Diagnosis of thyroid disorders











Assoc. prof. A. Punda,MD.,PhD. Assoc. prof. V. Marković,MD.,PhD. S. Gračan, MD., nucl. med. spec.

Thyroid

- Thyroid is single, endocrine gland situited in the lower part of the neck, in front of the trachea, weigh 20 g
- Upper limit of normal thyroid volume is around 18 ml



Development of the thyroid

Parafollicular or C-cells

They are formed from ultimobrachial body which is made from the epithelium of the fourth pharyngeal pouch.

Ultimobrachial body is incorporated in the thyroid lobes and from it are formed Ccells.





Slika 16.11. Shematski prikaz premještanja osnove timusa, epitelnih tjelešaca i ultimobranhijalnog tijela. Osnova štitne žlijezde nastaje u središnjoj crti u području foramena cekuma i spušta se do razine prvog hrskavičnog prstena dušnika.

Follicular cells

They are formed from endodermal epithelium in the bottom of the pharyngeal bowel, on the border of the anterior 2/3 and posterior 1/2 base of the tongue (foramen cecum).



A. Thyroid gland is developed from the epithelial outgrowth in the middle of the pharynx, caudal from the medial tongue lump. B. Position of the thyroid gland in adults. Discontinuous line represents migration path of thyroid basis



Schematic representation of posistions of ductus thyreogossal cysts: they are most often found near hyoid bone, but they are allways near central line of the neck



Ectopic – lingual thyroid

Tc-99m-perthechnetate scintigram



Ectopic – lingual thyroid I-131 scintigram: SPECT/CT of the neck and planar whole body scintigram



Ectopic – lingual thyroid Ultrasound: coronal and sagittal cross-section



Ectopic – lingual thyroid





Normal and aberrant locations of thyroid tissue

What is this?



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Dual Ectopic Thyroid Gland

Sonography and Scintigraphy of Lingual and Sublingual Thyroid

Vinko Marković, MD, PhD,* Gordana Glavina, MD, Davor Eterović, PhD,* Ante Punda, MD, PhD,* and Dubravka Brdar, MD*

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ultrasonography and scintigraphy



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Dual Ectopic Thyroid Gland



Histology and patohistology

- Functional unit of the thyroid is follicle, oval or round bag (sac) filled with colloid content, coated with one layer of squamose or cuboid epithelia cells
- Colloid thyroglobulin molecule to which thyroid hormones are attached to
- In the normal gland size of the follicles ranges from 200-300 μm, while some of them can be larger than half mm





Thyroid hormones

T4 TYROSINE - TETRAIODOTYRONINE



Thyroid hormones



Thyroid hormones



Regulation of function and synthesis of thyroid hormones

Hypothalamus

TRH

Pituitary *

TSH

Thyroid

T3+T4

Transporting proteins (globulin TBG (75%) prealbumin TBPA (5-20%), albumin (5-20%))

Periferal conversion (PTU)

FT4 FT3

100-200 µg iodine

 Iodide is transported actively into the thyroid by thyroid-iodide pump; competitive blocators: thiocyanate, perchlorate

2. lodide oxidation (iodide from the blood is oxidated to neutral iodine I₂) and then bounded to the tyrosine part of the thyreoglobulin molecule (organification) forming MIT and DIT – blocked by tionamide

3. **Coupling**: two molecules of DIT into T4 and one molecule of MIT and one molecule of DIT into T3 – **blocked by tionamide**

Synthesis of T3 (10%), T4 (90%)

Thyreoglobulin

4. Proteolysis of Tg and release of hormones into the circulation

→100-200 μg T3+T4

Metabolisam of thyroid hormones

- Daily production of T4 = 130 nmol (100 μg): 30 % is converted into T3 (40 nmol), 40 % is converted into inactive rT3 (50 nmol); rest is metabolized by different metabolic pathways, mostly by conjugation with sulphates and glucuronide acid (around 20% of T4 is excreted by stool as glucuronide conjugate) and by oxidative deamination
- Daily production of T3 = 50 nmol (33,5 μg): 40 nmol (80%) by extrathyroid conversion from T4, and 10 nmol (20%) by intrathyroid production [5 nmol (10%) by synthesis and 5 nmol (10%) by intrathyroid conversion from T4]; overall 90% of T3 is formed by conversion from T4.

Transport of thyroid hormones in the blood

Thyroid hormones in the blood are bounded to:

- **TBG** thyroxine binding globulin, Thyreopexin: 75% T4 and 75% T3
- **TBPA** thyroxine binding prealbumin, Transthyretin,

TTR: 20% T4 and 5% T3

HSA- human serum albumin: 5% T4 and 20% T3

Free thyroxine (FT4) = 0,03% T4

Free thriiodotyronine (FT3) = 0,3% T3



T3 biologiclly active hormon, T4 prohormon.

Hyper- and hypo-thyroxinaemia

Increased TBG (hyperthyroxinaemia): pregnancy, estrogens, opioid drugs, 5-fluorouracil.

Decreased TBG (hypothyroxinaemia): chronic disease, malnutrition, nephrotic syndrom, liver disease, corticosteroids, androgens.

Decreased transthyretine(hypothyroxinaemia): acute and chronic disease, liver disease, nephrotic syndrom, malnutrition.

Decreased albumin (hypothyroxinaemia): chronic disease, liver disease, nephrotic syndrom, malnutrition.

Thyroid hormones metabolism

- T3 is further metabolized by deiodinitation on the internal ring into 3,3'T2 (di-iodotyrosine).
- rT3 is further metabolized by deiodinitation on the external ring also into 3,3'T2 (di-iodotyrosine).
- Deiodinitation on the external ring transforming prohormon T4 into active hormon T3, while deiodinitation on the internal ring inactivates thyroid hormones (T4 into rT3, and T3 into 3,3'T3)

D1- deiodinase type 1

- Three enzymes catalyze deiodination of thyroid hormones: deiodinase type 1 (D1), type 2 (D2) and type 3 (D3)
- D1 is most commonly expressed in liver, kidneys and thyroid
- Deiodination on the external ring of thyroxine, T4 → T3 and rT3 → 3,3'T2, but also on the internal ring T4 → T3
- Deiodination on the internal ring of different derivates of iodotyronine because of reutilisation of iodine
- D1 provides forming of plasmatic T3, and is therefore main source of cirrculating T3
- D1 activity in hyperthyroidism is increased (that reduces concentration of T4 which leads to less arrival to the tissue and smaller cellular conversion of T4 into T3).
- D1 activity in hypothyroidism is decreased (insures for higher concentration of tissue T4 and therefore more T3)

D2- deiodinase type 2

- D2 is most commonly expressed in CNS, pituitary and brown adipose tissue (BAT), as well as in thyroid and sceletal muscles
- Deiodinitation can be performed only on the external ring of T4 (T4 ₹3).
- <u>D2 catalysis transformation of T4 to T3 in the cells</u>
- D2 activity is increased in hypothyroidism and decreased in hyperthyroidism
- D2 insures that brain, pituitary and BAT have adequate quantities of T3 in different functional states

D3- deiodinase type 3

- Inactivates thyroid hormones has only the ability for deiodinatation on the internal ring, T4→ rT3 and T3 — 3,3'T2.
- High activity of D3 is found in the brain, placenta, gravid uterus and fetal tissues, as well as in the skin, liver and bowel
- Expression of D3 is much higher in fetal tissues than in adult tissues
- D3 activity is increased in hyperthyroidism, and decreased in hypothyroidism
- D3 prevents to much exposure of the fetus and the brain to the thriiodotyronine (T3)

Deiodinase

- Hyperthyroidism: D1 acitivity overcome
- Hypothyroidism: D2 activity overcome
- "Low T3 syndrom" in nonthyroid diseases (low T3, increased rT3 and normal FT4): decreased D1 acitivity in the liver and induced D3 activity in the liver, sceletal muscles and other tissues)

Deiodinase – pharmalogical influence

- Some drugs can interfere with periferal conversion of T4 to T3 :
 - PTU: specific, uncompetitive inhibitor of D1.
 - Ipodate and iopanic acid are competetive D1 inhibitors.
 - Corticosteroids and beta-blockers also inhibit periferal conversion of T4 to T3, by unknown mechanisam.
 - Amiodaron and it's metabolit desethyl-amiodarone: also inhibit D1 deiodinase activity and by that reduce T3 levels.

Deiodinase

- Tissues criticaly dependent of T3, like brain, have expressed D2 activity and by that they ensure T3 despite the posible variations in serum cancentration levels of T3 (for example in hypothyroidism).
- D2 protects brain from hypothyroidism, and D3 from hyperthyroidism.
- Tissues that can balance fast T4 are liver and kidneys.
- After the balance is achieved, half-life of T4 is 7 days, and T3 1 day

Deiodinase

- Deiodinases have posability to increase or decrease influence of thyroid hormones by working as a very important mechanisam that can vary hormon levels in different tissues.
- Deiodinases can modulate in different ways hormone status of different tissues in states of iodine deficite, thyreotoxicosis or hypothyroidism.
- The entire thyroid hormons' metabolisam can be observed through the effectiveness of cellular supply of nuclear T3.

Deiodinase activity

	D1	D2	D3
Hyperthyrodism	increased	decreased	increased
Hypothyrodism	decreased	increased	decreased

Thyroid hormons effects

Primary effect is expressed on the <u>cellular nucleus</u> where by bounding to receptores they cause expression of different genes, and further increase in protein sinthesis and enzymatic activity.

Some thyroid hormon's activity on the cellular metabolisam is mediated by activity on cellular membrane, endoplasmatic reticulum and mitochondria.

Thyroid hormones regulate growth, development and metabolisam.

In adults their action is primary metabolical: they regulate overall production of energy and traffic of all the important supstrates: proteins, carbohydrates, fat, hormones and vitamines.

Diagnosis of thyroid diseases











DIAGNOSIS OF THYROID DISEASES

- 1. Anamnesis and clinical exam
- 2. Blood analasys (in vitro tests)
- 3. Thyroid ultrasonography
- 4. Thyroid scintigraphy
- 5. Radionuclide examination
- 6. Fine-needle aspiration cytology
- 7. Radiological testing

Anamnesis (History)

Symptoms of hypothyroidism

Symptoms of hyperthyroidism

Thyroid enlargement, neck swelling, difficulty of swalloving or breathing, pain, eye symptoms and signs...
Clinical examinaiton

Inspection Thyroid palpation

Heart rate

Skin state

Tremor

Eye signs,....



Thyroid palpation



Thyroid palpation



Goiter (struma) World health organisation division (WHO)

- **Grade 0:** No goiter: hardly palpable and visible (or unpalpabile or unvisible)
- Grade IA: clearly palpable, but unvisible with neck extension
- Grade IB: clearly palpable and visible with complete neck extension (head thrown). This stage involves nodular thyroid, even if the thyroid itself isn't enlarged
- Grade II: clearly visible when the head in normal position (palpation isn't neccessry for diagnosis)
- **Grade III**: thyroid seen from the distance (palpaiton isn't neccesery for diagnosis)

Revised goiter classification

Grade 0 Not enlarged by inspection or palpation
Grade 1 palpable goiter, but not seen when head and neck are in normal position (thyroid isn't visible by inspection). This category includes thyroid nodul in normal size gland).

Grade 2 thyroid visible when head is in normal position or enlarged thyroid by palpation.

WHO, UNICEF, and ICCIDD. 2001. Assessment of the Iodine Deficiency Disorders and monitoring their elimination. Geneva: WHO publ. WHO/NHD/01.1. 1-107 pp.

What is nodul?

- Inspection: thyroid formation-lump
- Palpation: formation of different consistency
- Ultrasound: formation of different echostructure or formation of the same echostructure but separated from the rest of the thyroid by hypoechogenic border (rim)
- Scintigram: formation of different function

<u>Ultrasound</u>

Inspection and palpation





Scintigraphy



Diagnosis with in vitro tests

TSH

- T3, T4, FT3, FT4
- Tg, Calcitonin, TBG, protein bounded iodine TSH receptor - antibodies, Tg-Ab, and TPO-Ab Urine iodine

Thyroid ultrasound

Ultrasound examination of the thyroid

- Ultrasound echos are formed on the border of different sound resistance tissues, mainly on the border of solid tissue and colloid.
- Normal thyroid: homogeneity allocated echos which are, in regard to the muscles, denser and of higher amplitudes – normoechogenic or isoechogenic image.

ULTRASOUND OF NORMAL THYROID



Ultrasound image of normal thyroid (normoechogenic), leftlongitudinal axis, right- cross-section.

ULTRASOUND EXAMINATION OF THE THYROID

Both thyroid lobes and isthmus are shown in longitudinal, cross-section and inclined sections (three dimensions).

Analasys: size

echostructure

present of nodule

relationship to the other structures on the neck and orientiational neck examination

NECK ANATOMY





Cross-section through the neck



Transverse image of the right thyroid lobe. Note the compressed internal jugular vein (IJV) lateral to the common carotid artery (CCA) (A) compared with the distended internal jugular vein (B) when the patient performs a Valsalva maneuver. Also well seen are the thyroid gland (THY), tracheal rings (TR), the sternocleidomastoid muscle (SCM), and the omohyoid (OH), sternohyoid (SH), and sternothyroid (ST) muscles all separated by a fascial layer (arrows).

THYROID SIZE

Normal dimension:

lenght 4-5 cm

widht 1,5-2 cm

thickness 1-1,5 cm

Isthmus thickness up to 0,3 cm

Thyroid volume 10-15-18 ml

Thyroid weight Tw(gr)=1,06 x V(ml)

Thyroid volume: according to formula for elipsoide vol. (for each lobe) $V=\pi/6$ abc = abc/2





π /6=0,523



Untreated diffuse toxic goiter

Because of increased cells proliferation and relatively empty follicules, there are less borders of which the ultrasound is reflected, and therefore less echoes reflected back to the ultrasound probe.

Accordingly, untreated diffuse toxic goiter is shown more or less hypoechogenic.

Ultrasonography of diffuse toxic goiter



Hypoechogenic image of the thyroid in Mb. Basedow, left – longitudinal section, right – cross-section

Normal thyroid

Diffuse changes

- 1. Diffuse goiter,
- 2. Struma lymphomatosa,
- 3. Diffuse toxic goiter,
- 4. Thyroiditis subacuta









NODULAR CHANGES

Number, size, echostructure, location

- 1. Cyst or cystic-degenerative changes
- Solitar nodule hypoechogenic, isoechogenic, degeneratively changed (benigne goiter)
- 3. Nodular (multinodular) goiter
- 4. Nodule in struma lymphomatosa,











NODULAR CHANGES

tumors – adenomas, carcinomas













Hypoechogenic nodule with irregular border



Hypoechogenic lymph node



Ca. papillare









Ca. papillare









Echogenic features suspected for malignancy

Hypoechogenic

Microcalcifications

No hypoechogenic edges, irregular borders

Intranodular vascularization

Regional lypmhadenopathy



Color Doppler



*Color Doppler can help deside on which lymph node to preform US giuded fine needle aspiration.

Functional assesment of thyroid tissue by using color-doppler in hyperthyroidism.

Flow stages on CD



Stage 1– minimal internal vascularization without periferal ring



Stage3 – periferal vascularization with little to medium internal flow.



Stage 2 – periferal vasclarization (>25% perimeter of the nodule), without or with minimal internal flow.



Stage 4 – high internl vascularizaiton with or without periferal ring.

Orientational neck examination





Metastatic lymph node



Lymph node metastasis on both sides of jugular vein



Enlarged - patologic neck lymph nodes





Enlarged – patologic neck lymph nodes and medial neck cyst





Medial neck cyst (cyst of ductus thyreoglossus)





Thyroid scintigraphy

Tc^{99m}- accumulation image

I¹³¹- accumulation and iodine organification image



*gamma camera, pin-hole collimator

Indications for thyroid scintigraphy

•Solitar or multiple nodules (nodular goiter): warm – cold nodules; especially with supressed TSH.

- Follicular tumor on fine needle aspiration.
- •Suspected subacute thyroiditis.
- •After partial (multinodular goiter) and total thyroidectomy (carcinoma).
- Ectopic thyriod, evaluation of substernal thyroid tissue.

"Warm or hot" nodule(s) are benigne (extremely rearly malignant).

"Cold" nodules – malignancy risk 5-8 %.

Nodular goiter – for differentiation of functional (warm, hot) from afunctional (cold) nodules.



Selective activity accumulation -Hot and warm nodule on scintigraphy



Selective activity accumulation -Warm or hot scintigraphic nodules




Scintigraphic "cold" nodule – fine needle aspiration

cytology



Scintigraphic "cold" nodule – fine needle aspiration cytology



<u>Multinodular goiter</u> – to select the nodule for fine needle aspiration cytology









Atipical findings



Fine needle aspiration cytology – follicuar tumor:

a)"cold" nodule on scint.

- extirpation

- a) "warm" nodule on scint.
 - opservation
- c) "hot" nodule

- therapy







Suspected subacute thyroiditis – dif.dg. – "empty scintigram"













Imaging of thyroid remnant after "total" thyroidectomy for thyroid ca.- I-131 scintigraphy



Thyroid isn't shown (agenesis, thyreoidectomy, subacute thyreoiditis, high iodine input)









Lingual thyroid



Lingual thyroid





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Preoperative Tc-99m-Pertechnetate Scan Visualization of Gross Neck Metastases From Microcarcinoma Papillare and Another Papillary Carcinoma of Tall Cell Variant Scintigraphically Presented Like Small Warm Nodule in Graves Disease Patient. Markovic, Vinko; MD, PhD; Eterovic, Davor; Punda, Ante; MD, PhD; Pesutic-Pisac, Valdi; MD, PhD; Kuna, Tihomir; PhD, DDS

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OvidSP

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Health

FIGURE 1. Tc-99m-pertechnetate pinhole scintigraphy showed a homogeneous distribution of activity in the thyroid with small, warm nodule in the upper pole of the left lobe and 3 gross metastatic nodules on the left side of the neck. The upper 2 metastatic nodules showed equally intensive accumulation of Tc-99m-pertechnetate in comparison with thyroid tissue with less intensive accumulation in the lowest nodule.

I'm not a rabbit. I'm a substernal goiter!



















Radionuclide examination – Diagnostic tests

- * I-131 thyroid accumulation, uptake test
- * Perchlorate test
- * TRH test
- * TSH test
- * Supression test

Radionuclide examinations

I-131 accumulation ("uptake" test)

- Patient is oraly given radioiodine dose (10 μCi; 370 kBq I-131) and after 2 h, 4 h, 24 h and 48 h percentage of the given dose, accumulated in the thyroid, is measured:
- a) Difference between hyperthyroidism and hypothyroidism.
- b) Difference between hyperthyroidism and thyreotoxicosis of different causes.
- c) Determining effective $T_{1/2}$ for calculating therapeutic dose of radioiodine.



Examples of thyroidal RAIU curves under various pathological conditions. Note the prolonged uptake in renal disease due to decreased urinary excretion of the isotope and the early decline in thyroidal radioiodide content in some patients with thyrotoxicosis associated with a small but rapidly turning over intrathyroidal iodine pool.

Radionuclide examinations

Perchlorate test

I-131 accumulation in thyroid is measured 2 hours after the diagnostic dose of I-131, and after that 1 g of pottasium perchlorate is given oraly and then accumulation measure is repeated after 30 and 60 minutes

Normaly accumulation of I-131 isn't reduced or is reduced till 10%.

Reduction greater then 10% shows organification defect (there is output, "wash-out" of nonorganificated iodine out of the thyroid): congenital enzymatic defect, acquired deffect (autoimune thyroiditis, hypothyroidism caused by overload of iodine, tionamide therapy, after radioiodine therapy of hyperthyroidism or after surgery).

i. v. 400 μg TRH, TSH in 0, 15, 30 and 60 $\,$ min.



Differntiation of: 1. hypothalamic from pituitary hypothyroidism 2. evidence of thyroid autonomy - thyreotoxicosis latens

Radionuclide examinations

- **Thyreotropin stimulating test (TSH)-** I-131 accumulation measuring repeated after im. given TSH.
- Normaly or in patients with pituitary hypothyroidism there is increase in 24-h accumulation for ≥50% in regard to first measure, while there is no increase in primary hypothyroidism.

TSH stimulation and scintigraphy:

- 1. enabled sc. visualization of supressed thyroid tissue in toxic adenoma,
- 2. detection and therapy of functional metastasis of thyroid carcinoma,
- 3. determining existence of functional thyroid tissue in patients on supstitutional- supressive therapy, but without its discontinuation

Radionuclide examinations

Supression test – repeated accumulation of I-131 measure 14 days after taking 200 μg of thyroxine or after seven days after taking 75-100 μg of threeiodotironin.

Normaly there is \geq 50% decrease in regard to first measurment.

Normal test excludes hyperthyroidism.

Test is positive (so there is no supression in uptake) in Graves-Basedow disease, toxic adenoma and toxic multinodular goiter, euthyroid patients with Graves-Basedow disease, after therapy of hyperthyroidism, nontoxic multinodular goiter and sometimes in family of patients with Graves-Basedow disease.

SUPRESSION TEST Thyroid scintigraphy with 99mTc





Before LT4

14 days after taking 100 ug LT4

Ultrasound guided fine needle aspiration (FNA)

- First used by Holm and as. in 1975. god.
- Guided by ultrasound exact area of different echostructure can be punctured and aspirated.
- Ultrasound can help to determine to which organ lesion belongs to – important in lesions on the border of two organs.

Techincs for FNA

 Before aspiration skin on the neck must be cleaned from the gel and desinfected.



- Desinfected ultrasound probe is then placed on the neck above the lesion which is ment for aspiration.
- Ultrasound of the needle in the neck is observed on the monitor of ultrasound; when the top of the needle is in the wanted lesion aspiration is done (needle 22-23 gage – fine needle).
- This way "free hand", even lesions smaller then 2-3 mm can be aspirated.

Fine needle aspiration



Top of the needle enters the lesion

Indications for fine needle aspiration citology

Thyroid nodules

Nodules outside the thyroid (lymph nodes, neck tumors, parathyroid glands).

Thyroiditis - dif.dg.

Advantages of ultrasound guided fine needle aspiration

- 1. Visualization of pathologic lesions: denifition of affiliation to certain organ and posibility to choose point for aspiration inside the lesion.
- 2. Reducing incidence of inappropriate material.
- 3. Enabling aspiration of unpalpable, small lesions up to 2 mm.
- 4. Early detection of possible complications (bleeding, perforation).
- 5. Good reproducibility.

Ethanol percutane therapy

- Autonomic functional thyroid tissue adenoma, synthesizes and secretes thyroid hormones independently to TSH secretion.
- When hyperthyroidism syndroms appear (nodule usually bigger then 3 cm) they require therapy (surgical, radioiodine or percutane ethanol injection).
- Percutane ethanol therapy was first used in parathyroid adenomas and small hepatocellular carcinomas.

Ethanol percutane therapy - technic

- According to the volume of the nodule, volume of 96% ethanol for injection is calculated.
- Injection is made by 22G needle (0,7 mm), with max. volume up to 20 ml every 3-4 days.
- Color-dopller is used for verification of decreased nodule vascularity- cirrculation.

Echografic criterion suspected for malignancy:

- Hypoechogenic nodule
- Uneven contours





- small crumbly calcifications

FNAC is mandatory!

In patients with thyroid carcinoma examination of the lateral sides of the neck is mandatory.

Enlarged lymph nodes on the neck, especially if rounded, unhomogenic, isoechogenic or with cystic-degenerative changes are allways suspected of metastasis and **they must be punctuated**.

Lymph node metastasis





Metastatic – isoechogenic lymph nodes





No need for FNAC:

- all nodules in multinodular goiter.
- **Small solitare nodules** (without ultrasound signes for malignacy) **<1 cm.**
- Scintigraphic warm and hot nodules (if not suspected for malignancy by ultrasound.).
- Colloid cysts, cysts <1,5 cm.

• If earlier aspiration finding was normal (benign) there is no need to repeat it.



 Assessment of thyreoglobulin, calcitonin and parathyroid hormon in thyroid nodule's and neck nodule's aspirations.

- Cytologic finding of thyroid nodule's and neck nodule's aspiration sometimes can be inconclusive.
- Punctuate is washed with 1 ml of physiological solution and thyreoglobulin, calcitonin and parathyroid hormon levels measured by usual methodes.
Radiological examination

X-ray of the trachea and soft tissues structures of the neck

- dislocation, compression, tracheomalatio of the trachea
- thyroid calcifications



CT, MR- rearly indicated examinations

X-ray examinations

Substernal goiter



CT, MR Ectopic- intratracheal thyroid



CT, MR Ectopic- intratracheal thyroid







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Retrotracheal Secondary Intrathoracic Goiter Presenting as Cervical Thyroid Nodules on Ultrasonography

> Vinko Marković,^{1,2} Davor Eterović,^{1,2} Ante Punda,^{1,2} Dubravka Brdar,¹ Juroslav Roglić,³ and Zoran Slobodnjak⁴



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Huge intrathoracic goiter in an asymptomatic patient

Vinko Marković¹, Ante Punda¹ and Nenad Ilić²



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Thank you for your attention!