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

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

Joint statement of:
Steering Committee

Dr. Ida Marie T. Lim, *Project leader*
Dr. Wenceslao S. Llauderes, *Project leader*
Dr. Bien J. Matawaran
Dr. Alfred Phillip O. de Dios
Dr. Christine Susean S. Sagpao
Dr. Cristina S. Nieves
Dr. Maria Cheryl L. Cucueco
Dr. Rodney B. Dofitas

Technical Working Group

*General Surgery*
Dr. Neresito T. Espiritu
Dr. Marwin Emerson V. Matic
Dr. Cherry Lyn V. Montealto

*Otorhinolaryngology*
Dr. Adrian F. Fernando
Dr. Milabelle B. Lingan

*Endocrinology*
Dr. Nemencio A. Nicodemus, Jr.
Dr. Elaine C. Cunanan
Dr. Erick S. Mendoza
Dr. Mark David D.G. Francisco

*Nuclear Medicine*
Dr. Francis Gerard M. Estrada
Dr. Arnel E. Pauco
Dr. Jeanelle Margareth T. Tang

*Radiology*
Dr. Lino Santiago S. Pabillo

*Radiation Oncology*
Dr. Michael Benedict A. Mejia
Dr. Johanna Patricia A. Cañal

*Medical Oncology*
Dr. Solidad L. Balete
Dr. Jhade Lotus P. Peneyra

*Pathology*
Dr. Jose M. Carnate, Jr.
Dr. Ann Margaret V. Chang

*Pain and Palliative Care*
Dr. Jocelyn C. Que
Dr. Maria Lilybeth R. Tanchoco

Department of Health Representative
Dr. Clarito U. Cairo, Jr.

Patient Perspectives
Erdaine Stiffany M. Tangco
Emily Dizon-Nacpil

Consensus Panel

*General Surgery*
Dr. Ramon S. Inso
Dr. Roberto A. Sarmiento
Dr. Jose Ravelo T. Bartolome
Dr. Jeffrey J.P. Domino
Dr. Fernando Lopez

*Otorhinolaryngology*
Dr. Arsenio Claro A. Cabungcal
Dr. Jeanette Marie S. Matsuo
Dr. Christine Joy S. Arquiza

*Endocrinology*
Dr. Sjoberg A. Kho
Dr. Jeremyjones F. Robles
Dr. Cecilia A. Jimeno

*Nuclear Medicine*
Dr. Emerita A. Barrenechea
Dr. Ruben V. Ogbac
Dr. Teofilo O.L. San Luis

*Radiology*
Dr. Lino Santiago S. Pabillo

*Radiation Oncology*
Dr. Michael Benedict A. Mejia
Dr. Johanna Patricia A. Cañal

*Medical Oncology*
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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, policy makers, 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 CPG development project was commissioned by the Department of Health to JRRMMC, it is still subject to approval by the DOH Guidelines Clearing house prior to public dissemination.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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</thead>
<tbody>
<tr>
<td>AACE</td>
<td>American Association of Clinical Endocrinologists</td>
</tr>
<tr>
<td>AAES</td>
<td>American Association of Endocrine Surgeons</td>
</tr>
<tr>
<td>ACE</td>
<td>American College of Endocrinology</td>
</tr>
<tr>
<td>AIHNS</td>
<td>African Head and Neck Society</td>
</tr>
<tr>
<td>AHNS</td>
<td>American Head and Neck Society</td>
</tr>
<tr>
<td>AJCC/UICC</td>
<td>American Joint Committee/Union for International Cancer Control</td>
</tr>
<tr>
<td>AME</td>
<td>Associazione Medici Endocrinologi</td>
</tr>
<tr>
<td>AGREE</td>
<td>Appraisal of Guidelines Research and Evaluation</td>
</tr>
<tr>
<td>ATA</td>
<td>American Thyroid Association</td>
</tr>
<tr>
<td>ATC</td>
<td>anaplastic thyroid cancer</td>
</tr>
<tr>
<td>AUS</td>
<td>atypia of undetermined significance</td>
</tr>
<tr>
<td>CN XI</td>
<td>spinal accessory nerve</td>
</tr>
<tr>
<td>CP</td>
<td>consensus panel</td>
</tr>
<tr>
<td>CPG</td>
<td>clinical practice guideline</td>
</tr>
<tr>
<td>CRT</td>
<td>chemoradiation</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>DFS</td>
<td>disease-free survival</td>
</tr>
<tr>
<td>DOH</td>
<td>Department of Health</td>
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<tr>
<td>DSS</td>
<td>disease-specific survival</td>
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<tr>
<td>DTC</td>
<td>differentiated thyroid cancer</td>
</tr>
<tr>
<td>EBRT</td>
<td>external beam radiation therapy</td>
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<tr>
<td>FLUS</td>
<td>follicular lesion of undetermined significance</td>
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<tr>
<td>FNAB/FNAC</td>
<td>fine-needle aspiration biopsy</td>
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<tr>
<td></td>
<td>fine-needle aspiration cytology</td>
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<tr>
<td>HA-WBRT</td>
<td>hippocampal avoidance whole brain radiation</td>
</tr>
<tr>
<td>HFSRT</td>
<td>hypofractionated stereotactic radiotherapy</td>
</tr>
<tr>
<td>ICER</td>
<td>incremental cost-effectiveness ratio</td>
</tr>
<tr>
<td>IJV</td>
<td>internal jugular vein</td>
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<tr>
<td>KTA</td>
<td>Korean Thyroid Association</td>
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<tr>
<td>LNMM</td>
<td>lymph node metastases</td>
</tr>
<tr>
<td>LT4</td>
<td>levothyroxine</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>MRND</td>
<td>modified radical neck dissection</td>
</tr>
<tr>
<td>NICCA</td>
<td>National Integrated Cancer Control Act</td>
</tr>
<tr>
<td>ORR</td>
<td>overall response rate</td>
</tr>
<tr>
<td>OS</td>
<td>overall survival</td>
</tr>
<tr>
<td>PhilHealth</td>
<td>Philippine Health Insurance Corporation</td>
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<tr>
<td>PET/CT</td>
<td>positron emission tomography/computed tomography</td>
</tr>
<tr>
<td>PTC</td>
<td>papillary thyroid cancer</td>
</tr>
<tr>
<td>QALY</td>
<td>quality-adjusted life year</td>
</tr>
<tr>
<td>RAI</td>
<td>radioactive iodine, radiiodine</td>
</tr>
<tr>
<td>RAIA</td>
<td>radioactive iodine ablation</td>
</tr>
<tr>
<td>rhTSH</td>
<td>recombinant human thyroid-stimulating hormone</td>
</tr>
<tr>
<td>RND</td>
<td>radical neck dissection</td>
</tr>
<tr>
<td>RR-DTC</td>
<td>radioiodine-refractory differentiated thyroid cancer</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>--------------</td>
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</tr>
<tr>
<td>RT</td>
<td>radiotherapy, radiation therapy</td>
</tr>
<tr>
<td>SC</td>
<td>steering committee</td>
</tr>
<tr>
<td>SCM</td>
<td>sternocleidomastoid</td>
</tr>
<tr>
<td>SFN</td>
<td>suspicious for a follicular neoplasm</td>
</tr>
<tr>
<td>SND</td>
<td>selective neck dissection</td>
</tr>
<tr>
<td>SPM</td>
<td>secondary primary malignancy</td>
</tr>
<tr>
<td>SRS</td>
<td>stereotactic radiosurgery</td>
</tr>
<tr>
<td>SRT</td>
<td>stereotactic radiotherapy</td>
</tr>
<tr>
<td>TBSRTC</td>
<td>The Bethesda System for Reporting Thyroid Cytopathology</td>
</tr>
<tr>
<td>Tg</td>
<td>thyroglobulin</td>
</tr>
<tr>
<td>TgAb</td>
<td>anti-thyroglobulin</td>
</tr>
<tr>
<td>THST</td>
<td>thyroid hormone suppression therapy</td>
</tr>
<tr>
<td>TLUS</td>
<td>transcutaneous laryngeal ultrasound</td>
</tr>
<tr>
<td>TMB</td>
<td>tumor mutational burden</td>
</tr>
<tr>
<td>TNM</td>
<td>Tumor Node Metastasis</td>
</tr>
<tr>
<td>TSH</td>
<td>thyroid-stimulating hormone</td>
</tr>
<tr>
<td>TWG</td>
<td>technical working group</td>
</tr>
<tr>
<td>UHC</td>
<td>Universal Health Coverage</td>
</tr>
<tr>
<td>US</td>
<td>ultrasound or ultrasonography</td>
</tr>
<tr>
<td>USPSTF</td>
<td>United States Preventive Services Task Force</td>
</tr>
<tr>
<td>WBRT</td>
<td>whole brain radiotherapy</td>
</tr>
<tr>
<td>WDTC</td>
<td>well-differentiated thyroid cancer</td>
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</table>
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)
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Box 1. List of clinical practice guidelines assessed using the AGREE-II tool
Box 2. Basis for strength of recommendations
### SUMMARY OF RECOMMENDATIONS

#### Screening

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

<table>
<thead>
<tr>
<th>Question</th>
<th>Recommendation</th>
<th>Certainty of evidence</th>
<th>Strength of recommendation</th>
</tr>
</thead>
</table>
| 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 |
## Diagnosis and preoperative evaluation

<table>
<thead>
<tr>
<th>Question</th>
<th>Recommendation</th>
<th>Certainty of evidence</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.3 What are the indications for doing thyroid biopsy?</td>
<td>a We recommend that FNAB should be performed on all nodules suspected of being malignant based on clinical or US findings.</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>b For thyroid glands with multiple nodules, we recommend that each nodule be evaluated separately and the decision to perform a FNAB be individualized.</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>c We do not recommend FNAB for nodules that are purely cystic and hyperfunctioning on thyroid scintigraphy.</td>
<td>Low</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>d We recommend FNAB for cervical lymph nodes with suspicious clinical and US findings</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
| 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 |
## Diagnosis and preoperative evaluation

<table>
<thead>
<tr>
<th>Question</th>
<th>Recommendation</th>
<th>Certainty of evidence</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.6 Among patients who underwent FNAC of a thyroid nodule, when molecular testing warranted and most helpful in diagnostic and therapeutic applications?</td>
<td>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.</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>2.7 Among patients suspected to have DTC, what are the indications for additional diagnostic imaging?</td>
<td>a. We do not recommend the routine use of CT scan, MRI, thyroid scintigraphy and PET/CT.</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>b. Use of CT scan and/or MRI with intravenous contrast may be considered in clinically advanced cases like bulky and fixed tumors.</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
</tbody>
</table>
| 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

<table>
<thead>
<tr>
<th>Question</th>
<th>Recommendation</th>
<th>Certainty of evidence</th>
<th>Strength of recommendation</th>
</tr>
</thead>
</table>
| 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.  
   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.  
   b We recommend therapeutic central neck dissection (Level VI) if there are LNM in the central compartment.  
   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                | a We recommend total thyroidectomy ± neck dissection for patients with DTC even with distant metastasis. | Moderate | Strong |
### Surgical management

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<tr>
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<tbody>
<tr>
<td>distant metastasis of DTC?</td>
<td>b We recommend surgical excision for resectable metastatic disease without adverse functional outcome in selected patients.</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>3.5 How should we manage perioperative complications after thyroidectomy?</td>
<td>a We recommend at least an overnight observation for patients at high risk for postoperative hematoma, when clinically appropriate.</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
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<td></td>
<td>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.</td>
<td>Low</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>c For patients at high risk for hypocalcemia, determination of ionized calcium or serum calcium and albumin should be requested post-operatively.</td>
<td>Low</td>
<td>Strong</td>
</tr>
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<td></td>
<td>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.</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>e We recommend formal laryngeal evaluation for patients with dyspnea and/or stridor, aspiration, dysphagia, and hoarseness.</td>
<td>Low</td>
<td>Strong</td>
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### Surgical management

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<tr>
<td>3.6 What is the role of surgery for pregnant patients with thyroid nodules?</td>
<td>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.</td>
<td>Low</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
| 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                     |
| 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

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<tbody>
<tr>
<td>4.1</td>
<td>What is the role of postoperative staging systems in the management of DTC?</td>
<td>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.</td>
<td>Moderate</td>
</tr>
<tr>
<td>4.2</td>
<td>What is the role of initial risk stratification in the management of DTC?</td>
<td>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.</td>
<td>Moderate</td>
</tr>
<tr>
<td>4.3</td>
<td>Should postoperative disease status be considered in decision-making for RAI therapy for patients with DTC?</td>
<td>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.</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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.</td>
<td>Moderate</td>
</tr>
<tr>
<td>4.4.1</td>
<td>What is the role of RAI (including remnant ablation, adjuvant therapy, or therapy for persistent disease) after thyroidectomy in the primary management of DTC?</td>
<td>a We recommend routine RAI adjuvant therapy after total thyroidectomy for ATA high risk DTC patients.</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b We recommend RAI adjuvant therapy after total thyroidectomy in ATA intermediate-risk level DTC patients.</td>
<td>Low</td>
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<tr>
<td></td>
<td></td>
<td>c We do not recommend routine RAI remnant ablation after thyroidectomy for ATA low-risk DTC patients.</td>
<td>Low</td>
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### Postoperative management

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<tr>
<td><strong>d</strong> 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.</td>
<td>Moderate</td>
<td>Strong</td>
<td></td>
</tr>
<tr>
<td><strong>e</strong> We do not recommend routine RAI remnant ablation after thyroidectomy for patients with multifocal papillary microcarcinoma, in absence of other adverse features.</td>
<td>Low</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td><strong>4.4.2</strong> How should post-thyroidectomy patients be prepared for RAI remnant ablation/treatment or diagnostic scanning?</td>
<td>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.</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td><strong>4.4.3</strong> Should a posttherapy scan be performed following remnant ablation or adjuvant therapy?</td>
<td>We recommend that RAI administration must be followed by WBS to stage the disease and document the $^{131}$I avidity of any structural lesion.</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td><strong>4.5</strong> Among patients with DTC post-surgery, what is the role of thyroid hormone suppression?</td>
<td>We recommend initial TSH suppression to &lt;0.1 mU/L for high-risk DTC patients.</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>We suggest initial TSH suppression to 0.1–0.5 mU/L for intermediate-risk DTC patients.</td>
<td>Low</td>
<td>Strong</td>
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## Postoperative management

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<tr>
<td>c</td>
<td>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.</td>
<td>Low</td>
<td>Strong</td>
</tr>
<tr>
<td>d</td>
<td>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.</td>
<td>Low</td>
<td>Strong</td>
</tr>
<tr>
<td>e</td>
<td>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.</td>
<td>Low</td>
<td>Strong</td>
</tr>
<tr>
<td>4.6.1</td>
<td>Among patients with DTC post-surgery, is there a role for adjunctive EBRT?</td>
<td>a</td>
<td>We do not recommend routine adjuvant EBRT to the neck in patients with DTC after initial complete surgical removal of the tumor.</td>
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### Postoperative management

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</table>
| 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?  

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<tbody>
<tr>
<td>a</td>
<td>We recommend post-operative EBRT with systemic therapy for resectable, non-metastatic, good performance status patients desirous of aggressive treatment.</td>
<td>Low</td>
<td>Strong</td>
</tr>
<tr>
<td>b</td>
<td>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.</td>
<td>Low</td>
<td>Strong</td>
</tr>
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### Postoperative management

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<tr>
<td>4.7.1 Among patients with DTC post-surgery, is there a role for chemotherapy in the adjuvant setting?</td>
<td>We do not recommend the use of chemotherapy in patients with DTC (beyond RAI and/or TSH suppressive therapy) in the adjuvant setting.</td>
<td>Very low</td>
<td>Strong</td>
</tr>
<tr>
<td>4.7.2 Among patients with ATC diagnosed postoperatively, is there a role for chemotherapy in the adjuvant setting?</td>
<td>We recommend the use of cytotoxic chemotherapy with or without RT in patients with ATC when clinically appropriate in the adjuvant setting.</td>
<td>Low</td>
<td>Strong</td>
</tr>
<tr>
<td>4.8.1 Among patients with DTC post-surgery, what is the role of targeted therapy and immunotherapy in the adjuvant setting?</td>
<td>We do not recommend the use of targeted treatment such as kinase inhibitors and immunotherapy in the adjuvant setting.</td>
<td>Low</td>
<td>Strong</td>
</tr>
<tr>
<td>4.8.2 Among patients with ATC, what is the role of targeted therapy and immunotherapy in the adjuvant setting?</td>
<td>We can consider the use of targeted agents in the presence of druggable mutations and genetic aberrations in the adjuvant setting, if accessible.</td>
<td>Low</td>
<td>Strong</td>
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## Surveillance

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<tr>
<td>5.1 Which criteria should be utilized to classify response to therapy of a patient with DTC?</td>
<td>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.</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
</tbody>
</table>
| 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.  

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

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

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

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.  

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   | Moderate   | Strong   | Moderate   | Strong   | Moderate   | Strong   |
### Surveillance

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<tr>
<td>g</td>
<td>We recommend that neck US should be performed at a 6- to 12-month interval depending on risk assessment.</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>5.3 How should a patient’s response to therapy after the first year of treatment be followed up?</td>
<td>a</td>
<td>We recommend increasing the time interval between repeat measurements of unstimulated Tg and TgAb for patients who achieve excellent response.</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>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.</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>c</td>
<td>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.</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>d</td>
<td>We recommend increasing the time interval between repeat neck US for patients who achieve excellent response.</td>
<td>Moderate</td>
</tr>
<tr>
<td>5.4 What are the roles of radiologic and nuclear imaging studies in the follow-up of DTC?</td>
<td>a</td>
<td>We recommend periodic neck US depending on the patient’s risk for recurrent disease and Tg status.</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>We recommend US-guided FNAB for ultrasonographically suspicious lymph nodes ≥10 mm in widest dimension.</td>
<td>Moderate</td>
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<tr>
<td>c</td>
<td>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.</td>
<td>Low</td>
<td>Strong</td>
</tr>
<tr>
<td>d</td>
<td>We recommend FDG-PET scanning in high-risk DTC patients with elevated serum Tg and with negative RAI imaging.</td>
<td>Moderate</td>
<td>Strong</td>
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</table>
| 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

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

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<tbody>
<tr>
<td><strong>6.4.2</strong> What is the role of systemic therapy in brain metastases?</td>
<td>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.</td>
<td>Low</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>b In low-resource settings, we do not recommend the use of cytotoxic chemotherapy for brain metastases.</td>
<td>Low</td>
<td>Strong</td>
</tr>
<tr>
<td><strong>6.4.3</strong> What is the role of systemic therapy in bone metastases?</td>
<td>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.</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>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.</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td><strong>6.5</strong> What is the role of systemic therapy in the palliative setting in ATC?</td>
<td>We recommend chemotherapy, targeted therapy or immunotherapy used alone or sequentially, when clinically appropriate.</td>
<td>Moderate</td>
<td>Strong</td>
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<tr>
<td>6.6 How should pain be managed among patients with thyroid cancer</td>
<td>a We recommend the use of the WHO 3-Step Ladder Approach to pain management across stages of thyroid cancer.</td>
<td>Moderate</td>
<td>Strong</td>
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<td></td>
<td>b We recommend a non-opioid analgesic combined with adjuvant drugs for thyroid cancer patients with mild cancer-related pain.</td>
<td>Moderate</td>
<td>Strong</td>
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<td></td>
<td>c For patients with moderate to severe pain, we recommend a trial of a strong opioid.</td>
<td>Moderate</td>
<td>Moderate</td>
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<tr>
<td></td>
<td>d For cancer-related pain that is non-responsive to conventional drugs, we recommend any of the following: interventional pain procedures (e.g., coeliac plexus block, rehabilitation and complementary/integrative treatment).</td>
<td>Moderate</td>
<td>Strong</td>
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<tr>
<td></td>
<td>e We recommend pain management using alternative routes when the conventional route is not tolerated or possible. This includes subcutaneous administration, transdermal opioid delivery system, morphine elixir by gastrostomy or jejunostomy tube, or rectal route (when indicated).</td>
<td>Low</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>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.</td>
<td>Low</td>
<td>Strong</td>
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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 6th 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. Upon approval of the application to be the lead guideline developer for thyroid cancer, the Dr. Jose R. Reyes Memorial Medical Center (JRRMMC) embarked on the development of the clinical practice guideline (CPG) following the DOH-PHIC Manual for Clinical Practice Guideline Development.⁵ To help align the implementation of NICCA with the Universal Health Coverage law, this guideline, if approved by the DOH CPG clearing house, may 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 (a) the screening, diagnosis, surgical management, postoperative management, surveillance and palliative care of well-differentiated thyroid cancer (WDTC) (both papillary and follicular), and (b) the postoperative management and palliative care of poorly differentiated or anaplastic thyroid cancer (ATC) based on existing local and international CPGs from 2012 to the present. More recent evidence that came out during the drafting of the guideline was included.
CHAPTER 2
GUIDELINE DEVELOPMENT METHODS
Guideline preparation

A steering committee (SC) was formed, composed of specialists from JRRMMC, 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 who are involved in the management of thyroid cancer. 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 technical working group (TWG) was composed of physicians from different specialties of medicine involved in the management of thyroid cancer. These individuals were recommended by their respective organizations based on their expertise, training and experience in the preparation of CPGs. Members of the TWG reviewed existing CPGs and drafted recommendations based on the gathered evidence. To prepare for evidence synthesis, a clinical epidemiologist was invited to an orientation workshop to discuss the ADAPTE process of CPG development.

The consensus panel (CP) included representatives of the 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. 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.

Declaration and management of conflicts of interest

All individuals involved in the development of the CPG were required to disclose potential conflicts of interest (COIs) that have existed in the past 12 months. A summary of these COIs can be found in Appendix 1.

Evidence synthesis

The TWG agreed that the CPG would cover aspects of management of 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.**

<table>
<thead>
<tr>
<th>Category</th>
<th>Question(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>• Among individuals at risk for thyroid cancer, which screening tools (physical exam and/or ultrasound) are accurate in detecting cancer?</td>
</tr>
</tbody>
</table>
| 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 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

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• About adults with WDTC and ATC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>• Older versions of the guideline</td>
</tr>
<tr>
<td>• Published in text or online</td>
<td>• Guidelines about medullary thyroid cancer</td>
</tr>
<tr>
<td>• Written in English or with English translations</td>
<td>• Guidelines involving pediatric patients</td>
</tr>
<tr>
<td>• Published in the last 10 years (2012 onwards)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>• Guidelines involving pregnant patients</td>
</tr>
<tr>
<td>• Must include a report on systematic literature searches and explicit links between individual recommendations and their supporting evidence</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Only recommendations for postoperative management and palliative care were considered for anaplastic thyroid cancer

<sup>b</sup> 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.

<table>
<thead>
<tr>
<th>Database</th>
<th>Keywords</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDLINE</td>
<td>“thyroid carcinoma”, “thyroid neoplasm”, “thyroid malignancy”, “thyroid tumor”, “thyroid nodule”, “thyroid neoplasm”, “practice guidelines”</td>
</tr>
<tr>
<td>Google Scholar</td>
<td>“thyroid cancer”, “thyroid neoplasm”, “thyroid mass”, “thyroid nodule”, “practice guidelines”</td>
</tr>
<tr>
<td>HERDIN Plus</td>
<td>“thyroid cancer”, “guidelines”</td>
</tr>
</tbody>
</table>

Assessment of guidelines using the AGREE 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.**

<table>
<thead>
<tr>
<th>Quality</th>
<th>Definition</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>The group is very confident that the true effect lies close to that of the estimate of the effect</td>
<td>Further research is very unlikely to change confidence in the estimate of effect</td>
</tr>
<tr>
<td>Moderate</td>
<td>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</td>
<td>Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate</td>
</tr>
<tr>
<td>Low</td>
<td>Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect</td>
<td>Further research is very likely to have an important impact on confidence in the estimate of effect and is unlikely to change the estimate</td>
</tr>
<tr>
<td>Very low</td>
<td>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</td>
<td>Any estimate of effect is very uncertain</td>
</tr>
</tbody>
</table>

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.**

<table>
<thead>
<tr>
<th>Vote &gt;75 of Consensus panel</th>
<th>Strong recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vote &gt;50 but &lt;75</td>
<td>Moderate recommendation</td>
</tr>
<tr>
<td>Vote &lt; 50</td>
<td>Weak recommendation</td>
</tr>
</tbody>
</table>

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 can comment and vote on the recommendations. The Delphi method was employed, and voting was repeated until consensus was reached.
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: Strong | Certainty of evidence: 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. The evidence assessed showed that the prevalence of thyroid cancer was low relative to the prevalence of cancers of other sites.

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.

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. 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. 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).

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%), 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. 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.\textsuperscript{8} Although not found to be associated with mortality,\textsuperscript{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.\textsuperscript{8}

**Diagnosis**

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

<table>
<thead>
<tr>
<th>a</th>
<th>Clinical features suggestive of increased risk for thyroid malignancy include:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Age &lt;14 years old or &gt;70 years old</td>
</tr>
<tr>
<td></td>
<td>• Male sex</td>
</tr>
<tr>
<td></td>
<td>• Family history of thyroid cancer</td>
</tr>
<tr>
<td></td>
<td>• Previous head or neck irradiation</td>
</tr>
<tr>
<td></td>
<td>• Rapid neck mass growth</td>
</tr>
<tr>
<td></td>
<td>• Recent onset hoarseness, dysphagia or dyspnea</td>
</tr>
</tbody>
</table>
|   | **Strength of recommendation:** Strong  
|   | **Certainty of evidence:** Low to Moderate                           |

<table>
<thead>
<tr>
<th>b</th>
<th>Physical examination findings suggestive of higher risk for thyroid malignancy include:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Firm or hard thyroid nodule consistency</td>
</tr>
<tr>
<td></td>
<td>• Fixed nodule</td>
</tr>
<tr>
<td></td>
<td>• Cervical adenopathy</td>
</tr>
</tbody>
</table>
|   | **Strength of recommendation:** Strong  
|   | **Certainty of evidence:** 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.\textsuperscript{10–13}

Malignancy rate is higher among younger patients compared to adult patients.\textsuperscript{14} In contrast, the risk of thyroid cancer is slightly higher in older persons and in males.\textsuperscript{15,16} In a meta-analysis of 41 studies,\textsuperscript{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: Strong  
   Certainty of evidence: 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: Strong  
   Certainty of evidence: Moderate

c We recommend a diagnostic neck US for all patients with thyroid nodule.
   
   Strength of recommendation: Strong  
   Certainty of evidence: 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: Strong  
   Certainty of evidence: 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
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, hypoechogeticity, irregular margins, and a taller-than-wide shape measured on transverse view. 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. US features of lymph nodes suspicious for malignant involvement include loss of fatty hilum; microcalcifications; cystic, peripheral vascularity; hyperechogenicity; and round shape. 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.
Figure 1. ATA nodule sonographic patterns and risk of malignancy. From Haugen et al12
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: Strong  | Certainty of evidence: 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: Strong  | Certainty of evidence: Moderate |
| c | We do not recommend FNB for nodules that are purely cystic or hyperfunctioning on thyroid scintigraphy. |
|   | Strength of recommendation: Strong  | Certainty of evidence: Low |
| d | We recommend FNAB for cervical lymph nodes with suspicious clinical and US findings. |
|   | Strength of recommendation: Moderate  | Certainty of evidence: Moderate |

FNAB is the diagnostic procedure of choice in confirming thyroid malignancy due to its accuracy and cost-effectiveness.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 nodulesa

<table>
<thead>
<tr>
<th>Sonographic pattern</th>
<th>US features</th>
<th>Estimated risk of malignancy, %</th>
<th>FNAB size cutoff (largest dimension)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High suspicion</td>
<td>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</td>
<td>&gt;70–90b</td>
<td>Recommend FNAB at ≥1 cm</td>
</tr>
<tr>
<td>Intermediate suspicion</td>
<td>Hypoechoic solid nodule with smooth margins without microcalcifications, ETE, or taller than wide shape</td>
<td>10–20</td>
<td>Recommend FNAB at ≥1 cm</td>
</tr>
<tr>
<td>Low suspicion</td>
<td>Isoechoic or hypoechoic solid nodule, or partially cystic nodule with eccentric solid areas, without microcalcification, irregular margin or ETE, or taller than wide shape</td>
<td>5–10</td>
<td>Recommend FNAB at ≥1.5 cm</td>
</tr>
<tr>
<td>Very low suspicion</td>
<td>Spongiform or partially cystic nodules without any of the sonographic features described in low, intermediate, or high suspicion patterns</td>
<td>&lt;3</td>
<td>Recommend FNAB at ≥2 cm</td>
</tr>
<tr>
<td>Benign</td>
<td>Purely cystic nodules (no solid component)</td>
<td>&lt;1</td>
<td>No biopsyc</td>
</tr>
</tbody>
</table>

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. 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. 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. 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: Strong  Certainty of evidence: 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.
Evidence showed that this strategy makes the procedure safer, more reliable and more accurate.\textsuperscript{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.\textsuperscript{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: Strong  | Certainty of evidence: 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).\textsuperscript{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.

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

Adapted from Cibas ES & Ali SZ\textsuperscript{46}

The 2017 revision reaffirms that every thyroid FNAB report should begin with one of six diagnostic categories,\textsuperscript{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.

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:** Strong  
**Certainty of evidence:** 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%). In follicular thyroid cancer (FTC), the most common genetic alterations found are *Ras* mutation (40–53%) and *PPARG* rearrangement (25–63%). About 25% of cases lack the common driver mutations. 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. 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 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: Strong  Certainty of evidence: 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: Strong  Certainty of evidence: 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 131I sodium iodide is useful to evaluate suspected retrosternal goiter. Pre-operative whole-body scintigraphy using 131I 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: Strong  
Certainty of evidence: Low to Moderate

AAES 2020 and the ATA 2015 enumerated indications for evaluating vocal fold function preoperatively with low to moderate qualities of evidences.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 endarterectomy, 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.\textsuperscript{12} Hence, it may then be necessary to perform other examinations aside from voice assessment to identify these patients.\textsuperscript{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. 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)?

- We recommend total thyroidectomy for all Category V and VI unifocal nodules measuring >1 cm.
  
  **Strength of recommendation: Strong**  
  **Certainty of evidence: Moderate**

- 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: Strong**  
  **Certainty of evidence: Moderate**

The basic goals of initial therapy for patients with DTC are the improvement of overall survival (OS) and disease-specific survival (DSS); 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:

- To remove the primary tumor, disease that has extended beyond the thyroid capsule, and clinically significant lymph node metastases (LNM).
- To minimize the risk of disease recurrence and metastatic spread. Adequate surgery is the most important treatment variable influencing prognosis.
- To facilitate postoperative treatment with radioiodine (RAI), where appropriate.
- To permit accurate staging and risk stratification of the disease.
- To permit accurate long-term surveillance for disease recurrence.
- 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. 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. 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%. 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>
<thead>
<tr>
<th>Name of procedure</th>
<th>Extent of resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobectomy</td>
<td>One entire thyroid lobe without isthmus</td>
</tr>
<tr>
<td>Lobectomy and isthmusectomy</td>
<td>One entire thyroid lobe with isthmus and pyramidal lobe</td>
</tr>
<tr>
<td>Isthmusectomy</td>
<td>Isolated isthmus resection</td>
</tr>
<tr>
<td>Subtotal thyroidectomy</td>
<td>Preservation of small posterior remnant(s) of the contralateral or bilateral lobe(s) (Rarely recommended today)</td>
</tr>
<tr>
<td>Near-total thyroidectomy</td>
<td>Resection of all but a very small posterior remnant, i.e., at the ligament of Berry</td>
</tr>
<tr>
<td>Total thyroidectomy</td>
<td>All visible thyroid tissue</td>
</tr>
<tr>
<td>Completion thyroidectomy</td>
<td>Reoperative resection of any remaining thyroid tissue</td>
</tr>
</tbody>
</table>

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:** Strong | **Certainty of evidence:** High |
| b | We recommend therapeutic central neck dissection (Level VI) if there are lymph node metastases in the central compartment. |
|   | **Strength of recommendation:** Strong | **Certainty of evidence:** 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:** Strong | **Certainty of evidence:** 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 OS 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.

<table>
<thead>
<tr>
<th>Level</th>
<th>Anatomic Boundaries</th>
<th>Likelihood of LNM</th>
</tr>
</thead>
</table>
| 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 superfully  
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.\textsuperscript{11}
A anterior, I inferior, 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. 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. 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: internal jugular vein (IJV), the spinal accessory nerve (CN XI), and the sternocleidomastoid (SCM). Radical neck dissection (RND) 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 (MRND) entails removal of Level I–V lymph node groups with preservation of one or more of the following non-lymphatic structures: IJV, CN XI, SCM. A compartment-oriented selective neck dissection (SND) involves removal of less than all five lymph node basins with preservation of the IJV, CN XI, and SCM, and it is the most commonly applied type of therapeutic lymph node resection for thyroid cancer. It should be reported to indicate the laterality and nodal levels removed.

In SND for PTC, Levels IIa, III, IV, and Vb are included (Table 8). To avoid injury to CN XI, 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 SND. Prophylactic lateral node dissection has not been shown to improve PTC survival or recurrence rates; thus, SND is typically performed only for clinically evident disease. Clearance of Levels II–V is associated with a lower risk of recurrence.

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

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>We recommend total thyroidectomy ± neck dissection for patients with DTC even with distant metastasis.</td>
</tr>
<tr>
<td></td>
<td>Strength of recommendation: Strong  Certainty of evidence: Moderate</td>
</tr>
<tr>
<td>b</td>
<td>We recommend surgical excision for resectable metastatic disease without adverse functional outcome in selected patients.</td>
</tr>
<tr>
<td></td>
<td>Strength of recommendation: Strong  Certainty of evidence: Moderate</td>
</tr>
</tbody>
</table>

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. Since most metastatic WDTC are considered as oligomestasis, 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?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
</table>
| a | We recommend at least an overnight observation for patients at high risk for postoperative hematoma, when clinically appropriate.  
**Strength of recommendation:** Strong  
**Certainty of evidence:** 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:** Strong  
**Certainty of evidence:** 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:** Strong  
**Certainty of evidence:** 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:** Strong  
**Certainty of evidence:** Moderate |
| e | We recommend formal laryngeal evaluation for patients with dyspnea and/or stridor, aspiration, dysphagia, and hoarseness.  
**Strength of recommendation:** Strong  
**Certainty of evidence:** 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: Moderate | Certainty of evidence: 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. 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. 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.

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. 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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age &lt;55 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Any tumor size</td>
<td>Any lymph node status</td>
<td>Absence of distant metastases (M0)</td>
</tr>
<tr>
<td>II</td>
<td>Any tumor size</td>
<td>Any lymph node status</td>
<td>Presence of distant metastases (M1)</td>
</tr>
<tr>
<td></td>
<td>Age ≥55 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Tumor of ≤4 cm limited to the thyroid (T2)</td>
<td>Absence of LNM (Nx/N0)</td>
<td>Absence of distant metastases (M0)</td>
</tr>
<tr>
<td>II</td>
<td>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)</td>
<td>Any lymph node status</td>
<td>Absence of distant metastases (M0)</td>
</tr>
<tr>
<td>III</td>
<td>Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve (T4a)</td>
<td>Any lymph node status</td>
<td>Absence of distant metastases (M0)</td>
</tr>
<tr>
<td>IVa</td>
<td>Gross extrathyroidal extension invading prevertebral fascia or encasing the carotid artery or mediastinal vessels (T4b)</td>
<td>Any lymph node status</td>
<td>Absence of distant metastases (M0)</td>
</tr>
<tr>
<td>IVb</td>
<td>Any tumor size</td>
<td>Any lymph node status</td>
<td>Presence of distant metastases (M1)</td>
</tr>
</tbody>
</table>

From Lamartina et al.\textsuperscript{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.

<table>
<thead>
<tr>
<th>Strength of recommendation:</th>
<th>Certainty of evidence: Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td></td>
</tr>
</tbody>
</table>

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

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;
No local study is available for reference; hence, further observational study is recommended.

**Table 10. 2015 ATA risk stratification system.**

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

| 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 $\text{BRAF}^{\text{V600E}}$ 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 $\geq$3 cm in largest dimension |   |   |
| Follicular thyroid cancer with extensive vascular invasion ($>4$ foci of vascular invasion) |   |   |

From Haugen et al.\textsuperscript{12}
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:** Strong  
  - **Certainty of evidence:** 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:** Strong  
  - **Certainty of evidence:** 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. 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. This should be done 3–4 weeks postoperatively, which is when postoperative Tg is at its lowest for nearly all patients. TgAb should be measured at least once to be used in ascertaining the reliability of the measured serum Tg.

Routine postoperative diagnostic whole-body scan (WBS) with $^{131}$I is not recommended as problems with detection sensitivity and post-imaging stunning may arise. However, these may be prevented by the use of low-activity $^{131}$I (about 1–3 mCi) or alternative isotopes such as $^{123}$I. 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?

<p>| | |</p>
<table>
<thead>
<tr>
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</table>
| **a** | We recommend routine RAI adjuvant therapy after total thyroidectomy for ATA high risk DTC patients.  
Strength of recommendation: Strong  
Certainty of evidence: Moderate |
| **b** | We recommend RAI adjuvant therapy after total thyroidectomy in ATA intermediate-risk level DTC patients.  
Strength of recommendation: Strong  
Certainty of evidence: Low |
| **c** | We do not recommend routine RAI remnant ablation after thyroidectomy for ATA low-risk DTC patients.  
Strength of recommendation: Strong  
Certainty of evidence: 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: Strong  
Certainty of evidence: 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: Moderate  
Certainty of evidence: 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. A local study by Espiritu et al. observed an increasing trend in the incidence of \( \text{BRAF} \ V600E \) mutation among patients with PTC, which is associated with a more aggressive type of PTC. The local incidence rate of \( \text{BRAF} \ V600E \) 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 \(^{131}\text{I} \) 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).
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. Evidence has shown that radiotherapy (RT) and chemotherapy could increase the risk for secondary primary malignancy (SPM). In a meta-analysis of two multi-centric studies, patients who underwent RAI therapy had a 1.19 times greater risk of developing SPM compared to patients who did not undergo RAI therapy. Thyroid cancer survivors treated with RAI also had a higher risk for leukemia.

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

Prior to RAIA, TSH stimulation must be done until serum TSH levels reach a minimum of 30 µIU/ml. 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. A cheaper alternative to rhTSH is the use of T3 (Tertoxine or Cytomel) which can be 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?

All patients who had RAIA should have a post-therapy WBS with I within 3–7 days of RAIA. 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: Strong  
  Certainty of evidence: Moderate

- **b** We suggest initial TSH suppression to 0.1–0.5 mU/L for intermediate-risk DTC patients.
  
  Strength of recommendation: Strong  
  Certainty of evidence: 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: Strong  
  Certainty of evidence: 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), and decreased likelihood of disease progression compared to patients with lesser degree of TSH suppression (p=0.03). OS 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). This also extends to NTCTCSG Stage II classification where those with a mean TSH score of 1.0–2.99 had better OS 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. DSS 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:

- 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
- 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 (DFS) rates (89% vs. 91%, p=0.39). 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 131I. 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). At different stages of thyroid cancer, there was an improvement in OS (RR stages I-IV: 0.13, 0.09, 0.13, 0.33) and DFS (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. Thus, the ATA 2015 suggested relaxing TSH targets may be considered for those with tachycardia, osteopenia, age older than 60, osteoporosis and atrial fibrillation.

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 or even excluded. 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 DFS regardless of TSH levels (p=0.63).

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: Strong    Certainty of evidence: 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: Strong    Certainty of evidence: 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\textsuperscript{12,54,55,85}
- inadequate RAI uptake\textsuperscript{12,54,85}
- extranodal extension or involvement of soft tissues\textsuperscript{12,85}
- tumors threatening vital structures\textsuperscript{11,85}
- rapid progression\textsuperscript{85}
- locally advanced disease\textsuperscript{12,54}
- older patients with extensive extrathyroidal extension\textsuperscript{12,54}
- tumors undergoing multiple and frequent serial reoperations for locoregionally recurrent disease\textsuperscript{12}

Two guidelines mentioned that EBRT should be considered for patients above age 60 with extensive thyroidal extension.\textsuperscript{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.\textsuperscript{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?

\textbf{a} We recommend post-operative EBRT with systemic therapy for resectable, non-metastatic, good performance status patients desirous of aggressive treatment.  
\hspace{1cm} Strength of recommendation: Strong \hspace{1cm} Certainty of evidence: Low

\textbf{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.  
\hspace{1cm} Strength of recommendation: Strong \hspace{1cm} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.  
\textbf{Strength of recommendation: Strong} \hspace{1cm} \textbf{Certainty of evidence: 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.\textsuperscript{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.  
\textbf{Strength of recommendation: Strong} \hspace{1cm} \textbf{Certainty of evidence: Low}

For patients who present with resectable tumors, we suggest complete resection followed by combined chemotherapy and RT.\textsuperscript{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/m²) 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/m²) and doxorubicin (60 mg/m²), 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/m²) 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: Strong  Certainty of evidence: 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: Strong  
Certainty of evidence: 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.
**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: Strong  Certainty of evidence: 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:

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*Figure 4. Initial treatment of stages IVA and IVB anaplastic thyroid cancer. From Bible et al. 87 Additional 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.*
- 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.

<table>
<thead>
<tr>
<th>Responses to treatment</th>
<th>Total thyroidectomy + radioactive iodine remnant ablation</th>
<th>Total thyroidectomy alone</th>
<th>Lobectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent response</td>
<td>No clinical evidence of tumor and</td>
<td>No clinical evidence of tumor</td>
<td>No clinical evidence of tumor</td>
</tr>
<tr>
<td></td>
<td>Negative imaging and Undetectable Tg antibody and unstimulated Tg &lt;0.2 ng/mL or stimulated Tg &lt;1 ng/mL</td>
<td>and Negative imaging and Undetectable Tg antibody and unstimulated Tg &lt;0.2 ng/mL or stimulated Tg &lt;2 ng/mL</td>
<td>and Negative imaging and Stable Tg levels and undetectable TgAb</td>
</tr>
<tr>
<td>Biochemical incomplete response</td>
<td>No clinical evidence of tumor and</td>
<td>No clinical evidence of tumor</td>
<td>No clinical evidence of tumor</td>
</tr>
<tr>
<td></td>
<td>Negative imaging and Unstimulated Tg &gt;1 ng/mL or stimulated Tg &gt;10 ng/mL or rising TgAb levels</td>
<td>and Negative imaging and Unstimulated Tg &gt;5 ng/mL or stimulated Tg &gt;10 ng/mL or rising TgAb levels</td>
<td>and Negative imaging and Unstimulated Tg &gt;30 ng/mL or rising Tg values with similar TSH levels or rising TgAb</td>
</tr>
<tr>
<td>Structural incomplete response</td>
<td>Clinical or imaging evidence of disease (regardless of Tg and TgAb levels)</td>
<td>Clinical or imaging evidence of disease (regardless of Tg and TgAb levels)</td>
<td>Clinical or imaging evidence of disease (regardless of Tg and TgAb levels)</td>
</tr>
<tr>
<td>Indeterminate response</td>
<td>Nonspecific imaging findings or</td>
<td>Nonspecific imaging findings or</td>
<td>Nonspecific imaging findings or</td>
</tr>
<tr>
<td></td>
<td>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.</td>
<td>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.</td>
<td>Unstimulated TgAb levels stable or declining in the absence of structural or functional disease.</td>
</tr>
</tbody>
</table>

Adapted from Momesso DP & Tuttle RM91; 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: Strong  Certainty of evidence: Moderate

b We recommend using Tg and TgAb assays that are calibrated with a reference standard.
   Strength of recommendation: Strong  Certainty of evidence: 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: Strong  Certainty of evidence: 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: Strong  Certainty of evidence: 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: Strong  Certainty of evidence: 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: Strong  Certainty of evidence: Moderate

g We recommend that neck US should be performed at a 6- to 12-month interval depending on risk assessment.
   Strength of recommendation: Strong  Certainty of evidence: 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](image-url)
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. 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. 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. 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.

<table>
<thead>
<tr>
<th></th>
<th>Stimulated Tg (thyroid hormone withdrawal)</th>
<th>Stimulated Tg (rTSH stimulation)</th>
<th>Unstimulated Tg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>96%</td>
<td>93%</td>
<td>78%</td>
</tr>
<tr>
<td>Specificity</td>
<td>95%</td>
<td>88%</td>
<td>98%</td>
</tr>
</tbody>
</table>

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. 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. 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.

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. 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.

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
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. 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.

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). 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.

<table>
<thead>
<tr>
<th>Risk of Recurrence</th>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tg (with TgAb)</td>
<td>Within 6 months</td>
<td>At 6-12 month</td>
<td>If Tg elevated or high clinical suspicion</td>
</tr>
<tr>
<td>Neck US</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>If Tg elevated or high clinical suspicion</td>
</tr>
<tr>
<td>CT or MRI</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>If Tg &gt;10 ng/mL</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>If Tg &gt;10 ng/mL</td>
</tr>
</tbody>
</table>

Data from Haugen BR, Alexander EK, Bible KC, et al.12; Filetti S, Durante C, Hartl D, et al.43; and Tuttle RM104

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

* 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. 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. 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 \(^{a,b}\).

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

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?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
</table>
| **a** | We recommend periodic neck US depending on the patient’s risk for recurrent disease and Tg status.  
   **Strength of recommendation:** Strong  
   **Certainty of evidence:** Moderate |
| **b** | We recommend US-guided FNAB for ultrasonographically suspicious lymph nodes >10 mm in widest dimension.  
   **Strength of recommendation:** Strong  
   **Certainty of evidence:** 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:** Strong  
   **Certainty of evidence:** Low |
| **d** | We recommend FDG-PET scanning in high-risk DTC patients with elevated serum Tg and with negative RAI imaging.  
   **Strength of recommendation:** Strong  
   **Certainty of evidence:** 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:** Strong  
   **Certainty of evidence:** 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:** Strong  
   **Certainty of evidence:** 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.\textsuperscript{39,106}

A WBS with \textsuperscript{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, \textsuperscript{123}I is preferred, but it is not readily available locally.

\textsuperscript{18}F-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-\textsuperscript{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). \textsuperscript{18}F-FDG PET/CT is correlated with poor survival and is a negative predictor for response to RAI treatment. It is complementary to \textsuperscript{131}I WBS (in the presence of detectable \textsuperscript{131}I uptake), because F-18 uptake may be present in neoplastic foci with no \textsuperscript{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, \textsuperscript{18}F-FDG PET/CT is more sensitive for retropharyngeal or retroclavicular metastases. Some studies show that TSH stimulation may increase sensitivity of \textsuperscript{18}F-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.\textsuperscript{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 \textsuperscript{18}F-FDG PET/CT or CT and MRI should be the first-line imaging of choice for metastatic DTC.\textsuperscript{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: Strong   Certainty of evidence: 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: Strong   Certainty of evidence: Low

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

   Strength of recommendation: Strong   Certainty of evidence: High

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

   Strength of recommendation: Strong   Certainty of evidence: 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. 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: Strong    Certainty of evidence: 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. 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.

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: Strong    Certainty of evidence: 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{110}. Best supportive care may be offered to patients with poor prognosis or poor performance status.\textsuperscript{12}

6.3.2 What is the role of radiotherapy in bleeding tumors?

<table>
<thead>
<tr>
<th>We can consider palliative RT to patients with bleeding tumors not amenable to surgery or other treatments.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strength of recommendation:</strong> Strong  <strong>Certainty of evidence:</strong> Moderate</td>
</tr>
</tbody>
</table>

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.\textsuperscript{86,111}

6.3.3 What is the role of radiotherapy in brain metastasis?

<table>
<thead>
<tr>
<th>We recommend EBRT to patients who develop brain metastasis.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strength of recommendation:</strong> Strong  <strong>Certainty of evidence:</strong> Moderate</td>
</tr>
</tbody>
</table>

The main management for brain metastasis from thyroid cancers is neurological resection and EBRT.\textsuperscript{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.\textsuperscript{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 whole brain radiation (HA-WBRT), and focal radiation in the form of stereotactic radiosurgery (SRS) and HFSRT. The choice between SRS, HFSRT, HA-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.\textsuperscript{115-118} There is also emerging data showing comparable survival in patients with limited versus multiple (≥5) brain metastasis treated with SRS alone.\textsuperscript{119,120} In patients who are not candidates for SRT but require RT, HA-WBRT provides better cognitive outcomes compared to conventional WBRT. The addition of memantine to WBRT lessens the neurocognitive toxicity associated with the conventional method.\textsuperscript{121-123}

Best supportive care alone may be considered in older patients with short life expectancy and poor performance status.\textsuperscript{124}

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

<table>
<thead>
<tr>
<th>Case</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| 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.  
  \textbf{Strength of recommendation: Strong} \textbf{Certainty of evidence: 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.  
  \textbf{Strength of recommendation: Strong} \textbf{Certainty of evidence: 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 (ORR) was 64.8% for lenvatinib while it was 1.5% for placebo. The median OS was not reached in either group, but a preplanned analysis demonstrated that among patients older than 65 years, lenvatinib had a significantly longer OS 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 ORR was 12.2% for sorafenib versus 0.5% with placebo. Median OS 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.

<table>
<thead>
<tr>
<th>Kinase inhibitor</th>
<th>Trial</th>
<th>Median PFS (vs. comparator)</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenvatinib</td>
<td>Phase III (SELECT)</td>
<td>HR 0.21; 99% CI 0.14–0.31</td>
<td>64.8%</td>
</tr>
<tr>
<td></td>
<td>18.3 months (vs. 3.6 months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Phase III (DECISION)</td>
<td>HR 0.59; 95% CI 0.45–0.76</td>
<td>12.2%</td>
</tr>
<tr>
<td></td>
<td>10.8 months (vs. 5.8 months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vandetanib</td>
<td>Phase II</td>
<td>11.1 months</td>
<td>-</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>Phase II</td>
<td>11.7 months</td>
<td>49%</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Phase II</td>
<td>13.1 months</td>
<td>22%</td>
</tr>
<tr>
<td>Axitinib</td>
<td>Phase II</td>
<td>16.1 months</td>
<td>35%</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>Phase III (COSMIC-311)</td>
<td>11.0 months (after progression on lenvatinib or sorafenib)</td>
<td>18%</td>
</tr>
</tbody>
</table>

CI confidence interval; HR hazard ratio; ORR overall response rate; PFS progression-free survival

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.\textsuperscript{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?

<p>| | |</p>
<table>
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</table>
| 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: Strong  
   Certainty of evidence: Low |
| b | In low-resource settings, we do not recommend the use cytotoxic chemotherapy for brain metastases.  
   Strength of recommendation: Strong  
   Certainty of evidence: 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.\textsuperscript{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: Strong  
   | Certainty of evidence: 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: Strong  
   | Certainty of evidence: 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: Strong  
   | Certainty of evidence: 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

Additional 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?

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</table>
| a | We recommend the use of the WHO 3-Step Ladder Approach to pain management across stages of thyroid cancer.  
   Strength of recommendation: Strong  
   Certainty of evidence: Moderate |
| b | We recommend a non-opioid analgesic combined with adjuvant drugs for thyroid cancer patients with mild cancer-related pain.  
   Strength of recommendation: Strong  
   Certainty of evidence: Moderate |
| c | For patients with moderate to severe pain, we recommend a trial of a strong opioid.  
   Strength of recommendation: Moderate  
   Certainty of evidence: 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: Strong  
   Certainty of evidence: 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: Strong  
   Certainty of evidence: 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: Strong  
   Certainty of evidence: Low |

The use of analgesic medications is the mainstay of cancer pain management. 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. 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 WHO139
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
   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

MONITORING AND EVALUATION
Dissemination

The recommendations of the Thyroid Cancer CPG may be presented by any member of the SC and TWG in the various conferences of the organizations which participated in its development. The SC will look for a suitable journal where the DOH-approved Thyroid Cancer CPG can be published.

Implementation

Once approved by the DOH CPG clearing house, a department order may be issued to introduce the Thyroid Cancer CPG to the different DOH hospitals for implementation. Likewise, the various organizations which contributed to the development of the Thyroid Cancer CPG may cascade the recommendations and endorse these for implementation in their respective healthcare units. The SC will be responsible in monitoring the implementation of the CPG and compliance of the stakeholders. This may be done through an annual survey.

Updating of the guidelines

This Thyroid Cancer CPG will undergo regular review to incorporate any new evidence which may affect the recommendations. This will be updated every three years.
CHAPTER 6
AUTHORSHIP, CONTRIBUTIONS, ACKNOWLEDGEMENT
This project would not have been possible without the initiative and funding from the DOH. The DOH neither imposed any condition nor exerted any influence in formulating the final recommendations.

**Steering Committee.** The steering committee 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 Steering committee will also be responsible in monitoring the implementation and compliance of clinicians with the CPG.

Dr. Ida Marie T. Lim, Dr. Wenceslao Llauderes, Dr. Bien J. Matawaran, Dr. Alfred Philip O. de Dios, Dr. Christine Susean S. Sagpao, Dr. Cristina S. Nieves, Dr. Maria Cheryl L. Cucueco, and Dr. Rodney B. Dofitas

**Technical Working Group.** JRRMMC 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.

Dr. Jose Modesto III B. Abellera, Dr. Orlino C. Bisquera, Jr., Dr. Angela P. Camacho, Dr. Elaine C. Cunanan, Dr. Neresito T. Espiritu, Dr. Francis Gerard M. Estrada, Dr. Adrian F. Fernando, Dr. Mark David D.G. Francisco, Dr. Mary Ondinee M. Igot, Dr. Joy Grace G. Jerusalem, Dr. Milabelle B. Lingan, Dr. Joshua A. Marcos, Dr. Marwin Emerson V. Matic, Dr. Erick S. Mendoza, Dr. Cherry Lyn V. Montealto, Dr. Nemencio A. Nicodemus, Jr., Dr. Arnel E. Pauco, Dr. Esther A. Saguil, Dr. Kenneth G. Samala, Dr. Jeanelle Margareth T. Tang, Dr. Gemma Leonora B. Uy, Dr. Cesar Vincent L. Villafuerte III, and Dr. Rowen T. Yolo

**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:

Dr. Christine Joy S. Arquiza, Dr. Solidad L. Balete, Dr. Emerita A. Barrenechea, Dr. Jose Ravelo T. Bartolome, Dr. Arsenio Claro A. Cabungcal, Dr. Clarito U. Cairo, Jr., Dr. Johanna Patricia A. Cañal, Dr. Jose M. Carnate, Jr., Dr. Ann Margaret V. Chang, Ms. Emily Dizon-Nacpil, Dr. Jeffrey J.P. Domino, Dr. Ramon S. Inso, Dr. Cecilia A. Jimeno, Dr. Sjoberg A. Kho, Dr. Fernando Lopez, Dr. Jeanette Marie S. Matsuo, Dr. Michael Benedict A. Mejia, Dr. Ruben V. Ogbac, Dr. Lino Santiago S. Pabillo, Dr. Jhade Lotus Peneyra, Dr. Jocelyn C. Que, Dr. Jeremyjones F. Robles,
Dr. Teofilo O.L. San Luis, Dr. Roberto A. Sarmiento, Dr. Maria Lilybeth R. Tanchoco, and Ms. Erdaine Stiffany M. Tangco

This project would not have been successful without the leadership and guidance of Dr. Emmanuel F. Montaña Jr., the Medical Center Chief II of Jose R. Reyes Memorial Medical Center. The developers of this guideline would also like to give special thanks to Dr. Leonila F. Dans for giving the orientation on the CPG development process and Ms. Isabel Teresa O. Salido for drafting the final manuscript.
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APPENDIX 1. DECLARATION OF CONFLICTS OF INTEREST

Steering Committee

Dr. Ida Marie T. Lim

Dr. Wenceslao S. Llauderes

Dr. Bien J. Matawaran

Dr. Alfred Phillip O. de Dios

Dr. Christine Susean S. Sagpao

Dr. Cristina S. Nieves

Dr. Maria Cheryl L. Cucueco

Dr. Rodney B. Dofitas
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<tr>
<td>Dr. Ida Marie T. Lim</td>
<td>Philippine College of Surgeons&lt;br&gt;Philippine Society of General Surgery&lt;br&gt;Philippine Academy for Head and Neck Surgery, Inc&lt;br&gt;Philippine Thyroid Association</td>
<td>None declared</td>
</tr>
<tr>
<td>Dr. Wenceslao S. Llauderes</td>
<td>• Philippine Thyroid Association&lt;br&gt;• Philippine Society of Nuclear Medicine</td>
<td>None declared</td>
</tr>
<tr>
<td>Dr. Maria Cheryl L. Cucueco</td>
<td>Philippine Society of General Surgery</td>
<td>None declared</td>
</tr>
<tr>
<td>Dr. Alfred Phillip O. de Dios</td>
<td>Philippine Society of General Surgery&lt;br&gt;Philippine Society of Ultrasound in Surgery</td>
<td>None declared</td>
</tr>
<tr>
<td>Dr. Rodney B. Dofitas</td>
<td>Philippine College of Surgeons (Committee on Research)</td>
<td>None declared</td>
</tr>
<tr>
<td>Dr. Bien J. Matawaran</td>
<td>• Philippine Thyroid Association&lt;br&gt;• Philippine Society of Endocrinology Diabetes and Metabolism</td>
<td>None declared</td>
</tr>
<tr>
<td>Dr. Cristina S. Nieves</td>
<td>Philippine Society of Otolaryngology-Head and Neck Surgery</td>
<td>None declared</td>
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<tr>
<td>Dr. Christine Susean S. Sagpao</td>
<td>Philippine Radiation Oncology Society</td>
<td>None declared</td>
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Consensus Panel

Dr. Christine Joy S. Arquiza  
Dr. Solidad L. Balete  
Dr. Emerita A. Barrenechea

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Dr. Clarito U. Cairo, Jr.

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<td>Philippine Society of Medical Oncology</td>
<td>None declared</td>
</tr>
<tr>
<td>Dr. Emerita A. Barrenechea</td>
<td>Philippine Society of Nuclear Medicine</td>
<td>Visiting consultant&lt;br&gt;• St. Luke’s Medical Center – 2021 to present&lt;br&gt;Personal advocacies:&lt;br&gt;• Multidisciplinary management for cancer patients&lt;br&gt;• Head and neck cancer awareness and prevention</td>
</tr>
<tr>
<td>Dr. Jose Ravelo T. Bartolome</td>
<td>• Philippine Society of General Surgery&lt;br&gt;• Philippine College of Surgeons&lt;br&gt;• Philippine Academy of Head and Neck Surgeons, Inc.&lt;br&gt;• Surgical Oncology Society of the Philippines</td>
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<td>Philippine Society of Otolaryngology-Head and Neck Surgery</td>
<td>None declared</td>
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<tr>
<td>Dr. Clarito U. Cairo, Jr.</td>
<td>Department of Health</td>
<td>None declared</td>
</tr>
<tr>
<td>Dr. Johanna Patricia A. Cañal</td>
<td>Philippine Radiation Oncology Society</td>
<td>None declared</td>
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<td>Dr. Jose M. Carnate, Jr.</td>
<td>Philippine Society of Pathologists, Inc.</td>
<td>None declared</td>
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<tr>
<td>Dr. Ann Margaret V. Chang</td>
<td>Philippine Society of Pathologists, Inc.</td>
<td>None declared</td>
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<tr>
<td>Dr. Emily Rose M. Dizon-Nacpil</td>
<td>N/A</td>
<td>None declared</td>
</tr>
<tr>
<td>Dr. Jeffrey J.P. Domino</td>
<td>• Philippine Society of General Surgery&lt;br&gt;• Philippine College of Surgeons&lt;br&gt;• Philippine Academy of Head and Neck Surgeons, Inc.&lt;br&gt;• Surgical Oncology Society of the Philippines</td>
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| Dr. Ramon S. Inso             | • Philippine Society of General Surgery  
                              | • Philippine College of Surgeons  
                              | • Philippine Academy of Head and Neck Surgeons, Inc.  
                              | • Surgical Oncology Society of the Philippines                                        | None declared                                                                       |
| Dr. Cecilia A. Jimeno        | • Philippine Thyroid Association  
                              | • Philippine Society of Endocrinology Diabetes and Metabolism                          | None declared                                                                       |
| Dr. Sjoberg A. Kho           | • Philippine Thyroid Association  
                              | • Philippine Society of Endocrinology Diabetes and Metabolism                          | None declared                                                                       |
| Dr. Fernando Lopez           | • Philippine Society of General Surgery  
                              | • Philippine College of Surgeons  
                              | • Philippine Academy of Head and Neck Surgeons, Inc.  
                              | • Surgical Oncology Society of the Philippines                                        | Speaker:  
                              | • Servier (MPFF; phlebotonic) – monthly (PHP 10,000.00)                              | |
| Dr. Jeanette Marie S. Matsuo | Philippine Society of Otolaryngology-Head and Neck Surgery                | None declared                                                                       |
| Dr. Michael Benedict A. Mejia| Philippine Radiation Oncology Society                                     | 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                                      | None declared                                                                       |
| Dr. Lino Santiago S. Pabillo | • Philippine College of Radiology  
<pre><code>                          | • Ultrasound Society of the Philippines                                              | None declared                                                                       |
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<td>Dr. Jocelyn C. Que</td>
<td>Philippine Society of Anesthesiologists</td>
<td>None declared</td>
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<tr>
<td>Dr. Jeremyjones F. Robles</td>
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<td>Research support:</td>
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<td>Iodine Global Network</td>
<td>Personal advocacy:</td>
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<td></td>
<td></td>
<td>• National Coordinator, Iodine Global Network</td>
</tr>
<tr>
<td>Dr. Roberto A. Sarmiento</td>
<td>• Philippine Society of General Surgery</td>
<td>None declared</td>
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<td>Philippine Society of Anesthesiologists</td>
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<td>• Menarini (pain management) – 2019 to present</td>
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Evidence Reviewers

Dr. Jose Modesto III B. Abellera
Dr. Orlino C. Bisquera, Jr.
Dr. Angela P. Camacho

Dr. Elaine C. Cunanan
Dr. Neresito T. Espiritu
Dr. Francis Gerard M. Estrada

Dr. Adrian F. Fernando
Dr. Mark David D.G. Francisco
Dr. Mary Ondinee M. Igot
Dr. Kenneth G. Samala

Dr. Jeanelle Margareth T. Tang

Dr. Cesar Vincent L. Villafuerte III

Dr. Gemma Leonora B. Uy

Dr. Rowen T. Yolo
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<td>Dr. Jose Modesto III B. Abellera</td>
<td>Philippine College of Surgeons (Committee on Research)</td>
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<tr>
<td>Dr. Orlino C. Bisquera, Jr.</td>
<td>Philippine Society of Ultrasound in Surgery</td>
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<td>Dr. Angela P. Camacho</td>
<td>Philippine Radiation Oncology Society</td>
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<td>Dr. Elaine C. Cunanan</td>
<td>- Philippine Thyroid Association</td>
<td>Speaker:</td>
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<td>- Philippine Society of Endocrinology Diabetes and Metabolism</td>
<td>Merck (levothyroxine) – March 2021</td>
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<td>Dr. Neresito T. Espiritu</td>
<td>Philippine Society of General Surgery</td>
<td>None declared</td>
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<tr>
<td>Dr. Francis Gerard M. Estrada</td>
<td>- Philippine Thyroid Association</td>
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<td>- Philippine Society of Nuclear Medicine</td>
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<td>Dr. Adrian F. Fernando</td>
<td>Philippine Society of Otolaryngology-Head and Neck Surgery</td>
<td>Gifts, non-research grant, sponsorships, or rewards:</td>
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<td>Dr. Mark David D.G. Francisco</td>
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<td>Dr. Mary Ondinee M. Igot</td>
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<td>Dr. Joshua A. Marcos</td>
<td>- Philippine Academy of Family Physicians</td>
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<td>Dr. Erick S. Mendoza</td>
<td>- Philippine Thyroid Association</td>
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<td>Dr. Cherry Lyn V. Montealto</td>
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| Dr. Nemencio A. Nicodemus, Jr.   | • Philippine Thyroid Association  
                                  | • Philippine Society of Endocrinology Diabetes and Metabolism              | None declared         |
| Dr. Arnel E. Pauco               | • Philippine Thyroid Association  
                                  | • Philippine Society of Nuclear Medicine                                  | None declared         |
| Dr. Esther A. Saguil             | Philippine College of Surgeons (Committee on Research)                    | None declared         |
| Dr. Kenneth G. Samala            | Philippine Society of Medical Oncology                                    | None declared         |
| Dr. Jeanelle Margareth T. Tang   | • Philippine Thyroid Association  
                                  | • Philippine Society of Nuclear Medicine                                  | None declared         |
| Dr. Cesar Vincent L. Villafuerte III | Philippine Radiation Oncology Society                                | None declared         |
| Dr. Gemma Leonora B. Uy          | Philippine College of Surgeons (Committee on Research)                    | None declared         |
| Dr. Rowen T. Yolo                | Philippine Society of Pathologists, Inc.                                  | None declared         |
APPENDIX 2. 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 3. 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)*


Fernando L. Lopez, M.D., F.P.C.S and Nilo C. De los Santos, M.D., F.P.C.S. for the Philippine Society of General Surgeons


The Philippine College of Surgeons (PCS) through its Committee on Surgical Research, in cooperation with the Philippine Society of General Surgeons (PSGS) and the Philippine Academy of Head and Neck Surgery, Inc. (PAHNSI) published the Evidence-based Clinical Practice Guideline on Thyroid Nodules in 2008 (PJSS Vol 63 No. 3). This guideline covers the comprehensive management of thyroid nodules -both benign and malignant. After five years, the PCS through its Committee on Cancer and Committee on Surgical Research, again in cooperation with the PAHNSI and the PSGS worked on updating its guidelines particularly those pertaining to the management of thyroid cancer, which is among the top ten cancers in the Philippines. This update focuses on the diagnostic and therapeutic aspects of the management of well-differentiated thyroid cancer including postoperative surveillance. It is based on the most recent available scientific evidence and the views of local experts. It is intended to guide surgeons (fellows, resident trainees) and general physicians involved in the management of thyroid cancer and practicing in the Philippines.

This project was funded solely by the PCS Foundation. The Technical Working Group (TWG), composed of fellows from the PCS, PAHNSI and PSGS was formed last May 2012.

Technical Working Group:

For PAHNSI:
Alfred Philip O. de Dios, MD
Arlene T. Fajardo, MD
Marwin Emerson V. Matic, MD
Ida Marie Tabangay-Lim, MD

For PCS:
Ma. Luisa D. Aquino, MD
Jose Modesto B. Abellera III, MD
Cheryl L. Cucueco, MD
Leonardo O. Ona III, MD

For PSGS:
Fernando L. Lopez, MD
Nilo C. de los Santos, MD

* Taken from the Philippine Journal of Surgical Specialties, Vol. 68, No. 1, January-March, 2013
The research questions from the 2008 guidelines were reviewed and modified as needed, focusing on well-differentiated thyroid cancer. Important new issues to update the working list of research questions were discussed and developed by the members of the TWG and the PCS Committee on Surgical Research. These include the role of thyroid ultrasound in detecting malignancy and the role of central node dissection in the management of well-differentiated thyroid cancer.

The search of the available literature included publications from 2007 onwards using the same electronic database used in the 2008 PCS EBCPG: Pubmed(Medline) plus Cochrane database and manual search of the following libraries: UST, UP and De La Salle Health Sciences. The search was guided by the clinical research questions using MESH terms as applicable. All existing clinical practice guidelines on thyroid cancer were likewise searched, and the references used in these guidelines were reviewed if applicable. A total number of 50 articles were used as reference for this update.

The evidences were appraised, and the initial draft of recommendations was prepared together with the PCS Committee on Surgical Research last October 13, 2012. The group agreed to apply the Levels of Evidence of the Oxford Centre for Evidence-Based Medicine, 2011 for the new recommendations. (See Appendix A)

The initial draft was presented to a multidisciplinary panel of experts and members of the PCS Board of Regents during the PCS Annual Clinical Congress on December 5, 2012, for some revisions, and for the strength of the recommendations.

The final draft was presented in a public forum during the Philippine Society of General Surgeons Annual Meeting on August 1, 2013 held at the SMX Convention Hall.

**Categories of Recommendations**

- **Category A** At least 75 percent consensus by expert panel present
- **Category B** Recommendation somewhat controversial and did not meet consensus
- **Category C** Recommendation caused real disagreements among members of the panel

**Members of the Expert Panel:**

1. Alejandro C. Dizon, MD
2. Jose Macario V. Faylona, MD
3. Ramon S. Inso, MD
4. George G. Lim, MD
5. Ramoncito C. Magnaye, MD
6. Maximo B. Nadala, MD
7. Enrico P. Ragaza, MD
8. Rhoel de Leon, MD
9. Mark R. Kho, MD
10. Daniel L. de la Paz, MD
11. Edgardo R. Cortez, MD
12. Rodney B. Dofitas, MD
13. Joselito F. David, MD
14. Juan P. Sanchez Jr., MD
15. Ray I. Sarmiento, MD
16. Jose Roberto V. Claridad, MD
17. Rowen Yolo, MD
18. Jonas Y. Santiago, MD
19. Sjoberg A. Kho, MD
20. Bien J. Matawaran, MD
21. Ruben L. Carreon, MD
22. Lino Santiago S. Pabillo, MD

**List of Clinical Questions:**

1. What is the appropriate diagnostic work-up in a patient with thyroid nodule?
   1.1 What is the role of thyroid function tests (TSH, T3, T4, FT4)?
   1.2 What is the role of ultrasonography?
      1.2.1 Who should undergo ultrasonography?
      1.2.2 What are the indications for doing ultrasound guided fine needle aspiration biopsy?
   1.3 What is the role of radioisotope scan?
   1.4 What is the role of fine needle biopsy (FNAC)?
   1.5 What is the role of frozen section in the intraoperative diagnosis of thyroid nodule?
2. What is the recommended treatment for well-differentiated thyroid cancer (WDTC)?
2.1 What is the recommended surgical procedure for the treatment of WDTC?
2.2 What is the role of central node dissection in the management of patients with well-differentiated thyroid cancer in improving overall and disease-free survival?
2.2.1 What is the role of therapeutic central node dissection?
2.2.2 What is the role of prophylactic central node dissection?
2.3 What is the role of radioactive iodine remnant ablation therapy in the treatment of WDTC?
2.4 What is the role of completion thyroidectomy in the treatment of WDTC?
2.5 What is the role of external beam radiation in the treatment of WDTC?
2.6 What is the role of TSH suppression therapy in the treatment of WDTC?

3. What is the recommended postoperative surveillance for patients with WDTC?
3.1 What is the role of thyroglobulin assay for postoperative surveillance in patients with WDTC?
3.2 What is the role of TSH for postoperative surveillance in patients with WDTC?
3.3 What is the role of ultrasonography for postoperative surveillance in patients with WDTC?
3.4 What is the role of whole body scan in the postoperative surveillance of patients with WDTC?

Recommendations with updated evidence:

1. What is the appropriate diagnostic work-up in a patient with thyroid nodule?
1.2 What is the role of ultrasonography in the diagnosis of thyroid nodule?
1.2.1 Who should undergo ultrasonography?
1.2.2 What are the indications for doing ultrasound-guided fine needle aspiration biopsy?

2. What is the recommended treatment for well-differentiated thyroid cancer?
2.1 What is the recommended surgical procedure for well-differentiated thyroid cancer?
2.2 What is the role of central node dissection in the management of patients with well-differentiated thyroid cancer in improving overall and disease-free survival?
2.2.1 What is the role of therapeutic central node dissection?
2.2.2 What is the role of prophylactic central compartment dissection?
2.3 What is the role of radioactive iodine remnant ablation therapy in the treatment of WDTC?
2.4 What is the role of TSH suppression therapy in the treatment of WDTC?
3. What is the recommended postoperative surveillance for patients with WDTC?
   3.1 What is the role of thyroglobulin assay in the postoperative surveillance of patients with WDTC?
   3.2 What is the role of TSH in the postoperative surveillance of patients with WDTC?

Recommendations

1. What is the appropriate diagnostic work-up in a patient with thyroid nodule?
   1.2 What is the role of ultrasonography in the diagnosis of thyroid nodule?
      1.2.1 Who should undergo ultrasonography?

Thyroid ultrasound is not recommended as a screening test for the general population.

It is recommended for the following:

1. Evaluation of the patient with nodular goiter.
2. Those with adenopathy suggestive of a malignant lesion.
3. Screening of High-risk patients (patients with history of familial thyroid cancer, previous diagnosis of MEN2, childhood cervical irradiation).

Level 5, Category B

Summary of Evidence

High-resolution ultrasound is the most sensitive test available to detect thyroid lesions, measure their dimensions accurately, identify their structure and evaluate diffuse changes in the thyroid gland. Ultrasound can identify thyroid nodules that have been missed on physical examination, isotope scanning and other imaging techniques. This study, however, should not be performed on an otherwise normal thyroid gland nor used as a substitute for a physical examination. The role of ultrasound as a screening test for thyroid nodules is limited. Due to the high prevalence of thyroid nodules and the high survival rate and good prognosis, the consensus made by the AACE is that a screening test for thyroid malignancy is not justified.

In all patients with palpable thyroid nodules or MNG, ultrasound should be performed to accomplish the following: help with the diagnosis in difficult cases (as in Hashimoto's thyroiditis), look for coincidental thyroid nodules, detect ultrasound features suggestive of malignant growth and select the lesions to be recommended for fine-needle aspiration (FNA) biopsy.

The physical finding of adenopathy suspicious for malignant involvement in the anterior or lateral neck compartments warrants ultrasound examination of the lymph nodes and thyroid gland because of the risk of a lymph node metastatic lesion from an otherwise unrecognized papillary microcarcinoma.

Ultrasound should be performed in all patients with a history of familial thyroid cancer (Familial Medullary Thyroid Carcinoma and Familial Non-medullary Thyroid Carcinoma), Multiple Endocrine Neoplasia type 2, or childhood cervical irradiation, even if palpation yields normal findings.

Familial non-medullary thyroid carcinoma (NMTC) refers to those neoplasms originating from the thyroid epithelial cell, and includes papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), anaplastic thyroid carcinoma, and insular thyroid carcinoma.

In patients with non-specific symptoms (cervical pain, dysphagia, persistent cough, voice changes), ultrasound evaluation of the thyroid gland should be performed only on the basis of findings on physical examination and the results of appropriate imaging and laboratory tests.

Standardized ultrasound reporting criteria should be followed, indicating position, shape, size, margins, content, echogenic pattern, and, whenever possible, the vascular pattern of the nodule. For multiple nodules, detail the nodule(s) bearing the ultrasound characteristics associated with malignancy (hypoechogenic pattern and/or irregular margins, a more-tall-than-wide shape, microcalcifications, or chaotic intranodular vascular spots) rather than describing the largest ("dominant") nodule.

Nodules with malignant potential should be identified, and fine needle aspiration biopsy should be suggested to the patient.
1.2.2. What are the indications for doing ultrasound guided fine needle aspiration biopsy?

Ultrasound-guided fine needle aspiration biopsy is indicated for:

1. Multinodular goiter with suspicious ultrasound findings for malignancy
2. Complex (mixed cystic-solid) appearing nodule/s
3. Posteriorly located nodule/s
4. Ultrasound detected solitary nodule with malignant findings
5. Nodules greater than 1cm with indeterminate ultrasound findings
6. Nodules that are less than 1cm with indeterminate ultrasound findings which increase in size in a 6-18 months interval (more than a 50% change in volume or a 20% increase in at least two nodule dimensions with a minimal increase of 2 mm in solid nodules or in the solid portion of mixed cystic-solid nodules)

Level 3, Category A

Summary of Evidence

With the advent of technology advancement, the application of ultrasound-guided fine needle aspiration biopsy has been deemed as both reasonable and appropriate as part of the diagnostic armamentarium of a general surgeon in the management of a possible thyroid malignancy.

Studies abroad have demonstrated that it is accurate and efficient in determining malignancy in a thyroid nodule.1,2,3

Locally, a retrospective study by Young, et al.3 in 2011 involving 2,239 nodules from 1,737 patients who underwent ultrasound guided FNAB showed that the procedure had a sensitivity of 70.3%, a specificity of 92.8%, a positive predictive value of 76.5%, a negative predictive value of 90.4%, and an accuracy rate of 87.2%.

The use of ultrasound becomes more apparent with its ability to detect characteristics that are suspicious for malignancy at its smallest/earliest dimension. In a retrospective study by Sahin, et al.1 in 2006 involving 145 patients, they were able to demonstrate the ability of the ultrasound to diagnose microcarcinoma (less than 1 centimeter in diameter) with a sensitivity of 96.3%, a specificity of 71.2%, a negative predictive value of 44.8%, a positive predictive value of 98.8% and an accuracy rate of 76.1%.

However, studies by Kim4 and Mazzaferri5 have recommended not to biopsy nodules smaller than 5 mm in size because of a high rate of false positive US findings as well as a high rate of inadequate cytology.

A retrospective study by Kim, et al. in 20094 involving 438 thyroid nodules that have been divided into groups A (<5mm), B (>5mm ≤10mm), and C (>10mm), demonstrated a decrease in sensitivity (85.7% vs 97.7% vs 100%), negative predictive value (94.9% vs 100% vs 100%), and accuracy (96.1% vs 99.1% vs 99.4%) in group A compared to the other groups.

Mazzaferri5 cites that doing a needle biopsy in such small nodules evokes major patient anxiety and is likely to yield cytology that is insufficient for diagnosis, especially when done by those lacking in technical experience. Their study recommends periodic ultrasound examination as likely to be a better option for such patients since their small nodules may spontaneously disappear or fail to grow over time.

However, in a retrospective study by Ga Ram Kim, et al.6, of 1,238 nodules with cytology and/or histologic confirmation which analyzed the ultrasound...
characteristics of large (> 10mm) versus small nodules (< 10mm), they found that there is a difference in the sonographic characteristics predictive of malignancy between small and big nodules. On multivariate analysis, the following sonographic features were shown to be independent factors for PTC in large nodules: irregular margin (OR = 37.788, P < 0.001), microcalcifications (OR = 17.799, P < 0.001), microlobulated margin (OR = 10.385, P < 0.001), and no vascularity (OR = 5.975, P < 0.001). On the other hand, the following were noted to be independent factors in small lesions: irregular margin (OR = 7.185, P < 0.001), microlobulated margin (OR = 5.952, P < 0.001), microcalcifications (OR = 3.722, P < 0.001), marked hypoechogenicity (OR = 2.873, P = 0.004), and taller than wide shape (OR = 2.698, P < 0.001). Hence, the need to do FNAC should be based on sonographic features and not on nodule size alone.

Woon-Jin Moon, et al. recommend that if a nodule has indeterminate findings on US and is larger than 1 cm in diameter, ultrasound guided FNA should be performed due to the fact that the possibility of malignancy cannot be ruled out. If a nodule has indeterminate findings and it is 1 cm or less in size, a follow-up US would be appropriate, 6-18 months following the initial. A growing nodule (more than a 50% change in volume or a 20% increase in at least two nodule dimensions with a minimal increase of 2 mm in solid nodules or in the solid portion of mixed cystic-solid nodules) necessitates a USFNA.

When multiple nodules are found on US, not all of the nodules have to be biopsied. The risk of malignancy for patients with multiple thyroid nodules is not greatly different from that for patients with a single thyroid nodule. According to the ATA guideline, in the presence of two or more nodules 1-1.5 cm or more in size, a FNA biopsy is recommended for nodules with suspicious US findings. If none of the nodules has suspicious US findings, then FNA should be done for the largest one.

**References**


**Summary of Evidence**

The general slow progression of well-differentiated carcinoma has limited the production of randomized controlled trials with regards to the extent of surgery of well-differentiated thyroid cancer. Review of cohort
studies has produced much controversy which is yet unresolved.

In the PCS Thyroid Guidelines of 2008, the recommendation regarding total or near total thyroidectomy as the surgical procedure of choice was based mainly on the works of Udelsman and Mazzaferri.\textsuperscript{1,2,3}

For papillary and follicular thyroid cancers, Mazzaferri, et al.\textsuperscript{2} reported that lobectomy alone resulted in a 5%-10% recurrence rate in the opposite lobe, a high tumor recurrence rate, and a high (11%) incidence of pulmonary metastases. They stated that bilateral thyroidectomy and I\textsubscript{131} ablation is justified by the high recurrence rates in patients with cervical LN metastasis and multicentric tumors. The 20-year rates for local recurrence and nodal metastasis after lobectomy were 14 and 19 percent, respectively, significantly higher (P=0.0001) than the 2 and 6 percent rates seen after bilateral thyroid resection. Patients treated with total or near-total thyroidectomy plus I\textsubscript{131} ablation and L-thyroxine had significantly fewer recurrences and distant recurrences than those treated with any other combination (Figure 1). However, some have stated that the increase in recurrence rate and decrease in survival were found to have an independent effect on survival on multivariate analysis. Mazzaferri, et al. also chose to exclude patients with lesions under 1.5cm from the analysis.\textsuperscript{4}

After total thyroidectomy, serial serum thyroglobulin measurements become a useful marker for recurrence. Postoperative iodine 131 (I\textsubscript{131}) scans can be performed to diagnose recurrent or metastatic disease, and I\textsubscript{131} can be used to ablate residual thyroid bed uptake or distant metastases. In addition, the total dose of I\textsubscript{131} required for ablative therapy is far less following total thyroidectomy. Importantly, the local recurrence rate following total thyroidectomy is decreased, and the re-operative thyroid surgery with its inherently increased risks is minimized.

Recent cohort studies however, suggest the possibility of performing a less than total thyroidectomy for selected patients. With the increase in performing ultrasound as a diagnostic test for thyroid lesions, small thyroid cancer lesions can be easily detected. Barney, et al.\textsuperscript{4} conducted a 19-year study of 23,605 subjects with well-differentiated cancer. They concluded that performing total thyroidectomy produced improved 10-year overall survival (OS) and cause-specific survival rates (CSS). However, performing lobectomy only produced higher OS and CSS but they were not statistically different (Figures 2 & 3).

![Figure 1. Recurrence rates following thyroid surgery and hormonal suppression +/- RAI. Source: Mazzaferri and Kloos. Current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metabol 2001; 86: 4.](image1)

![Figure 2. Overall survival by extent of surgery. NOS, not otherwise specified (Barney, 2011).](image2)
This was supported by a study of Nixon, et al.\textsuperscript{5} in 2012 of 889 patients of Memorial Sloan Kettering Cancer Center with T1 and T2 tumors with a follow-up of 99 months (Table 1). Univariate analysis showed that that there was no significant difference in the 10-year overall survival according to extent of surgery. There was also no difference in local (0\% for both) and regional recurrence (0\% vs 0.8 \% P = .96) between total thyroidectomy and subtotal thyroidectomy groups. Age over 45 and male gender were the independent predictors of poor overall survival. Based on the results of the above studies, thyroid lobectomy with isthmusectomy may be considered as a safe alternative to total thyroidectomy for T1 and T2 well-differentiated tumors (Table 2).

Another study by Mendelsohn, et al.\textsuperscript{6} was conducted among 22,724 patients with papillary thyroid carcinoma.

![Figure 3. Cause-specific survival by extent of surgery. NOS, not otherwise specified.](image)

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<td>166 (46)</td>
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RAI, Radioiodine ablation
Among these, 5,964 patients underwent only lobectomy. Even by performing subgroup analysis for tumors 1 cm or larger, they found no significant difference in the overall survival and disease-specific survival between the groups of lobectomy versus thyroidectomy (P = .05 for OS and P = .09 for DSS) (Table 4).

Despite recent data supporting performing a less than total thyroidectomy for small thyroid carcinomas, caution must be exercised and proper selection of such candidates is needed since it was found in a retrospective medical record review done in Canada that Filipino patients experienced a thyroid cancer recurrence rate of 25% compared with 9.5% for non-Filipino patients (OR, 3.20; 95% CI, 1.23-7.49; P = .004).7

A retrospective study by Pellegriti, et al.8 found that approximately 20 percent of small (< 1.5%) papillary thyroid cancer had extra thyroid invasion and/or bilateral foci which might have been overlooked in most previous studies where microcarcinoma patients where treated with lobectomy. This is important because multifocal thyroid cancers have a relapse rate higher than unifocal cancers, which is also true for microcarcinomas (8.6% vs. 1.2%).

The study showed that although small papillary cancers have a favorable outcome, it might present with signs of aggressiveness including multifocality (30%), LN metastases (30%), vascular invasion (4.7%), and even distant metastases (2.7%). Moreover, 77 (25.7%) of their patients showed evidence of persisting/relapsing disease during the follow-up period of 12.2 to 252.4

**Table 2.** 10 year overall survival for lobectomy and total thyroidectomy groups stratified by pT, pT size and risk group. (Nixon, 2012)

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
<th>Overall 10 year survival (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lobectomy</td>
<td></td>
</tr>
<tr>
<td>PT stage</td>
<td></td>
<td>Total Thyroidectomy</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>632 (71)</td>
<td>92</td>
<td>89</td>
</tr>
<tr>
<td>T2</td>
<td>252 (29)</td>
<td>96</td>
<td>94</td>
</tr>
<tr>
<td>PT size (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>354 (40)</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>1-2</td>
<td>263 (32)</td>
<td>94</td>
<td>87</td>
</tr>
<tr>
<td>2-4</td>
<td>164 (18)</td>
<td>98</td>
<td>94</td>
</tr>
<tr>
<td>4-5</td>
<td>89 (10)</td>
<td>94</td>
<td>92</td>
</tr>
<tr>
<td>Risk group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>373 (42)</td>
<td>97</td>
<td>96</td>
</tr>
<tr>
<td>Intermediate</td>
<td>477 (51)</td>
<td>90</td>
<td>85</td>
</tr>
<tr>
<td>High</td>
<td>58 (7)</td>
<td>90</td>
<td>90</td>
</tr>
</tbody>
</table>

Among these, 5,964 patients underwent only lobectomy. Even by performing subgroup analysis for tumors 1 cm or larger, they found no significant difference in the overall survival and disease-specific survival between the groups of lobectomy versus thyroidectomy (P = .05 for OS and P = .09 for DSS) (Table 4).

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**Table 3.** Cox proportional HRs for overall and disease specific survival (Mendelsohn,2010).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall Survival</th>
<th>Disease-Specific Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size</td>
<td>HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Extent, localized (vs extrathyroidal)</td>
<td>1.07 (1.03-1.10)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Node status, referent: negative</td>
<td>1.46 (1.33-1.62)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.50 (1.35-1.67)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.09 (1.06-1.09)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Race, white (vs all other races)</td>
<td>1.24 (1.18-1.30)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Surgical type, lobectomy (vs thyroidectomy)</td>
<td>1.06 (0.95-1.19)</td>
<td>.30</td>
</tr>
<tr>
<td>Isotopes or implants (vs no radiation)</td>
<td>0.93 (0.84-1.03)</td>
<td>.16</td>
</tr>
<tr>
<td>External beam radiation therapy (vs no radiation)</td>
<td>1.71 (1.42-2.07)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Histologic subtype, papillary not otherwise specified (vs follicular)</td>
<td>0.92 (0.88-0.97)</td>
<td>.002</td>
</tr>
</tbody>
</table>

**Table 4.** Recurrences according to treatment carried out for each classification system(Hurtado-Lopez,et al. 2011)

<table>
<thead>
<tr>
<th></th>
<th>AMES (n = 184)</th>
<th>MACIS (n = 170)</th>
<th>DeGroot (n = 92)</th>
<th>TNM (n = 150)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x2 = 9.98, p = 0.0016</td>
<td>x2 = 11.28, p = 0.008</td>
<td>x2 = 5, p = 0.0254</td>
<td>x2 = 7.6, p = 0.0058</td>
</tr>
<tr>
<td></td>
<td>n  %</td>
<td>n  %</td>
<td>n  %</td>
<td>n  %</td>
</tr>
<tr>
<td>Thyroidectomy</td>
<td>7/161</td>
<td>4.3</td>
<td>5/146</td>
<td>3.4</td>
</tr>
<tr>
<td>Hemithyroidectomy</td>
<td>5/23</td>
<td>21.7</td>
<td>5/24</td>
<td>20.8</td>
</tr>
</tbody>
</table>
months (median of 45.2). This study recommended near-total or total thyroidectomy as the first choice surgical treatment.

Studies done in other countries recently have supported the need for total thyroidectomy for low risk papillary thyroid cancer. An observational study by Hurtado, et al, involving 128 low risk papillary thyroid cases with 10 year follow up showed higher recurrence rates for those who have undergone hemithyroidectomy only as shown on Table 4. The recurrences were mainly regional metastases.

In another study in Romania by Varcus, which retrospectively reviewed 228 patients who had completion thyroidectomy after histological confirmation of thyroid cancer in the ipsilateral lobe. Only one patient with cancer < 1 cm in ipsilateral lobe had malignant lesions in the contralateral lobe (4/7%). However, in patients with tumors > 1 cm, the frequency of malignant lesions in the contralateral lobe was between 42.8% and 47.6%. This again supports the recommendation of doing a total thyroidectomy for tumors > 1 cm.

Minimal invasive and endoscopic techniques for thyroidectomy have already been performed in our country. More studies are desired before any guidelines can be recommended for such procedures.

References


2.2 What is the role of central node dissection in the management of patients with well differentiated thyroid cancer in improving overall and disease free survival?

2.2.1 What is the role of therapeutic central compartment lymph node dissection (CLND)?

Therapeutic CLND is recommended for those with clinically palpable or ultrasonographically detected nodes.

Level 2, Category A

Summary of Evidence

Clinically evident lymph node involvement is a well-established indication for therapeutic dissection. The removal of involved cervical lymph nodes is part of locoregional control of the disease. Two systematic reviews1,2 showed higher rates of persistent and recurrent disease on follow-up for patients with lymph node metastases. Compartment-oriented lymph node dissection is shown to result to lower recurrences as compared to ‘berry picking’. There are no clear evidences for its impact on over-all survival.

References

2.2.2 What is the role of prophylactic central compartment lymph node dissection?

Prophylactic central node dissection is not recommended because it does not improve overall and disease-free survival.

**Level 2, Category A**

**Summary of Evidence**

Fifteen journal articles (1 prospective cohort, 11 retrospective cohorts, 2 systematic reviews and 1 meta-analysis) reported on the incidence of metastasis in the harvested nodes among patients who underwent prophylactic central lymph node dissection (CLND), or on the recurrence rate or disease-free survival against complication rates of the added procedure. Also noted was the effect of the procedure on the parameters used for surveillance.

The incidence of micrometastases in central compartment nodes ranges from as low as 45.8% to as high as 60.9%. Most micrometastases can be found in the pretracheal (40%) and ipsilateral (34.5%) group of nodes while the contralateral group showed an incidence of 17.4%.

Several studies showed no significant difference in the recurrence rate between patients undergoing total thyroidectomy with CLND and those undergoing a total thyroidectomy only. But the best evidence comes from two systematic reviews which concluded that prophylactic CLND does not improve cancer survival and that there is no significant difference in recurrence rate in patients having total thyroidectomy and prophylactic CLND versus total thyroidectomy alone.

As to the complication rates, majority of studies showed an increased incidence of transient hypocalcemia and parathyroid autotransplantation among patients who underwent an additional CLND to their surgical treatment. The incidence of transient hypocalcemia ranges from 18%-51.9% for bilateral CLND, 20.5%-36.1% for unilateral CLND and 0.5%-27.7% for those without CLND. Wong gave the same conclusion and Chisholm gave a risk difference of 0.13 translating into one incident of temporary hypocalcemia for every 7.7 CLNDs performed. Moreover, White, et al. showed an increased incidence of permanent hypocalcemia and recurrent laryngeal nerve paralysis in patients undergoing total thyroidectomy and CLND. They reported a further increased risk of hypocalcemia and unintentional nerve injury, if the CLND was done as a second procedure. Giordano showed a higher incidence of transient hypocalcemia if a bilateral CLND instead of just an ipsilateral CLND was performed (51.9% vs 36.1%). It should be noted that most of these studies employed patients whose procedures were performed by endocrine surgeons.

**References**


2.3 What is the role of radioactive iodine remnant ablation therapy in improving overall and disease-free survival?

Radioactive iodine remnant ablation therapy is beneficial in decreasing locoregional recurrence and distant metastases.

For low risk patients who underwent total thyroidectomy, there is no benefit in giving RAI remnant ablation therapy in terms of improving disease-free survival.

Level I, Category A

Summary of Evidence

A meta-analysis by Sawka, et al in 2004 showed that RAI ablation may be beneficial in decreasing recurrence of WDTC. Although no randomized controlled studies were obtained, 23 studies were included out of 267 full-text papers independently reviewed. Pooled analysis showed a statistically significant treatment effect of ablation for the following 10-year outcomes: Locoregional recurrence (RR of 0.31); and distant metastases (absolute risk reduction of 3%) (Figures 1 & 2).

![Figure 1](image-url)
However, Sawka, et al. in 2008, published an updated systematic review on the effectiveness of RAI in well-differentiated thyroid cancer. They stated that the benefit of RAI is unclear among low risk patients who underwent total or near-total thyroidectomy and are receiving thyroid hormone suppressive therapy. A similar conclusion was reported by another systematic review by Sacks, et al. in 2010. Majority of very low-risk and low-risk patients who underwent post-operative RAI ablation did not demonstrate increased survival or disease-free survival.

This is further supported by a randomized phase 3 trial done by Schlumberger, et al. in 2012. A total of 752 patients were enrolled and 92% of the cases had papillary cancer. Their results showed that a low dose of post-operative RAI ablation may be sufficient for low risk cancer to lessen the complications brought about by radiation exposure.

However, it is important to consider that for the subsequent follow-up of patients who did not receive post-operative RAI ablation, monitoring through the use of serum Tg levels will be complicated.

The decision to give RAI ablation must be individualized, based on the risk profile of the patient, as well as patient and physician preference, while balancing the risks and benefits of such therapy.

References


<table>
<thead>
<tr>
<th>Study</th>
<th>Radioiodine Ablation n/N</th>
<th>Control n/N</th>
<th>RR (95% CI Random)</th>
<th>Weight %</th>
<th>RR (95% CI Random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Papillary Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hong Kong (P) 2002</td>
<td>4 / 444</td>
<td>5 / 143</td>
<td>21.1</td>
<td>-0.03 (-0.08, 0.01)</td>
<td></td>
</tr>
<tr>
<td>Zurich (Stg. IU: P)</td>
<td>0 / 43</td>
<td>0 / 54</td>
<td>12.9</td>
<td>0.00 (0.04, 0.04)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>4 / 487</td>
<td>5 / 197</td>
<td>34.0</td>
<td>-0.22 (0.04, 0.01)</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity chi-square = 1.13 df =1 p = 0.28</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z = 1.17 p = 0.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>02 Papillary and Follicular Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ohio, USAF 2001</td>
<td>2 / 230</td>
<td>34 / 769</td>
<td>80.3</td>
<td>-0.03 (0.05, -0.02)</td>
<td></td>
</tr>
<tr>
<td>03 Follicular Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hong Kong (F) 2002</td>
<td>9 / 123</td>
<td>1 / 12</td>
<td>0.8</td>
<td>0.01 (-0.17, 0.15)</td>
<td></td>
</tr>
<tr>
<td>Lahey (capsule: F, )</td>
<td>0 / 20</td>
<td>0 / 72</td>
<td>4.5</td>
<td>0.00 (-0.07, 0.07)</td>
<td></td>
</tr>
<tr>
<td>Zurich (Min inv. F)</td>
<td>0 / 17</td>
<td>1 / 9</td>
<td>0.4</td>
<td>-0.11 (-0.07, 0.05)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>9 / 180</td>
<td>2 / 93</td>
<td>5.7</td>
<td>-0.01 (-0.07, 0.05)</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity chi-square = 0.90 df = 2 p = 0.54</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z = 0.29 p = 0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>15 / 877</td>
<td>41 / 1079</td>
<td>100.0</td>
<td>-0.03 (-0.04, -0.01)</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity chi-square = 3.51 df = 5 p = 0.62</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z = 3.83 p = 0.0003</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Figure 2. Random effects model examining the RD of RAI ablation on development of distant metastases at 10 yr. n, Number of events; N, size of population studied; P, papillary; F, follicular; H, Hurthle cell; Stg I, II, stage I or II; Min inv, minimally invasive; capsule, only capsule invasion; node +, including cervical lymphadenopathy.

Figure 3. Pooled analysis examining risk difference for any thyroid cancer recurrence after radioactive iodine ablation (Sawka 2008).

Figure 4. Pooled analysis examining the risk difference for loco-regional thyroid cancer recurrence after radioactive iodine remnant ablation (Sawka 2008).
2.6 What is the role of TSH suppression therapy in the treatment of WDTC?

Thyroid hormone suppression therapy following a risk stratified approach may reduce recurrence and improve thyroid cancer-specific mortality rates and overall survival rate among high risk patients or those with stage III or IV disease.

Considering the adverse effects of TSH suppression therapy, there is no significant benefit for low risk patients especially for those with no residual or active disease.

**Level 2, Category A**

**Specific Recommendations:**

For high risk and intermediate risk* thyroid cancer patients, initial TSH suppression to below 0.1mU/L is recommended for 3 - 5 years.

For low risk* thyroid cancer patients who either received or did not receive remnant ablation, maintenance of the TSH at or slightly below the lower limit of normal (0.1-0.5 mU/L) is adequate so as to minimize the toxic effects of aggressive thyroid suppression therapy.

(*According to the Risk Stratification for Recurrence, ATA 2009)

**Level 5, Category A**

**Summary of Evidence**

Thyroid hormone suppression therapy after surgery with or without remnant ablation is an important part of the multimodal treatment of thyroid cancer. Theoretically, it is effective in stopping the growth of microscopic thyroid cancer cells or residual thyroid cancer.\(^1\)

A prospective cohort (n=2938) which stratified patients into low risk (Stage I and II by NTCTCSG criteria) or high risk (stage III and IV) compared overall survival, disease-specific, and disease-free survival according to treatment received including degree of thyroid hormone suppression therapy. Aggressive thyroid hormone suppression therapy was found to be associated with longer overall survival among high risk patients. Moderate thyroid hormone suppression therapy was found to be associated with improved overall survival in stage II patients. There was no impact of thyroid hormone suppression therapy among stage I patients.\(^2\)

In a retrospective cohort of patients with metastatic differentiated carcinoma who received initial treatment and follow up in a single institution, DTC-specific survival was found to be significantly better in patients with a median TSH level of ≤ 0.1 mU/l (median survival 15.8 years) than those with a non-suppressed TSH level (median survival 7.1 years; p<0.001). However, suppressing TSH further (≤ 0.03 mU/l; p= 0.24) did not result in improved survival.\(^3\)

A randomized controlled trial comparing patients with papillary thyroid cancer who received TSH suppression therapy with those who did not, showed that disease-free survival was not inferior by more than 10% among those whose did not receive TSH suppression.\(^4\)

There are still ongoing discussions on the duration of suppression therapy. According to the current guidelines by ESMO\(^5\), low-risk patients who are disease-free after initial treatment may be shifted from suppressive to replacement LT4 therapy, with the goal of maintaining serum TSH level within the low normal range. However, for patients determined as high risk at the time of diagnosis but has been determined to be disease free on their first follow up after initial treatment, it is advisable to maintain them on suppressive doses of LT4 therapy (TSH < 0.1 uU/ml) for 3-5 years because the risk of relapse in this subset of patients on long-term follow-up may still be significant.

Biondi and Cooper\(^6\) proposed initial serum TSH targets based on the ATA risk stratification for cancer recurrence and progression\(^7\), as well as the patients' risk
from adverse effects of LT4. The following must be taken into account: the age of the patient, and the presence of preexisting cardiovascular and skeletal risk factors that might predispose to the development of long-term adverse cardiovascular or skeletal outcomes, particularly increased heart rate and left ventricular mass, atrial fibrillation, and osteoporosis. Using this scheme, nine potential patient categories can be defined, with differing TSH targets for both initial and long-term L-T4 therapy (Tables 1 & 2).

### Table 1. Suggested initial thyrotropin targets in thyroid cancer patients according to risk assessment (Biondi, 2010).

<table>
<thead>
<tr>
<th>Risk from T4 therapy</th>
<th>High</th>
<th>Intermediate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>&lt;0.1 mU/L a</td>
<td>0.1 mU/La</td>
<td>0.5-1 mU/L</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&lt;0.1 mU/L b</td>
<td>&lt;0.1 mU/Lb</td>
<td>0.5-1 mU/L</td>
</tr>
<tr>
<td>Low</td>
<td>&lt;0.1 mU/L</td>
<td>&lt;0.1 mU/L</td>
<td>0.1-0.5 mU/L</td>
</tr>
</tbody>
</table>

a  With high risk from L-T4: consider cardiovascular drugs, calcium, vitamin D, and antiresorptive drugs.
b  With intermediate risk from L-T4 and high or intermediate risk of tumor progression: consider b-adrenergic blocking drugs, calcium, and vitamin D.
c  With low risk from L-T4 with persistent=metastatic disease: periodic cardiovascular and BMD assessment.

### Table 2. Suggested thyrotropin targets in thyroid cancer patients according to risk assessment during follow-up (Biondi, 2010).

<table>
<thead>
<tr>
<th>Risk from T4 therapy</th>
<th>High</th>
<th>Intermediate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>&lt;0.1 mU/L persistent or metastatic disease; 0.1-0.5 mU/L if disease free for 5-10 years (a)</td>
<td>0.5-1 mU/L if disease free for 5-10 years, then 1-2 mU/L</td>
<td>1-2 mU/L</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&lt;0.1 mU/L persistent or metastatic disease b; 0.1-0.5 mU/L if disease free for 5-10 years</td>
<td>0.1-0.5 mU/L if disease free for 5-10 years, then 1-2 mU/L</td>
<td>1-2 mU/L</td>
</tr>
<tr>
<td>Low</td>
<td>&lt;0.1 mU/L persistent or metastatic disease c; 0.1-0.5 mU/L if disease free for 5-10 years</td>
<td>0.1-0.5 mU/L if disease free for 5-10 years, then 0.3-2 mU/L</td>
<td>0.3-2 mU/L</td>
</tr>
</tbody>
</table>

a  With high risk from L-T4 with persistent=metastatic disease: TSH suppression should be adapted to the clinical situation.
b  With intermediate risk from L-T4 with persistent=metastatic disease: consider cardiovascular drugs, calcium, and vitamin D.
c  With low risk from L-T4 with persistent=metastatic disease: periodic cardiovascular and BMD assessment.
3. **What is the recommended postoperative surveillance for patients with well-differentiated thyroid cancer?**

Postoperative surveillance with the goal of detecting recurrence among disease free patients and progression of disease among those with residual disease can be accomplished by utilizing serum thyroglobulin, serum TSH, thyroid ultrasound, with or without whole body scan, according to the patient's risk stratification for recurrence and/or death.

**Level 5, Category A**

**Summary of Evidence**

After initial surgery and remnant ablation, the risk for recurrence and mortality in patients with well differentiated thyroid cancer should be determined based on the ATA 2009 risk stratification into low, intermediate, or high risk, and the AJCC TNM staging respectively (Table 1). This can be used as a guide in determining the need and frequency of doing surveillance tests.

The diagnostic tests employed for post operative surveillance of patients with WDTC should have a high negative predictive value, so that patients who are unlikely to experience disease recurrence could be identified, hence, less aggressive management strategies which are more cost effective and safe can be used. Similarly, patients with a higher risk of recurrence should be monitored more aggressively for early detection of recurrent disease, which offers the best opportunity for effective treatment.

<table>
<thead>
<tr>
<th>Table 1. ATA initial risk of recurrence classification (ATA 2009):</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low-risk patients have the following characteristics:</strong></td>
</tr>
<tr>
<td>1. no local or distant metastases;</td>
</tr>
<tr>
<td>2. complete removal of macroscopic tumor</td>
</tr>
<tr>
<td>3. there is no tumor invasion of locoregional tissues or structures nor vascular invasion</td>
</tr>
<tr>
<td>4. the tumor does not have aggressive histology (e.g., tall cell, insular, columnar cell carcinoma)</td>
</tr>
<tr>
<td>5. and, if I131 is given, there is no I131 uptake outside the thyroid bed on the first posttreatment whole-body RAI scan (RxWBS)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intermediate-risk patients have any of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. microscopic invasion of tumor into the perithyroidal soft tissues at initial surgery;</td>
</tr>
<tr>
<td>2. cervical lymph node metastases or</td>
</tr>
<tr>
<td>3. I131 uptake outside the thyroid bed on the RxWBS done after thyroid remnant ablation</td>
</tr>
<tr>
<td>4. tumor with aggressive histology or vascular invasion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High-risk patients have:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. macroscopic tumor invasion,</td>
</tr>
<tr>
<td>2. incomplete tumor resection,</td>
</tr>
<tr>
<td>3. distant metastases, and possibly</td>
</tr>
<tr>
<td>4. thyroglobulinemia out of proportion to what is seen on the posttreatment scan</td>
</tr>
</tbody>
</table>
3.1 What is the role of thyroglobulin assay for postoperative surveillance in patients with well differentiated thyroid cancer in detecting recurrence or progression of disease?

Serum thyroglobulin monitoring is essential in the follow up of patients with well differentiated thyroid cancer who underwent total thyroidectomy and radioactive iodine ablation to help detect recurrence or progression of disease.

Level 2, Category A

Specific Recommendations:

1. To ensure an accurate and reliable measurement of serum Tg, an immunometric assay calibrated against the CRM-457 international standard is recommended. If this is not possible, measurements in individual patients over time should be performed in the same laboratory and using the same assay. Quantitative determination of thyroglobulin antibodies should be likewise be done with every measurement of serum Tg.

Level 2, Category A

2. For low risk who underwent less than total thyroidectomy or total thyroidectomy without remnant ablation: periodic TSH-suppressed Tg and cervical ultrasound, followed by TSH-stimulated serum Tg measurements if the TSH-suppressed Tg testing is undetectable should be done. The change (increase) in Tg values over time should be used as a basis to work up a patient for possible progression or recurrence of disease rather than specific cut off levels of Tg (whether on TSH suppression or stimulation).

Level 4, Category A

3. For low risk DTC who underwent total thyroidectomy with remnant ablation with negative ultrasound and undetectable suppressed Tg within 1 year from treatment, TSH stimulated Tg (by hormone withdrawal or rhTSH) should be measured 1 year after the ablation to verify absence of disease. This subset of patients may be followed up with yearly clinical exam and serum Tg measurements while on hormone replacement.

Level 3, Category A

Summary of Evidence

Standardization thyroglobulin assays have not yet been achieved even with the development of an international standard which is the Certified Reference Material 457 (CRM -457). A study by Lee, et al. compared the concordance of three immunoradiometric assays (IRMA) to CRM-457, and suggested that laboratories should adopt IRMAs standardized to CRM - 457.

In a retrospective analysis of 290 consecutively diagnosed cases of low risk DTC treated with thyroidectomy alone and followed up with yearly neck ultrasound and serum thyroglobulin, final Tg levels were found to be undetectable (<1 ng/ml) in 274/290 (95%) of RRA negative patients. This was not significantly different compared to a matched group of 495 RRA positive patients who had undetectable levels of Tg in 492 cases (99%) after a median follow up of 5 years. It was concluded that in most RRA negative patients, serum thyroglobulin levels spontaneously drop to undetectable levels within 5-7 years after thyroidectomy.

Another retrospective study reported on 312 consecutively diagnosed papillary thyroid microcarcinoma (T1NOMO) patients classified as very low risk (no family history, no history of head and neck irradiation, unifocal, no extracapsular extension and classic papillary
types) who underwent total thyroidectomy, with radioactive remnant ablation in 44 percent of the subjects. Yearly follow-up with neck ultrasound and serum thyroglobulin was done with a median follow up of 6.7 years, which showed that final serum thyroglobulin levels were undetectable (< 1 ng/ml) in all patients with RAI ablation and in 93% of those who did not receive RAI. The first neck ultrasound (6-12 months after surgery) and the last sonograms were all negative. The study proves that strict selection and classification of patients according to their risk for recurrence could help guide a cost-effective follow up protocol.3

References


5.2 What is the role of TSH for postoperative surveillance in the patient with WDTC?

Serum TSH level monitoring is recommended as part of postoperative surveillance to determine the adequacy of suppression to maximize the benefits while minimizing the risks associated with TSH suppression therapy.

Level 5, Category A

Summary of Evidence

Thyroid hormone suppression therapy is an essential part of the postoperative management of patients with well-differentiated thyroid cancer. The level of suppression following a risk stratified approach may reduce recurrence and improve thyroid cancer-specific mortality rates and overall survival rate among high risk patients. It also has adverse effects on the bone (osteoporosis) and the heart (arrhythmias). Thus, it is also important to monitor its levels so as to maximize its benefits while minimizing treatment related morbidity.

According to the American Thyroid Association (ATA) and European Thyroid Association ETA), TSH should be indefinitely maintained at subnormal levels (<0.1 mU/L) in patients with persistent disease in the absence of contraindications (cardiac problem or osteoporosis). In patients initially classified as high risk but have become clinically and biochemically free of disease, ATA recommends TSH levels between 0.1-0.5 mU/l for for 5-10 years. For ETA, however, TSH should be maintained at < 0.1mU/L for 3-5 years for this subset of patients to avoid possible recurrence during this period. Thereafter, TSH may be maintained at low normal levels (0.1 - 0.5 mU/L). In patients initially classified as low risk but have become clinically and biochemically free of disease, ATA recommends TSH levels between 0.1-0.5 mU/L . If they remain disease-free on follow up, TSH levels may be maintained in the low normal range (0.3 - 2 mU/L).1,2,3

Biondi, et al. (2010) proposed a stratified approach in giving TSH suppression therapy according to the risk of cancer recurrence and progression as well as the risk of adverse side effects from LT4 therapy with age, cardiovascular status and skeletal factors taken into consideration. (See Table 2 under Recommendation 2.6).3

References

### Appendix A. Oxford centre for evidence-based medicine 2001 levels of evidence.

<table>
<thead>
<tr>
<th>Question</th>
<th>Step 1 (Level 1)</th>
<th>Step 2 (Level 2)</th>
<th>Step 3 (Level 3)</th>
<th>Step 4 (Level 4)</th>
<th>Step 5 (Level 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How common is the problem?</td>
<td>Local and current random sample surveys (or censuses)</td>
<td>Systematic review of surveys that allow matching to local circumstances**</td>
<td>Local non-random sample**</td>
<td>Case-series**</td>
<td>N/A</td>
</tr>
<tr>
<td>Is the diagnostic or monitoring test accurate?</td>
<td>Systematic review of cross sectional studies with consistently applied reference standard and blinding</td>
<td>Individual cross sectional studies with consistently applied reference standard and blinding</td>
<td>Non-consecutive studies, or studies without consistently applied reference standards**</td>
<td>Case-control studies, or poor or non-independent reference standard**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What will happen if we do not add a therapy?</td>
<td>Systematic review of inception cohort studies</td>
<td>Inception cohort studies</td>
<td>Cohort study or control arm of randomized trial**</td>
<td>Case-series or case-control studies, or poor quality prognostic cohort study**</td>
<td>N/A</td>
</tr>
<tr>
<td>Does the intervention help?</td>
<td>Systematic review of randomized trials or n-of-1 trials</td>
<td>Randomized trial or observational study with dramatic effect</td>
<td>Non-randomized controlled cohort/follow-up study**</td>
<td>Case-series, case-control studies, or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td><strong>What are the COMMON harms? (Treatment Harms)</strong></td>
<td>Systematic review of randomized trials or nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect</td>
<td>Individual randomized trial or (exceptionally) observational study with dramatic effect</td>
<td>Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**</td>
<td>Case-series, case-control or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td><strong>What are the RARE harms? (Treatment Harms)</strong></td>
<td>Systematic review of randomized trials or n-of-1 trial</td>
<td>Randomized trial or (exceptionally) observational study with dramatic effect</td>
<td>Non-randomized controlled cohort/follow-up study**</td>
<td>Case-series, case-control or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>Is the (early detection) test worthwhile?</td>
<td>Systematic review of randomized trials</td>
<td>Randomized trial</td>
<td>Non-randomized controlled cohort/follow-up study**</td>
<td>Case-series, case-control or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
</tbody>
</table>

* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small. Level may be graded up if there is a large or very large effect size.

** As always, a systematic review is generally better than an individual study.