Multidisciplinary Care for Well-Differentiated Thyroid Cancer

Singapore Consensus - August 2016
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Dear Colleagues

We successfully held the 1st Singapore Differentiated Thyroid Cancer Consensus Meeting on the management of differentiated thyroid cancer in August 2016. First, I would like to express my sincere thanks to all of you for participating in this meeting. This was the first time that specialists from the various disciplines of surgery, endocrinology, pathology, oncology, radiation oncology, nuclear medicine and radiology participated to discuss the changes in recent guidelines proposed by the American Thyroid Association Guidelines in 2016.

The meeting was necessary to harmonize the way clinicians manage thyroid cancer in Singapore. With clinicians working in different institutions, both public and private, and the varied exposure and training everyone had in the practice of thyroidology, it was essential to bring about a uniformity in clinical practice. The guidelines have been published now with the endorsement of Endocrine and Metabolic Society of Singapore, College of Surgeons and Singapore Society of Oncology.

Of course, these guidelines are only a guide to best manage patients with thyroid cancer in the local setting. However, there are times where clinicians would have to individualize treatment and in this scenario, it is best that the cases be discussed in their respective MDT’s to decide the course for such a patient. It is hoped that we will meet again in 3 years’ time, in 2019, to discuss any updates to the management guidelines.

I would take this opportunity to thank Sanofi Aventis (S) Pte. Ltd for their kind support and Bioquest for their contribution in the preparation of the guideline.

Respectfully yours

Asst. Prof. Rajeev Parameswaran
Chairman of the Organizing Committee for the 1st Singapore Differentiated Thyroid Cancer Consensus Meeting
Singapore
List of Attendees

Endocrine Surgery & ENT
- Dr Tan Hiang Khoon
- Dr Ngiam Kee Yuan
- Asst. Prof. Rajeev Parameswaran
- Prof. Soo Khee Chee
- Prof. Thomas Loh
- Assoc. Prof. Cheah Wei Keat
- Dr Jeremy Ng
- Dr Thomas Ho
- Dr Adrian Koh
- Dr Constance Teo
- Dr Lim Chwee Ming
- Dr Abu Rauff
- Dr Ranjiv Siva
- Dr Huang Sin Yong
- Dr Lim Ming Yen
- Dr Gopalakrishna Iyer
- Prof. Christopher Goh

Nuclear Medicine
- Dr Kelvin Loke
- Dr Loi Hoi Yin
- Dr Ong Seng Chuan
- Dr Aaron Tong
- Dr David Ng Chee Eng

Molecular Pathology
- Asst. Prof. Nga Min En
- Dr Jacqueline Hwang
- Dr Akhil Chopra
- Dr Yap Wai Ming
- Dr Vijay Desai
- Dr Anjula Thomas

Oncology
- Dr Joanne Ngeow
- Dr Goh Boon Cher
- Dr Kittasis Sommat
- Dr Daniel Tan

Endocrinology
- Dr Chionh Siok Bee
- Dr Loh Keh Chuan
- Dr Samantha Yang
- Dr Adoree Lim
- Dr Lim Ling Choo
- Dr Chng Chiaw Ling
- Dr Chia Su Ynn
- Dr Loh Keh Chuan
- Dr Vanessa Au
- Dr Vivian Lim
- Dr Winston Kon

Radiation Oncology
- Dr Soong Yoke Lin
- Dr Sanjaya Dissanayake
- Dr Timothy Cheo

Radiology
- Dr James Khoo
<table>
<thead>
<tr>
<th>GRADE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>STRONGLY RECOMMENDED (Based on good evidence)</td>
</tr>
<tr>
<td>B</td>
<td>RECOMMENDED (Based on fair evidence)</td>
</tr>
<tr>
<td>C</td>
<td>RECOMMENDED (Based on expert opinion)</td>
</tr>
</tbody>
</table>
SCREENING AND DIAGNOSIS
Objectives

- To review the 2015 American Thyroid Association Guidelines and 2014 British Thyroid Association Guidelines on the following:
  - Role of history, physical examination, serum thyrotropin, thyroid scan, and ultrasound in the evaluation of thyroid nodules
  - Indications for fine-needle aspiration cytology (FNAC) in the evaluation of thyroid nodules
  - Guideline recommendations on the role of ultrasound-guided FNAC in the evaluation of thyroid nodules
  - Guideline recommendations for nondiagnostic FNAC results
  - Guideline recommendations for indeterminate FNAC results
  - Diagnostic tests for multiple thyroid nodules
- To provide a context for drafting the Singapore consensus guidelines on the screening and diagnosis of patients with differentiated thyroid cancer.
1.1 Role of History and Physical Examination in the Evaluation of Thyroid Nodules

1.1.1 Role of History and Physical Examination

Factors predictive of malignancy

<table>
<thead>
<tr>
<th>History</th>
<th>Physical examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>• History of head and neck or total-body irradiation or exposure to ionising radiation from fallout during childhood or adolescence</td>
<td></td>
</tr>
<tr>
<td>• Rapid nodule growth and/or hoarseness</td>
<td>• Presence of any of the following:</td>
</tr>
<tr>
<td>• Personal and/or family history of thyroid cancer, cancer, or other conditions suggestive of a thyroid cancer predisposition syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Vocal cord paralysis</td>
</tr>
<tr>
<td></td>
<td>• Cervical lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>• Fixation of the nodule to surrounding tissues</td>
</tr>
</tbody>
</table>

1.1.2 Evaluation of Thyroid Nodules

Evaluation of thyroid nodules

- Thyroid nodules >1 cm: Should be evaluated
- Thyroid nodules <1 cm: May require further evaluation if associated with any of the following:
  - Suspicious findings on ultrasound scan
  - Cervical lymphadenopathy
- Further evaluation of small lesions without any suspicious ultrasound characteristics is likely to be more harmful than beneficial.

Urgency of referral

- Immediate/same-day referral is indicated when there is stridor associated with a thyroid mass. (Grade C)
- Urgent referral (1–2 weeks) is indicated when there is (Grade C):
  - Unexplained hoarseness or voice changes associated with goiter*
  - Thyroid nodule in a child*
  - Cervical lymphadenopathy associated with a thyroid mass*
  - A rapidly enlarging, painless thyroid mass over a period of weeks*
- Routine referral is indicated if there is (Grade C):
  - History of sudden onset of pain in a thyroid lump
  - Tracheal deviation or retrosternal extension
  - Any other nodule without the above characteristics (*)

1.2 Role of Serum TSH, Thyroid Scan, Ultrasound, and Fine-Needle Aspiration Cytology in the Evaluation of Thyroid Nodules

1.2.1 Role of Serum TSH and Thyroid Scan

Indications for Serum TSH Estimation

Initial evaluation of a patient with thyroid nodule (Grade A)

- Suppressed/Low TSH (Grade A)
  - Radionuclide Thyroid Scan
  - US thyroid
- Normal or elevated TSH (Grade A)
  - US thyroid

Nonfunctioning nodule (Cold nodule) (Grade C)

Hyperfunctioning nodule (Hot nodule)

Treat with antithyroid drugs and consider radiiodine ablation*

*If radiiodine is contraindicated, consider surgery.

1.2.2 Role of $^{18}$FDG-PET Scan

- Focal $^{18}$FDG-PET uptake within a sonographically confirmed thyroid nodule conveys an increased risk of thyroid cancer
- Diffuse $^{18}$FDG-PET uptake, in conjunction with sonographic and clinical evidence of chronic lymphocytic thyroiditis

- Fine-needle aspiration is recommended for nodules $\geq 0.5$ cm
- Does not require further imaging or fine-needle aspiration

Grade A
1.2.3 Ultrasound in the Evaluation of Thyroid Nodules

- Thyroid US* should be performed in all patients with known or suspected thyroid nodules. (Grade A)
- Any abnormal lymph node in the neck should undergo FNAC to facilitate accurate diagnosis or staging. (Grade A)

<table>
<thead>
<tr>
<th>Indications for thyroid US</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Suspected thyroid nodule, nodular goitre</td>
</tr>
<tr>
<td>• Radiographic abnormality suggesting thyroid nodule incidentally detected on CT/MRI/thyroidal uptake on 18FDG-PET scan</td>
</tr>
<tr>
<td>• Thyroid US is not indicated in routine multiphasic health screening in people without red flag symptoms and palpable nodules (Grade C)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Role of US examination (Thyroid US can answer the following questions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Is there truly a nodule corresponding to an identified abnormality?</td>
</tr>
<tr>
<td>• How big is the nodule?</td>
</tr>
<tr>
<td>• What is the nodule's pattern of US characteristics?</td>
</tr>
<tr>
<td>• Is suspicious cervical lymphadenopathy present?</td>
</tr>
<tr>
<td>• Is the nodule &gt;50% cystic?</td>
</tr>
<tr>
<td>• Are there any other non-palpable nodules?</td>
</tr>
</tbody>
</table>


1.2.4 Minimum Dataset for Ultrasound Reporting

- Location of nodule
- Size of nodule (in three dimensions)
- Margin (well defined/microlobulated or irregular)
- Composition (solid/cystic/mixed solid-cystic with percentage of cystic component)
- Echogenicity (isoechoic/hypoechoic/hyperechoic)
- Calcifications (micro-/macro-/disruption in rim calcifications)
- Colloid artifacts (“comet tails”)
- Taller than wide morphology (defined as ratio of anteroposterior to transverse diameter ≥1)
- Increased intra-nodular vascularity on color Doppler ultrasound
- Associated cervical lymphadenopathy
  - Abnormal cervical lymph nodes may have one or more of the following features: hyperechogenicity, cystic, peripheral vascularity, microcalcifications, or round shape

1.2.5 Ultrasound-Guided FNAC in the Evaluation of Thyroid Nodules

<table>
<thead>
<tr>
<th>Nodule size*</th>
<th>Sonographic pattern</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 cm</td>
<td>High-to-intermediate suspicion@</td>
<td>Grade A</td>
</tr>
<tr>
<td>≥1.5 cm</td>
<td>Low suspicion@</td>
<td>Grade A</td>
</tr>
<tr>
<td>≥2 cm</td>
<td>Very low suspicion@</td>
<td>Grade C</td>
</tr>
</tbody>
</table>

A diagnostic FNAC is not required for:

- Nodules that do not meet the above criteria (Grade A)
- Nodules that are purely cystic (Grade A)

1.2.6 Sonographic Patterns for Fine-Needle Aspiration Guidance of Thyroid Nodules

<table>
<thead>
<tr>
<th>Sonographic pattern¹</th>
<th>US features ¹</th>
</tr>
</thead>
</table>
| High-to-intermediate suspicion | Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule with or without 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 extrathyroidal extension |
| Low suspicion | Isoechoic or hyperechoic solid nodule; or partially cystic nodule with eccentric solid areas, without microcalcification, irregular margin or extrathyroidal extension, or taller-than-wide shape. |
| Very low suspicion | Spongiform or partially cystic nodules without any of the sonographic features described in low-, intermediate-, or high-suspicion patterns |

1.2.7 Categorisation of FNA Cytology Findings

Thyroid nodule cytology should be reported using the diagnostic groups that are outlined in the Bethesda System for Reporting Thyroid Cytopathology. (Grade A)

Bethesda System of Categorisation of FNA Cytology Findings²

<table>
<thead>
<tr>
<th>Cytological diagnosis</th>
<th>All FNAs</th>
<th>All FNAs with histological follow-up</th>
<th>Benign histology</th>
<th>Malignant histology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>% total</td>
<td>n</td>
<td>% total</td>
</tr>
<tr>
<td>Nondiagnostic</td>
<td>3,271</td>
<td>12.9</td>
<td>530</td>
<td>8.3</td>
</tr>
<tr>
<td>Benign</td>
<td>15,104</td>
<td>59.3</td>
<td>1,563</td>
<td>24.6</td>
</tr>
<tr>
<td>AUS/FLUS</td>
<td>2,441</td>
<td>9.6</td>
<td>957</td>
<td>15.0</td>
</tr>
<tr>
<td>FN/SFN</td>
<td>2,571</td>
<td>10.1</td>
<td>1,791</td>
<td>28.2</td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>680</td>
<td>2.7</td>
<td>501</td>
<td>7.9</td>
</tr>
<tr>
<td>Malignant</td>
<td>1,378</td>
<td>5.4</td>
<td>1,020</td>
<td>16.0</td>
</tr>
<tr>
<td>Total</td>
<td>25,445</td>
<td>100</td>
<td>6,362</td>
<td>100</td>
</tr>
</tbody>
</table>

¹Percentage of the 6,362 cases with follow-up. ²Percentage of cases operated in each DC. c Percentage of cases calculated of the total number of operated cases in each category.

1.2.8 Algorithm for Diagnosis of a Thyroid Nodule, Based on US Pattern and FNA Cytology

Suspected thyroid nodule/TSH normal or elevated

Thyroid/neck sonography

High-to-intermediate suspicion pattern

Low-suspicion pattern

Very low-suspicious pattern

Cystic

FNAC ≥1 cm

FNAC ≥1.5 cm

FNAC ≥2 cm

FNAC not required

Cytology Bethesda System

Nondiagnostic

Benign

AUS/FLUS

FN/SFN Hürthle cell neoplasm

Suspicious for malignancy

Malignant

FNAC: Fine-needle aspiration cytology; TSH: Thyroid-stimulating hormone; AUS: Atypia of undetermined significance; FLUS: Follicular lesion of undetermined significance; FN: Follicular neoplasm; SFN: Suspicious for follicular neoplasm.

1.2.9 Guideline Recommendations for Nondiagnostic FNAC Results

Recommendations

- Surgery should be considered for histopathologic diagnosis if the cytologically nondiagnostic nodule has a high-suspicion sonographic pattern, growth of the nodule (>20% in two dimensions) is detected during US surveillance, or clinical risk factors of malignancy are present. (Grade C)
- A repeat US-guided FNAC is recommended for nodules with an initial non-diagnostic cytology, followed by an on-site cytologic evaluation if available. (Grade A)
- Repeatedly nondiagnostic nodules without a high suspicion sonographic pattern require close observation or surgical excision for histopathologic diagnosis. (Grade C)


1.2.10 Guideline Recommendations for Malignant FNAC Results

If the nodule is diagnostic for primary thyroid malignancy, surgery is recommended. (Grade A)


1.2.11 Recommendations for Indeterminate FNAC Results

The suspicious for malignancy (SUSP) cytology is the highest risk category of indeterminate cytology in the Bethesda System (estimated cancer risk: 60%–75%).

**Recommendations for nodules with suspicious for malignancy (SUSP) cytology**

- If the cytology is reported as suspicious for papillary thyroid carcinoma (SUSP), surgical management is recommended depending on clinical risk factors, sonographic features, patient preference, and, possibly, results off mutational testing, if performed. *(Grade A)*
- Consider frozen section for intra-operative evaluation *(Grade C)*

**18FDG-PET is not routinely recommended for evaluating thyroid nodules with indeterminate cytology. *(Grade C)***

**Indeterminate cytology includes AUS/FLUS, FN, SUSP**

**Recommendations for molecular testing of FNA samples with AUS/FLUS, FN, SUSP cytology**

- Molecular testing is not validated in the local population. *(Grade C)*
- Due to cost considerations, it is not yet available for routine testing. *(Grade C)*

AUS: Atypia of undetermined significance; FLUS: Follicular lesion of undetermined significance; FN: Follicular neoplasm; SUSP: Suspicious for malignancy; CLIA/CAP: Clinical Laboratory Improvement Amendments/College of American Pathologists

**Recommendations for nodules with atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) cytology**

- After consideration of worrisome clinical and sonographic features, investigations such as repeat FNA or molecular testing may be used to supplement malignancy risk assessment instead of proceeding directly with surveillance or diagnostic surgery. Consider informed patient preference and feasibility in clinical decision-making. *(Grade C)*
- If repeat FNA cytology and/or molecular testing are not performed or inconclusive, either surveillance or diagnostic surgical excision may be performed, depending on the clinical risk factors, sonographic pattern, and patient preference. *(Grade C)*

AUS: Atypia of undetermined significance; FLUS: Follicular lesion of undetermined significance.

**Recommendations for nodules with follicular neoplasm/suspicious for follicular neoplasm (FN/SFN) cytology**

Diagnostic surgical excision is the established standard of care. However, after consideration of clinical and sonographic features, molecular testing may be used to supplement malignancy risk assessment data in lieu of proceeding directly with surgery. Informed patient preference and feasibility should be considered in clinical decision-making. *(Grade C)*

FN: Follicular neoplasm; SFN: Suspicious for follicular neoplasm; FNAC: Fine-needle aspiration cytology.

1.2.12 Role of Intraoperative Frozen Section for Follicular Lesions

An intraoperative frozen-section examination is not useful when a follicular neoplasm is diagnosed on fine-needle aspiration cytology. (Grade C)

1.2.13 Recommendation for Initial Follow-up of Nodules With Benign FNA Cytology

Guideline Recommendations

- Nodules with high-to-intermediate-suspicion US pattern: Repeat US with or without US-guided FNA within 12 months. (Grade A)*
- Nodules with low-suspicion US pattern: Repeat US at 12–24 months: If there is sonographic evidence of growth (20% increase in at least two nodule dimensions with a minimal increase of 2 mm or more than a 50% change in volume) or development of new suspicious sonographic features, the FNA could be repeated or observation continued with repeat US, with repeat FNA in case of continued growth. (Grade C)
- Nodules with a very low-suspicion US pattern (spongiform nodules): The utility of surveillance US and assessment of nodule growth as an indicator for repeat FNA is limited. (Grade C)
- If a nodule has undergone repeat US-guided FNA, with a second benign cytology result, it is associated with a low risk of malignancy (<1%–2%). (Grade C)

* Solid hypoechoic nodules with one or more additional suspicious US characteristics should be considered for repeat US-guided FNA; US: Ultrasound; FNA: Fine-needle aspiration.

1.2.14 Recommendation for Follow-up of Nodules That do not Meet FNA Criteria

Nodules detected on US that do not meet FNA criteria should be followed-up based on sonographic pattern

- Nodules with high-to-intermediate-suspicion US pattern: Repeat US in 6–12 months. (Grade C)
- Nodules with low-suspicion US pattern: Consider repeat US at 12–24 months. (Grade C)
- Nodules >1 cm with very low-suspicion US pattern and pure cyst: Utility and time interval of surveillance US for risk of malignancy is not known (If US is repeated, it should be at ≥24 months) (No recommendation, insufficient evidence).
- Nodules ≤1 cm, with very low-suspicion US pattern and pure cysts, do not require routine sonographic follow-up. (Grade C)

### 1.3 Diagnostic Tests for Multiple Thyroid Nodules

#### 1.3.1 Diagnostic Tests for Multiple Thyroid Nodules

<table>
<thead>
<tr>
<th>Guideline Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patients with multiple thyroid nodules ≥1 cm should be evaluated in the same fashion as patients with a solitary nodule &gt;1 cm; however, given that each nodule ≥1 cm carries an independent risk of malignancy multiple nodules may require FNA. <em>(Grade A)</em></td>
</tr>
<tr>
<td>• When multiple nodules ≥1 cm are present, those with a suspicious sonographic pattern should be aspirated preferentially. FNA should be performed preferentially, based upon the nodule sonographic pattern and respective size cut-off. <em>(Grade A)</em></td>
</tr>
<tr>
<td>• If none of the nodules has a suspicious sonographic pattern, and multiple nodules coalesce with no intervening normal parenchyma, the likelihood of malignancy is low, and it is reasonable to aspirate only the largest nodules or continue US surveillance without FNA while observing others with serial US. <em>(Grade C)</em></td>
</tr>
<tr>
<td>• A low or low-normal serum TSH concentration in patients with multiple nodules may suggest that some nodule(s) may be autonomous. A radionuclide thyroid scan should be considered in such cases and directly compared with the US images to determine functionality of each nodule &gt;1 cm. The nonfunctioning nodules with high suspicion should be preferentially aspirated. <em>(Grade C)</em></td>
</tr>
</tbody>
</table>

TREATMENT
2.1 Preoperative Staging of Patients With DTC

2.1.1 Preoperative Staging

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck ultrasound</td>
<td>Clinician-directed or formal radiological preoperative staging US of full neck (including thyroid and lateral neck) for cervical (central and especially lateral neck compartments) lymph nodes is recommended for all patients undergoing thyroidectomy for malignant or suspicious for malignancy cytologic or molecular findings. <em>(Grade A)</em></td>
</tr>
<tr>
<td>US-guided FNA</td>
<td>US-guided FNA of sonographically suspicious lymph nodes &gt;8–10 mm in the smallest diameter should be performed for confirming malignancy, as the findings could change the management plan. *(Grade A)*1</td>
</tr>
<tr>
<td>CT/MRI</td>
<td>Preoperative use of cross-sectional imaging studies (CT, MRI) with intravenous contrast is recommended as an adjunct to ultrasound for patients with clinical suspicion for advanced disease, including invasive primary tumor, or clinically apparent multiple or bulky lymph node involvement. <em>(Grade A)</em></td>
</tr>
<tr>
<td>18FDG-PET</td>
<td>Routine preoperative 18FDG-PET scanning is not recommended. <em>(Grade A)</em></td>
</tr>
<tr>
<td>¹³¹I therapy</td>
<td>A 2-month delay between the use of iodinated contrast media and subsequent ¹³¹I therapy is advised when CT is used in preoperative assessment. <em>(Grade A)</em></td>
</tr>
</tbody>
</table>

2.2 Eligible Patients and Preferred Choices for Surgical Management

2.2.1 Patients Eligible for Surgical Management

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobectomy¹</td>
<td>Thyroid cancer &lt;1 cm without extrathyroidal extension and cN0, and no other risk factors <em>(Grade A)</em></td>
</tr>
<tr>
<td>Hemithyroidectomy²</td>
<td>• FTC (excluding Hürthle cell microcarcinoma) ≤4 cm, in the absence of other adverse risk factors (age &gt;45 years, widely invasive, lymph node/distant metastases, and angioinvasion) <em>(Grade B)</em></td>
</tr>
<tr>
<td></td>
<td>• Oncocytic (Hürthle cell) microcarcinoma <em>(Grade B)</em></td>
</tr>
<tr>
<td>Personalised decision-making</td>
<td>• Thyroid cancer &gt;1 cm and &lt;4 cm without extrathyroidal extension and without clinical evidence of any lymph node metastases (cN0) <em>(Grade B)</em></td>
</tr>
<tr>
<td>(lobectomy or total thyroidectomy³)</td>
<td>• MicroPTC with history of neck irradiation <em>(Grade B)</em></td>
</tr>
<tr>
<td>Total thyroidectomy³</td>
<td>• Thyroid cancer &gt;4 cm <em>(Grade A)</em></td>
</tr>
<tr>
<td></td>
<td>• Gross extrathyroidal extension (clinical T4) <em>(Grade A)</em></td>
</tr>
<tr>
<td></td>
<td>• Clinically apparent metastatic disease to nodes (clinical N1) or distant sites (clinical M1) <em>(Grade A)</em></td>
</tr>
<tr>
<td>Completion thyroidectomy³</td>
<td>• Offered to patients for whom a bilateral thyroidectomy would have been recommended had the diagnosis been available before the initial surgery <em>(Grade B)</em></td>
</tr>
<tr>
<td></td>
<td>• To be done preferably within 2 weeks or more than 3 months after initial surgery</td>
</tr>
</tbody>
</table>

2.3 Role of Prophylactic and Therapeutic Neck Dissection in Patients With DTC

2.3.1 Guidelines for Prophylactic Central Compartment Neck Dissection

| Recommended | Unilateral PCCND should be considered in patients with papillary thyroid carcinoma with clinically uninvolved central neck lymph nodes (cN0) who have advanced primary tumours (T3 or T4), clinically involved lateral neck nodes (cN1b), or if the information will be used to plan further steps in therapy. (Grade C) |
| Not Required | Thyroidectomy in small (T1 or T2), non-invasive, clinically node-negative PTC (cN0) and for most follicular cancers¹ (Grade A) |
| Not Recommended | MicroPTC that is either multifocal involving both lobes or with minimal extrathyroidal extension through the thyroid capsule (pT3) (Grade A) |
| | In patients aged <45 years with classical-type PTC ≤4 cm, unifocal, no extrathyroidal extension on US and who have clinical or radiological evidence of lymph node involvement (Grade A)² |
| | In patients aged >45 years with PTC <1 cm, multifocal, with minimal extrathyroidal extension through the thyroid capsule (pT3) and who have no clinical/radiological evidence of lymph node involvement (Grade A)² |
| | Oncocytic (Hürthle cell) follicular carcinoma (Grade A)² |

2.3.2 Guidelines for Prophylactic Lateral Compartment Neck Dissection

Prophylactic lateral compartment neck dissection in patients with differentiated thyroid cancer is not recommended. (Grade A)

2.3.3 Therapeutic Central and Lateral Compartment Neck Dissection

| Therapeutic Lymph Node Dissection² | Therapeutic level VI/VII node dissection is recommended: |
| | In cases of overt disease in the central compartment discovered prior to/at surgery. (Grade A) |
| Dissection of levels 1, IIb, and Va is NOT recommended: |
| | In the absence of clear indications. (Grade B) |
| A therapeutic central and selective lateral neck dissection (levels IIa–Vb) preserving the accessory nerve, sternocleidomastoid muscle, and internal jugular vein is recommended: |
| | When suspicious/clinically involved nodes in the lateral neck are apparent preoperatively or are encountered at thyroidectomy and confirmed by needle biopsy or frozen section (Good practice point). |
| If there is doubt as to the pathological nature of the nodes, the frozen section has high sensitivity and specificity for detecting PTC (Good practice point). |

2.4 Postoperative Staging of Patients With DTC

2.4.1 Postoperative Staging for Risk Stratification for Mortality

AJCC/UICC (7th edition) staging is recommended for all patients with DTC, based on its utility in predicting disease mortality and its requirement for cancer registries. (Grade A)¹,²

2.4.2 Minimum Dataset for Histopathological Reporting of Thyroid Cancer

Diagnosis

<table>
<thead>
<tr>
<th>Site</th>
<th>Tumour size</th>
<th>Tumour type:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>• If PTC, include variants where possible</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Presence or absence of encapsulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Presence or absence of capsular invasion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Multi-focality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Extrathyroidal extension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular invasion (number of vessels)</th>
<th>Lymph node metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• No. of involved nodes</td>
</tr>
<tr>
<td></td>
<td>• Size of largest nodal metastasis: &lt;0.2 cm/ 0.2 – 3 cm/ &gt;3 cm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Presence or absence of extranodal extension</th>
<th>Uninvolved thyroid, e.g. thyroiditis</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Resection margins</th>
<th>Staging</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• AJCC / TNM</td>
</tr>
</tbody>
</table>

PTC: Papillary thyroid carcinoma; AJCC/TNM: American Joint Committee on Cancer/tumor node metastasis.

2.4.3 Favourable and Unfavourable Histologic Types of Differentiated Thyroid Cancer

<table>
<thead>
<tr>
<th>Favourable</th>
<th>Unfavourable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical papillary thyroid carcinoma</td>
<td>Poorly differentiated thyroid carcinoma</td>
</tr>
<tr>
<td>Papillary microcarcinoma</td>
<td>Widely invasive follicular carcinoma</td>
</tr>
<tr>
<td>Minimally invasive follicular carcinoma</td>
<td>Unfavourable papillary thyroid carcinoma variants</td>
</tr>
<tr>
<td>Encapsulated classical papillary thyroid carcinoma</td>
<td>• Tall cell</td>
</tr>
<tr>
<td></td>
<td>• Columnar cell</td>
</tr>
<tr>
<td></td>
<td>• Solid</td>
</tr>
<tr>
<td></td>
<td>• Diffuse sclerosing</td>
</tr>
<tr>
<td></td>
<td>• Hobnail</td>
</tr>
</tbody>
</table>

Note: There is growing evidence that the newly described entity, viz. “non-invasive follicular thyroid neoplasm with papillary-like nuclear features” (NIFTP), a diagnosis made on excision biopsy, is an indolent tumour with a low risk of aggressive behaviour with conservative management (lobectomy) advocated.¹

### 2.5 Risk Stratification of Patients With DTC

#### 2.5.1 Risk Stratification for Recurrence – Low Risk

<table>
<thead>
<tr>
<th>Low-risk patients include those with any of the following (Grade A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary thyroid cancer (with all of the following)</td>
</tr>
<tr>
<td>• No local or distant metastases</td>
</tr>
<tr>
<td>• All macroscopic tumour has been resected</td>
</tr>
<tr>
<td>• No tumour invasion of loco-regional tissues or structures</td>
</tr>
<tr>
<td>• The tumour does not have aggressive histology (e.g. tall cell, hobnail variant, columnar cell carcinoma)</td>
</tr>
<tr>
<td>• If $^{131}$I is given, there are no RAI avid metastatic foci outside the thyroid bed on the first post-treatment whole-body RAI scan.</td>
</tr>
<tr>
<td>• No vascular invasion</td>
</tr>
<tr>
<td>• Clinical N0 or ≤5 pathologic N1 micrometastases (&lt;0.2 cm in largest dimension)</td>
</tr>
</tbody>
</table>

- Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer
- Intrathyroidal, well-differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion
- Intrathyroidal, papillary microcarcinoma, unifocal, or multifocal, including V600E BRAF mutated (if known)

---

#### 2.5.2 Risk Stratification for Recurrence – Intermediate Risk

<table>
<thead>
<tr>
<th>Intermediate risk patients include those with any one of the following (Grade A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopic invasion of tumour into the perithyroidal soft tissues</td>
</tr>
<tr>
<td>RAI avid metastatic foci in the neck on the first post-treatment whole-body RAI scan</td>
</tr>
<tr>
<td>Aggressive histology (e.g. tall cell, hobnail variant, columnar cell carcinoma)</td>
</tr>
<tr>
<td>Papillary thyroid cancer with vascular invasion</td>
</tr>
<tr>
<td>Clinical N1 or &gt;5 pathologic N1 with all involved lymph nodes &lt;3 cm in the largest dimension</td>
</tr>
<tr>
<td>Intrathyroid, papillary thyroid cancer, primary tumour 1–4 cm, V600E BRAF mutated (if known)</td>
</tr>
<tr>
<td>Multifocal papillary microcarcinoma with extrathyroidal extension and V600E BRAF mutated (if known)</td>
</tr>
</tbody>
</table>

2.5.3 Risk Stratification for Recurrence – High Risk

High-risk patients include those with any of the following (Grade A)

- Macroscopic invasion of tumour into the perithyroidal soft tissues (gross extrathyroidal extension)\(^1\,\,^2\)
- Incomplete tumour resection\(^1\,\,^2\)
- Distant metastases\(^1\,\,^2\)
- Postoperative serum thyroglobulin suggestive of distant metastases\(^1\)
- Pathologic N\(_1\) with any metastatic lymph node \(\geq 3\) in the largest dimension\(^1\)
- Follicular thyroid cancer with extensive vascular invasion (>4 foci of vascular invasion)\(^1\)

2.5.4 Dynamic Risk Stratification for Recurrence During Follow-up

<table>
<thead>
<tr>
<th>Excellent response</th>
<th>Indeterminate response</th>
<th>Incomplete response</th>
</tr>
</thead>
<tbody>
<tr>
<td>All of the following</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suppressed Tg*</td>
<td>&lt;1 μg/L</td>
<td>&lt;1 μg/L</td>
</tr>
<tr>
<td>Stimulated Tg*</td>
<td>&lt;1 μg/L</td>
<td>(\geq 1) and &lt;10 μg/L</td>
</tr>
<tr>
<td>Neck US</td>
<td>No evidence of disease</td>
<td>Nonspecific changes/stable subcentimeter lymph nodes</td>
</tr>
<tr>
<td>Cross-sectional and/or nuclear medicine imaging</td>
<td>Negative (if performed)</td>
<td>Nonspecific changes, although not completely normal</td>
</tr>
</tbody>
</table>

- Low risk
- Intermediate risk
- High risk

## 2.6 Role of Postoperative RRA in Patients With DTC

### 2.6.1 Treatment With Radioactive Iodine

The primary goal of the first dose of RAI after total thyroidectomy varies depending on the risk stratification of the patient.

<table>
<thead>
<tr>
<th>Type of treatment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remnant ablation</td>
<td>To facilitate detection of recurrent disease and initial staging</td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td>To decrease risk of recurrence and disease specific mortality by destroying suspected but unproven metastatic disease</td>
</tr>
<tr>
<td>RAI therapy</td>
<td>To treat known persistent disease</td>
</tr>
</tbody>
</table>

From a theoretical point of view, this first dose of RAI may also be considered adjuvant therapy, because of the potential tumouricidal effect on persistent thyroid cancer cells that lasts even after appropriate surgery in patients at risk for recurrence or disease-specific mortality.

### 2.6.2 Indications for Postoperative RAI Remnant Ablation

#### No Indications

All criteria below should be met.

- Tumour ≤1 cm, unifocal or multifocal
- Histology (classical papillary/follicular variant of papillary carcinoma/follicular carcinoma)
- Minimally invasive, without angioinvasion
- No invasion of thyroid capsule (extrathyroidal extension)

#### Definite Indications

Any one of the criteria below should be met.

- Tumour >4 cm
- Widely invasive histology
- Any tumour size, with gross extra thyroidal extension
- Distant metastases present
- Multiple lymph node involvement (>5 nodes), large size of involved lymph nodes (>3 cm), high ratio of positive to negative nodes, extracapsular nodal involvement
- Unfavourable cell type (tall cell, columnar, or diffuse sclerosing papillary cancer, poorly differentiated elements)

#### Uncertain Indications

All other cases

One or more of the following risk factors may identify patients at higher risk of recurrence who may benefit from RRA:

- Tumour size (1–4 cm)
- Small (≤2 mm), multiple lymph node involvement (1–5 nodes)

RAI: Radioactive iodine; RRA: Radioactive iodine remnant ablation.

### 2.6.3 Conditions in Which Postoperative RAI Remnant Ablation is not Routinely Recommended

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendation Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>After total thyroidectomy for ATA low-risk DTC patients</td>
<td>Grade C</td>
</tr>
<tr>
<td>After lobectomy or total thyroidectomy for patients with unifocal papillary microcarcinoma, in the absence of other adverse features</td>
<td>Grade A</td>
</tr>
<tr>
<td>After total thyroidectomy for patients with multifocal papillary microcarcinoma, in the absence of other adverse features</td>
<td>Grade C</td>
</tr>
<tr>
<td>In lieu of completion thyroidectomy: However, it may be used to ablate the remnant lobe in selected cases</td>
<td>Grade C</td>
</tr>
</tbody>
</table>

### 2.6.4 Recommendations of RAI Remnant Ablation in Pregnancy/Conception

**Key recommendation:**

Pregnancy must be ruled out before RRA or $^{131}$I therapy is administered in women of reproductive age. (Grade C)

The dopamine agonist cabergoline can be considered for suppressing lactation, if necessary. (Grade C)

**Key recommendation:** Breastfeeding must be discontinued at least 8 weeks before RRA or $^{131}$I therapy, to avoid breast irradiation; breastfeeding should not be resumed until after a subsequent pregnancy. (Grade C)

**In male patients:**

- Pre-treatment sperm banking should be considered if the patient is likely to have more than two sessions of high-activity $^{131}$I therapy. (Grade C)

### 2.6.5 Indications for Postoperative RAI Adjuvant (High Dose) Therapy

**Radioactive adjuvant therapy is RECOMMENDED in the following conditions:**

- After total thyroidectomy for ATA high-risk differentiated thyroid cancer patients (Grade A)
- After total thyroidectomy in ATA intermediate-risk level differentiated thyroid cancer patients, use selectively (Grade C)

**Radioactive adjuvant therapy is NOT ROUTINELY RECOMMENDED in the following conditions:**

- In lieu of completion thyroidectomy: However, it may be used to ablate the remnant lobe in selected cases (Grade C)
- After thyroidectomy for ATA low-risk DTC patients (Grade C)

---

2.6.6 RAI Therapy in Patients With Metastatic Disease

Loco-regional or metastatic disease

- Recombinant human TSH–mediated therapy may be indicated in selected patients with underlying comorbidities. (Grade A)
  - High risk of iatrogenic hypothyroidism potentially risky
  - Pituitary disease whose serum TSH cannot be raised
  - Deleterious effects with delay in therapy

Bone metastasis

- RAI therapy of iodine-avid bone metastases has been associated with improved survival and should be employed, although RAI is rarely curative. (Grade A)
- Selection of activity of $^{131}$I is empirical - 100–200 mCi or determined by dosimetry (Grade C)

Brain metastasis

- RAI can be considered if CNS metastases concentrate RAI. (Grade C)
- Stereotactic EBRT and concomitant glucocorticoid therapy are recommended prior to RAI therapy, to minimise the effects of a potential TSH-induced increase in tumour size and RAI-induced inflammatory response. (Grade C)

Pulmonary micrometastasis

- Patients should be treated with RAI and it should be repeated every 6–12 months as long as disease continues to concentrate RAI and responds clinically. (Grade A)
- Treatment with higher $^{131}$I activities such as 100–200 mCi or 100–150 mCi for patients ≥70 years old is recommended. (Grade A)
- $^{131}$I treatment with activity estimated by dosimetry to limit whole-body retention to 80 mCi at 48 hours and 200 cGy to the bone marrow is recommended. (Grade A)

2.7 Preparation for RRA: Thyroxine Withdrawal vs. rhTsh vs. T3 Withdrawal

2.7.1 Preparation of Patients for RRA (Thyroxine Withdrawal vs. rhTSH vs. T3 Withdrawal)

<table>
<thead>
<tr>
<th>Levothyroxine (LT4) withdrawal</th>
<th>Triiodothyronine (LT3) withdrawal</th>
<th>rhTSH (Thyrogen') stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>If the period between surgery and RRA is expected to be longer than 4 weeks, the patient should be commenced on thyroid hormone replacement (levothyroxine), followed by substitution with LT3 treatment for 28 days prior to RRA; LT3 should be withdrawn 14 days prior to RRA. (Grade A)</td>
<td>If RRA is planned within 3–4 weeks of surgery, LT3 is commenced one day after surgery and withdrawn 14 days before RRA. (Grade A)</td>
<td>Patients with tumour characteristics pT1 to T3, pN0 or NX or N1, and M0 and R0 (no microscopic residual disease). (Grade C)</td>
</tr>
</tbody>
</table>

Personalised decision-making between thyroxine withdrawal and rhTSH should be done in high-risk patients or patients with recurrent or metastatic disease where the advantage of one over the other is uncertain. (Grade A)

Patients should be advised to adopt a low-iodine diet for 1–2 weeks prior to RRA (Grade A).

2.7.2 Use of rhTSH-Stimulated Tg

- In patients with ATA low-risk and ATA intermediate-risk DTC without extensive lymph node involvement (i.e. T1-T3, N0/Nx/N1a, M0) in whom radioiodine remnant ablation or adjuvant therapy is planned:
  - Preparation with rhTSH stimulation is an acceptable alternative to thyroid hormone withdrawal for achieving remnant ablation. *(Grade A)*
- In patients with ATA intermediate-risk DTC who have extensive lymph node disease (multiple clinically involved LN) in the absence of distant metastases:
  - Preparation with rhTSH stimulation may be considered as an alternative to thyroid hormone withdrawal, prior to adjuvant radioactive iodine treatment. *(Grade C)*
- In patients with ATA high-risk DTC with attendant higher risk of disease-related morbidity and mortality:
  - More controlled data from long-term outcome studies are needed before rhTSH preparation for RAI adjuvant treatment can be recommended *(No recommendation, insufficient evidence).*

2.7.3 Use of rhTSH-Stimulated Tg in Specific Patient Subgroups

- In patients with DTC of any risk level with a significant comorbidity that may preclude thyroid hormone withdrawal prior to iodine radioiodine administration, recombinant human thyrotropin preparation should be considered. *(Grade A)*
- Patients who are deemed to be at significantly increased risk of side effects/complications from undergoing thyroid hormone withdrawal are as follows (Good practice point):
  - Patients with h/o stroke, TIA, or underlying heart disease, especially heart failure
  - Patients with renal failure who have altered clearance of RAI owing to prolonged hypothyroidism
  - Patients with h/o active psychiatric disorders
  - Patients with severe compromise of overall performance status
  - Patients on medications with a narrow therapeutic index, as clearance is impaired
  - Patients with hypopituitarism or who have previously been unable to achieve an adequate increase in endogenous TSH levels
  - Patients >65 years of age (irrespective of other concurrent medical conditions)

Generally, paediatric patients are not considered to be within the medically necessary category, as they are more likely to tolerate a short period of hypothyroidism and can often achieve adequate endogenous TSH elevation within 2 weeks of levothyroxine withdrawal.

2.8 Activity of $^{131}$I Used for Remnant Ablation

2.8.1 Activity of $^{131}$I Used for Remnant Ablation or Adjuvant Therapy

<table>
<thead>
<tr>
<th>Activity</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lower activities</strong></td>
<td>Approximately 30 mCi is favoured over higher administered dose activities in patients with:</td>
</tr>
<tr>
<td></td>
<td>- ATA low risk thyroid cancer</td>
</tr>
<tr>
<td></td>
<td>- Intermediate-risk disease with lower-risk features after radioactive iodine remnant ablation and total thyroidectomy. <em>(Grade A)</em></td>
</tr>
<tr>
<td><strong>Higher activities</strong></td>
<td>Can be considered for patients receiving less than a total or near-total thyroidectomy where a larger remnant is suspected or where adjuvant therapy is intended. <em>(Grade C)</em></td>
</tr>
<tr>
<td></td>
<td>Up to 150 mCi is generally recommended when RAI is intended for initial adjuvant therapy, to treat suspected microscopic residual disease. <em>(Grade C)</em></td>
</tr>
</tbody>
</table>

## 2.9 Role of External Beam Radiation and Chemotherapy

### 2.9.1 Role of External Beam Radiation and Chemotherapy

**External beam radiation therapy**

**Not recommended**
- No role for routine adjuvant EBRT to the neck in patients with DTC after initial complete surgical removal of the tumour (Grade A).

**Recommended**
- As a treatment in unresectable advanced tumour and as a palliative modality in distant metastasis (Grade A).
- In patients with recurrent tumour that fails to concentrate radioiodine (Grade C).

**Consider**
- The timing of RRA and EBRT needs to be decided by a multi-disciplinary team, based on the patient's condition (Good practice point).

**Chemotherapy**

There is no role for routine systemic adjuvant therapy in patients with DTC (beyond RAI and/or TSH suppressive therapy using levothyroxine). (Grade A)

## 2.10 Kinase Inhibitor Therapy in DTC patients

### 2.10.1 Recommendations for Kinase Inhibitor Therapy

**Indications of kinase inhibitor therapy** (Grade C)
- RAI-refractory DTC patients with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease not otherwise amenable to local control using other approaches (Grade C).

**Prerequisites for initiating kinase inhibitor therapy** (Grade A)
- Patients should be thoroughly counselled on the potential risks and benefits of this therapy as well as alternative therapeutic approaches, including best supportive care.
- Appropriate informed consent should be obtained and documented in the medical record.

**Failure of first-line kinase therapy** (Grade C)
- Second-line kinase inhibitor therapy should be considered in patients who have disease progression while on initial kinase inhibitor therapy without prohibitive adverse effects.
- Should be undertaken within the context of therapeutic clinical trials.
## 2.10.2 Factors to Review When Considering Kinase Inhibitor Therapy

### Factors Favouring Kinase Inhibitor Therapy

- Imminently threatening disease progression expected to require intervention and/or expected to produce morbidity or mortality in <6 months (e.g. pulmonary lesions or lymphadenopathy likely to rapidly invade airways, produce dyspnea, or cause bronchial obstruction)
- Clinically significant anatomical disease progression in 6 months or less despite optimal TSH suppression in RAI-refractory disease not amenable to control using focal therapeutic approaches (e.g. surgery, radiation therapy, ablation)
- Symptomatic disease (e.g. exertional dyspnea, painful unresectable adenopathy) not adequately addressable using directed therapy
- Diffuse disease progression, in contrast to focal progression (as seen in multiple lung metastases vs. growth of few lesions)

### Factors Discouraging Kinase Inhibitor Therapy

**Comorbidity, including:**

- Active or recent intestinal disease (e.g. diverticulitis, inflammatory bowel disease, recent bowel resection)
- Liver disease
- Recent bleeding (e.g. ulcer/GI bleed) or coagulopathy
- Recent cardiovascular event(s) (e.g. CVA, MI)
- Recent tracheal radiation therapy (this is associated with an increased risk of aerodigestive fistula, with kinase inhibitor therapy)
- Cachexia/low weight/poor nutrition
- Poorly controlled hypertension
- Prolonged QTc interval/history of significant arrhythmia (includes ventricular and bradyarrhythmia)
- Untreated brain metastases (controversial)
- Recent suicidal ideation (suicide has been reported in depressed patient receiving TKIs)

**Life expectancy based on other comorbidity estimated to be too brief to justify systemic therapy**

### 3.1 Thyroxine Suppressive Therapy: TSH Targets and Duration of Therapy

#### 3.1.1 Thyroxine-Suppressive Therapy: TSH Targets and Duration

<table>
<thead>
<tr>
<th>Patient Subgroup</th>
<th>TSH levels</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial TSH suppression for high-risk thyroid cancer patients</td>
<td>&lt;0.1 mU/L</td>
<td>Grade A</td>
</tr>
<tr>
<td>Initial TSH suppression for intermediate-risk thyroid cancer patients</td>
<td>0.1–0.5 mU/L</td>
<td>Grade C</td>
</tr>
<tr>
<td>For low-risk patients who have undergone remnant ablation and have</td>
<td>At lower end of the reference range</td>
<td>Grade C</td>
</tr>
<tr>
<td>undetectable serum Tg levels, along with surveillance for recurrence</td>
<td>(0.5–2 mU/L)</td>
<td></td>
</tr>
<tr>
<td>For low-risk patients who have undergone lobectomy (along with</td>
<td>At lower end of reference range</td>
<td>Grade C</td>
</tr>
<tr>
<td>surveillance for recurrence)</td>
<td>(0.5–2 mU/L)</td>
<td></td>
</tr>
</tbody>
</table>

Tg: Thyroglobulin, TSH: Thyroid-stimulating hormone.

#### 3.2 Role of Neck Ultrasound, 18FDG PET/CT Scan, CT/MRI, and Whole-Body Scan in Follow-up

##### 3.2.1 Role of Neck Ultrasound in Follow-up

Following surgery, cervical US to evaluate the thyroid bed and central and lateral cervical nodal compartments should be performed at 6–12 months and then periodically, depending on the patient’s risk for recurrent disease and Tg status (Grade A)

- If a positive result would change management, ultrasonographically suspicious lymph nodes >1 cm in the smallest diameter can be considered for biopsy for cytology with Tg measurement in needle washout fluid. (Grade C)
- If the nodes <1 cm threaten vital structures, biopsy should be considered for the central neck compartment. (Grade C)
- US-guided FNAC should be considered in the presence of other factors, such as proximity to structures, pharyngeal nerve involvement, and rapidity of growth of nodes. (Grade C)

3.2.2 Role of Whole-Body Scan in Follow-up

- Low-risk and intermediate-risk patients (with lower risk features) having no uptake outside thyroid bed, undetectable Tg with negative antithyroglobulin antibodies, and negative US (excellent response to therapy) do not require routine diagnostic WBS during follow-up post RXWBS following RAI remnant ablation or adjuvant therapy. (Grade A)

- As one of the imaging modalities, DXWBS, either following thyroid hormone withdrawal or rhTSH, 6–12 months after remnant ablation adjuvant RAI therapy, can be useful in the follow-up of patients with high or intermediate risk (higher risk features) of persistent disease and should be done with low-activity 131I. (Grade B)

Tg: Thyroglobulin, US: Ultrasound, RXWBS: First posttreatment whole-body RAI scan, DXWBS: Diagnostic whole-body scintigraphy.

3.2.3 Role of 18FDG-PET and CT Scan in Follow-up

18FDG-PET scanning should be considered in all DTC patients with elevated serum stimulated Tg (generally >10 ng/mL) and/or rising antibodies with negative radioiodine imaging.

Appropriate imaging studies may be considered in other indicated regions in such patients. (Grade A)

18FDG-PET: Deoxy-2[18F]fluoro-d-glucose Positron emission tomography, Tg: Thyroglobulin, RAI: Radioactive iodine.

3.2.4 Role of CT and MRI Imaging in Follow-up

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
</table>
| CT/MRI        | Cross-sectional imaging of the neck (CT, MRI) with intravenous contrast or any other relevant imaging modalities should be considered:  
  - In the setting of bulky and widely distributed recurrent nodal disease where ultrasound may not completely delineate disease,  
  - In the assessment of possible invasive recurrent disease where potential aerodigestive tract invasion requires complete assessment, or  
  - When neck ultrasound is negative and to exclude mediasternal or retropharyngeal disease (high Tg). | Grade B |

CT: Computerised tomography, MRI: Magnetic resonance imaging, Tg: Thyroglobulin.

3.3 Significance of Assessing Serum Thyroglobulin Levels

During initial follow-up, serum Tg on thyroxine therapy should be measured every 6–12 months. More frequent Tg measurements may be appropriate for ATA high-risk patients. The frequency may be modified subsequently based on the patient’s risk category and the response to treatment. (Grade C)

### 3.4 Significance of Antithyroglobulin Antibody

#### 3.4.1 Significance of Antithyroglobulin Antibody Measurement

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Recommendation</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithryoglobulin antibodies</td>
<td>Thyroglobulin antibodies should be quantitatively assessed with every measurement of serum Tg levels. In ideal situations, both serum Tg and Tg antibodies should be assessed longitudinally in the same laboratory and using the same assay, for a given patient.</td>
<td>Grade A</td>
</tr>
</tbody>
</table>

### 3.5 Stimulated vs. Unstimulated Thyroglobulin Levels and Their Interpretation

#### 3.5.1 Stimulated vs. Unstimulated Thyroglobulin Levels and Their Interpretation

- Stimulated Tg may not be required to verify the absence of disease in low-risk patients who have had an excellent response to therapy, with negative findings on ultrasound. *(Grade A)*

- Subsequent TSH stimulated Tg testing may be considered to reassess response to therapy in patients with an indeterminate, biochemical incomplete, or structurally incomplete response following either additional therapies or a spontaneous decline in Tg values on thyroid hormone therapy over time. *(Grade C)*

### 3.6 Managing Tg-Positive, Scan-Negative Patients

#### 3.6.1 Managing Tg-Positive, Scan-Negative Patients

<table>
<thead>
<tr>
<th>Patient Subgroup</th>
<th>Recommendation</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tg-positive, scan-negative</td>
<td>In the absence of structurally evident disease, patients with stimulated serum Tg &lt;10 ng/mL with thyroid hormone withdrawal or &lt;5 ng/mL with rhTSH (indeterminate response) can be followed without empiric RAI therapy on continued thyroid hormone therapy alone, reserving additional therapies for those with rising serum Tg levels over time or other evidence of structural disease progression.</td>
<td>Grade C</td>
</tr>
</tbody>
</table>

**Rising Tg levels, scan-negative disease**

Empiric (100–200 mCi) or dosimetrically determined radioactive iodine therapy may be considered in patients with significantly elevated serum Tg levels or rapidly rising serum Tg/Tg antibody levels in whom imaging (anatomic neck/chest imaging and/or 18FDG-PET/CT) studies have failed to reveal a tumour source that is amenable to directed therapy. *(Grade C)*

3.7 Managing Non-Iodine-Avid Disease

3.7.1 Role of Non-Avid Disease

<table>
<thead>
<tr>
<th>Patient subgroup</th>
<th>Recommendation</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-iodine-avid disease</td>
<td>A patient is considered to have RAI-refractory disease if empiric RAI therapy is given and the post-therapy scan is negative and Tg remains unchanged/unreduced; in such cases, no further RAI therapy should be administered.</td>
<td>Grade C</td>
</tr>
</tbody>
</table>

RAI could be repeated in the presence of persistent nonresectable disease, which is localised after an empiric dose of RAI, and if there is objective evidence of significant tumour reduction, until the tumour has been eradicated or the tumour no longer responds to treatment. (Grade C)

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