**Clinical Management Guideline for Thyroid Nodules and Cancer in Adults**

**PREFACE**

Within this document there is information on drug treatments including chemotherapy and targeted therapy. These regimens are to be prescribed in accordance with the chemotherapy operational protocols and master prescriptions which are available on <http://intranet.lothian.scot.nhs.uk/NHSLothian/Healthcare/A-Z/CancerServices/Pages/CancerServices.aspx>

The radiotherapy protocols are subject to the IRMER regulations. Only Level 4 medical staff may deviate from the protocols contained within this document. For level 3 medical staff and below these documents should be regarded as procedures which should not be deviated from without authorisation from a level 4 member of staff.

1. **INTRODUCTION**

Thyroid nodules are a common clinical problem. Approximately 3-7% of adults have a palpable thyroid nodule, but using ultrasound, prevalence rates increase to 30-70% of adults. Frequency increases with age. The majority of thyroid nodules are benign – a combination of colloid cysts, hyperplastic nodules and follicular adenomas. Thyroid cancer occurs in 7%–15% of palpable nodule, the risk depending on age, sex, radiation exposure history, family history, and other factors. Impalpable nodules have a lower risk of malignancy, though ~30% of nodules detected by FDG-PET scanning will be cancers.

The majority of malignant thyroid tumours (>90%) are differentiated thyroid cancer (DTC). DTC incorporates both papillary and follicular thyroid tumours. Anaplastic and medullary thyroid cancers are treated differently (see below).

The incidence of thyroid cancer is increasing rapidly, although the mortality is not rising. This is likely to be due in part to an increase in imaging picking up tumours that wouldn’t ever have presented clinically.

* Approx 3,200 new cases of thyroid cancer in the UK p.a., making it the 19th most common cancer
* More than half (52%) of thyroid cancer cases in the UK each year are diagnosed in people aged 50 and over
* Over the last decade, thyroid cancer incidence rates have increased by more than two-thirds (71%) in the UK, which includes similar increases in females (73%) and males (70%).
* Thyroid cancer in England is not associated with deprivation.
* Thyroid cancer mortality rates in women in the UK have more than halved in the last 40 years. In men they have fallen by almost a third.
* In 2012, around 370 people in the UK died from thyroid cancer
1. **THYROID NODULES**

All patients with a thyroid nodule should have thyroid function assessed (TFTs). Functional nodules, associated with a low or undetectable TSH, have an extremely small chance of malignancy and should be assessed and managed through general endocrinology. Patients with thyroid nodule(s) and normal TFTs may be referred to the Thyroid Nodule Clinic (TNC) at the RIE (Strachan/Gibb) or the Neck Lump Clinic at Lauriston Building (Adamson/Nixon).

Initial assessment is by thyroid/neck ultrasound. This is a highly specialised area of radiology and should be undertaken by radiologists with particular expertise in this field and who can confidently grade thyroid nodules according to the U1-U5 classification recommended by the British Thyroid Association.



U1. Normal.

U2. Benign:(a) halo, iso-echoic / mildly hyper-echoic(b) cystic change +/- ring down sign (colloid) (c) micro- cystic / spongiform (d & e) peripheral egg shell calcification(f) peripheral vascularity.

U3. Indeterminate/Equivocal: (a) homogenous, hyper-echoic (markedly), solid, halo (follicular lesion). (b) ? hypo-echoic, equivocal echogenic foci, cystic change(c) mixed/central vascularity.

U4. Suspicious:(a) solid, hypo-echoic (cf thyroid) (b) solid, very hypo-echoic (cf strap muscle) (c) disrupted peripheral calcification, hypo-echoic (d) lobulated outline

U5. Malignant(a) solid, hypo-echoic, lobulated / irregular outline, micro-calcification. (? Papillary carcinoma) (b) solid, hypo-echoic, lobulated/irregular outline, globular calcification (? Medullary carcinoma) (c) intra-nodular vascularity (d) shape (taller >wide) (AP>TR) (e) characteristic associated lymphadenopathy

Fine-needle-aspiration cytology (FNAC) was traditionally performed on all palpable thyroid nodules and concerning nodules identified by imaging, but with the growing local expertise is increasingly reserved for nodules graded U3-U5. Pathological lymph nodes may also be an appropriate target for FNA. U2 nodules may be FNA’d if there is clinical concern, e.g. PET positive or nodule growing on interval imaging. FNA may be performed in clinic for a clearly palpable nodule or under USS guidance. Biopsies are performed using a variety of needle sizes (21-25G) depending on the clinician. Pathology require two air dried slides, two slides fixed in alcohol and a Cytolyt container with needle rinse. Cyst fluid should be placed only in the Cytolyt container. Core biopsies under USS guidance may be performed under certain circumstances, such as from pathological lymph nodes or if thyroid lymphoma/anaplastic thyroid cancer is suspected. Clopidogrel and DOACS (e.g. apixaban) should be stopped 5 days before a FNA and INR should be <1.5 for patients on warfarin. FNA may be performed safely in patients taking aspirin. All patients should be advised of the risk of bleeding following FNA and advised to seek urgent medical advice if any significant swelling or breathing difficulties afterwards.

Thyroid cytology normally has a two-week turn-around time, but the thyroid pathologists (Thomson/Conn) will provide a more rapid assessment in urgent cases. Thyroid cytology is graded Thy 1- Thy5:

* Thy 1 - technically unsatisfactory specimen
* Thy 1c - cyst fluid with insufficient colloid and epithelial cells
* Thy 2 - non-neoplastic
* Thy 2c - cyst fluid with adequate colloid
* Thy 3a - atypical features, but insufficient to place in a higher category
* Thy 3f - follicular cytology
* Thy 4 - suspicious for malignancy
* Thy 5 - diagnostic of malignancy

The BTA guidelines suggest that individuals with U2 nodules may be discharged with no further follow-up. Current practice in the TNC is to arrange a 12 month surveillance USS, though that depends on the individual patient; in the neck lump clinic, patients with U2 nodules may be discharged. Some patients will prefer surgery to USS surveillance and that is acceptable. The pros and cons of surgery v surveillance should be discussed in detail. Patients who are discharged should be advised to have an annual check of TFT’s and to seek medical advice if they notice any change in the size of the nodule(s).

Nodules which are U3 should generally be FNA’d. If the cytology is Thy2, then surveillance may be appropriate depending on the individual’s wishes. Thy 1 or Thy3a cytology would generally mandate a repeat FNA or surgery. Thy 3f - Thy5 cytology would indicate surgery in most instances.

U4 and U5 nodules will require surgery in most instances; FNA is important to plan the optimum surgical approach.

**Other investigations**

* Thyroid scintigraphy is recommended when a functional nodule is suspected.
* CT is indicated if there is concern about retrosternal extension of a goitre or to accurately stage a confirmed cancer (for papillary and thyroid cancers this is not required as a matter of routine in the absence of neck lymphadenopathy on USS or symptoms suggestive of distant metastatic disease)
* Pulmonary function tests – a flow volume loop may be used in some instances to diagnose tracheal compression and may also rarely be used as a surveillance tool for people with a known retrosternal goitre. Its utility has largely been superseded by CT.
* Barium swallow may occasionally be required if an individual with a retrosternal goitre has dysphagia, to help clarify the extent of external compression of the oesophagus.

**Nodules under radiological surveillance**

Growth of nodules across interval scans is not in itself an indicator of malignancy, as clearly both benign and malignant nodules can grow. However, re-evaluation of a growing nodule by FNA (or repeat FNA) should be considered and the diagnostic uncertainty discussed with the patient.

The decision on when to stop USS surveillance in an individual with a static nodule (or rarely one reducing in size) must be individualised, taking into account multiple factors such as the USS characteristics, FNA findings (where performed), age, co-morbidities and risk factors.

**MDT Referral**

The thyroid/endocrine MDT meets monthly at the RIE (generally 4th Monday of the month). VC facilities are available. All referrals require completion of the MDT proforma (available on the ECED website) and it is essential to highlight whether pathological and/or radiological review are required. All patients with confirmed thyroid cancer must be referred to the MDT. Patients with thyroid nodule without confirmed malignancy, but where there is diagnostic uncertainty or management uncertainty may also be referred for discussion.

There is currently no specific cancer nurse specialist support for patients with thyroid cancer. Support is given in the aftermath of surgery to patients undergoing surgery in ENT by the head and neck cancer nurse specialists. Patients under the age of 23 should be referred to Fiona Dawson, CNS for Young Adults with Cancer.

**3. DIFFERENTIATED THYROID CANCER**

**Pathology**

Thyroid malignancies are divided into papillary carcinomas (80%), follicular carcinomas (10%), medullary thyroid carcinomas (5-10%), anaplastic carcinomas (1-2%), primary thyroid lymphomas (rare), and primary thyroid sarcomas (rare). Hürthle cell carcinoma is a rare thyroid malignancy that is considered a variant of follicular carcinoma. Hürthle cell carcinomas account for 2-3% of all thyroid malignancies. Other cancers may also rarely metastasise to the thyroid.

*Staging of primary tumour*

* TX Primary tumour cannot be assessed
* T0   No evidence of primary tumour
* T1   Tumour ≤2 cm in greatest dimension limited to the thyroid
* T1a  Tumour ≤1 cm, limited to the thyroid
* T1b  Tumour >1 cm but ≤2 cm in greatest dimension, limited to the thyroid
* T2   Tumour >2 cm but ≤4 cm in greatest dimension, limited to the thyroid
* T3   Tumour >4 cm in greatest dimension limited to the thyroid or any tumour with minimal extra-thyroidal extension (e.g. extension to sternothyroid muscle or perithyroid soft tissues)
* T4a Tumour of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, oesophagus, or recurrent laryngeal nerve
* T4b  Tumour invades prevertebral fascia or encases carotid artery or mediastinal vessels

*Staging of Regional lymph nodes (cervical or upper mediastinal)*

* NX Regional lymph nodes cannot be assessed
* N0   No regional lymph node metastasis
* N1   Regional lymph node metastasis
* N1a  Metastases to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)
* N1b  Metastases to unilateral, bilateral, or contralateral cervical (Levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (Level VII)

*Distant metastases*

* M0   No distant metastasis
* M1   Distant metastasis

*Residual Disease*

* RX Cannot assess presence of residual primary tumour
* R0 No residual primary tumour
* R1 Microscopic residual primary tumour
* R2 Macroscopic residual primary tumour

**Investigations**

Imaging:

* Ultrasound scan of the neck including assessment of LN status
* Cross-sectional imaging in selected circumstances only (see above)

Blood tests:

* Thyroid function
* Thyroglobulin (Tg) (follow up only)

Cytology

* FNAC of thyroid nodule or pathological lymph node

**Surgery**

Initial treatment for DTC is surgery in almost all cases. For tumours ≥4cm, total thyroidectomy is indicated. In addition, those cases felt suitable for RAI will also require total thyroidectomy to facilitate adjuvant treatment. In the absence of such features, uninodular intrathyroid tumours <4cm may be treated with thyroid lobectomy or total thyroidectomy. Such patients should be considered on a case-by-case basis.

Therapeutic neck dissection should be performed for proven disease in the central (level VI and VII) or lateral (level II-V) neck. There is no role for prophylactic lateral neck surgery and prophylactic central neck dissection is controversial with no survival benefit and limited evidence of benefit in terms of recurrence. Prophylactic central neck surgery should be considered in the highest risk cases (e.g. T4 disease). In expert hands surgical complications such as laryngeal nerve palsy and hypoparathyroidism, are uncommon.

**Radio-iodine Therapy (RAI)**

Adjuvant

Surgery may be followed by the administration of 131I activities aimed at ablating any remnant thyroid tissue and potential microscopic residual tumour. Ablation is not recommended for patients who have not undergone thyroidectomy/completion thyroidectomy, as the residual normal thyroid cells will preferentially take up the RAI. In select cases, RAI may decrease the risk of locoregional recurrence; it facilitates long-term surveillance based on serum Tg measurement and diagnostic radioiodine whole body scan (WBS). In addition the high activity of 131I allows obtaining a highly sensitive post-therapeutic WBS.

Table 1. Indications for Ablative Radioactive Iodine (BTA Guidelines, 2014)

|  |
| --- |
| **NO INDICATIONS** *ALL CRITERIA BELOW SHOULD BE MET* * Tumour <1cm unifocal or multi focal
* Histology classical papillary or follicular variant of papillary carcinoma, or follicular carcinoma
* Minimally invasive without angioinvasion
* No invasion of thyroid capsule (extra thyroidal extension)

  |
| **DEFINITE INDICATIONS** *ANY ONE OF THE CRITERIA BELOW SHOULD BE MET* • Tumour >4cm * Any tumour size with gross extra thyroidal extension
* Distant metastases present
 |
| **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 RIA * Large tumour size
* Extra-thyroidal extension
* Unfavourable cell type (tall cell, columnar or diffuse sclerosing papillary cancer, poorly differentiated elements)
* Widely invasive histology
* Multiple lymph node involvement, large size of involved lymph nodes, high ratio of positive to negative nodes, extracapsular nodal involvement.
 |

The prognosis for differentiated carcinoma is better for patients younger than 40 years without extracapsular extension or vascular invasion. Age is the single most important prognostic factor. Adverse factors include: age older than 45 years, follicular histology, primary tumour larger than 4 cm (T3), significant extrathyroid extension (T4: extension into subcutaneous soft tissues, larynx, trachea, oesophagus, or recurrent laryngeal nerve) and distant metastases.

The MDT generally favours ablative RAI for patients with definite and uncertain indications. 3,700MBq is generally given for patients with higher risk tumours, i.e. pT3 (unless primary small and minimal extra-thyroidal extension), pT4, N1b, N1a with extra-nodal spread, M1, R1/R2 and high risk histological types, e.g. tall cell variant or components of poorer differentiation. 1,100MBq is given for all other patients.

RAI is administered by Medical Physics at the WGH and patients will need to remain in isolation in the Oncology Assessment Area after treatment. The duration of isolation is variable and depends on the dose of RAI given, the patient’s renal function and the extent of any residual malignancy. In general, most patient’s receiving 1,100 MBq will get home after 24 hours while most patients receiving 3,700 will get home after 48 hours. Radiation restrictions will remain in place following discharge for a variable time, again depending on the above factors. All patients must be counseled in detail about the restrictions that are in place following RAI. Specific written guidance for patients is available on the ECED website.

Pregnancy and breast feeding are absolute contraindications to RAI.

Patients may be prepared for RAI with Levothyroxine withdrawal or Thyrogen stimulation. The latter is favoured by the SES MDT and there are specific ECE protocols in the ‘Metabolic Unit Handbook’ on the intranet and the ECED website which deal with both scenarios. It is important that the patient is assessed for their physical and mental suitability for RAI. Patients with co-morbidities must be carefully considered as to their suitability for being in the isolation room. If there is any doubt as to their suitability, it is better to defer therapy than have a patient become unwell or distressed in the isolation room, as that will potentially pose a radiation hazard to medical and nursing staff. Renal function should be checked in all patients with CKD or aged over 65 years prior to RAI therapy, to help Medical Physics staff plan the likely duration of admission.

Therapeutic

Patients with evidence of persistent disease, or with detectable levels of serum Tg increasing with time may be considered for further RAI therapy. Activities given are generally higher, e.g. 6000MBq and so the duration of admission and the restrictions are in place for longer. If there is evidence of benefit of therapy (reducing or stable tumour bulk and or reducing or stable thyroglobulin levels) and evidence of RAI uptake by the tumour deposits, further therapeuatic doses may be given. The minimum interval between treatments is generally 6 months. There is no upper limit for the cumulative amount of RAI that may be given, but it is rare to exceed 30,000 MBq. There is a suggestion from older literature that very high cumulative exposures are associated with an increased risk of leukaemia.

Ablative doses of RAI are not associated with major toxicity. There may be some uptake in salivary glands which can lead to a transient dry mouth. There is probably a small increase in the risk of second malignancies. Higher cumulative doses of RAI are associated with xerostomia and salivary duct stones. Patients with pulmonary metastases are at risk of pulmonary fibrosis, and so where metastases are extensive a reduced dose of RAI may be considered.

RAI Refractory

In patients with stage IV thyroid cancer, consensus guidelines have been drawn up to define patients who will not benefit from further RAI.

* Patients with metastatic disease that doesn’t take-up 131I at the time of initial treatment.
* Patients whose tumours lose the ability to take-up 131I after previous evidence of uptake.
* Patients with 131I uptake retained in some lesions but not in others.
* Patients with metastatic disease that progresses within 12 months despite significant uptake of 131I.
* Less clear is the situation for patients with persistent visible 131I uptake in all residual lesions who are not cured despite several treatment courses but whose disease does not progress according to RECIST criteria. It is controversial as to whether these patients (particularly after receiving more than 22,000 MBq of 131I) should be considered 131I-refractory and whether 131I treatment should be abandoned.

Finally, patients with advanced disease for whom thyroidectomy is not feasible. In such patients, 131I treatment is usually not administered because 131I is ineffective when the thyroid gland is still present and 131I uptake status cannot be assessed. These patients could be managed as iodine-refractory patients, or if desired, treated with RAI to destroy the thyroid.

**External-Beam Radiotherapy**

External beam radiotherapy (EBRT) is reserved for selected patients with

* Locally advanced disease
	+ Grossly visible extra thyroid extension at time of surgery
	+ Inoperable disease
* High-risk surgical pathologic features
	+ Gross residual disease. A study from Royal Marsden showed complete response in 37% and partial response in an additional 25%
* Recurrent or metastatic disease nonresponsive to RAI therapy

Radiotherapy doses and techniques

* Adjuvant
	+ 60- 66 Gy in 2Gy per fraction using IMRT covering the thyroid bed and bilateral neck nodes
* Palliative
	+ Doses range from 30 Gy in 3 Gy per fraction to 45 Gy in 3 Gy per fraction for high dose palliation
	+ 20 Gy in 5 fractions and 8 Gy in 1 fraction for palliation of pain, discomfort , osseous metastasis and cord compression
	+ Techniques range from simple single field, parallel pair to IMRT
	+ Intra-cranial metastases should be considered for surgery/SRS. Following an MRI brain and CT CAP and neck, refer to ECNO MDM for discussion

**Systemic Anti-Cancer Therapy (SACT):**

Metastatic DTC can be asymptomatically stable for long periods of time, in particular in young patients with small lung metastases from a well differentiated papillary or follicular carcinoma and in such patients the benefits SACT may be outweighed by drug toxicities.

In general SACT should be reserved for patients with multiple lesions >1-2 cm and with progression within 12 months. Patients with few and/or small lung lesions <1cm, and those with no evidence of progression are considered for active follow-up. The exception would be patients with large tumor burden and lacking 131I uptake who may be considered for systemic treatment based on uptake of FDG on PET scanning or even on primary tumor histology, if there is a high risk of complications.

Sorafenib

[Sorafenib](http://reference.medscape.com/drug/nexavar-sorafenib-342260) is SMC-approved for DTC that is refractory to radioactive iodine treatment. In a study of 417 patients with progressive radioiodine-refractory DTC, treatment with sorafenib, significantly improved progression-free survival (10.8 months) compared with placebo (5.8 months) (Brose et al 2014). Tumour histology was 57% papillary, 25% follicular, and 10% poorly differentiated. The majority of the patients (96%) had metastatic disease, of which 71% of the target lesions were in the lung, 40% in lymph nodes, and 14% in bone. Sorafenib toxicity was similar to that seen when it is used in other tumour types.

Sorafenib 400mg bd until disease progression. Dose modification on the basis of toxicity.

Lenvatinib

Lenvatinib is SMC-approved for DTC that is refractory to radioactive iodine treatment. A randomised phase III trial (Schlumberger et al 2015) demonstrated an improvement in progression-free survival to 18.3 months in the lenvatinib group from 3.6 months in the placebo group (hazard ratio for progression or death, 0.21; 99% confidence interval, 0.14 to 0.31; P<0.001). progression-free survival benefit associated with lenvatinib was observed in all prespecified subgroups, even in those with previous TKI exposure. The median overall survival was not reached in either group.

Treatment-related adverse effects of any grade, which occurred in more than 40% of patients in the lenvatinib group, were hypertension (in 67.8% of the patients), diarrhea (in 59.4%), fatigue or asthenia (in 59.0%), decreased appetite (in 50.2%), decreased weight (in 46.4%), and nausea (in 41.0%). Discontinuations of the study drug because of adverse effects occurred in 37 patients who received lenvatinib (14.2%) and 3 patients who received placebo (2.3%). In the lenvatinib group, 6 of 20 deaths that occurred during the treatment period were considered to be drug-related.

Lenvatinib 24mg daily until disease progression. Dose modification on the basis of toxicity.

There is no study directly comparing sorafenib and lenvatinib for the management of advanced DTC and either option could be chosen for use. In general lenvatinib is the preferred first-line of therapy, however, in view of longer disease control in the clinical trial and fewer symptomatic toxicities. In the context of poorly controlled hypertension sorafenib may be a better choice of therapy.

Other TKIs

A randomized phase II trial of vandetanib in 145 patients with RAI-refractory DTC demonstrated a similar improvement in PFS to sorafenib. Patients who received vandetanib had median PFS of 11·1 months (95% CI 7·7–14·0) in comparison to 5·9 months (4·0–8·9) for patients in the placebo group. Vandetanib is currently not licensed in this disease.

There is also phase II data suggesting activity of other TKIs in this disease including axitinib, sunitinib and motesanib. There is also evidence of the activity of vemurafenib in the context of patients with b-raf mutations.

Cytotoxic chemotherapy

There is no randomized evidence for a survival benefit in relation to cytotoxic chemotherapy in DTC. Cisplatin and doxorubicin both have some activity in this disease, with a radiological response rate for the combination of up to 26% (Shimaoka et al 1985), so it may occasionally be appropriate to consider systemic chemotherapy in the context of rapidly progressing, symptomatic disease.

Clinical Trials

Patients with RAI-refractory disease that has progressed after standard TKI therapies may be considered for clinical trials of novel agents.

**Follow-Up**

The majority of patients are followed up at the Thyroid nodule/Cancer clinic at the RIE. Exceptions to this are patients undergoing external beam radiotherapy and SACT. Patients from outwith Lothian are generally followed up by their local teams. Patients with low-risk tumours, treated with surgery alone, do not require long-term follow-up or TSH suppression (see below).

Thyroglobulin

Patients should be seen at 3 months post-RAI, 6 months, 12 months and thereafter annually if they have had an excellent response to treatment (see below). TFT’s and Thyroglobulin should be measured at each clinic visit, using the Trak ‘Diff thyroid cancer’ orderset. Thyroglobulin is an excellent marker of tumour recurrence after total thyroid ablation. Thyroglobulin (Tg) is measured by two methods – the high-sensitivity radio-immunometric ‘Access’ assay in Edinburgh and the low-sensitivity radio-immunoassay in Birmingham. 10% of patients will have antibodies against Tg which interferes with and invalidates the TG results. Antibody interference is detected by looking for discordance between the two assays. The Edinburgh assay reads low in the presence of antibodies, while the Birmingham assay reads high. Therefore, a typical example of antibody interference would be Edinburgh <0.1 and Birmingham >5.0. The alternate pattern of discordance, with a detectable value on the Edinburgh assay and an undetectable value on the Birmingham assay is simply a consequence of the differential functional sensitivity of the two assays (very, very rarely this pattern can occur as a consequence of antibody interference). A detectable Tg (>0.1) on the Edinburgh assay has a 33% PPV for recurrent/residual disease; a rising Tg trend has much greater PPV for recurrent/residual disease. A Tg <0.1 on the Edinburgh assay has a NPV of almost 100%. There is no requirement for routine use of Thyrogen stimulation to enhance functional sensitivity of the Edinburgh assay, but it can be used to confirm antibody interference (though this is rarely required).

Imaging

Patients with an interference pattern on the Tg assay should have an early neck USS to look for residual disease. Patients with undetectable Tg by both assays should have a neck USS prior to the 12 month follow-up assay. The purpose of this scan is to detect the unlikely occurrence of Tg negative residual disease. Thyrogen-stimulated Tg measurements and repeat WBS are not routinely required.

Dynamic Risk Stratification: Excellent Response to Treatment and TSH Suppression

After thyroidectomy and radioiodine ablation, patients with well-differentiated thyroid carcinoma are maintained on T4 in daily doses sufficient to suppress TSH production (usually 150-200 mcg/day). At 12 months, patients risk of recurrence should be re-evaluated in light of the prevailing Tg levels and the USS neck findings; this is known as dynamic risk stratification. Patients with an ‘excellent response to treatment’, i.e. a normal 12 month neck USS and undetectable Tg by both assays, do not require TSH suppression beyond 12 months and a target TSH of 0.3-2 is appropriate. Patients with an excellent response, but with high risk histological subtypes may benefit from longer-term TSH suppression. TSH suppression in the long term is associated with an increased risk of atrial fibrillation and osteoporosis.

Patients with initial stage 1 disease and who have maintained undetectable Tg levels may be discharged to the Virtual follow-up clinic after 5 years.

Incomplete Response to Treatment

Patients with an incomplete response to RAI (detectable Tg in the absence of antibody interference) require initial investigation with neck USS. The extent of further investigation with cross-sectional imaging, RAI imaging and FDG-PET imaging depends on the trend of TG levels, the absolute levels and the general well-being of the patient. The majority of patients with an incomplete response to RAI will require additional therapy such as surgical resection, further RAI therapy, external beam irradiation and/or systemic therapies. All such patients should be referred to the MDT for discussion.

**4. MEDULLARY THYROID CANCER**

Medullary thyroid cancer (MTC) is rare, comprising only 3% to 4% of thyroid cancers.

Approximately 25% of reported cases of MTC are familial. Familial MTC syndromes include MEN 2A, which is the most common; MEN 2B; and familial non-MEN syndromes. Any patient with a familial variant should be screened for other associated endocrine tumours, particularly parathyroid hyperplasia and pheochromocytoma. MTC can secrete calcitonin and other peptide substances. Determining the level of calcitonin is useful for diagnostic purposes and for surveillance following treatment.

**Pathology**

MTC is a neuroendocrine tumour (NET) derived from C cells (formerly called parafollicular cells) of ultimobranchial body of neural crest. The malignant cells frequently will secrete calcitonin and CEA.

Staging is as for differentiated thyroid cancer.

**Investigations**

Imaging:

* USS
* CT neck, chest, abdomen, pelvis

Blood tests :

* Thyroid function
* Calcitonin (either basal or post calcium/pentagastrin stimulation)
* Chromogranin A, CEA (specific cases only)

Cytology

* FNAC of thyroid nodule

Genetic screening

* RET mutation screening should be undertaken in all cases

**Surgery**

Sporadic medullary thyroid carcinomas and familial medullary thyroid carcinomas are treated with total thyroidectomy and level VI-VII dissection. Therapeutic neck dissection of the lateral compartments should be performed in line with the recommendations for DTC. Prophylactic lateral neck surgery is controversial. Although biochemical cure is unlikely in the setting of lateral neck disease, high calcitonin can be used as a predictor of metastases in the lateral neck. Some authors therefore consider high calcitonin (>200) to be an indication for prophylactic surgery. In children with multiple endocrine neoplasia (MEN) type 2A and MEN 2B syndromes, prophylactic thyroidectomy with or without central-compartment lymph-node dissection is performed. The timing of this is determined in liaison with clinical genetics and is influenced by the specific RET genotype.

**TSH suppression and Radio-iodine Therapy**

There is no role for RAI or TSH suppression in the management of medullary thyroid cancer. Patients should receive physiological replacement with T4 following thyroidectomy.

**External-Beam Radiotherapy**

External beam radiotherapy may have a role in

* Gross extra thyroid extension encountered following surgical resection
* Positive surgical margins (in contrast to “R1” pathological report) and further surgery not possible
* Local control if disease becomes unresectable
* Treatment of osseous metastases
* Spinal cord compression

Doses and techniques

* Adjuvant
	+ 60-66 Gy in 2 Gy per fraction to surgical bed and bilateral cervical nodes
	+ Mediastinal nodes are not included unless suspicious
* Palliative
	+ High dose for local control : 45 Gy to 30 Gy in 3 Gy per fraction
	+ For symptom control, emergencies : 20 Gy in 5 fractions to 8 Gy in a single fraction

**Systemic Anti-Cancer Therapy (SACT):**

Radiopharmaceuticals

There are no randomised trials of radiopharmaceuticals in medullary thyroid cancer, but by extrapolation from other neuroendocrine tumours, patients with octreotide or MIBG-avid tumours have been managed with octreotide or MIBG radiopharmaceutical therapy with case reports of benefit.

Vandetanib

In a randomized trial (Wells et al 2011), 331 patients were randomized 2:1 between vandetanib 300mg daily or placebo. The study met its primary objective with a PFS prolongation of approximately 11 months with vandetanib versus placebo (hazard ratio [HR], 0.46; 95% CI, 0.31 to 0.69; P < .001). Statistically significant advantages for vandetanib were also seen for objective response rate (P < .001), disease control rate (P = .001), and biochemical response (P < .001). Biochemical response can be associated with significant symptom benefit in patients with calcitonin-related diarrhoea.

Vandetanib therapy was not been reviewed by the SMC due to lack of submission by the parent company. It is therefore not routinely funded for medullary thyroid cancer patients in Scotland.

Vandetanib 300mg daily until disease progression. Dose modification on the basis of toxicity.

Carbozantinib

In a randomised phase III trial in 333 patients with progressive metastatic MTC Elisei et al 2013), carbozantinib was associated with a significant increase in PFS (4.0 versus 11.2 months). Improvements in PFS were seen regardless of prior therapy and RET mutation status. Treatment was associated with significant gastrointestinal toxicity in the majority of patients.

Carbozantinib was assessed by the SMC including a PACES meeting and the submission was rejected. Funding is therefore only be available in exceptional cases via the IPTR process.

Carbozantinib 140mg daily until disease progression. Dose modification on the basis of toxicity.

Other TKIs

Phase II studies suggest that other TKIs may also be associated with disease stabilization in medullary thyroid cancer. These include sorafenib, sunitinib, motesanib, axitinib and pazopanib.

Other SACT

Due to the relative rarity of this disease, there are no other randomized trials to guide therapy. Patients have been managed with somatostatin analogues for diarrhoea, which may, by analogy with other NETs, also alter the natural history of the disease.

There is no good data about efficacy of cytotoxic chemotherapy in this disease. Small case series have reported some responses with agents used in other NETs such as dacarbazine, doxorubicin and cisplatin.

**Follow-Up**

Most patients from Lothian are followed-up by the endocrine service. Patients with genetic syndromes will usually be followed up by their endocrinologist as they will require ongoing surveillance for other issues. Sporadic patients are followed up by Strachan/Gibb. A calcium/pentagastrin test 3 months post therapy is useful in establishing the success of surgical resection. Thereafter, basal calcitonin/CEA levels are typically used for surveillance. Patients are typically reviewed 3, 6 and 12 months post resection and thereafter annually if no evidence of residual disease. A baseline neck USS should be performed in all patients post surgery, especially if there is detectable calcitonin. Cross-sectional imaging may also be required if there is detectable calcitonin, though recurrence an metastatic disease can be hard to detect when calcitonin levels are only borderline. CT/MRI may be used; FDG-PET is not that useful and DOTA-octreotate PET is probably a better option. Nuclear medicine imaging scans may also be used to detect recurrent or metastatic disease, e.g. octreotide, MIBG and DMSA (V).

**5. ANAPLASTIC THYROID CANCER**

**Pathology**

Undifferentiated (anaplastic) carcinomas are highly malignant cancers of the thyroid. They may be subclassified as small cell or large cell carcinomas. Both grow rapidly and extend to structures beyond the thyroid. Both small cell and large cell carcinomas present as hard, ill-defined masses, often with extension into the structures surrounding the thyroid. Small cell anaplastic thyroid carcinoma must be carefully distinguished from lymphoma. This tumour usually occurs in an older age group and is characterized by extensive local invasion and rapid progression. Five-year survival with this tumor is poor. Death is usually from uncontrolled local cancer in the neck, usually within months of diagnosis.

Poorly differentiated thyroid carcinoma represents a disease on the spectrum between differentiated thyroid cancer and anaplastic cancer. Little evidence is available upon which to base decisions and cases must be considered on an individual basis. Ideal therapy will include surgery to remove all macroscopic disease and adjuvant therapy with radioactive iodine and/or external bead radiation depending on the clinico-pathological findings. However, an individualised decision should be made depending on patient and tumour factors including the trajectory of local and distant disease.

**Staging**

All anaplastic carcinomas are considered pT4 tumours

* pT4a  Anaplastic carcinoma limited to thyroid
* pT4b  Anaplastic carcinoma extends beyond thyroid capsule

**Investigations**

Imaging:

* CT Scan neck/ thorax and abdo

Blood tests:

* FBC, U&E, LFTs, calcium, thyroid function, LDH

Cytology

* FNAC thyroid or core biopsy of metastatic lesion

**Surgery**

Surgery with adjuvant therapy should be considered in select cases deemed suitable. These will include patients who are deemed fit, and with limited loco-regional disease. Tracheostomy may sometimes be indicated in cases where the diagnosis is unclear and time is required to reach a diagnosis and afford the patient time to arrange their affairs. In most settings, tracheostomy should be avoided.

**TSH Suppression and Radio-Iodine**

There is no role for TSH suppression or RAI in the management of anaplastic thyroid cancer.

**External-Beam Radiotherapy**

In this setting, EBRT is mainly used for palliation and for slowing progression of disease to provide optimal quality of life for as long as possible. It does not provide overall survival or progression free survival benefit.

Treatment is highly individualized. In the setting where no metastasis are detected, disease is localized and resectable without significant morbidity and in a fit and well patient, the argument can be made for radical resection followed by adjuvant radiotherapy. But adjuvant radiotherapy alone carries high risk of local recurrence. Also, no clear survival benefit seen with this approach. There have been case reports of adding chemotherapy (mainly Doxorubicin). But these treatments are very toxic with varied results seen in small case series.

Palliative doses : as for Differentiated thyroid cancer EBRT

**Systemic Anti-Cancer Therapy (SACT):**

There is insufficient randomized evidence to guide SACT in anaplastic thyroid tumours. Shortlived responses have been reported with cisplatin, carboplatin, taxanes and doxorubicin, but no standard regimen has emerged from trials. If a decision is made to use systemic therapy, it would be appropriate to use similar protocols to those used in other high grade tumours.

**Follow-Up**

The risk of recurrence or progression of these tumours is high so, if patients are considered candidates for further therapies they should have close clinical and radiological follow up. This is usually in the thyroid nodule/cancer clinic at the RIE. Patients should be offered the option of being enrolled in the International Anaplastic Thyroid Cancer Tissue Bank and Database (iNATT).

**AUTHORS** Dr. Lucy Wall (LW)

Professor Mark Strachan (MS)

Dr Devraj Srinivasan (DS)

Mr Iain Nixon (IN)

Professor Nick Reed