patients, median survival was 10 months and 3-year survival was 27%. Although these reports support a possible survival advantage for combined modality therapy combining RT and chemotherapy, selection bias is a major confounding factor in determining the effect of treatment on outcome. Patients who undergo resection followed by adjuvant therapy often have less extensive disease. The optimal timing of the individual components and the selection of chemotherapy regimen are uncertain. Some studies have used single agent chemotherapy when RT was unavailable.

Randomized controlled trials are not available to definitively prove benefit for combined modality therapy. Thus, there are no standard regimens. However, the use of weekly doxorubicin (10 mg/m^2) concurrently with RT is both reasonable and commonly applied, while more aggressive regimens have combined docetaxel and doxorubicin or cisplatin and doxorubicin with radiation. Given the overall poor prognosis of current treatment modalities, consideration should always be given to referring a patient with ATC for participation in a clinical trial.

4.8.1 Among patients with differentiated thyroid cancer post-surgery, what is the role of targeted therapy and immunotherapy in the adjuvant setting?

We do not recommend the use of targeted treatment such as kinase inhibitors and immunotherapy in the adjuvant setting.

Strength of recommendation:	Certainty of evidence:
Strong	Low

Kinase inhibitors are reserved for RR-DTC patients with metastatic (e.g., lung, liver, muscle), rapidly progressive and symptomatic disease not amenable to other local therapies (e.g., resection of distant metastases – metastasectomy and/or RT). Immunotherapy is also only limited to RR-DTC with advanced, progressive, or threatening disease. Immunotherapy such as pembrolizumab is indicated after doing genomic testing (tumor mutational burden or TMB) and if the result is high (≥10 mut/Mb).[12,43,52,85]

4.8.2 Among patients with anaplastic thyroid cancer, what is the role of targeted therapy and immunotherapy in the adjuvant setting?

We can consider the use of targeted agents in the presence of druggable mutations and genetic aberrations in the adjuvant setting, if accessible.

Strength of recommendation:	Certainty of evidence:
Strong	Low

Dabrafenib plus trametinib combination or larotrectinib are options for *BRAF V600E* mutation-positive tumors or for *NTRK* gene fusion-positive tumors, respectively. Other druggable genetic aberrations are ALK fusion (crizotinib, ceritinib, alectinib) and *RET* mutation (pralsetinib, selpercatinib). All these data are supported by phase II clinical trials with PFS benefit.[12,43,85,87,88]

If a BRAF V600E mutation is present, most guidelines suggest neoadjuvant dabrafenib (150 mg twice daily) plus trametinib (2 mg daily) to improve the chance of complete tumor resection. In resectable disease and favorable response to dabrafenib plus trametinib, complete resection should be attempted as long as gross resection could be achieved with minimal morbidity. This would be followed by chemoradiation (CRT) as described for Stage IVA. Evidence shows prolonged survival (i.e., more than 2 years) in some patients when surgery is combined with postoperative adjuvant CRT. In unresectable disease, dabrafenib plus trametinib can be continued if associated with disease stability or improvement. Alternative management options include CRT, clinical trials, or best supportive care if the response is not favorable.

Nonrandomized small studies have reported improvements in outcomes with dabrafenib plus trametinib in a few cases. In a nine-cohort study enrolling patients with rare cancers with the BRAF V600E mutation (23 patients with ATC), the complete and partial response rates were 4% and 57%, respectively, with a response duration of at least 6 months in 64% of responding patients. Adverse effects included fatigue (38%), fever (37%), and nausea (35%). In another small study in patients with BRAF-mutated ATC who were treated with the BRAF inhibitor, vemurafenib, there was a 29% response rate.

Molecular testing is recommended to help inform decisions regarding systemic therapy and eligibility for clinical trials. See Figure 4 for the pathway.

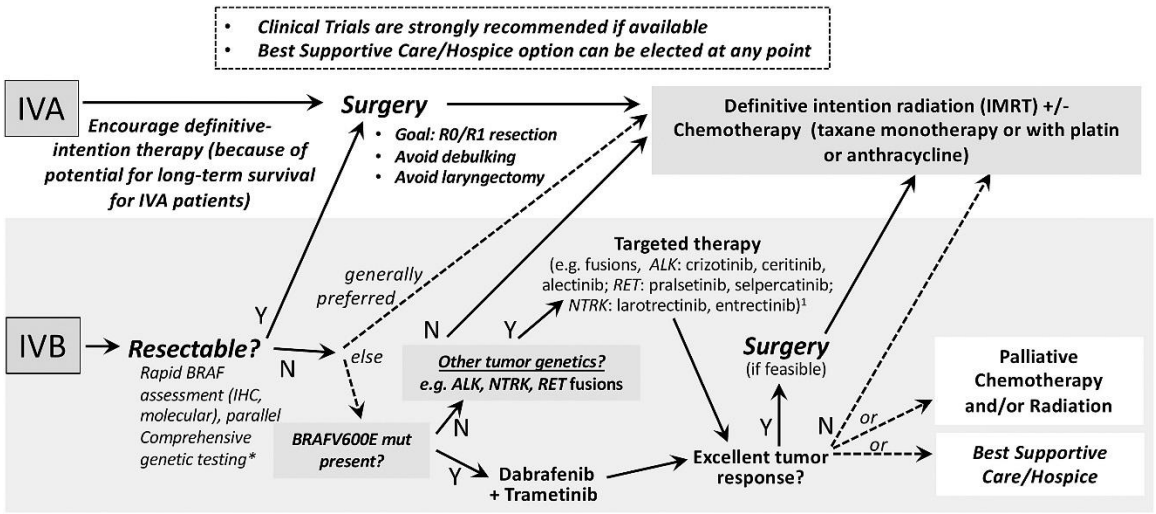

Figure 4. Initial treatment of stages IVA and IVB anaplastic thyroid cancer. From Bible et al.[87]
[1]Additonal agents exist and are in development, listing not meant to be comprehensive; clinical trials preferred if available; see text. *Cytotoxic chemotherapy may be started as a "bridge" while awaiting genomic information or while awaiting targeted therapy (e.g., dabrafenib and trametinib). Dashed arrows depict circumstances where competing therapeutic options may be of consideration.
ATC, anaplastic thyroid cancer.

Surveillance

5.1 Which criteria should be utilized to classify response to therapy of a patient with well-differentiated thyroid cancer?

We recommend to utilize the response to treatment categories based on the modified ATA dynamic or ongoing risk stratification system. Response to treatment is classified as any of the following: excellent, biochemical incomplete, structural incomplete or indeterminate response.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

Monitoring strategies are based upon the patient's risk of recurrence. While the initial staging systems can be used to guide initial and diagnostic follow-up strategy decisions, it is now recognized that initial risk estimates may need to change during follow-up based on clinical, laboratory and imaging parameters.[12,89,90] The original dynamic risk stratification described the best response to initial therapy during the first 2 years of follow-up. But as the classification became more acceptable, it is now being used to describe the patient's status at any point during follow-up.[90]

The precise definition of type of response is dependent on the extent of initial therapy. In general, the type of response is classified into four:

- Excellent response: no clinical, biochemical or structural evidence of disease
- Biochemical incomplete response: abnormal Tg or rising TgAb values in the absence of localizable disease
- Structural incomplete response: persistent or newly identified locoregional or distant metastases
- Indeterminate response: nonspecific biochemical or structural findings that cannot be classified as either benign or malignant

The best evidence and cut-off values are most consistent with those patients who underwent total thyroidectomy and RAIA. Novel responses to therapy definitions were proposed that can be used for dynamic risk stratification in thyroid cancer patients treated with lobectomy or total thyroidectomy without RAIA. The patient's response to therapy is reclassified at each follow-up visit. Aside from thorough clinical history and physical examination, the response to therapy is assessed primarily with measurements of serum Tg and neck US. The interpretation of the serum Tg level depends upon the initial therapy (see Table 11).

Table 11. Response to treatment categories in differentiated thyroid cancer patients

Responses to treatment	Total thyroidectomy + radioactive iodine remnant ablation	Total thyroidectomy alone	Lobectomy
Excellent response	• No clinical evidence of tumor and • Negative imaging and • Undetectable Tg antibody and unstimulated Tg <0.2 ng/mL or stimulated Tg <1 ng/mL	• No clinical evidence of tumor and • Negative imaging and • Undetectable Tg antibody and unstimulated Tg <0.2 ng/mL or stimulated Tg <2 ng/mL	• No clinical evidence of tumor and • Negative imaging and • Stable Tg levels and undetectable TgAb
Biochemical incomplete response	• No clinical evidence of tumor and • Negative imaging and • Unstimulated Tg >1 ng/mL or stimulated Tg >10 ng/mL or rising TgAb levels	• No clinical evidence of tumor and • Negative imaging and • Unstimulated Tg >5 ng/mL or stimulated Tg >10 ng/mL or rising TgAb levels	• No clinical evidence of tumor • and • Negative imaging and • Unstimulated Tg >30 ng/mL or rising Tg values with similar TSH levels or rising TgAb
Structural incomplete response	• Clinical or imaging evidence of disease (regardless of Tg and TgAb levels)	• Clinical or imaging evidence of disease (regardless of Tg and TgAb levels)	• Clinical or imaging evidence of disease (regardless of Tg and TgAb levels)
Indeterminate response	• Nonspecific imaging findings or • Faint uptake in thyroid bed on RAI scanning or • Tg 0.2–1 ng/mL or stimulated Tg 1–10 ng/mL or stable or declining in patients with no imaging evidence of disease.	• Nonspecific imaging findings or • unstimulated Tg 0.2–5 ng/mL or stimulated Tg 2–10 ng/mL or TgAb levels stable or declining in the absence of structural or functional disease.	• Nonspecific imaging findings or TgAb levels stable or declining in the absence of structural or functional disease.

Adapted from Momesso DP & Tuttle RM[91]; Haugen BR, Alexander EK, Bible KC, et al.[12]; and Filetti S, Durante C, Hartl D, et al.[43]
RAI *radioiodine*, Tg *thyroglobulin*, TgAb *anti-thyroglobulin*

5.2 How should a patient's response to therapy in the first year of treatment be followed up?

a We recommend that the initial dynamic risk stratification should be determined within 6 months after treatment.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

b We recommend using Tg and TgAb assays that are calibrated with a reference standard.

Strength of recommendation:	Certainty of evidence:
Strong	High

c We recommend that serum Tg and TgAb levels be checked every 3–6 months in the first year after treatment.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

d We recommend measurement of unstimulated or stimulated Tg and TgAb for patients who have undergone total thyroidectomy and radioactive remnant ablation therapy.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

e We recommend measurement of unstimulated Tg and TgAb for patients who have undergone total thyroidectomy but do not require radioactive remnant ablation, and who are at low risk of recurrence.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

f We do not recommend routine measurement of serum Tg and TgAb for patients who have not undergone total thyroidectomy and with low risk of recurrence.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

g We recommend that neck US should be performed at a 6- to 12-month interval depending on risk assessment.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

The publications of Tuttle *et al.* were adapted by most international societies and guidelines. Response to initial therapy is defined 6–12 months after therapy (surgery with/without RAIA) and during the subsequent follow-up of patients with DTC.[92]

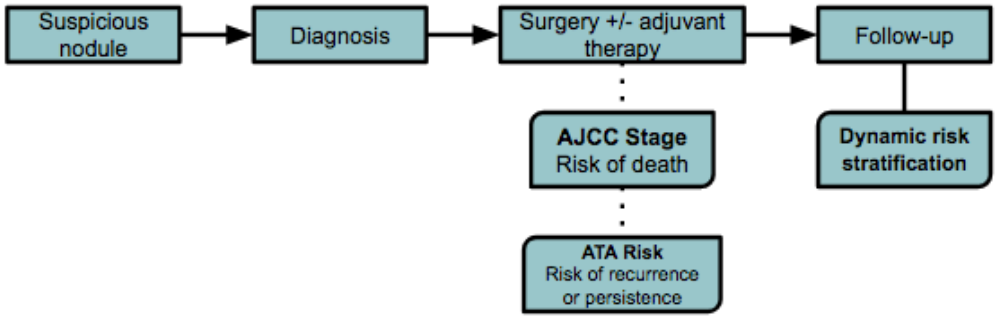

Figure 5. Role of dynamic risk stratification in thyroid cancer

The AJCC/TNM staging system predicts disease-specific mortality, and the ATA risk stratification system predicts the risk of persistent disease. These initial risk estimates are modified over time using the dynamic or ongoing risk stratification system during the follow-up. These modified risk estimates are then used to plan ongoing management.

In the United Kingdom National Multidisciplinary Guidelines, dynamic risk stratification is done 9–12 months after surgery and radioactive remnant ablation.[93] One local study showed that among Filipino patients with PTC, the proportions of incomplete responses for low-, intermediate-, and high-risk patients were 8.3%, 53.7% and 92.3%, respectively.[94] The result for low-risk patients was comparable with other studies abroad, but there was a greater number of patients with incomplete response among intermediate- and high-risk Filipino patients.

The same assay should be used when doing serial Tg measurements since inter-assay variability can be substantial.[95] This is observed for assays with lower functional sensitivity. The sources of variability are the anti-Tg used, and heterogeneity of Tg as consequence of processing and difference in iodination. Where the Tg result does not correlate with the clinical picture and risk of recurrence, clinician should communicate to the laboratory. Laboratories should also discuss with clinicians before changing the method for the assay. See Table 12.

Table 12. Sensitivity and specificity of thyroglobulin in detecting persistent thyroid cancer

	Stimulated Tg (thyroid hormone withdrawal)	Stimulated Tg (rTSH stimulation)	Unstimulated Tg
Sensitivity	96%	93%	78%
Specificity	95%	88%	98%

rTSH *recombinant thyroid-stimulating hormone*, Tg *thyroglobulin*

Functional sensitivity is the lowest Tg concentration that an assay can reliably and consistently measure under clinically relevant conditions with less than 20% coefficient of variation.[96] For many years, the functional sensitivity of most Tg assays had been

approximately 0.9 ng/mL. However, several assays with high functional sensitivities of (≤0.2 ng/mL) are now available. Unstimulated Tg level using this cut-off is acceptable to verify absence of disease (excellent response). To improve the sensitivity of serum Tg in the detection of persistent/recurrent thyroid cancer, serum Tg levels can be measured during TSH stimulation (either thyroid hormone withdrawal or with rhTSH). When using the less sensitive assays (≥1 ng/mL), TSH stimulation will result in a previously undetectable serum Tg value in about 25% of patients. Conversely, a stimulated Tg response above 2.0 ng/mL is highly unlikely when the unstimulated Tg is below 0.1 ng/mL using ultrasensitive assay with functional sensitivity of less than 0.05 ng/mL.

TgAb is detectable in as much as 10% of the general population and is present initially in about 25% of patients with thyroid cancer. It can interfere with all assays for Tg. Hence, TgAb should be measured, using the same assay over time with each measurement of serum Tg. If initial TgAb is detectable, measurements should be repeated at regular intervals (every 6 months) to document trends. The presence of TgAb should be suspected when the surgical pathology indicates the presence of background Hashimoto thyroiditis.[97,98] In patients with significantly detectable TgAb levels, serum Tg concentrations alone cannot be used as a marker to detect persistent or recurrent disease after thyroidectomy and ablation of residual normal thyroid tissue. These TgAb can cause false-negative, or less commonly, false-positive results. Immunometric assays, which can detect only free Tg, can result in falsely low values since anti-Tg complexes to Tg. Conversely, radioimmunoassays can result in falsely high values since both unbound and bound Tg are detected.[97,98]

We measure serum Tg and TgAb because disease recurrence can be heralded by a rise in TgAb with or without corresponding rise in serum Tg. On the other hand, a significant fall in these titers suggests future recurrence is unlikely. Even TSH-stimulated Tg measurements may fail to identify patients with clinically significant tumors because of TgAb, or less commonly, because of defective or absent production and secretion of immunoreactive Tg by tumor cells.[97,98] The earliest time to request for serum Tg and TgAb is 6 weeks after treatment . There is normally no need to measure serum Tg more frequently than every 3 months. Serum Tg can be measured while taking suppressive doses of thyroid hormone or with TSH stimulation (either after thyroid hormone withdrawal after administration of rhTSH). Stimulated Tg measurements are generally not necessary in ATA low-risk patients who do not receive RAI to ablate thyroid remnants, or in ATA intermediate or high-risk patients who have a detectable Tg on suppression.

Stimulated Tg values are useful in ATA intermediate- and high- risk patients with an undetectable suppressed Tg to document excellent response or to identify the presence of persistent/recurrent disease. Serum Tg should be measured when the serum TSH is greater than 30 mIU/L when thyroid hormone withdrawal is the method of stimulation.

rhTSH is recommended method of TSH stimulation prior to serum Tg determination in the patients with hypopituitarism, severe ischemic heart disease, previous history of

psychiatric disturbance precipitated by hypothyroidism and advanced disease/frailty. The use of rhTSH is associated with better quality of life in some studies but cost is a limiting factor in the local setting. Caution should be exercised in patients with large thyroid remnants or if there is known/suspected metastasis close to the central nervous system. Steroid cover is recommended in such cases. rhTSH (0.9 mg x 2 doses) should be administered by deep intramuscular injection into the buttock on Days 1 and 2 and serum Tg on Day 5. rhTSH should not be used if unstimulated serum Tg is elevated. Combining rhTSH stimulation with neck US improved sensitivity and negative predictive value to 93% and 99%, respectively, in a study of 340 consecutive patients. These data indicate that neck US will occasionally identify structural disease even when the Tg is undetectable.[99]

For patients who had a total thyroidectomy and RAIA, an excellent response is a non-stimulated Tg that is less than 0.2 ng/mL or stimulated Tg that is less than 1 ng/mL.[93] Interpretation of serum Tg is most informative in patients who have undergone total thyroidectomy are RAIA. A serum Tg that is less than 0.5 ng/mL after TSH stimulation has been shown to identify patients free of disease with 98-99.5% probability. A serum Tg greater than 1–2 ng/mL following TSH stimulation is highly suggestive in identifying patients with persistent disease, though the specificity is low. Stimulated Tg with neck US at 9–12 months following radioactive remnant ablation may be done among low-risk patients and is recommended among intermediate and high-risk patients with undetectable unstimulated Tg to document excellent response with improved sensitivity and negative predictive value.

For patients who had total or near-total thyroidectomy without RAIA, an excellent response is an unstimulated Tg that is less than 0.2 ng/mL or TSH stimulated Tg that is less than 2 ng/mL.[100] Many patients will not have undetectable basal Tg levels (less than 0.2 ng/mL) because of thyroid remnants. Hence, unstimulated serum Tg with TgAb levels should be measured as rising values over time are suspicious for growing thyroid tissue or cancer.

Among patients who underwent lobectomy, specific criteria for distinguishing normal residual thyroid tissue from persistent or recurrent thyroid cancer have not been defined. Some studies would claim that most patients with an excellent response should have a serum Tg level that is less than 30 ng/mL. Newer studies have demonstrated that changes in serum Tg over time are not reliable indicators of recurrent disease and that rising Tg levels are more likely related to residual thyroid tissue than to a true structural disease recurrence. Serum Tg used independently is of limited value for predicting or detecting disease recurrence following thyroid lobectomy.[101–103]

Neck US using a high-resolution system together with a skilled operator is most useful in identifying metastatic cervical lymph nodes which is noted to be the usual presentation of recurrent DTC (especially PTC).[40] The procedure can be performed without the need to discontinue LT4. All lymph node compartments and thyroid bed should be evaluated since most lymph node recurrences occur in previously involved compartments. Neck US is mandatory at 6–12 month after thyroidectomy to reassess the risk of recurrence. It may

be performed earlier for high-risk patients to reassess tumor extension or persistence. If there is biochemical and/or US evidence of recurrence, other imaging tests to identify the sites of disease such as diagnostic WBS, CT or MRI, skeletal radiographs, or skeletal radionuclide imaging may be needed. See Table 13 for a summary of methods used during monitoring.

Table 13. Monitoring during the first year of treatment[a]

	Risk of Recurrence		
	Low risk	Intermediate risk	High risk
Tg (with TgAb)	Within 6 months		
Neck US	At 6-12 month		
CT or MRI	Not indicated	Not indicated	If Tg elevated or high clinical suspicion
FDG-PET	Not indicated	Not indicated	If Tg >10 ng/mL

Data from Haugen BR, Alexander EK, Bible KC, et al.[12]; Filetti S, Durante C, Hartl D, et al.[43]; and Tuttle RM[104]

CT *computed tomography*, FDG-PET *fluorodeoxyglucose-positron emission tomography*, MRI *magnetic resonance imaging*, Tg *thyroglobulin*, TgAb *anti-thyroglobulin,* US *ultrasound*

[a] Monitoring should still be individualized

5.3 How should a patient's response to therapy after the first year of treatment be followed up?

a We recommend increasing the time interval between repeat measurements of unstimulated Tg and TgAb for patients who achieve excellent response.

Strength of recommendation: Strong — Certainty of evidence: Moderate

b We recommend measuring stimulated or unstimulated Tg at least every 6–12 months for high-risk and all patients with biochemical incomplete, structural incomplete or indeterminate response.

Strength of recommendation: Strong — Certainty of evidence: Low

c We do not recommend using stimulated Tg and TgAb in the follow up of these subsets of patients: those with excellent response, and those with incomplete structural response.

Strength of recommendation: Strong — Certainty of evidence: Low

d We recommend increasing the time interval between repeat neck US for patients who achieve excellent response.

Strength of recommendation: Strong — Certainty of evidence: Moderate

Ongoing follow-up is guided by assessment by individual patient's response to therapy. Most recurrences of DTC occur within the first 5 years after initial treatment, but recurrences may occur many years or even decades later. Monitoring interval may be increased to every 1–2 years for patients who achieve excellent response.

Serum Tg may remain detectable at low concentrations after RAIA. This could be indicative of residual/recurrent cancer, but in the majority of cases signify the presence of thyroid remnant. In the absence of structural evidence of persistent/recurrent disease, repeat assessments will usually reveal a gradual decline in serum Tg to the point of no detection. Increasing intervals of monitoring may then be performed. On the other hand, persistently detectable or rising Tg with subsequent assessments require further evaluation. Stimulated Tg may be required to establish excellent response among patients with biochemical incomplete or indeterminate response. Repeat stimulated serum Tg is not recommended if the initial test done showed stimulated Tg less than 1 ng/mL. The time interval between repeat measurements can be lengthened to 12–24 months for patients who achieve excellent response.

For low- and intermediate-risk patients with no evidence of disease, repeat neck US may be done every 3 years or longer. Continued routine use of surveillance neck US in ATA low- or intermediate-risk patients with no biochemical or clinical evidence of disease is more likely to identify false-positive findings than true structural disease recurrence.[105] For high-risk patients with no evidence of disease, repeat neck US may be performed more frequently (every 12 months for at least 3–5 years) depending on individual patient characteristics.

For those who underwent subtotal thyroidectomy or lobectomy, neck US is the principal monitoring tool since the serum Tg is of limited usefulness.[40] The thyroid bed and the contralateral lobe should be carefully examined for lesions. See Table 14.

Table 14. Monitoring after the first year of treatment[a, b]

	Response to therapy			
	Excellent	Biochemical incomplete	Structural incomplete	Indeterminate
Unstimulated Tg (with TgAb)	Every 1–2 years	Every 6 months	Every 6 months	Every 6–12 months
Stimulated Tg (with TgAb)	Not needed	May be repeated 2- to 3-year intervals if needed to establish excellent response to therapy	Not needed	May be repeated 2- to 3-year intervals if needed to establish excellent response to therapy
Neck US	Consider 3- to 5-year interval	1- to 5-year interval	1- to 5-year interval	Consider 6- to 12-month intervals for 5 years
CT or MRI	Not indicated	Not indicated*	6- to 12-month intervals depending on rate of progression	Not indicated*
FDG-PET	Not indicated	Not indicated*	To identify additional sites of disease and prognostic purpose	Not indicated*

Data from Haugen BR, Alexander EK, Bible KC, et al.[12]; Filetti S, Durante C, Hartl D, et al.[43]; and Tuttle RM[104]

CT *computed tomography*, FDG-PET *fluorodeoxyglucose-positron emission tomography*, MRI *magnetic resonance imaging*, Tg *thyroglobulin*; TgAb *anti-thyroglobulin*, US *ultrasound*

[a] Monitoring should still be individualized; [b] Consider if unstimulated Tg is greater than 10 ng/mL or Tg is rising.

5.4 What are the roles of radiologic and nuclear imaging studies in the follow-up of well-differentiated thyroid cancer?

a We recommend periodic neck US depending on the patient's risk for recurrent disease and Tg status.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

b We recommend US-guided FNAB for ultrasonographically suspicious lymph nodes >10 mm in widest dimension.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

c We do not recommend routine diagnostic WBS using low-dose ^{131}I in low-risk patients who have negative serum Tg, TgAb, and neck US during follow-up. WBS may be considered if persistent disease is suspected, despite a negative finding in the other tests.

Strength of recommendation:	Certainty of evidence:
Strong	Low

d We recommend FDG-PET scanning in high-risk DTC patients with elevated serum Tg and with negative RAI imaging.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

e We recommend neck and/or chest CT or MRI in the following settings:
- Bulky and recurrent nodal disease where US may not completely delineate disease;
- Possible invasive recurrent disease involving aerodigestive tract;
- Inadequacy of neck US in visualizing nodal disease (high Tg, negative neck US); and
- Possible involvement of lung parenchyma and/or mediastinum.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

f We recommend imaging of other organs including brain MRI, skeletal MRI, and/or CT or MRI of the abdomen in high-risk DTC patients with elevated serum Tg and negative neck and chest imaging who have symptoms referable to those organs.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

In low- and intermediate-risk patients, the risk of recurrent LNM is low (less than 2%) among patients with undetectable serum Tg.[12] Approximately, 1 gram of neoplastic thyroid tissue will increase serum Tg by 1 ng/mL during LT4 treatment, and by 2–10 ng/mL following TSH stimulation.

Serum Tg measurements obtained during suppression of TSH—and less commonly following TSH stimulation—may fail to identify patients with relatively small amounts of residual tumor. These minimal amounts of residual disease are often located in the neck, and performing neck US offers the best opportunity to recognize or exclude neoplastic disease even when the serum Tg is undetectable.

Cystic appearance, hyperechoic punctuations, loss of hilum, and peripheral vascularization are sonographic features with high specificity for malignancy. Minor criteria include round shape, hypoechogenicity, and the loss of hilum; these are not specific enough to suspect malignancy when taken as a single criterion. In another analysis, central neck location and size of the lymph node (≥7.5 mm) were significantly associated with the presence of metastatic involvement. Several characteristics rather than the single feature of a lymph node should be taken into consideration to guide the clinician.[39,106]

A WBS with ^{131}I will be done within 3–7 days post-therapy among all patients who underwent RAIA. Thereafter, patients with negative stimulated Tg levels, TgAb levels and cervical US do not require routine diagnostic WBS during follow up. Diagnostic WBS may be considered in patients with abnormal uptake outside the thyroid bed on posttherapy WBS; in patients with poorly informative post-ablation WBS; and in patients with TgAb at risk of false-negative Tg even without suspicious neck US finding. In these rare indications, ^{123}I is preferred, but it is not readily available locally.

18F-FDG PET/CT is recommended in high-risk patients with elevated serum Tg (generally greater than 10 ng/mL) and negative RAI imaging. It has a median sensitivity and specificity of 83% and 84%, respectively, in non-^{131}I-avid DTC, and is said to be more sensitive in patients with aggressive histologic subtype (e.g., poorly differentiated, tall cell, and Hurthle cell thyroid cancer). 18F-FDG PET/CT is correlated with poor survival and is a negative predictor for response to RAI treatment. It is complementary to ^{131}I WBS (in the presence of detectable ^{131}I uptake), because F-18 uptake may be present in neoplastic foci with no ^{131}I uptake. It is also not recommended to be performed in patients with low Tg (less than 10 ng/mL) because of its very low sensitivity in this subset of patients. While neck US is better in detecting LNM in the thyroid bed, 18F-FDG PET/CT is more sensitive for retropharyngeal or retroclavicular metastases. Some studies show that TSH stimulation may increase sensitivity of 18F-FDG PET scanning, there is no consensus evidence that it improves sensitivity of the latter.

CT or MRI may be used in patients with elevated Tg (generally greater than 10 ng/mL) or TgAb without evidence of disease.[12] This is most useful for bulky and invasive disease where anatomic delineation will affect treatment, especially surgery. RAI can be

administered after 4–8 weeks following injection of contrast medium. Iodine contamination would have disappeared in most patients after this period. Although MRI does not use iodine contrast and may better delineate the aerodigestive tract, it is less sensitive than CT for detection of lung micronodules.

There is still debate on whether 18F-FDG PET/CT or CT and MRI should be the first-line imaging of choice for metastatic DTC.[107] Modern PET/CT technique can offer several advantages, and the CT scan of the PET/CT is as reliable as a CT scan used for radiology without the need for iodine contrast. FDG-PET scanning can prognosticate thyroid cancer patients, assigning them to groups that are either at low (FDG-negative) or high (FDG-positive) risk of cancer-associated mortality.

Palliative care

6.1 What services/interventions can be provided for palliation?

We recommend consult with a multidisciplinary team that includes a pain medicine/ palliative care practitioner to address the needs of a thyroid cancer patient in the advanced stage of the disease.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

Thyroid cancer—specifically, the follicular cell-derived papillary and follicular cancers—generally has good prognosis. However, aggressive types such as the tall cell variant of PTC, and the poorly differentiated to undifferentiated type of cancer have bad prognosis and poor survival. In the staging of thyroid cancer, not all cases with distant metastases are considered stage 4 cancers. Patients who have distant metastases and are less than 55 years of age are still classified as stage 2 where treatment is curative. It is those patients with distant metastases and are older than 55 years old who are considered stage 4 cases.

This section of the CPG will cover recommendations for those with stage 4 DTC; with poor pathologic features (poorly differentiated, tall cell variant) that have undergone primary surgery but cannot be resected totally; and with recurrent symptomatic tumors wherein surgery and RAIA have previously been given (including tumors considered to be RAI-refractory).Patients who are symptomatic may have airway obstruction, bleeding, difficulty swallowing.

6.2 How do we treat advanced radioiodine-refractory thyroid cancer?

a We do not recommend further RAI when a patient with DTC is classified as refractory to RAI.

Strength of recommendation:	Certainty of evidence:
Strong	Low

b We recommend kinase inhibitors or immunotherapy for patients with RR-DTC.

Strength of recommendation:	Certainty of evidence:
Strong	High

c We recommend multidisciplinary discussion and enrollment in clinical trials for patients with RR-DTC.

Strength of recommendation:	Certainty of evidence:
Strong	Low

The European Society of Medical Oncologists (ESMO) defines RAI-refractory thyroid cancer as (a) the absence of initial RAI uptake in metastases, (b) the absence of RAI uptake in metastases after treatment with RAI, (c) the presence of RAI uptake in some metastases, but absence in others, and (d) RECIST progression (i.e., an increase of 20% in the sum of target lesions or the appearance of new lesions) despite RAI uptake in all metastases.[43] Other but controversial criteria may include high FDG uptake, aggressive histology, and persistence of disease after several RAI treatment courses. In the setting of overall poor anticipated outcome of patients with radiographically evident or symptomatic metastases that do not respond to RAI, the complexity of multidisciplinary treatment considerations and the availability of prospective clinical trials should encourage the clinician to refer such patients to tertiary centers with particular expertise.

6.3 What is the role of radiotherapy in the palliative setting?

We recommend EBRT to patients who develop metastasis that can cause symptoms that affect function and quality of life.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

EBRT may be given to patients with metastasis (i.e., brain, bone, lung, liver) to alleviate symptoms like pain, bleeding, obstruction and symptoms that cause neurologic compromise or compression. Most of the studies on the use of EBRT on thyroid cancer metastasis are limited to retrospective reviews of cases. Despite this, many guidelines support the use of EBRT for metastasis.[12,27,43,52,55] For patients with distant metastasis, it is important to discuss the treatment intent and goals with the multidisciplinary team considering the patient's overall prognosis and potential toxicities from EBRT.[86]

The use of stereotactic radiotherapy (SRT) has also been incorporated in the management of patients presenting with metastasis. SRT allows the delivery of precise, highly conformal, intense dose radiation in one to five fractions using specialized equipment. However, the available data on the use of this approach in thyroid cancer is limited, and the evidence that support its use is currently based on solid tumors.

6.3.1 What is the role of radiotherapy in spinal cord compression due to bone metastasis?

We recommend EBRT to patients who develop spinal cord compression secondary to bone metastasis.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

RT is given to the spine to alleviate pain or to provide durable local control that can improve or prevent neurologic compromise. The provision of RT in patients with spinal cord compression secondary to bone metastases is contingent on multiple factors, i.e., performance status, prognosis, and vertebral column stability.[108] The decision to use conventionally fractionated versus stereotactic regimens will depend on the patient's characteristics and preferences as well as the individual institutional protocols.

Surgery followed by RT is recommended for patients with fair to excellent performance status, good life expectancy, controlled or stable systemic disease, and available effective

systemic therapy options.[109] However, hypofractionated stereotactic radiotherapy (HFSRT) can be offered as definitive treatment among those with grade 2 epidural spinal cord compression, with intermediate spinal stability, with low rates of functional disability, and who are not candidates for surgery. It has been reported that HFSRT alone without surgery only had a 10.4% cumulative incidence of locoregional failure among patients who met these criteria.[110]. Best supportive care may be offered to patients with poor prognosis or poor performance status.[12]

6.3.2 What is the role of radiotherapy in bleeding tumors?

We can consider palliative RT to patients with bleeding tumors not amenable to surgery or other treatments.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

Multiple observational studies among patients with various head and neck malignancies have shown that RT is an effective treatment option for the palliation of bleeding, compression, or obstruction. The choice of fractionation regimen will depend on the prognosis and performance status of the patient. Short-course, cyclic, hypofractionated courses are preferred for patients with poor performance status and worse prognosis, while more protracted courses that deliver higher doses may be preferred for patients with good performance status and greater life expectancy.[86,111]

6.3.3 What is the role of radiotherapy in brain metastasis?

We recommend EBRT to patients who develop brain metastasis.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

The main management for brain metastasis from thyroid cancers is neurological resection and EBRT.[112,113] RT is given either upfront or postoperatively. Published experience with brain metastasis from DTC have shown that surgical management is reasonable for patients with solitary or oligometastatic disease, and/or patients with symptomatic metastasis.[112–114] In these studies, RT was given after surgery to enhance local tumor control.

Historically, whole brain radiotherapy (WBRT) with/without surgery has been standard of care. However, the toxicities associated with traditional WBRT, which include neurocognitive decline, have prompted the development and increased utilization of other

radiotherapeutic modalities such as hippocampal avoidance WBRT, and focal radiation in the form of stereotactic radiosurgery (SRS) and HFSRT. The choice between SRS, HFSRT, hippocampal avoidance WBRT, and conventional WBRT will depend on patient characteristics and preferences, and on the number, volume, size, and location of the lesions. The decision may also vary depending on individual institutional protocols.

In recent years, SRT has gained more traction over WBRT. Several phase III trials have shown that, although the addition of WBRT to SRS in limited brain metastases (1–4 lesions) improved local control, this was associated with worse neurocognitive outcomes with no survival benefit compared to SRS alone.[115–118] There is also emerging data showing comparable survival in patients with limited versus multiple (≥5) brain metastasis treated with SRS alone.[119,120] In patients who are not candidates for SRT but require RT, hippocampal avoidance WBRT provides better cognitive outcomes compared to conventional WBRT. The addition of memantine to WBRT lessens the neurocognitive toxicity associated with the conventional method.[121–123]

Best supportive care alone may be considered in older patients with short life expectancy and poor performance status.[124]

6.4.1 What is the role of systemic therapy in lung/visceral metastases?

a In high-resource settings, we recommend the use of kinase inhibitors or immunotherapy for RR-DTC patients with lung and/or other visceral metastases not otherwise amenable to local therapies.

Strength of recommendation:	Certainty of evidence:
Strong	High

b In low-resource settings, we can consider the use of cytotoxic chemotherapy in RR-DTC patients with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease when kinase inhibitors or immunotherapy are not available.

Strength of recommendation:	Certainty of evidence:
Strong	Low

Kinase inhibitors (lenvatinib, sorafenib, vandetanib, pazopanib, sunitinib, axitinib or cabozantinib) should be considered in RR-DTC patients with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease not otherwise amenable to local control using other approaches. Of these kinase inhibitors, only sorafenib and lenvatinib have phase III trials that showed prolongation of survival. There is no clinical trial directly comparing lenvatinib versus sorafenib for DTC.

Lenvatinib is a multitargeted kinase inhibitor of VEGFR, and to a lesser degree, of RET and fibroblast growth factor receptor kinases 1–4. In a phase III trial (SELECT), lenvatinib 24 mg OD was compared to placebo. The median PFS for lenvatinib was 18.3 months versus 3.6 months for placebo (HR 0.21; 99% CI 0.14, 0.31). The overall response rate was 64.8% for lenvatinib while it was 1.5% for placebo. The median overall survival was not reached in either group, but a preplanned analysis demonstrated that among patients older than 65 years, lenvatinib had a significantly longer overallsurvival than those who received the placebo (HR 0.53; 95% CI 0.31–0.91).

Sorafenib is a multitargeted kinase inhibitor of VEGFR 1–3, PDGFR, common RET/PTC subtypes, c-kit, and less potently, of BRAF. A phase III trial (DECISION) compared sorafenib at a starting dose of 400 mg BID with placebo. Median PFS was noted to be 10.8 months for sorafenib and 5.8 months for placebo (HR 0.59; 95% CI 0.45–0.76), while overall response rate was 12.2% for sorafenib versus 0.5% with placebo. Median overall sur had not been reached at the time of primary analysis.

At the time this guideline was written, other kinase inhibitors had phase II trial evidence of survival benefit (Table 15). If mutational studies have been performed and a targetable mutation is present, a mutation-specific kinase inhibitor may be considered.

Table 15. Summary of evidence for survival benefit of kinase inhibitors

Kinase inhibitor	Trial	Median PFS (vs. comparator)	ORR
Lenvatinib	Phase III (SELECT)	HR 0.21; 99% CI 0.14 –0.31 18.3 months (vs. 3.6 months)	64.8%
Sorafenib	Phase III (DECISION)	HR 0.59; 95% CI 0.45–0.76 10.8 months (vs. 5.8 months)	12.2%
Vandetanib[125]	Phase II	11.1 months	-
Pazopanib[126]	Phase II	11.7 months	49%
Sunitinib[127]	Phase II	13.1 months	22%
Axitinib[128]	Phase II	16.1 months	35%
Cabozantinib[129, a]	Phase III (COSMIC-311)	11.0 months (after progression on Lenvatinib or sorafenib)	18%

CI *confidence interval*; HR *hazard ratio*; ORR *overall response rate*; PFS *progression-free survival*
[a] after progression on at least one kinase inhibitor.

A cost effectiveness study done in the United States showed that lenvatinib was the most cost-effective treatment compared to sorafenib (incremental cost-effectiveness ratio [ICER]=$25,275/quality-adjusted life year [QALY]) and placebo (ICER=$40,869). Sorafenib is also more cost-effective compared to placebo (ICER=$64,067/QALY). No local studies on cost effectiveness were identified.

Immunotherapy such as pembrolizumab may be in RR-DTC patients with advanced, progressive or threatening disease if shown that results of genomic testing (TMB) are high (≥10 mut/Mb). This is supported by a phase Ib trial showing a PFS of 7.0 months for pembrolizumab at 10 mg/kg given IV every 2 weeks. A phase II trial was still ongoing at the time this guideline was written.

Cytotoxic chemotherapy (e.g., doxorubicin ± cisplatin) may be considered in RR-DTC patients with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease not otherwise amenable to control through other approaches (including kinase inhibitors or immunotherapy) or with contraindications to these treatment options. In a review of published series, 38% of patients had response to doxorubicin, and patients with pulmonary metastases seemed to benefit more from chemotherapy.[85] It is important to note that studies supporting the use of chemotherapy are small, underpowered and only showed minimal efficacy. Long-term responses are uncommon.

Multiple CPGs recognize that the survival of a cancer patient is best if treatment is administered in the context of a clinical trial, if available.

6.4.2 What is the role of systemic therapy in brain metastases?

a In high-resource settings, we may consider the use of kinase inhibitors or immunotherapy for brain metastases in RR-DTC patients not otherwise amenable to local therapies.

Strength of recommendation:	Certainty of evidence:
Strong	Low

b In low-resource settings, we do not recommend the use cytotoxic chemotherapy for brain metastases.

Strength of recommendation:	Certainty of evidence:
Strong	Low

Kinase inhibitors (e.g., sorafenib, pazopanib, sunitinib and lenvatinib) may be considered in RR-DTC patients with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease not otherwise amenable to local control using other approaches. Even so, evidence on responses of patients with brain metastases are limited to those found in case reports and case series, which showed stable or partial responses to kinase inhibitors.[85,130–132] Initial phase III trials found had excluded patients with brain metastases.

Immunotherapy such as pembrolizumab may also be considered in these patients if the result is high (≥10 mut/Mb) after doing genomic testing (TMB). Case reports have shown that chemotherapy did not show any objective responses in patients with brain metastases.

6.4.3 What is the role of systemic therapy in bone metastases?

a In high-resource settings, we recommend the use of denosumab in RR-DTC patients with diffuse and/or symptomatic bone metastases, either alone or concomitantly with other therapies.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

b In low-resource settings, we recommend the use of bisphosphonates in RR-DTC patients with diffuse and/or symptomatic bone metastases, either alone or concomitantly with other therapies.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

The use of bisphosphonates (zoledronic acid) or denosumab therapy in patients with diffuse and/or symptomatic bone metastases, either alone or in combination with locoregional treatments, is recommended. Prior to starting therapy, renal function (bisphosphonates) and calcium levels (both bisphosphonates and denosumab) should be determined. A dental evaluation before initial use is also needed.

In other solid tumors, bone-directed therapeutics such as bisphosphonates (especially zoledronic acid) and the RANK ligand–directed agent, denosumab, have been shown to delay time to occurrence of subsequent skeletal-related adverse events (fracture, pain, neurologic complications), to improve symptoms, and to provide benefits for patients with diffuse bone metastases. The determination of benefits across several tumor types suggests that they may be broadly generalizable, prompting FDA approval for their general use in patients with solid tumor bone metastases. Two small studies have suggested benefit from bisphosphonates specifically within the context of DTC bone metastases.

6.5 What is the role of systemic therapy in the palliative setting in anaplastic thyroid cancer?

We recommend chemotherapy, targeted therapy or immunotherapy used alone or sequentially, when clinically appropriate.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

There is no curative therapy for metastatic ATC, and the disease is uniformly fatal. It is considered the most lethal of all thyroid cancers, and median survival is poor (3–10 months), likely due to rapid growth (20–24 hours doubling time in cell culture).[88,133–135]

The choice of systemic therapy will depend on functional status, patient preference, prior systemic therapy used, result of molecular or genetic studies, and the side effect profile of available drugs. In patients who desire active therapy rather than palliative care, are fit, and are awaiting molecular or genetic studies, chemotherapy should be offered as treatment and should not be delayed given the aggressive nature of this disease.

Enrollment in clinical trials of BRAF-targeted therapy (based on molecular testing) is strongly encouraged (Figure 6). In the absence of clinical trials, multiple guidelines suggest the use of dabrafenib plus trametinib. Surgical resection for residual tumors can then be considered if the disease is responsive. If these tumors are resectable, surgery should then be followed by re-initiation of dabrafenib plus trametinib, provided that the distant metastases are stable or improved during prior therapy. However, if not resectable, dabrafenib plus trametinib may be continued if a favorable response to therapy is seen. Furthermore, other options include CRT, clinical trials, or best supportive care in cases where there is poor response to dabrafenib plus trametinib.

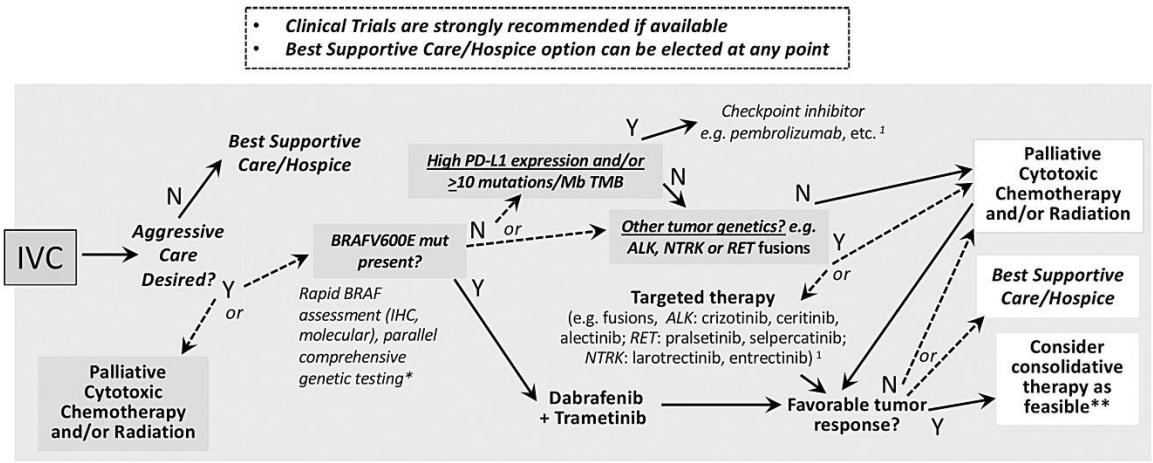

Figure 6. Initial treatment of stage IVC anaplastic thyroid cancer. From Bible et al.[87]
[1]Additonal agents exist and are in development, listings not meant to be comprehensive; clinical trials preferred if available; see text. *Cytotoxic chemotherapy may be started as a "bridge" while awaiting genomic information or while awaiting targeted therapy (e.g., dabrafenib and trametinib). **Consolidate Rx refers to focal therapy intended to control residual macrometastatic disease among those electing aggressive therapy. Dashed arrows depict circumstances where competing therapeutic options may be of consideration. TMB, tumor mutational burden.

In patients with adequate performance status, consider using targeted agents for druggable genetic aberrations such as larotrectinib or entrectinib for NTRK gene fusion-positive tumors; crizotinib, ceritinib, or alectinib for ALK fusion; pralsetinib or selpercatinib for RET mutation; and everolimus for TSC1/TSC2. As previously discussed, we recommend molecular testing to help inform decisions regarding systemic therapy and eligibility for clinical trials.

For non-druggable mutations, targeting the tumor microenvironment or common cancer signaling pathways is an alternative approach. Immunotherapy may be considered after doing genomic testing (TMB ≥10 mut/Mb).

Some data support the use of cytotoxic chemotherapy. In a randomized trial comparing cisplatin and doxorubicin in combination versus doxorubicin alone, the complete response rate was higher in the combination group (3 of 18 patients [17%] compared with none of 21 patients in the doxorubicin group). Paclitaxel as a single agent has been reported to have a response rate of 53%.

6.6 How should pain be managed among patients with thyroid cancer?

a We recommend the use of the WHO 3-Step Ladder Approach to pain management across stages of thyroid cancer.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

b We recommend a non-opioid analgesic combined with adjuvant drugs for thyroid cancer patients with mild cancer-related pain.

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

c For patients with moderate to severe pain, we recommend a trial of a strong opioid.

Strength of recommendation:	Certainty of evidence:
Moderate	Moderate

d For cancer-related pain that is non-responsive to conventional analgesic drugs, we recommend a multimodal approach to include any of the following pain management strategies: interventional pain procedures such as epidural block, rehabilitation and complementary/integrative therapies).

Strength of recommendation:	Certainty of evidence:
Strong	Moderate

e We recommend pain management using the alternative routes when the conventional (oral and intravenous)routes are not tolerated or possible. These alternative routes include subcutaneous administration, transdermal opioid delivery system, morphine elixir by gastrostomy or jejunostomy tube or sublingual route when indicated.

Strength of recommendation:	Certainty of evidence:
Strong	Low

f We recommend the use of non-pharmacologic modalities such as but not limited to cognitive behavioral therapy, support groups, acupuncture as part of the holistic approach to a patient with cancer related pain.

Strength of recommendation:	Certainty of evidence:
Strong	Low

The use of analgesic medications is the mainstay of cancer pain management.[136,137] Although concurrent use of other approaches and interventions may be appropriate in many patients and necessary in some, analgesic drugs are needed in almost every case. Drugs whose primary clinical action is the relief of pain are conventionally classified on the basis of their activity at opioid receptors as either opioid or non-opioid analgesics. A third class, adjuvant analgesics, are drugs with other primary indications that can be effective analgesics in specific circumstances. The major group of drugs used in cancer pain management is the opioid analgesics even in thyroid cancer.

When combined with appropriate dosing guidelines, this three-step ladder approach is capable of providing adequate relief to 70–90% of patients.[138] Emphasizing that the intensity of pain and the type/s of pain mechanisms involved , rather than its specific etiology, should be the prime consideration in analgesic selection, the approach advocates three basic steps (Figure 7). This strategy should be integrated with non-pharmacological methods of cancer pain control, including RT, chemotherapy, hormone therapy, surgery, anesthetic interventions, physiotherapy, and psychological/cognitive approaches.

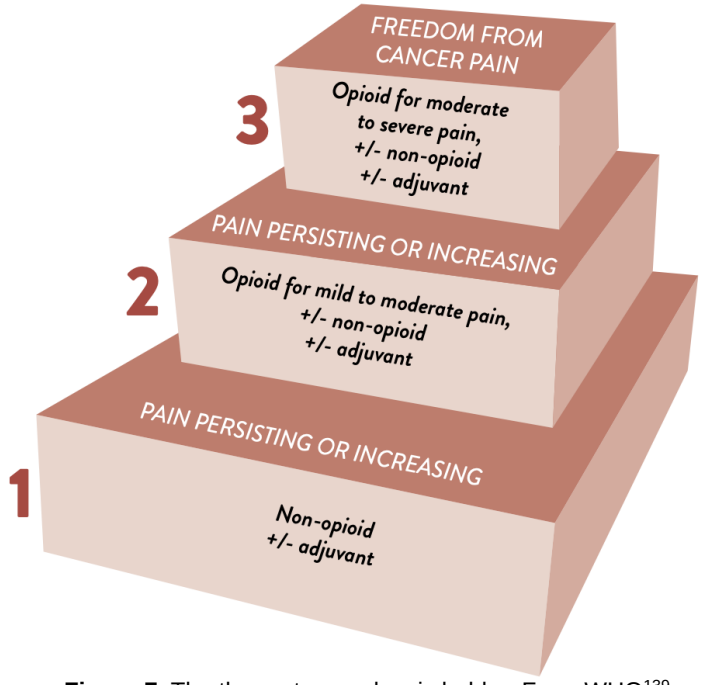

Figure 7. The three-step analgesic ladder. From WHO[139]

CHAPTER 4. RESEARCH GAPS

During the development of this CPG, the need for more research on thyroid cancer became more apparent. The following research questions for future study were identified:

1. Among high-risk individuals, what is the reliability of community health worker performed neck palpation as an initial screening tool for thyroid cancer?
2. Is there a role for a thyroid cancer risk assessment online tool in screening for thyroid malignancy?
3. What is the cost effectiveness of neck ultrasound as a diagnostic tool for malignant thyroid nodules?
4. What is the level of knowledge of clinicians on the TIRADS score applied in the evaluation of thyroid nodules?
5. What is the thyroid malignancy rate for each of the TIRADS score?
6. In clinically positive cervical lymphadenopathy with negative preoperative FNAC, what is the prevalence of metastasis?
7. What is the diagnostic accuracy of molecular testing of Bethesda III and IV nodules using a cytology specimen?
8. What is the cost effectiveness of routine preoperative and postoperative calcium determination to prevent hypocalcemic symptoms?
9. How much residual thyroid cancer can be effectively ablated with RAI?
10. What if the cost effectiveness of TKI's in the management of RAI refractory thyroid cancer?
11. What is the long-term outcome of management WDTC in the Philippines?
    a. Long-term outcome of surgical management applying the cut off size of 1 cm
    b. Long-term outcome of RAIA
    c. Long-term outcome of TSH suppression
    d. If the ATA 2015 risk stratification is applied
12. Which non-pharmacologic modalities are effective in pain control for thyroid cancer patients?

CHAPTER 5. FACILITATORS AND BARRIERS TO THE APPLICABILITY OF THIS GUIDELINE

Evidence on the diagnosis and management of thyroid cancer that (a) supported improvement in outcomes and (b) were regarded as applicable in the local setting were the foremost considerations in the development of the guideline. However, for the recommendations to be put into practice, barriers to implementation should be identified and addressed while facilitators need to be recognized and be utilized.

A major factor that can help facilitate the implementation and dissemination of this CPG is the involvement of representatives belonging to organizations involved in thyroid cancer management in the TWG and the CP. They occupy lead roles within their respective organizations as officers or fellows responsible for policymaking, or as trainers in clinical programs that can utilize these clinical guidelines. These individuals are also known clinicians who are looked up to in their respective fields of specialization and can influence practice. Another facilitating factor is the participation of the program manager of the NICCP including palliative and hospice care and Thyroid Disorders of the Department of Health in the consensus building process.

Through close collaboration between the CPG developers and the Cancer Control Division, the following steps to address barriers to full and effective implementation may be put in place were identified:

Table 16. Steps in addressing barriers to CPG implementation

STEP	**LEAD/RESPONSIBLE ORGANIZATION**	**TIMELINE**
1.Systematic dissemination of the Thyroid CPG to users and stakeholders	Various specialty organizations Training programs	First 6 months
2. establishment of baseline knowledge and practice across the country and monitor impact of the CPG	Various specialty organizations Training programs	1 year
3.Establish an integrated national thyroid cancer database	DOH NICCP including palliative and hospice care and Thyroid Disorders	1 year
4.Translate feedback from the CPG dissemination into policy such as PHIC packages for thyroid cancer	DOH NICCP PHIC	2nd year
5. Fund allocation to implement certain aspects of the recommendation (make diagnostic procedures and treatment available)	DOH	

CHAPTER 6. DISSEMINATION, MONITORING, EVALUATION, AND UPDATING OF THE GUIDELINE

Dissemination

The dissemination of the guideline may be done through the following avenues: (a) webinars and scientific fora of the collaborating specialty organizations; (b) websites of the collaborating specialty organizations; (c) lay fora to be conducted by specialty societies; (d) publication in a reputable scientific journal; (e) incorporation of key recommendations in medical curricula; (f) training; and (g) social media platforms.

Implementation, Monitoring & Evaluation

Once approved by the quality review panel of the NGC, a department order may be issued to introduce this CPG to the different DOH hospitals for implementation. Likewise, the various organizations that contributed to the development of the CPG may cascade and endorse the recommendations for implementation in their respective healthcare units.

The SC will be responsible in monitoring the implementation of the CPG and the compliance of the stakeholders. Part of the monitoring and evaluation activities will include a survey to determine (a) baseline knowledge and practices of target users, (b) feedback on the guideline recommendations, and (c) assessment of applicability and feasibility (Appendix 5). These surveys will be regularly performed to determine if there are any changes in knowledge and practices of the target users.

Updating of the guidelines

This CPG will be updated every three years. The SC and TWG will do quarterly reviews of available evidence that may affect the initial recommendations stated in the guideline. If new, high-certainty evidence on thyroid cancer diagnosis and management would become available before the scheduled update, the TWG will evaluate the evidence and the SC may convene the CP if there would be a need to issue amendments to the recommendations. Feedback from the target users of the CPG will also be reviewed annually to guide implementors and policymakers on matters pertaining to the CPG.

Table 17. Steps involved in the Updating of the Thyroid Cancer CPG

PROCESS	RESPONSIBLE UNIT/ORGANIZATION	FREQUENCY	TIMELINE
1. Review of current evidence relevant to thyroid cancer management	SC and TWG	Quarterly	2022-2024
2. Review of feedback on the 2021 Thyroid cancer CPG by end users	SC	Annual	2022-2024
4. Amendment to the recommendations if new strong evidence becomes available	SC, TWG, and CP	N/A	2022-2024
5. Major update of the 2021 Thyroid cancer CPG based on recent evidence and feedback obtained using the questionnaire	SC, TWG, and CP DOH	N/A	2024-2025

CHAPTER 7. AUTHORSHIP, CONTRIBUTIONS, ACKNOWLEDGEMENT

Authorship and Contributions

Steering Committee

The SC was indispensable in creating working groups and coordinating the preparatory work, evidence review, and formulation of the recommendations. It organized the consensus panel and facilitated the *en banc* meeting. The SC was responsible for the overall organization and management and is accountable for the overall quality of this CPG. The SC will also be responsible in monitoring the implementation and compliance of clinicians with the CPG.

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The TWG undertook extensive technical work in searching and summarizing the evidence while ensuring objectivity in each stage of the process, in presenting the evidence in the panel meeting, and in documenting and writing the final output.

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Consensus Panel

This CPG is invaluable because of the involvement and active participation of the panelists from various sectors of healthcare who dedicated their time and effort to share their expertise, experience, and knowledge in scrutinizing the scientific evidence with consideration of other critical factors such as patient values and preferences and current healthcare system in the Philippines. The Panel is composed of the following individuals:

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External Review Panel

The applicability, feasibility and ease of use of this CPG were assessed by a multisectoral group composed of practicing clinicians (both generalist and specialist), a hospital administrator, and a clinical epidemiologist. These reviewers are exposed to different healthcare settings to bring in their perspectives and hopefully assure a cost-effective application of the guidelines to benefit thyroid cancer patients.

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GALLERY

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APPENDIX 1. CPG ACTIVITY PLAN

JOSE R. REYES MEMORIAL MEDICAL CENTER
Clinical Practice Guidelines for Thyroid Cancer Committee

November 8, 2021

EMMANUEL F. MONTAÑA JR., M.D, MHA, FPCS, FACS
Medical Center Chief II
This Medical Center

Through: **WENCESLAO S. LLAUDERES, MD**
Chief, Medical Professional Staff

Dear Dr. Montaña:

Good day.

May I respectfully request for your approval on the Revised 2021 Action Plan dated November 8, 2021 for the Clinical Practice Guidelines for Thyroid Cancer. We revised the activity under **"Consultancy Services and Other Supplies and Materials Expenses.**

Thank you for your continued support in this endeavor.

Truly yours,

IDA MARIE TABANGAY-LIM, MD
Program Manager
Thyroid Cancer

JOSE R. REYES MEMORIAL MEDICAL CENTER
Office of the Medical Center Chief
APPROVED

cc budget >

ACTION PLAN FOR CY 2021
MEDICAL DIVISION
CLINICAL PRACTICE GUIDELINES for THYROID CANCER

OBJECTIVE/ MILESTONE	STRATEGY/ ACTIVITY	EXPECTED RESULTS	PERSON/S RESPONSIBLE	TIME FRAME	POTENTIAL OBSTACLES./ CONSTRAINTS	PREVENTIVE /	BUDGET	STATUS
Office Supplies (60k) ***Account Code:*** **5020301002**	Printing and distribution of Draft to Expert panel for review	25 copies of the draft have been sent to members of the Expert panel	CRU secretary	July 16-31,2021	Delay in response of the expert panel member	The soft copy of the draft was sent by email	P500/draft x 25 copies = **P12,500**	Will not be done
	Printing and distribution of Draft for Public Forum	200copies of the draft have been printed and give to the stakeholders (medical societies, PHICl DOH)	Head of TWG	September 13-30,2021	Delay in finalizing manuscript which needs to be reviewed by DOH prior to Public Forum	Soft copy to be sent through email	P237.50/draft x 200 copies =**P47,500**	Not yet done
Consultancy Services (1,104k) ***Account Code :*** **5021103002**	Preliminary meeting to discuss the clinical questions; to discuss the method of doing the CPG	The clinical questions to be addressed by a PG have been written	Head of TWG	March 1-15, 2021			Members of the TWG P1,600 x 4 hours = P6,400.00 P6,400.00 x 30consultant = **P192,000**	**March 13** – orientation meeting and workshop on CPG development **April9, 2021** Formulation of Question by TWG

Revised 11.8.2021

ACTION PLAN FOR CY 2021
MEDICAL DIVISION
CLINICAL PRACTICE GUIDELINES for THYROID CANCER

	Critical appraisal and Review of Evidences per group A . Screening in the general population B. Diagnosis of Thyroid Cancer C. Surgical Management D. Adjuvant treatment (Radioactive Iodine Ablation, Radiation, Targeted Treatment) E. Post operative Surveillance F. Palliative care	The journals/CPGs have been critically appraised and evaluated.	TWG members	(April-June 30, 2021)			Members of the TWG P1,600 x 10 hours = P16,000.00 per consultant (10 hours cumulative) P16,000 x 30 consultants = **P480,000**	**1. May 1, 2021** Presentation of the Search for Thyroid Clinical practice Guidelines and Appraisal using AGREE tool by Dr. Elaine Cunanan 2.**May 15 and May 29, 2021** TWG meeting regarding recommendation statements
	Presentation of the Draft of CPG to the whole TWG		Respective TWG members	July 1-15 2021			Members of the TWG P1,600 x 6 hours = P9,600.00	**Done: June 12, 2021** Presentation of draft of recommendations (Screening

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ACTION PLAN FOR CY 2021
MEDICAL DIVISION
CLINICAL PRACTICE GUIDELINES for THYROID CANCER

							P9,600 x 30 consultants **P288,000.00**	and Diagnosis) **June 26,2021** Presentaion of drafts of recommendations on Surgical treatment **July 10, 2021** Presentation of drafts of reommendations for Post surgical treatment **July 27-** Presentation of drafts of recommendations for surveillance of thyroid cancer

Revised 11.8.2021

ACTION PLAN FOR CY 2021
MEDICAL DIVISION
CLINICAL PRACTICE GUIDELINES for THYROID CANCER

								July 29, 2021 - presentation of drafts of recommendations on Palliative Care for thyroid cancer
	Meeting to finalize the Thyroid CPG* Corrected : First Consensus Panel meeting with TWG		TWG members	Sept 1-15,2021* corrected August 28 – September 30,2021			Members of the TWG (1 hour) P1,600 x 30 = **P48,000**	**Done: August 28,2021** First Consensus panel (Expert Panel Meeting)for their orientation regarding review and voting process on the draft of recommendations
	Presentation of Final CPG in a Public Forum *		TWG members	(Sept.16-30,2021)			Members of the TWG (2 hours)	Done: **Sept. 18, 20 and 27, 2021**

Revised 11.8.2021

ACTION PLAN FOR CY 2021
MEDICAL DIVISION
CLINICAL PRACTICE GUIDELINES for THYROID CANCER

	Corrected: Presentation of Draft of Recommendations to the Consensus Panel (Expert Panel) for voting						P1,600 x 2 hours= P3,200.00 P3,200.00 x 30 consultants **P96,000.00**	Presentation of draft of recommendations to the Consensus Panel (Expert Panel)for voting and approval
Other Professional Services (600k) ***Account Code:*** **5021199000**	CPG development workshop	Members of the TWG have been refreshed as to how conduct an appraisal of CPG's	Dr. Leonila "Inday" Dans	March 1-15,201			**P8,800.00**	**Done Conducted the workshop on March 13, 2021**
	Review of the draft by the Expert panel	Draft received by the Expert panel and reviewed					Honoraria (other professional) P1,600 x 6 hours = P9,600.00 P9,600 x 25= **P240,000**	August 7 to August27,2021 (personal review) **August 28,2021** First Consensus panel (Expert Panel Meeting)for their orientation regarding

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ACTION PLAN FOR CY 2021
MEDICAL DIVISION
CLINICAL PRACTICE GUIDELINES for THYROID CANCER

								review and voting process on the draft of recommendations
	Presentation of Final CPG in a Public Forum * Corrected: Review and Voting on Draft of Recommendations by Consensus Panel (Expert Panel)	The Thyroid CPG was presented in a public Forum* Corrected: The Thyroid CPG was presented in the Consensus Panel Meeting and recommendations approved		November 1-30, 2021* Corrected: September 1- 30 ,2021			Expert panel P1,600 x 2 hours = P3,200.00 P3,200 x 25 experts = **P80,000.00**	Done: **September 18, 20 and 27, 2021** Presentation of draft of recommendations to the Consensus Panel (Expert Panel)for voting and approval
	Contracting an individual who can perform secretary duties- for coordination and meeting	Dedicated secretary to the making of Thyroid CPG is allowed		March 1 to November 30, 2021			P20,000 per month x9 **P180,000.00**	ongoing
	Contracting a Technical writer	Finalized full text of CPG documents		October to November 30, 2021* Corrected:			**P85,000.00**	**Ongoing** **October 8-Nov. 8**

Revised 11.8.2021

ACTION PLAN FOR CY 2021
MEDICAL DIVISION
CLINICAL PRACTICE GUIDELINES for THYROID CANCER

				October 8 – Dec 8, 2021				Review of documents and writing of Introduction to Methods
Other Supplies and Materials Expenses (150k) ***Account Code:*** **5020399000**	Proceedings of the CPG for Thyroid Cancer (DOH approved)	Printed Journals		Dec 31,2021	Approval of the final manuscript by DOH	Will ask Office of Budget Department to obligate funds	Cost of journals **P122,500**	
	Printer, all-in-one, printer/scanner/copier, with continuous ink supply system	Printed documents					P13,750.00 x 2 = **P27,500.00**	
Other MOOE (86k) ***Account Code:*** **5029999099**	1.Zoom subscription 2. Printing of the Finished CPG 3. Transportation			March to November 2021			Zoom subscription P3,000/ month x 9 = P27,000 Transportation P5,000 P300.00/ draft x 200 copies P60,000 Subtotal: **P92,000.00**	
						Grand Total	**P1,999,800.00**	

Revised 11.8.2021

ACTION PLAN FOR CY 2021
MEDICAL DIVISION
CLINICAL PRACTICE GUIDELINES for THYROID CANCER

Submitted by:

IDA MARIE TABANGAY-LIM, MD
Program Manager, Thyroid Cancer

Approved by:

WENCESLAO S. LLAUDERES, MD
Chief, Medical Professional Staff

Revised 11.8.2021

APPENDIX 2. DECLARATION OF CONFLICTS OF INTEREST

Steering committee

Name	Affiliation	Institution	Geographic location	Summary of Disclosure
Dr. Ida Marie T. Lim	• Philippine College of Surgeons • Philippine Society of General Surgeons, Inc. • Philippine Academy for Head and Neck Surgery, Inc	• Jose R. Reyes Memorial Medical Center • University of Santo Tomas	NCR	None declared
Dr. Wenceslao S. Llauderes	• Philippine Thyroid Association • Philippine Society of Nuclear Medicine	• Jose R. Reyes Memorial Medical Center • University of Santo Tomas • St. Martin de Porres Charity Hospital	NCR	None declared
Dr. Maria Cheryl L. Cucueco	Philippine Society of General Surgeons, Inc.	• University of Santo Tomas • Gat Andres Bonifacio Medical Center	NCR	None declared
Dr. Alfred Phillip O. de Dios	• Philippine Society of General Surgeons, Inc • Philippine Society of Ultrasound in Surgery	• Jose R. Reyes Memorial Medical Center • Sanitarium • Our Lady of Lourdes Hospital	NCR	None declared
Dr. Rodney B. Dofitas	Philippine College of Surgeons (Committee on Research)	Philippine General Hospital	NCR Palawan	None declared
Dr. Bien J. Matawaran	• Philippine Thyroid Association • Philippine Society of Endocrinology Diabetes and Metabolism	• University of Santo Tomas • Jose R. Reyes Memorial Medical Center	NCR	None declared
Dr. Cristina S. Nieves	Philippine Society of Otolaryngology-Head and Neck Surgery	• Jose R. Reyes Memorial Medical Center • East Avenue Medical Center • Ospital ng Makati • Unihealth Parañaque Hospital and Medical Center	NCR	None declared
Dr. Christine Susean S. Sagpao	Philippine Radiation Oncology Society	• Jose R. Reyes Memorial Medical Center • Philippine General Hospital • San Juan de Dios • Cardinal Santos Medical Center • Mediatrix	NCR Batangas	None declared

Consensus panel

Name	Affiliation	Institution	Geographic location	Summary of Disclosure
Dr. Christine Joy S. Arquiza	Philippine Society of Otolaryngology-Head and Neck Surgery	Philippine General Hospital	NCR (Manila)	None declared
Dr. Solidad L. Balete	Philippine Society of Medical Oncology	Jose R. Reyes Memorial Medical Center	NCR (Manila)	None declared
Dr. Emerita A. Barrenechea	Philippine Society of Nuclear Medicine	St. Luke's Medical Center	NCR (Quezon City)	Visiting consultant • St. Luke's Medical Center – 2021 to present Personal advocacies: • Multidisciplinary management for cancer patients • Head and neck cancer awareness and prevention
Dr. Jose Ravelo T. Bartolome	• Philippine Society of General Surgeons, Inc • Philippine College of Surgeons • Philippine Academy of Head and Neck Surgery, Inc.	• FEU-NRMF • Fatima Medical University Antipolo • Bulacan Medical Center	NCR, Bulacan	None declared
Dr. Arsenio Claro A. Cabungcal	Philippine Society of Otolaryngology-Head and Neck Surgery	Philippine General Hospital	NCR (Manila)	None declared
Dr. Clarito U. Cairo, Jr.	Department of Health	Department of Health	NCR (Manila)	None declared
Dr. Johanna Patricia A. Cañal	Philippine Radiation Oncology Society	Philippine General Hospital	NCR (Manila)	None declared
Dr. Jose M. Carnate, Jr.	Philippine Society of Pathologists, Inc.	Philippine General Hospital	NCR (Manila)	None declared
Dr. Ann Margaret V. Chang	Philippine Society of Pathologists, Inc.	St. Luke's Medical Center	NCR (Quezon City)	None declared
Emily Rose M. Dizon-Nacpil	N/A	University of Santo Tomas	Pampanga	None declared
Dr. Jeffrey J.P. Domino	• Philippine Society of General Surgeons • Philippine College of Surgeons • Philippine Thyroid Association	St. Luke's Medical Center	NCR (Quezon City)	None declared

Consensus panel

Name	Affiliation	Institution	Geographic location	Summary of Disclosure
Dr. Ramon S. Inso	• Philippine Society of General Surgeons, Inc. • Philippine College of Surgeons	Perpetual Help Biñan Laguna	Laguna	None declared
Dr. Cecilia A. Jimeno	• Philippine Thyroid Association • Philippine Society of Endocrinology Diabetes and Metabolism	Philippine General Hospital	NCR (Manila)	None declared
Dr. Sjoberg A. Kho	• Philippine Thyroid Association • Philippine Society of Endocrinology Diabetes and Metabolism	University of Santo Tomas	NCR (Manila)	None declared
Dr. Fernando Lopez	• Philippine Society of General Surgeons, Inc. • Philippine College of Surgeons;	• University of Santo Tomas • The Medical City	NCR (Manila, Quezon City)	Speaker: Servier (MPFF; phlebotonic) – monthly (PHP 10,000.00)
Dr. Jeanette Marie S. Matsuo	Philippine Society of Otolaryngology-Head and Neck Surgery	Philippine General Hospital	NCR (Manila)	None declared
Dr. Michael Benedict A. Mejia	Philippine Radiation Oncology Society	• University of Santo Tomas • The Medical City	NCR (Manila)	Research support: • USTHBCI-RCNAS Head and Neck Collaborative Project (FTIR signal detection in head and neck cancer) – pending Authorship: • Co-author (The role of postoperative external beam radiotherapy for differentiated thyroid carcinoma: a systematic review and meta-analysis)
Dr. Ruben V. Ogbac	Philippine Society of Nuclear Medicine	Philippine General Hospital	NCR (Manila)	None declared
Dr. Lino Santiago S. Pabillo	• Philippine College of Radiology • Ultrasound Society of the Philippines	• Amang Rodriguez Memorial Medical Center • UERM	NCR (Manila)	None declared

Consensus panel

Name	Affiliation	Institution	Geographic location	Summary of Disclosure
Dr. Jhade Lotus P. Peneyra	Philippine Society of Medical Oncology	• San Juan De Dios Hospital • De La Salle University Medical Center • Our Lady of the Pillar Medical Center • Asian Hospital and Medical Centre • Medical Center Paranaque	NCR (Pasay, Muntinlupa, Parañaque), Cavite	None declared
Dr. Jocelyn C. Que	Philippine Society of Anesthesiologists	• University of Santo Tomas • Chinese General Hospital	NCR (Manila)	None declared
Dr. Jeremyjones F. Robles	• Philippine Thyroid Association • Philippine Society of Endocrinology Diabetes and Metabolism	• Chong Hua Hospital • Cebu Velez General Hospital	Cebu	Research support: • Diabetes Registry (Astrazeneca) – 2021 • Clinical trial, soliqua (Sanofi) – 2021
Dr. Teofilo O.L. San Luis	Iodine Global Network	St. Luke's Medical Center	NCR (Quezon City)	Personal advocacy: National Coordinator, Iodine Global Network
Dr. Roberto A. Sarmiento	• Philippine Society of General Surgeons, Inc. • Philippine College of Surgeons • Philippine Academy of Head and Neck Surgeons, Inc.	Mother Seton Hospital	Bicol	None declared
Dr. Maria Lilybeth R. Tanchoco	Philippine Society of Anesthesiologists	MCU-FD Tanchoco Medical Foundation Hospital	NCR (Caloocan)	Advisory Board member • Menarini (pain management) – 2019 to present Membership in speaker's bureau: • Mundipharma (pain management) – 2018 to present
Erdaine Stiffany M. Tangco	N/A	San Juan Manila	NCR	None declared

Technical working group

Name	Affiliation	Institution	Geographic location	Summary of disclosure
Dr. Jose Modesto B. Abellera III	Philippine College of Surgeons (Committee on Research)	• Philippine General Hospital • National Children's Hospital • Jose R. Reyes Memorial Center	NCR (Manila)	None declared
Dr. Orlino C. Bisquera, Jr.	• Philippine Society of Ultrasound in Surgery • Surgical Oncology Society of the Philippines	• Rizal Medical Center • Philippine General Hospital	NCR (Manila)	None declared
Dr. Angela P. Camacho	Philippine Radiation Oncology Society	• St. Luke's Medical Center QC and BGC • Manila Doctor's • Medical Center Dagupan	NCR, Pangasinan	None declared
Dr. Elaine C. Cunanan	• Philippine Thyroid Association • Philippine Society of Endocrinology Diabetes and Metabolism	University of Santo Tomas	NCR (Manila)	Speaker: • Merck (levothyroxine) – March 2021 Medchoice (levothyroxine) – March 2021
Dr. Neresito T. Espiritu	• Philippine Society of General Surgeons, Inc • Philippine College of Surgeons	• Jose B. Lingad Memorial Regional Hospital • Philippine General Hospital	NCR, Pampanga	None declared
Dr. Francis Gerard M. Estrada	• Philippine Thyroid Association • Philippine Society of Nuclear Medicine	• Mt. Carmel Medical Center	Pampanga	None declared
Dr. Adrian F. Fernando	Philippine Society of Otolaryngology-Head and Neck Surgery	• UERM, • Cardinal Medical Center • University of Santo Tomas	NCR (Manila, Quezon City)	Gifts, non-research grant, sponsorships, or rewards: • Merck Philippines (head and neck cancer) – 2021 to 2022 Personal advocacy: • Multi-disciplinary team for cancer, cancer awareness, prevention, and early detection
Dr. Mark David D.G. Francisco	• Philippine Thyroid Association • Philippine Society of Endocrinology Diabetes and Metabolism	St. Paul Hospital Bulacan, Inc.	Bulacan	None declared

Technical working group

Name	Affiliation	Institution	Geographic location	Summary of disclosure
Dr. Mary Ondinee M. Igot	Philippine Society of Medical Oncology	• De la Salle University Medical Center • Asian Hospital	Cavite, NCR (Muntinlupa City)	None declared
Dr. Joy Grace G. Jerusalem	Philippine College of Surgeons (Committee on Research)	Perpetual Help - Biñan	Laguna	None declared
Dr. Milabelle B. Lingan	Philippine Society of Otolaryngology-Head and Neck Surgery	• Jose R. Reyes Memorial Medical Center • University of Santo Tomas	NCR (Manila)	None declared
Dr. Joshua A. Marcos	• Philippine Academy of Family Physicians • Pain Society of the Philippines	Jose R. Reyes Memorial Medical Center	NCR (Manila)	None declared
Dr. Marwin Emerson V. Matic	Philippine Society of General Surgeons, Inc Philippine Academy for Head and Neck Surgery, Inc.	• Asian Hospital and Medical Center • De La Salle Medical Center • Cabrini Hospital	NCR (Muntinlupa), Cavite, Batangas	None declared
Dr. Erick S. Mendoza	• Philippine Thyroid Association • Philippine Society of Endocrinology Diabetes and Metabolism	University of Santo Tomas	NCR (Manila)	None declared
Dr. Cherry Lyn V. Montealto	• Philippine Society of General Surgeons, Inc. • Philippine Academy for Head & Neck Surgery Inc.	Cebu Velez General Hospital	Cebu	None declared
Dr. Nemencio A. Nicodemus, Jr.	• Philippine Thyroid Association • Philippine Society of Endocrinology Diabetes and Metabolism	Philippine General Hospital	NCR (Manila)	None declared
Dr. Arnel E. Pauco	• Philippine Thyroid Association • Philippine Society of Nuclear Medicine	Philippine General Hospital	NCR (Manila)	None declared
Dr. Esther A. Saguil	Philippine College of Surgeons (Committee on Research)	Philippine General Hospital	NCR (Manila)	None declared
Dr. Kenneth G. Samala	Philippine Society of Medical Oncology	• Philippine General Hospital • Jose R. Reyes Memorial Medical Center	NCR (Manila)	None declared

Technical working group

Name	Affiliation	Institution	Geographic location	Summary of disclosure
Dr. Jeanelle Margareth T. Tang	• Philippine Thyroid Association • Philippine Society of Nuclear Medicine	Rizal Medical Center	NCR (Manila)	None declared
Dr. Cesar Vincent L. Villafuerte III	Philippine Radiation Oncology Society	Philippine General Hospital	NCR (Manila)	None declared
Dr. Gemma Leonora B. Uy	• Philippine College of Surgeons (Committee on Research) • Surgical Oncology Society of the Philippines	• Philippine General Hospital • St. Luke's Medical Center	NCR (Manila, Taguig)	None declared
Dr. Rowen T. Yolo	Philippine Society of Pathologists, Inc.	University of Santo Tomas	NCR (Manila)	None declared

External review panel

Name	Specialty and Qualifications	Institution	Geographic Location	Summary of disclosure
Dr. Nilo C. de los Santos	General Surgeon Past president Philippine Society of General Surgeons,Inc. Chairman, Department of Surgery, EAMC Chief Medical Officer, De los Santos Medical Center Past Chair, Department of Clinical Epidemiology , UST FMS	EAMC, UST De los Santos Medical Center	NCR Manila	None declared
Dr. Leilani B. Mercado-Asis	Internist, Endocrinologist Past president PTA Past president PSEDM, Professor, USTFMS	UST Hospital	NCR Zambales	None declared
Dr. Lucy Ann Wee-Yap	Internist Endocrinologist	St. Elizabeth Hospital	General Santos City South Cotabato	None declared

External review panel

Name	Specialty and Qualifications	Institution	Geographic Location	Summary of disclosure
Dr. Irene S. Bandong	Nuclear Medicine Radiologist Training Officer and Head of Research Committee, Department of Nuclear Medicine, St. Luke's Medical Center-Quezon City Consultant and member of Radiology Research Committee, Institute of Radiology, St. Luke's Medical Center-Quezon City Assistant Professor 1, St Luke's Medical Center-College of Medicine Assistant Professor, Chinese General Hospital - College of Medicine Research Coordinator and Head of Publication Committee, Clinical Trial and Research Division, Philippine Heart Center	Philippine Heart Center St. Luke's Medical Center Chinese General Hospital College of Medicine	NCR	None declared
Dr. Eric B. Cruz	Nuclear Medicine President Philippine Thyroid Association 2022	Angeles University St. Luke's	Pampanga NCR	None declared
Dr. Warren R. Bacorro	Radiation Oncologist Consultant, Breast and Colorectal CPG	UST Manila Doctor's	NCR	None declared
Dr. Yasmin Dapit	Head and Neck Surgeon	Zamboanga Medical Center	Zamboanga City	None declared
Dr. Chrisanthydel Tiu	Former Doctors to the Barrios Masters in Public Management, Major in Health Systems and Development,2019 Resident in training, Radiology, starting January 2022	DTTB Program Liloan Leyte, 2018 Sto. Niño, Samar, 2019 Rizal Medical Center	Samar and Leyte (DTTB)	None declared

APPENDIX 3. APPRAISAL USING AGREE-II

External review panel

Detailed Appraisal Using AGREE-II Instrument

	Domain 1: Scope and purpose			Domain 2: Stakeholder involvement		
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6
Appraiser 1	7	7	7	7	7	7
Appraiser 2	7	7	6	6	7	7
Appraiser 3	7	7	7	7	7	7
Appraiser 4	7	7	7	7	7	7
Appraiser 5	7	7	7	7	6	6
Appraiser 6	7	7	7	7	7	1
Appraiser 7	7	7	7	7	7	7
Appraiser 8	6	6	6	6	6	6

	Domain 3: Rigor of development							
	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14
Appraiser 1	7	7	7	7	7	7	7	7
Appraiser 2	7	7	6	7	7	7	7	6
Appraiser 3	7	7	7	7	7	7	7	7
Appraiser 4	7	7	7	7	7	7	7	7
Appraiser 5	7	7	7	7	7	7	7	6
Appraiser 6	7	7	7	7	5	7	7	1
Appraiser 7	7	7	7	7	7	7	7	7
Appraiser 8	6	6	6	6	5	6	6	6

	Domain 4: Clarity of presentation			Domain 5: Applicability				Domain 6: Editorial independence		Global assessment	
	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall quality	Recom, Use?
Appraiser 1	7	7	7	7	7	7	7	7	7	7	Yes
Appraiser 2	6	7	7	7	7	7	7	7	7	7	Yes
Appraiser 3	7	7	7	7	7	7	7	7	7	7	Yes
Appraiser 4	7	7	7	7	7	7	7	7	7	7	Yes
Appraiser 5	7	7	7	6	7	6	7	7	7	7	Yes
Appraiser 6	7	7	7	5	7	7	0	7	0	6	Yes, with mod
Appraiser 7	7	7	7	7	7	7	7	7	7	7	Yes
Appraiser 8	6	6	6	6	5	5	6	7	6	6	Yes

Domain	Average (%)
Scope and purpose	97.22%
Stakeholder involvement	91.67%
Rigor of development	94.79%
Clarity of presentation	97.22%
Applicability*	91.15%
Editorial independence	91.67%
Overall quality (out of 7)	6.75
Recommend use?	7 out of 8

Comments from the external review panel

- Despite the number of thyroid cases in Zamboanga Peninsula, there is a decrease in the number of cases seen (specifically in Zamboanga City Medical Center) due to patients' concerns of potential COVID-19 infection while they are in the hospital, as well as because of financial and logistical constraints.
- There is also a small percentage of candidate patients for RAI who undergo this procedure since there are no functional RAI facilities in the region and patients requiring this procedure are usually referred to institutions from nearby provinces such as Davao or Cagayan de Oro.
- Include facilitators and barriers to application of the recommendations.
- Provide more detailed process of updating the CPG

Department of Health

Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

Screening Assessment for the National Guidelines Quality Review Panel

CPG APPRAISED: 2021 The Philippine CPG for the Diagnosis and Management of Well-Differentiated Thyroid Cancer
LEAD CPG DEVELOPER: Dr. Jose R. Reyes Memorial Medical Center
DATE APPRAISED: January 14, 2021

PART I. DETAILED APPRAISAL USING AGREE-II INSTRUMENT
Number of Appraisers: 5

	Domain 1: Scope and Purpose			Domain 2: Stakeholder Involvement			Domain 3: Rigor of Development							
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14
Appraiser 1	7	7	6	5	1	7	6	6	7	7	7	7	1	7
Appraiser 2	7	7	5	7	6	6	7	7	7	7	7	7	1	7
Appraiser 3	7	7	6	7	7	3	7	7	6	7	6	7	3	6
Appraiser 4	7	7	7	7	7	6	7	7	7	7	5	7	3	7
Appraiser 5	7	6	5	6	6	3	7	7	7	7	7	7	1	6

	Domain 4: Clarity of Presentation			Domain 5: Applicability				Domain 6: Editorial Independence		Global Assessment	
	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall Quality	Recom. Use?
Appraiser 1	7	7	7	7	7	7	1	7	6	6	Yes, with mod
Appraiser 2	7	7	7	6	7	6	6	7	7	6	Yes
Appraiser 3	7	7	7	5	7	7	6	7	5	6	Yes, with mod
Appraiser 4	7	7	7	4	6	6	7	7	7	6	Yes
Appraiser 5	7	7	7	5	7	7	4	7	7	7	Yes

PART II. SUMMARY OF APPRAISAL

Domain	Average (%)	Remarks
Scope and Purpose	92.22	Passed
Stakeholder Involvement	76.67	Passed
Rigor of Development	85.00	Passed
Clarity of Presentation	100.00	Passed
Applicability	81.67	Passed
Editorial Independence	95.00	Passed
Overall Quality (out of 7)	6.20	
Recommend Use?	3/5 Yes	

PART III. SUGGESTIONS FOR IMPROVEMENT

Domain	Comment/s
Scope and Purpose	Specify age groups and if special population is involved in the scope of this CPG.
Stakeholder Involvement	State the institution, and geographical location (if applicable) of the guideline development group. Explicitly mention the target users of the CPG.
Rigor of Development	State explicit external review process. Mention the full methodology on how the CPG will be updated.
Clarity of Presentation	
Applicability	Explicitly mention the facilitators and barriers to the application of the recommendations in a separate section.
Editorial Independence	State explicit COI management.
Other Comments	

**Please refer to https://bit.ly/AGREE-Checklist for the complete CPG reporting checklist of AGREE*

Prepared by:

MIGUEL GASTON M. AGCAOILI, RND
Health Program Officer II, Evidence Generation and Management Division
Disease Prevention and Control Bureau

Noted by:

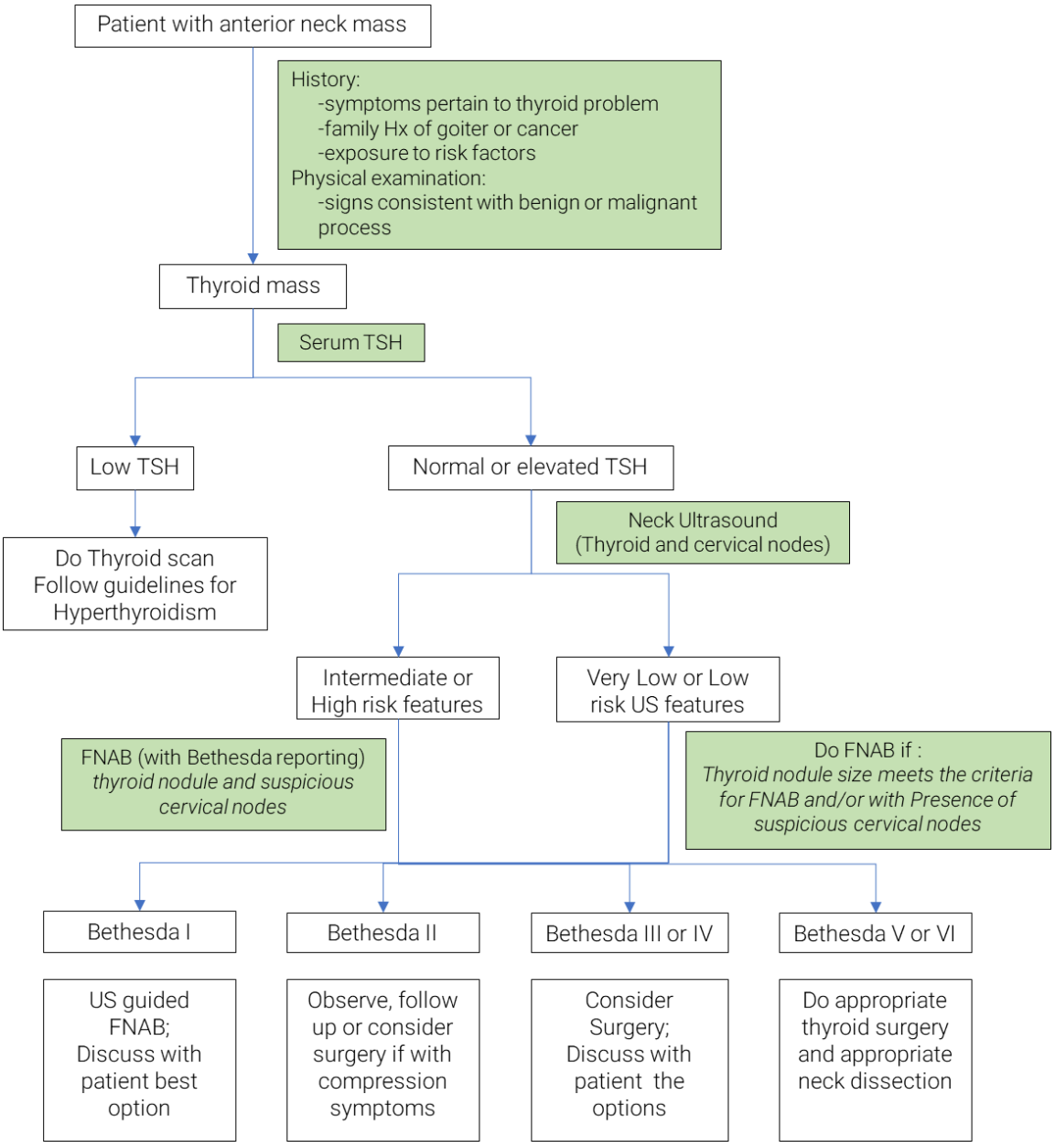
JOSE GERARD B. BELIMAC, MD, MPH
Division Chief, Evidence Generation and Management Division
Disease Prevention and Control Bureau

JAN DEREK D. JUNIO, RND, MD-MBA, MPH
Medical Officer IV, Evidence Generation and Management Division
Disease Prevention and Control Bureau

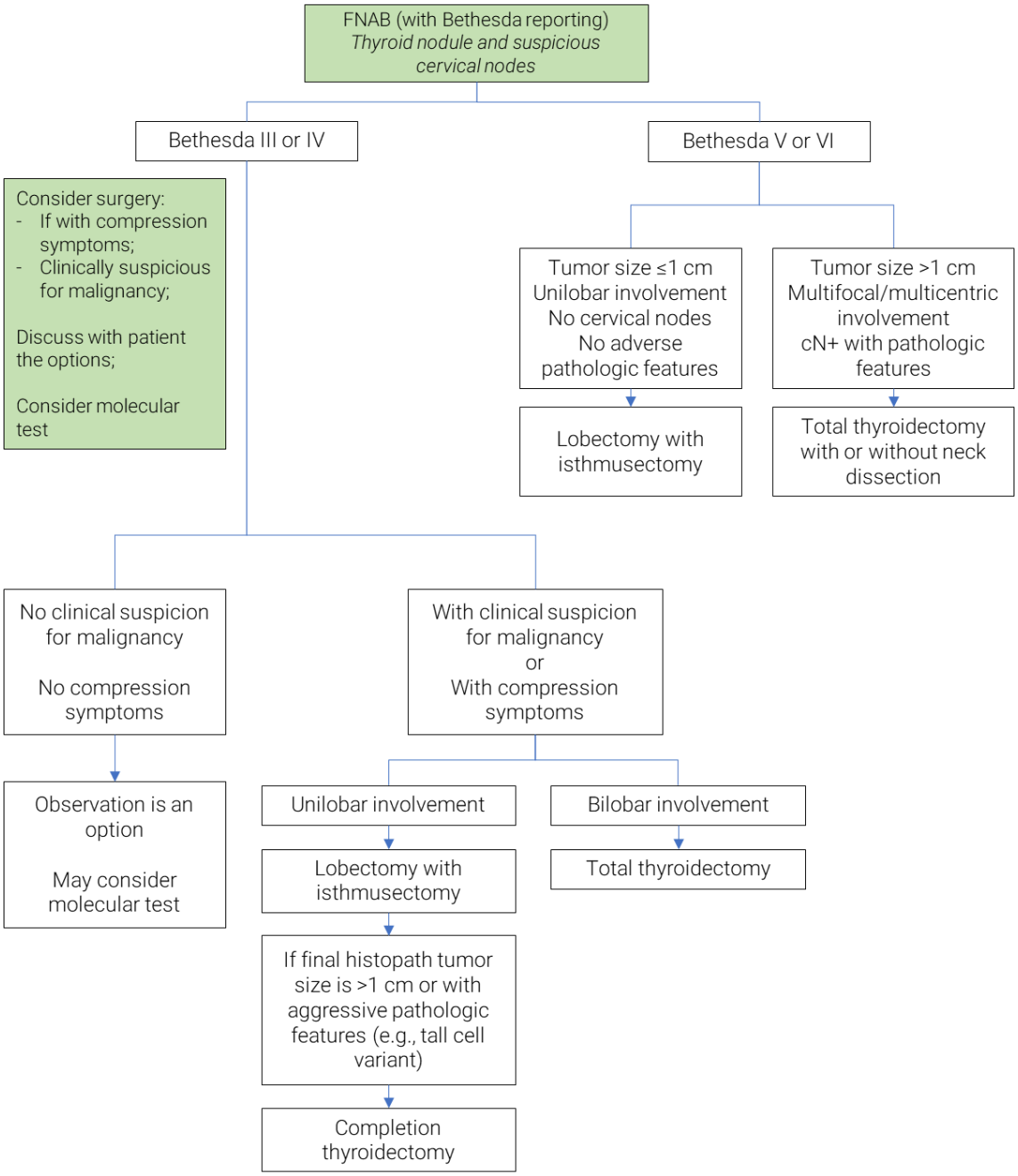
Approved by:

RAZEL NIKKA M. HAO, MD-MBA, MSc
OIC-Director III
Disease Prevention and Control Bureau

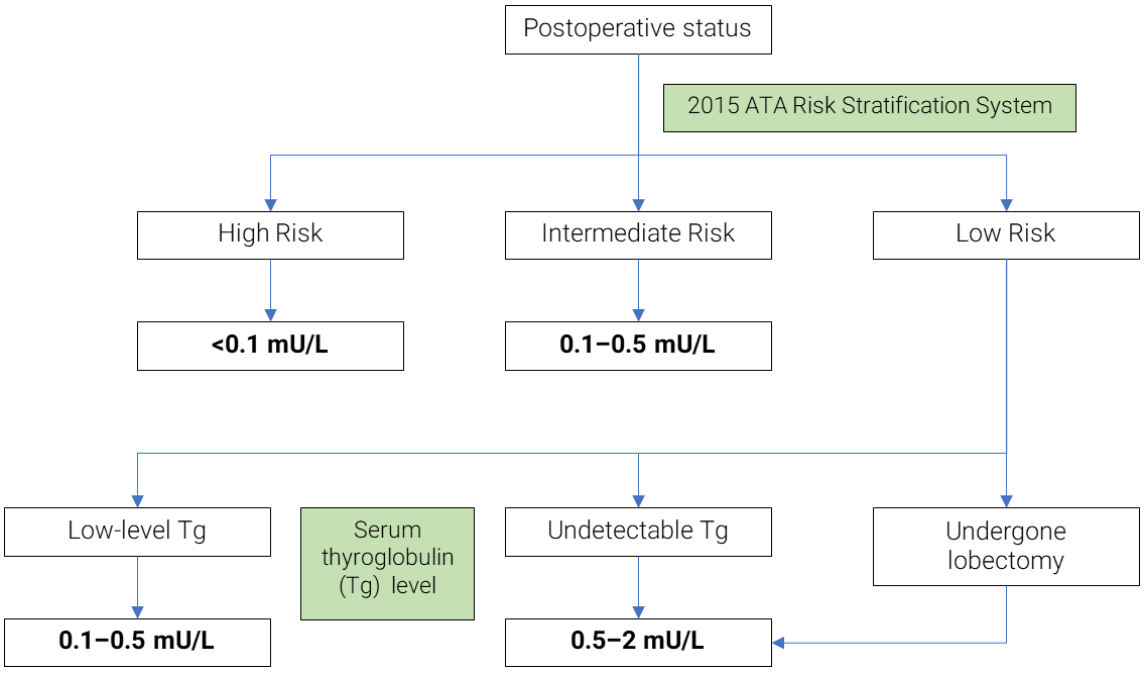
APPENDIX 4. ALGORITHMS FOR THE DIAGNOSIS AND MANAGEMENT OF THYROID CANCER



Algorithm for the approach to diagnosing thyroid cancer



Algorithm for the surgical treatment of WDTC



Algorithm for TSH suppression therapy

APPENDIX 5. QUESTIONNAIRE FOR THE DOH THYROID CPG

Check the appropriate response.

___Consultant ____Resident/Trainee

Internist ___ Endocrinology ___ Other specialty ___
Surgeon ___ GS ___ ENT ___
Nuclear medicine ___
Family Physician ___
General Practitioner ___
Others___ (specify)_____

1. Which of the following CPGs on Thyroid Nodules / Cancer are you aware of?

   ___2021 DOH Thyroid Cancer CPG
   ___PCS 2013 Update on certain aspects of EBCPG focused on diagnosis and management.
   ___UP-PGH 2012 Thyroid CPG
   ___American Thyroid Association guidelines
   ___AACE guidelines
   ___Others _____

2. Which of the choices above do you frequently refer to when managing thyroid nodules? Rank from 1 as the most often used to the least often used:
   ___2021 DOH Thyroid Cancer CPG
   ___PCS 2013 Update on certain aspects of EBCPG focused on diagnosis and management.
   ___American Thyroid Association guidelines
   ___AACE guidelines
   ___Advice from mentor or senior staff
   ___our own department/institution treatment protocol
   ___Others _____

Feedback on the CPG

1. The recommendations are specific and unambiguous.
   ___ Agree ___ Disagree ___ Neutral

2. The different options for management of the condition or health issue are clearly presented.
   ___ Agree ___ Disagree ___ Neutral

3. The recommendations are applicable in my setting.
   ___ Agree ___ Disagree ___ Neutral

4. The DOH Thyroid Cancer CPG provides advice and/or tools on how the recommendations can be put into practice.
   ___ Agree ___ Disagree ___ Neutral

5. The DOH Thyroid Cancer CPG encompasses important aspects of management of thyroid cancer
   ___ Agree ___ Disagree ___ Neutral

Knowledge and Practice

1. When I encounter a patient with an anterior neck mass, the initial thing I do is a thorough history and complete physical exam. (P)
   _/_ Agree ___ Disagree ___ Neutral

2. I request for serum TSH in all patients with thyroid nodules. (P)
   _/_ Agree ___ Disagree ___ Neutral

3. Only those with symptoms of hyperthyroidism should have a serum TSH level determination. (K)
   ___ Agree _/_ Disagree ___ Neutral

4. All patients with an anterior neck mass should undergo neck ultrasound. (K)
   _/_ Agree ___ Disagree ___ Neutral

5. I request for a thyroid ultrasound in all cases of anterior neck mass. (P)
   ___ Agree _/_ Disagree ___ Neutral

6. I request for thyroid ultrasound only if the mass is unilateral on PE. (P)
   ___ Agree _/_ Disagree ___ Neutral

7. I do FNAC on all cases of thyroid nodules. (P)
   ___ Agree _/_ Disagree ___ Neutral

8. I get a higher biopsy yield f I do US guided FNAC than blind biopsy. (P)
   ___ Agree ___ Disagree ___ Neutral

9. The advantage of having a thyroid ultrasound includes the ff: allows me to determine which nodule to biopsy based on US characteristics , determine whether there are nodules in a nonpalpable thyroid lobe. (K)
   _/_ Agree ___ Disagree ___ Neutral

10. If I get a reading of follicular tumor on FNAC, I would request for an intraop FS. (K)
    ___ Agree _/_ Disagree ___ Neutral

11. If I get a reading of follicular tumor on FNAC, lobectomy and isthmusectomy is the minimum surgery to establish pathology (K)
    _/_ Agree ___ Disagree ___ Neutral

12. I do total thyroidectomies for all thyroid cancer bigger than 1 cm (P)
    ___ Agree ___ Disagree ___ Neutral

13. One indication for total thyroidectomy is a malignant thyroid nodule more than 1 cm. (K)
    ___ Agree ___ Disagree ___ Neutral

14. The recommended neck dissection for clinically palpable nodes is therapeutic lateral neck dissection level 2 – 5
    ___ Agree ___ Disagree ___ Neutral

15. After surgery for thyroid malignancy, I give thyroxine replacement immediately even w/o biopsy result. (P)
    ___ Agree ___ Disagree ___ Neutral

16. Thyroid hormone as suppression therapy should be given for all cases of well differentiated thyroid cancer (K)

___ Agree _/_ Disagree ___ Neutral

17. Post op surveillance utilizes a dynamic risk stratification utilizing TG , TSH levels and ultrasound (K)
___ Agree ___ Disagree ___ Neutral

18. If indicated, radioactive iodine remnant ablation should be done 4 to 6 weeks after total thyroidectomy (K)
___ Agree ___ Disagree ___ Neutral

19. Patients with well differentiated thyroid cancer who need to undergo RAI remnant ablation after surgery are able to avail of the TX most of the time (P)
___ Agree ___ Disagree ___ Neutral

20. I use serum thyroglobulin to monitor my patients with well differentiated thyroid cancer after treatment. (P)
___ Agree ___ Disagree ___ Neutral

21. For advanced thyroid cancer including RAI refractory cancers, there is a role for tyrosine kinase inhibitors (K)
___ Agree ___ Disagree ___ Neutral

22. Patients with advanced and RAI refractory thyroid cancer are treated with chemotherapy and/ or tyrosine kinase inhibitors in our setting. (P)
___ Agree ___ Disagree ___ Neutral

23. Pathologists in our institution reports thyroid cytopathology following the Bethesda system (P)
___ Agree ___ Disagree ___ Neutral

24. Consult with a multidisciplinary team that includes a pain medicine/ palliative care practitioner to address the needs of a thyroid cancer patient in the advanced stage of the disease is practiced in our setting (P)
___ Agree ___ Disagree ___ Neutral

25. There is a palliative role for systemic chemotherapy and/ or radiotherapy in advanced and metastatic thyroid cancer including anaplastic cancers (K)
___ Agree ___ Disagree ___ Neutral