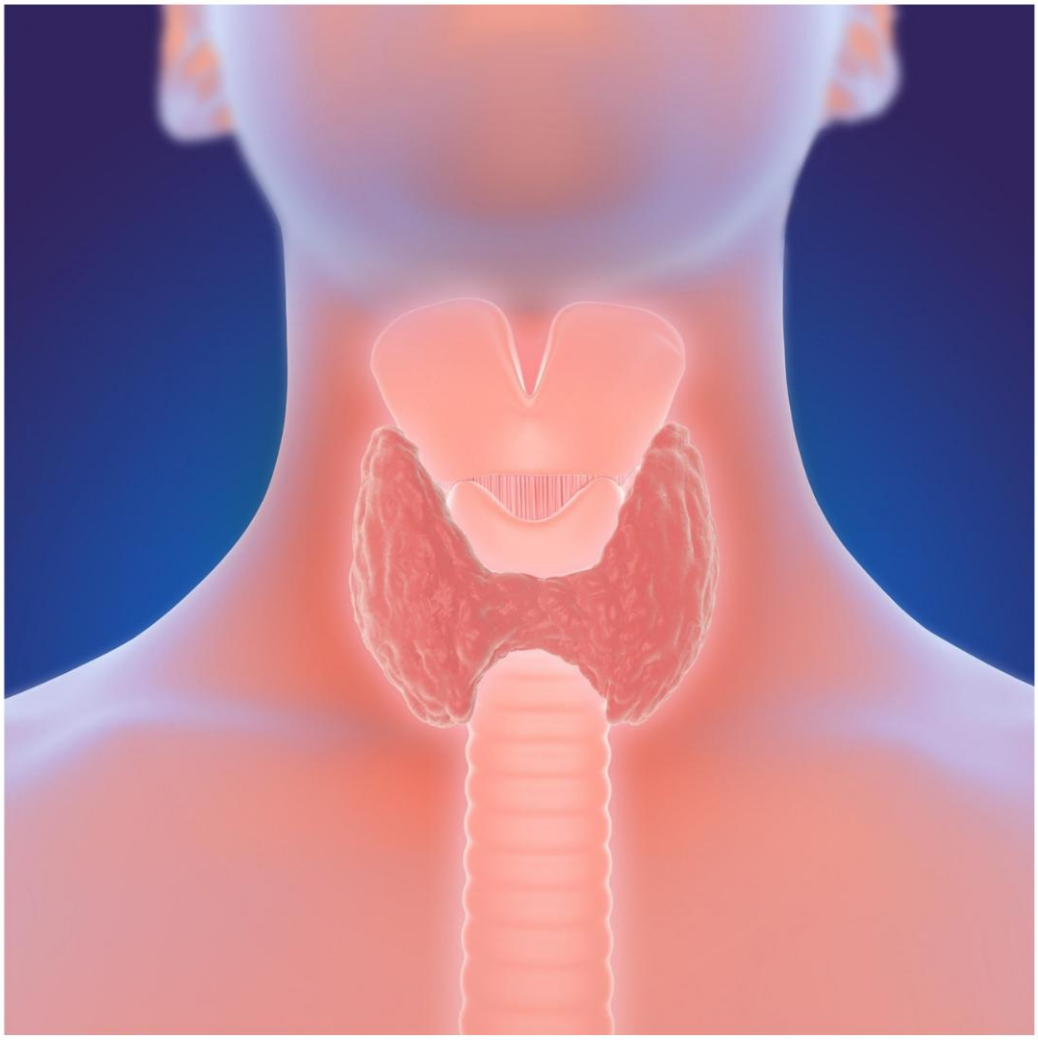
NATIONAL GUIDELINE ON THE DIAGNOSIS AND MANAGEMENT OF THYROID CANCER 2026



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Foreword

Thyroid cancer is among the most readily curable solid malignancies when diagnosed early and managed within a structured, evidence-based pathway. The biology of the disease is heterogeneous ranging from indolent papillary microcarcinomas, in which active surveillance may suffice, to anaplastic carcinoma, where management is measured in days rather than months.

Care of patients with thyroid cancer in the Maldives takes place across a geographically dispersed and resource-constrained healthcare system. Initial evaluation is increasingly possible at the atoll and regional hospital level, while definitive surgical care is concentrated in tertiary centres in Malé. Radioiodine ablation is not yet available in-country, and patients requiring it are referred overseas through Aasandha-empanelled centres. Multidisciplinary tumour board (MDT) review now takes place at our tertiary hospitals, and access to systemic agents including tyrosine kinase inhibitors and targeted therapies has expanded through Aasandha and the National Social Protection Agency (NSPA).

This guideline has been compiled to provide Maldivian clinicians with a practical, locally relevant standard for the diagnosis, staging, treatment, and follow-up of thyroid cancer. International standards NCCN, ESMO, ATA, and the WHO Classification of Endocrine Tumours form the technical basis. Wherever a recommendation requires interpretation in the Maldivian context, a section titled “Maldives Practice Note” has been added.

A dedicated section on the national referral pathway maps the journey of a patient from a regional hospital nodule presentation to definitive surgery, RAI, systemic therapy, and follow-up. It is intended to bring clarity to clinicians at every level of the system and to support a more uniform standard of care across atolls.

This is the first edition; it will be revised periodically as the evidence evolves and as oncology services in the Maldives continue to grow.

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1. Introduction and Epidemiology

Thyroid cancer is a malignant neoplasm arising from the epithelial cells of the thyroid gland. It comprises several histological subtypes with markedly different biological behaviour and prognosis. Globally, differentiated thyroid cancers (DTC), particularly papillary thyroid carcinoma (PTC), account for the great majority of cases. Reported incidence has risen steadily over recent decades in part due to genuine increases in disease, and in part due to wider access to neck imaging and fine-needle aspiration cytology (FNAC), which together detect small, indolent tumours that would not previously have come to attention.[5,17]

1.1 Classification

Thyroid cancers are categorised by cell of origin and biological behaviour:

- **Differentiated thyroid cancer (DTC) derived from follicular epithelium:**
  - Papillary thyroid carcinoma (PTC), including its subtypes (classic, follicular, tall cell, columnar cell, diffuse sclerosing, hobnail, etc.).
  - Follicular thyroid carcinoma (FTC), minimally invasive or widely invasive.
  - Oncocytic (Hürthle cell) carcinoma, now classified as a distinct entity in the 2022 WHO classification.
- **High-grade follicular cell-derived non-anaplastic thyroid carcinoma**: a category newly recognised in the 2022 WHO classification, encompassing differentiated high-grade thyroid carcinoma and poorly differentiated thyroid carcinoma; behaviour is intermediate between DTC and anaplastic carcinoma.
- **Medullary thyroid carcinoma (MTC)**: derived from parafollicular C cells; sporadic (~75–80%) or hereditary as part of MEN 2A or MEN 2B.
- **Anaplastic (undifferentiated) thyroid carcinoma (ATC)**: highly aggressive, often arising from a pre-existing differentiated tumour through dedifferentiation.

1.2 Global Epidemiology

Globally, thyroid cancer was estimated to account for **821,214 new cases** and **47,507 deaths** in 2022 (GLOBOCAN), making it the seventh most commonly diagnosed cancer worldwide.[1,6]

- Thyroid cancer accounts for approximately 1-2% of all malignancies and is roughly three to four times more common in women than men.

- Peak incidence occurs between 30 and 55 years of age.
- Papillary carcinoma is the most common subtype (80-85% of cases), followed by follicular carcinoma; medullary carcinoma constitutes 3-5% and anaplastic carcinoma <2%.
- Prognosis varies dramatically by subtype: DTC has a 10-year disease-specific survival exceeding 90%, whereas ATC has a median overall survival of 3-6 months.
- Reported age-standardised incidence is highest in Cyprus, the Republic of Korea, and parts of East Asia, reflecting both genuine differences and the impact of intensive screening and ultrasound use.

1.3 Epidemiology in the Maldives

Cancer is an emerging public health priority in the Maldives. The IARC/WHO Global Cancer Observatory estimated approximately **496 new cancer cases and 264 cancer-related deaths** in the Maldives in 2020, with breast, colorectal, lung, lymphoma, and thyroid cancers among the most frequently encountered malignancies in clinical practice.[2,4]

The Ministry of Health, in collaboration with WHO, launched the **National Cancer Control Plan of Maldives 2022-2026** in February 2023. The Plan sets out priorities for cancer prevention, early detection, treatment, palliative care, and surveillance, and recognises the need to strengthen the National Cancer Registry (NCR) and standardise national clinical guidelines.[3]

Thyroid cancer in the Maldivian population shares the global features of female predominance and a peak in the third to fifth decades, but several local factors warrant attention:

- A high background prevalence of benign thyroid nodular disease and goitre is encountered in routine endocrinology and surgical clinics, prompting frequent FNAC referrals.
- Cytology and surgery are concentrated in Malé, while initial detection occurs across atolls; this creates the principal logistic challenge of the national pathway.
- Radioiodine therapy is not yet available within the country, requiring overseas referral via Aasandha for a substantial proportion of patients with intermediate- or high-risk DTC and for selected metastatic cases.
- Iodine intake patterns in a fish-rich, sea-influenced population differ from many South Asian neighbours; the impact on histological subtype distribution has not been formally characterised in published Maldivian data.

Until robust national data are published, clinical estimates may be guided by GLOBOCAN regional figures for South Asia in conjunction with hospital-level case-series from IGMH and Tree Top Hospital.

1.4 Purpose and Scope of the Guideline

This guideline provides standardised national recommendations for the diagnosis, staging, treatment, and follow-up of thyroid carcinoma in the Maldives. It applies to all forms of primary thyroid malignancy in adults: differentiated, medullary, and anaplastic.

The guideline is adapted from the most recent international standards, namely:

- **NCCN** Clinical Practice Guidelines in Oncology: Thyroid Carcinoma, version 1.2025.
- **ESMO** Clinical Practice Guidelines (Filetti et al., 2019) and ESMO update on systemic therapy in advanced thyroid cancer (Filetti et al., 2022).
- **ATA 2015** Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer (Haugen et al.) and ATA Revised Guidelines for the Management of Medullary Thyroid Carcinoma (Wells et al., 2015).
- **WHO 2022** Classification of Endocrine and Neuroendocrine Tumours, 5th edition.

Specific objectives are to:

- Promote early and accurate diagnosis of thyroid malignancies across all levels of the Maldivian healthcare system.
- Standardise histopathological reporting, staging, and risk stratification.
- Define evidence-based management pathways adapted to locally available resources.
- Define the national referral pathway between atoll, regional, tertiary, and overseas centres.
- Guide long-term surveillance, survivorship, and palliative care planning.

2. Evaluation and Initial Assessment of Thyroid Nodules

Evaluation of a thyroid nodule should be comprehensive and multidisciplinary, integrating clinical, biochemical, radiological, and cytopathological findings to estimate malignancy risk and direct further management.[7]

2.1 Clinical Evaluation

A focused history should record:

- Duration and rate of growth of the nodule.
- Compressive symptoms dysphagia, dyspnoea, hoarseness, stridor.
- Prior neck or head irradiation, including therapeutic radiation in childhood.
- Family history of thyroid cancer, MEN 2, or familial MTC.
- Symptoms suggestive of hyperthyroidism or hypothyroidism.

Examination should include:

- Palpation of the thyroid gland for size, consistency, fixation, tenderness, and tracheal deviation.
- Examination of the central and lateral cervical lymph node basins.
- Assessment of voice quality; persistent hoarseness raises concern for recurrent laryngeal nerve (RLN) involvement and warrants laryngoscopy prior to surgery.

2.2 Biochemical Evaluation

- **Serum TSH** - first-line laboratory test for any thyroid nodule. A suppressed TSH suggests autonomous function and warrants a radionuclide scan when available; hyperfunctioning nodules carry a low risk of malignancy.
- **Free T4 / T3** - only if TSH is abnormal.
- **Thyroglobulin (Tg) and anti-Tg antibodies (TgAb)** - not diagnostic of malignancy; reserved as a postoperative tumour marker in DTC. TgAb must be measured alongside Tg because antibodies interfere with assay accuracy.
- **Serum calcitonin and CEA** - indicated where MTC is suspected (family history, MEN 2 stigmata, calcified thyroid mass with atypical FNA), as elevated levels are highly suggestive of MTC.

2.3 Imaging

2.3.1 Neck Ultrasound (USG)

Ultrasound is the first-line and preferred imaging modality for thyroid nodules. Every report should describe:

- Nodule size, echogenicity, margins, shape, composition (solid/cystic/mixed), and calcifications.
- Vascularity pattern.
- Presence and characterisation of cervical lymphadenopathy.
- Suspicion of extrathyroidal extension.

Ultrasound features suggestive of malignancy include:

- Marked hypoechogenicity.
- Irregular or infiltrative margins.
- Microcalcifications.
- Taller-than-wide shape on the transverse view.
- Disorganised intranodular vascularity.
- Suspicious lymph nodes (round shape, loss of fatty hilum, microcalcifications, cystic change, peripheral vascularity).

A standardised risk-stratification system (ATA categories or ACR TI-RADS) should accompany the ultrasound report. Central and lateral neck lymph nodes must be evaluated in every patient with suspected or confirmed thyroid malignancy.

Maldives Practice Note: Neck ultrasound is available at every atoll-level hospital, all regional hospitals, and in Malé. FNAC is typically performed by radiologists under ultrasound guidance at regional and Malé-based hospitals. Nodules detected at island health centres should be referred upward for ultrasound and FNAC.

2.3.2 Cross-Sectional Imaging

Contrast-enhanced CT or MRI of the neck and upper mediastinum should be considered when:

- Disease is locally advanced and airway, oesophageal, or vascular involvement is suspected.
- Vocal cord paralysis is identified preoperatively.

- Ultrasound is inadequate (retrotracheal or substernal extension).

Chest CT should be performed if pulmonary metastases are clinically or radiologically suspected. Iodinated contrast may delay subsequent radioiodine therapy by ~2-3 months - a relevant consideration when planning RAI in DTC.

2.4 Fine-Needle Aspiration Cytology (FNAC)

FNAC remains the gold standard for cytological evaluation of thyroid nodules. Indications include:

- Nodules ≥1 cm with one or more sonographically suspicious features.
- Nodules ≥1.5 cm with intermediate-suspicion features.
- Nodules ≥2 cm with low-suspicion features.
- Any nodule, regardless of size, when there is suspicious cervical lymphadenopathy or strong clinical suspicion of malignancy (e.g. fixed mass, vocal cord paralysis, family history of MTC).

2.4.1 The Bethesda Reporting System (2023)

All FNAC results should be reported using the 2023 Bethesda System for Reporting Thyroid Cytopathology (TBSRTC, 3rd edition).[12]

Cat.	Diagnostic Category	Risk of Malignancy (avg.)	Usual Management
I	Non-diagnostic / unsatisfactory	13%	Repeat USG-guided FNAC
II	Benign	4%	Clinical/USG follow-up
III	AUS / FLUS (now simplified into 2 subgroups based on molecular profile)	22%	Repeat FNAC, molecular testing, or diagnostic lobectomy
IV	Follicular neoplasm / suspicious for follicular neoplasm	30%	Diagnostic lobectomy ± molecular testing
V	Suspicious for malignancy	74%	Lobectomy or near-total / total thyroidectomy
VI	Malignant	97%	Near-total / total thyroidectomy ± central neck dissection

The 2023 update aligns nomenclature with the 2022 WHO Classification, simplifies AUS/FLUS subcategories, and incorporates expanded guidance on molecular ancillary testing. Pediatric risk-of-malignancy estimates and management algorithms are now included.

2.4.2 Molecular Testing

Molecular testing (BRAF, RAS, RET/PTC, PAX8/PPARγ, TERT, NTRK fusions; commercial multigene classifiers where accessible) may be considered for indeterminate cytology (Bethesda III or IV) to refine malignancy risk and guide the decision between active surveillance, diagnostic lobectomy, and total thyroidectomy.[16]

Maldives Practice Note: Routine commercial molecular testing platforms (Afirma, ThyroSeq) are not currently available locally; samples may be sent overseas at cost in selected indeterminate cases when the result would change management. For most patients with Bethesda III/IV cytology, repeat FNAC and conservative diagnostic lobectomy remain the practical default.

2.5 Diagnostic Integration

Diagnosis should rest on integration of:

- Clinical assessment.
- Biochemical findings.
- Imaging characterisation.
- Cytology and, where available, molecular testing.

A multidisciplinary team approach is recommended for all indeterminate cytology, advanced lesions, and atypical presentations.

3. Histopathology, Staging and Risk Stratification

3.1 Histopathological Classification

All thyroid tumours should be diagnosed and classified according to the WHO Classification of Endocrine and Neuroendocrine Tumours, 5th edition (2022). The 2022 edition introduces several important changes most notably the recognition of **high-grade follicular cell-derived non-anaplastic thyroid carcinoma** as a distinct category encompassing both poorly differentiated thyroid carcinoma and differentiated high-grade thyroid carcinoma, and the formal separation of **oncocytic carcinoma** from follicular carcinoma. Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is retained as a low-risk follicular cell-derived neoplasm.[13]

3.1.1 Major Histological Categories

Category	Subtype / Variant	Key Features
Differentiated thyroid carcinoma (DTC)	Papillary carcinoma - classic, follicular, tall cell, columnar cell, diffuse sclerosing, hobnail, solid/trabecular, oncocytic	80–85% of cases; lymphatic spread; generally excellent prognosis; aggressive subtypes (tall cell, columnar, hobnail, diffuse sclerosing) carry higher recurrence risk
	Follicular carcinoma - minimally invasive, encapsulated angioinvasive, widely invasive	10–15%; predominantly haematogenous spread (lung, bone)
	Oncocytic (Hürthle cell) carcinoma - now a separate entity	Often less RAI-avid; mitochondrial-rich cells
Low-risk neoplasm	NIFTP (non-invasive follicular thyroid neoplasm with papillary-like nuclear features)	Indolent; lobectomy alone usually sufficient
High-grade follicular cell–derived carcinoma	Poorly differentiated thyroid carcinoma; differentiated high-grade thyroid carcinoma	Behaviour intermediate between DTC and ATC; partial loss of differentiation
Medullary thyroid carcinoma (MTC)	Sporadic (75–80%) or hereditary (MEN 2A, MEN 2B, FMTC)	Parafollicular (C) cell origin; secretes calcitonin and CEA
Anaplastic (undifferentiated) carcinoma (ATC)	-	Highly aggressive; rapid progression; often arises from pre-existing DTC

3.2 Pathological Parameters to be Reported

Pathology reports for thyroid carcinoma should include:

- Tumour type and subtype (per WHO 2022).
- Tumour size (largest dimension) and focality (unifocal vs. multifocal).
- Extrathyroidal extension - microscopic (capsular) versus gross (extending into perithyroidal soft tissues, larynx, trachea, oesophagus, RLN).
- Margin status (involved vs. clear; distance to nearest margin).
- Lymphovascular invasion.
- Lymph node involvement - number examined, number positive, size of largest deposit, presence of extranodal extension.
- Background thyroid pathology (thyroiditis, nodular hyperplasia, lymphocytic infiltrate).
- For MTC: presence of amyloid stroma and C-cell hyperplasia in adjacent thyroid; mitotic count and necrosis.
- For DTC: tumour grade where applicable (high-grade features per WHO 2022 - mitoses ≥5 / 2 mm² and/or necrosis).

Resected specimens should be reviewed by an experienced histopathologist, ideally one with endocrine pathology experience.

3.3 Staging

Thyroid carcinoma is staged according to the AJCC/UICC TNM Classification, 8th Edition (2017). The 8th edition raised the age cut-off for DTC staging from 45 to 55 years and removed minor extrathyroidal extension and regional lymph node metastases from the definition of T3, downstaging a substantial proportion of patients and improving prognostic discrimination.[14,15]

3.3.1 Key Principles

- Separate staging systems apply to differentiated/medullary thyroid carcinoma and to anaplastic thyroid carcinoma (ATC is always considered Stage IV due to aggressive biology).
- Age-specific staging is used for DTC: <55 years - Stage I (M0) or Stage II (M1); ≥55 years - full TNM Stage I–IV.
- For MTC, staging does not depend on age.

3.3.2 Summary of TNM Definitions

Parameter	Definition
T - Primary tumour	T1a: ≤1 cm intrathyroidal • T1b: >1–2 cm intrathyroidal • T2: >2–4 cm intrathyroidal • T3a: >4 cm intrathyroidal • T3b: gross extrathyroidal extension into strap muscles only • T4a: gross ETE into subcutaneous tissue, larynx, trachea, oesophagus, or RLN • T4b: invasion of prevertebral fascia or major vessels
N - Regional lymph nodes	N0a: cytologically/histologically confirmed benign nodes • N0b: no clinical or radiological evidence • N1a: level VI / VII (central) • N1b: levels I–V (lateral neck) or retropharyngeal nodes
M - Distant metastasis	M0: absent • M1: present
Stage grouping	For DTC: depends on age and TNM; for MTC: full TNM regardless of age; for ATC: always Stage IV (IVA intrathyroidal; IVB gross ETE without M1; IVC distant metastasis).

3.4 Risk Stratification for Differentiated Thyroid Carcinoma

Following surgery, DTCs should be classified into low, intermediate, or high risk for recurrence using the modified ATA 2015 criteria. This classification - distinct from TNM staging - guides decisions on completion thyroidectomy, RAI, and TSH suppression intensity.[7]

Risk Category	Clinical / Pathological Features
Low risk	Intrathyroidal DTC, ≤4 cm, no aggressive histology, no vascular invasion, no nodal metastases (or ≤5 micrometastases <0.2 cm), no gross ETE, complete resection, no distant metastases. Postoperative Tg appropriate for thyroid remnant.
Intermediate risk	Microscopic ETE; cervical lymph node metastases (clinical N1, or >5 pathological N1 with deposits <3 cm); aggressive histology (tall cell, hobnail, columnar, diffuse sclerosing); vascular invasion (FTC); RAI-avid foci outside the thyroid bed on first post-therapy scan.
High risk	Gross extrathyroidal extension; incomplete tumour resection; distant metastases (M1); postoperative Tg suggestive of distant disease; pathological N1 with any node ≥3 cm; FTC with extensive vascular invasion (>4 foci).

Risk classification is dynamic and should be reassessed at each follow-up visit using the “response to therapy” framework (Section 6).

3.5 Multidisciplinary Review

All cases with indeterminate pathology, high-risk features, advanced stage, or anticipated need for RAI / overseas referral should be discussed at a multidisciplinary tumour board (MDT) involving surgery, endocrinology, radiology, pathology, nuclear medicine (where accessible), and oncology.

Maldives Practice Note: Tumour board meetings are conducted at most tertiary hospitals (IGMH, Tree Top Hospital, ADK), bringing together pathology, radiology, surgery, and the relevant medical teams together with oncology. All cases requiring overseas referral for radioiodine therapy or for advanced surgery should ideally be discussed at MDT prior to onward referral, both to confirm indication and to standardise documentation that travels with the patient.

4. Primary Tumour Management

Surgical resection is the principal treatment for thyroid cancer. The type and extent of surgery depend on tumour size, histological subtype, stage, and risk category. Surgical decisions should be made within an MDT framework and operations should be performed by surgeons with sufficient thyroid case volume.

4.1 Principles of Surgical Management

- Surgery remains the cornerstone of curative therapy for differentiated, medullary, and selected anaplastic thyroid cancers.
- The objective is complete macroscopic clearance of the primary disease, with preservation of the recurrent laryngeal nerves, parathyroid glands, and adjacent structures wherever possible.
- In carefully selected low-risk cases, active surveillance may be an acceptable alternative to immediate surgery.
- Preoperative laryngoscopy is recommended in any patient with vocal change or with bulky/posterior disease.

4.2 Active Surveillance

Active ultrasonographic surveillance may be considered, in lieu of immediate surgery, for:[7]

- Unifocal papillary microcarcinoma ≤10 mm.
- Absence of extrathyroidal extension or nodal/distant metastases.
- No cytological evidence of aggressive histology.
- No history of childhood neck irradiation or familial thyroid carcinoma.
- Patient preference and ability to comply with long-term follow-up.

Surveillance protocol:

- Neck ultrasound at 6, 12, 18, and 24 months, then every 12 months.
- Repeat FNAC for any new suspicious lymphadenopathy or significant nodule growth (≥3 mm in two dimensions or new aggressive sonographic features).
- Convert to surgery for documented progression, patient preference, or development of nodal disease.

4.3 Lobectomy (Hemithyroidectomy)

Indications

- Unifocal low-risk papillary or follicular carcinoma confined to one lobe, ≤4 cm (T1-T2), N0.
- No evidence of nodal disease, ETE, or radiation exposure.
- No aggressive histology on cytology or definitive pathology.
- Patient suitable for surveillance of the remaining lobe and where postoperative RAI is unlikely to be required.

Post-lobectomy Monitoring

- Thyroid and neck ultrasound at 6-12 months, then annually.
- FNAC of any new suspicious contralateral nodule or lymph node.
- Serum Tg and TgAb may be tracked for trend purposes; absolute Tg values are less informative when a thyroid lobe remains in situ.
- TSH should be maintained in the low-normal range with levothyroxine supplementation as required.

Indications for Completion Thyroidectomy

Completion thyroidectomy should be considered when final histology reveals:

- Tumour >4 cm.
- Gross extrathyroidal extension.
- Positive resection margins.
- Aggressive histological subtype (tall cell, hobnail, columnar, diffuse sclerosing, poorly differentiated).
- Lymphovascular invasion.
- Pathologically involved cervical lymph nodes.
- Bilateral or contralateral disease on imaging.

4.4 Total (or Near-Total) Thyroidectomy

Indications

- Tumour >4 cm.
- Gross extrathyroidal extension.
- Multifocal bilateral disease.
- Clinically or radiologically evident nodal metastases.
- Distant metastases at presentation.
- Prior head and neck irradiation.
- Aggressive histology or known BRAF-mutant tumour with adverse clinical features.

Surgical Considerations

- Intraoperative neuromonitoring (IONM) is recommended where available, particularly in revision surgery, large goitres, and any case with anticipated technical difficulty.
- Parathyroid identification and preservation are essential; auto transplantation should be performed if the blood supply of a gland is compromised or it cannot be left in situ.
- Routine measurement of postoperative serum calcium (and ionised calcium where available) and PTH is recommended to detect early hypocalcaemia.

Maldives Practice Note: Thyroid surgery is performed at the tertiary hospitals - IGMH, Tree Top Hospital, and ADK Hospital. Intraoperative nerve monitoring is currently available at IGMH; intraoperative frozen-section pathology is available at Tree Top Hospital. Definitive histopathology is reported in-house at the operating hospital.

4.5 Lymph Node Dissection

4.5.1 Therapeutic Neck Dissection

- Performed for clinically or biopsy-proven lymph node metastases.
- Central compartment (level VI ± VII) clearance is standard for N1a disease.
- Lateral compartment (levels IIa–Vb) dissection - preserving non-lymphatic structures - is performed for biopsy-proven N1b disease.

4.5.2 Prophylactic Central Neck Dissection

- Routine prophylactic central neck dissection in low-risk DTC (T1-T2 N0) remains controversial and is generally not recommended.
- It may be considered for advanced T3-T4 tumours or when intraoperative nodal involvement is suspected, in order to improve regional control and refine staging.

4.6 Surgical Management of Medullary Thyroid Carcinoma

Detailed in Section 8. In summary:[8]

- Total thyroidectomy with bilateral central compartment dissection is recommended for all patients with MTC.
- Therapeutic lateral neck dissection should be performed when nodal involvement is documented preoperatively or intraoperatively.
- Prophylactic dissection in hereditary disease is guided by RET mutation risk category and serum calcitonin level.
- RAI is not effective in MTC and should not be administered.
- Pheochromocytoma must be excluded - and if present, treated first - before thyroid surgery in MEN 2.

4.7 Surgical Management of Anaplastic Thyroid Carcinoma

Detailed in Section 9. Surgery should only be attempted when complete (R0/R1) resection is feasible, generally limited to Stage IVA and selected IVB disease in patients of acceptable performance status. Airway evaluation is mandatory; tracheostomy may be required.

4.8 Postoperative Considerations

- Voice assessment within the first 24 hours; flexible laryngoscopy if any change is detected.
- Serum calcium ± PTH monitoring for hypocalcaemia; oral calcium and active vitamin D supplementation as required, and intravenous calcium for symptomatic hypocalcaemia.
- Initiate levothyroxine postoperatively; the TSH target is determined by the postoperative risk category (Section 5).

- Refer for nuclear medicine consultation to assess eligibility for RAI; for Maldivian patients, this means MDT discussion and Aasandha referral preparation.
- Document operative findings, resection margins, completeness of resection, parathyroid status, and nodal yield in both the operative note and the formal pathology report.

5. Adjuvant Radioiodine Therapy and Hormone Suppression

5.1 Purpose and Rationale

Radioiodine (I-131) ablation, given after total thyroidectomy, is used to (a) destroy residual normal thyroid tissue and microscopic disease, (b) facilitate sensitive follow-up using serum thyroglobulin and whole-body iodine scanning, and (c) treat known iodine-avid metastatic disease. The decision to administer RAI must balance the recurrence risk against potential adverse effects (sialadenitis, xerostomia, lacrimal dysfunction, secondary malignancy, and gonadal effects).[7,11]

5.2 Indications for RAI Ablation in DTC

RAI ablation is not routine for every patient with DTC. The decision depends on postoperative risk stratification, biochemistry, and ultrasound findings.

5.2.1 Not Typically Recommended

Low-risk patients in whom all of the following apply:

- Classic papillary carcinoma confined to thyroid parenchyma.
- Largest tumour <2 cm, intrathyroidal, with negative margins and no aggressive features.
- No lymphovascular invasion or nodal metastases.
- Postoperative unstimulated Tg <1 ng/mL (or stimulated <2 ng/mL) with negative TgAb.
- Negative postoperative neck ultrasound.

5.2.2 Selectively Recommended (typical activity 30–100 mCi / 1.1–3.7 GBq)

- Tumour 2–4 cm intrathyroidal.
- Microscopic positive margins.
- Microscopic extrathyroidal extension.
- Lymphovascular invasion.
- Limited cervical lymph node metastases (N1a, ≤5 nodes, deposits <0.2 cm).
- Multifocal disease with at least one focus >1 cm.
- Postoperative unstimulated Tg 1-10 ng/mL.
- High-risk histology (tall cell, hobnail, columnar, insular, diffuse sclerosing variants).

5.2.3 Typically Recommended (typical activity 100–200 mCi / 3.7–7.4 GBq)

- Gross extrathyroidal extension.
- Primary tumour >4 cm.
- Extensive cervical nodal metastases (N1b, >5 positive nodes, or any node ≥3 cm).
- Incomplete resection or positive margins beyond microscopic.
- Distant metastases (M1).
- Postoperative unstimulated Tg >10 ng/mL.

5.3 Preparation for RAI Therapy

- **TSH stimulation:** withdraw levothyroxine for 3-4 weeks (T3 cover with liothyronine for 2 weeks then off for 2 weeks may be used to shorten the hypothyroid interval), or use recombinant human TSH (rhTSH) where available. Serum TSH should be >30 mIU/L before dosing.
- **Low-iodine diet:** for 1-2 weeks prior to RAI to maximise iodine uptake.
- **Pregnancy:** mandatory β-hCG testing within 48 hours before RAI in any woman of reproductive potential. RAI is contraindicated in pregnancy and lactation; lactation must have ceased ≥6 weeks before treatment.
- **Iodine-containing agents:** discontinue amiodarone (long washout required), iodinated contrast (≥6–8 weeks), and topical iodine antiseptics where feasible.
- **Counselling:** regarding contraception (typically 6-12 months for women, 3-4 months for men), salivary protection, and travel/radiation precautions.

Maldives Practice Note: There is no I-131 facility in the Maldives at the time of writing. Patients requiring RAI are referred to Aasandha-empanelled hospitals - predominantly in India and selected centres in Sri Lanka. Local arrangements for the low-iodine diet and for thyroid hormone withdrawal are coordinated through the endocrinology and oncology clinics at IGMH and Tree Top Hospital. Patients should travel with a complete clinical summary, operative note, histopathology report, postoperative ultrasound, baseline Tg/TgAb, and TSH at the time of dosing.

5.4 Post-RAI Follow-Up

- A post-therapy whole-body scan (WBS) should be performed 5–10 days after dosing to document iodine uptake and to detect previously occult metastatic disease.
- Serum Tg and TgAb measurement at 6-12 weeks post-ablation.
- Repeat RAI is considered only when there is demonstrable iodine uptake in known or suspected lesions and persistent or recurrent disease; cumulative activities are usually kept below 600 mCi (22 GBq) over a lifetime.

5.5 RAI-Refractory Disease

A tumour is considered RAI-refractory when any of the following applies:[10]

1. No iodine uptake on diagnostic or post-therapy WBS.
2. Loss of iodine avidity over time despite previously demonstrated uptake.
3. Mixed avidity with progression in non-avid lesions.
4. Disease progression within 6-12 months despite documented iodine uptake.
5. Persistent disease after a cumulative activity exceeding ~600 mCi (22 GBq) without response.

Such patients require systemic therapy (Section 7) and locoregional palliative options (Section 7.4).

5.6 TSH Suppression Therapy

5.6.1 Objectives

TSH stimulates growth of normal and malignant thyroid follicular cells. Suppression with levothyroxine (LT4) is therefore used postoperatively to reduce recurrence risk; the intensity of suppression is matched to the patient’s recurrence risk and response to therapy.

5.6.2 Target TSH Levels

Risk / Response Category	TSH Target (mIU/L)	Notes
Low risk; excellent response	0.5–2.0	Maintain TSH in the low-normal range.
Intermediate risk; biochemical incomplete or indeterminate response	0.1–0.5	Mild suppression.
High risk; structural incomplete response or persistent metastatic disease	<0.1	Strong suppression unless contraindicated by cardiac disease or osteoporosis.

5.6.3 Duration

- Suppressive therapy should be continued for 3-5 years after definitive therapy and then reassessed using dynamic risk stratification (Section 6).
- Lifelong suppression may be required in patients with persistent structural disease.

5.6.4 Monitoring of Therapy

- Serum TSH and free T4 at 6-8 weeks after each dose change, then 6-12 monthly when stable.
- Surveillance for atrial fibrillation, particularly in patients aged >60 years on long-term suppression.
- Bone density (DEXA) consideration in postmenopausal women on prolonged suppressive therapy; calcium and vitamin D supplementation as appropriate.
- Individualisation of suppression intensity in patients with cardiovascular comorbidity.

6. Follow-Up and Long-Term Surveillance

Effective follow-up after initial therapy is essential for the early detection of persistent or recurrent thyroid cancer, dynamic reassessment of recurrence risk, and optimisation of suppressive therapy. Surveillance should be coordinated through a dedicated thyroid cancer clinic, led by endocrinology or oncology, with input from surgery, nuclear medicine, radiology, and pathology.

6.1 Objectives of Follow-Up

- Detect biochemical or structural recurrence at the earliest possible stage.
- Monitor adequacy of TSH suppression and thyroid hormone replacement.
- Identify and manage late effects of treatment.
- Provide psychosocial and survivorship support.

6.2 Dynamic Risk Stratification

Patients should be re-classified at every visit using the ATA 2015 “response to therapy” framework. Risk categories evolve over time, and initial high-risk patients with an excellent response can subsequently be managed less intensively.[7]

Response Category	Definition	Implications
Excellent response	No clinical, biochemical, or structural disease; suppressed Tg <0.2 ng/mL or stimulated Tg <1 ng/mL; negative imaging	Continue low-normal TSH; routine follow-up; consider relaxing suppression
Biochemical incomplete response	Elevated Tg or rising TgAb without structural disease	Continue TSH suppression; trend Tg/TgAb; cross-sectional or PET imaging if persistently rising
Structural incomplete response	Persistent or recurrent disease on imaging	Maintain strong TSH suppression; consider surgery, RAI, EBRT, or systemic therapy
Indeterminate response	Non-specific findings: borderline Tg, low-level antibodies, or equivocal imaging	Close observation; serial monitoring; tailored imaging

6.3 Schedule of Follow-Up

Time since treatment	Clinical evaluation	Biochemical	Imaging
0–12 months	At 6–12 weeks post-RAI; then at 3, 6, and 12 months	TSH, fT4, Tg, TgAb	Neck US at 6–12 months; post-therapy WBS for those treated with RAI
Years 2–5	Every 6–12 months	TSH, Tg, TgAb	Neck US annually or as indicated
After 5 years	Annually for low-risk; 6-monthly for intermediate/high risk	TSH, Tg, TgAb	Imaging as clinically indicated

Maldives Practice Note: Long-term follow-up is currently coordinated through the endocrinology and oncology clinics at the Malé tertiary hospitals. Patients in the atolls should be linked to a named follow-up clinician and provided with a written long-term plan that includes the indicated investigations and the next clinic visit. Tg, TgAb, and TSH testing should be available locally; results that fall outside expected ranges should trigger early referral.

6.4 Surveillance Tools

6.4.1 Serum Thyroglobulin (Tg) and Anti-Tg Antibodies (TgAb)

- Tg is the most sensitive marker of recurrence in DTC after total thyroidectomy and RAI.
- High-sensitivity Tg assays (functional sensitivity <0.2 ng/mL) on suppressive therapy can replace stimulated Tg testing in many low-risk patients.
- TgAb must be measured in every Tg sample; a rising TgAb trend, even with “undetectable” Tg, is itself a marker of possible disease.
- Tg interpretation differs after lobectomy alone - values are not directly comparable to post-total-thyroidectomy benchmarks.

6.4.2 Neck Ultrasonography

- First-line imaging for detection of residual or recurrent cervical disease.
- Should systematically evaluate the thyroid bed and cervical nodal basins (levels II–VI).
- FNAC ± Tg washout of any suspicious node ≥8–10 mm short axis.

6.4.3 Other Imaging Modalities

- Diagnostic WBS - useful in high-risk or RAI-treated patients with rising Tg.
- CT/MRI - when extrathyroidal, mediastinal, or substernal extension is suspected.
- 18F-FDG PET/CT - for RAI-refractory or Tg-positive/scan-negative disease, and for prognostic stratification of advanced disease.

6.5 Criteria for Remission and Recurrence

Remission

- No clinical, biochemical, or structural evidence of disease.
- Undetectable Tg with negative TgAb on suppressive therapy.
- Negative neck ultrasound and, where performed, negative cross-sectional imaging.

Recurrence

- **Structural recurrence:** imaging evidence of disease in the thyroid bed, lymph nodes, or distant sites.
- **Biochemical recurrence:** newly detectable or persistently rising Tg (typically >1 ng/mL on suppression, or >2 ng/mL after stimulation) without an imaging correlate.

6.6 Long-Term Management

6.6.1 Hormone Replacement and TSH Suppression

- Adjust levothyroxine to the updated dynamic risk category.
- Periodically reassess the level of suppression to limit long-term cardiovascular and skeletal effects.

6.6.2 Late Effects of Treatment

- **Hypocalcaemia:** monitor calcium and vitamin D; adjust supplementation; check parathyroid function if ongoing.
- **Bone health:** consider DEXA scanning in postmenopausal women and in patients on prolonged suppressive therapy.
- **Cardiovascular:** monitor for atrial fibrillation; maintain heart rate control where suppression is prolonged.

- **Salivary and lacrimal dysfunction after RAI:** encourage hydration, sialagogues, frequent dental care, and ophthalmological assessment if symptomatic.
- **Second malignancy:** low absolute risk after standard cumulative RAI doses; patients should be informed and surveillance maintained.

6.7 Survivorship and Patient Support

- Patient education on the disease course, self-monitoring, and the importance of regular follow-up.
- Address fatigue, anxiety, body-image concerns, and treatment-related symptoms through counselling.
- Early referral to nutrition, rehabilitation, and psychological services where indicated.
- Encourage participation in patient-support networks (e.g. through the Cancer Society of Maldives).

7. Management of Advanced or Metastatic Differentiated Thyroid Carcinoma

Patients with recurrent or metastatic DTC require individualised management guided by disease biology, RAI avidity, tumour burden, and pace of progression. Care should be coordinated by a multidisciplinary thyroid cancer team with access to surgery, nuclear medicine, oncology, radiation oncology, and palliative care.

7.1 Principles of Management

- For iodine-avid disease, repeated RAI therapy and continued TSH suppression remain the foundation.
- For RAI-refractory disease, options include observation of asymptomatic indolent disease, locoregional therapies, and systemic therapy with multikinase or mutation-specific agents.
- The therapeutic goals are durable disease control, symptom relief, and preservation of quality of life.

7.2 Pre-Therapy Assessment

- Complete staging with neck and chest CT (and abdomen/pelvis when clinically indicated) to define locoregional and distant disease.
- Whole-body diagnostic RAI scan to confirm iodine avidity in patients being considered for further RAI.
- 18F-FDG PET/CT for non-RAI-avid or progressive disease.
- Performance status, comorbidities, and updated TSH/Tg/TgAb.
- Assessment of suitability and willingness for overseas travel (where RAI is required).

7.3 Radioactive Iodine for Metastatic DTC

7.3.1 Indications

- Iodine-avid distant metastases (lung, bone, lymph nodes, soft tissue).
- Resectable locoregional recurrence where adjuvant RAI may improve control.

7.3.2 Protocol

- I-131 doses of 100–200 mCi (3.7–7.4 GBq) following TSH stimulation (TSH >30 mIU/L).
- rhTSH may be used in fragile patients, the elderly, or those with significant comorbidity if available; otherwise levothyroxine withdrawal for 3–4 weeks.
- Repeat treatment at 6–12-month intervals while disease remains iodine-avid and continues to respond.

7.4 Locoregional and Palliative Therapies

7.4.1 Surgery

Resection or debulking may be appropriate for isolated recurrent disease in the central or lateral neck, mediastinum, or solitary distant sites in selected patients.

7.4.2 External Beam Radiotherapy (EBRT)

Indicated for:

- Unresectable locoregional disease threatening vital structures.
- Painful bone metastases, brain metastases, or impending pathological fracture.
- Symptomatic visceral metastases not amenable to surgery or systemic therapy.

Typical doses: 60–70 Gy in 30–35 fractions for definitive intent; lower fractionation regimens (e.g. 30 Gy / 10 fractions, 20 Gy / 5 fractions, 8 Gy / 1 fraction) for palliation.

7.4.3 Ablative and Stereotactic Interventions

- Radiofrequency ablation, cryotherapy, or percutaneous ethanol injection may control limited recurrent or metastatic deposits, particularly in the neck or bone.
- Stereotactic body radiotherapy (SBRT) provides durable local control for oligometastatic lesions in lung, bone, brain, and adrenal glands where available.

7.4.4 Bone Metastases Management

- Combine systemic therapy with bone-targeted agents: zoledronic acid (4 mg IV every 4 weeks; renal monitoring) or denosumab (120 mg SC every 4 weeks).
- Calcium and vitamin D supplementation must accompany bone-resorption inhibitors.
- Surgical stabilisation or vertebroplasty for impending or actual pathological fracture.
- Single-fraction palliative EBRT for painful localised lesions.

Maldives Practice Note: External beam radiotherapy and SBRT are not currently available within the Maldives. Patients requiring radiotherapy are referred overseas through the Aasandha pathway. Bone-targeted therapy can be administered locally through the day-care chemotherapy units at IGMH and Tree Top Hospital.

7.5 Systemic Therapy

Systemic therapy is reserved for patients with progressive, symptomatic, or unresectable RAI-refractory disease.[10]

7.5.1 Multikinase Inhibitors

Agent	Targets	Indication	Evidence
Lenvatinib	VEGFR1–3, FGFR1–4, RET, KIT, PDGFRα	First-line for progressive RAI-refractory DTC	SELECT trial - improved PFS (ref. 18)
Sorafenib	RAF, VEGFR2/3, PDGFR, RET	Alternative first-line; if lenvatinib not tolerated	DECISION trial - improved PFS (ref. 19)

- Continue MKI until disease progression or unacceptable toxicity.
- Common toxicities (hypertension, diarrhoea, fatigue, hand-foot skin reaction, proteinuria, weight loss) require proactive supportive care, regular blood pressure and renal monitoring, and early dose modification.
- Maintain TSH suppression during therapy unless contraindicated.

7.5.2 Mutation-Specific Targeted Therapy

Where molecular profiling identifies an actionable alteration, targeted therapy is preferred:

Alteration	Preferred Agents	Notes
RET fusion (DTC) or RET mutation (MTC)	Selpercatinib; pralsetinib	High response rates with favourable toxicity profile (ref. 20, 21)
NTRK1/2/3 fusion	Larotrectinib; entrectinib	Tumour-agnostic approval; rare in thyroid cancer
BRAF V600E mutation	Dabrafenib + trametinib (in selected DTC; standard in BRAF-mutant ATC)	Rapid responses; consider redifferentiation strategies (ref. 22)

Maldives Practice Note: Molecular profiling is not routinely available in-country and is generally arranged through overseas reference laboratories at the time of overseas referral. Most multikinase inhibitors and the principal mutation-specific agents (lenvatinib, sorafenib, selpercatinib, dabrafenib + trametinib) are accessible to Maldivian patients through Aasandha and the National Social Protection Agency (NSPA), with procurement through hospital pharmacies and the State Trading Organisation (STO). Treatment supervision and toxicity monitoring should be performed by the local oncology service even when the indication is established overseas.

7.5.3 TSH Suppression During Systemic Therapy

Continue levothyroxine with TSH maintained <0.1 mIU/L unless cardiac comorbidity or advanced age dictates a less aggressive target.

7.6 Monitoring and Response Assessment

- Clinical review every 4-8 weeks during MKI initiation; every 8-12 weeks once tolerance is established.
- Imaging (CT or MRI) every 12 weeks during initiation, then every 3-4 months, using RECIST 1.1 criteria.
- Regular blood pressure, renal function, urine protein:creatinine ratio, liver function, full blood count, electrolytes, and TSH monitoring.
- Baseline ECG and QTc surveillance for selpercatinib, pralsetinib, and vandetanib.

7.7 Palliative and Supportive Care

- Early integration of palliative-care principles for symptom relief, pain control, and emotional support.
- Proactive management of fatigue, anorexia, mucositis, diarrhoea, and skin toxicity.
- Psychological counselling and family support throughout the disease trajectory.

See Section 11 for palliative-care considerations specific to the Maldivian context.

7.8 Prognosis

- Iodine-avid distant disease has 10-year survival rates of 60-70% in many series.
- RAI-refractory disease has historically had a median overall survival of 3-5 years; outcomes are improving with MKI and mutation-specific therapy.

8. Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) is a neuroendocrine malignancy arising from the parafollicular (C) cells of the thyroid gland. C cells secrete calcitonin and CEA, both of which serve as reliable tumour markers. MTC may be sporadic or part of an inherited syndrome — Multiple Endocrine Neoplasia type 2A or 2B, or familial MTC. Early diagnosis and complete surgical clearance offer the only chance of cure; MTC is not iodine-avid and does not respond to RAI.

8.1 Epidemiology and Genetics

Key features:[8]

- MTC accounts for approximately 3-5% of all thyroid cancers.
- Approximately 75-80% of cases are sporadic; 20-25% are hereditary, driven by activating germline RET proto-oncogene mutations.
- All patients with MTC should undergo germline RET testing; first-degree relatives of carriers should be offered genetic counselling and predictive testing.
- Hereditary MTC is associated with phaeochromocytoma (MEN 2A and 2B) and primary hyperparathyroidism (MEN 2A); MEN 2B includes a marfanoid habitus, mucosal neuromas, and intestinal ganglioneuromatosis.

8.2 Clinical Presentation

- Palpable thyroid nodule or neck mass (often firm and centrally located).
- Cervical lymphadenopathy at presentation in roughly half of patients.
- Symptoms of local invasion - hoarseness, dysphagia, dyspnoea.
- Secretory symptoms (flushing, diarrhoea) from high circulating calcitonin in advanced disease.
- In hereditary cases, presentation may follow predictive RET testing in an asymptomatic relative.

8.3 Diagnostic Evaluation

8.3.1 Laboratory Assessment

- **Serum calcitonin:** elevated and broadly proportional to tumour burden; basal levels >100 pg/mL in the presence of a thyroid nodule are virtually diagnostic. Calcitonin is also used for postoperative monitoring.
- **CEA:** supportive marker; particularly useful when serial trends and doubling times are tracked together with calcitonin.
- **Calcium and metanephrines:** serum calcium and plasma fractionated metanephrines (or 24-hour urinary metanephrines) must be measured to exclude phaeochromocytoma in all hereditary cases (and in any patient pending RET results) before thyroid surgery.
- **Germline RET testing:** mandatory in every MTC patient.

8.3.2 Imaging

- Neck ultrasound - for the primary tumour and central/lateral nodal evaluation.
- Contrast CT/MRI of the neck and chest - for mediastinal extension and pulmonary metastases.
- Contrast-enhanced abdominal imaging (and bone imaging) - when systemic spread is suspected, particularly with calcitonin >500 pg/mL.
- 18F-DOPA PET/CT (where available) - sensitive for recurrent or advanced disease; FDG-PET/CT is an alternative.
- Adrenal imaging if biochemistry suggests phaeochromocytoma.

8.4 Staging

Staging follows the AJCC/UICC TNM 8th Edition (with a system distinct from DTC). Unlike DTC, MTC staging does not depend on age. Prognosis correlates with extent of disease (T and N stage) and with the postoperative basal calcitonin and CEA levels.

8.5 Management

8.5.1 Surgery

Surgery is the only curative treatment for MTC and should be undertaken by an experienced endocrine or head-and-neck surgeon.

Extent of Surgery

- Total thyroidectomy is recommended for all patients.
- Routine bilateral central (level VI ± VII) compartment dissection should be performed.
- Therapeutic lateral neck dissection (levels IIa–Vb) for clinically, radiologically, or biochemically documented lateral nodal disease (or with basal calcitonin >200 pg/mL with ipsilateral disease).
- Prophylactic lateral neck dissection in hereditary MTC is guided by RET mutation risk category and serum calcitonin level.

Special Considerations

- Phaeochromocytoma, if present, must be addressed surgically before thyroidectomy to prevent intraoperative hypertensive crisis.
- Parathyroid identification and preservation, or autotransplantation, are essential - primary hyperparathyroidism may need synchronous management in MEN 2A.
- Recurrent laryngeal nerve preservation with intraoperative neuromonitoring where available.

8.5.2 Adjuvant Therapy

- RAI is not effective in MTC and should not be administered.
- External beam radiotherapy may be considered postoperatively for gross residual disease, unresectable disease, or locoregional recurrence not amenable to further surgery.
- Levothyroxine replacement at physiological doses (TSH normal range) - TSH suppression is not required for MTC since C cells are not TSH-responsive.

8.6 Management of Advanced or Metastatic MTC

8.6.1 Systemic Therapy

Systemic therapy is indicated for symptomatic, progressive, or unresectable metastatic disease.

Patient Group	Preferred Agents	Notes
RET-mutated (MEN 2 or sporadic)	Selpercatinib or pralsetinib	Preferred first-line targeted therapy; high response rates; favourable tolerability
RET wild-type / RET status not available	Vandetanib or cabozantinib	Multikinase inhibitors with activity in MTC; require careful management of QT prolongation, hypertension, diarrhoea, and hepatic toxicity

- Selpercatinib and pralsetinib have higher response rates and a more favourable toxicity profile than older multikinase inhibitors.
- Cytotoxic chemotherapy (e.g. dacarbazine-based regimens) has limited efficacy and is rarely indicated in modern practice.

8.6.2 Locoregional and Palliative Measures

- Surgery or EBRT for local recurrence threatening the airway or causing compression.
- Embolisation, RFA, or selected resection for limited hepatic metastases.
- Bone-targeted therapy (zoledronic acid or denosumab, with calcium/vitamin D) for osseous metastases with pain or fracture risk.
- Symptomatic management of secretory diarrhoea (loperamide, octreotide where available).

8.7 Follow-Up

Schedule

- Calcitonin and CEA every 3–6 months for the first 2 years, then every 6–12 months.
- Neck ultrasound annually.
- Cross-sectional imaging (neck, chest, abdomen, bone) when calcitonin exceeds ~150 pg/mL or doubles in <6 months, or with new symptoms.

Postoperative Prognosis

- Complete biochemical remission (undetectable calcitonin) occurs in approximately 40–50% after early surgery for localised disease.
- Persistent or rising calcitonin indicates residual or metastatic disease.
- Calcitonin and CEA doubling times are powerful prognostic indicators - doubling time <6 months indicates aggressive disease.

8.8 Genetic Counselling and Family Management

- All individuals with MTC should undergo germline RET testing.
- First-degree relatives of RET-positive patients should be offered genetic counselling and predictive RET testing.
- Carriers identified by predictive testing should be offered prophylactic thyroidectomy at an age dictated by mutation risk category - within the first year of life for the highest-risk M918T (MEN 2B); before 5 years for high-risk codon 634 mutations; later for moderate-risk mutations, guided by calcitonin trends.
- Lifelong surveillance for phaeochromocytoma and primary hyperparathyroidism in MEN 2 syndromes (annual plasma metanephrines and calcium from age 8-11 years onwards depending on genotype).

Maldives Practice Note: Germline RET testing is not currently performed in-country. Samples should be sent to an empanelled reference laboratory; the Aasandha pathway can support testing as part of overseas referral. Family members of identified carriers should be offered counselling locally and onward testing as appropriate.

9. Anaplastic Thyroid Carcinoma

Anaplastic thyroid carcinoma (ATC) is a rare, highly aggressive malignancy representing fewer than 2% of all thyroid cancers. It commonly arises from a pre-existing differentiated tumour through dedifferentiation. Median overall survival is in the order of 3-6 months, but a meaningful subset of patients now achieve durable disease control with rapid molecular profiling and targeted therapy. Management requires urgent multidisciplinary coordination focused on airway protection, locoregional control, and prompt initiation of mutation-directed therapy where indicated.

9.1 Epidemiology and Clinical Features

- Predominantly affects older adults (typically >60 years) with a slight female predominance.
- Typically presents as a rapidly enlarging, hard, fixed neck mass.
- Local symptoms: pain, hoarseness, dyspnoea, dysphagia, stridor, superior vena cava obstruction.
- Cervical nodal involvement is common; up to 50% of patients have distant metastases (lung, bone, brain) at diagnosis.

9.2 Pathogenesis and Molecular Profile

- Frequently arises from previously undiagnosed or treated DTC (papillary or follicular).
- Common molecular alterations include BRAF V600E (≈40% of cases), TP53, TERT promoter, PIK3CA / PI3K/AKT/mTOR pathway, RAS, and (rarely) NTRK or RET fusions.
- **Rapid molecular profiling - minimally for BRAF V600E, plus broader actionable targets (NTRK, RET, NRG1) - should be initiated at diagnosis, ideally before discharge from the diagnostic admission.**

9.3 Diagnostic Evaluation

Investigation	Purpose
Core needle biopsy or open incisional biopsy	Required to confirm diagnosis; FNAC is often insufficient for definitive ATC diagnosis
Histology	Undifferentiated giant, spindle, or squamoid cells with high mitotic index and necrosis
Immunohistochemistry	Typically negative for thyroglobulin and TTF-1; positive for cytokeratins; PAX8 retained in many cases
Molecular profiling	BRAF V600E (rapid IHC/PCR); broader NGS panel (BRAF, RET, NTRK, NRG1, RAS, TP53, TERT, PIK3CA) where available
CT / MRI of neck and chest	Local invasion, airway compression, regional metastases
Whole-body CT or 18F-FDG PET-CT	Distant metastases; staging and treatment planning

9.4 Staging

All ATC is considered Stage IV (AJCC 8th Edition) by virtue of its aggressive biology:

- IVA - disease confined to the thyroid (intrathyroidal).
- IVB - gross extrathyroidal extension without distant metastases.
- IVC - distant metastases.

Staging informs communication and planning but does not by itself dictate treatment intent (curative vs palliative), which is determined by resectability, performance status, comorbidities, and patient/family preferences.

9.5 Principles of Management

- Immediate evaluation of airway and swallowing is critical. A secured airway (early flexible laryngoscopy and consideration of tracheostomy) takes priority over diagnostic staging.
- Rapid molecular profiling - particularly BRAF V600E status - should be requested at diagnosis.
- Treatment intent (curative vs palliative) should be clarified explicitly with patient and family at the outset.

- Care should be coordinated through a specialised centre or MDT experienced in aggressive thyroid malignancy.

9.6 Curative-Intent Therapy

Curative intent is appropriate only for resectable disease (Stage IVA and selected IVB) in fit patients.

9.6.1 Surgery

- Total thyroidectomy with en-bloc resection of involved structures (strap muscles, trachea, oesophagus) where complete (R0/R1) resection is feasible.
- Prophylactic tracheostomy when airway compromise is anticipated.
- Therapeutic neck dissection of clinically involved nodal levels.

9.6.2 Adjuvant Therapy

- External beam radiotherapy (typically IMRT) to 60-70 Gy to the tumour bed and at-risk nodal regions.
- Concomitant chemoradiation (weekly paclitaxel or docetaxel; doxorubicin-based regimens are alternatives) may improve local control.
- Continuation or initiation of mutation-directed therapy (e.g. dabrafenib + trametinib for BRAF-mutant disease) as soon as molecular results are available.

9.7 Unresectable or Metastatic Disease

9.7.1 Mutation-Directed Systemic Therapy

Treatment selection is guided by molecular profiling.[22]

Molecular Alteration	Preferred Therapy
BRAF V600E mutation	Dabrafenib + trametinib (preferred first-line; rapid responses; consider neoadjuvant use to render initially unresectable disease operable)
RET fusion	Selpercatinib or pralsetinib
NTRK fusion	Larotrectinib or entrectinib
No actionable mutation identified	Lenvatinib or pembrolizumab-based combinations (in selected patients) or systemic chemotherapy; eligibility for clinical trials should be considered

- Targeted therapy should be initiated rapidly - within days of diagnosis where possible - to stabilise disease and improve survival.
- Responses to BRAF-directed therapy can be dramatic and may permit subsequent definitive surgery and radiotherapy.

9.7.2 Radiotherapy

- Definitive EBRT for unresectable local disease.
- Palliative EBRT for bleeding, pain, or threatened airway.
- SBRT or fractionated radiotherapy for limited brain, bone, or lung metastases where available.

9.7.3 Cytotoxic Chemotherapy

- Weekly paclitaxel, docetaxel, or doxorubicin-based regimens, often combined with radiotherapy when targeted agents are unavailable.
- Response rates with chemotherapy alone are <20%; the principal role is concurrent use with radiotherapy or palliation.

9.8 Palliative and Supportive Care

- Early integration of palliative-care principles - symptom control, communication, and family support.
- Airway management: tracheostomy where indicated; consider stenting if appropriate expertise is available.
- Nutritional support: nasogastric or PEG feeding for dysphagia.
- Multimodal analgesia, including opioids, neuropathic agents, and corticosteroids; bone-targeted therapy for symptomatic skeletal metastases.
- Psychosocial support for patient and family is essential given the rapid disease trajectory.

Maldives Practice Note: Patients with anaplastic thyroid carcinoma should be discussed at the tertiary MDT at the earliest opportunity. Where dabrafenib + trametinib or other targeted agents are indicated and available through Aasandha/NSPA, treatment should not be delayed by diagnostic logistics. For patients in whom curative intent is not feasible, in-hospital palliative-care principles - symptom control, family communication, and home support - should be applied by the oncology team in conjunction with the relevant medical specialties (see Section 11).

9.9 Prognosis

- Overall, 1-year survival is <20% in unselected series.
- Long-term remission is possible only in the small subset achieving complete resection followed by chemoradiation and/or sustained molecular response.
- Survival is markedly improved in molecularly selected patients treated with BRAF, RET, or NTRK inhibitors.

9.10 Key Management Summary

Clinical Scenario	Recommended Approach
Resectable IVA / selected IVB	Total thyroidectomy ± en-bloc resection → adjuvant chemoradiation; targeted therapy if molecular alteration identified
Unresectable or metastatic with targetable mutation	Mutation-directed therapy (BRAF, RET, NTRK) - initiate within days of diagnosis
Unresectable / non-targetable	EBRT ± chemotherapy for local control or palliation; lenvatinib in selected patients
Airway compromise	Urgent tracheostomy and locoregional control
End-stage disease	Symptom-directed palliative care

10. Referral Pathways for Thyroid Cancer in the Maldives

This section maps the journey of a patient with a suspected or confirmed thyroid cancer through the Maldivian healthcare system, from first presentation in an atoll to definitive multimodality treatment. Clear pathways reduce delay, support uniform standards across the country, and minimise repeat investigations during transitions of care.

10.1 Healthcare Structure and Levels of Care

Care for thyroid cancer in the Maldives is delivered across three levels:

- **Atoll-level hospitals:** initial clinical assessment, neck ultrasound, basic biochemistry. (Island health centres do not currently provide thyroid imaging or FNAC and refer suspected nodules upward.)
- **Regional hospitals:** neck ultrasound and ultrasound-guided FNAC by radiologists, basic biochemistry, and onward referral.
- **Tertiary hospitals (Malé and Hulhumalé):** IGMH (Indira Gandhi Memorial Hospital), Tree Top Hospital (TTH), and ADK Hospital - providing thyroid surgery, in-house histopathology, multidisciplinary tumour board review, day-care chemotherapy, endocrinology and oncology follow-up.
- **Overseas referral (Aasandha-empanelled centres in India and Sri Lanka):** radioiodine therapy (I-131), external beam radiotherapy / SBRT, advanced surgery beyond local capability, and selected molecular profiling.

10.2 Step-by-Step Pathway

10.2.1 Step 1 - Detection and Initial Assessment

- Patients presenting with a thyroid nodule, neck swelling, or compressive symptoms at an island health centre should be referred to the nearest atoll hospital.
- At atoll-level: history, examination, serum TSH, and neck ultrasound.
- Suspicious sonographic features (per Section 2.3.1) → onward referral to a regional hospital or to Malé for ultrasound-guided FNAC.
- Bethesda category assigned per the 2023 system; results communicated to the referring physician with an interpretation and recommended next step.

10.2.2 Step 2 - Surgical Referral

- Bethesda V or VI cytology, or Bethesda IV with high-risk features → referral to a tertiary hospital (IGMH, TTH, or ADK) for surgical evaluation.
- Pre-operative work-up: TSH, calcium, vocal cord assessment if voice changes, chest X-ray and neck CT/MRI when indicated.
- Surgery - lobectomy or total thyroidectomy ± central neck dissection - performed at IGMH, TTH, or ADK by surgeons with sufficient case volume.
- IONM (intraoperative nerve monitoring) is currently available at IGMH; intraoperative frozen-section pathology is available at TTH.
- Histopathology is reported in-house at the operating hospital and should follow the standardised reporting set in Section 3.2.

10.2.3 Step 3 - Risk Stratification and MDT Review

- Postoperative risk stratification per Section 3.4 by the surgical team in conjunction with endocrinology / oncology.
- Tumour board review (pathology, radiology, surgery, endocrinology, oncology) for: intermediate- and high-risk DTC, all MTC, all ATC, indeterminate pathology, and any case in which RAI or overseas referral is anticipated.
- A standardised MDT summary should be prepared for any patient being referred onward.

10.2.4 Step 4 - Radioiodine Therapy (Overseas Referral)

- Radioiodine (I-131) facilities are not currently available in the Maldives.
- Patients meeting RAI criteria (Section 5.2) are referred to Aasandha-empanelled hospitals - predominantly in India, with selected Sri Lankan centres also used.
- Aasandha is responsible for approval of the receiving hospital and for funding of treatment under the universal health insurance scheme; documentation requirements should be confirmed at the time of MDT planning.
- Local arrangements for the low-iodine diet and for thyroid hormone withdrawal are coordinated through the endocrinology and oncology clinics at IGMH and TTH prior to travel.

- A complete clinical packet - operative note, definitive histopathology, postoperative neck ultrasound, baseline Tg and TgAb, current TSH and fT4, and MDT summary - should accompany the patient.
- On return: post-therapy WBS report, copy of Tg/TgAb at follow-up, and a long-term plan should be entered into the patient's record at the local hospital.

10.2.5 Step 5 - Systemic Therapy Access

- For patients with RAI-refractory disease, MTC, or ATC requiring systemic therapy, treatment should be initiated under the supervision of the local oncology service.
- Multikinase inhibitors (lenvatinib, sorafenib, vandetanib, cabozantinib) and the principal mutation-specific agents (selpercatinib, pralsetinib, larotrectinib, entrectinib, dabrafenib + trametinib) are accessible through Aasandha and NSPA.
- Drugs are procured through the hospital pharmacies and through the State Trading Organisation (STO).
- Where molecular profiling is required to determine eligibility, samples may be sent overseas as part of the Aasandha referral pathway.
- Toxicity monitoring (blood pressure, renal function, urine protein, LFTs, ECG/QTc as required) and supportive care are provided by the local chemotherapy day-care units at IGMH and TTH.

10.2.6 Step 6 - Long-Term Follow-Up

- Long-term follow-up is coordinated through the endocrinology and oncology clinics at the Malé tertiary hospitals.
- Stable patients in remission should be linked to a regional follow-up clinician with a written long-term plan: schedule of TSH, fT4, Tg, TgAb, and ultrasound; trigger criteria for early referral; and named tertiary contact.
- Patients on long-term TSH suppression require monitoring for atrial fibrillation, osteoporosis, and adequacy of suppression.

10.3 Schematic Pathway

The pathway is summarised below. Each row represents a transition of care; investigations and decisions at each level are shown in the right-hand column.

Level	Setting	Activities and Decision Points
1. Detection	Island health centre / atoll hospital	Clinical evaluation; TSH; neck ultrasound (atoll level and above). Refer suspicious nodules upward.
2. Diagnosis	Regional hospital / Malé tertiary	USG-guided FNAC by radiologist; Bethesda 2023 reporting; cross-sectional imaging if indicated.
3. Surgery	IGMH / TTH / ADK	Lobectomy or total thyroidectomy ± neck dissection. IONM at IGMH; frozen section at TTH. In-house histopathology.
4. MDT review	Tertiary MDT	Risk stratification (Section 3.4); decision on RAI, completion surgery, systemic therapy; documentation pack for onward referral.
5. RAI (if indicated)	Overseas (Aasandha-empanelled India/Sri Lanka centres)	Local low-iodine diet and LT4 withdrawal coordinated by IGMH/TTH. Post-therapy WBS report returned to local team.
6. Systemic therapy (if indicated)	IGMH / TTH chemotherapy day care	MKIs and targeted agents via Aasandha/NSPA, procured through hospital pharmacy / STO. Toxicity monitoring local.
7. Follow-up	Endocrinology / Oncology clinics, Malé	Dynamic risk reassessment; TSH/Tg/TgAb; neck ultrasound; long-term plan documented and shared with the patient and regional clinician.

10.4 Documentation Standards

To minimise repeated investigations and to support continuity of care, a minimum dataset should accompany every referral:

- Patient demographics, contact details, and Aasandha number.
- Relevant history including prior neck irradiation, family history of thyroid cancer or MEN.
- Imaging - neck ultrasound report (with images where possible), CT/MRI as indicated.
- Cytology / histology report with Bethesda or WHO classification.
- Operative note (where applicable).

- Postoperative biochemistry: TSH, fT4, Tg, TgAb (and calcitonin/CEA where MTC).
- MDT summary and current management plan.
- Allergy and current medication list.

10.5 Linkage to the National Cancer Registry

All confirmed cases of thyroid cancer should be notified to the **National Cancer Registry (NCR)** as part of routine cancer surveillance, in line with the National Cancer Control Plan of Maldives 2022–2026. Accurate notification - including histological subtype, stage, and treatment received - is essential for the development of country-specific epidemiological data and will support future iterations of this guideline.[3]

11. Palliative and Supportive Care in the Maldivian Context

Palliative and supportive care should be integrated early into the management of patients with thyroid cancer, particularly those with anaplastic disease, advanced medullary disease, RAI-refractory differentiated disease, and high symptom burden at any stage.

11.1 Current Service Capacity

At present, the Maldives does not have dedicated palliative medicine specialists, hospital palliative care units, or formal hospice or community-based palliative care services. In-hospital palliative care is delivered by the relevant medical teams and the oncology service. Important practical implications follow:

- Palliative-care planning should begin at the point of diagnosis for advanced or symptomatic disease, rather than at end-of-life.
- The oncology team will often act as the de-facto palliative-care lead and should coordinate symptom management, communication, and family support.
- Discharge planning for symptomatic patients must include written guidance to the family on medication use, symptom red flags, and contact arrangements.

11.2 Core Symptom Management

11.2.1 Pain

- WHO analgesic ladder principles, with rapid escalation to opioids for moderate-to-severe cancer pain.
- Long-acting and immediate-release opioid formulations (morphine, oxycodone) should be made available; appropriate regulation and prescriber training is essential.
- Adjuvants - corticosteroids, anticonvulsants, and antidepressants - for neuropathic pain.
- Bone-targeted therapy (zoledronic acid or denosumab) and palliative radiotherapy (overseas) for symptomatic skeletal metastases.

11.2.2 Airway and Respiratory Symptoms

- Early ENT assessment for stridor; tracheostomy where indicated and consistent with goals of care.
- Opioids and benzodiazepines for dyspnoea where airway intervention is not appropriate.

- Oxygen for symptomatic relief; corticosteroids for airway oedema.

11.2.3 Nutritional and Swallowing Support

- Dietetic input and texture modification for dysphagia.
- NG / PEG feeding where prolonged dysphagia is anticipated and consistent with goals of care.

11.2.4 Other Symptoms

- Antiemetics for nausea; laxatives for opioid-induced constipation.
- Anxiolytics, antidepressants, and sleep support as needed.
- Skin care for fungating lesions; wound care; haemostatic dressings for bleeding.

11.3 Communication and Decision-Making

- Honest, culturally appropriate communication about diagnosis, prognosis, and treatment options is essential.
- Goals-of-care conversations should occur early - at diagnosis of advanced disease - and be revisited at major transitions.
- Written documentation of agreed plans (including ceilings of treatment, resuscitation status, and preferred place of care) should be entered into the medical record and shared with family caregivers.
- Religious and cultural considerations should be respected; involvement of the family unit is central to Maldivian practice.

11.4 Caregiver Support

- Caregivers should receive education in symptom monitoring, medication administration, and emergency contact pathways.
- Practical support - including written information in Dhivehi where possible - improves adherence and reduces avoidable presentations.
- Bereavement support is a recognised gap; oncology teams should provide compassionate follow-up after a patient’s death and offer information on community support resources where available (e.g. the Cancer Society of Maldives).

11.5 Future Direction

Building palliative-care capacity is a national priority. Steps endorsed by this guideline include:

- Training of designated nurses and physicians in palliative-care principles.
- Development of pathways for community and home-based palliative-care delivery, particularly for atoll-resident patients.
- Engagement with regional centres of palliative-care excellence for clinical attachment and curriculum development.
- Integration of palliative-care indicators into the National Cancer Control Plan and into routine oncology audit.

12. Abbreviations

Abbreviation	Definition
AJCC	American Joint Committee on Cancer
ATA	American Thyroid Association
ATC	Anaplastic thyroid carcinoma
Aasandha	National universal health insurance scheme of the Maldives
CEA	Carcinoembryonic antigen
DTC	Differentiated thyroid carcinoma
EBRT	External beam radiotherapy
ESMO	European Society for Medical Oncology
ETE	Extrathyroidal extension
FNAC	Fine-needle aspiration cytology
FTC	Follicular thyroid carcinoma
GBq	Gigabecquerel
IGMH	Indira Gandhi Memorial Hospital, Malé
IONM	Intraoperative neuromonitoring
mCi	Millicurie
MDT	Multidisciplinary team
MEN	Multiple Endocrine Neoplasia syndrome
MKI	Multikinase inhibitor
MTC	Medullary thyroid carcinoma
NCCN	National Comprehensive Cancer Network
NCR	National Cancer Registry (Maldives)
NIFTP	Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
NSPA	National Social Protection Agency (Maldives)

Abbreviation	Definition
PTC	Papillary thyroid carcinoma
RAI	Radioactive iodine (I-131)
RECIST	Response Evaluation Criteria in Solid Tumours
rhTSH	Recombinant human thyroid-stimulating hormone
RLN	Recurrent laryngeal nerve
SBRT	Stereotactic body radiotherapy
STO	State Trading Organisation (Maldives)
TBSRTC	The Bethesda System for Reporting Thyroid Cytopathology
Tg / TgAb	Thyroglobulin / anti-thyroglobulin antibody
TSH	Thyroid-stimulating hormone
TTH	Tree Top Hospital, Hulhumalé
UICC	Union for International Cancer Control
WBS	Whole-body scan
WHO	World Health Organization

13. References

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