THYROID GOITRE

Enlargement of thyroid gland:
1. Simple (diffuse or multinodular)
2. Toxic (diffuse ie Grave's/early viral thyroiditis or multinodular)
3. Neoplastic (benign or malignant)
4. Inflammatory ie thyroiditis (autoimmune/Granulomatous ie DeQuervain's/Fibrosing ie Riedel's/Infective ie viral etc/Amyloid)

Indications for surgery: cosmesis/compressive/toxic/rapid growth/malignant/recurrent cyst/patient wishes

SIMPLE GOITRE (DIFFUSE NON-TOXIC GOITRE)

Arises usually due to TSH stimulation:-
1. Iodine deficiency (low intake in area of low soil iodine levels; Himalayas, Pyrenees, Andes, Sydney)
2. Dyshormogenesis: enzyme deficiencies affecting thyroid-hormone synthesis; often family history
3.Goitrogens: thiocyanate (cassava and brassica family vegetables)
4. Hypothyroidism
5. Drugs (lithium, carbimazole)
6. Pituitary adenoma
7. Radiotherapy

NON-TOXIC (SIMPLE) GOITRE

1. **DIFFUSE** (hyperplastic) GOITRE: early stimulus for thyroid hyperplasia → follicular cells fill with colloid; **hypo/euthyroid**
Treatment: in early stages, thyroxine replacement will regress goitre
2. **MULTINODULAR GOITRE**: **euthyroid** with palpable colloid nodules (gland is firm but not hard)
Treatment: **Total thyroidectomy(TTx)** for cosmesis/compressive symptoms/rapid growth$_{(?anaplastic)}$/suspicious FNA from nodule
*STx = 50% recurrence
*Pain/sudden growth of a nodule is suspicious for carcinoma

TOXIC GOITRE

1. MULTINODULAR GOITRE (TMNG)
Disorganised response to hyperstimulation → juxtaposed areas of **hyper/hypoplasia**
(a)Mildly **hyperthyroid** from hyperplastic nodules + atrophy of rest of gland; (b) hyperplastic nodules atrophy→ **hypothyroidism**
Treatment: Total **thyroidectomy** always indicated (don't respond well to RAI/ATDs)
2. DIFFUSE TOXIC GOITRE = Grave's *or early viral thyroiditis*
Treatment: >45: RAI || <45: RAI/ATDs if small, surgery if large

SOLITARY TOXIC NODULE

Follicular adenoma autonomously secretes **excess hormone**→mildly **hyperthyroid** (50%: isolated T3-toxicosis)
Atrophy of rest of gland (50% actually have toxic MNG with palpable dominant nodule!)
Treatment: **131^{I}** taken up by nodule but not by atrophied gland

THYROID CYSTS

1. Usually benign; 50%= colloid degeneration
2. 10% of mixed solid/cystic thyroid lesions are malignant
3. Rest are involution of follicular adenomas

Surgery if –malignant or suspicious cytology
-large cyst >4cm
-history of head and neck irradiation
-rapid refill after aspiration
-heavily blood-stained aspirate

History	Investigations	Pre-op
Compressive/pain	TFTs	Must be Euthyroid (carbimazole)
Thyroid function	TRAbs	Lugol's iodine/potassium iodide to reduce vascularity
PMHx: H&N radiation	USS + FNA of nodules	Laryngoscopy only if vocal changes
FHx: thyroid cancer/disease fam endo disease	CT if retrosternal for pre-op planning Ca^{2+}	HRA: may need fibre-optic intubation
Medx: goitrogens etc		

THYROID CANCERS

Incidence rising due to increased diagnosis of PTC (especially microcarcinomas)/women 4x more likely to be diagnosed with thyroid cancer

PAPILLARY (80%)

Children/young adults; iodine-rich areas; 90% of radiation-induced thyroid Ca (related to level of exposure)

Pathology:

-Arises from **thyroid follicular cells**//**grow and spread slowly**(lung/bone) (cervical nodes)/ **90% cervical lymph node** mets at time of diagnosis
-Blood-borne spread unusual cf FTC, only if extrathyroidal spread; nodal spread more common than FTC
-Unique nuclear features (cf FTC) (clear or ground-glass "Orphan Annie" nuclei, irregular papillary contours) so **can diagnose on cytology**

Histopathological variants:

Microcarcinomas (PTMC): nodal involvement in 30% at presentation
Follicular variant: follicular architecture but nuclear features of PTC → easily confused with follicular adenoma/carcinoma
Aggressive variants: tall cell variant often found in older patients with more aggressive clinical behaviour eg extrathyroidal extension

Molecular biology: Genetic lesions that activate MAPK (mitogen-activated protein kinase) pathway
1. RET/PTC chromosomal rearrangement :RET proto-oncogene encodes receptor-type tyrosine kinase
2. BRAF valine-glutamate substitution at reside 600 ($BRAF^{V600E}$) in 70% PTCs
Other: rearrangements in TRK and AKAP9/BRAF oncogenes or point mutations in RAS oncogene

FOLLICULAR (15%)

Middle-age (30-50)/unrelated to radiation exposure/takes up 131^{I}

Pathology:

-Arises from **follicular cells**; lacks diagnostic nuclear features → only possible to **diagnose on histological examination**
-**Blood: brain/bone** (commoner + **earlier** than PTC)(cervical node spread rare)
-Difficult to distinguish **carcinoma vs. adenoma** (both hypercelullar aspirates w/ microfollicular pattern + scant colloid)

Histopathological Variants:

1. **Conventional**: lymph node mets in <5% (unlike HCC ie 30%)
2. **Hurthle Cell Carcinoma** 75% oncocytic cells in tumour; node mets in 30%

Molecular biology:

1.RAS oncogene mutations (adenoma-carcinoma sequence →FTC)
2.PAX8/PPAR-g rearrangement
3. PI3K/Akt (phosphoinositide 3-kinase)/(protein kinase B)

WORKUP

History: symptoms esp compressive,invasive, pain/PMHx: H&N radiation/FHx: thyroid disease/cancer, familial endocrine disease/SHx: radiation/I_2 in diet
Examination: neck for mass/nodes; chest+neuro; laryngoscopy if voice change
Bloods: TFTs/Ca^{2+}/anti-Tg Abs
Imaging: USS neck for nodes, CXR for chest spread

RISK FACTORS FOR DTCs

1.Ionising radiation

-most well-established environmental risk factor; most pronounced in children; latency period up to 30 years
-Induces cellular DNA damage (commonly RET-PTC chromosomal rearrangements)
history of radiation + nodule = malignancy risk = 3-40% → TTx recommended

2.Hereditary non-medullary thyroid cancer (HNMTC)

-more aggressive than sporadic form
-no susceptibility gene identified so suspicion depends on family history
-risk of cancer 5-10x higher if first degree relative with thyroid cancer
-suspect if young, male preponderance in family, large, multicentric tumour, aggressive tumour biology

STAGING OF DIFFERENTIATED THYROID CANCERS

AJCC/UCC 6th edition unique: includes age and nodal status
Start with US-FNAC for diagnosis then MRI/CT for invasion/nodes ie planning surgery

MANAGEMENT OF DIFFERENTIATED THYROID CANCERS

(A)Resection
PTC confirmed on FNA (Thy4/5) → TTx
(i)TTx if >4cm, FHx of PTC, radiation exposure, extrathyroidal spread, bilateral lesions, cervical lymph node mets, distant mets
(ii)Unifocal, intrathyroidal micro PTC w/o high risk features of spread → HTx

FTC
(i)Atypia/FLUS/FN /SFN(Thy3a/f) → diag. HtX → completion Tx if capsular or angio-invasion/Hurthle cell
(ii)TTx upfront if >4cm, marked atypia on FNA, FHx thy ca, radiation exposure, wish to avoid completion TTx, bilateral nodules

(B)Lymph node dissection:
Central compartment (level VI): prelarygneal (Delphian), pretracheal, paratracheal nodes (90% PTCs at diagnosis so do in all)
Lateral compartment (levels II-V): intraoperative frozen section → LLND only if mets proven

(C1)Adjuvant therapy: RADIOACTIVE REMNANT ABLATION (RRA)
WDTC take up I_2 so can use 131^I as radiotherapy (driven by TSH) to obliterate residual tumour cells (if well-differentiated only)
Indications: high-risk features/primary tumour >4cm/gross extrathyroidal extension/lymph node mets/distant mets/recurrence/unresectable
Not for unifocal cancer <1cm without risk features //multifocals if all <1cm without high risk-features
Stimulated Tg and US neck 9-12mths post-RRA

(C2)EXTERNAL BEAM RADIOTHERAPY
(i)Gross invasion w/ macroscopic residual disease
(ii)Residual tumour falls to concentrate radio-iodine

(D)Thyroxine replacement and TSH Suppression
*TSH suppression therapy with thyroxine recommended for all DTCs
Discharge on T3 for 4 weeks then stop for 2wks for TSH to rise
Radioiodine scan at 6 weeks (i)residual thyroid, continue T3 and rescan 3mths (ii)negative, switch to T4 to suppress TSH <0.1mU/L for 5 yrs
If scan positive , RAI until clear

*Patients with mets need repeated RAI; give T3 as shorter acting (can stop, TSH recovers for RAI therapy, no need for long periods hormone-free)

FOLLOW-UP
Discharge on T3 for 4 weeks then stop for 2wks for TSH to rise
Radioiodine scan at 6 weeks (i)residual thyroid, continue T3 and rescan 3mths (ii)negative, switch to T4 to suppress TSH <0.1mU/L for 5 yrs
If scan positive , RAI until clear

3 things in follow-up
Calcium: (i)check Ca2+/PTH post-op (ii)monitor Ca^{2+} 12 monthly by serum, urinary excretion + creatinine, US kidneys
TSH: (i)post-op T3 4wks, stop 2 wks, RI scan 6 wks → switch to T4 to suppress TSH to <0.1mU/L in all TTX w> RRA (for 5yrs if not risk-stratified);
(ii)If residual thyroid remnant on 6 wk scan → continue T3 and rescan in 3mths
(iii)If TSH rises → RRA dose KABOOM
TgAB/Tg: do annually (detect recurrence/mets on TSH-suppressive T4); repeat in 6mths if detected (stimulate Tg with rTSH)

Thyroglobulin (detect recurrence or mets but must suppress TSH)/whole body NM scan/neck US
Disease-free = no clinical evidence of disease/absence on imaging/undetectable Tg in TSH suppression/stimulation in absence of Tg antibodies
Surveillance: dependence based on ATA risk category: Tg, NM scan, neck US
Discharge: 5yrs disease free + no longer require TSH suppression

THYROID NODULE GUIDELINES (BTA 2014)

Definition: discrete lesion within thyroid gland distinct from surrounding parenchyma

Clinical features

History: thyroid function, pain PMHx: radiation exposure FHx: thyroid disease/FTC/polyposis syndromes/MEN2
Examination: neck mass, cervical nodes, thyroid status

Investigations (>1cm)

Bloods: TSH normal/high needs no scan; TSH suppressed needs ^{131}I scan
USS nodule + nodes : size (1cm threshold) + risk features for malignancy **hypoechoic, loss of halo, irreg margins, LNs, micro Ca^{2+}**
FNA cytology: >1cm high suspicion/>1.5cm low suspicion/>2cm v low suspicion → Thy 1-5

Surveillance (<1cm)

v low suspicion= no follow-up; low-intermediate= repeat 12-24mths; high suspicion= repeat 12mths

Management of cytology

Thy1 (non-diagnostic): (a)REPEAT FNA (or US if only cyst)
(b)if repeatedly non-diagnostic → US low suspicion = observe or surgery (grows 20%/malig)
→ US high suspicion= surgery

Thy2 (benign): discharge (thyroiditis/colloid reassuring)
Thy3a (atypia/FLUS): DIAGNOSTIC HEMITHYROIDECTOMY (can do repeat FNA) (ii)TTx upfront if high risk
Thy3f (follicular neoplasm/suspicious for FN): (i)HEMITHYROIDECTOMY (ii)TTx upfront if high risk
Thy4 (suspicious for malignancy): TOTAL THYROIDECTOMY (75% cancer risk)
Thy5 (malignancy): TOTAL THYROIDECTOMY

"High risk"= >4cm, marked atypia, radiation history, fam hx thyroid cancer, bilateral nodules
Thy3: only suspicious for FN as cannot able to ascertain capsular invasion ie carcinoma features

AFTER HEMITHYROIDECTOMY →COMPLETION THYROIDECTOMY?

Histology examined
(i)No capsular invasion/angioinvasion/non-Hurthle → no further treatment
(ii)capsular invasion/angioinvasion/Hurthle cell → completion thyroidectomy **Hurthles don't take RAI well**

MEDULLARY (10%)

Pathology:
Arises from **parafollicular C cells** (neuroendocrine-derived calcitonin-producing cells)
Spread: lymph nodes in 60% (non-curative) ||blood: liver/lung/bone

Genetics:
(i)**Hereditary** (25%) are bilateral and multicentric and (ii)Sporadic (75%)
Associations with MEN2 (RET) and familial non-MEN syndromes (Men2A: Phaeo, pHPT:MGD, MTC) (Men2B:MTC +phaeo+ neuromas)
Constitutive phosphorylation of tyrosine kinase receptor → unregulated cellular proliferation → c-cell hyperplasia

Clinical features:
1. Hereditary: present **earlier**; often discovered by genetic testing/MEN testing
2. Sporadic: present **later**; **neck lump**/**metastatic** sx (bone, liver, lung)/**calcitonin** sx in 10% (carcinoid: flush, diarrhoea, bone pain)

BLOODS: calcitonin/CEA/investigations for MEN2 (phaeo and hyperPTH) before operating!
IMAGING (primary and mets): (i)Diagnosis= USS-FNAC (ii)Staging= CTNCAP + US neck$_{(nodes)}$
GENETICS: Identify RET mutation (all FDRs of individual with MTC → genetic testing for RET mutation)

MANAGEMENT **Depends on (1) extent at presentation (2) histological examination of resected thyroid**
Resection: TTx + CLND (level VI) + thymectomy
Nodes: lateral nodal disease →ipsilateral LLND (level II-IV)
Parathyroids: (i)autografts in neck for MEN2B, RET-negative and FMTC (ii)Heterotopic site in MEN2A

Prophylactic thyroidectomy in RET-positive families (depends on level of risk from RET mutation; 4-7yrs in kids)
Must exclude phaeo before surgery and treat hyperPTH

F**ollow-up:**
4mthly for 2 yrs/6mthly for 3yrs/annually therafter months: **Calcitonin/CEA** + **clinical examination**
Raised biomarkers = (i)recurrence (ii)mets → imaging

ANAPLASTIC
Epid: **elderly women** (typically); <6 month prognosis
Path: arise from **follicular** cells
Spread: aggressive to **nodes/blood**
Feat: hard, irregular, infliltrating
Management: **chemoradiotherapy** for **palliative** disease control (surgery rarely performed unless very localised → curative)
Isthmusectomy > tracheostomy in compression

LYMPHOMA (5%)
Epid: elderly
Features: rapidly enlarging, painless neck mass → compressive symptoms
Path: (a)Autoimmune thyroiditis (? is how lymphoid aggregates develop in thyroid parenchyma)
(bDIffuse lymphoma disease
FNA: mixed results; lymphocytes arouse suspicion *difficult to distinguish from Hashimoto's disease*
Core biopsy essential to determine curative intent
Treatment: chemoradiation
Surgery: palliative debulking of compressive neck disease
Prognosis: -depends on subtype of lymphoma, grade and stage of disease but overall 60% 5 year survival
-good if cervical node-free

Other: SCC rare and aggressive with poor prognosis//Metastatic carcinoma to thyroid

AIRWAY COMPROMISE IN PATIENT WITH GOITRE

Causes:
Large/retrosternal goitre
Haemorrhage into nodule/goitre
Airway invasion by cancer

Symptoms:

Signs:
I= (i)Compressive: resp distress; stridor; hoarseness, SVC obstruction (ii)Thyroid: thyroid function/Graves' signs
Pa= mass, nodes, tracheal deviation
Pe= retrosternal extension
Ausc= bruit

Investigations:
Bloods: TFTs/TRAbs + routines + Ca^{2+}
Imaging: CT neck + chest
Endoscopy: bronchoscopy (?tracheal invasion) + laryngoscopy (RLNs)

Management:
1. ABCDE with early anaesthetic involvement -→GA (awake fibreoptic)
2. TTx + Level VI node dissection ?lateral frozen section
Tracheal stent/resection (shaving/window resection/segmental and anastomosis)
RLN repair

Post-operative concerns:
Airway compromise (i)bleeding/haematoma (ii)RLN palsy (iii)tracheomalacia
Hypocalcaemia
MDT to discuss adjuvant therapy

POST-THYROIDECTOMY COMPLICATIONS

Airway obstruction (i)haematoma (ii)bilateral RLN palsy – adducted (iii)tracheomalacia
(history will determine likelihood of each; esp note if voice was normal post-op to rule out RLN complication)

Assessment
As for "A" ie look (agitated vs drowsy, resp distress), swelling) listen (dysphonia, stridor) feel (swelling)

Management
ABCDE + Anaesthetist
Open clips → theatre for definitive opening of skin/platysma strap + haemostasis –> close +/- drain

THYROTOXIC CRISIS

Uncontrolled thyrotoxicosis + precipitating event → massive release of T4
Clinical features: hyperthermia, tachycardia, diarrhoea, jaundice, derilium/com
Management: (i)supportive: fluids, steroids, B-blocker, sedation, cooling (ii)reduce thyroid secretion (PTU/carb + Lugol's iodine)