Endocrine Organs

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Contents

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6.1 Anatomy and Physiology of the Thyroid Gland

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Key Points

Thyroid gland (Thyroid):
- Cervical endocrine gland (normal weight 15–20 g)
- Blood supply via 4 anastomosing arteries
- Closely related to: recurrent laryngeal nerve, parathyroid glands
- Regulatory circuit: TRH (thyrotropin-releasing hormone)—TSH (thyroid-stimulating hormone)—T3 (triiodothyronine), T4 (thyroxine)—TRH/TSH

6.1.1 Embryology and Anatomy

- Large cervical endocrine gland

Macroscopy

- Two lateral lobes connected by isthmus
- Pyramidal lobe: Cranial process from isthmus; inconstant (50% of cases)
- Total adult weight = 15–20 g

Microscopy

- Thyroid follicle = structural and functional unit
- follicular epithelium = source of thyroid hormones
- C cells: Release of calcitonin (= regulation of the blood calcium level; ► Sect. 6.1.2)

Localization

- Isthmus at the level of the 2nd–4th tracheal cartilage
- Lateral lobes adjacent to the cricoid and thyroid cartilage

Blood Supply

- 4 arteries + inconstant vessels
  - Superior thyroid artery: Paired, from external carotid artery
  - Inferior thyroid artery: Paired, from thyrocervical trunk (subclavian artery)
  - A. thyreoidea ima: Unpaired from aorta or truncus brachiocephalicus; inconsistent
- Venous drainage: Variable; drainage into internal jugular vein + brachiocephalic vein

Surgical-Relevant Anatomical Relationships
- Superior laryngeal nerve: from the inferior ganglion of the vagus nerve; divides at the level of the hyoid bone into the external branch (pharyngeal musculature) and internal branche (plica vocalis)
- Recurren laryngeal nerve: branch of the vagus nerve; course between trachea and esophagus, directly behind the thyroid gland; division into anterior branche (for Mm. vocalis) and posterior branche
- Parathyroid glands: dorsal to the thyroid gland; variable location (► Sect. 6.4)
- Lymph node groups (◘ Table 6.1 and ◘ Fig. 6.1)

Development

- During development, displacement of thyroid caudally with formation of thyroglossal duct.
- regression of the thyroglossal duct in the course (possible peristence = pyramidal lobe)

6.1.2 Physiology

Thyroid Hormones (Thyroxine, T4, and Triiodothyronine, T3)

- Production and release by follicular epithelial cells
- Active form = T3
- Function (on almost all body cells):
  - Metabolism increase
  - Important role in growth + development of the nervous system

Table 6.1 Classifications of locoregional thyroid lymph nodes (LN)

Compartment classification (Dralle et al. 1994)	US classification (Robbins et al. 2008)	UICC classification (Wittekind et al. 2003)	Japanese classification (Qubain et al. 2002)
Compartment 1 (1a cervicocentral right, 1b cervicocentral left)	Without side assignment: Level 1 (submental, submandibular), Level 6 (central), Level 7 (central caudal)	Without side assignment: LN groups 1 and 2 (submental, submandibular), and 8 (central)	Without side assignment: Regional LN groups 1–4
Compartment 2 (cervicolateral right) Compartment 3 (cervicolateral left)	Without side assignment: Level 2A, 2B (cranial jugular), Level 4 (caudal jugular), Level 5A, 5B (lateral jugular)	Without side assignment: LK groups 2, 3 (cranial jugular), 4 (middle jugular), 5 (caudal jugular), 6 (dorsal lateral), and 7 (lateral supraclavicular).	Without side assignment: Regional LN groups 5–7
Compartment 4 (4a upper infrabrachiocephalic mediastinum right, 4b left)	–	–	–

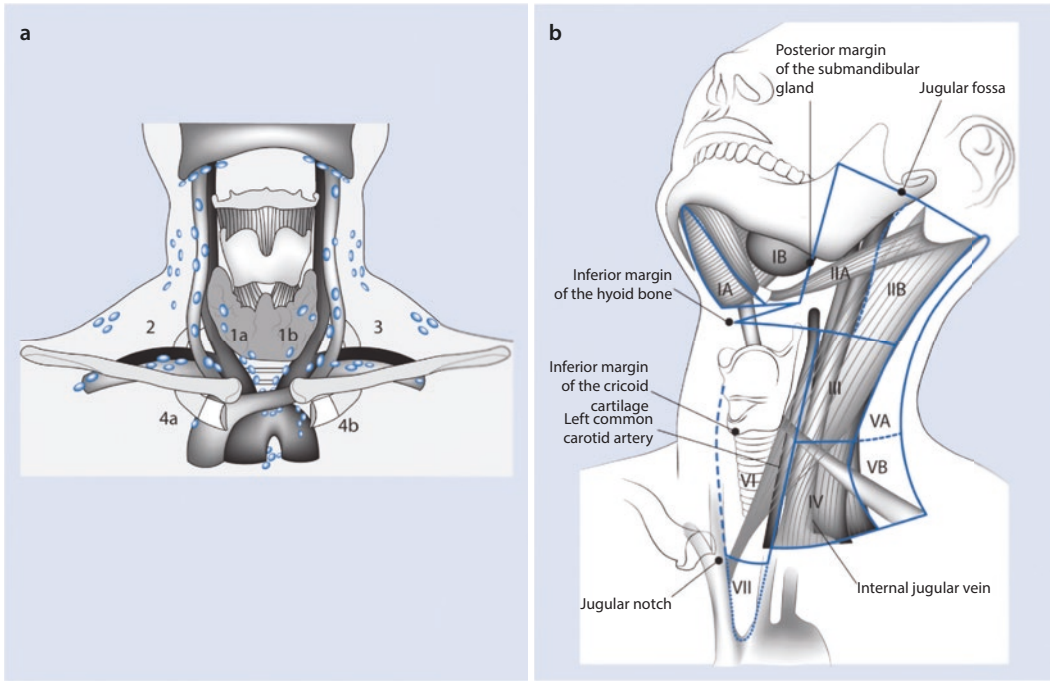

Fig. 6.1 **a**–**d** Classifications of locoregional thyroid lymph nodes. Comparison between **a** compartment classification according to Dralle, **b** US classification according to Robbins, **c** UICC/TNM classification and **d** Japanese classification

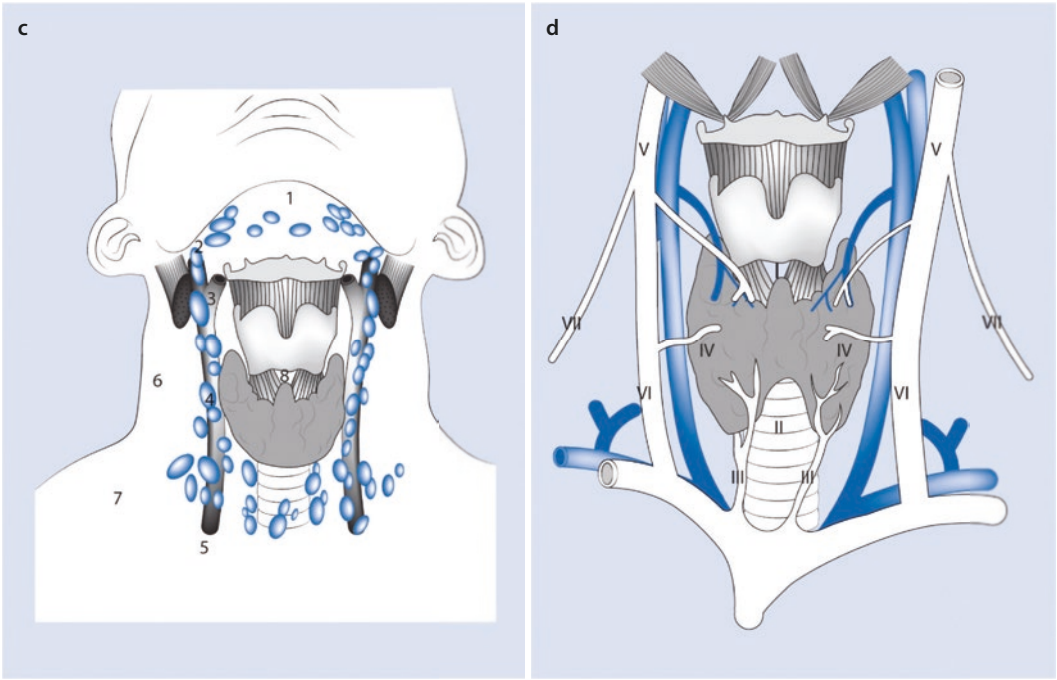

Fig. 6.1 (continued)

Control Loop (Negative Feedback)

- Goal = accurate control of T3, T4
- Control of thyroid by hypothalamus + hypophysis (pituitary gland): mediators (TRF and TSH)

Calcitonin

- Produced and released by C cells
- Physiological antagonist of parathyroid hormone (PTH; ► Sect. 6.4 Parathyroid)
- Calcium regulation

6.2 Diseases of the Thyroid Gland

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6.2.1 Epidemiology

Goiter and Multinodular Goiter

- Prevalence: 33.1% of the working population
- Incidence of thyroid nodules:
  - 23.2% of patients with goiter (approx. 20 million people in Germany)
  - Age-dependent

Hyperthyroidism (Thyroid Autonomy)

- Prevalence: subclinical hyperthyroidism = 1.8%, manifest hyperthyroidism = 0.4%.
- Etiology:
  - Graves' disease: leading cause in regions without iodine deficiency
  - toxic nodular goiter/toxic adenoma: In regions with iodine deficiency
  - Iodine-induced hyperthyroidism (acute high iodine intake): Increasingly rare
  - Amiodarone (high iodine) induced hyperthyroidism: 30–40% of amiodarone treated patients

Autoimmune Diseases

- Prevalence: No precise data
- possibly associated with autoimmune diseases of other organs

- Autoimmune thyroiditis: women:men = 10:1
- Graves' disease:
  - 5–20 cases/100,000 inhabitants per year
  - Women:Men = 6–8:1

Thyroid Cancer

- Most common endocrine tumor
- Prevalence: men = 4/100,000 per year; women = 8.7/100,000 per year
- Women:Men = 2:1
- Germany: 5000 new cases/year
- Mortality declining (by 40% in recent years)

6.2.2 General Methods of Investigation

Key Points

- Standard examinations: clinical examination + laboratory thyroid function tests (TSH) + ultrasound (sonography)
- FNA (fine needle aspiration cytology): To exclude malignancy
- Scintgraphy, CT, MRT: Only for special questions

Clinical Examination

- Medical history: signs of hyper- or hypothyroidism (◘ Table 6.2)
- Inspection, palpation (position, size, consistency, swallowing displacement of the thyroid), auscultation (blood flow)
- Exclusion: globus sensation, voice change, stridor, dysphagia.
- Search for cervical lymph nodes

Laboratory Thyroid Function Tests

Basic Diagnosis (For Each Patient)

- TSH: Examination of thyroid function (see below: Overview of normal levels)
  - Euthyroid
  - Hyperthyroidism (subclinical/manifest)
  - Hypothyroidism (subclinical/manifest)

Specific Diagnosis (For Further Clarification)

- Free thyroid hormones (fT3, fT4)
- TRH test
- Thyroglobulin (Tg)
- Antibodies (in autoimmune thyroiditis): TRAb (TSH receptor autoantibodies), TgAb (thyroglobulin antibodies), TPO-MAb (thyroid peroxidase antibodies, microsomal antibodies)
- Calcitonin

Normal Levels of Thyroid Metabolism

- Serum TSH = 0.3–6 mU/L
- Serum fT3 = 3–9 pmol/L (2–6 ng/L)
- Serum fT4 = 9–29 pmol/L (7–23 ng/L)
- Serum calcitonin <2.8 pmol/L (<10 ng/dL)

Imaging Studies

Ultrasound

- Orienting study
- High resolution linear transducers (7.5–18 MHz)
- Display of nodules from 0.5–1 mm
- Special Techniques:
  - Color-coded duplex sonography: vascularization of the thyroid nodules
  - Elastography: degree of hardness of the thyroid/a nodule
  - Contrast-enhanced sonography (under evaluation)
  - "Acoustic Radiation Force Impulse-Imaging" (under evaluation)

Imaging Studies

- Ultrasound = key examination
- Cross-sectional imaging (CT/MRT) = environmental diagnosis + therapy planning
- CT, MRI, nuclear medicine procedures: Only for further clarification

Computer Tomography (CT)

- Assessment of the thyroid environment (trachea, esophagus, vessels)
- Good retrosternal/intrathoracic assessment

Table 6.2 Comparison of symptoms of hyperthyroidism and hypothyroidism

Symptoms	Hyperthyroidism	Hypothyroidism
General	Rapid fatigue	Fatigue
	Anorexia	
	Cycle Irregularity	
	Weight loss	Weight gain
	Weakness	Muscle weakness
	Heat intolerance	Hypothermia
	Increase appetite	Hypercholesterolemia
Cardiovascular	Tachycardia	Bradycardia
		Hypotension
Neurological	Nervousness/restlessness	
	Insomnia	
	Hyperreflexia	Hyporeflexia
	Tremor	
	Apathy	Adynamics
	Depression	Depression
	Confusion	
		Deep hoarse voice
Gastrointestinal	Diarrhea	
	Polydipsia	
	Constipation	Constipation
Pulmonology	Dyspnea	
Musculoskeletal	Muscular atrophy	
	Muscle cramps	
Dermatological	Sweating	Hair loss
		Facial Edema
		Pale yellowish skin coloration

- Detection of metastases (lymph nodes from 1 cm, lung +++)

Contrast Medium Containing Iodine

- In case of manifest autonomy/hyperthyroidism only approved in case of vital indication
- Radioiodine therapy through this administration for several months impossible

Magnetic Resonance Imaging (MRI)

- Mostly for surgery planning
- Good sensitivity with regard to compression/infiltration of adjacent structures
- Detection of abnormal lymph nodes
- Postoperative tumor follow-up: differentiation of scar vs. tumor recurrence

Nuclear Medicine Diagnosis

- Use of radioactively labelled substances (involved in the metabolism of Thyroid) (^{99m}Tc-pertechnetate scintigraphy)

Table 6.3 Possible causes of cold and hot nodules

Cold nodules	Hot nodules
Cancer	Compensated toxic thyroid adenoma
Cyst	Decompensated toxic thyroid adenoma
Hemorrhage	
Nonstoring adenoma	
Regressive change	
Focal inflammations	

  - Exploration of the function of the thyroid/nodules (semiquantitative)
- Relatively poor image resolution
- Differentiation between cold and hot nodules (possible causes: Table 6.3)
- Specific investigations: for specific questions
  - ^{131}I-scintigraphy (whole body scintigraphy)
  - ^{18}F-fluorodeoxyglucose positron emission tomography (^{18} F-FDG-PET) (whole-body tomography, possibly CT-coupled)
  - ^{124}I-Positron Emission Tomography
  - "Medullary Thyroid Carcinoma" section: ^{111} indium-pentetreotide; ^{99} Tc-Tyr3-octreotide scintigraphy; ^{68} Ga-DOTATOC; ^{68}Ga-DOTATATE-PET; ^{18}F-DOPA-PET; ^{18}F-FDG-PET.

- Well-differentiated iodine-storing metastases = usually only low FDG enrichment
- De-differentiated metastases no longer storing iodine = intensive FDG enrichment

Fine Needle Aspiration Cytology (FNA)

- Objective = selection of lesions suspicious of malignancy to avoid unnecessary surgery
- Accuracy: Depending on the experience of the examiner/pathologist
- Inexpensive, easy to perform, low complications

Principle

- Contraindication = haemorrhagic diathesis
- Local anesthesia
- Puncture with disposable cannula (25–23 G)
- Ultrasonic control, monitoring
- Transfer of the punctate onto slides, air drying, staining

Interpretation of the Cytological Findings

- Quality control
- Interpretation: current consensus between Italian/UK Royal College of Pathologists/Bethesda classifications (Table 6.4)
- Diagnostic reliability (see malignancy rate Table 6.4)

Diagnostic Strategy

- Geographic variation in the prevalence of thyroid nodules = different strategies
  - USA: FNA = primary diagnostic procedure (with clinical examination and sonography)
  - Germany: FNA = additional method as part of a differentiated approach
- Clinical history-oriented procedure (► Sect. 6.2.6 Workup of a solitary thyroid nodule)

6.2.3 Basics of Surgical Therapy, Complications and Postoperative Care

Preoperative Measures

- Control/achievement of a euthyroid metabolic state
- Laboratory chemistry parameters: Blood count, electrolytes, coagulation, eventually blood type and Packed red blood cells (PRBCs) if large retrosternal goitre
- Calcitonin: For the early detection of medullary thyroid cancer
- Cervical ultrasound: complementary to the clinical examination
- FNA: For suspicious nodules >1.0 cm
- Preoperative laryngoscopy: examination of vocal cord function

Table 6.4 Interpretation of fine needle aspiration cytology (*FNA*; comparison (consensus) Italian/UK Royal College of Pathologists/Bethesda classifications)

Italian system	Bethesda System	UK Royal College of Pathologists System	Cytology category	Malignancy risk	Therapy recommendation
TIR 1	I	Thy 1	Non-diagnostic or insufficient test material[a]	1–4%	Repeat FNA under sonographic control[c]
TIR 1C	Ic	Thy 1c	Non-diagnostic with cystic fluid	dependent on clinical presentation	Repeat FNA under sonographic control[c]
TIR 2	II	Thy 2/Thy 2c	Benign	0–3%	Annual control: clinical examination+TSH + sonography Renewed FNA if size progression
TIR 3A	III	Thy 3a	Atypia of undetermined significance or follicular lesion of undetermined significance[b] (A/FLUS)	5–15%	Repeat FNA (3–6 months) Surgery for persistent A/FLUS, with frozen section examination
TIR 3B	IV	Thy 3f	Follicular or Hurtle cell neoplasia[b]	15–30%	Surgery due to high risk of malignancy Frozen section no further benefit
TIR 4	V	Thy 4	Suspicious for Malignancy[b]	60–75%	Surgery due to high risk of malignancy with frozen section
TIR 5	VI	Thy 5	Malignant	97–99%	Surgery with definitive thyroidectomy Preoperative sonography to exclude lymph node metastases (neck dissection)

[a] Non-diagnostic or inadequate if quality criteria not met: At least 6 groups, each group with at least 10 follicular cells, at least 2 aspirates for each nodule examined
[b] Categories III, IV and V are collectively referred to as "intermediate" and require repeat FNA (III) or surgical exploration (IV and V)
[c] After renewed non-diagnostic FNA, surgery should be performed (risk of malignancy = 8%)

- Imaging procedures for mechanical impairments (CT, MRI)
- chest X-ray
- Patient education
- Marking of the skin incision directly preoperatively

Basics of Surgical Therapy

Key Points

- Gold standard = open hemithyroidectomy/thyroidectomy (■ Table 6.5)
- Caution:
  - Protection of the parathyroid glands
  - Visualisation of the recurrent laryngeal nerve (= necessity of a dry operation field) to avoid injury
- Minimally invasive techniques: Cosmetic benefits only
- Lymphadenectomy: Compartmental/regional only
- Postoperative Complications (informed consent):
  - Bleeding
  - Recurrent laryngeal nerve lesion
  - Hypoparathyroidism
- Rarely thyrotoxic crisis, tracheomalacia
- Quality Criteria: Magnifying loupes/microsurgical technique.

Open Surgical Technique (= Procedure of Choice)

- Obligatory compromise: finding-oriented/preservation of function/minimization of complications (recurrent laryngeal nerve, parathyroid glands)

■ **Table 6.5** Clinical factors in favour of/against initial total thyroidectomy

In favor of total thyroidectomy	1. Planned radioiodine therapy due to known (or suspicion of) differentiated thyroid cancer: a. Malignant FNA with lesion >4 cm b. Relevant extrathyroidal extension on US or intraop. c. Clinical, intraop. or ultrasound signs of LN metastases d. Known distant metastases e. Abnormal result of the molecular examination
	2. Medullary thyroid cancer
	3. Bilateral thyroid disease: a. Euthyroid/toxic goiter b. Graves' disease c. Contralateral dominant nodule d. Radiotherapy in anamnesis e. Familial predisposition syndrome f. Indication of contralateral parathyroidectomy
	4. Struma ovarii
Controversial/no consensus	1. Known or suspected unilateral differentiated thyroid cancer 1–4 cm with low-risk signs on ultrasound
	2. Index lesion under known thyroid hormone therapy
	3. Unilateral differentiated thyroid cancer with need for Tg/ultrasound surveillance
	4. Unilateral lesion in complex medical situation
	5. Unilateral lesion and patient preference for total thyroidectomy.
In favor of hemithyroidectomy with isthmus resection	1. Unilateral papillary thyroid microcarcinoma low-risk on ultrasound
	2. Unilateral lesion with inconspicuous molecular examination
	3. Unilateral goiter

- Standard technique = extracapsular lobectomy with isthmus resection
- Subtotal resection = inadequate (higher risk of injury to the recurrent laryngeal nerve and parathyroid glands).
- Ideal: Operation in centres with adequate expertise
- Rules:
  - Good exposure (= excellent visualization of the recurrent laryngeal nerve + parathyroid glands)
  - Systematic identification of the anatomical structures + careful dissection
  - Preoperative informed consent (operation, alternative procedures, possible complications)
  - Preoperative confirmation of the euthyroid metabolic state

Surgical Procedure

Open Hemithyroidectomy/Thyroidectomy

- General anaesthesia (only rarely locoregional anaesthesia possible)
- Cervical spine extension, roll or vacuum mattress under the shoulders
- Access: 4–5 cm Kocher collar incision, in skin fold approx. 1 finger width above the jugulum (preoperative marking)
- Transection of the platysma muscle, formation of a subplatysmal flap which is retracted cranially (holding suture)
- Incision of the linea alba, lateral retraction of the strap muscles (infrahyoid muscles)
- Preparation only on the side of the nodule(s)
- Neuromonitoring of the vagus nerve before resection
- Finding the right plane on the thyroid capsule (crucial)
- Dissection of the upper thyroid pole; visualization of the upper pole vessels: transection + ligation (close to the capsule); mobilization of the upper pole
- Mobilization to lateral + caudal; transection of the Kocher veins; mobilization of the lower pole
- Medial retraction of the thyroid and central preparation
- Exposure of the inferior thyroid artery and the recurrent laryngeal nerve; neuromonitoring prior to resection; exposure of the inferior thyroid artery (close to thyroid capsule)
- Identification of both parathyroid glands and assessment of blood flow; if insufficient blood flow: parathyroidectomy and autotransplantation into the sternocleidomastoid muscle
- Complete mobilization of the SD lobe while sparing the recurrent laryngeal nerve
- Subtle hemostasis; close to the nerve, PDS (polydioxanone)-6/0 sutures (no electrocoagulation)
- Final neuromonitoring of the recurrent laryngeal nerve and the vagus nerve after resection
- Thyroidectomy: Only justified if neuromonitoring is unremarkable on the primary side; analogous procedure on the opposite side
- Suture of the strap muscles; suture of the platysma muscle; continuous subcutaneous suture; skin closure (suture, glue)

Minimally Invasive Surgical Techniques

- Only in centres with adequate expertise
- Purely aesthetic benefits (evidence-based)
- New complications (vascular injury, nerve injury) = critical use of these techniques.
- 3 groups of procedures:
  - Purely endoscopic procedures (collar, prethoracic, axillary, perimammillary or supramandibular approach)
  - Open video-assisted procedures (MIVAT)
  - Open procedures with minimum incision length
- Indications, relative and absolute contraindications (◘ Table 6.6)

Table 6.6 Indications, relative and absolute contraindications for MI (minimally invasive) techniques

Indications	Absolute contraindications	Relative contraindications
Nodule, diameter < 3 cm	History of cervical surgery	History of neck irradiation
Thyroid volume < 20 mL	Large goiter	Hyperthyroidism
Benign nodule	Locally advanced cancer	Thyroiditis
Low-risk papillary carcinoma	Lymph node metastases	

Surgical Procedure

Minimally Invasive Video-Assisted Thyroidectomy (MIVAT) According to Miccoli

- General anesthesia
- No hyperextension of the cervical spine
- Access: 1–2 cm transverse skin incision, in jugular fossa (preoperative marking)
- transection of the platysma muscle and formation of a subplatysmal flap
- Incision of the linea alba (3 cm) and retraction of the strap muscles to the lateral side, medial retraction of the thyroid
- After exposure of the thyroid: Further preparation videoscopically-assisted (30°, 5-mm endoscope)
- Mobilization and resection of the thyroid: Following the rules of open surgery
- supply of the vessels: ligation impossible, therefore electrosurgery (bipolar vessel sealing devices, ultrasound dissection devices) or stapling devices
- Conversion to open surgery always possible
- Continuous subcutaneous suture; skin closure (suture, glue)

Surgical Procedure

Complete Endoscopic Thyroidectomy According to Gagner

- General anesthesia
- Moderate extension of the cervical spine
- Access: 5 mm transverse neck incision, above the jugulum (preoperative marking)
- Opening of the cervical fascia; preparation below the platysma
- Insertion of 5-mm trocar into the subplastysmal space; CO_2 insufflation (10 mmHg)
- Dissection along the anteromedial border of the sternocleidomastoid muscle (SCM), using a 0° endoscope via the 5 mm trocar; then use a 30° endoscope as soon as sufficient space is created.
- 3 additional working trocars: 3-mm trocar on the midline, 3-mm trocar on the ipsilateral SCM, 5-mm trocar on the anterior border of the SCM
- Opening of the linea alba; retraction of the sternohyoideus and sternothyroideus muscles medially
- Mobilization of the thyroid lobe
- Sealing/Transection of the Kocher veins (clip, ultrasound)
- Identification and dissection of the parathyroid glands and the laryngeal recurrent nerve
- Identification and Sealing/Transection of the inferior thyroid artery (clip, ultrasound)
- Isolation of the upper pole vessels and Sealing/Transection of the same (clip, ultrasound)
- Isolation of the lower pole vessels and Sealing/Transection of the same (clip, ultrasound)
- Transection of the Berry ligament and isthmus; extraction of the specimen
- Continuous subcutaneous suture; skin closure (suture, glue)

Cervical Lymphadenectomy (LAD) for Thyroid Cancer

Surgical Anatomy and Classification Systems

- ► Section 6.1, ◘ Fig. 6.1 and ◘ Table 6.1

Pathophysiology

- Lymphadenectomy for thyroid cancer (limited to the neck)
  - = curative intervention: resection of the LN (lymph node) metastases
  - = preventive intervention: prevention of LN metastases
- Lymphadenectomy: the most important curative treatment modality for locoregional LN metastases
- Indication + extent = depending on tumor biology
  - Tumour type (papillary, follicular, low-differentiated, undifferentiated, medullary)
  - Tumor extension (intrathyroidal vs. extrathyroidal; locoregional vs. distant metastases)
- Currently no consensus due to lack of studies: prophylactic vs. therapeutic LAD
- Adjuvant therapy modalities (= no replacement of surgery):
  - Radioiodine therapy (for differentiated thyroid cancers)
  - External radiation (for undifferentiated cancers or locally advanced differentiated cancers)

Sentinel Node Biopsy Technique

- Only in the context of studies
- Not routine use because of: High variability of lymphatic drainage/Frequent multiple primary tumours.

Selective LAD ("Berry Picking")

- Contraindicated
- In case of locoregional recurrence: after already performed compartment-oriented LAD

◘ **Table 6.7** Forms of cervical lymphadenectomies

Forms of neck dissection	Resection extension
Radical neck dissection	Removal of the lymph node groups 1–5 including the sternocleidomastoid muscle, internal jugular vein and vagus nerve
Modified radical neck dissection	Removal of lymph node groups 1–5 leaving at least one of the following structures: sternocleidomastoid muscle, internal jugular vein and vagus nerve
Selective neck dissection	Removal of groups of cervical lymph nodes, leaving at least one group intact. Classically, one distinguishes: Central neck dissection: removal of the lymph nodes of groups 1a and 1b according to Dralle (6 according to Robbins) Lateral neck dissection: removal of the lymph nodes of groups 2 and 3 according to Dralle (2–5 according to Robbins)
Extended neck dissection	The above resection procedures extended to include other groups of lymph nodes (deep mediastinal) or other structures (muscles or nerves)

Compartment-Oriented LAD

- Classification + definition of cervical lymph node dissections (◘ Table 6.7)
- Standard procedure for LN-positive thyroid cancer
- Surgical strategy: In case of preoperatively confirmed locally advanced thyroid cancer:
  - Centripedal tactics
  - Centrifugal tactics
  - Mediastinal LAD (sternotomy): Only in case of confirmed LN metastasis.

Surgical Procedure
Central Lymph Node Dissection

- General anesthesia
- Resection Boundaries:
  - Lateral = medial aspect of the carotid artery
  - medial = trachea
- Central LAD always with thyroidectomy (ideally "en bloc")
- Protection of the upper PG (parathyroid glands) extremely important (possibly autotransplantation)

Surgical Procedure
Lateral Lymph Node Dissection

- General anaesthesia; following thyroid resection or as an independent procedure
- sternocleidomastoid muscle, strap muscles pulled laterally dorsally
- transection of the omohyoid muscle
- Visualization of carotid artery, internal jugular vein, vagus nerve (vessel loop)
- Exposure of hypoglossal nerve (= cranial dissection landmark and border)
- Exposure of the accessorius nerve in its course (important for its protection) at the upper edge of the sternocleidomastoid muscle
- En bloc resection of the entire compartmental fibro-fatty tissue with LN
- Dorsal landmark and border = dorsal cervical fascia
- Dorsal to note and spare: C3 to C7 fibers of the brachial plexus…
- Dorsal to note and spare: cervical sympathetic trunc (mediodorsal; avoid Horner's syndrome).
- Visualization of the subclavian vein dorsal to the clavicle (= caudal dissection landmark and border)
- Caudomedial left: Protection of the thoracic duct…

Postoperative Complications

Bleeding Needing Revision

- Incidence = 0.3–5%
- Bleeding within a few hours to 24 h postoperatively
- Clinical signs: cervical swelling of the throat; dyspnoea; dysphagia
- Therapy: Immediate revision

Recurrent Laryngeal Nerve Lesion

- Temporary vs. permanent (passing after 6 months = permanent)
- Causes: transection, contusion, strain, electrocoagulation, pressure damage (edema, hematoma)
- High rate of spontaneous remission of the paresis
- Unilateral lesion: often late diagnosis/unnoticed
  - Clinical signs: Absence of glottis closure on coughing; discrete hoarseness; deeper voice; usually only evident on postoperative laryngoscopy.
  - Therapy: Speech therapy
- Bilateral lesion: Usually early and markedly symptomatic
  - Clinical presentation: Stridor, dyspnea
  - Therapy: In mild clinical condition: conservative (calcium, glucocorticoids, if necessary NSAIDs, O_2 administration); in case of respiratory impairment (reintubation, if necessary translaryngeal laterofixation of the vocal cord, if necessary tracheotomy).

Parathyroid Hypofunction (= Hypoparathyroidism; ◘ Fig. 6.6)

- Temporary vs. permanent (passing after 6 months = permanent)
- Prophylaxis: Intraoperative exposure/imaging of the parathyroid glands, autotransplantation in case of reduced blood flow
- Clinical presentation, diagnosis and therapy (► Sect. 6.5.1)

Thyrotoxic Crisis

- Rare; on the ground of hyperthyroidism.

Table 6.8 Akamizu criteria for the diagnosis of thyrotoxic crisis

Main criterion 1	Main criterion 2	Secondary criterion 1	Secondary criterion 2
Elevated fT4 or fT3 levels	CNS manifestations (agitation, delirium, psychosis, seizure, impaired consciousness)	Body temperature ≥ 38 °C, heart rate ≥ 130, cardiac decompensation, gastrointestinal and hepatic manifestations	Thyroid disease in history, goiter, exophthalmos
Definite thyrotoxic crisis	Both main criteria + one of the Secondary criteria **or** main criterion 1 + at least three of the secondary criteria		
Suspicion of thyrotoxic crisis	Main criterion 1 and exactly two of the secondary criteria, **or** main criterion 2 + one of the secondary criteria 1 + all of the secondary criteria 2, **or** at least three of the secondary criteria 1 + all of the secondary criteria 2		

Table 6.9 Staging of thyrotoxic crisis according to Hermann

Stage	Clinical criteria
1	Tachycardia, arrhythmias, hyperthermia, adynamia, diarrhea, dehydration, tremor, agitation, hyperkinesia, possibly increased thyroid hormone levels.
2	Stage 1 + disorientation, somnolence, stupor or psychosis
3	Stage 1 + coma
1–3a	Age < 50 years
1–3b	Age > 50 years

- Life-threatening due to decompensation of the organism
- Diagnosis: Purely clinical (Akamizu criteria Table 6.8)
- Clinical presentation: (Classification according to severity: staging according to Hermann Table 6.9)
- Prognosis: Overall lethality >15%; in stage 3 up to 30%
- Prophylaxis:
  - Consistent preoperative preparation in patients with hyperthyroidism (thyrostatic drugs, α/β-blockade if necessary) until euthyroidism is achieved.
  - Avoidance of Iodin exposure
  - Resection of all autonomies
- Therapy:
  - Interdisciplinary intensive medical treatment
  - Sedation + thyrostatic drugs + β-blockade + corticosteroids
  - Symptomatic measures: Reduction of temperature, fluid and electrolyte balance, high-calorie diet, possibly plasmapheresis
  - In case of uncontrollable crisis: emergency thyroidectomy

Tracheomalacia

- Rare
- Postoperative collapse of the trachea during inhalation
- Therapy:
  - Intraoperative: Atraumatic lateral submucosal stabilization sutures (pillar sutures) to sternocleidomastoid muscle
  - Postoperative: Postoperative mechanical ventilation
  - Endoluminal stenting

Postoperative Care

- Monitoring in the recovery room: HF (heart rate), SpO_2 (pulse oximetric oxygen saturation), neck circumference, hypocalcemia signs.
- Postoperative pain therapy (analogic pain scale)
- Workflow:
  - On the first postoperative day: calcemia and PTH
  - Calcium substitution if symptomatic hypoparathyroidism or very low level
  - Before discharge: Postoperative laryngoscopy

- 1 week postoperatively: clinical follow-up (with discussion of the definitive histopathology); possible initiation of substitution therapy; planning of possible radioiodine therapy
- 3–4 weeks postoperatively: TSH control and eventual adaptation of substitution
- Cervical ultrasound: after 6 months

6.2.4 Benign Thyroid Diseases

Hypothyroidism

Definition

- Insufficient central thyroid hormone production
- Limited peripheral activity of thyroid hormones

Symptoms

- During growth
  - Delayed growth to dwarfism
  - Mental retardation
  - Rare: Rectal prolapse, umbilical hernia…
- In adults (incidious and slowly progressive; ◘ Table 6.2)

Diagnosis

- Laboratory diagnosis: Elevated TSH, low fT3 and fT4

Therapy

- Purely substitution therapy (levothyroxine)

Hyperthyroidism

Key Points

- Increased thyroid hormone secretion: hypermetabolism
- Extrathyroidal vs. thyroidal (toxic nodules, Graves' disease, thyroiditis) causes
- Definitive therapy possible only under euthyroidism
- Therapy: Medical and/or radioiodine and/or surgical therapy

Definition

- Increased thyroid hormone secretion
- As a consequence = hypermetabolism

Etiology

- Diseases of the thyroid (toxic nodules, autoimmune thyreopathy)
- central nervous system disease (increased TSH secretion or thyroid hormone resistance)
- Exogenous thyroid hormone supply
- Molar pregnancy
- Thyroid cancer (► Sect. 6.2.5)

Symptomatology (◘ Table 6.2)

Toxic Nodules (= Autonomies)

Definition

- Thyroid cell clusters with autonomous (= TSH-independent) hormone secretion
- Forms: Unifocal vs. multifocal vs. multifocal disseminated

Epidemiology

- In regions with iodine deficiency: prevalence up to 65%
- In regions without iodine deficiency: prevalence <2–5%
- Prevalence increases with age

Symptoms

- Symptoms of hyperthyroidism (◘ Table 6.2) in up to 20% of patients (in Germany, 4.1%/year hyperthyroidism in patients with unifocal autonomy)

Diagnosis

- Laboratory tests:
  - TSH (low)
  - Exclusion of an immunothyreopathy (Graves' disease)
- Thyroid ultrasound: nodules; however, cannot prove/exclude an autonomic area
- Thyroid suppression scintigraphy with quantification of uptake: method of choice to prove/exclude functional autonomy (toxic nodules)

Normal TSH (in 70% of patients with relevant autonomy) does not exclude the diagnosis of hyperthyroidism.

Therapy

- Principle: Definitive therapy only in case of euthyroidism

Pretherapeutic/Preoperative Hyperthyroidism Treatment

- Thyrostatic agents: Thiamazole (initially 10–40 mg/day, then 2.5–10 mg/day), or carbimazole (initially 15–60 mg/day, then 5–15 mg/day), or thiouracil (initially 25–150 mg/day, then 10–50 mg/day)
- Inhibitors of iodine uptake: (e.g. perchlorate) Inhibition of iodine uptake prior to planned iodine contamination/contrast medium (CM) administration: Irenate drops (1 mL = 300 mg sodium perchlorate), 3 × 25 drops/day
- Adjunctive therapy: β-blockers (attenuation of sympathetic activity and reduction of peripheral conversion of T4; e.g. propranolol 3 × 20–40 mg/day for 3–6 days before surgery), possibly benzodiazepines (to alleviate symptoms)
- Lugol's iodine solution (Plummer and Boothby 1923): If thyrostatic not suitable because of side effects

- **Radioiodine Therapy**
  - Indications/contraindications (limit = goiter >80–90 mL; ◘ Table 6.10)
  - Low side effects + high success rate (85–95%)
  - Principle:
    - In-patient (2–5 days), with radiation protection measures (= isolation in special departments)
  - Per os intake from ^{131}I
- Risks/Side Effects:
  - Sialadenitis
  - Posttherapeutic hyperthyroidism (due to disintegration of the follicles)
  - Radiation-induced thyroiditis
  - Hypothyroidism: When excessive destruction of normal functional tissue
- **Surgical Therapy**
  - Medical pretreatment obligatory (see above; exception: uncontrollable thyrotoxic crisis)

◘ **Table 6.10** Indications and contraindications for ^{131}I therapy

Indications	Contraindications
Small to medium sized autonomous goiter	Very large goiter with existing mechanical complications
Focal toxic nodules (autonomous volume treatable with one radioiodine session)	Very large volume of autonomous tissue
Toxic nodules in recurrent goiter	Low iodine uptake of the thyroid in scintigraphy
Toxic nodules in patients with increased surgical risk	Children and young people with toxic nodules
	Gravidity and lactation
	Large cold nodules with suspected malignancy

  - Indication for surgical therapy:
    - Large goiter (volume > 80 mL); small strumen with poor iodine uptake.
    - Goiter with persistent symptoms under medication
    - Goiter with additional cold nodules
    - For children, women of childbearing potential, pregnant women (when medication is no longer possible or desirable)
    - Autonomous adenomas (toxic nodules) with diameter > 3 cm
    - Refusal of radioiodine therapy
    - Iodine-induced thyrotoxicosis; thyrotoxic crisis that cannot be controlled despite drug therapy
    - Principle: High risk of recurrence: Therefore rather aggressive therapy
    - Complications of surgery (Section "Cervical Lymphadenectomy (LAD) for thyroid Cancer")
- Posttherapeutic/postoperative therapy: objectives: Prophylaxis of recurrence + treatment of postoperative hypothyroidism

Immunothyreopathy: Graves' Disease

Definition

- Merseburg Triassic
  - Goiter
  - Tachycardia (sinus tachycardia)
  - Exophthalmos
- Hyperthyroidism

Epidemiology

- Prevalence = 0.5–2%; second most common cause of thyroid hyperfunction (in Europe)
- Mostly between 20 and 50 years of age
- Most common reason for hyperthyroidism in children and adolescents
- Annual incidence = 40–60/100,000 population per year
- Women:Men = 5:1
- Association with other autoimmune diseases (5–10% of patients):
  - Vitiligo
  - Pernicious anaemia
  - myasthenia gravis
  - Diabetes mellitus type 1
  - Addison's disease
  - Rheumatoid arthritis

Pathophysiology

- Pathogenesis not fully understood
- Autoantibodies: anti-TSH receptor = increased hormone production = hyperplasia, hypertrophy
- Risk factors
  - Genetic predisposition (familial clustering)
  - Nicotine consumption
- Triggering factors: stress; iodine exposure to jodes; viral infection; influence of sex hormones

Symptoms

- **Caution:** Oligosymptomatic courses
- Clinical presentation: (◘ Table 6.2 Symptoms of hyperthyroidism), in addition:
  - Overheated moist skin
  - Systolic hypertension
  - Auscultatory murmur over the thyroid (increased blood flow)
  - Enlarged thyroid (80% of patients)
  - Endocrine ophthalmopathy (not always synchronous), pathognomonic
  - Pretibial myxedema, rare (4% of patients)
  - Hypertrophic osteoarthropathy, rare
  - Acropachy, rare

Diagnosis

- Laboratory Diagnosis:
  - Low TSH: Hyperthyroidism
  - Increased fT4 and/or fT3 (if TSH low and T4/T3 normal = subclinical hyperthyroidism)
  - Antibody determination: TSH receptor antibodies (= TRAb) elevated (grey range = 1–1.5 IU/L)
  - Blood count and liver values: Required if drug therapy is used
- Ultrasound:
  - Hypoechogenicity with/without goiter
  - Doppler: Diffusely increased perfusion
  - Exclusion of focal findings
- Complementary Diagnosis:
  - Scintigraphy: Not absolutely necessary
  - Ophthalmological examination of an ophthalmopathy: measurement of the protrusio
  - In case of symptoms: cardiological examination, osteodensitometry

Therapy

- Primary (initial manifestation): Thyrostatic long-term therapy
- After completion: regular follow-up to exclude recurrence
- In case of recurrence/unsuccessful therapy: definitive therapy (surgery vs. radioiodine therapy)
- **Thyrostatic long-term therapy**:
  - 30–60% remission after long-term thyrostatic therapy
  - Therapy duration at least 12 months (= better remission rate)
  - Contraindications:
    - Mechanical impairment due to thyroid volume
    - Suspicion of malignancy
    - Severe side effects
    - Multimorbid patient (if stable euthyroidism cannot be achieved by drug therapy)

  - Lack of compliance
  - Desire to have children (= relative contraindication)
  - Recurrence after long-term thyrostatic therapy
- Practical implementation (◘ Table 6.11)

- **Radioiodine Therapy**
  - Indications:
    - Graves' disease with small or moderate goiter
    - Increased risk of surgery, recurrent laryngeal nerve palsy, postoperative hypoparathyroidism
    - refusal of an operation
    - Special occupations (using the voice): Singer, teacher, speaker
  - Contraindications:
    - Pregnancy (should be avoided 4 months after therapy)
    - Breastfeeding women (wean at least 6–8 weeks before radioiodine)
    - Suspected malignancy
  - Practical implementation:
    - Ablative concept: Complete thyroid ablation (about 250 Gy)
    - Function-optimized concept: function-preserving therapy (about 150 Gy)

◘ **Table 6.11** Thyrostatic long-term therapy of Graves' disease (practical implementation)

Substance	Initial therapy (mg/day)	Maintenance therapy (mg/day)
Monotherapy[a,b]		
Thiamazole	10–40	2.5–10
Carbimazole	20–60	5–15
Propylthiouracil	150–300	50–200
Combination therapy [a,b]		

[a] Combination therapy with thyroid hormones (levothyroxine 100 µg/day) possible: lower thyrostatic doses
[b] Pregnancy: Absolutely monotherapy, as only thyreostatics pass the blood-placental barrier. Multidisciplinary monitoring

- **Surgical therapy**:
  - Indications:
    - Compression symptoms (tracheomalacia, tracheastenosis, stridor)
    - Malignancy suspected
    - Need for immediate therapeutic effect (e.g. severe side effects to thyrostatic or radioiodine therapy)
    - Therapy refractory hyperthyroidism
    - Highly-active endocrine orbitopathy
    - Lack of patient compliance
    - Desire to have children
    - For children/adolescents (relative indication)
  - Preoperative preparation: (see above: Overview: Pretherapeutic/preoperative hyperthyroidism treatment); Glucocorticoids: In Graves' disease hyperthyroidism with suspicion of endocrine ophthalmopathy
  - Total/almost total thyroidectomy: therapy of choice
  - Intraoperative specific features:
    - Increased blood flow = bleeding tendency
    - Difficult identification of recurrent laryngeal nerve/parathyroid glands
  - Follow-up: Specific features:
    - Frequently postoperative hypocalcemia (disturbed bone metabolism)
    - Discontinue thyrostatic medication immediately postoperatively
    - Hormone replacement: levothyroxine (1.5 µg/kg BW/day)

Thyroiditis

Key Points

- Inflammatory diseases of the thyroid = histological evidence of inflammatory cells in the thyroid
- Diagnosis based on clinical presentation + laboratory diagnosis (+++) + ultrasound
- Therapy depending on entity (acute/subacute/Riedel's/autoimmune thyroiditis)

Acute Thyroiditis

Pathogenesis

- Rare
- Acute infection due to fungi/bacteria
- Especially in case of immunodepression (HIV, tuberculosis)
- Pathogen: Frequently Streptococcus pyogenes, Staphylococcus aureus

Symptoms

- Pain:
  - Mostly one-sided
  - Radiating pain (ears, lower jaw, retrosternal)
- Acute onset
- Fever
- Local redness, swelling, possible fluctuation
- Difficulty swallowing
- possibly hoarseness

Diagnosis

- Medical history: chronic diseases (HIV, tuberculosis)
- Palpation: pain/fluctuation
- Laboratory: leukocytosis, CRP elevation, temporary hyperthyroidism
- Ultrasound: Inhomogeneous image with hypoechogenic areas (= pus)
- CT: exclusion of a process involving more than one organ
- Contrast medium swallow: exclusion of a fistula with pyriform sinus/esophagus
- FNA: Confirmation of diagnosis + microbiological examination

Therapy

- No pus collection
  - i.v. antibiotics, pathogen-oriented, at least 14 days
  - Analgesia, cooling measures
- In case of pus collection
  - Additional surgical drainage

Subacute Thyroiditis (De Quervain)

Pathogenesis

- Granulomatous disease
- Inclusions of multinucleated giant cells
- Often a few weeks to several months after viral infection (especially respiratory tract)
- Predominantly women in the fourth and fifth decade
- Seasonal accumulation in early autumn
- Genetic predisposition (HLA B35)

Symptoms

- Acute onset with pain (radiating into the ears)
- subfebrile temperature
- Dysphagia
- Mild hoarseness
- Viral prodromes: muscle pain, general feeling of illness
- First mild hyperthyroidism then euthyroidism and possibly discrete hypothyroidism

Diagnosis

- Palpation: Firm consistency, pressure pain
- Laboratory: mild leukocytosis, CRP elevated, extremely accelerated blood sedimentation (>100 mm/h, almost pathognomonic), inflammation-related anemia
- Ultrasound: Typical: Map-like (hypo/hyperechogenic areas)
- Scintigraphy: Decreased Tc uptake (in the affected thyroid)
- FNA: Granulomatous change with multinucleated giant cells

Therapy

- Mild course: Aspirin 2–3 × 500 mg/day; alternatively, diclofenac 50–150 mg/day.
- Pronounced symptoms: glucocorticoid therapy (over 6–12 weeks)
- If hyperthyroidism: symptomatic (β-blocker, e.g. propranolol 3 × 40 mg).
- Surgical therapy: in case of therapy resistance (rarely necessary)

Autoimmune Thyroiditis

- Lymphocytic organ infiltration
- Women:Men =7–10:1

- Genetic predisposition (HLA DR3, DR4, DR5, B8), environmental influences, nutrition, infections, age, sex
- Autoimmune thyroiditis:
  - Hypertrophic autoimmune thyroiditis (Hashimoto's thyroiditis)
  - Atrophic autoimmune thyroiditis (primary myxedema)
  - Post-partum thyroiditis: In 3–11% of women after childbirth
  - Asymptomatic "silent thyroiditis": almost always an incidental finding
- Riedel's goiter: extracapsular and infiltrating thyroiditis

Symptoms

- Often incidental finding when organ enlargement is detected
- Feeling of pressure or slight pain
- Hypothyroidism symptoms (Hashimoto's and atrophic thryoiditis = most frequent cause of hypothyroidism in adults; ◘ Table 6.2)

Diagnosis

- Positive family history
- Presence of other autoimmune diseases
- Mild cervical pressure sensation
- Palpation: Firm consistency of the thyroid
- Laboratory tests:
  - Antibody elevation: anti-TPO (anti-thyroid peroxidase; frequent), anti-Tg (anti-thyroglobulin)
  - hyperthyroidism (at the beginning of the disease, short-term) then hypothyroidism
- Ultrasound: Diffuse hypoechogenicity
- Scintigraphy: Diffuse low uptake

Therapy

- If hypothyroidism: L-thyroxine substitution therapy
- If hyperthyroidism: symptomatic therapy
- If Riedel's thyroiditis: glucocorticoid therapy + surgery (to exclude cancer).

Special Forms of Thyroiditis

Traumatic Thyroiditis

- Thyroiditis induced by exogenous lesion (including radiation thyroiditis, radioiodin-induced thyroiditis)
- Therapy: analgesia + anti-inflammatory drugs, local cooling, rarely glucocorticoids

Drug-Induced Thyroiditis

- Drugs: e.g. cytokines such as interferons, Il-2, GM-CSF ("granulocyte macrophage colony-stimulating factor"), amiodarone
- In case of hyperthyroidism, surgical therapy may be necessary

Goiter and Nodular Goiter

Key Points

- Organ enlargement of the thyroid with/without nodule
- Etiopathogenesis: iodine deficiency + genetic predisposition
- Surgical therapy depending on: thyroid morphology, clinical presentation, nodule behavior, FNA

Definition

Goiter

- organ enlargement over 18 mL in women, 25 mL in men

Nodular Goiter

- Enlargement of the thyroid due to multifocal thyrocyte proliferation
  - Thyroid nodules: Clearly delineated clonal/polyclonal heterogeneous thyroid formation
  - Thyroid adenoma: histologically homogeneous monoclonal nodule with own structure + capsule

Pathogenesis

- Genetic predisposition + acquired alterations: Direct influence on the progenitor cells
- Iodine deficiency = hyperplasia-inducing

Diagnosis

Clinical Examination

- Inspection: Classification of goiter (grading, symmetry)
- Grading of goiter according to WHO
  - 0a: No goiter
  - 0b: Palpable, but not visible
  - 1: Palpable and visible with head reclination
  - 2: Visible goiter without reclination
  - 3: Large visible goiter
- Palpation: estimation of thyroid volume; relationship to landmarks (e.g., retrosternal goiter); number and consistency of nodules; swallowing displacement; presence of cervical lymph nodes.

Ultrasound

- Determination of the thyroid volume
- Localization, dimension and character (echogenicity, margins, vascularization, calcifications) of the nodules (◘ Table 6.12 Ultrasound signs of malignancy)

◘ **Table 6.12** Ultrasound signs of malignancy

Malignancy sign	Signs of benign node
Hypoechogenicity	Purely cystic mass
Increased intranodal vascularization	Spongiform mass
Irregular border	
Microcalcifications	
Absence of a halo	
Nodule larger than wide in transverse image	
Abnormal cervical lymph nodes	

Scintigraphy (► Sect. 6.2.2)

- Only if there's a nodule >1 cm on ultrasound…

Endemic euthyroid goiter: scintigraphy not required, neither for indication nor for planning surgery.

FNA

- For the differentiation of benign/malignant thyroid nodules
- Indications: ► Sect. 6.2.2

Laboratory (Standard Levels, ► Sect. 6.2.2, Laboratory Thyroid Function Tests)

- Basal TSH (sufficient if normal)
- In case of suppressed or elevated TSH: fT3 and fT4 for the detection of hyperthyroidism/hypothyroidism
- In case of disseminated functional autonomy (scintigraphy): TPO + TSH receptor antibodies to exclude Graves' disease
- If malignancy is suspected: calcitonin to exclude medullary thyroid cancer (**caution:** proton pump inhibitor (PPI) therapy and renal insufficiency)

Therapy

Medical Therapy and Prophylaxis

- Levothyroxine or iodide
  - Limited therapeutic influence on the progression of nodular goiter
  - Large nodules, large goiter = less sensitive to medical therapy
  - In iodine deficiency endemic areas: Early prophylaxis of nodular goiter indicated
- Radioiodine therapy: ultima ratio, only if surgical treatment is not possible

Surgical Therapy

- Procedure oriented to thyroid morphology and nodules
- Possible surgical procedures: Hemithyroidectomy, thyroidectomy…
- Indications:
  - Large thyroid volume (grade III, volume > 60 mL)
  - Suspicion of nodules (◘ Table 6.12)

  - Patient's request for pathology with smaller volume goiter
  - Waiver of the patient for long-term control examinations
- Section "Preoperative Measures"
- Procedural choice:
  - Hemithyroidectomy: When nodules localized on one side
  - Hartley-Dunhill procedure: hemithyroidectomy + contralateral subtotal resection
  - Thyroidectomy: standard procedure for euthyroid multinodular goiter

Highly Recommended For All Thyroid Operations

- Use of magnifying loupes
- Visual identification of recurrent laryngeal nerve (gold standard)
- Intraoperative neuromonitoring (recurrent laryngeal nerve + vagus nerve)
- Visual identification of the parathyroid glands

Recurrent Goiter

- Prophylaxis in case of incomplete resections = drug-based recurrence prophylaxis (administration of iodide/levothyroxine)
- Radical resection in primary surgery = thyroidectomy = most important factor for recurrence prophylaxis
- Surgery on recurrent goiter: only by very experienced surgeons; intraoperative neuromonitoring + readiness for frozen section obligatory

6.2.5 Malignant Thyroid Diseases

Key Points

- 1% of human malignancies
- 99% = epithelial tumours (carcinomas)
- Increase in incidence of thyroid cancers in the last 25 years (better diagnosis + absolute increase)
- Mortality declining (differentiated cancers = excellent prognosis)
- Evidence (RCT, meta-analyses): in the past 3 years in favour of limited resection or surveillance without surgery for "low-risk" differentiated thyroid cancers (not yet integrated in the current guideline)

German S3 guideline "Thyroid carcinoma": currently in development with planned completion by 30.04.2021.

Cancers of the Thyroid Gland

Definition (■ Table 6.13)

- Differentiation: cancers with follicular epithelial cells vs. C-cell differentiation
- Distinction based on the different biological course:
  - Differentiated cancers (papillary = PTC, follicular = FTC)
  - Poorly differentiated cancers (medullary cancer = MTC, anaplastic carcinoma)
- Specific features of thyroid cancers:
  - Congenital (familial) or acquired in the course of life (sporadic)
  - From childhood to old age
  - Strong predominance in the female gender (especially PTC and FTC)
  - Geographical differences = genetic, environmental factors
  - Differentiated cancers = very good prognosis; anaplastic carcinomas = very poor prognosis
  - Incidence of thyroid microcarcinoma (carcinoma <1 cm) up to 35%.

Papillary Thyroid Cancer (PTC)

Epidemiology

- Most frequent malignant thyroid cancer (60–85%)
- Age peak = 40 years of age
- Women:Men = 3:1

Table 6.13 Classification of thyroid cancers

Carcinomas with follicular epithelial cell differentiation	Differentiation according to biological course	Cell differentiation	Subdifferentiation
	Differentiated carcinoma	Papillary carcinoma	Conventional type
			Variants
		Follicular carcinoma	Minimally invasive
			Broadly invasive
		Other	
	Anaplastic carcinoma[a]		
Carcinoma with C-cell differentiation	Medullary carcinoma[a]	Sporadic	
		Autosomal dominant inheritance (MEN 2, fam. MTC)	
	Mixed type (C-cell follicle differentiation)		
Rare primary thyroid carcinomas	Squamous cell carcinoma Mucinous carcinoma Mucoepidermoid carcinoma Mucoepidermoid carcinoma with eosinophilia Spindle epithelial tumor with thymus-like differentiation (SETTLE) Carcinoma with thymus-like differentiation (CASTLE)		

MEN 2 multiple endocrine neoplasia type 2, *MTC* medullary thyroid carcinoma
[a] Low-differentiated carcinoma = medullary + anaplastic carcinoma

Molecular Pathology BRAF Mutation: Approx. 50% of PTC

- RET/PTC rearrangements: 10–20% of the PTC
- NTRK1 rearrangements: 10% of the PTC

Prognosis

- Regional LN metastasis: Already with tumor sizes of a few mm (microcarcinoma)
- distant metastases significantly later (= mainly lung)
- Normal life expectancy even with metastases
- Prognostic factors:
  - Large PTC = poor prognosis
  - High age = poor prognosis
  - Radioiodine storage = good prognosis

Therapy Principles

- ► Section 6.2.3 "Principles of surgical therapy" and "Cervical lymphadenectomy for thyroid cancer":
- Total thyroidectomy + central lymphadenectomy
- Subsequent radioiodine therapy
- Lateral lymph node dissection:
  - if positive lateral LN
  - In case of special histology (poorly differentiated cancer)
- In case of recurrent PTC: primary therapy = surgery; in case of mediastinal LN metastases or distant metastases: Primary radioiodine therapy

Hemithyroidectomy = sufficient for papillary/follicular thyroid microcarcinoma (< 1 cm nodule) without extrathyroidal tumor manifestation.

Follicular Thyroid Cancer (FTC)

Epidemiology
- 10–30% of thyroid cancers
- High incidence in iodine deficient areas
- Women:Men = up to 5:1
- Age peak: 50 years of age

Molecular Pathology
- Adenoma-carcinoma sequence: FTC develops from an adenoma (genetic alterations)
- Vascular invasion/metastasis: From tumor size of 1–2 cm
- No specific genetic change (= no marker)

Prognosis
- Hematogenous metastasis mainly (lung, bone): 10% in encapsulated tumors, 50% of broadly invasive FTC
- Lymph node metastases together with organ metastases
- Minimally invasive FTC = excellent prognosis; broadly invasive FTC = 40–60% 10-year survival; oncocytic FTC = poorer prognosis.

Therapy Principles
- ► Section 6.2.3 "Principles of surgical therapy" and "Cervical lymphadenectomy for thyroid cancer"
- Total thyroidectomy + central lymphadenectomy
- Subsequent radioiodine therapy
- Lateral lymph node dissection:
  - if positive lateral LN
  - In case of special histology (poorly differentiated cancer)
- In case of FTC recurrence: primary therapy = surgery; in case of mediastinal LN metastases or distant metastases: Primary radioiodine therapy

Poorly Differentiated Thyroid Cancer

Epidemiology
- 4–7% of thyroid cancers (geographical differences)
- Women:Men = 2:0

Molecular Pathology
- Largest part = development de novo
- No specific genetic characteristic features

Prognosis
- 5-year survival rate = 50
- 10-year survival rate = 25–35%.

Therapy Principles
- ► Section 6.2.3 "Principles of surgical therapy" and "Cervical lymphadenectomy for thyroid cancer"
- Total thyroidectomy + central lymphadenectomy
- Lateral lymph node dissection
- Subsequent radioiodine therapy

Anaplastic Thyroid Cancer

Epidemiology
- <5% of thyroid malignancies; 90% of deaths from thyroid cancers
- Predominantly older people
- Mostly in nodular goiters
- Women:Men = 1.5:1

Molecular Pathology
- Often de novo

Prognosis
- Mortality >90%
- Mean survival <6 months (= one of the most aggressive human malignancies)
- Short history, rapid metastasis (hematogenous + lymphogenous)
- At diagnosis: already extensive extrathyroidal extension (trachea, esophagus, cervical vessels)

Therapy Principles
- Perioperative radiochemotherapy
- Operative therapy: If operable, ideally R0 resection
- Molecular genetic testing always indicated
- New targeted therapies/checkpoint inhibitor therapy: in evaluation within studies

Medullary Thyroid Cancer (MTC)

Epidemiology
- 1–3% of all thyroid cancers
- Sporadic MTC (75%): Mostly in patients >45 years
- Familial MTC (FMTC; 25%): In patients from childhood to old age

Molecular Pathology

- Tumor markers: calcitonin, chromogranin A, CEA
- Familial MTC: Autosomal dominant in the context of the MEN-2 syndrome (2a or 2b; ► Sect. 6.2.3)
- Familial MTC: detection/exclusion of the rearranged-during-transfection (RET)-protooncogene mutation obligatory

Prognosis

- MTC without metastasis: Excellent prognosis
- MTC with metastasis: generally poor prognosis

Therapy Principles

- Sporadic MTC: thyroidectomy + central LN dissection + ipsilateral lateral LN dissection ± contralateral lateral LN dissection (if calcitonin level > 200 pg/mL)
- Familial MTC: timing of therapy depends on mutation type: thyroidectomy + LN dissection; in MEN 2B: surgery immediately after diagnosis

Familial Non-Medullary Thyroid Cancer (► Sect. 6.3)

- 5% of the differentiated PTC, FTC
- In the context of defined autosomal dominant syndromes (e.g. Gardner syndrome, Cowden syndrome, Carney complex) or non-syndromic

Rare Thyroid Cancers

- Squamous cell carcinoma
- Mucinous carcinoma
- mucoepidermoid carcinoma
- Mucoepidermoid carcinoma with eosinophilia
- Spindle cell tumor with thymus-like differentiation (SETTLE)
- Carcinoma with thymus-like differentiation (CASTLE)

Primary Malignant Lymphoma of the Thyroid Gland

- Patients with Hashimoto's thyroiditis = 70 times higher risk
- Predominant part = extranodal mucosa-associated lymphoid tissue (MALT) marginal zone B-cell lymphoma
- Other lymphomas (non-Hodgkin or Hodgkin) very rare

Primary Sarcomas of the Thyroid Gland

- Rare
- Differential diagnosis with anaplastic thyroid cancer difficult
- Special type: angiosarcoma (poor prognosis)

Metastases in the Thyroid Gland

- Incidence of thyroid metastases in autopsies = 25%
- Origin tumors:
  - Lung Cancer
  - Breast Cancer
  - Renal cancer
  - Cancers of the GI tract
  - Malignant melanoma

6.2.6 Workup of a Solitary or Dominant Thyroid Nodule

Key Points

- High prevalence of thyroid nodes in Germany (25–50%)
- Necessity of a rational workup for differential diagnosis (workup diagram)
- Central = anamnesis + clinical examination + laboratory thyroid function tests + ultrasound
- Increasing importance: FNA

Epidemiology

- Prevalence (25–50%) depending on: Geography (endemic area), age, sex
- In Germany approx. 16 million people with nodules; 2/3 = cold nodules
- Diagnostic workup = **evidence-based rational approach** (◘ Fig. 6.2: ATA guideline 2015)

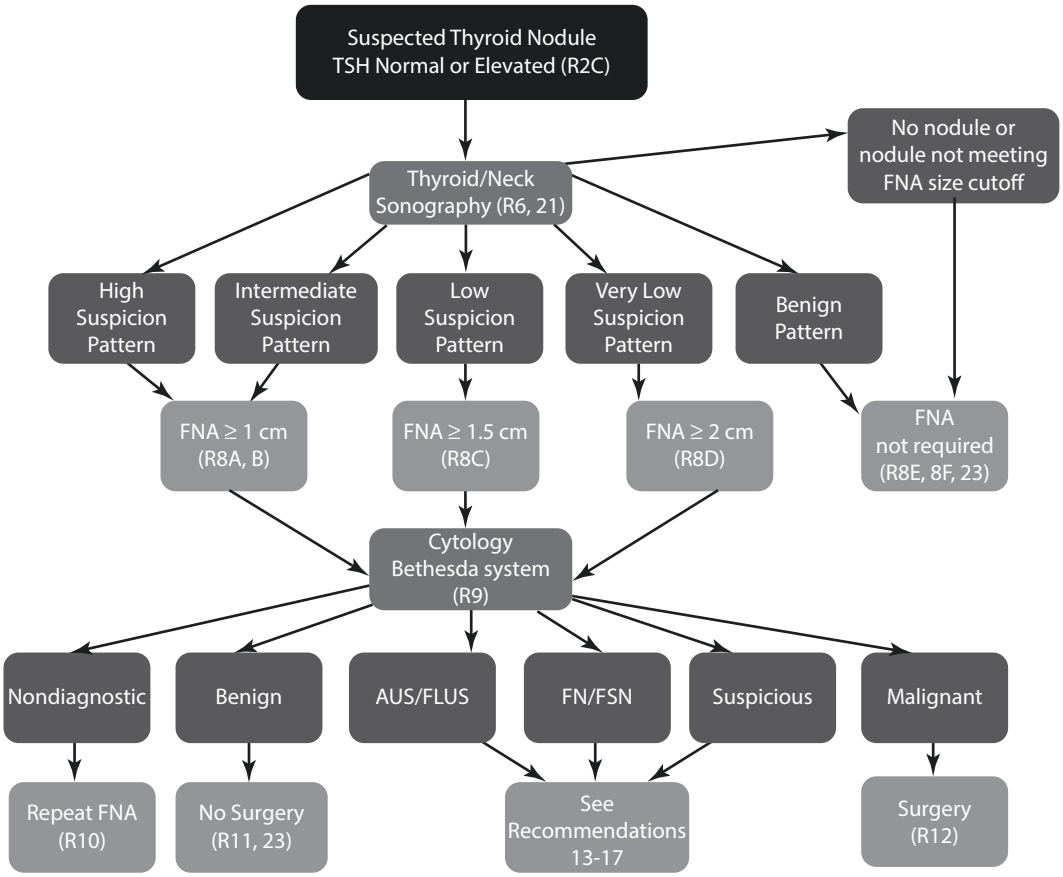


Fig. 6.2 ATA guidelines

- Prevalence-oriented differential diagnosis of the solitary/dominant thyroid nodule (with decreasing prevalence)
  - Colloid Nodules
  - Thyroid adenoma, hormonally inactive (mostly follicular adenoma)
  - Thyroid adenoma, hormonally active, toxic adenoma (autonomous adenoma)
  - Thyroid Cyst
  - Thyroiditis (Hashimoto)
  - Thyroid cancer (papillary, follicular)
  - Non-epithelial thyroid tumors and metastases
  - Abscess

Symptoms

- Mostly asymptomatic
- Mild symptoms/symptomatic: Only if large nodule
  - Subjective globus sensation
  - Swallowing disorders, to dysphagia
  - Stridor with tracheal compression

Diagnosis

- Rational approach

Medical History and Clinical Examination

- Age, sex, cervical radiation history, family history, familial thyroid disease patterns (► Sect. 6.3, e.g., MEN, poliposis coli, Gardner and Cowden syndromes).
- Time course of occurrence, growth
- Clinical examination:
  - Solitary nodule: Isolated nodular finding
  - Dominant nodule: Sudden change in a nodule in a nodular goiter.
  - Local symptoms

- Metabolic activity
- Exclusion of malignant signs

Clinical Signs of Malignancy in Thyroid Nodules

- Rough consistency
- Palpable cervical lymphadenopathy
- Non-displaceable Thyroid
- Hoarseness (expression of a recurrent laryngeal nerve impairment)
- Horner's syndrome = late sign

Laboratory Diagnosis (► Sect. 6.2.2 Laboratory Thyroid Functuon Tests)

Ultrasound

- Most sensitive examination method for solitary/dominant thyroid nodes
- Presentation of clinically inapparent nodules
- Best method for monitoring the progress of a nodule
- Guidance of the FNA
- Sonographic signs of malignancy (◘ Table 6.12)

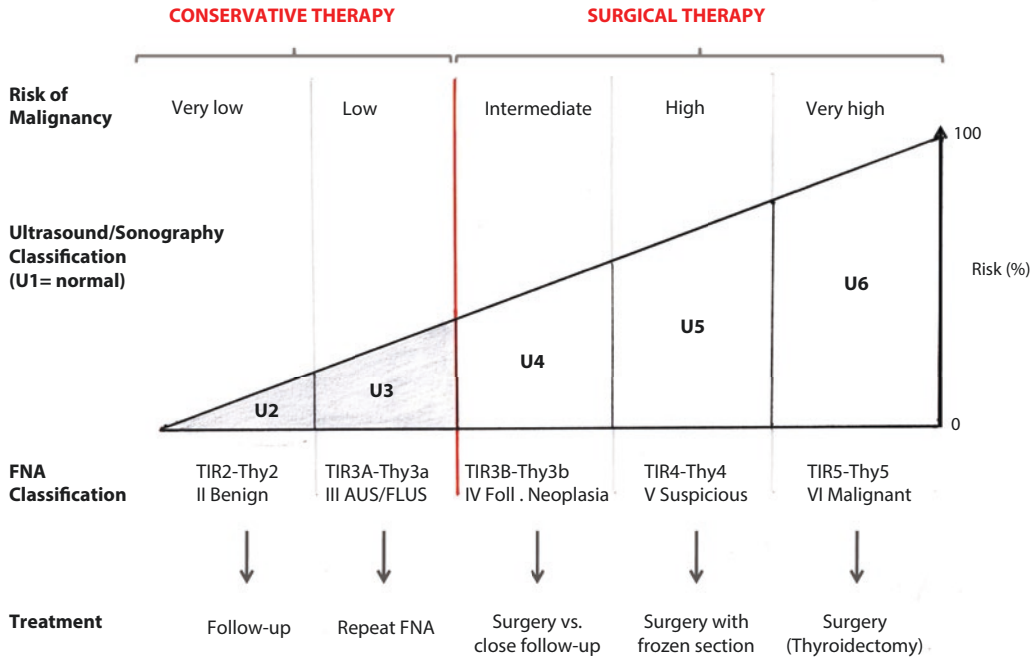
Scintigraphy

- If low TSH
- In nodule endemic areas (even if TSH normal)
- To distinguish hot nodule (autonomous area) vs. cold nodule
- Diagnostic consequence: autonomous area (= no further diagnosis) vs. cold nodule (= indication for FNA); check possibility of radioiodine therapy

FNA (► Sect. 6.2.2 Fine Needle Aspiration Cytology) (◘ Fig. 6.3)

Therapy

- Oriented to:
  - Knowledge of the underlying disease/its prognosis (diagnosis)
  - Risk factors of the patient
  - Function of the thyroid
  - Expectations of the patient
  - Health condition of the patient



◘ **Fig. 6.3** Ultrasound and cytological FNA categories (classes) and recommended treatment

Indications for Surgical Therapy

- Higher-grade suspicion in FNA (Bethesda groups IV, V, and VI, TIR 3B/thy 3f to TIR 5/Thy 5 ◘ Table 6.4)
- Benign nodule with compression symptoms
- Newly appeared growing nodule with cervical radiation history
- Solitary autonomous adenoma >3 cm
- Suspicious nodule in the absence of follow-up

Indications for Conservative Therapy

- Operation criteria not fulfilled
- Patient not fit for anaesthesia/surgery

With conservative therapy:

- Always plan regular follow-up (interval = 6–18 months)
- In case of nodule growth: reschedule follow-uo sooner and possibly indicate surgery

Operative Therapy Principles

- Basically hemithyroidectomy + isthmus resection
- Enucleation: no longer justifiable; subtotal resection: actual controversial discussion
- In case of suspected malignancy: intraoperative frozen section
- In case of malignancy: thyroidectomy (exception = microcarcinoma)
- Prophylactic central lymphadenectomy: controversy

6.2.7 Guidelines

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6.3 Familial Malignant Syndromes of the Thyroid Gland

C. E. Gibson and R. Udelsman

6.3.1 Introduction (■ Table 6.14)

Genetics

- Thyroid cancer three times more frequent in women than men
- Earlier age at diagnosis in women (40–50 s) versus men (60 s–70 s)
- Certain inherited mutations associated with different types of thyroid cancer:
  - RET gene mutations: associated with medullary thyroid cancers/syndromes such as MEN 2A, MEN 2B and FMTC
  - APC gene mutations: associated with FAP and Gardner syndrome
  - PTEN gene mutations: associated with Cowden disease
  - PRKAR1A gene mutations: associated with Carney Complex, type I

6.3.2 Hereditary Medullary Thyroid Carcinoma

Medullary Thyroid Carcinoma (MTC)

Key Points

- Tumor of the parafollicular C cells
- accounts for ~5% of all thyroid cancers
- 25% = hereditary, 75% = sporadic
- responsible for disproportionate number of thyroid cancer deaths
- all patients with MTC should be screened for germline mutations:
  - linked to germ line activation of the Rearranged during Transfection (RET) proto-oncogene
  - several RET mutations identified; aggressiveness of MTC differs by mutation (i.e. genotype-phenotype correlation)

Clinical Presentation

- Neck mass; cervical lymphadenopathy
- Asymptomatic/incidental finding (e.g. during work-up for unrelated medical issues)
- Evidence of distant metastases: Liver, lung, bone and mediastinum

Diagnosis

- Neck ultrasound (US)
- Fine needle aspiration biopsy (FNA)
- Tumour markers: Elevated serum calcitonin + carcinoembryonic antigen (CEA) levels
- Cytology: plasmacytoid cell pattern, spindle cells, stromal amyloid deposits, positive calcitonin antibody

Treatment

- Surgery (total thyroidectomy; central and/or lateral neck lymph node dissection)
- External beam radiation (rarely used)
- Chemotherapy (rarely used)
- Tyrosine kinase inhibitor therapy

Multiple Endocrine Neoplasia 2A (MEN 2A)

Epidemiology

- Identified in <1000 kindreds to date
- High penetrance for the MTC
- accounts for 90% of MEN-2 cases

Genetics

- Germline mutation of the RET proto-oncogene
- Mutation in codon 609, 611, 618, 620, 630, 631 and 634 (most common; mutation at extracellular cysteine residues)
- Autosomal dominant (AD); localized on chromosome 10q11.2
- Neoplastic cell proliferation (C-cell hyperplasia) = precursor lesion
- Characteristic features:
- MTC (often multifocal and bilateral)
  - Pheochromocytoma
  - Parathyroid neoplasia (typically benign asymmetric multiglandul hyperplasia)
  - Hirschsprung's disease and cutaneous lichen amyloidosis (uncommon associations).

Table 6.14 Hereditary predisposition syndromes for thyroid cancer

	Familial adenomatous polyposis	PTEN hamartoma tumor (Cowden)	Carney complex type 1	RET-associated	DICER1
Gene	**APC**	**PTEN**	**PRKAR1A**	**RET**	**DICER1**
Pathognomonic criteria	>100 colorectal adenomatous polyps	Mucocutaneous lesions, cerebellar tumors (Lhermitte-Duclos)	Multiple pigmented skin lesions (e.g. nevi, blue nevi, lentiginous N)	Medullary thyroid carcinoma)	Pleuropulmonary blastoma)
Other main manifestations	–	Breast, endometrial, thyroid carcinoma, macrocephaly	Blue nevi, pigmented nodular adrenal gland, cardiac myxoma…	Primary hyperparathyroidism, pheochromocytom, mucous neuromas	Germline stromal tumors, cystic nephromas, multinodular goiter
Ancillary manifestations	Extracolic polyps, congenital hypertrophy of the retinal pigment epithelium, thyroid nodules, SD carcinoma, soft tissue tumors, desmoid tumors, osteomas	Fibrocystic mastopathy, gastrointestinal hamartomas, lipomas, fibromas, renal cell carcinomas, uterine fibromas	Thyroid nodules, melanotic schwanomas, adrenal or pituitary adenomas, HCC, pancreatic carcinoma	Hirschsprung's disease, cutaneous lichen, amyloidosis…	Wilms tumor, rhabdomyosarcoma, ciliary body medulloepithelioma, pituitary gland blastoma, nasal chondromesenchymal hamartoma
Prevalence of thyroid diseases	40%	75%	Up to 75%		Up to 30%
Benign	0.4–12%	35%	<5%	–	Up to 30%
Malignant subtypes	CMV-PTC 63% FV-PTC 25% PTC 12%	PTC 50% FV-PTC 28% FTC 14%	PTC FTC	100% MTC	FTC FV-PTC

CMV cribriform-morulare variant, *FV* follicular variant

Clinical Presentation

- Often asymptomatic
- If symptomatic, linked to hyperparathyroidism or pheochromocytoma.
- No correlation between extent of hypercalcemia and extent of symptoms

Diagnosis

- thorough family history
- Genetic testing = **gold standard** for diagnosis
  - can detect >30 variants of RET mutations
- FNA biopsy:
  - 85–99% specific for MTC
  - Cytologic features: Plasmacytoid cells, spindle cells, stromal amyloid deposits, eccentrically located nuclei, positive calcitonin staining.
- Tumor markers:
  - Calcitonin levels >100 highly suggestive of MTC
  - Elevated CEA levels may denote advanced disease

Treatment (■ Table 6.15)

- Mostly level 2 risk (codon 634):
  - Highest rate of pheochromocytoma and hyperparathyroidism
  - **Must rule out pheochromocytoma prior to neck surgery**
  - MTC development at earlier age than other codon mutations
  - Prophylactic total thyroidectomy (± central LN dissection) prior to age 5 recommended
- Modified radical (= functional) neck dissection --> if clinical or cytologic evidence of cervical metastases

Multiple Endocrine Neoplasia 2B (MEN 2B)

Epidemiology

- Less common cause of inherited MTC (<5% of cases)
- MTC presents at earlier age than in MEN 2A
- Worst prognosis

Genetics

- Germline mutation in the RET proto-oncogene
- mutation in codon 804, 806, 883 and 918 (most common: methionine → threonine)
- Autosomal dominant (AD); located on chromosome 10q11.2
- Neoplastic cell proliferation (C-cell hyperplasia); precursor lesion
- Characteristic features:
  - MTC (early onset; infancy—early childhood)
  - Pheochromocytoma (40% penetrance)
  - Mucosal neuromas, gangliomas, megacolon, Marfanoid-like body habitus.

Clinical Presentation

- Often asymptomatic
- If symptomatic, linked to tumor compressive symptoms, high calcitonin levels, or pheochromocytoma

Diagnosis

- Thorough family history

■ **Table 6.15** Management of patients with RET germline mutation detected on genetic screening. (From Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma 2015)

MEN Type	RET mutation	Age at presentation (years)	Recommended procedure
MEN 2A	C609/F/G/R/S/Y	Variable	Thyroidectomy when serum calcitonin ↑, or based on patient/parent preference
MEN 2A	C611/F/G/S/Y/W	Variable	
MEN 2A	C618/F/R/S	Variable	
MEN 2A	C620F/R/S	Variable	
MEN 2A	C634F/G/R/S/W/Y	≤ age 5	Thyroidectomy by age 5 years
MEN 2B	A883F	≤ age 5	
MEN 2B	V804M + Y806C	20–30 years	Thyroidectomy when serum calcitonin ↑, or based on patient/parent preference
MEN 2B	V804M + S904C	20–30 years	
MEN 2B	V804M + E805K	20–30 years	
MEN 2B	V804M + Q781R	20–30 years	
MEN 2B	M918T	Infancy	Thyroidectomy ± Level VI LN dissection within first year of life

- Genetic testing = **gold standard** for diagnosis
- Can detect >30 variants of RET mutations
- FNA biopsy:
  - 85–99% specific for MTC
  - Cytologic features: Plasmacytoid cells, spindle cells, stromal amyloid deposits, eccentrically located nuclei, positive calcitonin staining.
- Tumor markers:
  - Calcitonin levels >100 highly suggestive of MTC
  - Elevated CEA levels may denote advanced disease

Therapy (◘ Table 6.15)

- Mostly level 3 risk (codon 918):
  - Highest rate of advanced disease (locally advanced or widely metastatic)
  - C-cell hyperplasia or MTC development during infancy
  - must rule out pheochromocytoma prior to neck surgery
  - Prophylactic total thyroidectomy (± central LN dissection) by age 1 recommended
- Total thyroidectomy + central neck dissection + modified radical (functional) neck dissection → if clinical or cytologic evidence of cervical metastases
- consider prophylactic functional neck dissection if clinically negative cervical LN but high calcitonin and/or CEA levels

Familial Medullary Thyroid Carcinoma (FMTC)

Epidemiology

- Clinical variant of MEN 2A
- Affected patients suffer **exclusively** from MTC

Genetics

- Germline mutation in RET proto-oncogene
- Similar codon mutations as those found in MEN 2A; also codons 768 and 790
- Autosomal dominant (AD); located on chromosome 10q11.2
- Neoplastic cell proliferation (C-cell hyperplasia); precursor lesion
- Least aggressive form of MTC

Clinical Presentation

- Often asymptomatic
- Incidentally found
- Presents in second or third decade of life

Diagnosis

- RET mutation
- Thorough family history
  - **Must** demonstrate the absence of pheochromocytoma or hyperparathyroidism in ≥2 generations within a family

Treatment

- Mostly level 1 risk (codon 918):
  - Total thyroidectomy ± central neck dissection
  - Add functional neck dissection → if clinical or cytologic evidence of cervical metastases

6.3.3 Familial Papillary Thyroid Carcinoma (FPTC)

Key Points

- First reported in monozygotic twins in 1955
- Now recognized as a distinct clinical entity
- Prevalence = 5–10% of well-differentiated thyroid cancer
- To date, no identifiable responsible genes, however heritability of FNMTC (familial non medullary thyroid cancer) considered to be one of the highest of all carcers

Clinical Presentation

- Neck mass; cervical lymphadenopathy
- May occur as a minor component of other familial cancer syndromes:
  - Familial adenomatous polyposis (FAP)
  - Gardner Syndrome
  - Cowden's disease
  - Carney complex type I

Diagnosis

- Neck ultrasound (U/S)
- Fine needle aspiration (FNA) biopsy
- **Genes: to date, none identified**
- Cytology: trabecular struma with oxyphilia (some cases)

Screening Recommendations

- all first degree relatives of affected families to be screened; consider screening of second degree relatives (nearly 50% of second degree relatives also affected)
- fine needle aspiration (FNA) biopsy
- Tumor markers: None
- Cytology: trabecular struma with oxyphilia (some cases)

Treatment

- Total thyroidectomy + prophylactic central neck lymph node dissection

FPTC felt to be more aggressive than sporadic cases:

- Earlier age of onset
- Higher incidence of:
  - Multifocality
  - Bilaterality
  - Nodal involvement
  - Intraglandular dissemination
  - Extrathyroidal invasion
  - Recurrence

6.3.4 Rare Genetic Syndromes Associated with Thyroid Cancer

Key Points

- 5% of well-differentiated thyroid cancers (WDTC) have familial disease, most of which are NMFTC
- Some rare syndromes associated with WDTC include familial adenomatous polyposis (FAP), Gardner syndrome, Cowden syndrome, and Carney complex I
- Inheritance is likely autosomal dominant with reduced penetrance
- Most common type of thyroid cancer associated with these syndromes is PTC

Familial Adenomatous Polyposis (FAP)

- ► Section 3.3.3

Epidemiology

- Occurs in approximately 1:10,000 to 1:30,000 live births
- Men:Women = 1:1
- Accounts for <1% of all colorectal cancer cases in the U.S.
- 0.5–2% of cases associated with thyroid cancer; cribriform variant classically associated with FAP

Genetics

- Germline mutation in the adenomatous polyposis coli (APC) tumor suppressor gene
- Autosomal dominant (AD); located on chromosome 5q21–q22
- Near complete penetrance of colonic manifestations; variable penetrance of extracolonic manifestations (◘ Table 6.16).

Clinical Presentation

- Often asymptomatic
- If symptomatic, linked to iron-deficiency anemia due to occult bleeding.

Diagnosis

- Suspect any patient with ≥10 colorectal polyps on colonoscopy

◘ **Table 6.16** Colonic and extracolonic manifestations of familial adenomatous polyposis (FAP)

Colonic manifestation	Extracolonic manifestation
Adenomatous colorectal polyps (>100) by second to third decade of life Colorectal carcinoma: 100% of cases (if not treated)	Gastric polyps: Rarely progress to gastric cancer Duodenal polyps: Up to 12% risk of duodenal cancer Desmoid tumours Cysts Other benign tumors: lipomas, osteomas, fibromas, adrenal adenomas

- Genetic testing for germline mutation in the APC gene = required for **DEFINITIVE DIAGNOSIS**

Treatment

- total colectomy
- Excision of desmoid tumors:
  - Destruction of adjacent vital intra-abdominal organs
  - Leading cause of death in patients with FAP
- Thyroidectomy (if thyroid cancer present)

Gardner Syndrome

Definition and Epidemiology

- Considered a variant of FAP
- Combination of:
  - Inherited colonic adenomatosis
  - Along with extracolonic lesion (◘ Table 6.17)

Genetics

- Germline mutation in adenomatous polyposis coli (APC) tumor suppressor gene
- Autosomal dominant (AD); located on chromosome 5q21–q22 (same as in FAP)

Clinical Presentation

- Based on which extra-intestinal manifestation(s) present

Diagnosis

- Suspicion in any patient with known FAP and additional extra-colonic lesion:
  - Genetic examination for germline mutation of the APC gene = required for **DEFINITIVE DIAGNOSIS**

Treatment

- Total colectomy (as in FAP)
- Additional therapy based on presence of other extra-intestinal lesions

◘ Table 6.17 Extracolonic and extraintestinal manifestations of Gardner syndrome

Benign extra-intestinal lesions	Extra-colonic malignancies
Osteomas, dental abnormalities Desmoid tumours Cutaneous lesions Adrenal adenomas Nasal angiofibromas Congenital hypertrophy of the retinal pigment epithelium	Duodenum/periampullary (5%) **Thyroid (2%)** Pancreastic (2%) Gastric (<1%) CNS (<1%) Hepatoblastoma (2%) Adrenal (rare)

Cowden Syndrome

Epidemiology

- First reported in 1963
- Estimated prevalence = 1/200,000–250,000

Genetics

- Germline mutation in phosphatase tensin homolog (PTEN) tumor suppressor gene
- Autosomal dominant (AD); located on chromosome 10q23
- Other mutations:
  - Hypermethylation of the promoter of the Killin (KLLN) gene, also located on chromosome 10q23
  - Mutations in succinate dehydrogenase (SDH) gene, subunits B and D
  - Germline PIK3CA and AKT1 mutations
- Characteristic features:
  - Enlarged cranium
  - Benign tumors on face, hands and feet
  - Breast, renal and thyroid malignancies

Clinical Manifestations

- Mucocutaneous
  - Distinctive and common manifestation of Cowden syndrome
  - Trichilemmomas, acral keratoses, facial papules
- Breast
  - Breast cancer = most common malignancy in Cowden syndrome
  - Early onset (third and fourth decades of life)
  - Lifetime risk = 25–50%
- Thyroid
  - Thyroid disease: incidence in >50% of patients
  - Risk of thyroid malignancy = 3–35%
  - incidence of non-medullary thyroid cancer (NMTC) = 70-fold increased

- Genitourinary
  - Endometrial Cancer
  - Renal Cell Cancer
- Gastrointestinal
  - Gastric, duodenal, colon polyps
  - Colorectal cancer
- Other manifestations
  - Macrocephaly
  - Mental retardation
  - Immune dysfunction
  - Vascular tumors

Diagnosis

- Thorough family history
- Genetic testing for PTEN, KLLN or other associated gene mutations

Management

- Genetic counselling
- Cancer surveillance:
  - Annual physical exam (PE): with particular attention to skin, breast and thyroid
  - Thyroid ultrasound: beginning at age 18
  - Colonoscopy: at age 35, then every 5 years
  - Consider renal ultrasound by age 40

Treatment

- Therapy based on organ system(s) involved

Carney Complex I

Epidemiology

- Approximately 600 cases reported to date
- Incidence: Men:Women = 1:1
- Mean age at diagnosis = 20 years

Genetics

- Germline mutation in PRKAR1A gene on chromosome 17q22–q24; codes for the type 1α regulatory subunit of protein kinase A
  - Other associated mutations: PDE11A gene mutation; involved in cAMP signaling
- Autosomal dominant (AD) inheritance; can also occur sporadically
- Characteristic features:
  - Multiple endocrine disorders: Cushing syndrome, adrenocortical hyperplasia, acromegaly, thyroid gland tumors (often WDTC= "well differentiated thyroid cancers")
  - Other features: Atrial myxomas, schwannomas, osteochondromyxomas, pigmented skin/mucosa lesions

Presentation

- Variable:
  - Cushing's
  - Acromegaly
  - Thyroid gland tumors
  - Other lesions (see characteristic features)
- Numerous pigmented lesions (lentigenes, blue nevi), noted during adolescence

Diagnosis

- Detailed patient history with identification of 2 or more of the following: (◘ Table 6.18)
- Genetic testing = **gold standard** for diagnosis:
  - PRKAR1A or PDE11A mutations
- Echocardiogram:
  - To detect cardiac myxoma = **life-threatening condition!**
- Biochemical analysis:
  - Hormones: cortisol, insulin-like growth factor, prolactin.

◘ **Table 6.18** Diagnostic features of Carney complex I

Endocrine abnormalities	Non-endocrine abnormalities
Primary pigmented nodular adrenocortical disease (PPNAD) Thyroid tumors Acromegaly	Cardiac myxomas Lentiginosis Multiple Blue Nevi Testicular tumors Schwannoma Osteochondromyxoma Skin myxoma

Treatment

- Treatement directed toward specific symptoms:
  - Cardiac myxoma requires open heart surgical removal
  - Pituitary adenoma → transphenoidal resection
  - thyoid cancer (typically well-differentiated) → Thyroidectomy ± lymph node dissection

6.3.5 Guidelines

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6.4 Anatomy and Physiology of the Parathyroid Gland

F. Billmann

6.4.1 Anatomy

- 4 Parathyroid glands (PG)

Localization

- Variable (embryological):
  - Lower PG: Posterior to the inferior pole of the thyroid gland, medial and anterior to the recurrent laryngeal nerve; wide variability.
  - Upper PG: posterior to the superior pole of the thyroid gland, lateral and superior to the recurrent laryngeal nerve (1 cm around the junction of the inferior thyroid artery and recurrent laryngeal nerve); relatively constant
  - approx. 90% of the PGs in "normal position

Blood Supply

- Inferior thyroid artery (A. thyroidea inferior)
- Variations = A. thyroidea superior/A. thyroidea ima

6.4.2 Physiology (Fig. 6.4)

Parathormone (PTH)

- Production + distribution by PG
- Function: Regulation of calcium-phosphate balance together with vitamin D_3/calcitonin (thyroid gland)
- PTH receptors:
  - Type 1: Bones, kidneys, intestines
  - Type 2: brain, intestine

Calcium (Ca++)

- Functionally active calcium (Ca^{++}) = non-albumin-bound Ca^{++} = ionized Ca^{++}
- "CaSR" = Calcium Sensing Receptor (PG cells): Binding site for Ca^{++}
- Regulation of calcium = central to cell signaling pathways, cranial nerve function, muscle function, bone metabolism

Control Loop (Negative Feedback)

- Accurate control of calcium levels:
  - Hypocalcemia → lower Ca^{++} receptor binding → increase in PTH secretion.
  - Vitamin-D_3-receptor (PG cells): Vitamin D_3 deficiency → secretion of PTH
  - PTH → PTH receptor → bone resorption + absorption from small intestine + reabsorption in kidney → increase Ca^{++} level
  - Increase in Ca^{++} level → higher Ca^{++} receptor binding → reduction in PTH secretion

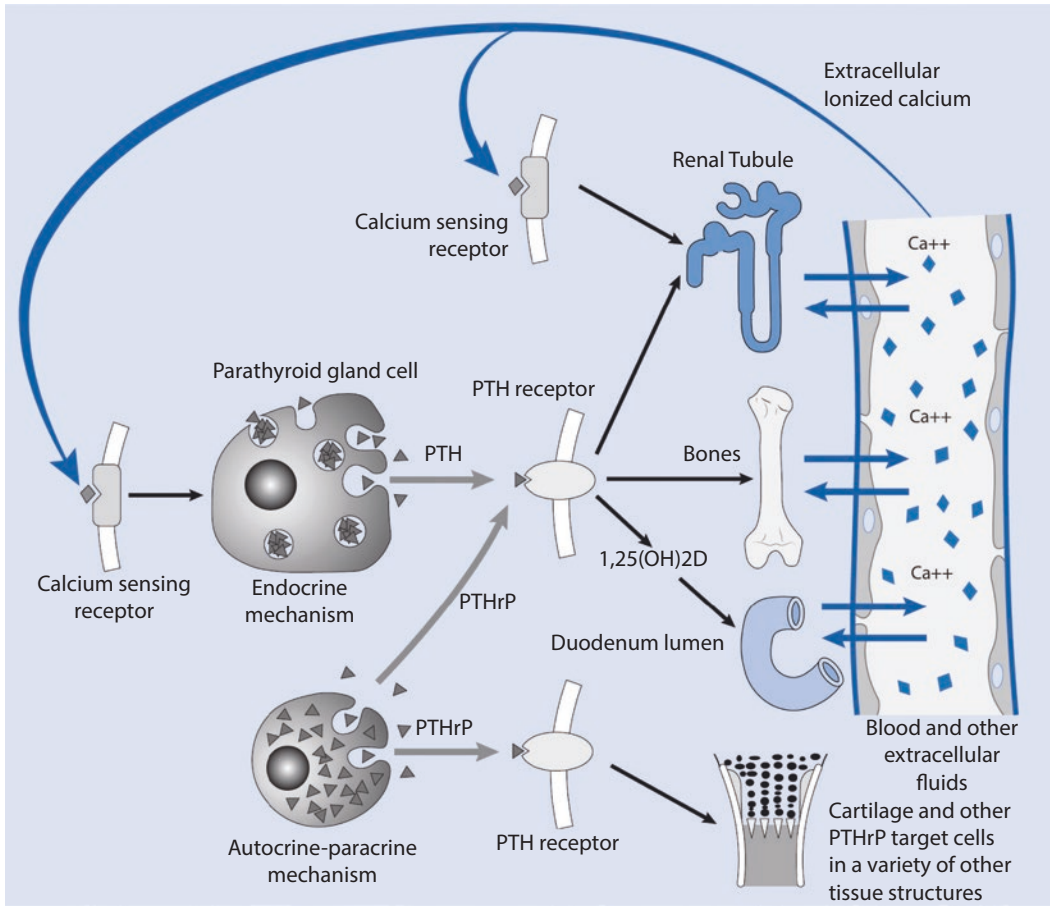


Fig. 6.4 Regulation of the calcium balance

Normal Levels of Calcium Metabolism

- Serum PTH: 1.5–6.0 pmol/L (12–72 ng/L)
- Serum calcitonin: <2.8 pmol/L (<10 ng/dL)
- Serum calcium (total): 2.15–2.75 mmol/L
- Serum calcium (ionized): 1.0–1.5 mmol/L
- Urine calcium: 4.02–4.99 mmol/L in 24-h urine
- Serum phosphate: 0.84–1.45 mmol/L

6.5 Diseases of the Parathyroid Gland

F. Billmann

6.5.1 Benign Parathyroid Diseases

Primary Hyperparathyroidism (pHPT)

Key Points

- Most common cause of hypercalcemia; prevalence = 1–5/1000 (increasing with age)
- Often asymptomatic

- Elevated/unexpected normal parathyroid hormone + elevated ionized serum calcium
- Imaging diagnosis for localization before planned parathyroidectomy
- Indication for parathyroidectomy:
  - Symptomatic pHPT patients
  - Asymptomatic pHPT patients with compliance with the guidelines (■ Table 6.20)
  - Monitoring impossible
- Monitoring without therapy = in asymptomatic patients (guidelines) = obligation of regular controls (progression of the disease)

Definition

- One or more hyperactive PG
- Continuous hypersecretion of PTH

Forms

Sporadic pHPT

- Solitary adenoma (65–85%)
- Multiglandular hyperplasia (10–30%)
- Double adenoma (5–10%)
- Carcinoma (approx. 0.1%)

Hereditary pHPT (► Sect. 6.3)

- Multiple endocrine neoplasia type 1 (MEN 1)
- Multiple endocrine neoplasia type 2A (MEN 2A)
- Neonatal severe hyperparathyroidism (NSHPT; mutation CaSR, chromosome 3q13.3–q21)
- Hyperparathyroidism jaw tumor syndrome (HPT-JT, mutation parafibromin, chromosome 1q25)

Epidemiology

- Prevalence: 1 per 1000 (USA), 3 per 1000 (Norway), 4.3 per 1000 (Sweden), 2–4 per 1000 (Germany)
- Incidence: 27–30 new cases/100,000 population years (increases with age)
- Third most common endocrinological disease (after thyroid disease, diabetes mellitus)
- Women:Men = 3:1
- Average age = 55 years

Caution

Radioiodine therapy = no pHPT incidence increase with currently used radioiodine doses.

Symptoms

- Associated with hypercalcemia (not with elevated PTH)
- Mostly few symptoms/asymptomatic (truly asymptomatic patients <5%)
- Affected systems ■ Table 6.19

■ **Table 6.19** Symptoms of pHPT

Bones and muscles	Muscle weakness Myalgia Bone pain Osteoporosis/penia Osteitis fibrosa cystica Brown tumor
Kidneys	Kidney stones/renal colic Nephrocalcinosis Dehydration/thirst Polyuria/oliguria/anuria Renal insufficiency
Neuropsychiatry	Concentration problems Poor memory Restlessness Depression Confusion Dementia/Paranoia Ataxia Hyporeflexia Coma
Gastrointestinal tract	Nausea/vomiting Abdominal pain Anorexia Ulcer disease Pancreatitis Constipation Weight loss
Cardiovascular system	Hypertension Vascular calcifications QT interval reduction Bradycardia Myocardial block Lethal arrhythmias
Other	Visual changes Linear keratopathy (corneal calcification) Conjunctivitis Pruritus

Caution

Hypercalcemic crisis:

- Metabolic emergency (calcium >3.5 mmol/L)
- Symptoms: Dehydration, metabolic encephalopathy (stupor to coma), gastrointestinal symptoms (distended abdomen, bloating, constipation, vomiting, ileus), renal (acute renal failure), cardiovascular symptoms (tachyarrhythmia)
- Intensive medical treatment (rarely haemodialysis necessary)

Diagnosis

- 2 stages (laboratory diagnosis + imaging diagnosis)

Laboratory Diagnosis (Fig. 6.5)

- Goal = Confirmation of the pHPT
  - In serum: Ionized Ca^{++} + PTH + Vitamin D
  - In urine: Ca^{++} + phosphate + creatinine
  - In 24-h urine: Ca^{++} + phosphate + creatinine (ratio creatinine clearance/Ca^{++} clearance)
  - 2 independent determinations (eventually after vitamin D deficiency treatment)
- Strategy:
  - PTH high/unusually normal = pHPT until proven otherwise.
  - Phosphate, electrolytes, creatinine, 24-h urine: calcium and phosphate: to exclude Differential diagnoses
  - s. Normal levels (► Sect. 6.4.2)

Diagnostic Imaging

- Goal = Localization: Essential for minimally invasive surgery (= no exploration of all 4 parathyroid glands)
- Standard = Ultrasound (US) + Scintigraphy
- Ultrasound (linear transducer 7.5–15 MHz)
  - Adenoma: Hypoechogenic, peripheral blood circulation (Doppler)
  - Possibility of US-guided fine needle aspiration (FNA)
- Scintigraphy: $^{99\ m}$Tc-Sestamibi-Scintigraphy
  - SPECT (Single Photon Emission Computed Tomography): Tomographic examination
  - Dual $^{99\ m}$Tc- and ^{123}I-scintigraphy: contrast enhancement by subtraction imaging (subtraction of thyroid uptake)
- 4D-CT/MRI (not first-line method)
- Fusion possible: SPECT + CT, SPECT + MRT, PET + CT
- Invasive investigations (not first-line methods): Selective vein sampling; Selective angiography; Fine needle aspiration (FNA)

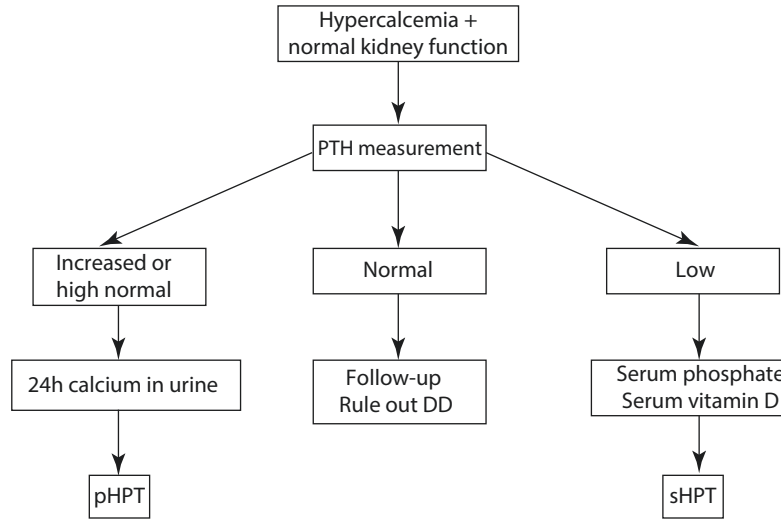


Fig. 6.5 Positive diagnosis of primary (pHPT) and secondary hyperparathyroidism (sHPT). *DD* differential diagnosis

Genetic Workup

- In young patient <40 years with pHPT + multiglandular disease + family history or syndromic signs

Ectopic Parathyroid Glands

- Ectopic location = 4–16% of cases
- Necessity of a standardized neck exploration (localization OP technique)
- If adenoma not identifiable by exploration: abort surgery + need for further imaging (MRI, CT, SPECT, selective vein sampling)

Differential Diagnosis (◘ Fig. 6.6)

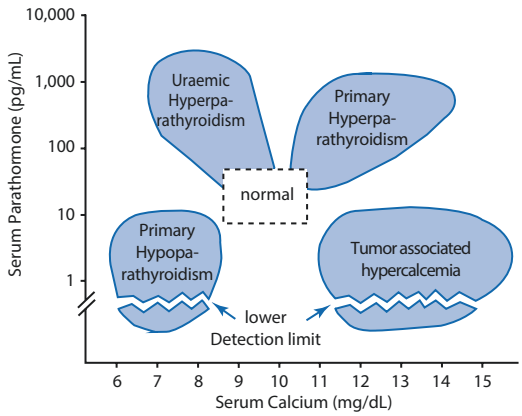
Secondary (sHPT), Tertiary HPT (tHPT) (See Below)

Familial Hypocalciuric Hypercalcemia (FHH)

- Mutation of CaSR = loss of function of the receptor (kidney and parathyroid gland) leads to a reduction in calciuria
- Findings: hypercalcemia, PTH normal or high, 24-h calciuria decreased, Ca^{++}/Crea clearance <0.01

Milk-Alkali Syndrome

- Caused by an excess of easily absorbable alkalis (e.g. bicarbonates) + calcium (e.g. milk)



◘ **Fig. 6.6** Laboratory test results in hyper- and hypoparathyroidism

- Findings: hypercalcemia, metabolic alkalosis, decreased PTH, impaired renal function

Lithium Therapy

- Especially psychiatry: depression, mania, schizophrenia, cluster headaches
- Elevated PTH, increased bone turnover

Malignancy-Associated Hypercalcemia

- Calcium release by osteodestructive metastases of a malignant tumor or by tumor production and release of a parathyroid hormone-related peptide (paraneoplastic; PTHrP)
- Findings: Elevated tumor markers, elevated PTHrP and calcitriol

Granulomatous Disease

- e.g. sarcoidosis, berylliosis, tuberculosis, histoplasmosis
- Renal involvement = increased hydroxylation of vitamin D = hypercalcemia (increased absorption and reabsorption of calcium)
- Findings: hypercalcemia, PTH decreased, 24-h calciuria decreased

Endocrinopathies

- e.g. hyperthyroidism, adrenal insufficiency, pheochromocytoma, VIPoma
- Increased bone turnover
- Findings: Elevated calcium, low PTH

Drugs

- e.g. thiazides, vitamin D, calcium, vitamin A intoxication
- Elevated PTH, increased bone turnover.

Immobilization, Bed Rest

- Lack of stress on the musculoskeletal system = increased osteoclastic activity = hypercalcemia

Therapy

Indications for Medical Therapy

- OP criteria not met
- Patient not fit for anaesthesia/surgery
- Monitoring absolutely necessary: Ca^{++} + creatinine + PTH control every 6–12 months (once PTH target level is reached).
- Therapeutic options:

- Hormonal therapy (especially postmenopausal women): e.g. raloxifene 60 mg daily
- Bisphosphonates (e.g. alendronate): 70 mg once a week
- Calcimimetic (e.g. Cinacalcet): Starting at 30 mg/day (increase until PTH goal is reached).
- Dietary recommendations: Sufficient water intake (at least 2–3 L/day), calcium intake <1000 mg/day.

Indications for Surgical Therapy

- Symptomatic pHPT = always OP indication
- If monitoring is not desired/not possible
- For neurocognitive/neuropsychiatric symptoms
- Asymptomatic pHPT (75% of patients): Early surgery if OP criteria are met (■ Table 6.20), for prophylaxis of morbidity/mortality
- Multiglandular hyperplasia: persistence and recurrence rate high; sporadic or in the context of MEN; therapy = subtotal parathyroidectomy (± cryopreservation)

■ **Table 6.20** Criteria for determining the indication for surgery in asymptomatic pHPT patients. (According to Wang and Udelsman 2007 and 2016 AAES guideline)

Measured level	Criteria for surgery	Monitoring without surgery
Serum calcium (above the upper normal level)	>1.0 mg/dL (0.25 mmol/L) above the upper normal level	Annual
24 h urine calcium	>400 mg/day (>10 mmol/day) or nephrocalcinosis on imaging	Annual
Creatinine clearance	Reduced <60 mL/min	Annual
Bone density	T-score < 2.5 (lumbar, femoral, or wrist), and/or fracture risk	Every 1–2 years (lumbar, femoral and wrist)
Age	<50 years	–

- Ectopic PG (up to 4–16% of patients): Treatment success depending on treatment algorithm (■ Fig. 6.7)

Guideline Criteria for Determining the Indication for Surgery (■ Table 6.20)

- Progressive disease (= only 25% of asymptomatic patients)
- Weighing morbidity/mortality of surgery vs. expected benefit
- If monitoring is not desired/not possible
- For neuropsychological/neuropsychiatric symptoms
- Caution: in Germany only S1 guideline

Operative Therapy Principles

- Bilateral neck exploration
  - Indication: No definite localization, or suspicion of 4-gland hyperplasia
  - Principle = exploration/visualization of all 4 parathyroid glands
  - Resection of enlarged, abnormal TG (based on morphology)
  - Intraoperative aids: Intraoperative PTH measurement, intraoperative frozen section, localization by gamma probe
- Minimally invasive parathyroidectomy:
  - Current method of choice
  - Only if positive localization (sonography, sestamibi scan)
  - Intraoperative aids: Intraoperative PTH measurement, intraoperative frozen section, localization by gamma probe

Surgical Therapy

- Need for careful hemostasis: "Only a dry situs guarantees the identification of the parathyroid glands"
- Advantage operative vs. medical: improvement of bone density and mass: back to baseline (lasts up to 10 years postoperatively)
- Early: prevention of cardiovascular morbi/mortality

- If 3 or more PGs are enlarged or PTH does not decrease adequately after removal of

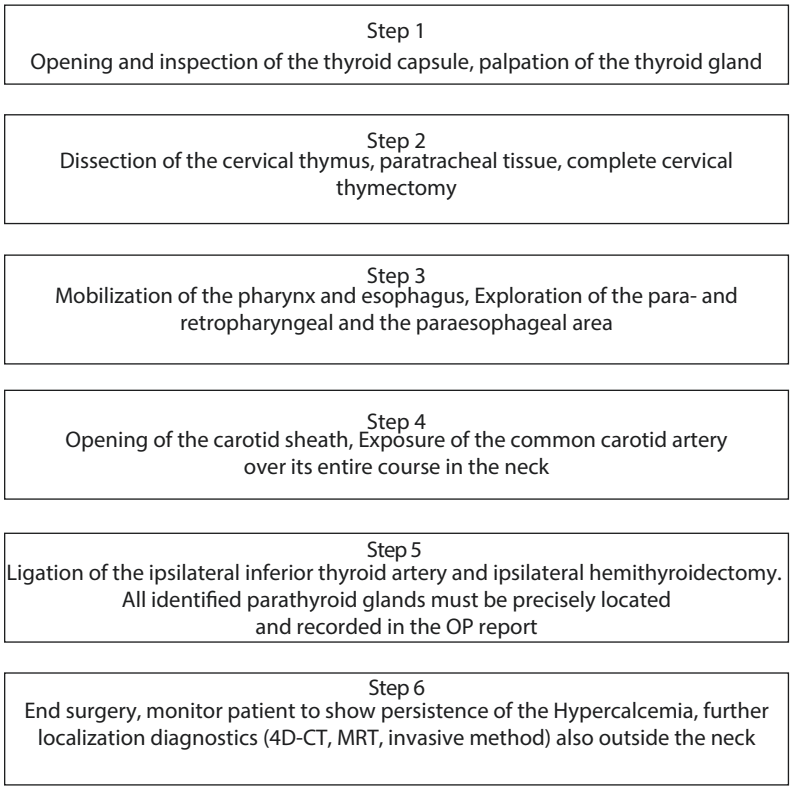


Fig. 6.7 Treatment algorithm for intraoperative identification of missing parathyroid glands (failure to find a PG). (After Wang and Udelsman 2007)

the first PG = 3½-gland resection or total parathyroidectomy + autotransplantation of part of the most inconspicuous PG into sternocleidomastoid/brachioradialis muscle

- Postoperative aftercare
  - Postoperative calcium controls (1 time daily)
  - Search for clinical signs of hypocalcaemia (see "Hypoparathyroidism" below)
  - Eventual substitution of temporary hypocalcemia:
    - Calcium per os 1.5–3 g/day +1,25-dihydroxy vitamin D_3 0.5–2 µg/day
    - i.v. calcium administration in case of persisting symptoms
  - Before discharge: PTH determination + videolaryngoscopy

Surgical Procedure

Bilateral Neck Exploration

- General anaesthesia (rarely locoregional anaesthesia possible)
- Extension of the cervical spine, roll or vacuum mattress under the shoulders
- Access: 4–5 cm Kocher collar incision, in skin fold approx. 1 finger width above the jugular notch (preoperative marking)
- transection of the platysma muscle, formation of a subplatysmal flap (cranial retraction by suture)
- Opening of the linea alba and retraction of the strap muscles laterally
- Start surgery on the side of the localization (if negative localization, start on the right side)
- Visualization of the thyroid gland, ligation and transection of the middle thyroid veins, mobilization of the thyroid gland anteromedially
- Identification and sparing of the recurrent laryngeal nerve and inferior thyroid artery
- Lower PG = usually in the cervical thymus; upper PG = usually in a 1-cm radius around the point where the

recurrent laryngeal nerve inserts into the cricothyroid membrane.
- Removal of the conspicuous PG (+ intraoperative PTH determination + frozen section examination of the specimen)

Surgical Procedure
Minimally Invasive Open Parathyroidectomy
- Local/regional anaesthesia/general anaesthesia
- Moderate extension of the cervical spine
- Access: 2–4 cm Kocher collar incision, in skin fold approximately 1 finger width above jugular notch (preoperative marking)
- transection of the platysma muscle + formation of a subplatysmal flap (cranial retraction by suturing)
- Opening of the linea alba + retraction of the strap muscles to the lateral side
- Targeted preparation in the area of localization
- Mobilization of the thyroid gland (transection of the middle thyroid veins not necessary)
- Identification + protection of the recurrent laryngeal nerve and the inferior thyroid artery
- Visualization of the conspicuous PG, mobilization, ligation of the blood supply and excision of the adenoma
- Intraoperative PTH measurement

Surgical Procedure
Minimally Invasive Video-Assisted Parathyroidectomy (MIVAP)
- General anesthesia
- Thyroid positioning: Moderate extension of the cervical spine
- Access: 15 mm transverse neck incision, approx. 2 cm above the jugular notch (preoperative marking); lateral access possible in case of reoperation
- transection of the platysma muscle
- Opening of the linea alba over 3 cm + retraction of the strap muscles to the side
- Targeted dissection in the area of localization, mobilization of the thyroid gland + transection of the middle thyroid veins
- Insertion of a 5 mm 30° endoscope through the access and purely endoscopic continuation of the operation
- 2–3 surgeons required for surgery: Surgeon, first assistant (laparoscope guidance + suction), second assistant (holding the retractor).
- Identification + protection of the recurrent laryngeal nerve and the inferior thyroid artery (easier due to laparoscopic magnification effect)
- Visualization of the conspicuous PG, mobilization, ligation of the blood supply and exheresis of the adenoma
- Intraoperative PTH measurement

Complications (Section "Postoperative Complications")

Reoperation
- Indications
  - pHPT persistence: persisting hypercalcemia after neck exploration/recurrence of hypercalcemia within 6 months of initial surgery.
  - pHPT recurrence: recurrence of hypercalcemia later than 6 months after initial surgery
  - Causes of persistence/recurrence ◘ Table 6.21
- Preoperative strategy ◘ Table 6.22
- Surgical strategy ◘ Table 6.23

Table 6.21 Causes of pHPT persistence or recurrence

pHPT Persistence	Failure to identify or resect the PG adenoma Failure to identify or resect all adenomas or 4-gland hyperplasia Inadequate subtotal resection of a 4-gland hyperplasia Subtotal resection of a parathyroid adenoma Residual or metastatic parathyroid carcinoma Parathyromatosis Inadequate percutaneous ablation
pHPT Recurrence	Recurrent growth of hyperplastic PG tissue (especially familial pHPT) Recurrent growth of autotransplanted PG tissue Recurrence of PG carcinoma or metastatic PG carcinoma Parathyromatosis

Table 6.22 Preoperative strategy in case of reoperation

1. Reconfirmation of the diagnosis	Complete medical history and clinical examination again Repetition of laboratory diagnosis Exclusion of a differential diagnosis (see Differential diagnoses, Fig. 6.6)
2. Re-evaluation of the old localization diagnosis, operation report, pathology findings	(Essential information for planning the surgical strategy and the possible location of the adenoma)
3. Planning of additional localization examinations	(Only if 1. and 2. did not provide further information) Ultrasound + Sestamibi 4D CT/MRI Selective vein sampling Selective arteriography

Table 6.22 (continued)

4. Discussion of the operative risk with the patient	Injury to recurrent laryngeal nerve during reoperation 4–20% (preoperative laryngoscopy); if bilateral, need for tracheostomy Transient/permanent postoperative hypocalcemia (transient: 10–20%, permanent: 5–10% after reoperation)

Table 6.23 Surgical strategy for reoperation

1. Selection of an adequate time window and adequate access for the reoperation	Ideal time window: within the first week or 3 months after initial surgery Optimal strategy = targeted minimally invasive re-exploration (reducing the risk of laryngeal recurrent nerve injury and postoperative hypocalcaemia) Lateral access ("back door"): due to adhesions in the central neck Planning of the surgery on the basis of the localization diagnosis, the operation and pathology report
2. Exploration of ectopic and unusual PG localizations	Most unidentified PG (40%) are found in normal anatomical localization Fig. 6.7 in the other cases
3. Consider intraoperative localization methods	Intraoperative PTH measurement Intraoperative ultrasound examination Gamma probe examination (with radioactively labelled sestamibi)

Secondary Hyperparathyroidism (sHPT)

Key Points

- Renal etiology = 90% of patients with sHPT
- Mostly asymptomatic
- sHPT: elevated parathyroid hormone + low/normal ionized serum calcium; **caution:** differential diagnoses
- Primary therapy = conservative, medical
- Indications for surgical therapy:
  - Failure of conservative therapy
  - Hypercalcemia
  - Normocalcemia, if PTH > tenfold elevated, refractory hyperphosphatemia, advanced renal osteopathy, spontaneous fractures, calciphylaxis

Definition

- Compensatory hypersecretion of PTH in response to hypocalcemia

Etiology (Table 6.24)

- Always outside the PG (= malfunction of one/several components of the calcium control loop)

Renal sHPT

- 90% of patients with sHPT
- Renal insufficiency → increased phosphate level → inhibition of renal calcitriol production → decreased serum Ca^{++} (hypocalcaemia) → stimulation of PTH production and release
- Renal insufficiency → hyperphosphatemia, acidosis, hyperuricemia → inhibition 1α-hydroxylase → hypocalcemia → compensatory hypersecretion of PTH + hyperplasia of PG

Extrarenal sHPT (= Differential Diagnosis) (Table 6.23)

Symptoms

- Initially no symptoms
- Symptoms of pHPT (see above "Primary hyperparathyroidism")
- Extraosseous calcifications (perarticular with gout-like symptoms, vessels, kidneys, myocardium)
- Calciphylaxis: extreme form of extraosseous calcifications (vessels, subcutis) → vasculitis + paniculitis → necrosis

Diagnosis (Fig. 6.5)

- Same as in pHPT (see above "Primary hyperparathyroidism")

Therapy

Conservative/Medical = Primary Therapy of sHPT

- Compensation of hyperphosphatemia: diet (reduction of intake) + phosphate binders + withdrawal by dialysis
- Calcium administration as required
- Vitamin D_3 substitution
- Calcimimetics (Cinacalcet): Receptor blockade of parathyroid cells (= prevention of PTH release).

Surgical Therapy

- Indication for surgery: Only 5% of patients with sHPT
- Indications:
  - Failure of conservative/medical therapy
  - Hypercalcemia = absolute indication for surgery
  - Normocalcemia and:
    - PTH > tenfold above the norm
    - Hyperphosphatemia resistant to therapy with extraosseous calcifications or
    - Advanced renal osteopathy or
    - Bone pain refractory to treatment or
    - Spontaneous fractures or
    - Calciphylaxis
- Standard operations
  - Subtotal parathyroidectomy: Smallest PG is left in situ with intact circulation (recurrence risk = 16%)
  - Parathyroidectomy + simultaneous orthotopic/heterotopic autotransplantation

Table 6.24 Differential diagnosis of sHPT

Gastrointestinal causes	Inadequate diet	Food intolerance Dietary restriction Phytic acid (legumes, cereals, oilseeds)
	Malabsorption	Celiac disease Pancreatic diseases (exocrine pancreatic insufficiency) Inflammatory bowel disease Cystic fibrosis (mucoviscidosis) Gastric bypass surgery Cortisone therapy Age
Vitamin D-associated causes	Lack of sunlight	Dark skin in northern latitudes Cultural habits, clothing
	Inadequate diet	Vegan or lactovegan diet
	liver or biliary disease	Malabsorption, 25-hydroxylase deficit. Liver cirrhosis Cholestasis
	Antiepileptic therapy	Modified vitamin D metabolism
Vitamin D-dependent osteomalacia		Hypophosphatemia
Nephrological causes	Chronic kidney disease	Hyperphosphataemia 1α-hydroxylase deficiency: Decreased 1,25-dihydrovitamin-D Reduction of PTH clearance: (C-terminal) PTH resistance
Cellular/tissue-associated causes	Bones	Growth
Genetic causes	Pseudohypoparathy-reoisism	Abnormal PTH receptor G protein/PTH resistance(s)
"Hungry Bone Syndrome"		
Bisphosphonate therapy		
Lactation, postlactation period		
Metastatic prostate carcinoma	Kidneys	Diuretics Increased natriuresis Idiopathic hypercalciuria
	Soft Tissue	Rhabdomyolysis: calcium deposition, hyperphosphatemia, acute renal failure. Acute pancreatitis Sepsis

Postoperative Follow-Up: Like pHPT (See Above "pHPT")

Surgical Procedure
Parathyroidectomy with Simultaneous Orthotopic/Heterotopic Autotransplantation

- General anaesthesia (rarely locoregional anaesthesia possible)
- Extension of the cervical spine, roll or vacuum mattress under the shoulders
- Bilateral neck exploration (see above)
- A portion of the least modified PG is divided into small, 1-mm pieces = implantation into the brachioradialis muscle of the non-shunt-bearing forearm; clip marking
- Thymectomy + central LK dissection (due to possibility of supernumerary PGs).

Tertiary Hyperparathyroidism (tHPT)

Definition

- PG function escaping the negative feedback within the framework of an sHPT
- Consequence of chronic sHPT (= PG hyperplasia):
  - Under-expression of CaSR
  - Reduction of vitamin D receptors

Etiology

- Chronic kidney disease (= most frequent cause)
- X-linked dominant hypophosphatemic rickets
- Autosomal dominant hypophosphatemic rickets

Therapy

- Always surgical therapy = parathyroidectomy + simultaneous orthotopic/heterotopic autotransplantation (see above "Surgical procedure")
- Postoperative follow-up like pHPT (see above "pHPT")

After kidney transplantation (= etiological treatment of sHPT)

- PG hyperplasia remains (= increased PTH secretion)
- Development of PTH-induced hypercalcemia in 1/3 of patients after kidney transplantation = risk for kidney transplant function!

Hypoparathyroidism

Epidemiology

- Incidence: Very controversial (especially for postoperative hypoparathyroidism)

Symptoms

- Symptoms of hypocalcemia:
  - Paresthesias
  - Muscle spasms (up to tetany) (Chvostek/Trousseau sign)
  - seizures (especially in acute hypoparathyroidism)
  - Chronic hypocalcemia: Mostly and long asymptomatic

Chvostek/Trousseau sign:

- Chvostek: contraction of facial muscles on tapping the facial nerve trunk (1 cm ventral to the ear lobe).
- Trousseau: carpopedal spasm (paw position) after inflation of a blood pressure cuff above systolic pressure for 3 min

Diagnosis

- Serum Ca^{++} + PTH levels

Etiology

- Intraoperative iatrogenic damage to the PG
  - Damage to PG blood flow
  - Unintentional parathyroidectomy
- Other: Developmental defect of parathyroid gland: autoimmune, genetic (e.g., mutation PTH gene).

Therapy

- Calcium + vitamin D (or vitamin D analogues)
- Thiazides: stimulation of renal calcium reabsorption
- In acute hypoparathyroidism (e.g. postoperative hypoparathyroidism): i.v. calcium and vitamin D administration
- PTH substitution in case of failure of other treatments

6.5.2 Parathyroid Cancer

Epidemiology

- Women:Men = 3:1
- Frequency peak: 40–60 years of age
- approx. 0.1–0.5% of HPT patients

Symptoms

- Symptoms of pHPT

Diagnosis

- Very high PTH levels
- Rarely preoperative diagnosis, mostly intraoperative (= infiltration of the tumor into the surrounding area)/postoperative diagnosis (= histology)

Therapy

- Always surgical therapy
  - Parathyroidectomy + ipsilateral hemithyroidectomy
  - En bloc resection of the infiltrated soft tissues
- Systematic ipsilateral lymphadenectomy
- Postoperative follow-up like pHPT (see above "pHPT")
- Palliative approach: chemotherapy ± radiotherapy

6.5.3 Guidelines

Bilezikian JP, Brandi ML, Eastell R et al. (2014) Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab 99:3561–3569.

Wilhelm SM, Wang TS, Ruan DT et al. (2016) The American Association of Endocrine Surgeons Guidelines for definitive management of primary hyperparathyroidism. JAMA Surg 151:959–968.

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6.6 Anatomy and Physiology of the Adrenal Gland

F. Billmann

6.6.1 Embryology

- Each adrenal gland = 2 different glands in one capsule
  - Adrenal cortex (cortex)
  - Adrenal medulla

Aberrant adrenal tissue is possible along the migratory route of the urogenital crest.

Extraadrenal chromaffin cells: Persistence of part of these cells = Zuckerkandl organ (usually left of aortic bifurcation) + possibly paraganglion.

6.6.2 Anatomy

Topographic Anatomy

- Pairs gland (endocrine cells)

Location

- Retroperitoneal position
- Superomedially from the upper pole of the respective kidney
- Right adrenal gland:
  - Often contact with right crus of the diaphragm
  - Close to inferior vena cava
- Left adrenal gland:
  - Between kidney and aorta
  - Contact/relationship with pancreas tail + splenic artery

Adrenal glands = usually not directly visible in the retroperitoneum. Therefore dissection + mobilization of the adjacent organs necessary.

Blood Supply

- Arterial blood flow:
  - Branches of the inferior phrenic artery + renal artery + aorta
  - Right adrenal gland: superior + inferior adrenal arteries
  - Left adrenal gland: middle + inferior adrenal arteries

- Venous drainage:
  - Right adrenal vein: drainage into inferior vena cava (short vein)
  - Left adrenal vein: drainage into the left renal vein (variant: directly into the inferior vena cava)
- Lymphatic drainage:
  - Lymphatic plexus of the adrenal gland
  - Drainage: Paraaortic + renal lymph node groups

Innervation

- Cortex: No direct innervation
- Medulla: Through preganglionic sympathetic nerves
- No parasympathetic component

Histological Anatomy

Adrenal Cortex

- 3 zones:
  - Zona glomerulosa (outer zone)
  - Zona fasciculata (intermediate zone)
  - Zona reticulata (inner zone)

Adrenal Medulla

- 10% of the weight of the adrenal gland
- Cells: Content = catecholamines (fix chromium salts = chromaffin cells).

Positional Relationships

- Right adrenal gland:
- Posterior: right diaphragmatic crus, diaphragm
  - Anterior: right lobe of the liver
  - Medial: Inferior vena cava (medial and anterior)
  - Cranial: diaphragm (cranial and posterior)
  - Caudal: Right renal upper pole
- Left adrenal gland:
  - Posterior: Left diaphragm, kidney
  - Anterior: peritoneum from the bursa omentalis (further: stomach, spleen)
  - Medial: left inferior phrenic artery, left gastric artery
  - Lateral: Left kidney
  - Cranial: diaphragm (cranial and posterior)
  - Caudal: pancreatic tail and splenic artery

6.6.3 Physiology

- Adrenal glands: Synthesis + secretion of 2 groups of hormones:
  - Steroid hormones (adrenal cortex)
  - Catecholamines (adrenal medulla)

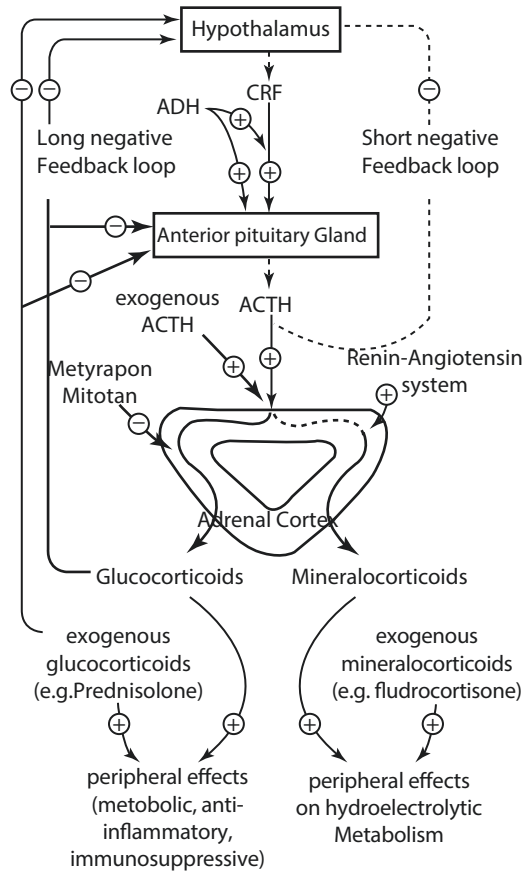
Steroid Hormones

Glucocorticoids

Effects of Glucocorticoids

Regulation (◘ Fig. 6.8)

- On almost all organ systems of the human body
- Alteration of the metabolism of proteins, lipids, carbohydrates: increase of blood sugar



◘ Fig. 6.8 Feedback regulation of glucocorticoid production and secretion in humans

- Preservation of intravascular volume, blood pressure
- Sensitization of β-adrenergic stimulation.
- Anti-inflammatory and immunosuppressive effect
- To summarize: Glucorticoids = response to stress
  - Short-term exposure = anabolism
  - Long-term exposure = catabolism

10–15% of cortisol in plasma unbound = active.

Mineralocorticoids

Effects of Mineralocorticoids

Regulation (■ Fig. 6.9)

- Regulation of water + electrolyte balance: expansion of intravascular volume

40% of aldosterone in plasma unbound = active.

Adrenal Sexual Steroids

Effects of Adrenal Sexual Steroids

- Regulation ACTH-dependent
- Other mechanisms (not yet fully understood)

Regulation

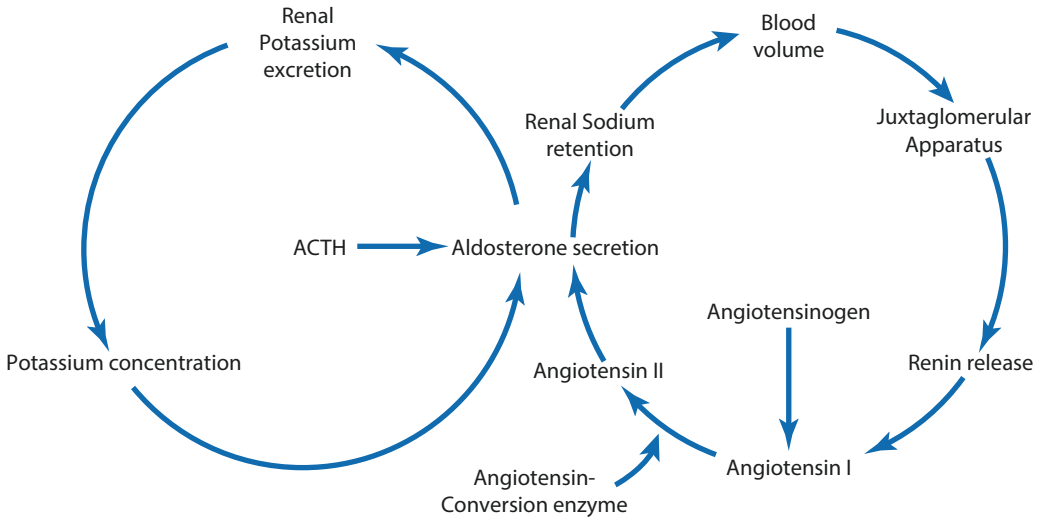
- In adults: Mild peripheral effects:
  - Development of secondary sexual characteristic features in men
  - female virilization
- During development:
  - development of the external male genitalia (vas deferens, epididymis, seminal vesicles, prostate)
- During puberty:
  - Development phallus, muscle mass, body hair

- Effects after peripheral transformation to testosterone
- Absence of androgens = development of female genitalia + vagina
- Adrenal gland = secondary source of secretion of sexual steroids (main source = gonads)

Catecholamines

Regulation

- Basal state: Low catecholamine secretion
- Autonomic sympathetic nervous system: stimulation = catecholamine secretion
- Activation of the autonomic sympathetic nervous system = response to stress
  - Physiological stress
  - Psychological stress



■ Fig. 6.9 Feedback regulation of mineralocorticoid production and secretion in humans

Effects of Catecholamines

- β-adrenergic effects:
  - Heart (β_1-receptors): Increase heart rate, increase contractility
  - Smooth muscle (uterus, bronchi, muscle vessels; β_2-receptors): Smooth muscle relaxation (= bronchodilation, increase muscle blood flow, etc.).
- α-adrenergic effects:
  - Vessels (skin, GI tract, etc.; α_1-receptors): Vasoconstriction
  - Presynaptic receptors (CNS; α_2-receptors): Reduction of sympathetic outflow

Action of the catecholamines

- Increase of blood supply and oxygen supply to brain, heart, muscle ("fight-and-flight response")
- Reduction of the supply to the other organs

6.7 Diseases of the Adrenal gland

F. Billmann

- In this chapter only adrenal diseases treated by surgery will be presented.

6.7.1 Primary Hyperaldosteronism (Conn Syndrome)

Definition

- Hypersecretion of aldosterone (► Sect. 6.6.3)
- Etiologies within or outside the adrenal gland

Etiopathogenesis

Etiologies

- Two main etiologies:
  - Unilateral aldosterone-producing adrenal adenoma (= Conn's adenoma) = 60%
  - Bilateral adrenal hyperplasia or idiopathic hyperaldosteronism = 40%
- Rare etiologies:
  - Unilateral primary adrenal hyperplasia
  - Adrenocortical carcinoma (aldosterone-producing)
  - Familial hyperaldosteronism
  - aldosterone-producing ovarian tumor

Pathogenesis (► Sect. 6.6.3)

Clinical Presentation

- Mostly mild/unspecific
- Most common symptoms:
  - Headache
  - Muscle weakness
  - Fatigue
  - Polydipsia, polyuria and nocturia
  - Arterial hypertension: Almost always, but mild (diastolic blood pressure usually <120 mmHg)

Diagnosis (See Algorithm ◘ Fig. 6.10)

Laboratory Adrenal Function Tests

- To confirm primary hyperaldosteronism

Caution

Discontinue all diuretics 2 weeks prior to blood sampling in cases of suspected hyperaldosteronism.

- aldosterone in plasma
- Plasma aldosterone/renin ratio

Aldosteronemia >20 ng/dL + plasma aldosterone/renin ratio > 30 (ng/dL:ng/mL/h); sensitive + specific in screening and diagnosis.

- Salt suppression test or 3-day sodium test: If aldosterone/renin not conclusive

Etiological Diagnosis

- To distinguish unilateral adenoma vs bilateral hyperplasia vs rare etiologies.
- Central to the decision-making process of therapeutic strategy:
  - Unilateral Conn's adenoma: surgery
  - Bilateral hyperplasia: non-surgical (medical) therapy

Diagnostic Imaging

- CT abdomen or MRI abdomen
- Visualization of a tumour/mass of the adrenal gland (suspicion of adenoma)

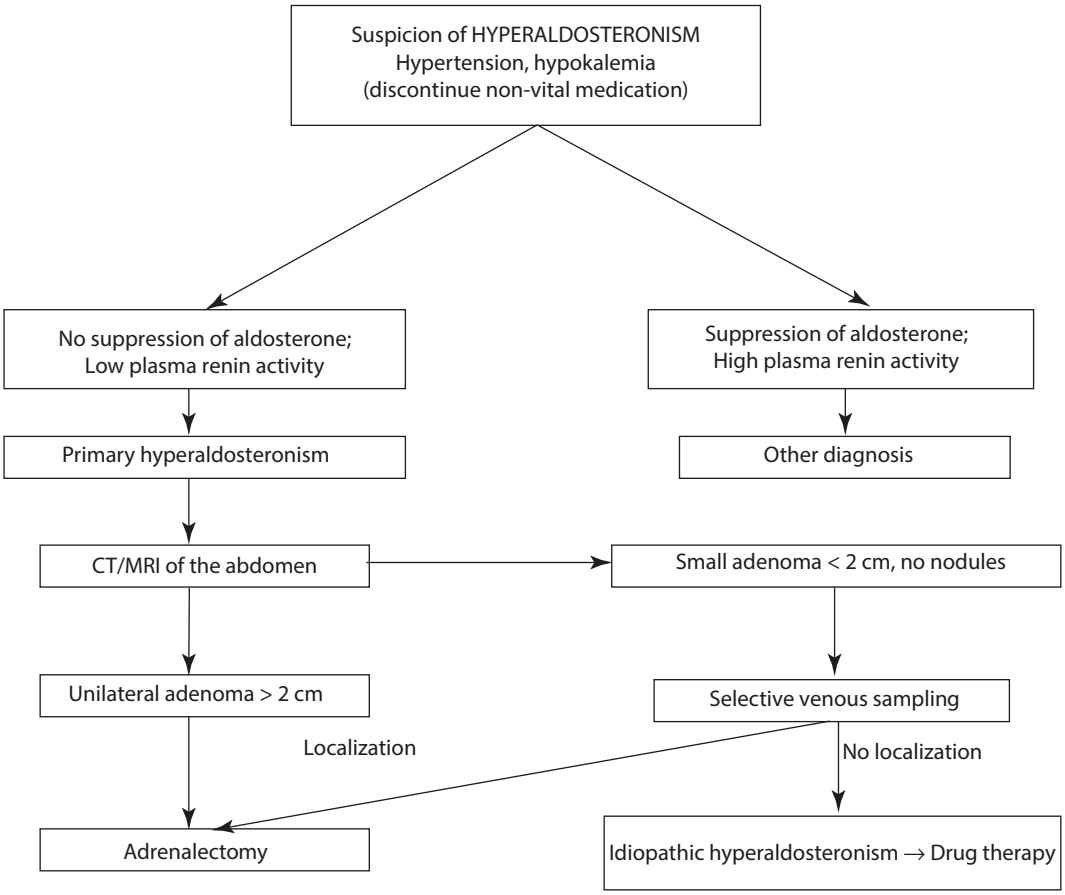


Fig. 6.10 Diagnostic algorithm in patients with suspected primary hyperaldosteronism

Caution
Adrenal tumour may also be nonfunctional (2–8%).

Selective Venous Sampling

- Invasive examination (only in centres with expertise)
- Localization (right/left) of aldosterone hypersecretion
- Indication:
  - None/Small adrenal tumor on imaging
  - Bilateral tumour of the adrenal gland
- Complications:
  - Adrenal Vein Thrombosis
  - Adrenal Infarction

Therapy

- Depending on etiology

Medical (Drug) Therapy

- In bilateral hyperplasia/idopatic hyperaldosteronism
  - Spironolactone (aldosterone antagonist) = therapy of arterial hypertension
  - Possible combination with other antihypertensive drugs

Surgical Therapy

- Indication = aldosterone-producing adenoma
- Preoperative Preparation:
  - Spironolactone: normalization hypertension
  - Potassium substitution: normalization of electrolyte/fluid balance
  - About 3–4 weeks
- Technique: (► Sect. 6.7.7) Minimal-invasive surgery

Aldosterone-producing adenomas = mostly small + benign: minimally invasive surgery = ideal modality.

- Low morbidity (fewer postoperative complications)
- Analogue success rate (vs. open)

Results

- Cure of hypokalemia: Almost all patients
- Cure of hypertension: 70% of patients (30% need further antihypertensives)

6.7.2 Cortisol-Producing Adrenal Adenoma

Definition

Cushing's Syndrome

- Hypercortisolism (overproduction of cortisol)
- Different etiologies (see below)

Exogenous steroid use = most common cause of Cushing's syndrome.

Cushing's Disease

- Hypercortisolism (overproduction of cortisol)
- Small pituitary adenoma: stimulation of the normal adrenal gland

ACTH Syndrome

- Ectopic ACTH secretion (outside the pituitary gland; 15% of Cushing's cases)
- Mostly malignant tumors (lung, pancreas, carcinoid tumor, thymoma)

Epidemiology and Etiology

- Exogenous steroid use (most common cause!)
- Endogenous causes:
  - Cushing's disease (pituitary adenoma, 70% of endogenous causes)
  - ACTH syndrome due to ectopic ACTH secretion (malignant tumors; 15% of endogenous causes)
  - Cortisol-producing adrenal disease (10–20% of endogenous causes).
    - Adrenal adenoma (50–60% of cases)
    - Bilateral adrenal hyperplasia (20–30% of cases)
    - Adrenocortical carcinoma (20–25% of cases)
  - Primary adrenal hyperplasia
  - Ectopic CRH (corticotropin releasing hormone) syndrome

Clinical Signs

- Weight gain = most common sign: Mostly on the trunk = centripetal obesity.
- muscular atrophy of the extremities
- Fat deposits on head ("moon face") + neck
- Dorsal kyphosis ("bull neck" = "buffalo hump")
- Abdominal striae (dark red, broad)
- Hypertonus
- Hyperglycemia

Subclinical Cushing's syndrome: Absent or poorly developed clinic, usually in patients with adrenocortical tumors.

Diagnosis

Laboratory Adrenal Function Tests

- To confirm Cushing's syndrome

Diurnal variation in cortisol secretion: cortisol high early morning, low evening: important for test interpretation.

Overnight Cortisol Suppression Test

- Most sensitive diagnostic test
- Principle: p.o. administration of 1 mg dexamethasone at 22 h or 23 h + cortisol determination in the blood the next morning at 8 h
- False negative = 3%; false positive = 30%.
- Interpretation:
  - Suppression (cortisol ≤5 µg/dL): Reliable exclusion of hypercortisolimsus
  - Absence of suppression: suspicion of hypercortisolism

Free Cortisol 24 h Urine Test

- In patients with suspected hypercortisolism in the suppression test
- Less sensitive, higher specificity
- Normal: Urinary cortisol <80 µg/day

48-h Low-Dose Dexamethasone Test

- For patients with ambiguous results
- Administration of 0.5 mg dexamethasone every 6 h for 2 days
- Determination of pre- and post-dexamethasone 24-h-cortisol in urine
- Interpretation:
  - No suppression: Autonomous cortisol secretion

Patients with adrenal incidentaloma: Always perform tests to exclude Cushing's syndrome.

Etiological Diagnosis

- To find the etiology

ACTH in Plasma

- ACTH secretion: diurnal variations parallel to cortisol (approx. 1–2 h earlier)
- Suppressed ACTH in patients with:
  - Adrenal Adenoma
  - Adrenocortical carcinoma
  - Cortisol-producing bilateral adrenal hyperplasia
- ACTH elevated/upper normal range: Cushing's disease
- ACTH markedly/very elevated: Ectopic ACTH secretion (tumor)

Therapy

- Depending on etiology

Surgical Therapy

Cushing's Disease

- Transsphenoidal pituitary adenoma resection (if resectable)
- Bilateral adrenalectomy:
  - In patients with no improvement after drug therapy + transsphenoidal pituitary adenoma resection.
  - In patients with end-organ insufficiency in relation to hypercortisolism.

Caution

In the case of bilateral adrenalectomy: perioperative steroid therapy (Table 6.25) + lifelong substitution.

Ectopic ACTH Secretion Syndrome

- Identification of the secreting tumor + treatment
- Bilateral adrenalectomy: Only if tumor irresectable or consequences of hypercortisolism not treatable with medication

Cushing's Syndrome in Adrenal Tumor (Adenoma or Carcinoma)

- Unilateral adrenalectomy (of the affected side)
- Adenoma: Almost all adenomas = resectable
- Adrenocortical carcinoma: resectable in only 25–35% of cases

Table 6.25 Recommendations for perioperative steroid therapy

Surgical stress	Example	Hydrocortisone Equivalency (mg).	Duration (days)
Small	Hernia surgery	25	1
Medium	Open cholecystectomy Revascularization of the lower extremity Segmental colon resection Total joint replacement Abdominal hysterectomy	50–75	1–2
Large	Pancreaticoduodenectomy Esophagogastrectomy Total proctocolectomy Cardiac surgery + cardiopulmonary bypass	100–150	2–3

Medical (Drug) Therapy

- Chemotherapy: Poor results
- In case of metastases/non-resectable tumor: drugs with direct effect on adrenal gland or on steroid synthesis (mitotane, aminoglutethimide, metyrapone, ketoconazole)

6.7.3 Pheochromocytoma

Definition

- Neuroectodermal tumor; from chromaffin cells of the adrenal medulla
- Treatable form of endocrine hypertension
- Secretion of catecholamines: symptoms
- High morbidity/mortality if not treated

Epidemiology

- Incidence = 0.005–0.1% of the general population
- Incidence = 0.1–0.2% of hypertensive adults
- Bilateral tumor = 10% of cases; possibility of multiple tumors
- Extraadrenal localization: 10% of cases (= paragangliomas)
- Non-functional pheochromocytomas = rare (mostly extraadrenal)
- Malignant pheochromocytoma: 10% of cases (metastases: bone, liver, lung, less frequently lymph nodes)
- 5-year survival rate:
- Benign phaeochromocytoma = 97%
- Malignant pheochromocytoma = 43%
- Familial pheochromocytoma: 10% of cases (currently more like 25%):
- MEN 2A or 2B (► Sect. 6.3): Often bilateral pheochromocytoma
- Neurofibromatosis type I or MEN 1 (► Sect. 6.3): Pheochromocytoma risk <1%
- Hereditary paraganglioma syndrome (mutations in SDHD, SDHB and SDHC genes)

In familial pheochromocytoma: Mandatory follow-up + regular screening.

Clinical Signs

- Variable clinical presentation: Over time and from one patient to another (up to dramatic situations)

Arterial Hypertension

- Constant hypertension + paroxysmal peaks (variable frequency and severity)
- Paroxysmal symptoms due to e.g. physical stress, food containing tyramine (chocolate, cheese, red wine)

Other Symptoms

- Excessive sweating
- Tachycardia
- Trembling
- Inner restlessness
- Thoracic pain
- Impaired glucose tolerance: with diabetes mellitus signs (polydypsia, polyuria)

Impaired glucose tolerance = consequence of catecholamine secretion.

Diagnosis

Laboratory Function Tests

- Confirmation of excessive catecholamine secretion
- In the blood:
  - Free metanephrines in plasma: more sensitive than punctual metanephrines in urine
- In the urine:
  - Free catecholamines + metabolites in 24-h urine: to confirm elevation in plasma
    - Free catecholamines: Dopamine, epinephrine, norepinephrine…
    - Metabolites: normetanephrines, metanephrines, vanillinmandelic acid
- Elevated levels in more than 90% of patients with pheochromocytoma

Phenylethanolamine-N-transferase = enzyme only in adrenal gland: conversion of norepinephrine to epinephrine; as consequence: extraadrenal pheochromocytoma = no epinephrine production.

Etiological Diagnosis = Localisation Diagnosis

- Goal = localization of the pheochromocytoma
- Only if laboratory diagnosis is confirmed (see above)

CT Scan

- Imaging of first choice for suspected pheochromocytoma
- Detects 95% of tumors >6–8 mm

MRI

- In selected cases
- T2 weighting: visualization of chromaffin cells (T2 adrenal/liver ratio > 3 in pheochromocytoma)

MIBG Scintigraphy

- Localization of extraadrenal pheochromocytomas + metastases + bilateral pheochromocytomas
- Method of choice in case of:
  - positive Laboratory function tests and negative CT + MRI examinations
  - Follow-up of patients with recurrent/metastatic disease

In (suspected) malignant pheochromocytoma: staging by standard imaging + MIBG scintigraphy.

Therapy

Preoperative Preparation

Background

- Preoperative preparation = central to prophylaxis of intraoperative cardiovascular crisis
- Intraoperative cardiovascular crisis: due to the release of catecholamines.

Principle

- α-adrenergic blockade
- β-adrenergic blockade for the prophylaxis of arrhythmias/tachycardia

Caution

β-adrenergic blockade: inhibition of α-blocker-induced vasodilation; β-blocker alone: increase in hypertension + left ventricular congestion.

- Restoration of a normal electrolyte-fluid balance

Dosages for Pheochromocytoma

- Phenoxybenzamine (non-selective α-blocker): 10 mg 3 times/day
- Prazosin (selective α_1 blocker): 0.5–1 mg titrated to 3–20 mg/day
- Metyrosine (tyrosine hydroxylase inhibitor): 250 mg 3 times/day titrated to a maximum of 1.5–4 g/day
- Propranolol (non-selective β-blocker): 10–40 mg 3 times/day.

Surgical Therapy

Strategy

- Laparoscopic/retroperitoneoscopic adrenalectomy:
  - In the case of unilateral small, benign appearing tumour with normal opposite side
  - Patients with MEN 2 or von Hippel-Lindau syndrome with small unilateral findings (<6 cm)
  - Bilateral minimally invasive adrenalectomy: For MEN 2 or von Hippel-Lindau syndrome with small bilateral findings

Adrenal cortex-sparing adrenalectomy (subtotal) = method of choice for bilateral benign disease (e.g. MEN 2 or von Hippel-Lindau syndrome): prophylaxis of adrenal insufficiency.

- Open adrenalectomy:
- For findings >6 cm (high risk of malignancy = approx. 25%)
- In case of primary suspicion of malignancy
- Malignant pheochromocytoma + limited metastasis: resection possible in well-selected patients

Principles of Surgical Therapy (► Sect. 6.7.7)

- Avoid intraoperative manipulation of the tumor
- Early ligation of the adrenal vein (interruption of the venous outflow of the tumor)

Postoperative Monitoring/Follow-Up

- 24-h monitoring: blood pressure (compensatory hypotension due to vasodilation), arrhythmias
- Annual: Plasmatic free metanephrines or urinary catecholamines

Chemotherapy

- Therapy regime
  - High dose streptozocin
  - Alternative: Cyclophosphamide + Vincristine + Darcarbazine
- Response rate = 50%

Radiotherapy

- For bone metastases

Palliative Therapy

- α-Methyltyrosine
- α-blockade + β-blockade

6.7.4 Adrenocortical Carcinoma

Definition

- Rare malignant endocrine tumor
- Surgical resection = only curative therapy

Epidemiology and Prognosis

Epidemiology

- Incidence = 0.5–2/1 million inhabitants per year in USA
- Bimodal age distribution:
  - Peak in young children <5 years
  - Peak in adults at 40–50 years

Prognosis

- Bad because of late diagnosis
- Most important prognostic factor = complete resection
  - With complete resection: 5-year survival = 40%, median = 43 months
  - In case of incomplete resection: Median survival = 12 months

Clinical Signs

Unclear Abdominal Complaints

- Secondary
- Due to progressive retroperitoneal mass.

Symptoms of Overproduction of Adrenocortical Hormones

- Majority of these tumors = functional
- Cushing's syndrome: due to cortisol secretion (50% of tumors)
- Virilization/Feminization/Hypertension: due to androgen/estrogen or aldosterone secretion (10–20% of tumors)

Diagnosis

Biochemical Screening

- Cortisol, aldosterone, androgens, estrogens
- Biochemistry = indicator for perioperative substitution therapy
- Exclusion of a pheochromocytoma: catecholamines + metabolites in plasma + urine

Imaging

- High-resolution CT/MRI:
  - MRI especially for the evaluation of a vena cava inferior infiltration
  - With thorax: For detection of pulmonary metastases
- PET-CT: For detection of metastases + recurrence

Therapy

- 50% of tumors = localized at the time of diagnosis

Surgical Therapy

Strategy

- Complete resection = only curative option for local adrenocortical carcinoma
- Open resection:
  - Adequate exposure
  - Reduction of malignant cell spillage
  - Better control of the vessels (inferior vena cava, aorta, renal vessels)
  - Radical en bloc resection (possibly multivisceral resection, if necessary)
- Laparoscopic resection technically possible, **but** high recurrence rate. **Caution:** tumor fracture + peritoneal contamination.
- Recurrence/Metastases: Complete resection of recurrence + metastases
- Prolonged survival
- Reduction of hormone-associated symptoms

Postoperative Follow-Up

- Regular control of hormone levels
- Abdominal CT examinations (thorax + abdomen)

Chemotherapy

- For unresectable cancer(s)/metastases
- No chemotherapy active in terms of improving survival
- Reduction of symptoms due to anti-hormonal effect
- Mitotan:
  - steroid inhibitor
  - Inducer of atrophy of adrenocortical cells
  - Side effects: Gastrointestinal + neuromuscular

Mitotan

- Need for close monitoring of hormone levels!
- Adjuvant mitotane therapy: currently being evaluated (in the context of studies)
- Neoadjuvant mitotane therapy: currently being evaluated (in the context of studies)
- Combinations of etoposide + doxorubicin + cisplatin + mitotane (EDP-M): Currently being evaluated (in the context of studies), possible advantages in recurrence-free survival/overall survival.
- Other active agents:
  - Suramin, Ketoconazole
  - Cisplatin, doxorubicin, vincristine

Radiotherapy

- Palliative therapy for bone metastases

6.7.5 Adrenal Incidentaloma

Definition

- Asymptomatic adrenal lesion as an incidental finding during imaging for another reason
- Increasing frequency with use of abdominal CT

Epidemiology

- Frequency = 4% of routine abdomen imaging
- Frequency = 9% in autopsy series
- Most lesions = benign; hormone active vs. hormone inactive.

Clinical Evidence

Functional Incidentalomas

- All incidentalomas >1 cm: need for Hormonal workup
- All hormone-active lesions: Resection
- In case of radiological suspicion of malignancy: resection
- In case of size progression during follow-up: resection

Non-functional Incidentalomas

- Malignancy risk dependent on:
  - Size of the mass: Best clinical indicator
    - <4 cm: risk of malignancy = 2%
    - 4.1–6 cm: risk of malignancy = 6%
    - >6 cm: risk of malignancy = 35%
- Nonfunctional incidentalomas <3 cm: surveillance; nonfunctional incidentalomas 3–5 cm: controversial.
- Radiological malignancy criteria/etiology (Table 6.26)

Evaluation Algorithm

- In patients with adrenal incidentaloma (Fig. 6.11)
- In patients with adrenal incidentaloma and extraadrenal carcinoma (Fig. 6.12)

Therapy

- Therapy = surgical therapy vs. monitoring

Indications for Surgical Therapy

- Hormone-active incidentalomas
- Incidentalomas with radiological signs of malignancy (regardless of size)
- Incidentalomas >6 cm

Incidentalomas 3–6 cm: Individual decision for surgery based on age + general condition.

Table 6.26 Characteristic features of adrenal incidentalomas in imaging ("imaging phenotype")

	Adrenocortical adenoma	Adrenocortical carcinoma	Pheochromocytoma	Metastases
Size	Small, mostly ≤3 cm	Large, mostly >4 cm	Large, mostly >3 cm	Variable, often <3 cm
Form	Round or oval with smooth margin	Irregular with unclear margin	Round or oval with clear margin	oval, irregular with unclear margin
Texture	Homogeneous	Heterogeneous, with different densities	Heterogeneous, with cystic areas	Heterogeneous, with different densities
Laterality	Mostly solitary, one-sided	Mostly solitary, one-sided	Mostly solitary, one-sided	Often bilateral
Density (CT without CM)	≤10 HU	>10 HU (mostly >25)	>10 HU (mostly >25)	>10 HU (mostly >25)
Vessels in CM-CT	Not highly vascular	Mostly vascular	Mostly vascular	Mostly vascular
Washout	≥50% after 10 min	<50% after 10 min	<50% after 10 min	<50% after 10 min
MRI image	Isointens in T2 weighting	Hyperintensity in T2 weighting	Significantly hyperintensive in T2 weighting	Hyperintensity in T2 weighting
Necrosis, hemorrhage, calcification	Rarely	Frequently	Bleeding + cystic areas frequent	Regular bleeding + cystic areas
Size increase	Mostly stable in progression or very slow (<1 cm/year)	Mostly fast (>2 cm/year)	Mostly slow (0.5–1.0 cm/year)	Different, slow–fast

HU Hounsfield units, *CM* contrast medium

Strategy

- Laparoscopic adrenalectomy for:
  - Incidentalomas without malignancy criteria on imaging
  - Incidentalomas <4 cm
- Open adrenalectomy: All other incidentalomas with indication for surgery

Background = Risk of capsular rupture and cell spillage during laparoscopic adrenalectomy: Not adapted in the presence of malignancy.

6.7.6 Adrenal Metastases

Epidemiology

- Adrenal metastases = frequent
- In autopsies, adrenal metastases present in:
  - 42% of lung cancers
  - 16% of gastric cancers
  - 58% of breast cancers
  - 50% of malignant melanomas
  - High percentage of prostate and kidney cancers

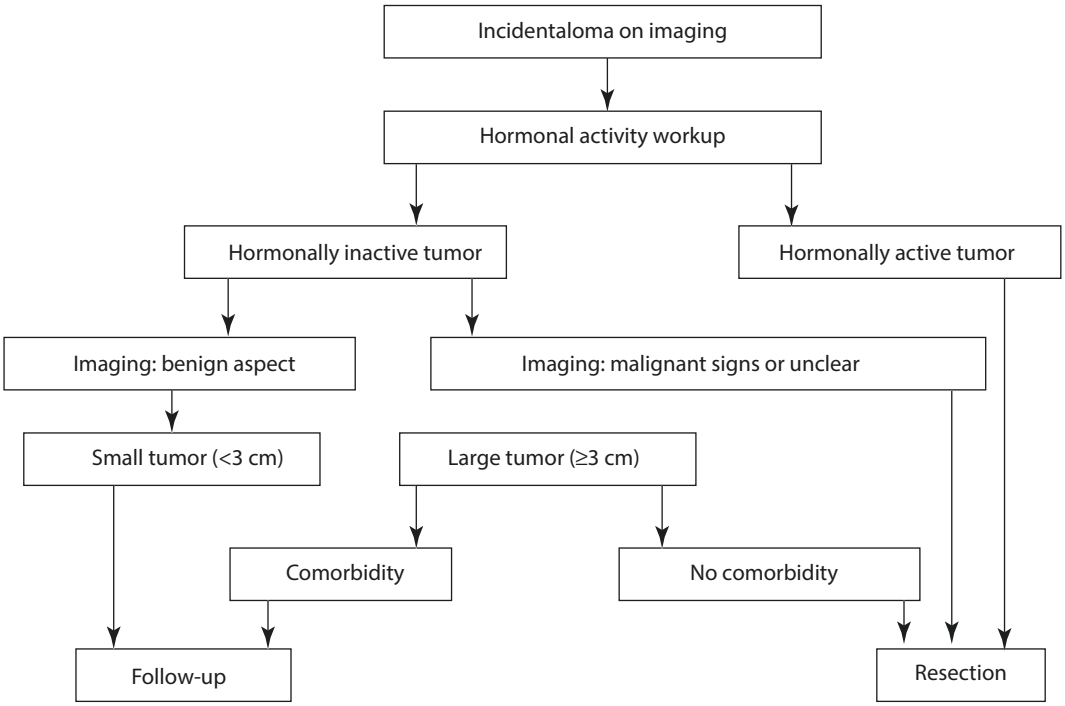


Fig. 6.11 Algorithm for the evaluation of a patient with an isolated adrenal incidentaloma

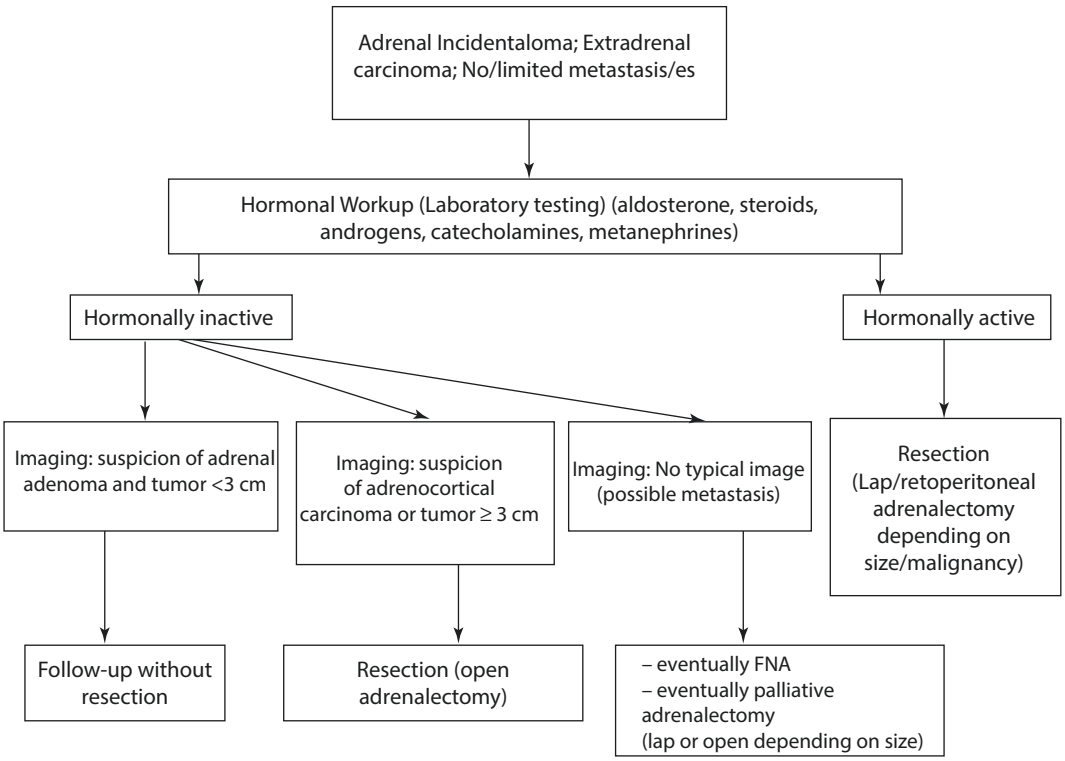


Fig. 6.12 Algorithm for the evaluation and therapy of a patient with an adrenal incidentaloma in the context of an extraadrenal carcinoma

Clinical Signs

- Mostly asymptomatic
- If symptomatic:
  - Unclear complaints
  - Adrenal insufficiency: Very rare

Adrenal insufficiency: At least 90% of the adrenal cortex affected (massive enlargement of the adrenal gland on CT).

Diagnosis

- Workup of patients with adrenal tumour in the context of extraadrenal malignant disease (◘ Fig. 6.12)

Therapy

Surgical Therapy

- Resection of adrenal metastasis: in selected patients
- Selection Criteria:
  - Prolonged disease-free interval
  - Adequate tumor biology: good response to systemic therapy, history of isolated metachronous metastasis, long disease-free interval
  - Primary tumour localisation: better results for metastases from lung, colon, kidney cancers and melanomas (worse for oesphagus, liver tumours or sarcomas)

6.7.7 Principles of Adrenal Surgery

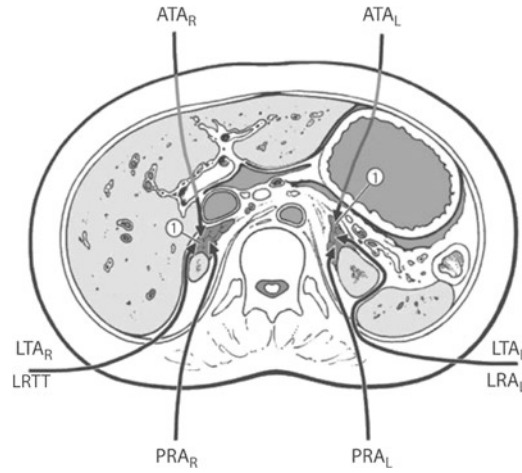
General (◘ Fig. 6.13)

Decisive Factors for the Choice of a Procedure

- Size and localization of the tumor
- Malignant potential of the lesion
- Unilateral vs. bilateral lesion
- Presence of extraadrenal manifestations
- Surgical procedure in the anamnesis
- Habitus of the patient
- Surgeon's experience

General Rule

- Open access for large tumors and, if necessary, for tumors with malignant potential



◘ **Fig. 6.13** Access routes in adrenal surgery. (After Walz 2012)

Open Adrenalectomy

Indications

- Known or suspected primary adrenocortical carcinoma
- Large tumors
- Tumor Recurrence
- Extension to adjacent organs

Technique

- 4 possible accesses:
  - Anterior: Preferred for adrenocortical carcinoma
  - Lateral: Ideal for obese patients
  - Posterior: Rarely used; for small tumors
  - Thoracoabdominal: Ideal for tumors requiring en bloc resection of adjacent organs + lymphadenectomy

Surgical Procedure

Open Anterior Left Adrenalectomy

- Mostly longitudinal laparotomy
- Mobilization of the left colonic flexure + descending colon
- Entering retroperitoneum through incision along the lower edge of the pancreas
- Medial visceral rotation of the spleen + pancreas tail (dissection on Gerota's fascia)

- Visualization of renal hilus and following renal vein to confluence with left adrenal vein
- Left adrenal gland = left to the aorta, above the left renal vein
- Early ligation of the adrenal vein
- Supply of thin-caliber collaterals of the aorta, inferior diaphragmatic vessels and renal vessels
- adrenalectomy
- No drainage

Surgical Procedure
Open Anterior Right Adrenalectomy

- Mostly longitudinal laparotomy
- Mobilization of the right ligamentum triangulare of the liver and anteromedial rotation of the liver = access to the right adrenal gland
- Kocher maneuver: mobilization of the duodenum if necessary; thereby better access to the right kidney + inferior vena cava
- Right adrenal vein: Mostly direct drainage into inferior vena cava; ligation of the adrenalvein
- Control of the arterial inflow of the adrenal gland
- adrenalectomy
- No drainage

Surgical Procedure
Open Posterior Adrenalectomy

- Patient in prone position; table bent 35°
- Oblique incision over the 12th rib; retraction of the sacrospinalis muscle medially
- Resection of the 12th rib; reflection on pleura cranially
- Left: Cranial resection border = diaphragm; Right: Cranial resection border = liver
- Adrenalectomy is performed like anterior technique

Surgical Procedure
Thoracoabdominal Approach

- Allows the best exposure: ideal for tumors requiring en bloc resection of adjacent organs + lymphadenectomy
- Incision over tenth rib on the right and 11th rib on the left, with rib resection
- If infiltration V. cava or hepatic veins: Need for additional sternotomy

Surgical Procedure
Lateral Access

- Patient in lateral decubitus: using gravity for organ retraction
- Extraperitoneal approach to the adrenal gland
- sparing of extensive adhesiolysis in patients with postop. Adhesions
- Vascular control usually more difficult

Laparoscopic Adrenalectomy

- Standard access for small benign adrenal tumors

Advantages (Compared to Open Access)

- Less pain and less postoperative restrictions
- Shorter hospital stay
- Faster recovery
- Better cosmetic result

Good Candidates for Laparoscopic Adrenalectomy

- Patients with Conn adenoma
- Small functional adrenal tumors (<4 cm)
- Unilateral sporadic benign tumors
- MEN 2 or von Hippel-Lindau syndrome, patients with unilateral pheochromocytoma
- Selected patients with adrenal metastasis

Laparoscopic Adrenalectomy

- Tissue-sparing subtotal adrenalectomy: Possible using laparoscopy
- In case of suspected malignancy: No laparoscopy
- In case of unclear incidentaloma: open approach recommended (potential malignancy)

Surgical Procedure

Laparoscopic Left Adrenalectomy

- Patient in right lateral decubitus
- Operating table adequately padded; abdomen and thorax washed down from areola to below the spina iliaca, and from right of umbilicus to spine
- Infracostal trocar 10–15 cm anterior to the anterior axillary line (open technique)
- 3 × 10 mm trocars under direct vision: anterior axillary line, posterior axillary line and one 5-cm posterior to posterior axillary line port, medial to left kidney
- Dissection (e.g., ligasure, ultracision): Mobilization left colonic flexure, using gravity; inferior and medial dissection
- Mobilization of the spleen by incision of the peritoneum lateral to the spleen
- Rotation of the spleen medially with pancreatic tail
- Dissection of the left adrenal gland from retroperitoneal fat
- Transection of the adrenal vein after mobilization of the gland and shortly before complete resection (difference to the open technique): Vascular stapler, energy sealing device (e.g.Ligasur) or clip (currently some authors advise against clips: slippage of clips)
- Extraction of the adrenal gland in sterile plastic bag via umbilical caltrocar

Surgical Procedure

Laparoscopic Right Adrenalectomy

- Patient in left lateral decubitus
- Trocar positions analogous to left
- Medial port for liver retraction
- Dissection of the adrenal gland caudally along the renal vein and medially along the inferior vena cava
- Right adrenal vein usually short and thick-lumened
- Transection of the adrenal vein obligatory, by means of vessel stapler, energy sealing (Ligasur), or vessel clips (currently some authors advise against clips: slipping of the clips)
- Remaining dissection analogous to left

Retroperitoneoscopic Adrenalectomy

Indications

- Small benign adrenal tumors
- Isolated adrenal metastases

Caution

Positioning in knee-elbow position.

Advantages

- Minimally invasive method
- Reduction of hemodynamic or respiratory instability (vs. capnoperitoneum)
- No need for adhesiolysis or transperitoneal access
- Possibility of hemostasis by increasing the pressure (insufflator pressure up to 20–25 mmHg)
- Possibility of bilateral adrenalectomy without repositioning the patient

Contraindications

- Suspicion of adrenocortical carcinoma/malignant pheochromocytoma
- Adjacent Organ Infiltration
- Lesion >6 cm
- Morbid obesity
- Limited distance between costal arch and iliac crest

Surgical Procedure

Retroperitoneoscopic Adrenalectomy

- Patient in knee-elbow position
- Palpation of the 12th rib, 1.5-cm incision just below the tip of the 12th rib.
- Opening of the retroperitoneum with scissors and widening of the access with the finger
- Palpation with index finger and insertion of the 10 mm and 5 mm trocar (possibly also possible under visual control): Medial trocar 5 cm medial to the 12-mm trocar, lateral to the paraspinal muscles; the lateral trocar 5 cm lateral to the 12-mm trocar under the tip of 11th rib.
- Insertion of a 12 mm trocar with balloon and CO_2 insufflation with pressure 20–24 mmHg
- 30° 10 mm videoscope into the 12 mm trocar and start of blunt dissection: retroperitoneal space
- Opening of the Gerota fascia + visualization of the renal upper pole. Visualization of landmarks: paraspinal muscles, diaphragm, liver, peritoneum parietale, inferior vena cava
- videoscope into paravertebral trocar
- Dissection along the renal upper pole
- Identification of inferior vena cava on right side
- Exposure of adrenal vein and supply by means of sealing (e.g. Ligasur)
- Complete mobilization of the adrenal gland and salvage using a plastic salvage bag via 12-mm access
- haemostasis after reduction of pressure
- Removal of the trocar and closure of the accesses

6.7.8 Guidelines

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