THYROID DISORDERS

Minsk BSMU 2022

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ЗАБОЛЕВАНИЯ ЩИТОВИДНОЙ ЖЕЛЕЗЫ

THYROID DISORDERS

Учебно-методическое пособие

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LIST OF ABBREVIATIONS

Antithyroid drugs — ATD

Autoimmune thyroid disease — AITD

Autoimmune thyroiditis — AT

Computer tomography — CT

Graves' disease — GD

Graves' ophthalmopathy — GO

Fine-needle aspiration biopsy — FNAB

Magnetic resonance imaging — MRI

Medullary thyroid carcinoma — MTC

Radioactive iodine — RAI

Radiofrequency ablation — RFA

Recurrent laryngeal nerve — RLN

Thyroglobulin — Tg

Thyroid-stimulating hormone — TSH

Thyroid peroxidase — TPO

Thyrotropin-releasing hormone — TRH

Thyroxin (tetraiodothyronine) — T4

Triiodothyronine — T3

INTRODUCTION

Thyroid disorders and their complications are of great importance for doctors of different specialties. The widespread prevalence of various forms of thyroid pathology urgently necessitates the study of diagnostic and treatment methods. The rapid development of endocrine surgery, new concepts of the etiology and pathogenesis of endocrine disorders, approaches to the examination and treatment of patients with thyroid diseases that have changed recently, made this manual necessary.

The purpose is to study etiology, pathogenesis, clinical presentation, diagnostics and management of thyroid disorders.

Objectives:

1. To acquire the general and special methods for the diagnosis of thyroid disorders.
2. To study the classification of thyroid disorders.
3. To study the clinical presentation of various thyroid disorders.
4. To study modern methods of treatment and indications for their choice for various thyroid disorders.

Requirements to the initial level of knowledge

To learn the topic completely student should know:

– normal and topographic anatomy of the thyroid gland

– thyroid physiology.

Test questions from related disciplines

1. Anatomy and topography of the thyroid gland.
2. Blood supply, routes of venous outflow and regional lymph nodes.
3. Physiological role of thyroid hormones, regulation of synthesis and secretion.

Test questions

1. Non-toxic (euthyroid) goiter. Definition, etiology, clinical presentation, indications for and extent of surgery.
2. Diffuse toxic goiter (Graves' disease). Definition, etiology, clinical presentation, indications for and extent of surgery.
3. Toxic goiter. Indications for and extent of surgery.
4. Acute infectious (suppurative) thyroiditis. Etiology and pathogenesis. Clinical presentation, diagnosis, differential diagnosis, management. Indications for and extent of surgery.
5. Subacute de Quervain's thyroiditis. Etiology and pathogenesis. Clinical presentation, diagnosis, management. Indications for and extent of surgery.
6. Hashimoto's thyroiditis (Chronic lymphocytic thyroiditis, Autoimmune thyroiditis). Etiology and pathogenesis. Clinical presentation, diagnosis, management. Indications for and extent of surgery.

7. Invasive fibrous thyroiditis (Riedel's thyroiditis). Etiology and pathogenesis. Clinical presentation, diagnosis, management. Indications for and extent of surgery.

8. Thyroid tumors. Clinical presentation, diagnosis, management. Extent of surgery.

9. Principles of thyroid surgery and postoperative complications.

THYROID ANATOMY AND PHYSIOLOGY

The thyroid gland (glandula thyroidea) is an endocrine gland that is located on the front surface of the neck and is a parenchymal organ consisting of two lobes and an isthmus. In 30–50 % of cases there is an additional pyramidal lobe. Lateral lobes are located at the level of the thyroid and cricoid cartilages, the lower pole is located at the level of V–VI tracheal rings. The posterior surface of the lobes borders the neurovascular bundle of the neck, trachea, larynx, pharynx and esophagus. Four parathyroid glands are located on the posterior surface of the thyroid gland — two on each side.

The blood supply to the thyroid gland is carried out by four main arteries: two superior thyroid arteries from the external carotid arteries, and two inferior thyroid arteries, from the subclavian arteries. Sometimes (5–10 % of observations), an additional unpaired artery can be found, a single thyroid ima artery that arises from the brachiocephalic artery. Venous outflow occurs through paired superior, middle and inferior thyroid veins draining into the internal jugular veins.

Lymphatic vessels drain to the regional lymph nodes: jugular chain of nodes to the digastric nodes and inferiorly to the pretracheal and brachiocephalic nodes, located in the pretracheal and paratracheal tissue, in the tracheoesophageal groove, in the mediastinum, along the jugular vein, as well as pharyngeal and paraesophageal lymph nodes.

The thyroid is surrounded by a sleeve of pretracheal fascia sometimes called the perithyroid sheath. Posteriorly, a thickening of this fascia attaches the gland to the cricoid cartilage. This fascia is the lateral ligament of the thyroid (ligament of Berry).

The thyroid gland is encased by a thin capsule that sends out septa that invaginate into the gland, forming lobules. Lobules consist of follicles, the walls of which are lined with a single-layer cubic epithelium. Functional unit of the thyroid is a follicle. Its average size is around 20μm in diameter. The follicle is enveloped by a basal lamina and is surrounded by numerous capillaries and lymphatics. The follicular lumen contains colloid, composed of thyroglobulin and enzymes.

Thyroid parenchyma is composed mainly of 3 types of cells:

– A-cells (follicular epithelium, thyrocytes), that constitute the majority of thyroid cells, form follicles, participate in iodine metabolism and thyroid hormone synthesis.

– C-cells (parafollicular cells) — located between the follicles and are involved in the synthesis of the hormone calcitonin. C-cells belong to the neuroendocrine system; tumors from parafollicular cells can produce hormones of the APUD system.

– Oncocytic cells (oxyphils, Askanazy cells, Hürthle cells) are altered/metaplastic follicular cells. They are common in long-standing Graves' disease, autoimmune thyroiditis, thyroids affected by radiation, follicular-derived neoplasms, and some adenomatous nodules.

The thyroid gland secrets iodinated hormones L-thyroxine (T4) and to a much lesser extent L-triiodothyronine (T3), as well as calcitonin. Basic components necessary for thyroid hormone production are iodine and amino acid tyrosine.

Iodine is ingested with food and water. The physiological consumption of iodine is 110–150 μg/day; excess is excreted with urine and bile. Iodine is absorbed into the blood from the gastrointestinal tract in the form of potassium and sodium iodides. The latter are transported into the thyrocytes. After that iodine is oxidized and with the the help of the thyroid peroxidase (TP) incorporated into tyrosyl residues in thyroglobulin (TG), which is stored in the colloid space at the center of the thyroid follicles. Iodinated tyrosines (monoiodotyrosine and diiodotyrosine) couple to form T3 and T4.

Regulation of the thyroid hormones synthesis and secretion mainly controlled by the hypothalamic-pituitary-thyroid axis. Hypothalamic thyrotropin-releasing hormone (TRH) stimulates the synthesis and release of anterior pituitary thyroid-stimulating hormone (TSH), which in turn stimulates growth and hormone secretion by the thyroid gland.

Between hypothalamus, the pituitary and the thyroid there is a negative feedback loop mediated by T4 and T3. T4 and especially T3 excess suppress TSH and TRH release.

Synthesized thyroid hormones are stored in thyroglobulin-bound state inside the follicles. With a decrease in the concentration of thyroid hormones hydrolysis of thyroglobulin occurs, releasing T4, T3 into the circulation. The released hormones are bound to carrier proteins. Only 0.04 % of T4 and 0.4 % of T3 are free (FT4 and FT3), which represents the fraction that is enough for hormonal activity.

In peripheral tissues, T4 is converted by deiodination to T3, which is 3–8 times more potent than T4 and mainly provides the biological effect of thyroid hormones.

The physiological role of thyroid hormones is diverse. T3 interacts with the nuclear thyroid hormone receptor, which binds to regulatory regions in various gene-regulated processes. This increases oxygen consumption, basal metabolic rate, and heat production. Thyroid hormones influence all types of metabolism — water-electrolyte, protein, fat, carbohydrate. The presence of an adequate level of thyroid hormones is a necessary condition for the normal fetal brain development.

The third thyroid hormone, calcitonin, is synthesized by C-cells and participates in calcium metabolism, inhibiting calcium absorption and lowering peripheral serum calcium levels. In normal human physiology, calcitonin does not have a significant role, but this is a sensitive marker of medullary thyroid carcinoma (MTC).

EVALUATION OF PATIENTS

Clinical methods

Complains. Complains of patients with the thyroid disorders can be divided into 2 groups. First one is due to gland enlargement and compression of nearby structures, second one is because of alteration of thyroid function (hypothyroidism or hyperthyroidism). Gland enlargement leads to such complains, like presence of neck tumor, feeling of foreign body during swallowing (dysphagia), "inconvenience" around neck on its movement, buttoning up collar, subjective or positional dyspnea, coughing, dysphonia.

Symptoms of altered thyroid function will be described later.

Clinical examination. Examination allows confirming the presence of goiter, type of enlargement (diffuse or nodular) and its localization, consistence (firm or soft), mobility on swallowing or palpation. Regional lymph nodes should be palpated (neck lymph nodes, supra- and subclavicular). In case of retrosternal goiter a positive Pemberton's sign — facial flushing and dilatation of cervical veins upon raising the arms above the head can be found.

The thyroid enlargement is assessed using WHO classification (Table 1).

Table 1

Grade	Characteristics
0	No palpable or visible goitre.
I	A goiter that is palpable but not visible when the neck is in the normal position (i. e. the thyroid gland is not visibly enlarged). Nodules in a thyroid that is otherwise not enlarged fall into this category.
II	A swelling in the neck that is clearly visible when the neck is in a normal position and is consistent with an enlarged thyroid gland when the neck is palpated.

Laryngoscopy is indicated in case of voice hoarseness. It allows revealing vocal folds paresis due to involvement of recurrent laryngeal nerves (RLN).

Laboratory evaluation. To estimate thyroid status and extent of secretion impairment, serum concentrations of T3, T4, TSH and calcitonin are evaluated using chemiluminescent assay or radioimmunoassay. To evaluate autoimmune thyroid disorders level of serum antibodies against various cellular components is used: antibodies against TG, TP and TSH receptors.

Thyroid imaging.

Ultrasound. Ultrasound (US) is the leading method of the thyroid imaging. It allows to assess thyroid size and volume, location, type of lesion and extent of blood supply.

Its normal volume ranges up to 18 ml in women and up to 25 ml in men. After determining its volume and location, ultrasonographer assesses its contour and echogenicity. The latter one can be increased (hyperechogenic) or decreased (hypoechogenic), homogeneous or heterogeneous. All focal lesions are examined: size, contour, echogenicity and echotexture, blood supply, extrathyroidal extension, if present. Examination protocol also includes assessment of regional lymph nodes and surrounding structures. The normal thyroid has a smooth contour and shows a fine granular homogeneous, slightly hyperechogenic sonographic pattern.

Currently there are no absolute US criteria that can differentiate benign and malignant lesions, but thyroid ultrasound allows effective and safe examination of the thyroid tissue, reveals nonpalpable lesions and guides fine-needle aspiration biopsy (FNAB).

Radioisotope Scanning. Radionuclide imaging allows simultaneous evaluation of anatomical and topographic details of the thyroid gland, presence of aberrant tissues and thyroid functional activity. However, scanning doesn't differentiate benign and malignant lesions. Iodine-123 (^{123}I) and iodine-131 (^{131}I), technetium Tc 99m pertechnetate (^{99m}Tc) are used to image the thyroid gland. More recently, 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) combined with computed tomography (CT) is being increasingly used to screen for metastases in patients with thyroid cancer in whom other imaging studies are negative.

Indications for scanning:

– Autonomously functioning nodule(s) and differential diagnosis with Graves' disease.

– Dystopic localization of thyroid tissue.

– Screening of patients with differentiated thyroid cancers for recurrent/metastatic disease.

X-ray neck and mediastinum examination and barium esophagography. Allows assessment of retrosternal goiter, esophageal compression and/or deviation, presence of calcifications. Currently mostly has been substituted by other imaging modalities.

CT and MRI of neck and mediastinum. High resolution methods that are mostly used for evaluating lymphadenopathy, local tumor extension, and extension into the mediastinum or retrotracheal region. They can't differentiate benign and malignant nodules and have no role in assessing thyroid function.

Fine-needle aspiration biopsy (FNAB) is performed under US-guidance. It is valuable tool for morphological preoperative diagnostics. Material is aspirated and is placed on the slide, fixed and stained. FNAB is indicated in case of nodular/multinodular goiter. This method has changed dramatically goiter management, allowed canceling a great number of unnecessary operations. Additional examinations of aspirated material (polymerase chain reaction and other molecular techniques) allow to reveal rare tumors, clarify the diagnosis in case of inde-

terminate cytology. Needling the thyroid allows to perform cyst aspiration and ethanol injection into those cysts to achieve their sclerosing as well.

Intraoperative morphological examination includes cytological (smears) and histological (frozen tissue) examination of resected specimen. These methods can be utilized in specialized oncological hospitals for intraoperative defining extent of operation.

Postoperative histological examination is a final step of morphological diagnostics with the best sensitivity and specificity. It can be improved by such adjuncts like immunohistochemistry and different molecular techniques.

THYROID FUNCTION ABNORMALITIES

Hypothyroidism — is a clinical syndrome caused by long-term insufficiency of thyroid hormones. At present time classification includes *primary hypothyroidism* (*congenital and acquired*), due to absence of the thyroid gland or congenital deficiency of thyroid hormones synthesis; *secondary* (*central*) hypothyroidism, which is the consequence of reduced TSH and/or thyrotropin-releasing hormone (TRH) production, as observed in several pituitary and hypothalamic diseases. Clinical signs and symptoms of hypothyroidism may rarely be observed in conditions associated with reduced thyroid hormone activity at the tissue level, even in the presence of normal or increased thyroid hormone production — *peripheral hypothyroidism*.

Classification of hypothyroidism severity:

– Mild (subclinical): elevated TSH without decreased FT4 concentrations, clinical signs are absent;

– Severe (overt): elevated TSH levels associated with subnormal levels of FT4, clinical signs are present;

– Complicated (myxedema): long-term severe hypothyroidism associated with the nonpitting edema caused by accumulation of glycosaminoglycans in derma and other tissues; this condition is associated with multiple complications (cretinism, coma etc).

Primary acquired hypothyroidism is the most frequent type in clinical practice.

Clinical presentation usually varies among individuals and depends on duration and severity of thyroid hormone deficiency, age and cause. It often lacks specific symptoms; complaints are scarce and don’t correspond with the severity of condition.

Several syndromes can be identified:

– Metabolic changes — obesity, hypothermia, dyslipidemia;

– Myxedema — swelling, most marked around the eyes and hands, enlarged tongue results in a husky, low-pitched, and coarse voice, as well as in a low and deliberate speech; skin is pale, rough, dry, and cool, covered with scales; the hair is dry, coarse, and slow growing;

– Nervous system — somnolence, lethargy, slow speech, delayed relaxation of deep tendon reflexes, ataxia, sensory-motor polyneuropathy, EEG changes, dizziness, vertigo, and tinnitus, deafness, anxiety and depression, memory deficits, calculation difficulties, myxedema madness and coma;

– Cardiovascular system — arrhythmias, reduction of pulse rate, stroke volume, cardiac output, cardiac preload, increase of systemic vascular resistance, systolic and diastolic, dysfunction, sinus bradycardia, cardiomegaly;

– Gastrointestinal system — weight gain (modest), increased liver function tests, oropharyngeal dysphagia, esophagitis, and hiatus hernia, increased esophageal transit time and gastric emptying time — nausea and vomiting, constipation, increased risk for nonalcoholic fatty liver disease;

– Musculoskeletal system — pain, cramps, muscle hypertrophy, stiffness, proximal muscle weakness, easy fatigability and weakness, increased risk of fracture;

– Reproductive system — decreased libido or impotence in men, oligomenorrhea and increased risk of obstetrical/neonatal morbidity in women; healthy children born to hypothyroid mothers have been reported to achieve a lower IQ later in life;

– Increased prevalence of pernicious anemia, celiac disease, inflammatory bowel disease, primary biliary cirrhosis when hypothyroidism is dependent on an autoimmune thyroid disease.

Diagnosis is based on laboratory examination of TSH and FT4 levels; to reveal central hypothyroidism additional tests are required.

Treatment consists of replacement therapy with levothyroxine (L-T4). Dosage is decided upon age, body weight, comorbidities and adjusted by serum TSH and FT4 concentrations.

Thyrotoxicosis — clinical syndrome, caused by thyroid hormones excess in blood independently of its origin. According to its origin, there are 3 types of thyrotoxicosis:

– overproduction of the thyroid hormones (hyperthyroidism). Graves' disease, toxic adenoma and toxic multinodular goiter are the most frequent causes. Such entities like iodine-induced thyrotoxicosis, TSH-secreting adenomas, neonatal thyrotoxicosis (each < 1 %) are also included in this group;

– destructive — develops as a result of thyroid destruction and release of stored hormones. Such type develops in case of autoimmune Hashimoto thyroiditis, subacute de Quervain's thyroiditis, post-partum and radiation-induced thyroiditis;

– thyrotoxicosis of nonthyroidal origin — very rare situation due to thyroid hormone poisoning, struma ovarii, metastatic thyroid cancer.

Classification of the thyrotoxicosis severity:

– Subclinical thyrotoxicosis — suppressed TSH, normal values of T3 and T4, clinical signs are absent;

– Overt thyrotoxicosis — suppressed TSH, increased concentration of T4 and/or T3 and typical clinical presentation;

– Complicated thyrotoxicosis — suppressed or absent TSH, significantly elevated level of T3 and T4, vivid clinical presentation and presence of complications: atrial fibrillation, heart failure ("thyrotoxic heart"), worsening of psychiatric conditions, stupor, coma, weight loss and adrenal insufficiency.

Thyroid storm — life-threatening complication, characterized by an exacerbation of thyrotoxic symptoms with possible systemic decompensation (heart failure, liver failure, psychosis, coma), usually triggered by precipitant events (e. g., infections or other acute illnesses, thyroid or nonthyroidal surgery in undiagnosed or inadequately treated hyperthyroid patient), and with a substantial mortality rate (Angell et al. 2015).

Clinical presentation of thyrotoxicosis includes several syndromes:

Cardio-vascular system — result of direct influence on cardiac muscle and indirect influence of hemodynamic alterations. It results in tachycardia, cardiomegaly, heart failure, rhythm disturbance. Tachycardia is a compensatory respond on increased oxygen consumption by peripheral tissues, but it increases risk of subsequent complications.

Central nervous system — irritability, worsening of psychiatric conditions, stupor, coma in advanced cases.

Metabolic alterations — hyperglycemia, hypercalcemia, weight loss, tremor, myopathy, paralysis, reduced bone mineral density.

Skin and hair — warm, moist palms, hyperhidrosis, urticaria, itching, exacerbation of eczema, hair loss.

Gastrointestinal system — diarrhea, hyperdefecation.

Reproductive system — gynecomastia, infertility, light or absent menstrual periods.

Hemostasis system — hypercoagulability, increased risk of clot formation.

EUTHYROID GOITER

Goiter is a general definition of any enlargement of the thyroid gland. It can be nodular or diffuse enlargement and the pathologic changes include one or more of the following: (1) hyperplasia (increase of the thyrocytes quantity), (2) colloid accumulation (colloid goiter), and (3) nodularity (adenomatous goiter). Clinical term "goiter" includes various pathology, both benign and malignant. It means, that given patient has thyroid enlargement, and doctor should diagnose the exact reason.

The most frequent cause of goiter is iodine shortage — iodine deficiency goiter (endemic goiter). This condition leads to the thyroid hormone deficiency, which in turn stimulates TSH production; latter leads to the thyroid gland enlargement. In most instances enlargement is due to both colloid accumulation and thyrocytes hyperplasia. This leads to formation of colloid hyperplastic goi-

ter. Gland can be enlarged diffusely (diffuse goiter), or in case of persistence of the zones of epithelial hyperplasia will develop nodules (nodular/multinodular goiter). In many cases enlargement has a combined nature.

Besides iodine deficiency, etiology of euthyroid goiter also includes congenital (genetic) or acquired errors of the thyroid hormones' synthesis or secretion, (dyshormonogenetic goiter), dietary goitrogens, and goitrogenic drugs and chemicals (sporadic goiter).

Diffuse euthyroid goiter. In most instances is a result of iodine insufficiency. Clinically neck deformity may be visualized; large goiter can cause compression of surrounding structures. Goiter size is measured using ultrasound (normal values: women — 18 ml; men — 25 ml); function is assessed by blood concentration of thyroid hormones and TSH. Surgery is indicated only in case of compressive syndrome; extent of operation — subtotal or total thyroidectomy. In majority of patients iodine supplementation will be sufficient.

Nodular euthyroid goiter — is a collective entity, which includes various nodular thyroid lesions with normal thyroid function. The term "multinodular goiter" is used when two or more nodular lesions are discovered within the thyroid gland. It is necessary to distinguish pathological and clinical meanings this term. Pathological meaning implies nodular lesion as a result of excessive colloid accumulation and/or follicular hyperplasia, i. e. nodular colloid or adenomatous goiter. Clinical meaning before examination includes presence of various pathological forms. Besides colloid or adenomatous goiter (60–70 %) it includes adenomas (10–15 %), nodular forms of the autoimmune thyroiditis (1 %), cysts (2–4 %) and thyroid malignancy (5–10 %). Proper examination is necessary to clarify the situation and make clinical diagnosis.

In the case of colloid goiter clinical signs can be absent during long time; only neck deformity may be visualized. With the course of time after becoming enough large, goiter begins to dislocate and compress surrounding structures. Especially dangerous is tracheal compression, which may lead to the tracheomalacia or acute respiratory compromise in retrosternal goiter. Possible final step of goitrogenesis is the development of focal autonomy and development of toxic multinodular goiter. The risk of such transformation constitutes about 10 % during patient's life span. Malignization of colloid goiter is virtually impossible.

Diagnosis is based on the results of clinical examination, visualizing (US, CT/MRI), cytology (FNAB) and assessment of the thyroid function (T3, T4, TSH) and additional methods, when indicated (laryngoscopy, barium esophagography, esophagoscopy, bronchoscopy etc).

The most important aim of examination is to exclude thyroid malignancy. It can be suspected basing on clinical data (hard on palpation and fixed nodule with fast growth (twice or more in 6 months), regional lymphadenopathy, hoarseness), US examination (solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule with one or more of the following features: irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim

calcifications with small extrusive soft tissue component, evidence of extrathyroidal extension), vocal fold paresis on laryngoscopy, extrathyroidal extension on CT. Diagnosis is confirmed by FNAB.

Indications for surgery in benign colloid/adenomatous euthyroid goiter include:

– Compression of surrounding structures
– Substernal localization (threat of acute respiratory compromise)
– Cosmetic reasons.

Extent of surgery. As subtotal thyroidectomy is associated with recurrence in up to 20–50 % of patients, and in 3–16,6 % of goiters, malignancy was revealed with necessity of completion thyroidectomy in one-third of the cases, for patients with a unilateral compressive mass thyroid lobectomy and for patients with bilateral goiter or nodules total thyroidectomy is recommended as the procedure of choice.

When operation is not indicated, management includes observation using US and TSH evaluation once a year. Repeated FNAB is indicated in case of significant growth of the nodule and changes of its sonographic pattern. In case of iodine deficits iodine supplementation is indicated.

Previously widely used suppressive levothyroxine therapy is not used now because of low efficacy, quick relapse after its withdrawal and multiple complications.

GRAVES' DISEASE

Graves' disease (GD, diffuse toxic goiter) — genetically predisposed autoimmune thyroid disorder, which is characterized by production of thyroid-specific autoantibodies against TSH receptors on the surface of thyrocytes. GD is characterized by diffuse thyroid enlargement, increased synthesis of thyroid hormones resulting in thyrotoxicosis, thyroid ophthalmopathy (40–50 %), pretibial myxedema and acropathy (2 %).

GD is the most frequent cause of thyrotoxicosis. Its prevalence is approximately 0.5 % in the population, with approximately 3 % of women and 0.5 % of men developing GD during their life span.

At present GD origin is believed to be associated with synthesis of thyroid-stimulating antibodies against TSH receptors. They cause thyroid hyperfunction ahd thyrocytes hyperplasia, which leads to the thyroid enlargement.

Typical clinical presentation is described by classic triad: tachycardia — typical sign of thyrotoxicosis; presence of neck tumor and dysphagia; ophthalmopathy (Graves' ophthalmopathy — GO) and typical eye symptoms — ocular motility abnormalities. The latter are caused by the failure of antagonist muscles to relax. These symptoms are:

von Graefe's sign — when the patient looks downward, the upper lid lags behind the globe (lid lag), exposing more sclera.

Kocher symptom — when the patient gazes upward, often with difficulty, the globe may lag behind the lid.

Dalrymple's sign — spasm of the upper eyelid revealing the sclera above the corneoscleral limbus.

Graves' ophthalmopathy (GO) (exophthalmos, proptosis), when present, is frequently asymmetric and associated with a feeling of pressure behind the globes. It should be distinguished from eye symptoms. It occurs together with hyperthyroidism in 46–60 % of patients; in 30 % of patients, hyperthyroidism may occur several years before any eye symptoms are present; and only in about 10 % of cases may the eye symptoms precede the thyroidal symptoms. Clinical signs are (in descending frequency): lid retraction, edema, exophthalmus, motility disorders, and visual impairments. The pathogenesis of the orbitopathy is now better understood. The extraocular muscle and adipose tissue are swollen by the accumulation in the extracellular matrix of glycosaminoglycans and new fat cell development (adipogenesis) within the orbit. As a result, the volume of orbital contents is enlarged because of an increase both in retrobulbar connective tissue and adipose tissue and in the total extraocular muscle mass. This accumulation of glycosaminoglycans disrupts and impairs the function of the extraocular muscles. Later the damaged muscles become fibrosed.

The early GO signs include a sense of irritation in the eyes, and excessive tearing that is often made worse by exposure to air or wind. In active disease, the conjunctivae and eyelids are generally injected and swollen, and the patient may complain of pain with eye motion. Double vision can be intermittent, inconstant (at extremes of gaze only), or constant. Exophthalmos (proptosis), when present, is frequently asymmetric and associated with a feeling of pressure behind the globes. In advanced cases, the eyes may not close well during sleep (lagophthalmos) that leads to corneal dryness. In severe cases, an exposed cornea may ulcerate or become infected. Anterior displacement of the globe out of the orbit (subluxation), is another manifestation of extreme proptosis that can be catastrophic if not promptly treated. Dysthyroid optic neuropathy is a sight-threatening condition that develops as the optic nerve is compressed by enlarged extraocular muscles. This can occur with or without proptosis and may present as subtle changes in color vision or increased eye pressure symptoms. If not properly treated, dysthyroid optic neuropathy can lead to decreased visual acuity and even sight loss.

Standardized clinical assessment of the severity and activity of GO is mandatory for successful treatment and evaluation of outcome (modified from Bartalena et al. (2016)) (Table 2).

GD is diagnosed on the basis of typical clinical presentation, laboratory data (TSH suppression and increased T4 serum concentration, autoantibodies against TPO, thyroglobulin and TSH receptors) and visualizing examinations (US — diffuse or combined thyroid enlargement, enhanced vascularization; radionuclide scanning –increased diffuse uptake).

Table 2

Grade	Characteristics
Mild GO	Patients whose features of GO have only a minor impact on daily life insufficient to justify immunosuppressive or surgical treatment. They usually have one or more of the following: minor lid retraction (< 2 mm), mild soft tissue involvement, exophthalmos < 3 mm above normal for race and gender, no or intermittent diplopia, and corneal exposure responsive to lubricants
Moderate-to-severe GO	Patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). They usually have two or more of the following: lid retraction ≥ 2 mm, moderate or severe soft tissue involvement, or exophthalmos ≥ 3 mm above normal for race and gender, inconstant or constant diplopia
Sight-threatening GO (very severe GO)	Patients with dysthyroid optic neuropathy and/or corneal breakdown

Main aim in GD management is an elimination of thyrotoxicosis and appropriate complications. Currently 3 treatment modalities are used: antithyroid drugs, thyroidectomy and thyroid ablation with radioactive ^{131}I (radioactive iodine, RAI).

Antithyroid drugs (ATD) are indicated in case of initially discovered GD for achieving euthyroid state; it can be curative for (a) small, nontoxic goiters less than 40 g; (b) mildly elevated thyroid hormone levels; (c) negative or low titers of thyroid hormone receptor antibodies; and (d) rapid decrease in gland size with antithyroid medications.

Two types of ATD are commonly used: propylthiouracil (PTU) and methimazole. Both reduce thyroid hormone production by inhibiting the organic binding of iodine and the coupling of iodotyrosines. Methimazole is administered up to 60 mg per day, PTU — up to 400 mg per day. After euthyroid state is achieved one of two regimens should be chosen: the "titration method" and the "block-and-replace method". First one implies that daily dosage is reduced to the lowest dose maintaining euthyroidism (usually 2.5–10 mg/day), and the treatment is continued for 12–18 months. In the block-and-replace regimen, after restoration of euthyroidism, ATD are continued at the initial high doses, but levothyroxine is added to prevent hypothyroidism. This treatment is usually not continued for more than 6 months. The two regimens do not differ substantially in terms of risk of recurrences after drug withdrawal; the block-and-replace seems to bear a slightly higher risk of side effects.

Also, management includes β-blockers (they block the response to catecholamines at the receptor site (e. g., propranolol) and ameliorate some of the manifestations of thyrotoxicosis) and glucocorticoids in case of active GO.

Relapses occur in 30–70 % of ATD-treated patients. Predictive factors of relapsing hyperthyroidism include large thyroid volume, young age, smoking, the postpartum period and high levels of antibodies against TSH receptors.

Surgical intervention is the oldest modality used in GD treatment, still important nowadays. Main advantage — rapid elimination of thyrotoxicosis. Indications for operation are: inability to achieve stable remission with adequate ATD treatment within 12–24 months, intolerance of ATD treatment, large size of the thyroid (> 60 ml), presence of suspicious nodules, patient's refusal from RAI, unavailability of RAI treatment, active GO. Surgery is performed in euthyroid state to prevent postoperative thyroid storm. In case of ineffectiveness (intolerance) of ATD treatment iodinated drops (Lugol's solution), glucocorticoids, β-blockers or plasmapheresis can be used to achieve a rapid control of hyperthyroidism.

Radioiodine treatment — relatively easy, noninvasive, effective and cheap method of GD treatment. RAI therapy is performed using ^{131}I which has short half-life (8 days). It is indicated in case of ineffective ATD treatment, recurrent thyrotoxicosis, ATD intolerance, contraindications for surgery of patient's refusal from surgical intervention. RAI treatment is contraindicated in case of thyroid nodules, childhood (under 18 y.o.), pregnancy and lactation, huge goiter and compression of adjacent organs. Most studies have found no significant increase in the prevalence of thyroid or other carcinomas in adults patients treated with radioiodine.

Severe complication of thyrotoxicosis is thyroid storm (TS). TS is accompanied by rapid exacerbation of thyrotoxicosis and development of life-threatening condition. Its mechanism is unclear and may be related to cytokine release and acute immunologic disturbance caused by the precipitating condition, such as infection, trauma, surgical emergencies, or operations and, less commonly, by radiation thyroiditis, diabetic ketoacidosis, toxemia of pregnancy, or parturition.

TS is characterized by acute onset of all symptoms of thyrotoxicosis. Patients develop agitation, fever, dyspnea, tachycardia. Nausea, vomiting, abdominal pain may simulate "acute abdomen". Later on agitation switches to delirium with development of sopor and coma. Unfavorable prognostic signs are anuria, jaundice followed by acute hepatic failure. Most dangerous complication is acute cardiovascular collapse due to dystrophia of myocardium, increased by hypoxia, microcirculatory and metabolic alterations, mortality reaches as high as 50 %.

TS management is performed in the ICU, includes prescription of glucocorticoids, ATD, infusion and correction of electrolytes, cardiovascular management, sedation.

Adequate preoperative preparation of patients including plasmaferesis, hemosorption, and hyperbaric oxygenation allowed to decrease postoperative TS incidence down to 0.01 %.

TOXIC GOITER

Focal autonomy of the thyroid gland (toxic nodular and multinodular goiter) — mostly iodine-deficient condition, characterized by signs of thyrotoxicosis due to presence of autonomously functioning thyrocytes. Iodine deficiency leads to the thyroid hyperplasia, and as a result of clonal mutations functioning

independently of serum TSH levels pool of thyrocytes is produced. Final step of iodine-deficient goiter formation is a toxic goiter consisting of one or several hot nodules. Since this process takes decades, multinodular toxic goiter is usually encountered in senior population.

A separate entity is a toxic adenoma (Plammer disease). Usually it is discovered in younger patients. Toxic adenomas are characterized by somatic mutations in the TSH receptor gene, although G-protein–stimulating gene mutations may occur also.

Clinical presentation of nodular or multinodular goiter consists of signs of thyrotoxicosis and, in case of large size, — compression of adjacent structures (trachea, esophagus). Extrathyroidal manifestations are absent.

Evaluation includes physical examination (neck deformity and nodules may be revealed), laboratory data (serum levels of T3, T4, TSH), visualizing methods (US, FNAB, scintigraphy).

Surgical therapy is often recommended after adequate preoperative preparation in patients with large goiters or obstructive manifestations. In case of nodular goiter hemithyroidectomy is performed, in case of multinodular goiter — total thyroidectomy is preferred. Radioiodine treatment and ablative procedures are alternatives, especially in case if surgery is contraindicated. In elderly patients who are not candidates for either radioiodine therapy or surgery, lifelong low dose ATD therapy remains an option.

ACUTE THYROIDITIS (STRUMITIS)

Acute thyroiditis — rarely encountered inflammatory disease of unchanged thyroid gland. Although the thyroid gland is remarkably resistant to infection, congenital abnormalities of the piriform sinus, underlying autoimmune disease, or immunocompromise of the host may lead to the development of an infectious disease of the thyroid gland, acute infectious thyroiditis. In individuals with midline infections, persistence of the thyroglossal duct should be considered. Similar inflammation of goiter is called strumitis.

Most frequent bacteria are Staphylococcus, Pneumococcus, Salmonella, or Mycobacterium tuberculosis. In addition, infections with certain fungi, including Coccidioides immitis, Candida, Aspergillus, and Histoplasma, have been reported.

Onset is acute, accompanied by fever, headache, neck pain and neck edema. Neck pain is due to the thyroid edema and thyroid capsule distension. On examination goiter may be found on the anterior surface of neck, skin redness. Enlarged painful thyroid may be found on palpation, in case of abscess formation — fluctuation. Neck lymph nodes are enlarged, painful.

Diagnosis is made primarily on clinical data; laboratory evaluation is of lesser importance. Leukocytosis is typical, serum levels of thyroid hormones are usually within normal range. On US diffuse heterogeneity and hypoechogenicity

of thyroid tissue can be found. In case of abscess formation cavity with fluid content and enlarged lymphatic nodes will be found.

Differential diagnosis includes subacute de Quervain's thyroiditis, neck phlegmon, acute intracystic hemorrhage, thyroid adenoma or cancer, pharyngitis, esophagitis, otitis, parodontal abscess.

Management of the acute thyroiditis is performed in the department of purulent surgery. Initially conservative management (antibiotics, NSAIDs, infusion) is done until recovery or abscess formation. If abscess has appeared, it should be drained. Serious complication of acute thyroiditis — its spontaneous drainage into trachea, esophagus or mediastinum with subsequent mediastinitis.

SUBACUTE DE QUERVAIN'S THYROIDITIS

Subacute de Quervain's thyroiditis (granulomatous, giant cell) — transient inflammatory and destructive disease of the thyroid gland of viral etiology.

It is thought to be caused directly or indirectly by a viral infection of the thyroid gland and often follows an upper respiratory illness. The mumps virus has been implicated in some cases, and coxsackievirus, influenza virus, echovirus, and adenoviruses may also be etiologic agents. A tendency to appear in the spring in the Northern latitudes has been noted and it predominates in the female.

Subacute thyroiditis is characterized by moderate inflammation, accompanied by destruction and degeneration of the follicles, partial or complete loss of colloid. A characteristic feature is the well-developed follicular lesion that consists of a central core of colloid surrounded by the multinucleated giant cells. The follicular changes progress to form granulomas. Interfollicular fibrosis and an interstitial inflammatory reaction are present to varying degrees. When the disease subsides, an essentially normal histologic appearance is restored.

Clinical presentation consists of 4 phases:

– Initial (thyrotoxic) lasts 2–12 weeks, characterized by pain and mild thyrotoxicosis. Administration of glucocorticoids interrupts this phase;

– Euthyroid phase lasts 1–3 weeks;

– Hypothyroid phase lasts up to 2 months, may be revealed in half of patients. During this phase replacement therapy with LT4 is applied;

– Recovery phase.

Diagnosis includes past history, physical examination, laboratory data (the erythrocyte sedimentation rate is increased, white blood cell count is normal, amount of lymphocytes is increased, elevation in CRP is present; hormonal: elevated serum T4 and T3 and suppressed TSH, the serum Tg level is characteristically high).

On US subacute thyroiditis is characterized by the thyroid gland enlargement and hypoechogenic area at the site of thyroid gland pain. Many of these patients may develop multiple small nodules. On follow-up, the majority of these nodules spontaneously resolve.

Radionuclide thyroid scanning typically shows markedly reduced or absent tracer uptake during the acute phase of subacute thyroiditis. In the recovery phase, the thyroid gland has an increased iodine-trapping ability, which can result in irregular or diffusely increased tracer uptake on scanning before eventually normalizing.

To confirm the diagnosis one can use Crile test — 20–40 mg of prednisolone daily. In subacute thyroiditis inflammation will subside in 1–3 days.

Management is conservative, includes NSAIDs and b -blockers in severe cases with hyperthyroidism. Corticosteroids are useful (about 40 mg hydrocortisone equivalents daily) when the NSAID alone is not successful. However, in some patients, it may take about 4 weeks for the disappearance of the thyroid enlargement.

HASHIMOTO'S THYROIDITIS

Chronic lymphocytic thyroiditis, autoimmune thyroiditis (Hashimoto's thyroiditis) — an organ-specific autoimmune disease, characterized by autoimmune-mediated destruction of the thyroid gland. Definite genetic associations have been shown to contribute to the development of autoimmune thyroid diseases (AITD), including Hashimoto's thyroiditis. Distinct pathologic phenotypes are recognized: goitrous and atrophic variants, IgG4-related variant, hashitoxicosis, juvenile thyroiditis, and silent or painless thyroiditis.

The cause of the disease is believed to be associated with the breakdown of self-tolerance against thyroid antigens that leads to thyroid autoimmunity. As a result, cytotoxic CD8+ T-cells directed against TPO and Tg mediate thyroid gland destruction, either by the granule exocytosis pathway or apoptosis (programmed cell death). Contribution of the environment of the liability to developing Hashimoto's thyroiditis is considered to be around 20–30 %. Among environmental factors that were proven: high iodine intake, smoking, low selenium intake.

The pathologic features of autoimmune hypothyroidism vary from mild focal thyroiditis to extensive lymphocytic infiltration and fibrosis. In classical Hashimoto thyroiditis (originally termed struma lymphomatosa), the thyroid gland may be diffusely enlarged or nodular; the tissue is pale and firm and has a rubbery texture. Destruction of thyroid epithelial cells occurs as disease progresses from euthyroidism to hypothyroidism.

Autoimmune thyroiditis is a very frequently encountered thyroid disorder, especially involving women 40–60 years old. Male-to-female ratio is 1:4–1:8.

Hashimoto's thyroiditis doesn't have specific clinical signs. Hypothyroidism develops gradually, majority of patients at presentation usually are euthyroid or have subclinical hypothyroidism. Approximately 10 % of patients may develop transitory hyperthyroidism (hashitoxicosis). It evolves into permanent hypothyroidism after 3–24 months.

Chronic autoimmune thyroiditis has a goitrous (classic) form often referred to as Hashimoto's disease (in agreement with the presence of a goiter in

the patients described by Hashimoto himself in 1912) and an atrophic form sometimes referred to as Ord's disease (as first reported by W. M. Ord in 1888).

Diagnosis relies on family history (presence of autoimmune disorders, especially AITD), examination (signs of hypothyroidism, firm gland on palpation), laboratory data (hypothyroidism, antibodies against TPO and Tg), US data (diffuse or inhomogeneous hypoechogenicity or patchy echo pattern), reduced RAI uptake. The combination of thyroid ultrasound, thyroid function tests, and thyroid antibodies usually allows to make a reliable diagnosis of Hashimoto's thyroiditis. Cytology and histopathology are nowadays rarely required to ascertain the diagnosis.

In euthyroid patients with Hashimoto thyroiditis, no treatment is required because the goiter is usually asymptomatic. Replacement doses of thyroid hormone should be given when hypothyroidism is present, appropriate to the degree of hormone deficiency. Surgery may be justified if compressive symptoms or unsightly enlargement persists after a trial of levothyroxine therapy.

INVASIVE FIBROUS THYROIDITIS

Riedel's thyroiditis is a rare disease of undetermined etiology with characteristic progressive fibrosis of the thyroid gland. It involves not only thyroid gland itself, but also surrounding structures — trachea, esophagus, vessels, nerves.

Etiology is unclear, but the systemic autoimmune hypothesis has the most support, due to elevated titers of thyroid autoantibodies. Retroperitoneal, orbital, and mediastinal fibrosis, as well as rarer fibrotic syndromes, are associated with Riedel's thyroiditis.

Disease is progressing gradually, initially patients are presenting with a rapid indolent enlargement of the thyroid that becomes very hard on palpation and difficult to delineate. Symptoms are usually related to tracheal and/or esophageal compression. Other local effects include hoarseness because of recurrent laryngeal nerve affection, reduction of blood flow due to compression of large veins, and Horner's syndrome through involvement of the cervical sympathetic trunk. A proportion of 30–40 % of patients develop overt hypoparathyroidism due to involvement of the parathyroid glands.

Physical examination, laboratory analysis, and imaging features are not helpful for differentiating between Riedel's thyroiditis and neoplastic diseases or the fibrotic variant of Hashimoto's thyroiditis. FNAB is almost always nondiagnostic. Therefore, histological examination is necessary to establish the final diagnosis, and surgical biopsy is mandatory.

Surgical treatment may be necessary when compressive signs and symptoms become intolerable. Thyroidectomy may be extremely difficult if there is extensive extrathyroidal fibrosis and involvement of the parathyroid glands and/or recurrent laryngeal nerves. Tamoxifen, 10 to 20 mg/day (with or without corticosteroids), has been successful in many of these patients.

THYROID TUMORS

Histological classification of thyroid tumors
1. Epithelial tumors
1.1. Benign: follicular adenoma, others
1.2. Malignant:
Papillary carcinoma
Follicular carcinoma
Medullary carcinoma (C-cell carcinoma)
Poorly differentiated carcinoma
Undifferentiated (anaplastic) carcinoma
Others
2. Nonepithelial tumors
3. Malignant lymphomas
4. Miscellaneous tumors
5. Secondary tumors
6. Unclassified tumors
7. Tumor-like lesions

Follicular adenoma is a benign tumor derived from the follicular cells. The incidence of follicular adenoma in autopsy series has ranged from 3 to 4 %.

The most common clinical presentation of follicular adenoma is a painless nodule in the thyroid, which may sometimes show gradual increase in size and become painful because of hemorrhage and necrosis. The patients are usually euthyroid except in rare cases of toxic adenoma that present with hyperthyroidism.

Toxic adenoma is developing mainly due to mutations of genes, encoding synthesis of TSH receptors or G-protein. In contrast, the molecular etiology of non-functioning follicular adenomas is still largely unknown.

Diagnosis includes physical examination (tumor-like round-shaped lesion, smooth, painless, retractable), laboratory data (TSH, T3, T4), US (round-shaped, well-defined, hypoechogenic lesion with pronounced hypervascularization). Usually confirmation of preoperative diagnosis in case of nodular lesion is achieved with the help of FNAB. Unfortunately, FNAB is unable to distinguish follicular adenoma from follicular carcinoma. The reason for this limitation is that the diagnostic distinction between follicular adenoma and carcinoma is based on the presence or absence of thyroid capsular and/or vascular invasion by the neoplastic cells. This determination requires evaluation of the resected neoplastic tissue. Thyroid nodules in this category are triaged for surgery, usually lobectomy, given that 14–32 % may represent a follicular (or Hürthle cell) carcinoma.

Thyroid cancer — malignant epithelial tumor, which is presented by following main histological types: papillary carcinoma, follicular carcinoma, medullary carcinoma, poorly differentiated carcinoma and undifferentiated (anaplastic) carcinoma.

Papillary and follicular carcinomas originate from follicular cells, are considered as differentiated cancers and characterized by relatively favorable prognosis; 10-years survival rate reaches up to 94 %. Medullary cancer originates from C-cells; its clinical course is more aggressive. 10-years survival rate reaches up to 80–90 % in cases when metastases are absent and doesn't exceed 40 % in metastatic cases.

Differentiated thyroid carcinoma of both papillary and follicular type may progress to a more poorly differentiated phenotype. Poorly differentiated thyroid carcinoma is a heterogenous group that that may present as insular carcinoma or a group of less well-defined morphologic phenotype; it is characterized by presence of solid/trabecular/insular growth pattern, absence of nuclear features of papillary thyroid cancer, and presence of at least one of the following: convoluted nuclei; mitotic activity of 3 or more per 10 fields of view; and tumor necrosis. Poorly differentiated thyroid carcinoma has a behavior that is intermediate between differentiated cancer and anaplastic carcinoma, with a mean survival of approximately 3 years.

Anaplastic carcinoma of the thyroid is a highly undifferentiated and highly aggressive tumor that constitutes less than 2 % of all thyroid cancers and is almost invariably fatal within 1–2 years of diagnosis. Its incidence is higher in regions endemic for goiter. The patients are usually elderly in their seventh or eight decade of life, with a female preponderance of around 2.5:1. Personal history of goiter may be seen in approximately 25 % of cases and prior exposure to radiation in 9.4 % cases. Survival was best in early stage patients treated with aggressive surgery and both external radiation and chemotherapy.

There are no specific clinical signs of thyroid cancer. Clinical presentation of thyroid cancer includes rapidly enlarging neck mass associated with compressing symptoms such as dysphagia, hoarseness, and stridor. Every nodule that is firm, fixed to the adjacent structures in the neck, and associated with cervical lymphadenopathy and/or paralysis of the vocal folds is highly suspicious for thyroid cancer.

Occasionally, a metastatic tumor manifests as a painless lateral neck mass that is clinically detected before detecting the primary thyroid lesion. Frequently metastases can be found in lungs, skull, spine, sternum and ribs, as well as in skin liver and kidney.

In many cases diagnosis is difficult because of presence of concomitant thyroid pathology (adenomas, colloid nodules, thyroiditis).

Several clinical features must be considered during thyroid nodule evaluation: age, sex, status of thyroid function, history of radiation exposure, family history, and pre-existing thyroid disorders.

Relatives of papillary thyroid cancer (PTC) patients have a significant increased risk of developing the same cancer. Radiation to the head and neck region leads to the development of benign and malignant thyroid nodules and hyperparathyroidism. The risk of a malignancy is 33 %. Patients < 20 or > 70 years

with thyroid nodules have an increased risk of malignancy, as do men. Symptoms of hyperthyroidism (weight loss, tremor, palpitations, increased sweating, heat intolerance, and insomnia) suggest autonomously functioning nodule with relatively low risk of malignancy.

On physical examination presence of hard, gritty, or fixed to surrounding structures such as the trachea or strap muscles nodules and the cervical chain of lymph nodes are assessed.

Laboratory examination is necessary only for diagnosing medullary thyroid cancer. Calcitonin is a marker of this type of carcinoma.

US is the main method of the thyroid gland and lymph nodes examination. Ultrasound findings within a nodule that are considered suspicious for malignancy include microcalcifications, hypervascularity, infiltrative margins, being hypoechoic compared with surrounding parenchyma, and having a shape that is taller than its width on transverse view.

FNAB is a key diagnostic technique in the evaluation of thyroid nodules. It allows to diagnose thyroid cancer in 80–96 % of cases, reveal its type in 60–70 % of cases. In case of non-diagnostic FNAB it should be repeated. Usually it is performed in nodules 1 cm in diameter or larger. In case, when nodule is highly suspicious judging by US data, FNAB can be performed for smaller lesions.

CT and MRI are necessary to evaluate extrathyroidal extension and local or distant metastases.

Aim of treatment — curative surgery of locally advanced cases and combined treatment of disseminated forms.

Extent of surgery is defined by histological type of tumor and stage of disease.

In case of papillary or follicular microcarcinomas, absence of extrathyroidal extension and metastases hemithyroidectomy will be sufficient. In other cases, total thyroidectomy should be performed. Lymphadenectomy should be considered during operative planning because thyroid cancer has a high frequency of lymph node metastasis. Majority of protocols include obligatory central neck dissection. In the presence of pathologically confirmed lateral neck nodal disease, an ipsilateral therapeutic lateral neck dissection is indicated.

In postoperative period RAI therapy may be indicated for ablation of thyroid tissue remnants and possible micrometastases.

To prevent thyroid cancer recurrence suppressive LT4 therapy postoperatively may be applied. Its duration is defined by disease stage.

PRINCIPLES OF THYROID SURGERY

For a long period of time the most frequent type of thyroid operation has been subcapsular partial resection. Modern surgical treatment of hyperthyroidism consists of a differentiated approach with either near-total or total extracapsular thyroidectomy for immunogenic hyperthyroidism and with lobectomy for toxic

adenomas. Systematic identification of anatomic structures and meticulous dissection are necessary for excellent visualization which is the main way to avoid RLN or parathyroid injury.

The standard Kocher's incision is placed 1.5–2 cm above the sternal notch. The incision is carried out through the skin and the subcutaneous layer through the platysma muscle. The two skin flaps are created by dissecting them away from the strap muscles upward to the thyroid cartilage and downward to the suprasternal notch. The approach to the thyroid capsule is done by splitting the strap muscles in the midline. After that the thyroid becomes achievable for inspection, that allows deciding further maneuvers. Typically, next steps include mobilization of the upper pole and ligation of superior thyroid artery. Inferior pole is mobilized next; this allows gland retraction upward and medially. As a result, thyroid capsule and ligaments are pulled on and RLN can be visualized. Simultaneously mobilization of superior and inferior parathyroid glands is performed. After that Berry ligament is transected and final mobilization of thyroid lobe is over. Removal of one entire lobe and isthmus of the thyroid is called hemithyroidectomy. In case of total thyroidectomy, similar intervention is performed from the contralateral side. After completion of thyroidectomy hemostasis is ensured, thyroid bed is washed with saline and wound is closed, usually leaving drain inside.

Recently minimally invasive interventions have gained popularity. These methods can be classified into 2 groups: nonoperative ablative procedures and surgical modalities.

Nonoperative ablative procedures are used as an alternative to traditional surgery in case of thyroid nodules.

This group includes following modalities:

– ethanol destruction,
– transcutaneous laser ablation,
– radiofrequency ablation,
– ultrasound destruction,
– microwave destruction.

Ethanol destruction is one of the earliest ablative procedures, which has been described in the 1990s. Ethanol is injected into the nodule under ultrasound guidance. Mechanism of its action consists in protein coagulation and thrombus formation in microcirculatory vessels, which leads to nodule shrinking.

This method is used in case of functionally autonomous nodules and for cysts sclerosing. This method is already well adopted and included in treatment protocols of a number of countries.

Transcutaneous laser ablation initially was introduced in clinical practice in 2000. During multiple researches effectiveness and safety of this procedure, as well as early and delayed postoperative results were well studied. Mechanism of its action consists in tissue coagulation under laser emission. Cell death lasts up to 72 hours due to microthrombi formation and tissue ischemia.

Most typical indications are benign nonfunctioning nodules causing local compression, cosmetic complaints, refusal from traditional operation or intolerance of surgical operation because of high anesthetic risk. Recently indications have included functionally autonomous nodules.

One more rapidly developing method is radiofrequency ablation (RFA). In spite of long history of its use in the treatment of tumors of different localization, firstly its application in thyroid surgery was described in 2006. Since that time a number of studies were performed to evaluate its effectiveness and safety in benign thyroid nodules.

Mechanism of its action consists in electrode introduction into the nodule and subsequent administration of high-frequency current. This leads to local heating of tissues around the electrode up to 60–90 ºC, which leads to tissue necrosis.

Laser and radiofrequency ablation have been introduced recently and currently are under investigation and in the process of adoption by numerous specialized endocrine surgery units.

Ultrasound and microwave destruction now are largely experimental methods.

Minimally invasive thyroid surgery has emerged in 1997, following the first report of endoscopic thyroid resection by Huscher C. S. Within several years these operations have been introduced almost simultaneously in various centers and by various authors. Initially, indications were restricted to solitary nodules less than 3.5 cm in diameter and lobes up to 15 ml of volume. In time, the indications have expanded and now include small goiters, Graves' disease, and even low-risk malignancies or RET mutation carriers. According to the most recent literature, some authors have embarked on full oncologic resections with prophylactic central compartment node dissection. Currently there are more than 20 various modalities, that have been proposed for minimally invasive thyroid surgery.

By type of access all these modalities can be classified into 2 main groups: cervical access (main incision is performed on the neck) and extracervical (main incision is performed beyond the neck).

Most frequent criterion for minimally invasive operation is maximal incision length of 3 cm, which allows direct access to the thyroid and surrounding structures.

Minimally invasive endoscopic procedures — are interventions, which are performed solely through endoscopic ports; video-assisted operations — some manipulations are performed without endoscope.

"Minimally invasive video-assisted thyroidectomy" (MIVAT) was introduced by P. Miccoli in 1999 and is the most widely applied video-endoscopically assisted type of thyroidectomy. It can be utilized both for hemithyroidectomy or total thyroidectomy and for central lymph node dissection.

Operations that are performed from the remote extracervical access are much more sophisticated and challenging, but as a result patient avoids a visible scar in the neck for cosmetic reasons.

Most frequently applied extracervical approaches for endoscopic thyroidectomy are axillary and breast, for video-assisted thyroidectomy — VideoAssisted Neck Surgery (VANS) from anterior chest approach. Working space is maintained by a mechanical lifting system or by insufflation of carbon dioxide.

Main advantages of minimally invasive methods are: reduced trauma and postoperative pain, reduced hospital stay, better cosmetic result.

POSTOPERATIVE COMPLICATIONS

Typical complications are: bleeding, recurrent laryngeal nerve (RLN) injury, postoperative hypoparathyroidism.

Postoperative bleeding usually occurs between 6 and 12 h after the initial operation. It is characterized by respiratory distress, pain, cervical pressure, dysphagia, and increased blood drainage. Blood loss itself usually is less dangerous, as far as hematoma causes compression of RLN and trachea that leads to respiratory distress. Once recognized, the wound should be reopened and the hematoma evacuated. In case of significant respiratory distress, emergency bedside hematoma evacuation, if necessary, in combination with endotracheal intubation, is required. After that, definite hemostasis should be ensured.

RLN injury leads to vocal cord paresis from the appropriate side. It leads to hoarseness or aspiration. Bilateral RLN injury leads to variable degrees of airway obstruction. Sometimes it can prompt tracheostomy. Transient cord paresis seldom lasts more than 4–6 weeks. When no restitution of function is notable within 6–12 months postoperatively, permanent damage should be assumed. Treatment by a speech and language pathologist or invasive interventions such as injection laryngoplasty or medialization laryngoplasty are necessary.

Occurrence of postoperative hypoparathyroidism may be attributed to inadvertent removal of the parathyroid glands or their devascularization. Depending on number of the involved glands and trauma mechanism hypoparathyroidism can be clinically latent or overt, temporary or permanent. It leads to the decrease of serum calcium level, which is accompanied by paresthesia, in severe cases — seizures. Treatment includes calcium and vitamin D supplementation.

CLINICAL CASES

1. A 63-year-old patient with moderate severity Graves' disease. The volume of the gland is 21 cm^3, there are no nodules in the gland, concomitant chronic diseases in the stage of decompensation are also not revealed. What is the preferred treatment strategy?

2. The patient has a retrosternal goiter with compression syndrome (compression of the trachea). What management are you going to choose?

3. The patient has a cytologically verified colloid euthyroid goiter with a 5 cm nodule in the left lobe. What is the best treatment option?

4. The next day after thyroidectomy for Graves' disease, psychomotor agitation of the patient, tachycardia and hyperthermia were noted. What is your diagnosis and treatment?

5. A patient of 35 years of age was diagnosed to have a focal mass in the right lobe of the thyroid gland 2.0 cm in diameter. Nodule is invisible; thyroid hormones are within normal range, according to the FNA biopsy — a colloid goiter. What is your further management?

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