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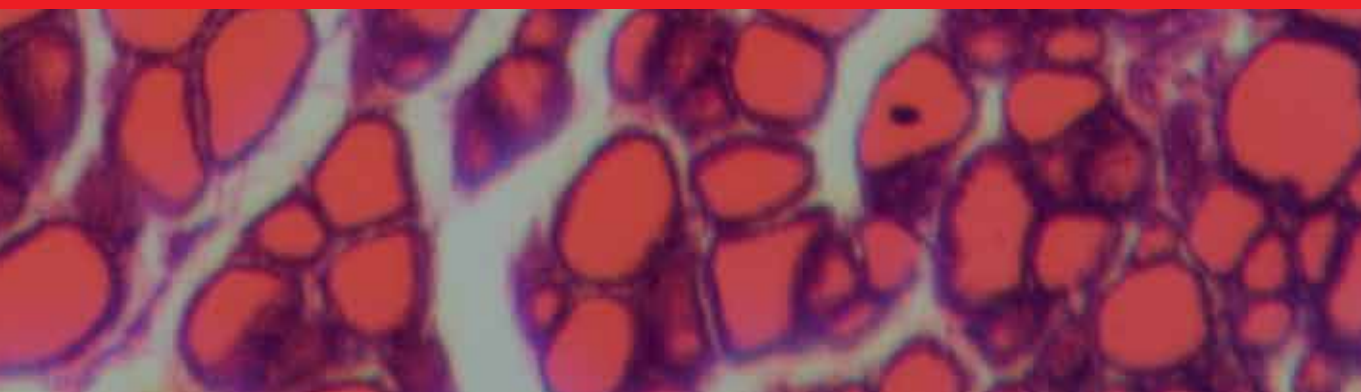
Thyroid Disorders

Edited by Poondy Gopalratnam Raman



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Contributors

Maryam Vaezi, Elena Espinosa Muñoz, Lulu Sakafu, Mira Siderova, Sanjay Saran, Lei Xie, Jianbiao Wang, Liang Zhou, Poondy Gopalratnam Raman

Notice

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Meet the editor

Dr. P. G. Raman graduated in 1962 and received his MD (Medicine) in 1965, both from M.G.M. Medical College, Indore, MP. He has been practicing in diabetes since 1970. Between 1972-75, he worked as a fellow at the Joslin Clinic Boston USA and had intensive training in Diabetes and Endocrinology.

In 1967, he joined as a Lecturer in Medicine at the Medical College, Rewa. He worked at Indore and held different positions. In 2002, he retired from the post of Head of the Dept. and Professor of Medicine from M. G. M. Medical College, Indore. M.P.

He was a teacher both for undergraduate and post-graduate studies for over 30 years. He has more than 100 publications in National and International journals. He is a fellow of the All India Institute of Diabetes as well as of the Indian College of Physicians. He is exclusively devoted to the clinical practice of diabetes and diabetic patient education. He has written several medical books for undergraduate and post-graduate students.

He was Professor and Head of the Department of Medicine, at R.D. Gardi Medical College, Ujjain, after his retirement. He worked as professor and HOD at Shri Aurobindo Institute of Medical Science (SAIMS) for 2 years between 2004-2005. He was awarded B.C. Roy oration in 2007 and he was elected as Fellow of the Royal College of Physicians, Edinburgh in 2005. He is also the recipient of Master-Teacher Award by Indian College of Physicians, a wing of Association of Physicians in India, in 2014.

Contents

Preface

Thyroid disorders are common endocrinal problems more common in women. This book presents various aspects of thyroid disorders as seen in clinical practice. Book will be useful for clinicians, medical students and nursing staff. The purpose of the book is to disseminate knowledge on thyroid diseases. The book contains articles on congenital hypothyroidism, radio diagnostic techniques, thyroid carcinoma and preservation of parathyroid gland and during surgical resection of thyroid gland.

I would like to thank all the contributing authors for their cooperation in submitting their articles in time. I am also grateful to Kristina Kardum, Author Service Manager for her time to time guidance and cooperation.

Dr. P.G. Raman
MD, FRCP (Edin)
Ex-Professor of Medicine
M.G.M. Medical College,
DAVV, lndore (M.P.), India

Chapter 1

Introductory Chapter: Introduction to Thyroid Disorders

Poondy Gopalratnam Raman

Additional information is available at the end of the chapter

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1. Physiological considerations

Thyroid disorders are most common endocrine problem next to diabetes mellitus. Thyroid disorders affect women more compared to men. Thyroid glands secrete, store, and release triiodothyronine (T3) and thyroxine (T4). The hormone T4 gets converted into T3 at tissue level and produces its effect. Iodine is necessary for production of thyroid hormone. Iodine in food is trapped by thyroid gland and is utilized in hormone production. Pituitary and hypothalamus control thyroid gland hormone secretion. TRH from hypothalamus modulates through pituitary to produce TSH, which in turn controls thyroid hormone production. If T4 and T3 are low, TSH level increases to stimulate thyroid gland to secrete more hormone. T3 and T4 hormones have profound effect on the body. Almost all the tissues are stimulated, and body metabolism is increased. T3 and T4 affect cardiovascular system, GI tract, brain, metabolism, weight, bone, etc. With increased T4 and T3, there is tachycardia, diarrhea, hyperglycemia, lowering of cholesterol, increased growth rate in infant, normal brain development, and sexual function. Undiagnosed hypothyroidism in infants not only affects physical and bony growth but also damages brain growth. If untreated, it leads to permanent damage.

Thyroid functions are affected by congenital absence of thyroid glands, autoimmune thyroid disease, surgical removal, infiltrative diseases, and after radiation to neck. Drugs like amiodarone, lithium, interferon alpha, and interleukin 2 prevent thyroid glands from making hormone and causing hypothyroidism.

Pituitary damage by tumor radiation or surgery can affect thyroid glands and cause secondary hypothyroidism.

For brain maturation and brain function, thyroid hormone is necessary. Thyroid diseases like hypothyroid can cause lethargy, hyporeflexia, depression, memory impairment, weight gain, dry

skin, and constipation along with dyslipidemia. Hyperthyroidism produces weight loss, tremors, irritability, and hyperreflexia. Glucose intolerance can also be caused by hyperthyroidism.

Thyroid hormone acts through T3 with nuclear receptors and regulation of gene expression. Hormone deficiency can cause retarded brain maturation and neurological impairment. Thyroid hormone deficiency is caused by congenital and maternal hypothyroidism. Hypothyroidism causes lethargy, hyporeflexia, poor motor coordination, and memory impairment. Hypothyroidism is also associated to bipolar affective disorders, depression, or loss of cognitive functions, especially in the elderly. Thyroid hormone deficiency, even of short duration, may lead to irreversible brain damage.

There is suggestion that reduction in circulating thyroid hormone concentrations is one of the factors mediating impaired neurological development in intrauterine growth retardation and premature babies. More research is required to resolve these questions and ultimately shows if thyroid hormone or iodide supplementation in hypothyroid mothers in the antenatal period and in premature neonates can reduce the prevalence of neurodevelopmental delay.

2. Hyperthyroidism

Hyperthyroidism, which is usually due to autoimmune thyroiditis, clinically presents with tachycardia, increased systolic BP, weight loss in spite of increased appetite, and tremors in both hands. The cardiovascular system reveals fast pulse and sometimes irregular pulse known as auricular fibrillation. Auscultation of chest reveals systolic murmur. Neurological examination reveals brisk knee jerk, and patients show anxiety. There is history of diarrhea. In thyrotoxicosis, bone resorption leads to hypercalcemia. There is decreased PTH, decreased urinary, and fecal calcium excretion. There is hyperphosphatemia. Bone mineral density is decreased due to osteoporosis. Forearms are more affected.

3. Hypothyroidism

In hypothyroidism, patient has a puffy and pallor look. Skin is dry, BP may be increased, and tongue is bigger and voice is hoarse and has constipation due to poor bowel moments. In hypothyroidism, PTH and vitamin D are increased due to low urinary calcium excretion. Decreased bone resorption and formation occurs. Serum osteocalcin and alkaline phosphatase are decreased. Bone turnover is also decreased.

4. Effect of thyroid disorders on bone

Skeletal growth is influenced by thyroid hormone and growth hormone. In thyroid deficiency, there is decreased skeletal growth due to decreased growth hormone and insulin growth factor. Osteoblastic activity is decreased. In childhood thyrotoxicosis, there is advanced bone age due to premature fusion of epiphysis.

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5. Thyroid carcinoma

Thyroid carcinoma like anaplastic, follicular, and adeno may eventually cause hypothyroidism. Diabetes mellitus is associated more with hypothyroidism. In Grave's disease, eyes are involved which is termed as thyroid ophthalmopathy.

Thyroid diseases affect both mother and child before and after delivery. Untreated thyroid dysfunctions can affect neurointellectual development of fetus.

6. Thyroid disorders in pregnancy

During pregnancy, human chorionic gonodotrophin is produced from placenta. This is structurally similar to TSH. Hence, this stimulates thyroid gland, leading to increase in T4 and T3 and decrease in TSH. Thyroid binding globulin is increased due to estrogen and in turn binds T4 and increases T4 level and increases T4 to T3 conversion. There is increased iodine consumption and increased renal iodine clearance. There is increase of iodine transfer to fetus.

7. Thyroid function test in pregnancy

1. Increased TBG, T4, and iodine clearance, decreased thyrotropin, and increased placental type 3 deiodinase leading to decreased thyroxin level
2. TSH level varies with trimester

- 2.5 μg in the first trimester
- Less than 3 μg in the second trimester
- Less than 5 μg in the third trimester
- T4 = 1.5 times higher

8. Factors influencing thyroid functions in pregnancy

1. Increase in human chorionic gonodotrophin in the first trimester stimulates TSHR. This leads to transient gestational hyperthyroidism or hyperemisisgravidorum. Antithyroid drugs are not needed in this situation.
2. Increase in estrogen leads to increased TBGT level.
3. Altered immune reaction leads to autoimmune phenomenon.
4. Increased thyroid hormone metabolism occurs in placenta.

5. Increased urinary excretion of iodine in pregnancy impairs thyroid hormone production. This in turn leads to goiter, maternal, and fetal hypothyroidism. Maternal hypothyroidism is seen in 2–3%. Thyroid hormone requirement increases by 25–50 μg/day.

The current open access book on thyroid disorders covers many interesting topics. On the whole, various titles are interesting and provide additional information. I am sure this online book on thyroid disorders will be read by readers with great enthusiasm.

Author details

Poondy Gopalratnam Raman

Address all correspondence to: drpgraman@yahoo.com

M.G.M. Medical College, DAVV, lndore, MP, India

Chapter 2

Congenital Hypothyroidism

Sanjay Saran

Additional information is available at the end of the chapter

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Abstract

Congenital hypothyroidism is one of the commonest preventable causes of mental retardation is also the most common congenital endocrine disorder of childhood. The subtlety of clinical features and protective effect of the maternal hormone on fetal brain after crossing the placenta mask the clinical features. The incidence varies from 1 in 4000 to 1 in 1000 in newborn infants in various parts of world and is increasing worldwide. Thyroid agenesis remains the most common etiology of CH and other causes are dyshormonogenesis, defects in peripheral thyroid hormone transport, metabolism, or action. CH is usually diagnosed after neonatal screening tests and if treatment started with in few weeks of birth neurodevelopmental outcome is usually normal. Levothyroxine (T4) remains the treatment of choice as most brain T3 is derived from local monodeiodination of T4 and studies have shown normal serum level of T3 in infant treated with T4 alone.

Keywords: congenital, hypothyroidism, levothyroxine, TSH, thyroid

1. Introduction

Congenital hypothyroidism (CH), one of the commonest preventable causes of mental retar dation is also the most common congenital endocrine disorder of childhood [1]. Neurodevelopmental outcome is usually better if treatment is started within in few weeks of birth [2]. The subtlety of clinical features and the maternal hormone crossing the placenta provides a protective effect on the fetal brain masking the clinical signs [3]. In addition to this even the most severe forms of CH have some functioning residual thyroid tissue further making clinical diagnosis difficult [4]. As the age of the neonate progresses so does the hypothyroxinemia leading to progression of the clinical signs and symptoms which increases the risk for irreversible brain injury. To prevent this, treatment needs to be started as soon as possible after

birth. For all the above reasons, screening has evolved as the best way to detect infants with CH in developed countries. In North America, more than 1400 infants out of the 5 million newborns screened are diagnosed with CH annually.

2. Epidemiology

The incidence of CH varies from 1 in 4000 to 1 in 1000 in newborn infants as has been reported from various parts of world [5]. Developing countries like India and Iran have a higher incidence of CH [6, 7]. In countries like The US, Canada, New Zealand, Italy, Greece and Argentina the incidence of CH has nearly doubled since the introduction of newborn screening programmes [5, 8–12]. Widespread lowering of screening cutoffs in newborn screening programs [5, 8], increase detection of milder cases of CH, increase screening of higher risk newborn preterm and low birth infants, increased number of birth among Hispanic and of low birth weight [13] are some of the supposed causes that have been proposed as a possible cause for the increase in the incidence of CH. The incidence of CH is higher among Hispanic and Asian individuals and lower in black individuals [10, 13]. There has been a dramatic increase in the incidence of congenital hypothyroidism detected by the newborn screening programs, the incidence has risen from 1:3985 (in 1987) to 1:2273 (in 2002) [14]. This dramatic increase may be attributed to a spurt in the Asian (37%) and Hispanic (53%) births over the same period [13].

3. Etiology

Abnormal development of thyroid gland (thyroid dysgenesis) is the most common cause of CH. Thyroid dysgenesis accounts for 85% of cases of CH and is usually sporadic. It has three major forms thyroid ectopy, athyreosis and thyroid hypoplasia. Thyroid ectopy: it is the most common form and accounts for two thirds of cases of thyroid dysgenesis and is twice more common in females [15]. The exact etiology of thyroid dysgenesis is not known but largely its considered a sporadic disease and although the etiology remains elusive in most of cases some mutations in transcription factor genes i.e. TSHR, PAX8, NKX2-1, FOXE1, that regulate thyroid gland development have been reported, but only 2–5% of cases with thyroid dysgenesis are found to have such genetic mutations [16]. Recently, several other genes have found to be associated with thyroid gland dysgenesis, including NKX2-5, JAG1 and GLIS3 although each of them contributes to only a small fraction of cases [17–21]. Each of these transcription factors has a role in the development of organ systems too, and mutations of these genes are generally associated with additional congenital defects. In remaining one-third of cases, CH results from absence of thyroid (athyrosis) and thyroid hypoplasia. Dyshormonogenesis, or defects in peripheral thyroid hormone transport, metabolism, or action are accounted in approximately 15% of cases [22]. Defects in thyroid hormone biosynthesis are familial and usually autosomal recessive in inheritance [23]. These include mutations in the genes coding for the sodium-iodide symporter (NIS; SLC5A5), thyroid peroxidase (TPO), thyroglobulin (Tg), apical iodide transporter pendrin (PDS; SLC26A4), iodotyrosine deiodinase (IYD), dual oxidase (DUOX2) and its necessary protein(DUOXA2) [23]. Defective thyroid hormone

transport (mutations in monocarboxylase transporter 8), metabolism (selenocysteine insertion sequence-binding protein 2), or resistance to action (mutations of thyroid hormone receptor) are some rare causes. Among the aforementioned defects, mutations of the thyroid peroxidase (TPO) gene form the most prevalent cause of inherited defects in CH [24]. The incidence of thyroid dyshormonogenesis has been increasing and now accounts for 30–40% case of CH but thyroid dysgenesis remains the most common cause of CH [12].

Maternal thyrotropin receptor–blocking antibodies, exposure to maternal antithyroid medications, iodine deficiency or iodine excess are the major causes of transient CH in children.

Central congenital hypothyroidism is rare and is usually associated with and is usually associated with developmental anomaly of the pituitary gland and is usually associated with other pituitary hormone deficiencies like adrenocorticotropin and gonadotropins [25]. If isolated, it usually results from a mutation in the thyroid stimulating hormone β TSHβ subunit gene or TRH receptor gene. Less often it is due to mutation in transcription factor gene regulating pituitary development i.e. HESX1, LHX3, LHX4, OTX2, SOX3, PIT1 and PROP1 [1].

4. Diagnostic evaluation

In countries with newborn screening programs CH is diagnosed after neonatal screening tests. However, only 25% of the world wide birth population has the access and undergoes the said screening tests [26]. For the remaining 75% infants, particularly concentrated in developing countries, clinical suspicion of hypothyroid leads to thyroid function evaluation.

4.1. Newborn thyroid screening protocols

48–72 h after birth is the ideal time for the newborn screening tests, the reason being that the physiological surge in TSH that occurs after the first hours after birth to a peak serum level of 80 mIU/L slowly starts to decrease over the next several days [27]. Sample taken within 48 h of birth may lead to false positive results whereas screening done in very sick newborn or following blood transfusion may lead to false negative result.

In case of a critically ill new born, preterm birth or in case of a home delivery sample should be collected by 7 days of age. Capillary blood samples taken by heel prick method are placed on circles of specialize filter paper, dried at room temperature, then sent to a centralized laboratory. Second blood sample taken at 2–4 week is a part of the protocol in some screening programs. The additional incidence of CH based on a second screening at 2 weeks of age is approximately 1 in 30,000 [28, 29]. Preterm and LBW infants, critically ill infants, same-sex twins, and infants whose initial screen was performed in the first 24 h of life are some examples where a routine second screening must be performed [30].

Earlier the screening protocol for CH was T4 estimation followed by TSH only if t4 was low however with increasing accuracy of TSH assays on small volumes of blood, initial TSH testing has become the sine qua non of most screening protocols [31]. Both methods allow for the detection of most of the infants having CH but each method has its own merits and demerits. Measuring T4 first and then TSH detects some cases of secondary hypothyroidism and

infants that might have "delayed TSH elevation" whereas measuring TSH first and then T4 also detects mild or subclinical forms of hypothyroidism. Broadly speaking, if the screening T4 value is less than 10th percentile of cut off and/or the TSH is greater than 40 mU/L, the infant should be called again for confirmatory serum testing. In cases having "intermediate results," TSH 20–40 mU/L, recommendation is to repeat TSH screening in early second week of life. A TSH value <20 mIU/L is considered as normal.

4.2. Confirmatory serum thyroid testing

Diagnosis must not be completely and solely reliant on the screening tests only they must be confirmed by serum testing, venipuncture blood should be drawn and serum should be sent for TSH and free T4, or total T4 and T3 resin uptake as some measure of binding proteins. These serum based results must be compared with age normalized values as during the first week of life TSH and T4 are fluctuant [32]. Most confirmatory serum tests could be obtained in first 2 weeks of life, as during this upper TSH range has fallen to an around 10 mU/L. Although all hormones are higher during first week of age they come down to infancy range within 2–4 weeks.

5. Test results

5.1. Low T4 and elevated TSH values

A low total serum T4 or free T4 level along with an elevated serum TSH level confirms the diagnosis of primary hypothyroidism and levothyroxine (L-T4) must be started immediately after the confirmatory tests are done even before the results are available. Before age of 2 weeks, venous TSH >20 mIU/L and after 2 weeks, TSH > 10 mIU/L, suggests primary CH [33]. Serum T4 < 10 μg/dL (<128 nmol/L) or FT4 < 1.17 ng/dL (<15 pmol/L) is considered low in infancy.

5.2. Normal T4 and elevated TSH values

A transient or permanent thyroid dysfunction or delayed maturation of the hypothalamic–pituitary axis is indicated by normal levels of total T4 or free T4 along with elevated TSH. Initiating levothyroxine in such cases is still controversial. Since TSH concentration is the most sensitive indicator of hypothalamic-pituitary-thyroid axis therefore when confirmatory serum TSH level is between 6 and 20 mIU/L with normal FT4 levels, it is reasonable to watch serum thyroid function tests closely (every 1–2 weeks) and not start LT4 and if TSH is increases or if FT4 decreases to below normal level, treatment should be initiated. After 2 weeks of age a TSH > 10 mU/L is considered abnormal [34, 35]. And if TSH elevation persists, the infant must be treated.

5.3. Low T4 and normal TSH values

Hypothalamic immaturity particularly in preterm infants, in infants during illness, in central hypothyroidism or in primary hypothyroidism and delayed TSH elevation low T4 with normal TSH may be seen. No guidelines exists for the follow-up of these patients, but they

can be followed with serial filter-paper screening tests until the T4 value becomes normal, or a second blood sample for measurement of serum FT4 and TSH can be obtained. Such infants are usually found to have normal thyroid profile on subsequent screening tests. Their treatment (except those with central hypothyroidism) with L-T4 has not yet been shown to be beneficial [36].

6. Diagnostic studies to determine an underlying etiology

Since additional investigations for etiology do not alter the treatment plan they can be delayed. Treatment of CH should never be deferred after confirmation pending the determination of etiology.

6.1. Thyroid radionuclide uptake and scan

Thyroid radionuclide uptake and scanning is the most accurate imaging modality to determine the size and location of thyroid tissue. Iodine-123 (I-123) or sodium pertechnetate 99 m (Tc99m) are tracers of choice as I-131 delivers a higher dose of radioactivity. Radionuclide uptake and scan is used to identify thyroid aplasia (absent uptake), hypoplasia (decreased uptake, small gland in a eutopic location) or an ectopic gland. Other conditions not showing any uptake include; TSHβ gene mutations, TSH receptor inactivating mutations, iodide trapping defects and in those with maternal thyrotropin receptor blocking antibodies (TRB-Ab). Dyshormonogenesis beyond trapping of iodide results in a large gland in a eutopic location with increased uptake on the scan. A perchlorate discharge test can be performed to confirm the diagnosis of dyshormonogenic CH.

6.2. Thyroid ultrasound

When it comes to etiology determination thyroid ultrasound is usually the first modality performed. It confirms thyroid aplasia when radionuclide scan show absent uptake. TSHβ gene mutations, TSH receptor inactivating, iodide trapping defect and maternal TRB-Ab shows the absence of radionuclide uptake in the presence of thyroid gland in the normal position. Dyshormonogenesis is associated with absent uptake in radionuclide scan and large thyroid in ultrasound. Color Doppler flow may be able to detect up to 90% of cases of ectopic thyroid [37].

6.3. Serum thyroglobulin (Tg) measurement

Serum thyroglobulin is reflective of the thyroid mass and is usually raised in increased activity of the thyroid gland. In a recent study, Beltrão et al., suggested that color Doppler ultrasound combined with serum thyroglobulin measurement may become very valuable tools for the diagnosis of the cause of CH and will also help minimize more harmful tests, like radionuclide scan [38]. Increased thyroglobulin levels and absent uptake on radionuclide scan suggests presence of thyroid gland along with a TSH receptor inactivating mutation, a trapping defect, or maternal TRB-Ab, rather than aplasia.

6.4. Thyroid receptor antibody

Transient CH in children can also be caused by maternal thyroid receptor blocking antibodies TRB-Ab. Absent radionuclide uptake with small or normal sized eutopic gland suggests transient congenital hypothyroidism as a result of transplacental passage of the antibody from the mother to the child. For confirmation the measurement of serum TRB-Ab in mother and/or infant may be done by a thyrotropin-binding inhibitor immunoglobulin (TBII) assay.

6.5. Urinary iodine estimation

24 h urinary iodine excretion approximates the iodine ingestion. For neonates the normal range is approximately 50–100 mg/24 h. Urinary iodine measurement may provide confirmation regarding iodine deficiency or excess.

7. Management

CH remains the most common preventable cause of mental retardation. Studies have shown that timing and dosing of thyroid hormone replacement are both crucial for neurological outcome. The infant must be rendered euthyroid as early as possible by starting the treatment promptly and at sufficient dose, as there is an inverse relationship between intelligence quotient (IQ) and the age of diagnosis. Despite early diagnosis the neurological outcome may be poor due to delay in starting treatment, lower starting thyroid hormone dosing and severity of the hypothyroidism, which itself correlates with the underlying etiology [39].

7.1. Formulation

Levothyroxine (L-thyroxine) remain the treatment of choice. Although biologically active form is triiodothyronine (T3) but most brain T3 is derived from local monodeiodination of T4. As studies have shown normal serum level of T3 in infant treated with T4 alone, so treatment with T3 is not essential for normal neurological outcome/brain development [40]. Currently, only tablets form of L-thyroxine are approved for use owing to inconsistent delivery of liquid formulations. However, in some countries in Europe, L-thyroxine suspension is also available and is used to normalize thyroid function.

7.2. Administration

Crushed levothyroxine (L-thyroxine) tablet is mixed with 1–2 ml of breast milk, formula or water and resultant suspension is squirted into cheek pad or put on open nipple for infant to feed. Various substances like such as calcium and iron preparation, soy protein formula, sucralfate, aluminum hydroxide and cholestyramine interfere levothyroxine (L-thyroxine) absorption through gut and thus should not be given together [41, 42]. Although, recommendation is to take levothyroxine (L-thyroxine) empty stomach but for infant it may not be feasible.

7.3. Dosages

For the optimal neurodevelopmental outcome, the treatment goal is to normalize T4 and TSH within 2 and 4 weeks respectively [33, 43, 44]. In a study infants had significant lower cognitive, attention and achievement scores who took more than 2 weeks to normalize thyroid function compared to infants who attained normal thyroid function at 1 or 2 weeks of treatment [45]. Adequacy and the timing of treatment determines optimal neurodevelopmental outcome and thus American academy of pediatrics and European society of pediatric endocrinology recommend 10–15 μgm/kg/day as initial dose [46]. Studies show that this dose normalizes serum T4 within 3 days and TSH within 2–4 weeks. To achieve these goals, it is important to start higher initial dose of the recommended range in case of severe CH. In a study infants who were started on higher initial doses of 50 μgm had full-scale IQ scores 11 points higher than those started on lower initial doses of 37.5 μgm [45].

7.4. Target concentrations

The target T4 concentrations lies in the upper half of reference range according to the Guidelines issued by the American academy of pediatrics and European society for pediatric endocrinology [30, 47–49]. Target values for T4 being 10–16 μgm/dl; FT4 1.4–2.3 ng/dl and TSH <5 μU/dl (optimally 0.5–2.0 μU/dl) for initial 3 years of life following this T4 should be kept in the upper half of normal range. Low IQ in infants with T4 concentration below 10 μgm/dl and TSH above 15 μU/dl was seen during the first year of life compared to those had serum T4 more than 10 μgm/dl [50]. Better intellectual outcome in children with CH was seen with higher doses of levothyroxine (L-thyroxine) [51]. Contrary to this other studies have shown behavior problems like increased anxiety, social withdrawal and poor concentration with higher doses in children at age of 8 years. Thus demonstrating potential dangers of overtreatment with levothyroxine in CH children [52].

8. Follow-up

Congenital anomalies are also more frequent in CH than in general population (10% in CH compared to 3% in general population) most common of these anomalies is cardiac malformation particularly pulmonary stenosis, atrial septal defect and ventricular septal defect. Adequate monitoring is required to maintain the thyroid functions within the recommended levels. The American Academy of Pediatrics recommends the following monitoring schedule [53].

- At 2 and 4 weeks after the initiation of L-thyroxine treatment.
- Every 1–2 m during the first 6 m of life.
- Every 3–4 m between 6 m and 3 years of age
- Every 6–12 m thereafter until growth is complete

- Four weeks after any change in dose or more frequently if results are abnormal or non-compliance is suspected.

To ensure adequate growth and neurological development of the infant clinical evaluation should be carried out even more frequently than lab investigation.

8.1. Unresolved controversy

The incidence of congenital hypothyroidism is seemingly on the rise. Whether this increase is absolute or the result of lowering of screening test cutoff or changes in the racial and demographic profile or something else remains to be determined. This rise may also be the result of a larger reach of the screening test or the detection of infants with mild hypothyroidism and those with "delayed TSH rise". As already mentioned the most common cause of CH is thyroid dysgenesis, but the underlying etiology of thyroid dysgenesis remains an enigma. Only 2% cases of thyroid dysgenesis caused by genetic mutation in genes that encode for thyroid transcription factors. The other issue at hand is whether the rise of TSH is permanent or temporary we require more studies in affected infants detected by abnormalities on a second screening test to resolve this controversy.

9. Conclusion

Congenital hypothyroidism (CH) is one of the most common preventable cause of mental retardation. Screening of large populations of newborns is best method to diagnose infants with CH. If the diagnosis is made and treatment started within a few weeks of birth, neurodevelopmental outcome generally is normal. The underlying etiology of the most common cause of CH, thyroid dysgenesis, is largely unknown.

Author details

Sanjay Saran

Address all correspondence to: drsanjaysaran@gmail.com

Department of Endocrinology, SMS Medical College and Associated Group of Hospitals, Jaipur, India

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Chapter 3

Inferior Parathyroid Gland Preservation In Situ during Central Neck Dissection for Thyroid Papillary Carcinoma

Lei Xie, Jianbiao Wang and Liang Zhou

Additional information is available at the end of the chapter

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Abstract

Hypoparathyroidism is the most common and a potentially serious complication of thyroid surgery; therefore, it becomes very important for thyroid surgeons to preserve the parathyroid glands in situ during the thyroid operation. Because of the application of "meticulous capsular dissection," the problem about how to preserve the parathyroid gland in thyroidectomy has become minor. Because inferior parathyroid glands enjoy a more variable position in the adult neck and they are located in the area of central neck lymph node dissection, how to preserve them in situ during central neck dissection is regarded as a major problem. To solve it, a new operation concept, "a layer of thymus-blood vessel-inferior parathyroid gland," is mainly introduced in this chapter.

Keywords: inferior parathyroid gland, thyroid papillary carcinoma, thyroidectomy, central neck dissection, hypoparathyroidism

1. Introduction

Prof. Richard Owen firstly identified the parathyroid gland in an Indian rhinoceros in 1850 [1]. Ivar V. Sandström also found this gland in humans and firstly named it as "glandulae parathyroidae" in 1887 [1]. Because Gley observed that animals whose parathyroid glands were removed subsequently developed tetany in the 1890s, the parathyroid gland and their function became widely appreciated [2]. After that, surgeons understood that the parathyroid glands were vital organs to be treated cautiously during thyroidectomy.

Hypoparathyroidism is the most common and a potentially serious complication of thyroid surgery, which can lead to metabolic and physiologic disturbance, prolonged hospitalization and medical supplementation [3–6]. In general, the prevalence of transient and permanent hypoparathyroidism is reported to range from 14–60% and 4–11%, respectively [7]. Total thyroidectomy (TT) with central neck dissection (CND) significantly increases the rate of transient and permanent hypoparathyroidism in comparison with total thyroidectomy.

In this chapter, a new operation concept, "a layer of thymus-blood vessel-inferior parathyroid gland (TBP)," is mainly introduced to preserve the inferior parathyroid gland (IPTG) *in situ* during CND for papillary thyroid carcinoma (PTC).

2. Classification of the IPTG

1. According to the location relationship between the IPTG and thymus, four groups were classified by J. Grisoli in 1979 [8]. Group 1: the parathyroid gland in the usual classic position, in contact with the terminal branches of the inferior thyroid artery, behind or below the inferior poles of the thyroid lobes (65% of cases); Group 2: the parathyroid gland in a thyrothymic position, more or less equidistant from the inferior thyroid lobe and the thymic cornu (17.5% of cases); Group 3: the superior thymic parathyroid gland, situated in the cornua of the thymus or their immediate vicinity (15.5% of cases); Group 4: intrathymic parathyroid (2% of cases) (**Figure 1**).

2. Based on the relationship between the parathyroid gland and the thyroid gland as well as the color change in the parathyroid glands after separation from the thyroid, different categories of parathyroid gland are as follows [9]:

   Type A, no dependency on the thyroid, and with adequate blood supply and no color change after thyroidectomy; B1, partial blood supply from the thyroid but retains adequate blood supply after removal of the thyroid; B2, partial blood supply from the thyroid and becomes devascularized after the removal of the thyroid; B3, blood supply mostly from the thyroid; difficult to preserve in situ and C, blood supply completely dependent on the thyroid. The classifications were used to decide between in situ preservation and auto-transplantation (**Figure 2**).

3. According to the positional relationship between IPTG and the thyroid gland, JQ Zhu classified IPTG into two types [10], namely type A (close contact) and type B (non-close contact). Type A includes A1 (planar attachment), A2 (embedded attachment), and A3 (intra-thyroid); type B includes B1 (around thyroid), B2 (intra-thymus), and B3 (blood supply from thymus or mediastinum) (**Figures 3** and **4**)

During TT and CND, IPTG typically undergoes "dissection" twice. At first instance, the IPTG is exposed and preserved by meticulous capsular dissection during thyroid lobectomy; at second instance, the IPTG is identified and preserved in situ while the central neck fibro-fatty tissue with lymph nodes is removed. The first instance is the premise and basis of the second instance, because in situ preservation of IPTG in CND becomes impossible if IPTG has been devascularized or resected during thyroid lobectomy. The identification and preservation of IPTG in the first instance of dissection facilitates the preservation of the IPTG in situ in CND

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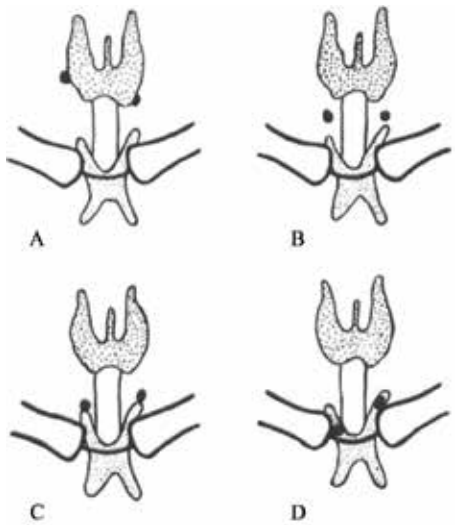

Figure 1. Position of inferior parathyroid gland (by J Grisoli). (A) Usual position; (B) thyro-thymic position; (C) superior thymic position; (D) intrathymic.

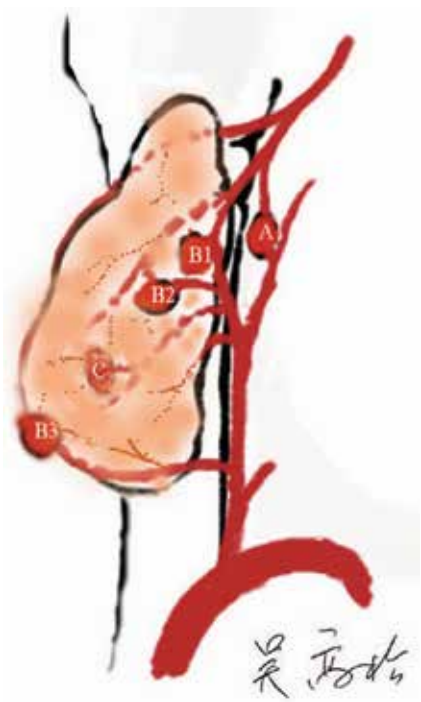

Figure 2. The three main types of parathyroid gland (by GS Wu). Type A, nonattachment to the thyroid and has adequate blood supply; type B1, attached lightly to the thyroid and retains adequate blood supply after thyroid removal; type B2, attached tightly to the thyroid and changes color easily, in which case, the distal tissue is cut in half for autograft; type B3, blood supply is derived mostly from the thyroid gland and may be treated as either type B2 or type C according to the surgeon's skill; type C, under cover of the thyroid capsule and can only be preserved by total auto-transplantation.

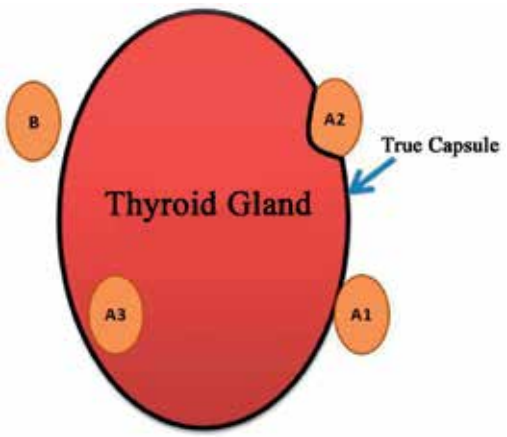

Figure 3. Classification of inferior parathyroid gland (by JQ Zhu). Type A (close contact) includes A1 (planar attachment), A2 (embedded attachment) and A3 (intra-thyroid); type B (non-close contact) includes B1 (around thyroid), B2 (intra-thymus) and B3 (blood supply from thymus or mediastinum).

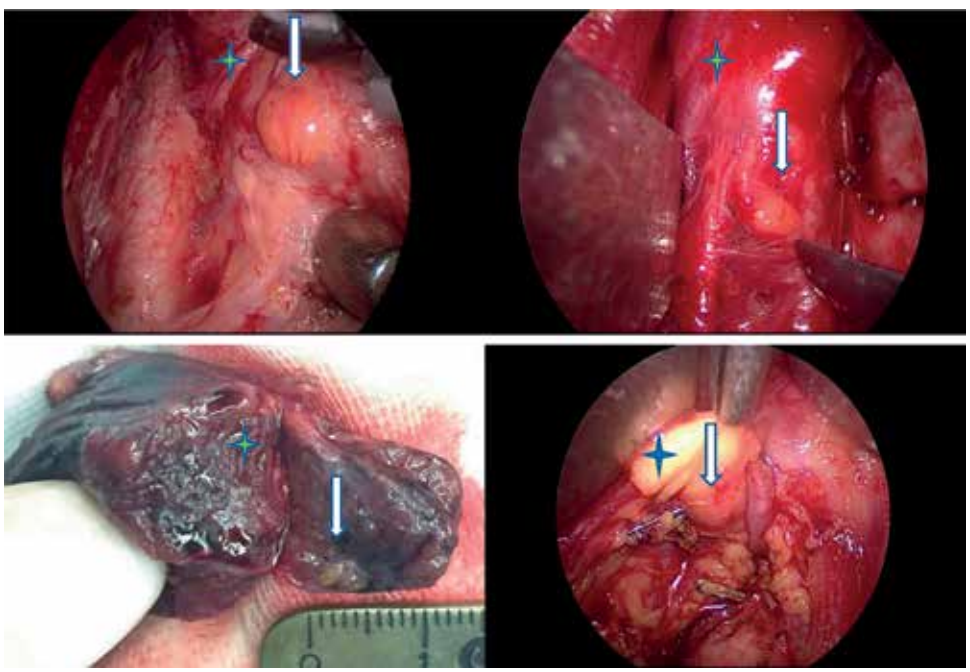

Figure 4. Intraoperative views of inferior parathyroid gland according Zhu's classification. Type A1 (left upper), A2 (right upper), A3 (left down) and B2 (right down) are included. White arrow: Inferior parathyroid gland; green star: thyroid; blue star: thymus.

(in the second instance of dissection). Therefore, the inferior parathyroid gland can be actually classified into exposure type and unexposure type according to whether the IPTG is identified and preserved during the thyroidectomy (at the first instance). As to the unexposure type, the

in situ preservation of the IPTG in CND could be very difficult. This can be attributed to the fact that IPTGs assume a more variable position in the adult neck, thus making their detection difficult. Moreover, IPTGs are located in the area of central neck lymph node dissection and have to be distinguished from lymph nodes, fatty tissue, and so on.

3. Two operation concepts during TT and CND

3.1. "Meticulous capsular dissection" in thyroid lobectomy

How to preserve the IPTG during the thyroid lobectomy, a concept "meticulous capsular dissection" was put forward by NW Thompson in 1973 [11], and further explanation was given by Attie and other scholars [12]. The protection of the parathyroid glands and to the recurrent laryngeal nerve is achieved by using capsular dissection, hugging the gland and dividing the tertiary branches (i.e., the third order of division) of the vessels while dissecting the parathyroid glands with their vascular pedicles free from the thyroid surface, with minimal exposure of the recurrent laryngeal nerve and disturbance of its blood supply (**Figure 5**).

3.2. "A layer of thymus, blood vessels and inferior parathyroid gland" in CND

Because of the application of "meticulous capsular dissection," how to preserve the parathyroid gland in thyroidectomy has become a minor problem. Because IPTGs enjoy a more variable position in the adult neck and locate in the area of central neck lymph node dissection, how to preserve IPTG during CND is a major problem.

Some methods are recommended to identify and preserve the IPTG [13, 14]. For example, IPTG is superficial to RLN coronal plane and does not dissect the triangular region in order to protect laterally based blood supply of the IPTG (**Figure 6**). However, actually it is not easy to practice.

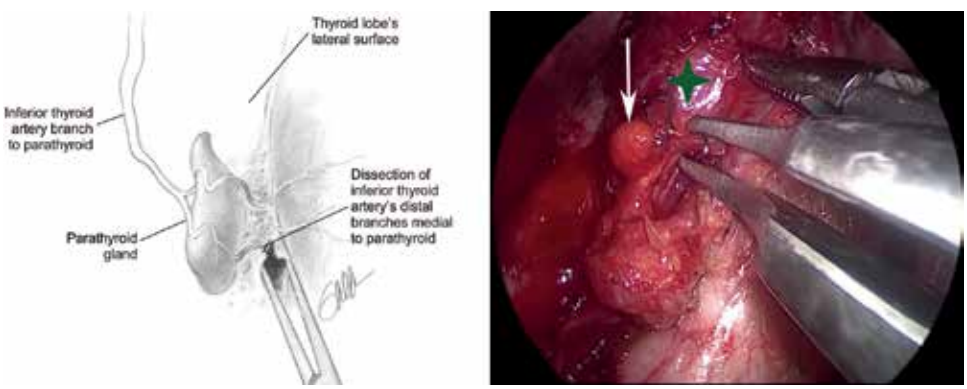

Figure 5. "Meticulous capsular dissection." The distal branches of the inferior thyroid artery medial to the parathyroid at the level of the thyroid capsule, are identified and controlled. Attie's drawing (left); intraoperative view (right); white arrow: Inferior parathyroid gland; green star: thyroid.

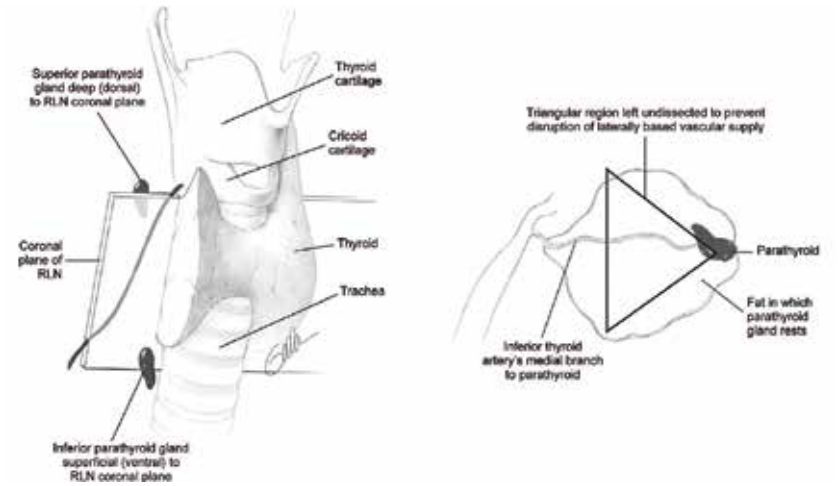

Figure 6. Some methods recommended to identify and preserve the inferior parathyroid gland (IPTG). IPTG superficial to recurrent laryngeal nerve coronal plane (left); triangular region left undissected to prevent disruption of laterally based vascular supply of IPTG (right).

3.2.1. The meanings of "a layer of TBP"

To solve this main problem, "a layer of TBP" was firstly put forward by Lei Xie in 2014 [15]. This new concept has two meanings: (1) the thymus, IPTG and blood vessels connecting them are located in one layer; (2) the layer covers the common carotid artery (innominate artery), the trachea, and the area of paratracheal lymph nodes between them (**Figure 7**).

3.2.2. Theoretical basis of "a layer of TBP"

Embryologically, the IPTGs are derived from the dorsal part of the third pharyngeal pouch, and the thymus arises from the ventral part of the third pharyngeal pouch. As the IPTGs and the thymus migrate together toward the mediastinum, they eventually separate. In most cases, the inferior parathyroid glands become localized near the inferior poles of the thyroid, and the thymus continues to migrate toward the mediastinum (**Figure 8**) [16]. In an anatomical study of the adult thymus, Di Marino et al. [8] described the true sheath of the thymus and its relative structures in detail. In the cervical region, adhesion between the thymic sheaths and thyroid is via the thyrothymic ligaments, in which the superior vascular pedicle of the thymus is contained. The superior vascular pedicle mainly includes the superior thymic artery arising from the ITA as well as the inferior and median thyroid veins, which also supply blood to the IPTG. In addition, from the midline cervicothoracic sagittal section, the thymus, blood vessels within the thyrothymic ligament and the posterior layer of thyroid sheath are in the same plane (**Figure 9**), which could be regarded as an anatomical basis for the TBP layer.

3.2.3. How to practice "a layer of TBP" during CND

According to the ATA guidelines, bilateral CND involves removal of the prelaryngeal, pretracheal, and both the right and left paratracheal nodal basins; and unilateral CND involves

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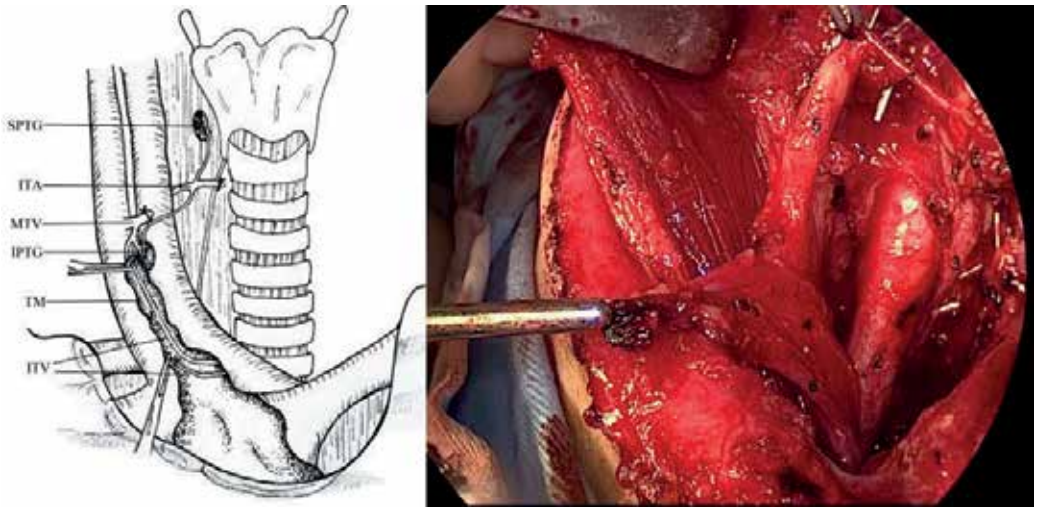

Figure 7. "A layer of thymus-blood vessel-inferior parathyroid gland (TBP)." The thymus, the inferior parathyroid gland, and the blood vessels connecting them are located in one layer. This layer covers the common carotid artery (innominate artery), the trachea, and the area of paratracheal lymph nodes between them. Diagram of this concept (left); intraoperative views of "a TBP layer" preserved after central neck dissection. SPTG, superior parathyroid gland; ITA, inferior thyroid artery; MTV, middle thyroid vein; IPTG, inferior parathyroid gland; TM, thymus; ITV, inferior thyroid vein; 1, trachea; 2, common carotid artery; 3, recurrent laryngeal nerve; 4, Thymus; 5, inferior parathyroid gland; 6, branches of inferior thyroid vein; 7, a branch of inferior thyroid artery.

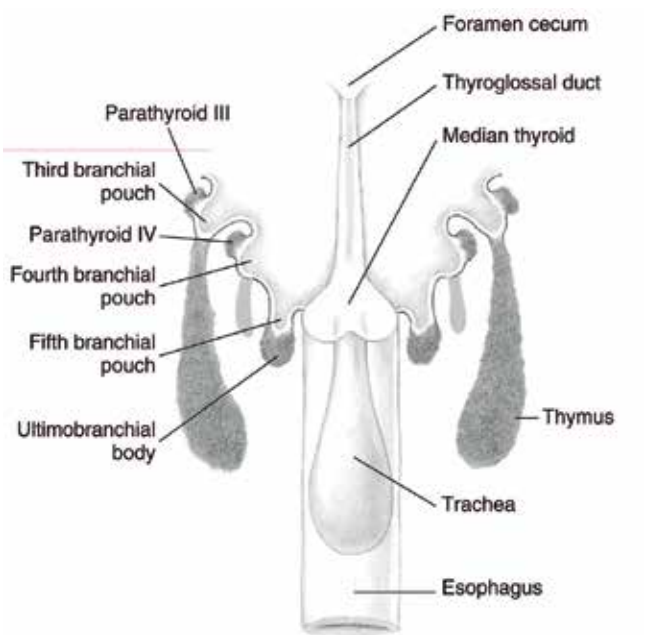

Figure 8. Schematic view of primitive pharynx of an 8- to 10-mm embryo. The inferior parathyroid glands are derived from the dorsal part of the third pharyngeal pouch, and the thymus arises from the ventral part of the third pharyngeal pouch.

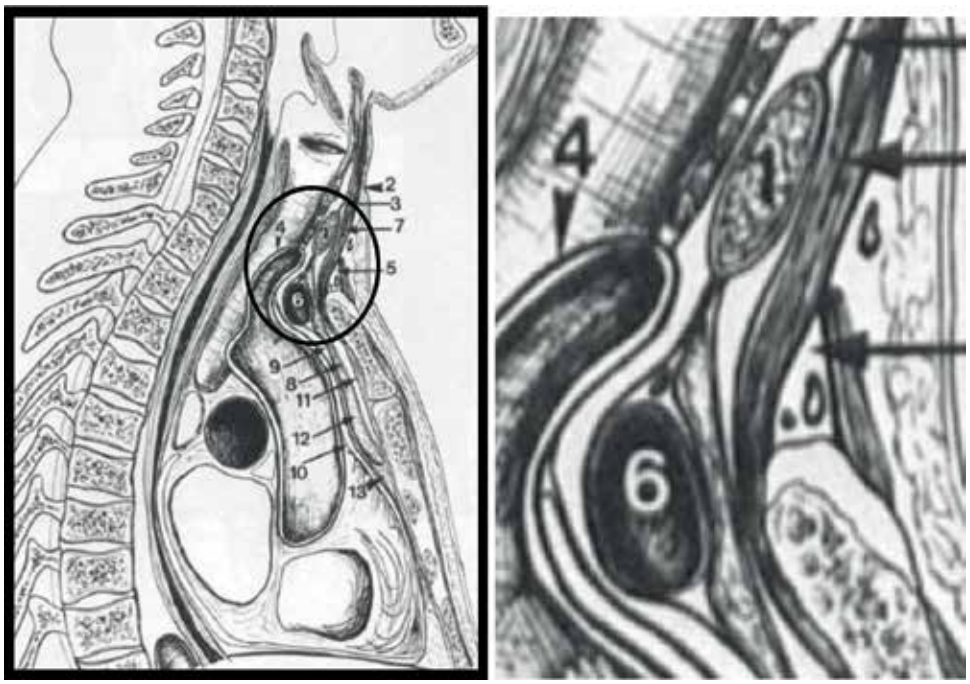

Figure 9. Midline cervicothoracic sagittal section. The thymus, blood vessels within the thyrothymic ligament and the posterior layer of thyroid sheath are in the same plane, which could be regarded as an anatomic basis of the "TBP layer". 1, thyroid isthmus; 2, superficial layer of cervical fascia; 3, pretracheal cervical fascia; 4, brachiocephalic trunk; 5, pretracheal space; 6, left brachiocephalic vein; 7, sternothyroid muscle; 8, anterior wall of thymic sheath; 9, thyropericardial layer; 10, serous pericardium; 11, anterior interpleural ligament; 12, thymus; 13, subthymic fatty tissue.

removal of the prelaryngeal, pretracheal and one paratracheal nodal basins. In addition, "a layer of TBP" is mainly applied in lateral margin dissection of paratracheal nodal basin.

During the paratracheal lymph node dissection, the medial dissection margin is defined using electrocautery along the tracheal lateral wall from Berry's ligament to the brachiocephalic vessels. Lateral margin dissection aims to identify and preserve the TBP layer first (**Figure 10**) rather than directly exposing the common carotid artery. The thymus, inferior thyroid blood vessels and their branch stumps are regarded as reference points, with the fibrofatty tissue removed by electrocautery. During this process, the TBP layer is slowly identified and lifted upwards; the common carotid artery (innominate artery) beneath the layer is exposed. The medial border of the common carotid artery is dissected down to the prevertebral fascia. The TBP layer and the common carotid artery are retracted laterally, whereas the trachea is retracted medially, exposing the paratracheal compartment. The recurrent laryngeal nerve (RLN) is freed from the fibrofatty tissue and retracted laterally. The envelope of level VI lymph nodes is then retracted medially and excised en bloc [17].

The relationship between the TBP layer, inferior thyroid artery (ITA) and RLN can be further clarified. Because the TBP layer is superficial to the common carotid artery, whereas the ITA

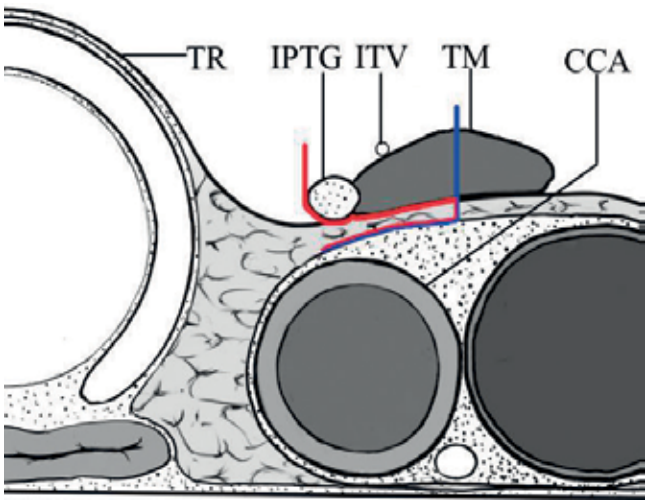

Figure 10. Lateral margin dissection approaches in paratracheal lymph node dissection. The blue line shows the traditional approach to directly expose the common carotid artery (CCA), which could lead to the inferior parathyroid gland injury due to the destruction of the TBP layer. The blue line shows the new dissection approach based on the TBP layer (layer of thymus-blood vessel-inferior parathyroid gland) concept. The thymus (TM), inferior thyroid blood vessels and inferior parathyroid gland (IPTG) are lifted upwards and laterally, exposing the CCA (innominate artery) underneath. TR, trachea; ITV, inferior thyroid vein.

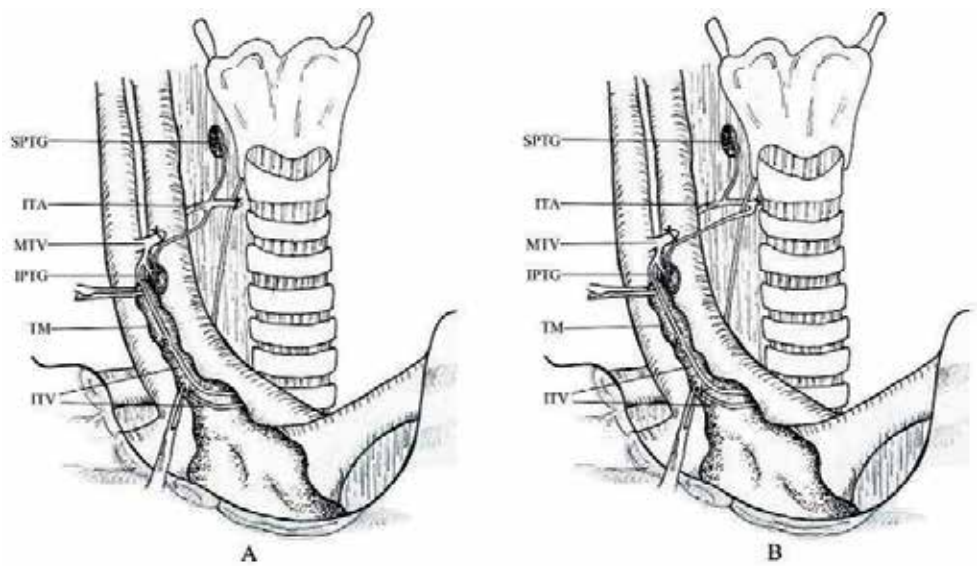

Figure 11. The relationship between the TBP layer, inferior thyroid artery (ITA) and recurrent laryngeal nerve (RLN). A is ITA branches lateral to RLN; B is ITA branches medial to RLN. MTV, middle thyroid vein; IPTG, inferior parathyroid gland; TM, thymus; ITV, inferior thyroid vein. Red cycle means that the dissection in this region (between the cricoid cartilage and ITA level) should be emphasized, especially when the concept of "a layer of TBP" is performed.

enters the central neck compartment posterior to the carotid sheath, branches of the ITA need to traverse paratracheal fibrofatty tissue anteriorly to the TBP layer. In general, these branches of the ITA abut against the carotid artery medially and run into the TBP layer; therefore, the TBP layer, carotid artery and ITA branches can easily be retracted laterally, allowing en bloc excision of the paratracheal fibrofatty tissue (**Figure 11A**). The alternative situation is that the ITA branches are not very close to the carotid artery, and the RLN traverses between them (**Figure 11B**). For completeness of dissection and RLN preservation, it is suggested that the paratracheal dissection should be divided into two parts according to the level of the ITA: a dissection cranial to the ITA (between the cricoid cartilage and ITA level) and one caudal to the ITA (between the innominate artery and ITA level).

4. Clinical application results of "a layer of TBP"

A retrospective chart review was authorized and drawn from all 487 patients with PTC who underwent TT with ipsilateral or bilateral CND or plus lateral neck dissection between January 1, 2012 and December 31, 2014 [15]. The study group consisted of 181 patients with using the new surgical concept "a layer of TBP," from January 2014 to December 2014, whereas the control group included 306 sex- and age-matched patients who underwent conventional method from January 2012 to December 2013. There were no significant differences between the groups in tumor size, multifocality, extrathyroidal extension, and number of harvested and metastatic central lymph nodes. The rate of inferior parathyroid gland preservation in situ was significantly improved from 37.9 to 76.3% on the left side (P < 0·001), and from 52.0 to 77.9% on the right side (P < 0.001), in the study group compared with the control group (**Figure 12**). The incidence of transient hypoparathyroidism decreased

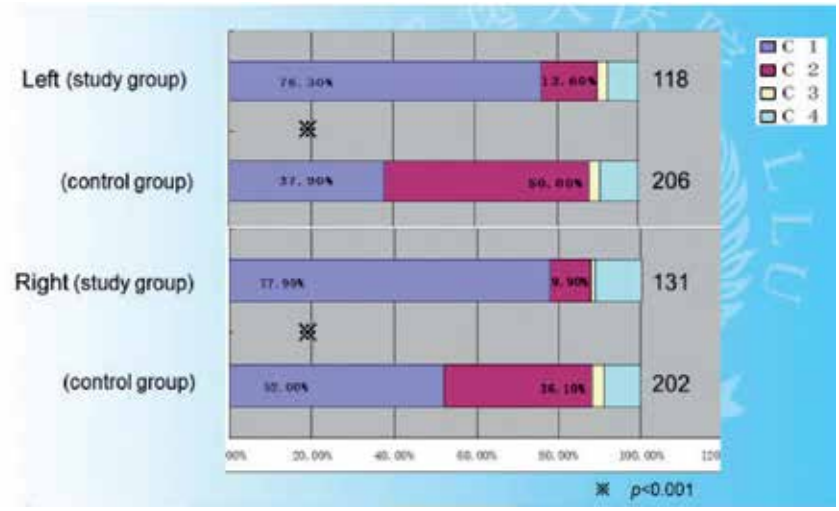

Figure 12. The status of inferior parathyroid glands after TT and CND. It was classified into four categories: C1, preserved in situ (vascularized); C2, autotransplanted (devascularized); C3, removed owing to infiltration by the tumor; and C4, not identified. The rate of inferior parathyroid gland preservation in situ was significantly improved on both sides (P < 0.001) in the study group compared with the control group.

Variables	Control group (n = 306)	Study group (n = 181)	*P*
No. retrieved lymph nodes	12.74 ± 6.16 (1-30)	13.83 ± 7.07 (3-43)	0.186
No. metastatic lymph nodes	1.94 ± 2.83 (0-14)	1.95 ± 2.75 (0-13)	0.826
No. retrieved lymph nodes in unilateral CND	11.08 ± 5.71	11.33 ± 5.89	0.756
No. metastatic lymph nodes in unilateral CND	1.52 ± 2.20	1.67 ± 2.28	0.393
No. retrieved lymph nodes in bilateral CND	16.04 ± 5.70	18.10 ± 7.00	0.036
No. metastatic lymph nodes in bilateral CND	2.79 ± 3.66	2.41 ± 3.37	0.342

Table 1. The excised lymph nodes in the unilateral and bilateral central neck dissections.

significantly from 35.0 to 7.2% ($P < 0.001$). In addition, the excised lymph nodes in the unilateral and bilateral CNDs were compared between the groups. The result showed that significantly more lymph nodes were removed in bilateral CND in the study group than in the control group; however, there was no difference in lymph nodes in unilateral CND between the groups (**Table 1**). Therefore, applying the proposed surgical concept improved the rate of inferior parathyroid gland preservation in situ and decreased the incidence of transient postoperative hypoparathyroidism, along with ensuring the completeness of lymph node dissection.

1. Some special considerations relative to "a layer of TBP."

2. Although the success rate of IPTG preservation in situ can be considerably improved using the concept "a layer of TBP" in CND, it is important that the surgeons have the abilities to identify the parathyroid glands and evaluate their blood supply. Some techniques such as no black stain in parathyroid gland by carbon nanoparticles [18] and the intraoperative near-infrared autofluorescence imaging of parathyroid gland [19] are recommended, but we suggest that it is necessary to clinically train the identification of the parathyroid gland by the naked eyes.

3. Parathyroid autotransplantation has been considered a salvage method to avoid permanent hypoparathyroidism. Although the incidence of IPTG preservation in situ was increased greatly after using the concept of "a TBP layer," still about 10% of IPTGs were removed inadvertently or devascularized during thyroid surgery. Therefore, the technique of parathyroid autotransplantation should be mastered by thyroid surgeons.

4. The IPTG and its blood supply are frequently involved in the dorsal extrathyroidal invasion of primary tumor or extranodal metastasis of paratracheal lymph nodes; therefore, the preservation of IPTG in situ is unsuitable, and en bloc resection of the thyroid and central neck lymph nodes is recommended. In addition, although the paratracheal area is full of excessive fatty tissue in obese patients, it is also possible to identify and build up "a layer of TBP" by clinical training.

5. Preservation of the IPTG in situ using the approach "a layer of TBP" requires meticulous manipulation during the operation. The requirements for meticulous manipulation include good operation vision, wide operation space, antagonistic traction (the first assistant's), and

refined operational instruments. In this study, TT and CND were mostly performed under direct vision with the operator's headlight (mPack LL, HEINE Optometrik, Germany), and the first assistant's coordinated traction was emphasized; in addition, the use of a high-frequency electric knife with a needle-shaped head (Changzhou Yanling Electronic Equipment Co. Ltd., Jiangsu, China) and a small titanium ligating clip (Horizon; Weck Drive, Research Triangle Park, NC 27709, USA) are strongly recommended to preserve the parathyroid gland and its blood supply.

6. As mentioned earlier, when the RLN traverses between the ITA branches and the carotid artery, the paratracheal dissection can be divided into two parts according to the level of the ITA: a dissection cranial to the ITA (between the cricoid cartilage and ITA level) and one caudal to the ITA (between the innominate artery and ITA level), for completeness of dissection and RLN preservation (**Figure 11B**). Actually, the dissection between the cricoid cartilage and ITA level is a challenge because superior parathyroid gland and its blood supply from ITA and RLN are on this area. Although some surgeons declare that performing the dissection inferiorly from the trunk of ITA could achieve the equal completion of the dissection in safety [20, 21] because the metastatic lymph nodes are rarely found above the ITA trunk, the recurrence can be observed in this region between the cricoid cartilage and the ITA trunk. Therefore, the dissection in this region (between the cricoid cartilage and ITA level) should be emphasized, especially when the concept of "a layer of TBP" is performed. In addition, the usage of carbon nanoparticles, as a lymph tracer, can facilitate this procedure (not published).

5. Conclusion

The prevention of postoperative hypoparathyroidism entails several issues, including the concept of meticulous operation, the ability of parathyroid gland identification, the technique of parathyroid gland autotransplantation, and the principle of "the preservation of at least one vascularized parathyroid gland" [10, 22]. This chapter shows that the concept of "a layer of TBP" during CND can greatly improve the success rate of IPTG preservation in situ, thereby efficiently decreasing the incidence of temporary postoperative hypoparathyroidism, along with ensuring the completeness of lymph node dissection.

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Disclosure

The author declares no conflict of interest.

Author details

Lei Xie*, Jianbiao Wang and Liang Zhou

*Address all correspondence to: xiel@srrsh.com

Department of Head and Neck Surgery, Institute of Micro-Invasive Surgery of Zhejiang University, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, P.R. China

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Chapter 4

Nuclear Medicine in the Assessment of Thyrotoxicosis Associated with Increased Thyroid Function and Radioiodine 131 Ablative Therapies

Elena Espinosa Muñoz

Additional information is available at the end of the chapter

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Abstract

Nuclear medicine is directly involved in both the diagnosis and treatment of benign thyroid disease. Thyroid scintigraphy (most commonly with technetium-99 m pertechnetate) should be used as the imaging modality of choice for assessment of thyrotoxicosis, since it demonstrates the functional state of the thyroid gland. An adequate understanding of the pathophysiological mechanisms and characteristics of the patient is essential, as well as the different treatments of thyroid disorders that present with hyperthyroidism (*Graves' disease*, toxic multinodular goiter, and toxic adenoma-Plummer's disease). Therapeutic modalities include antithyroid drugs, radioiodine and surgery. Antithyroid drugs are the first line of therapy and regarding the use of radioiodine, current recommendations consider it a safe and effective therapeutic alternative in hyperthyroidism. Finally, we highlight the existence of some special situations (children, pregnancy, thyroid eye disease, chronic renal failure and dialysis patients) and the importance of radiation protection measures to the patient, the public and professionals.

Keywords: nuclear medicine, thyrotoxicosis, thyroid hyperfunction, radioiodine 131

1. Introduction: thyroid anatomy and physiology

Thyroid gland is the first organ to develop in human embryo. Its development begins 22 days after conception. The thyroid gland develops in the floor of the primitive foregut, between the first and second pharyngeal pouches from the endoderm. It descends to its habitual position, by the anterior neck to the level of the trachea, connecting to the tongue's base by the thyroglossal duct. The thyroglossal duct starts from the foramen caecum and normally involutes

throughout the development of the embryo when the thyroid occupies its final position in the neck, but sometimes becomes into a pyramidal lobe which is contiguous with the thyroid isthmus [1].

The TSHR is a G-protein coupled receptor present in thyroid, lymphocytes, fibroblasts and adipocytes. The binding of TSH to TSHR results in signaling pathway downstream that results in actions of thyroid hormone production [2].

Approximately 94% of thyroid hormones are secreted by the thyroid gland as tetraiodothyronine (T4) and 6% as triiodothyronine (T3). T4 is catalytically converted to T3 (more metabolically active) in peripheral tissues by deiodinases enzymes. Both T4 and T3 are mostly bound to carrier thyroxine-binding globulin proteins (TBG) in the serum [3].

At the cellular level, the function of thyroid hormones is mediated by the free hormones (free T4 (fT4) and free T3 (fT3)), principally by the binding of triiodothyronine (T3) to its receptors. In addition, the subsequent expression of genes is regulated by the binding of the T3-receptor complexes to DNA. This is specifically important, for example, for those genes that regulate the calcium cycling in cardiac cells [3, 4].

2. Radiopharmaceuticals principles

Radiopharmaceuticals are substances that contain one or more radioisotopes (radionuclides). They are nonencapsulated sources of artificial ionizing radiation, which are used for both diagnostic and therapeutic medical applications in the field of nuclear medicine.

It is important to mention certain general characteristics, such as the type of radioactive emission (gamma photons, alpha or beta particles and mixed, with emission of gamma photons and charged particles), the emission energy measured in KeV and the physical half-life (T ½ f), that help us to know and properly choose the type of radiotracer that we should use at all times. Radioiodine isotopes and ^{99m}Tc-pertechnetate (TCO4-) are the most commonly used radiopharmaceuticals for thyroid imaging.

^{99m}Tc-pertechnetate is used worldwide to study the thyroid function because of its advantages, such as a short retention in the gland due to half-life (6 h) and no beta-radiation, thus providing low dosimetry to the thyroid gland and the rest of the body. Its gamma photon of 140 keV is ideal for imaging using scintillation cameras, really cost effective and it can be done fast (readily available), safe and no side effects [5, 6]. A disadvantage is that ^{99m}Tc is only trapped and not organified in the follicles [7].

Iodine-123 (^{123}I) is both trapped and organified by the thyroid gland, it has a relatively short half-life of 13.6 h, a gamma photon suitable for imaging using conventional scintillation cameras (159 keV) and no beta-radiation [5, 7]. Therefore, it is considered the ideal agent for thyroid imaging. However, the reality is that its availability is limited and costly due to its expensive and complex production in a cyclotron. As the information is mostly the same as that obtained by ^{99m}Tc-pertechnetate scintigraphy, specific indications include evaluation of organification defects [5–7].

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Iodine-131 (^{131}I) was frequently used in the past in thyroid diagnosis imaging because of both gamma emission (364 keV) and beta particle emission [7]. Its special characteristics of energy emission, its long half-life (approximately 8.1 days) and high radiation doses to the gland (1–3 rad/mCi) makes 131-Iodine less satisfactory for thyroid imaging (poor quality images are produced) [5]. Currently, 131-Iodine is a radiopharmaceutical used mainly for metabolic therapy in benign thyroid disorders (thyroid hyperfunction) and ablation of tumor remnants of differentiated thyroid carcinomas, in addition to the staging and follow-up of patients with such tumors (using a lower dose of ^{131}I than in the ablation of possible thyroid remnants) [6].

3. Clinical presentation

A thorough cervical examination is important. The palpation of the thyroid gland should be done with the patient sitting (never in supine position) and helping with swallowing movements. We must be careful in the search for possible goiters and their correlation with size (from small goiters, grade-I, to large goiters of endothoracic clinical characteristics, grade-IV), palpation of thyroid nodules and/or adjacent adenopathies (mobile/fixed, painful/not painful, reactive, etc.).

In addition, it is necessary to pay special attention to the size and weight of the patient, heart rate and blood pressure, body temperature, skin adnexa such as hair and nails, skin characteristics or menstrual changes in cases of women of childbearing age.

In patients with thyroid hyperfunction, there is usually weight loss (accompanied by nausea, vomiting, diarrhea and often an increased appetite), excessive urination and thirst, along with remarkable associated hyperactivity.

The cardiovascular system is altered by thyroid hormones which have important effects on cardiac muscle, the peripheral circulation, and the sympathetic nervous system. There is an important correlation between the hyperthyroid state and cardiac morbidity, with cause–effect determination. Cardiac symptoms such as tachycardia, heart failure, or arrhythmia and atrial fibrillation are most frequent [3, 4].

About psycho-neurological manifestations, we have to highlight detected cases of tremors, chorea, myopathy, myasthenia gravis, ophthalmopathy (exophthalmos), delirium, emotional lability, psychosis, paranoia, irritability, exhaustion, depression and panic attacks among others.

Fine and brittle hair or a diffuse hair loss due to an acceleration of capillary cycles is common. The skin is usually smooth, thin, moist and hot, with marked redness of the palms of the hands and tendency to facial flushing, due in large part to heat intolerance. Loss of libido and amenorrhea are other alterations that can be generated over time.

Some laboratory alterations in addition to the thyroid profile such as high blood sugar, low cholesterol or calcium-phosphorus metabolism's alterations (with osteoporosis tendency) can be visualized.

Regarding pediatric age, a high index of suspicion is required due to its important effects on the organism. Thyroid hormones play an important role in the development of the central nervous system and growth. A situation of thyroid hyperfunction can interfere with growth

and development, result in growth retardation, brain damage due to craniosynostosis and cognitive impairment [8].

Although the manifestations are mostly similar to adults, the initial clinical presentation may be different in the pediatric age and even the symptoms may vary within this age group according to (prepubertal or pubertal population). A highlight of certain symptoms as an example of such atypical presentation and that are subject to confusion are mood changes and emotional lability, fatigue, sleep disturbance and increased appetite (prepubertal children more commonly present with poor weight gain and frequent bowel movements), attention-deficit hyperactivity disorder, poor school performance, irritability, fatigue, palpitations, heat intolerance, fine tremor and a goiter [2].

Definitive diagnosis can be more challenging in pregnancy. A diffuse goiter, ophthalmopathy, hyperthyroid symptoms prior to pregnancy and serum thyroid hormone receptor antibody (TRAb) positivity favor the diagnosis of *Graves' disease*. Transient gestational thyrotoxicosis is more common in women with morning sickness, especially those with the most severe form, hyperemesis gravidarum [9].

4. Diagnostic methods in the evaluation of hyperthyroidism

The normal thyroid gland and anatomic variants can be visualized by numerous imaging modalities including scintigraphy, ultrasound and computed tomography. Although magnetic resonance imaging (MRI) is capable of providing excellent anatomic detail of the thyroid gland using proton density imaging, it is not usually used in routine clinical practice [7].

Thyroid ultrasonography utilizes reflected sound waves that allow to identify and evaluate gland size, location, the presence of nodules and to differentiate between cystic and solid lesions [7].

There are certain echographic characteristics such as echogenic behavior of the thyroid nodule (as purely cystic or hyperechoic nodules), good demarcation and external vascularization suggesting signs of benign course (e.g., a thyroid adenoma). On the contrary, solid hypoechogenic nodules, irregular borders, internal vascularization, presence of microcalcifications or recent increase in size on follow-up are associated with malignancy [10].

Ultrasound is, therefore, an image modality from which morphological information of the thyroid gland is obtained. On the other hand, thyroid scintigraphy is a functional imaging test that visualizes the distribution of active thyroid tissue and is used as a complementary test for definite diagnosis [6, 10].

American Thyroid Association (ATA) and other guidelines have published their recommendations suggesting that thyroid scintigraphy is useful in the assessment of diffuse goiter *(Graves' disease)*, the simple thyroid nodule and multinodular goiter, acute or chronic local inflammation (thyroiditis), suspected ectopic thyroid (such as lingual thyroid), the study of cervical embryonic development anomalies of thyroid origin (thyroglossal cysts) to evaluate the extent of retroesternal goiter and patients undergoing treatment with radioactive iodine, which is important to know about the anatomical distribution, active thyroid tissue information and select the appropriate therapeutic dose/activity of 131-Iodine [6].

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Regarding the evaluation of thyroid nodules by thyroid scintigraphy, it plays an important role in the identification of the functional state of the nodule. Non-functioning thyroid nodules do not present radiotracer uptake ("cold nodules") and present a higher risk of malignancy, while functioning thyroid nodules have tracer uptake ("hot nodules") and are usually benign nodules [10].

Laboratory tests play a fundamental role in the initial diagnosis and follow-up of thyroid hyperfunction, in the assessment of possible autoimmunity associated with thyrotoxicosis, in the control and adjustment of adequate pharmacological dose to each patient, as well as in the detection of pharmacological response (drug resistance) or clinical relapse.

In the presence of typical signs and symptoms, a TSH suppressed with excess thyroid hormone production—thyroxine (T4), free thyroxine (FT4) and/or triiodothyronine (T3)—indicates clinical-analytic findings of hyperthyroidism. In the case of *Graves' disease*, these hormonal alterations are attributed to the presence of thyroid stimulating antibodies (TSHR-Ab), specifically thyroid stimulating immunoglobulins (TSI) [2, 11]. This existence of antibodies in the bloodstream explains the autoimmune and genetic component of this syndrome, as well as its relationship with other autoimmune entities.

5. Thyroid scintigraphy: patient preparation, instrumentation and image acquisition. Evaluation of thyrotoxicosis associated with thyroid hyperfunction (clinical examples)

5.1. Patient preparation, instrumentation and image acquisition

Usually no prior patient preparation is needed for thyroid scintigraphy [6]. It is not necessary to carry out any special diet or suspend the usual medication. In case the patient is taking thyroid hormone replacement therapy (levothyroxine), it is necessary to stop taking such medication at least 30 days before the imaging study.

That medication can be restarted as usual once the image is acquired. If the patient is taking an iodine supplement or has recently had an intravenous iodine test (such as a CT scan with intravenous contrast), the study should be delayed 4–6 weeks later [6].

On the other hand, women who are pregnant or breastfeeding should inform the nuclear medicine physician before any testing of the service. Although the exposure to the radiation involved is very low with ^{99m}Tc-pertechnetate, the benefit/risk of the test must be compared, using the lowest possible dose to obtain an adequate image (optimization criterion) [6].

Breastfeeding will be suspended for 24 h after performing the thyroid scan and the importance of drinking plenty of water for an early elimination of the radiotracer will be reported, which will reduce the exposure time of the embryo/fetus to radiation.

About radiation protection measures, it is recommended not to be in contact with pregnant women or young children for 24 h after the scintigraphy. If this condition cannot be met, a distance of at least 1 m from the patient should be maintained.

Regarding scintigraphic technique, the images begin 20 min after the intravenous injection of 5 mCi (185 MBq) of ^{99m}Tc-pertechnetate [12]. In pediatric population, these fixed doses are not used (5–10 mCi [185–370 MBq]); the dose administered to make the image is adjusted to the weight of the patient.

The acquisition is done with gamma cameras, which are composed of collimators of scintillation crystals and photomultipliers, which allow the image obtained to be the projection of the radiotracer distribution. In our department, we use a pinhole collimator with a 3.5 mm opening, as well as an energy setting of 140 keV photopeak for ^{99m}Tc. Images are obtained on a 128 x 128 matrix with a zoom 5 and at 100,000 counts in the anterior and 30° anterior oblique views (right and left anterior oblique) with the collimator placed as close as possible to the patient's extended neck [5, 12]. The duration of the image is usually about 5 min.

In cases where we want to visualize more specifically the thyroid gland and adjacent structures (as in the case of intrathoracic goiters), we can perform the SPECT/CT hybrid technique *(Tomography by Emission of a Single Photon)*. Several rotating gantry are incorporated to the gamma cameras and they rotate around a central axis of the patient, what allows a rotation arc of 180° to 360°. Finally three-dimensional images are obtained, unlike the two-dimensional planar images of the scintigraphy.

5.2. Evaluation of thyrotoxicosis associated with thyroid hyperfunction (clinical examples)

The biodistribution of ^{99m}Tc-O4 in the body is taken up by the thyroid, but this is also taken up by other structures such as salivary glands. Its secretion by saliva, sweat or urine may give false positive image [10].

Therefore, in a normal thyroid scintigraphy, the gland is symmetrical and the lateral borders of lobes are straight to convex. Tracer is normally seen in salivary glands and in capillary network of the neck tissue also, called as 'blood pool' (i.e., seen as a light background along the neck contour) [6].

In the case of diffuse goiter due to *Graves' disease*, thyroid scintigraphy shows a diffuse enlargement of thyroid with a homogeneous distribution of the radiotracer and markedly increased uptake of both thyroid glands suggestive of hyperfunction [8]. Activity throughout the gland is increased relative to the background due to both increased stimulation and function of the gland (**Figure 1**). Such stimulation at times results in visualization of the pyramidal lobe (a remnant of the thyroglossal duct). Owing to its relatively small size, the pyramidal lobe is normally not seen unless the gland is overly stimulated [12].

The toxic multinodular goiter is shown as an enlarged thyroid with a heterogeneous distribution of the radiotracer. Non-functioning and uptake-tracer thyroid nodules are both present, whose activity is above normal (hyperfunction) (**Figure 2**).

With respect to the pretoxic nodular goiter, the thyroid gland usually presents a hyperfunctioning nodulation in one of its thyroid lobes, while the rest of the thyroid parenchyma presents a slight decrease in the uptake of the radiotracer, which suggests the existence of braking phenomena (**Figure 3**).

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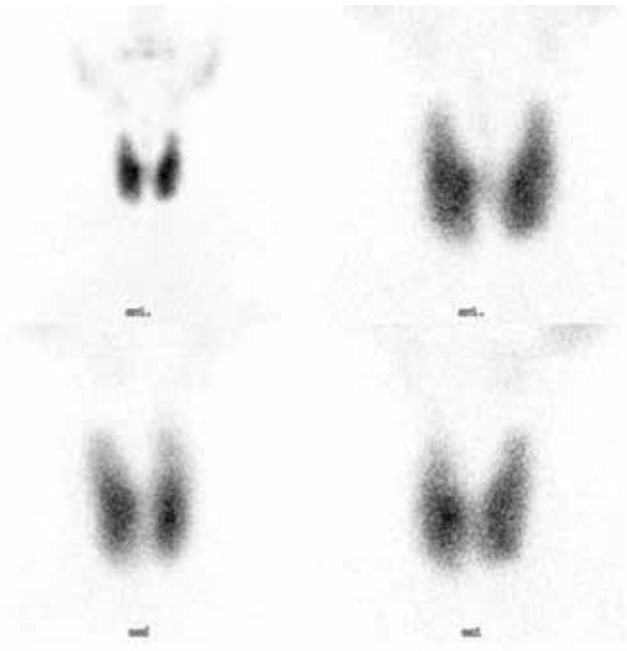

Figure 1. It is noted a diffuse enlargement of thyroid with a homogeneous distribution of the radiotracer and markedly increased uptake of both thyroid lobes, suggestive of hyperfunction. *Courtesy of H.R.U. Málaga, Spain. Nuclear Medicine Department.*

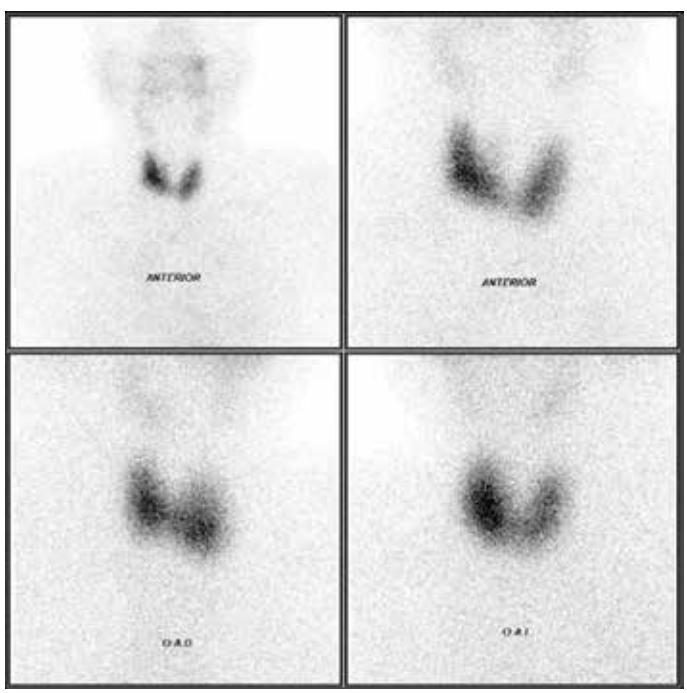

Figure 2. Thyroid scintigraphy shows an uptake-tracer nodule at the base of the right thyroid lobe and another non-functioning nodule at the base of the left thyroid lobe. *Courtesy of H.R.U. Málaga, Spain. Nuclear Medicine Department.*

Figure 3. Hyperfunctioning nodulation is seen at the base of the right thyroid lobe. *Courtesy of H.R.U. Málaga, Spain. Nuclear Medicine Department.*

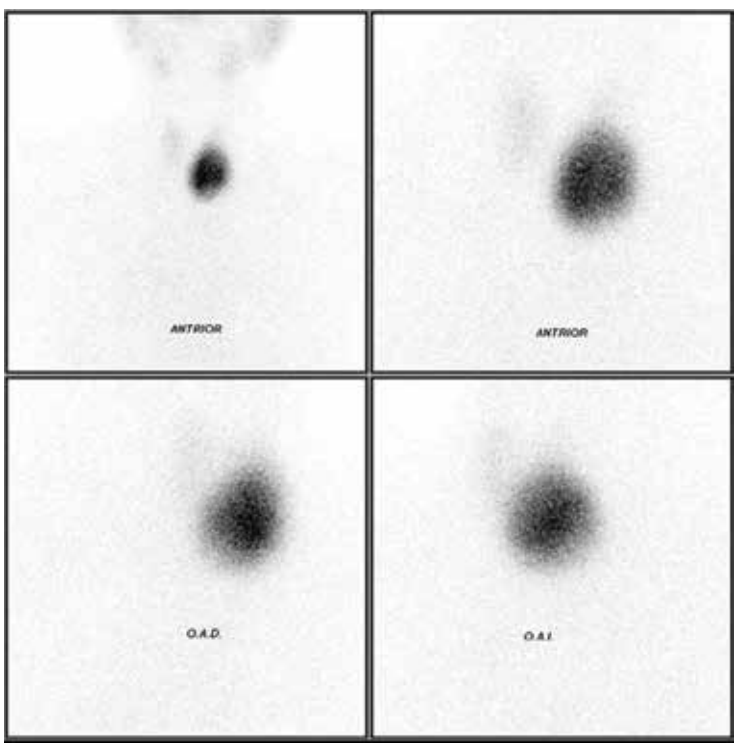

Figure 4. We can see the existence of a large hyperfunctioning nodulation that occupies the left thyroid lobe. *Courtesy of H.R.U. Málaga., Spain. Nuclear Medicine Department.*

As for the toxic adenoma, the thyroid gland appears enlarged at the expense of a thyroid lobe, which is occupied by a hyperfunctioning nodulation. The contralateral thyroid shows a notable decrease in uptake, due to more advanced braking phenomena than in the previous case (**Figure 4**).

The most common reason for hyperthyroidism is *Graves' disease*. Toxic nodular goiter is a clinical situation that includes toxic multinodular goiter and toxic adenoma and is the second most common reason of hyperthyroidism [13].

6. Treatment in hyperthyroidism: different therapeutic options. Radioiodine (^{131}I) administration protocol in our center

6.1. Different therapeutic options in hyperthyroidism

Current therapeutic options for these pathologies include antithyroid drugs (ATD), radioactive iodine and thyroidectomy. The choice of treatment depends on the type of pathology (*Graves' disease*, toxic multinodular goiter, pretoxic or toxic adenoma), physiological characteristics of the patient (age, pregnancy, breastfeeding), co-morbidities (advanced age, heart failure, large compressive intrathoracic goiters, thyroid ophthalmopathy), as well as refractoriness to the treatment administered [8, 14].

Antithyroid drugs (ATD) therapy is usually recommended as the initial treatment for hyperthyroidism (especially in *Graves' disease*), achieving normalization of thyroid function in 4–6 weeks [8].

There are several antithyroid drugs, the most used in our environment are methimazole and propylthiouracil. For several reasons, propylthiouracil is preferred during pregnancy. Avoidance of the use of propylthiouracil (PTU) was recently recommended in childhood because of the high risk of PTU-induced hepatitis. Because methimazole (active metabolite of carbimazole) has a longer half-life and is effective as a single daily dose, it is particularly helpful in younger children. Daily loading doses of 10–30 mg of methimazole or 100–300 mg of propylthiouracil are appropriate for most patients [15, 16].

The medication is prescribed for 12–18 months normally, with the aim of achieving remission of the disease. However, the frequency of recurrences (more frequently in young males) and severe side effects like cytopenias, vasculitis, liver failure or agranulocytosis (higher in pediatric patients than adults) are a main limitation of ATD treatment [8, 14, 16].

Radioiodine therapy and surgery are usually the second-line treatments in *Graves' disease*. It does not happen in the case of toxic nodular goiter (toxic multinodular goiter and toxic adenoma), where definite and effective treatment can be achieved only with radioiodine or surgery [13]. So, both are considered as the first line of treatment for these pathologies and not the second line as in *Graves' disease* [17].

The use of 131-Iodine in the treatment of hyperthyroidism is increasing, as it is easy to administer, relatively inexpensive, safe and highly effective with a cure rate approaching 100% after one or more activity [18].

In our department, we administer single doses of radioiodine, which are prepared in individual capsules to be taken orally. The said capsules are specifically detailed with the data of the patient who is going to receive the metabolic treatment, as well as the amount of dose that the capsule carries. That way, it is possible to reduce failures in the administration of doses between patients.

There is no consensus regarding the optimum dose of radioiodine [17]. There are fixed doses regimens of 10 mCi (370 MBq) generally used to treat *Graves 'disease*, in addition to capsules with a dose of 12 mCi (444 MBq) at 15 mCi (555 MBq), for cases of pretoxic and toxic multinodular goiter and adenoma, respectively. Also, calculated-dose strategies (doses adjusted to patient's weight) can be used, which is considered the most specific option, since the patient is prevented from receiving a higher or lower dose than necessary. In a study conducted by Rokni H et al., it was observed that, interestingly, permanent hypothyroidism was not significantly different between calculated and fixed dose regimens [17].

Once the dose of ^{131}I is administered, the patient may present three situations. The goal of treatment of hyperthyroidism is to bring patients to the euthyroid state.

Hypothyroidism is recognized as an important and more frequent side effect of treatment for hyperthyroidism. Hypothyroidism may be transient (usually 2–4 months after therapy) or permanent [17, 18]. Patients with permanent hypothyroidism usually need additional treatment with thyroid hormones (levothyroxine), whose doses are increased or decreased according to clinical and analytical controls.

On the other hand, it may happen that once the dose of 131-Iodine is administered, the patient persists in hyperthyroidism. In this case, refractoriness is discussed at the initial dose of metabolic therapy and it may be necessary to administer a second dose of ^{131}I after 6 months from the initial dose.

Risk factors such as the presence of thyroid antibodies, age and sex of the patient, etiology of hyperthyroidism, administration of antithyroid drugs and goiter size can influence the outcome of ^{131}I treatment [18]. Patients with antithyroid antibodies, young males, *Graves' disease* (more frequent than multinodular goiter and pretoxic/toxic adenoma), long period of time with high doses of antithyroid drugs or relapse after its suspension, large intrathoracic compressive goiters or *Graves´ophthalmopathy*, have more risk of failure to the initial treatment with 131-Iodine.

These fixed dose regimens of 131-Iodine (^{131}I) for each pathology: 10 mCi [370 MBq] *(Graves' disease)*, 12 mCi [444 MBq] (multinodular goiter and adenoma in "pre-toxic situation"), 15 mCi [555 MBq] (toxic multinodular goiter and toxic adenoma) have been previously studied, increasing the probability of healing and providing the lowest possible radiation to the rest of the body. Calculated-dose strategies (doses adjusted to patient's weight) have the advantage that they are individualized for each patient. In our department, calculated-dose strategies are used in childhood and adolescent patients, as well as in adults of low weight. However, the optimal way is to use adjusted doses to the weight of the patient and to a lesser extent the fixed doses.

Surgery (total thyroidectomy) is recommended when there are side effects of antithyroid drugs, non-adherence to pharmacological treatment, non-remissions in hyperthyroidism's recurrences after prolonged medical treatment, patients with severe exophthalmos, very large

goiters, multinodular goiters, large nodules on thyroid or refuse treatment with 131-Iodine. Although the treatment rate is high with surgery, serious complications such as recurrent laryngeal nerve injury and hypoparathyroidism may be seen [8, 13].

6.2. Radioiodine (^{131}I) administration protocol in our center

In all cases of treatment with 131-Iodine (*Graves' disease*, pretoxic/toxic multinodular goiter or pretoxic/toxic adenoma), treatment is performed in our department on an outpatient basis if the dose of ^{131}I is less than 30 mCi (1110 MBq).

Prior to the administration of the radioiodine dose, metabolic treatment is explained, as well as all the radiological protection measures to be followed, possible side effects such us fever due to radiation-thyroiditis (which usually remits at 48 h); cervical/pharyngeal complaints, that usually remit with analgesics or tachycardia. Additional treatment with β-blockers (except in patients with asthma or cardiac failure) during the first 2 weeks of management may help to reduce the patient's symptoms. This treatment can be given orally twice daily, at a dose of 2 mg/kg/day, and stopped when the patient becomes euthyroid [15]. After a detailed explanation, informed consent is signed.

If there are women of childbearing age, it is mandatory to ask the date of last menstruation and request pregnancy tests. To receive a therapeutic dose of ^{131}I, it is also necessary to have a thyroid scintigraphy in the last year.

As for the preparation, the patient should come fasting for at least 4 h and have stopped the medication with antithyroid drugs 2 days before. The medication with antithyroid drugs will be reintroduced 72 h after taking the radioiodine and half the dose scheduled until the next revision by endocrinology. There is another option such as discontinuing antithyroid drugs 1 week before treatment and starting again 1 week after treatment [13].

Once the patient has ingested the capsule, it is not necessary to carry out any diet low in iodine. However, it is mandatory that the patient stays for 2 more h fasting and performs the radiological protection measures (already explained previously) for 7–10 days following the administration of ^{131}I. This is due to a reasonable 131-Iodine half-life of 8 days [8, 13].

Following treatment, patients must be evaluated at 1, 3, 6 and 12 months for thyroid function tests, clinical symptoms and physical examination by endocrinology physicians to observe the response to metabolic therapy. Patients who develop euthyroidism and hypothyroidism in the sixth month are accepted as cured [13].

7. Radiation protection: ionizing radiation and radiobiology. Objective, pillars and radiological protection measures

7.1. Ionizing radiation and radiobiology

Nuclear medicine is the medical speciality that uses non-encapsulated sources of artificial ionizing radiation with diagnostic-therapeutic use and research. In these cases, the patient is the source of radiation. For these reasons, there is a risk of external radiation to health personnel,

patients' relatives and the general public. In addition, special attention is paid to the possibility of contamination because these tracers are excreted physiologically by tear secretions, saliva, sweat, urine, feces, genital fluids or breastfeeding.

Radiobiology studies the effects of ionizing radiation on cells. These effects are diverse and are classified into three large groups:

- According to the time of appearance: early or late effects.
- Depending on its action on cells: direct effects on DNA (breakage of DNA strands) or indirect effects (cellular damage by free radicals).
- From a point of view of dose dependence: deterministic effects ("dose-dependent", which can be prevented if this dose threshold is not exceeded) and stochastic effects (due to chance, cannot be prevented since they do not present dose threshold).

7.2. Objective, pillars and radiological protection measures

The main objective of radiation protection is to prevent the appearance of deterministic effects and limit the possibility of stochastic effects. The pillars of radiological protection are based on:

- Justification: obtain positive net benefit. Benefit/risk balance, where the benefit of the test must be greater than the risk.
- Optimization: exposure to ionizing radiation should be as low as reasonably achievable *("ALARA principle")*. It is because of that calculated-dose method may be more acceptable, due to considering that principle and an increasing desire for lowering annual dose of the general population [17].
- Limitation of doses: use the lowest possible dose to obtain good image quality and limit the radiological tests to be performed. Maximum doses (mSv) are established for members of the public, caregivers of the patient and health personnel, as well as specifically for the lens, skin and limbs.

The general measures in radiological protection are:

- Time: the shorter the time in contact with the radiation source (patient), the lower the received dose.
- Distance: it must be as far as possible from the radiation source (patient), since the dose received will be lower. The physical law of the *"inverse of the square of the distance"* is applied in such a way that if we move away twice the distance of the patient, we will decrease the dose 1/22 (1/4); if we go three times, the received dose will decrease 1/33 (1/9), and so on.
- Shielding: separation between the issuing source (patient) and the rest of people (operators / public). There are "primary shields" such as lead tubes used as a protector for the injection of the radiotracer. Also, mention the existence of "secondary shields", such as leaded aprons, thyroid protectors, eye protectors for lenses, gloves, glass or special screens.

When a patient is treated with ^{131}I and released, it is important that members of the public, including the family, are not exposed to significant radiation. The regulations vary between countries, but there are certain general conditions under which outpatient therapy can be arranged. Between them, no adult can be exposed to 5 mSv (500 mrem), patients can be released when the administered dose is <1.22 GBq (33 mCi) [1221 MBq] and the emitted radiation must be <7 mrem/h at 1 m [16].

Several studies have measured radiation rates to family members and have confirmed that simple measures, such as sleeping in a separate bedroom and remaining more than 2 m from family members for a few days, ensure that the regulations are fulfilled [16]. In our nuclear medicine department of the *Regional University Hospital of Málaga*, we have prepared an informative document with the recommendations and precautions that patients should follow in treatment with radioiodine, which is explained and delivered to each of these patients (Appendix 1).

8. Special situations in nuclear medicine and radiation protection

8.1. Pregnancy and breastfeeding

"In nuclear medicine, a woman of childbearing age is considered pregnant until proven otherwise". In the nuclear medicine services, there are visible information leaflets to the public, especially for women of childbearing age who may be pregnant and whose duty it is to inform the center's health personnel.

In addition, it is mandatory to ask the date of last menstruation and about the possibility of pregnancy in the clinical history. Also, all women in this age group who are to be treated with radionuclides of iodine must have a negative pregnancy test, prior to the administration of the radiopharmaceutical as therapy [16]. The result of the pregnancy test will be recorded in the patient's health history.

Pregnant women with untreated overt hyperthyroidism are at increased risk for spontaneous miscarriage, congestive heart failure, thyroid storm, preterm birth, pre-eclampsia, fetal growth restriction, and increased perinatal morbidity and mortality [9].

Regarding the use of radioiodine, fertility could be reduced and abnormalities offspring will be increased. Several studies are related to larger doses of ^{131}I that are used to treat thyroid cancer [16]. Medical personnel should warn patients to avoid becoming pregnant during the time following the procedure with radionuclides. The time required depends on the type of radiopharmaceutical used; in the case of ^{131}I (either used for the treatment of hyperthyroidism or as ablative therapy of possible thyroid remnants in differentiated thyroid carcinoma) the consensus is that the conception should be deferred for 12 weeks (minimum 6 months) and that maternal thyroid function should be normal [16].

By avoiding pregnancy during this period, the objective is achieved to reduce the probability that the dose received to an embryo or fetus is greater than 1 mSv (dose limit to the public). Keep in mind that these compounds cross the placental barrier and there is a risk of an exposure of the fetus that can reduce the intelligence quotient by 30 points per gray (100 rads), and

may be associated with attention deficit disorders and impairment of figurative memory in the offspring and also a slightly increased cancer-risk possibility. According on the gestation period the patient is in, there is a greater probability of risk of [3, 16]:

- Pre-implantation stage (second week): abortions *("all-or-nothing law")*.
- Stage of organogenesis (second–eighth week): congenital malformations.
- Early fetal stage (8th–15th week): neurological alterations such as decrease of the intellectual coefficient.
- Late fetal stage (15th–25th week): neurological alterations and risk of developing radio-induced cancer that will be suffered before the age of 15 years.
- Special mention with the use of ^{131}I, therapeutic administration of radioiodine to the mother after the fetal gland is formed (after about 10 weeks into gestation) can result in fetal hypothyroidism. This is because after the eleventh week, the fetal thyroid concentrates iodine, and if the fetus is exposed, it will be born athyrotic.

For these reasons, radioiodine therapy is contraindicated in pregnancy, being the pharmacological treatment with oral antithyroid drugs the first line of therapy, mainly with propylthiouracil. Radioiodine would be acceptable when pregnancy is contemplated after at least 6 months, and thyroidectomy if conception is envisaged within a 6 month interval and/or if there is a large goiter [3]. It must also be borne in mind that these possibilities of therapy are considered second line, in the case of contraindication, refractoriness or failure to adherence to pharmacological therapy with anti-thyroid drugs.

Regarding breastfeeding, there are general guidelines on the time of interruption depending on the radiopharmaceutical used. In the case of ^{131}I for therapeutic purposes, breastfeeding should be completely suppressed after administration of ^{131}I. This condition does not occur with antithyroid drugs, since studies have shown that only limited amounts of propylthiouracil or carbimazole are secreted in breast milk, which explains that the neonatal exposure to these drugs is insignificant. Therefore, the use of low-moderate doses of carbimazole (<20 mg) or propylthiouracil (<300 mg) during breastfeeding is recommended [3].

8.2. Chronic renal failure and dialysis

Patients with chronic renal failure do not have a contraindication to receive treatment with 131-Iodine.

Holst et al. reviewed the medical literature and concluded that the ^{131}I dose does not need to be adjusted in patients who have end-stage renal disease and who are referred for the therapy of hyperthyroidism. However, they recommended ^{131}I administration as soon as possible after dialysis and a delay in subsequent dialysis until the maximum ^{131}I uptake has occurred in the thyroid [16].

Some cases of contamination of dialysis machines have been reported. In these cases where there may be a slight contamination with 131-Iodine in disposable items such as syringes or waste bags, these can be stored for several half-life periods until activity declines. Also these

patients should undergo dialysis in a private room and monitored by radiophysics personnel. Apart from this, no additional precaution is needed.

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Conflict of interest

The authors declare that they have no conflict of interest.

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A. Appendix 1

Nuclear medicine service.

Regional university hospital of Málaga.

Patients in radioiodine treatment.

Name and surname:

Dear SR / SRA:

For the treatment of your illness, we have given you a radioactive substance called 131-Iodine. This substance will remain in your body for several days until it disappears completely through the urine, because it eliminates itself. While this is beneficial for you, certain precautions must be taken in order to protect the people with whom you live. Therefore, we recommend that you follow these instructions for the next 7–10 days (from xx-xx-xxxx to xx-xx-xxxx):

- Avoid being around pregnant women and young children.
- If you stay in a room with your family for a long time, try to be as far away from them as possible (at least 1 meter away).

- When using the toilet, you must pull the cistern several times (approximately 4 times).
- Use your own napkin, towel, toothbrush, glass, plate, cutlery, and so on.
- Drink plenty of fluids.
- Daily shower and brushing of teeth after each meal.
- Wash your underwear and bedding in a different laundry from your family.
- Avoid having sex during these days.
- Sleep in a different room from the rest of your family.
- If you are of childbearing age, avoid becoming pregnant during the next 12 months.
- If you are the one who cooks at home, do it with rubber gloves (to avoid touching the food with your own skin).
- You can go out to the street only to walk and away from places with crowds of people. You should not enter closed places such as cafes, bars, shops, cinemas, and so on.

If you have any questions, do not hesitate to contact us by calling 0–00-000000. Thank you very much for your help.

Remember that you must continue fasting for 2 h after the administration of the dose of iodine.

Author details

Elena Espinosa Muñoz

Address all correspondence to: elenaespinosamunoz@gmail.com

Nuclear medicine physician, Hospital Regional Universitario, Málaga, Spain

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Chapter 5

Thyroid Cancer: Diagnosis, Treatment and Follow-Up

Mira Siderova

Additional information is available at the end of the chapter

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Abstract

Thyroid cancer is the most common malignancy of the endocrine system and it is usually presented as nodular goiter, the last being extremely a common clinical and ultrasound finding. The widespread use of ultrasonography during the last decades has resulted in a dramatic increase in the prevalence of clinically inapparent thyroid nodules, which only in 5.0–10.0% harbor thyroid carcinoma. The goal of the initial sonographic assessment of thyroid nodules is to distinguish benign nodules that could be managed conservatively from those with suspicious or malignant features requiring further management, including fine needle aspiration biopsy (FNAB), some axillary molecular techniques and thyroid surgery. Since over 90% of malignant thyroid nodules are differentiated thyroid carcinomas (DTCs) with good prognosis, it is necessary to establish strict criteria for diagnosis, treatment and follow-up in order to minimize the potential harm of over-treatment of low-risk patients and to provide adequate therapy to patients at high risk. This often requires an interdisciplinary approach involving endocrinologists, surgeons, pathologists, radiologists and oncologists.

Keywords: thyroid cancer, thyroid nodules, ultrasound, fine needle aspiration biopsy, surgery, radioiodine, follow-up

1. Introduction

Nodular thyroid disease is a common clinical problem and palpable thyroid nodules are found in approximately 3–7% of the population [1]. Comparing to palpation as the detection method, ultrasound (US) increases the prevalence 10-fold, reaching between 20 and 76% with higher rates in women, older age groups and endemic areas [2, 3]. Thyroid carcinoma is the most common endocrine cancer [4], diagnosed in about 5–10% of thyroid nodules [1, 5]. An American survey predicts that by 2019, papillary thyroid carcinoma will be the third most common malignancy in women [6]. Over the last 30 years, the annual incidence of thyroid carcinoma in the

USA has nearly tripled from 4.9 to 14.3/100,000 [7]. It is believed that this increase is largely due to the improved diagnosis and detection of carcinomas smaller than 2 cm, whereas the mortality rate of this disease has not changed and remains at a level of 0.5/100,000 [8]. However, an analysis by Lim et al. of 77,276 thyroid cancer patients published in 2017 estimates an increase in the mortality rate for advanced-stage papillary thyroid cancer [9].

The Chernobyl accident in 1986 marked a new era in thyroid carcinoma incidence. The risk of developing thyroid cancer, especially in Ukraine, Belarus, Western Russia and neighboring countries, is estimated to be highest for those who were then under the age of 9, and especially under the age of 5, and probably have taken a large dose radioactive iodine through milk and dairy products [10]. It is estimated that the Chernobyl accident will result in 16,000 new cases of thyroid cancer by 2065 [10]. In the coming years, an increasing number of newly diagnosed thyroid carcinomas is expected in Japan, related to the Fukushima accident in April 2011. All these factors led to the development in 2015 of the American Thyroid Association (ATA) management guidelines for adults with thyroid nodules and differentiated thyroid cancer [5].

Differentiated thyroid carcinoma (DTC), including papillary (classical and variants) and follicular carcinoma, accounts for over 90% of cases of thyroid cancer and is the main subject of this review. Medullary and anaplastic carcinomas are rare and prognostically less favorable.

2. Preoperative diagnosis of thyroid carcinoma

Two diagnostic procedures play a major role in the preoperative diagnosis of thyroid cancer—the ultrasound (US) examination of the neck, revealing one or more thyroid nodules and the fine needle aspiration biopsy (FNAB).With the discovery of a thyroid nodule, a complete history and physical examination focusing on the thyroid gland and cervical lymph nodes should be performed. Family history of thyroid carcinoma, prior head or neck irradiation, a growing or fixed nodule with neck lymphadenopathy, male gender as well as some age groups (< 18 and > 70 years of age are clinical factors that are associated with a higher risk of thyroid carcinoma [11, 12].

The next diagnostic step is the clarification of thyroid function by obtaining a serum TSH. If the serum TSH is subnormal, besides serum levels of free T4 and T3, a radionuclide thyroid scan should be performed to document whether the nodule is hyperfunctioning ("hot"), isofunctioning ("warm") or nonfunctioning ("cold") [12]. Autonomously functioning thyroid nodules (toxic or hyperfunctioning nodules) do not need further cytologic evaluation because the incidence of malignancy is exceedingly low [5, 12]. On the contrary, a higher serum TSH level, even within the upper part of the reference range, is associated with an increased risk of malignancy [13]. Experimental studies have shown that thyroid cell proliferation is TSH dependent and that highly differentiated thyroid carcinomas retain this response to TSH. Suppressive thyroxine treatment for differentiated thyroid cancer is also based on this TSH dependence [14].

2.1. Ultrasound examination

Most guidelines do not recommend routine population US screening. However, thyroid ultrasound is mandatory for individuals with a family history of thyroid carcinoma, previous

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head or neck irradiation (e.g., radiotherapy for concomitant lymphoma), palpable nodules in the neck, symptoms of dysphonia, dysphagia, dyspnea and cervical lymphadenopathy [12].

Neck US is a key examination in the management of thyroid nodules and in the last two decades, it has become an indispensable tool for detecting thyroid nodules and for accurately determining their size, number and structure [15]. By definition, a thyroid nodule is a discrete lesion within the thyroid gland that is radiologically distinct from the surrounding thyroid parenchyma [16]. The US examination should select the suspicious nodule for subsequent FNAB according to the "degree of suspicion" determined by the presence of some of the following malignancy-specific characteristics [17]:

- a solid hypoechoic structure and especially marked hypoechogenicity;
- irregular margins—if more than 50% of the circumference of the nodule is unclearly separated from the surrounding parenchyma, the margins are considered irregular, as well as if microlobulations or spiculae exist. The missing "halo" sign, which indicates that it is difficult to delineate margins, is not equivalent to irregular margins, the last being clearly visible but showing an infiltrative course [5];
- the presence of microcalcifications—tiny hyperechoic spots that are equal to or less than 1 mm in diameter without posterior acoustic shadowing. They are common in papillary thyroid carcinoma and pathologically represent psammoma bodies.
- "taller-than-wide" shape, anterior–posterior diameter exceeds the transversal diameter of the nodule (AP/T ratio > 1) on a transverse or longitudinal plane [18, 19].
- intranodular blood flow detected by color or power Doppler is explained by the formation of new blood vessels needed for the fast proliferating tumor cells [20, 21]. Although intranodular hypervascularity is observed in about half of thyroid carcinomas, it is a nonspecific finding. Perinodular blood flow is usually seen in benign nodules, but 22% of malignant nodules also show perinodular blood flow. The results of previous studies are somewhat contradictory regarding Doppler [19].
- presence of enlarged cervical lymph nodes with suspicions for malignancy characteristics (e.g., round shape, absence of hilus, thyroid-like structure, presence of microcalcifications, cystic degeneration, abnormal vascularity pattern).

Other US characteristics are still debatable, for example, an increase in nodular size/volume (50% increase in volume), large coarse and irregular-shaped dystrophic calcifications (frequently seen in all types of nodules and may reflect previous hemorrhage and tissue necrosis) and rim or "egg-shell" calcifications (malignancy is suspected if the "egg-shell" is interrupted, with small extrusive soft-tissue component). According to most studies, the nodule size and number (solitary nodules or multinodular goiter) are not suggestive of malignancy, although a meta-analysis of Campanella indicates a higher malignancy risk for single nodules (OR, 1.43) and for nodule size ≥4 cm (OR, 1.63) [11].

There are also some US features suggestive of benignity of the nodule—pure cysts with anechoic structure, spongiform nodules, halo sign, smooth margins, dorsal acoustic enhancement, presence of a gentle continuous halo, dorsal acoustic enhancement, hyperechoic structure, uninterrupted eggshell calcifications as well as significant decrease in size over time [22].

Apart from the interobserver variation in the assessment, the US criteria associated with malignancy have various sensitivity and specificity, and unfortunately, none of them alone is strong enough to prove or rule out malignancy efficiently (**Table 1**). This is why some teams have tested certain combinations of US features to increase the diagnostic accuracy of this imaging technique. The concurrent presence of two sonographic criteria doubles the probability of malignancy; a combination of three raises the malignancy risk to 72.7% [30]. According to Papini et al. the combination of a hypoechoic structure and at least one of the following US features—irregular borders or microcalcifications or intranodular blood flow—reaches 87% sensitivity and would miss only 13% of the carcinomas among the nonpalpable nodes [25].

In 2017 the European Thyroid Association (ETA) created a novel European Thyroid Imaging and Reporting Data System, called **EU-TIRADS**, providing a risk stratification of thyroid nodules [31]. It consists of a 6-point scale for risk stratification with increasing risks of malignancy and is based on the "classic pattern" concept [31]:

- **EU-TIRADS 1** category refers to a US examination where no thyroid nodule is found; there is no need for FNAB.
- **EU-TIRADS 2** category comprises benign nodules with a risk of malignancy close to 0%, presented on sonography as pure/anechoic cysts (**Figure 1A**) or entirely spongiform nodules (**Figure 1B**). Both of these US appearances are sufficient to rule out malignancy without the need for FNAB, unless the last is performed for therapeutic purposes—that is, cyst evacuation in case of compressive symptoms. The benign cyst is a purely cystic nodule which does not have any wall thickening or any solid component that could be identified by Doppler US. Cysts which are divided into separate compartments by septa also belong to this benign category. Bright echogenic spots with posterior comet-tail artifact represent a benign finding, in fact a reverberation of the US signal related to presence of microcrystals in colloidal nodules. The spongiform nodule (also "puff pastry" structure) is composed of tiny cystic spaces involving the entire nodule, separated by numerous isoechoic septa, and is considered benign [5, 12, 22, 31].
- **EU-TIRADS 3** is the low-risk category (malignancy risk: 2–4%) which includes oval-shaped, isoechoic or hyperechoic nodules with smooth margins and no high-risk features (**Figure 1C** and **D**). FNA is recommended only for nodules >20 mm [31, 32]. For nodules with an inhomogeneous structure, the presence of any hypoechoic areas classifies the nodule as intermediate risk (see below).
- **EU-TIRADS 4** is the intermediate-risk category with an estimated risk of malignancy between 6 and 17% [31, 32]. This category is presented by mildly hypoechoic nodules with oval shape, smooth margins and without any features of high risk (**Figure 1E**). FNA should be performed if nodule's diameter is >15 mm. As it is evident, the difference between the low-risk (EU-TIRADS 3) and the intermediate-risk category (EU-TIRADS 4) lies in the echogenicity of the solid part of the nodule. The estimated risk of malignancy varies between 6 and 17% and some US features may modulate it. For example, cystic areas, the presence of comet-tail artifacts, peripheral vascularity or high elasticity lowers the malignancy risk, whereas interrupted rim macrocalcifications, a thick or discontinuous halo, predominantly central vascularity, and low elasticity may increase the risk [31].

US feature	Author	Year	Nodules (number)	Sensitivity (%)	Specificity (%)
Solid	Kim et al. [23]	2002	155	26.5	94.3
hypoechoic	Peccin et al. [24]	2002	289	44.0	83.0
structure	Papini et al. [25]	2002	494	87.1	43.4
	Capelli et al. [26]	2007	5198	81.0	47.0
	Moon et al. [27]	2008	8024	41.4	92.2
	Brito et al.* [28]	2014	18288	73.0	56.0
	Remonti et al ** [29]	2015	12786	62.7	62.3
Irregular	Kim et al. [23]	2002	155	55.1	83.0
margins	Peccin et al. [24]	2002	289	56.0	80.0
	Papini et al. [25]	2002	494	77.5	85.0
	Capelli et al. [26]	2007	5198	53.0	81.0
	Moon et al. [27]	2008	8024	48.3	91.8
	Brito et al.* [28]	2014	18288	56.0	79.0
	Remonti et al ** [29]	2015	12786	50.5	83.1
Microcalci-	Kim et al. [23]	2002	155	59.2	85.8
fications	Peccin et al. [24]	2002	289	56.0	94.0
	Papini et al. [25]	2002	494	29.0	95.0
	Capelli et al. [26]	2007	5198	72.0	71.0
	Moon et al. [27]	2008	8024	44.2	90.8
	Brito et al.* [28]	2014	18288	54.0	81.0
	Remonti et al ** [29]	2015	12786	39.5	87.8
Intra-	Papini et al. [25]	2002	494	74.2	80.8
nodular	Capelli et al. [26]	2007	5198	62.0	50.0
blood flow	Brito et al.* [28]	2014	18288	48.0	53.0
	Remonti et al ** [29]	2015	12786	49.5	78.0
Taller-than-	Kim et al. [23]	2002	155	32.7	92.5
wide shape	Moon et al. [27]	2008	8024	40.0	91.4
	Brito et al.* [28]	2014	18288	53.0	93.0
	Remonti et al ** [29]	2015	12786	26.7	96.6
Size >10 mm	Papini et al. [25]	2002	494	61.3	32.0
	Capelli et al. [26]	2007	5198	77.0	35.0
	Brito et al.* [28]	2014	18288	57.0	40.0

*a metaanalysis of 31 studies
**a meta-analysis of 41 studies

Table 1. Sensitivity and specificity of different US characteristics, studied by different research groups.

- **EU-TIRADS 5** encompasses the high-risk category nodules with at least one of the following US features: marked hypoechogenicity, nonoval shape, irregular margins and microcalcifications. The risk of malignancy varies between 26 and 87% [33, 34], generally increasing with the number of suspicious US characteristics. FNA is recommended for high-risk nodules if they exceed 10 mm in size. In case of benign cytology of such a suspicious nodule, FNAB should be repeated within 3 months to reduce the rate of false-negative samples. Patients with subcentimeter nodules with highly suspicious US features (microcarcinomas) and no abnormal lymph nodes can have the choice of active surveillance or FNAB. The last is recommended if the nodule shows enlargement or is accompanied by abnormal lymph node/s, highly suspicious of lymph node metastatic disease [31].

2.1.1. The problem of thyroid incidentalomas

A thyroid incidentaloma is defined as an unexpected, asymptomatic thyroid tumor discovered during the investigation of an unrelated condition. The widespread use of various high-sensitive imaging methods (US, CT, MRI, FDG PET) leads to accidental detection of nonpalpable thyroid nodules, some of which may prove to be malignant [35]. It is believed that the

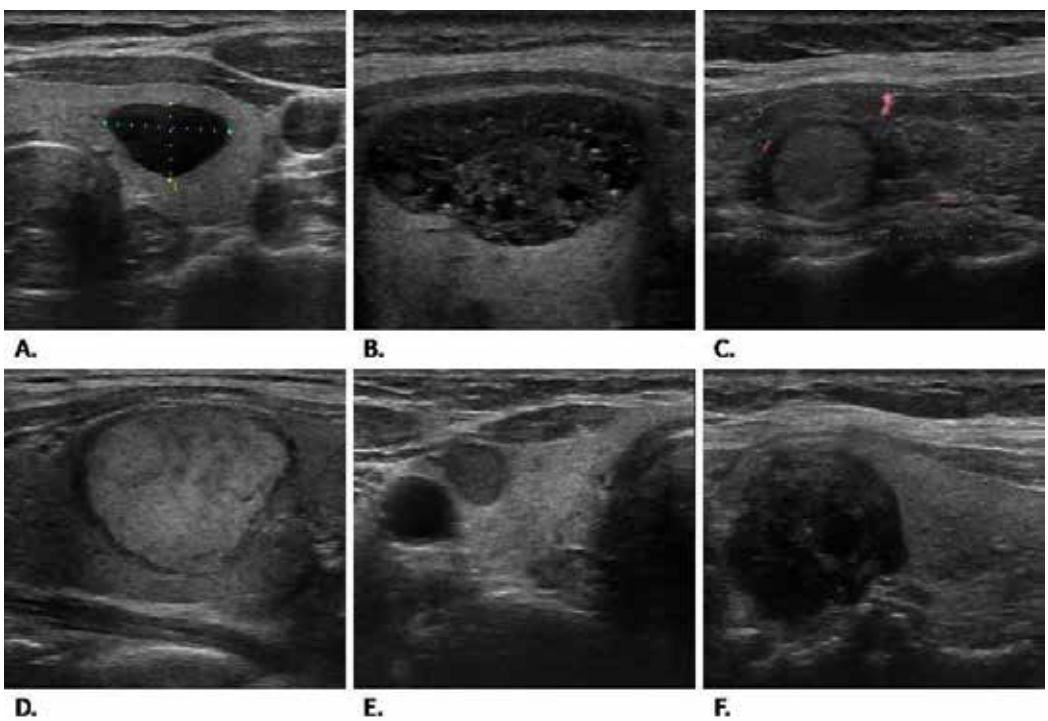

Figure 1. US images of different thyroid nodules, classified according to EU-TIRADS. A. A pure cyst in the left thyroid lobe (EU-TIRADS 2). B. A spongiform nodule with comet-tail artifacts (EU-TIRADS 2). C. An isoechoic nodule with continuous halo (EU-TIRADS 3). D. A hyperechoic nodule with a hypoechoic halo (EU-TIRADS 3). E. A hypoechoic nodule with borderline anterio-posterior to transversal ratio (EU-TIRADS 4). F. A highly suspicious nodules with marked hypoechogenicity, non-oval shape, irregular margins, and microcalcifications (EU-TIRADS 5).

increased incidence of thyroid carcinoma is mainly due to detection of microcarcinomas ≤ 1 cm as incidentalomas [36]. The estimated risk of malignancy varies according to the method of discovery. In the absence of clinical risk factors, the risk of malignancy in thyroid incidentalomas diagnosed on neck US, CT or MRI is 5–13%, which is more or less the same as the risk among all thyroid nodules [31, 32, 36, 37]. This implies a mandatory US assessment before the decision for FNAB. In contrast, the risk of malignancy when diagnosed by focal FDG uptake on a PET scan (F-18 fluoro-deoxy-glucose positron emission tomography) is much higher, around 30% [38]. Although the FDG PET is performed in the context of another oncological disease, most FDG PET-positive thyroid incidentalomas are differentiated thyroid cancers and not intrathyroidal metastases from other malignancies [38].

2.1.2. US elastography

Sonoelastography is a noninvasive dynamic technique that uses US to provide an estimation of tissue stiffness by measuring the degree of distortion under the application of an external force. US elastography has been applied to study the hardness/elasticity of nodules to differentiate malignant from benign lesions [39]. Real-time ultrasound elastography (RTE) is the most commonly used method in thyroid clinics. The nodule chosen by the operator and taken in to the area of interest is subjected to repeated pressure pulses applied by the probe. Tissue distortion is then processed by a special software and presented by a US elastogram over the B-mode image in a color scale that ranges from red, for components with greatest elastic strain (*i.e.,* softest components), to blue for those with no strain (*i.e.,* hardest components). The US elastographic image is then matched with an elasticity color scale and classified as: score 1—elasticity in the whole nodule; score 2—elasticity in a large part of the nodule; score 3—elasticity only at the periphery of the nodule; score 4—no elasticity in the nodule; score 5—no elasticity in the nodule and part of the surrounding tissue [39, 40]. The probability of malignancy raises with increasing hardness of the nodule and decreasing elasticity, respectively. A strain index (SI) could be calculated as a ratio of the nodule strain divided by the strain of the softest part of the surrounding normal tissue. The cut-off of SI for malignancy was estimated to be 2.9 in a study of Magri in 661 nodules [41]. Others proposed a higher cut-off of 3.85 for detecting malignant thyroid nodules [42].

2.2. Fine needle aspiration biopsy (FNAB) with cytology assessment

Fine needle biopsy (with or without aspiration) is the most accurate preoperative diagnostic method for distinguishing malignant from benign thyroid nodules [43]. It is a minimally invasive and safe method, which can be performed to hospitalized patients as well as in outpatient settings. It is recommended that the yielded cytological material is then evaluated according to the Bethesda classification in one of the following six categories [44]:

1. **Nondiagnostic or unsatisfactory** are specimens that do not meet the criteria for adequacy due to different reasons—an insufficient number of follicular cells, obscuring blood or clotting artifact, thick smears, air drying of alcohol-fixed smears and others. A thyroid FNA specimen is considered satisfactory for evaluation if it contains at least six groups of follicular cells, each group composed of at least 10 cells [45]. Cyst-fluid-only (CFO) cases

representing cystic thyroid nodules, richly vascularized nodules and pronounced fibrosis in Hashimoto thyroiditis may also result in nondiagnostic specimens. A repeated biopsy with ultrasound guidance is recommended for the unsatisfactory specimens. The risk of malignancy in this category is from 1 to 4%.

2. **Benign cytology** comprises benign follicular nodules (adenomatoid nodules, colloid nodules, etc), lymphocytic (Hashimoto) thyroditis and granulomatous (subacute) thyroiditis. A "benign" or "negative for malignancy" result is obtained from 60 to 70% of all thyroid FNABs, thus avoiding unnecessary surgery in the majority of the patients. Surgery is indicated for very big nodules (usually over 4 cm) causing compression or cosmetic concerns. The benign category carries very low risk of malignancy (0–3%) and if during the US follow-up the nodule shows more than 50% increase in volume or "suspicious" sonographic changes, a repeated FNAB is indicated [44].
3. **Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS)** refers to cytological specimens with follicular arrangement and scant colloid that do not fulfill the criteria for the other categories (4, 5, rarely 6). The estimated risk of malignancy varies between 5% and 15%. The recommended management is clinical correlation and a repeated FNA which may lead to a more definitive interpretation. However, the physician may choose not to repeat the FNA but observe the nodule clinically or, alternatively, refer the patient to operation due to clinical and/or sonographic concerns [44, 46].
4. **Follicular neoplasm (FN) or suspicious for a follicular neoplasm** (SFN)—the specimens typically have high cellularity, and colloid is scant or absent. Since the differentiation between follicular carcinoma and adenoma is made on the basis of capsular and/or vascular invasion, that are visible only on histology, FNAB reports them by this summary term "follicular neoplasm," requiring a definitive diagnostic histology procedure, usually lobectomy. The risk of malignancy in the category of FN/SFN amounts to 15–30% [44, 47].
5. **Suspicious for malignancy** is a cytology suggestive of malignancy without meeting all criteria for the definitive diagnosis of papillary or medullary carcinoma or very rarely lymphoma. The likelihood of definitively confirmed malignancy is approximately 70% and a surgery is recommended [44, 46].
6. **Malignant cytology** indicates that the cytomorphologic features of the cells are conclusive for malignancy—usually papillary thyroid carcinoma (PTC), more rarely anaplastic, medullary cancer, lymphoma or a metastatic lesion of another origin. Thyroidectomy is indicated for this category. The positive predictive value of a malignant FNA interpretation is from 97–99% [44].

Most guidelines recommend surgical removal of nodules with cytology corresponding to Bethesda categories 3, 4, 5, and 6 [5, 13]. Preoperatively, clinical staging is performed through US and/or CT for neck cervical lymph nodes engagement [5, 12]. A CT/MRI is also indicated in selected cases to determine the local invasion of trachea and surrounding structures. In cases of suspicious neck lymphadenopathy, an FNAB of the lymph node with cytological assessment can be combined with a measurement of thyroglobulin/calcitonin in the wash out of the needle [48].

2.3. Molecular testing

Bethesda indeterminate categories 3 and 4 comprise the so-called "gray zone" in thyroid cytopathology. Further stratification of malignancy risk and, respectively, the decision for surgery could be made by some ancillary techniques as molecular testing. The largest studies of preoperative molecular markers in patients with indeterminate FNA cytology have, respectively, evaluated a seven-gene panel of genetic mutations and rearrangements (BRAF, RAS, RET/PTC, PAX8/PPRAγ) [49], a gene expression classifier (167 GEC, mRNA expression of 167 genes) [50] and galectin-3 immunohistochemistry (cell blocks) [51]. Due to the lack of a single optimal molecular test to exclude malignancy and the high cost of these ancillary techniques, they are still not routinely recommended. In the absence of molecular diagnosis, surgical removal of all undetermined lesions and follicular neoplasms is recommended [5].

3. Role of staging and risk stratification in differentiated thyroid carcinoma (DTC) patients

Disease staging is recommended for all patients with DTC not only as a requirement of the cancer registries but also as a factor determining the following treatment, risk assessment, and prediction of disease recurrence or persistence as well as disease mortality. Moreover, in the last years, risk stratification for thyroid cancer patients has changed from a single-point assessment at the time of the diagnosis and initial treatment to a more dynamic and changing overtime risk evaluation [16, 52].

TO	No evidence of primary tumor
T1a	Tumor < 1 cm in greatest dimension. limited to the thyroid. without extrathyroidal extension
T1b	Tumor between 1 cm and 2 cm, without extrathyroidal extension
T2	Tumor between 2 cm and 4 cm, without extrathyroidal extension
T3	Tumor > 4 cm in its greatest dimension. limited to the thyroid gland or
	Any tumor with minimal extrathyroidal spread (e.g., extension into sternothyroid muscle or perithyroid soft tissues)
T4a	Any tumor. with extension beyond the thyroid capsule and invasion of subcutaneous tissue. larynx. trachea. esophagus. or recurrent laryngeal nerve
T4b	Tumor of any size, with invasion of prevertebral fascia or encasing carotid artery or mediastinal vessels
NO	No metastatic lymph nodes (LNs)
N1a	Metastases to LNs in level VI (pretracheal, paratracheal, and prelaryngeal LNs)
N1b	Metastases to unilateral, bilateral, or contralateral cervical LNs (levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal region (level VII)
MO	No distant metastases
Ml	Distant metastases

Table 2. AJCC 7th edition of TNM classification system for differentiated thyroid carcinoma (adapted from the AJCC cancer staging manual. Seventh edition (adapted from edge et al. [53]).

The initial staging of each patient is performed post-operatively mainly on the basis of the histology report, according to the seventh edition of the TNM classification of the American Joint Committee of Cancer (AJCC), presented on **Table 2** [53]. Additionally to the TNM score, the age of the patient is also important, as young age (≤ 45 years) is considered a favorable factor upstaging the young patients with any T, any N and M0 in stage I and, respectively, young patients with distant metastases in stage II. However, some studies have questioned this "young age benefit" in the presence of lymph node metastases [54].

The initial risk stratification is based on the TNM staging, as well as the type of tumor histology. ATA guidelines from 2015 proposed some additional prognostic variables as the extent of lymph node involvement presented as the number and size of lymph metastases, mutational status and degree of vascular invasion as the number of affected vessels that were not present in previous stratification systems (**Table 3**).

Low ATA risk	Papillary thyroid carcinoma (with all of the following): • No local (LNs) or distant metastases • Complete resection of the primary tumor (assessed macroscopically) • No tumor invasion of local tissues and structures • The histological subtype does not belong to the aggressive ones (e.g., tall cell, columnar cell or hobnail cell variant) • No vascular invasion • Clinical N0 or < 5 N1 micrometastases (< 2 mm) • If ^{131}I is administered, there are no uptake outside the thyroid bed (no metastatic foci) on the post-therapeutic whole-body scan (WBS)
	Intrathyroidal encapsulated follicular variant of papillary carcinoma
	Intrathyroidal, well differentiated follicular carcinoma with capsular invasion and no or minor (< 4 vessels) vascular invasion
	Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including $BRAF^{V600E}$ mutated (if known)
Intermediate ATA risk	Microscopic invasion of tumor into the soft tissues surrounding the thyroid
	RAI uptake outside the thyroid bed (metastatic foci) on the posttherapeutic whole-body scan (WBS)
	Aggressive histology (e.g., tall cell, columnar cell or hobnail cell variant, diffuse sclerosing variant)
	PTC with vascular invasion
	Clinical N1 or > 5 metastatic LNs with size < 3 cm
	Multifocal papillary microcarcinoma with extrathyroidal extension and $BRAF^{V600E}$ mutated (if known)
High ATA risk	Macroscopic invasion of tumor into the perithyroidal soft tissues Incomplete tumor resection Distant metastases
	High postoperative serum thyroglobulin suggestive of distant metastases LN metastasis with any of the LNs > 3 cm
	Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion)

Table 3. Initial risk stratification (adapted from ATA 2015 guidelines [5]).

Ongoing (dynamic) risk stratification reflects the changes of recurrence risk during the follow-up period, which depends on the natural history of the disease and the patient's response to therapy (see Section 5 on the follow-up of patients with DTC).

4. Treatment

Initial treatment of DTC includes surgery and post-operative administration of radioiodine (if indicated) and the initiation of levothyroxin therapy. In rare cases (locally aggressive thyroid cancer), external beam radiotherapy to the neck is also indicated.

4.1. Surgery

4.1.1. Thyroid surgery

Thyroid surgery is an important element of the initial therapy for thyroid carcinoma. The recommended extent of thyroid surgery in patients with FNAB and cytology of malignant thyroid nodule (not medullary carcinoma) depends on the nodule size:

- A tumor larger than 4 cm, or with a gross extrathyroidal extension, or clinically metastatic lymph nodes or proven distant metastases, requires a total or near-total thyroidectomy as initial surgical intervention in order to remove all primary tumor mass [5].
- For tumors >1 cm and < 4 cm without extrathyroidal invasion, with no clinical data of lymph node metastases, the initial surgical procedure can be either bilateral (total or near-total thyroidectomy) or unilateral (lobectomy). Lobectomy may be sufficient for low-risk papillary and follicular carcinomas. Total thyroidectomy (TT) can be considered by the treatment team, especially if consequent radioiodine ablation (RAI) is planned. TT also enables a reliable follow-up, since thyroglobulin used as a tumor marker is expected to be undetectable if the thyroid is removed.
- For tumors <1 cm (small, unifocal and intrathyroidal carcinoma), without extrathyroidal extension and without lymph nodes involvement, thyroid lobectomy is sufficient unless there are other indications to remove the contralateral lobe as concurrent Graves' disease or benign nodules in the contralateral lobe [5, 52].

4.1.2. Lymph node dissection

- Therapeutic central-compartment (level VI) lymph dissection of the neck is recommended in addition to the total thyroidectomy for patients with clinical evidence of involved central lymph nodes [5].
- Prophylactic central-compartment neck dissection should be considered in patients with PTC with no clinical data on central neck LNs' involvement in cases that lateral neck nodes are involved or when the primary tumor is advanced (T3 or T4).

- Thyroidectomy without prophylactic central neck lymph dissection is suitable for small (T1 or T2), noninvasive, PTC without clinically engaged LNs and for most follicular carcinomas [5].
- Therapeutic lateral-compartment lymph node dissection is recommended for patients with biopsy-proven metastatic lateral lymph nodes [55].

4.1.3. Completion thyroidectomy

Completion thyroidectomy is a reoperation to completely remove residual thyroid parenchyma and should be offered to patients for whom total thyroidectomy would have been indicated if the diagnosis was known prior to the initial surgery. This underlines the importance of routine referral of patients with nodular goiter to FNAB, since malignant or suspicions for malignancy cytology suggests a one-step operation (total or near-total thyroidectomy) in contrast to a suboptimal operation (lobectomy) for preoperatively unspecified carcinoma which could require a second operation (completion thyroidectomy), the latter being often difficult to perform due to adhesions and neck changes after the previous operation [4, 5].

4.2. Post-operative radioiodine (RAI) treatment

Post-operative administration of ^{131}I aims to destroy the remnant in the thyroid bed, as well as microscopic tumor foci, thus reducing the likelihood of recurrence [56, 57]. The ablation of residual normal thyroid tissue allows adequate long-term follow-up and early detection of recurrence based on serum Tg and whole-body scintigraphy (WBS). The high activity ^{131}I, given as a therapeutic dose (from 30 to 100 mCi), can also be used for diagnostic purposes by conducting a WBS from 2 to 5 days after the iodine administration, thus detecting small invisible with diagnostic doses (from 1 to 3 mCi) foci [57].

However, RAI remnant ablation is not routinely recommended after thyroidectomy for all DTC patients. For patients with low ATA risk and tumor ≤1 cm, there is no evidence that RAI improves disease-related survival and is not recommended [5, 56, 57]. For patients with low ATA risk and tumor size between 1 and 4 cm, RAI is not routinely recommended, but it can be considered in aggressive histology and vascular invasion. Moreover, for low-risk patients, preference is given to the use of lower activities (30 mCi). For intermediate risk patients, the data on the survival benefits of RAI is controversial, and RAI is recommended for larger tumor size (> 4 cm) and age above 45 years [5]. In high-risk patients (with LN metastases, extrathyroidal spreading and distant metastases), RAI is generally indicated and in doses of 100 mCi [5].

If RAI therapy or diagnostic testing (WBS, stimulated thyroglobulin measurement) is planned, a TSH stimulation should be achieved before these procedures. TSH level may rise through two methods: thyroid hormone withdrawal or application of recombinant human TSH (rhTSH, Thyrogen). Levothyroxine (LT4) should be withdrawn for 4–6 weeks to induce transient hypothyroidism with TSH > 30 mU/l that can stimulate iodine uptake (diagnostic or therapeutic) and Tg release. Liothyronine (LT3) may be substituted for LT4 in the initial weeks, but LT3 should be withdrawn for at least 2 weeks before testing/therapy. During the withdrawal period, patients experience signs and symptoms of hypothyroidism which may

be severe and substantially impair their quality of life [58]. Cardiovascular, respiratory, CNS and psychiatric diseases worsen, as well as renal and liver function, requiring dose adjustment of concomitant medications in comorbid patients [59]. Besides, prolonged TSH stimulation may be associated with increased growth of metastatic tissue [16].

Alternatively, to overcome the inconvenience of this thyroid hormone withdrawal, rhTSH has been developed, and numerous studies have demonstrated its safety, noninferiority of remnant ablation efficacy and Tg secretion, a definite superiority regarding quality of life, especially in patients with significant comorbidities, and also benefits for patients unable to mount an endogenous TSH rise [60, 61].

4.3. Hormonal therapy

Treatment with thyroid hormone is well established and its goal is (1) to correct the post-operative/post-radiation hypothyroidism and (2) to suppress the growth of neoplastic cells by reducing TSH levels [62]. Thus, thyroid hormone treatment provides replacement and suppressive therapy at the same time.

Since thyroid cell proliferation and differentiation is TSH dependent and the presence of functional TSH receptors has been documented in most DTCs, the rationale for thyroid hormone administration is to inhibit TSH secretion. According to 2015 ATA guidelines the initial TSH suppression is considered as the following:

- High-risk DTC patients require initial TSH suppression to below 0.1 mU/L [4, 5].
- For intermediate-risk DTC patients, initial TSH suppression of 0.1–0.5 mU/L is recommended [5, 61].
- Low-risk patients who have undergone remnant ablation should maintain TSH at the lower end of the reference range (0.5–2 mU/L) if Tg is undetectable or TSH at or slightly below the lower limit of normal (0.1–0.5 mU/L) if Tg is low but detectable. For low-risk patients who have undergone lobectomy, TSH may be maintained in the mid-to-lower reference range (0.5–2 mU/L) while surveillance for recurrence is continued [5, 61].

4.4. Other therapies

In the very rare cases of RAI refractory DTC patients with metastatic, rapidly progressive and symptomatic disease, kinase inhibitors may be considered after a careful evaluation of the potential risks and benefits of such therapies [5].

5. Follow-up of patients with DTC

Most differentiated thyroid cancers are characterized by an indolent course with low morbidity and mortality. The methods used in the long-term follow up of patients with DTC are clinical examination, US (with special focus on the thyroid bed and lymph node status of the

neck), serum thyroglobulin measurement with anti-Tg-antibodies, ^{131}I WBS and in selected cases CT, MRI and positron emission tomography (^{18}F-FDG-PET).

It is recommended that Tg is always assessed together with anti-Tg antibodies. In the presence of positive anti-Tg-antibodies, the interpretation of thyroglobulin is complicated [62, 63]. Often, this necessitates a WBS that can visualize recurrence in negative Tg (false negative due to the presence of anti-Tg-antibodies). In the positive for anti-Tg-antibodies' patients (e.g., PTC on the background of Hashimoto thyroiditis), the dynamic changes in serum levels of these antibodies may serve as an indirect marker for remission (decreasing titers of antibodies) or recurrence of the disease (rising titers) [64].

^{18}F-FDG-PET is indicated in the case of high-risk patients with elevated thyroglobulin and negative radioiodine WBS [65].

Based on the clinical, laboratory and imaging results, a novel nomenclature was introduced in order to describe the status of the patient during follow-up, excellent response, biochemical incomplete response, structural incomplete response and indeterminate response to treatment [5]. Thus, the response to therapy determines the ongoing risk stratification, which further guides the long-term follow-up and the management decisions.

- **Excellent therapeutic response** or absence of persistent disease for patients who have undergone surgery and RAI ablation is defined by the presence of all following three criteria (4, 5, 63):

1. no clinical evidence of tumor;
2. no imaging evidence of tumor

   a. no RAI uptake outside the thyroid bed on the post-treatment or subsequent diagnostic WBS

   and/or

   b. no US data for recurrence in thyroid bed or suspicious neck LNs
3. Low serum Tg during TSH suppression (Tg < 0.2 ng/mL) and after stimulation with thyroxin withdrawal or rhTSH (Tg < 1 ng/mL) in the absence of anti-Tg antibodies.

- **Biochemical incomplete response** is characterized by abnormal thyroglobulin (Tg > 1 ng/ml during suppressive therapy and > 10 ng/mL after stimulation) in the absence of a localizable disease. If associated with stable or declining serum Tg values, a biochemical incomplete response should lead to continued observation with ongoing TSH suppression. Rising Tg or anti-Tg antibody values requires prompt additional imaging and potentially additional therapies [5, 16].
- **Structural incomplete response is determined by persistence or new identification of loco-regional or distant metastases. The management (additional treatment or ongoing observation) depends on** the size, location, rate of growth, RAI avidity, ^{18}F-FDG avidity and specific pathology of the structural lesions [5].

- **Indeterminate response** constitutes nonspecific biochemical or structural findings. This includes patients with Tg between 0.2 and 1 ng/ml during suppressive therapy and stimulated Tg between 1 and 10 ng/mL or nonspecific imaging findings as US data of subcentimeter avascular thyroid bed nodules or atypical LNs, faint uptake in the thyroid bed on WBS [5]. If these nonspecific findings become suspicious during the follow-up or if Tg or anti-Tg antibody levels are rising, additional imaging or biopsy with cytology evaluation and wash-out Tg measurement in suspicious LNs are indicated [66].

The initial LT4 treatment is reassessed during the long-term follow-up of DTC patients and the following **long-term serum TSH levels** are recommended:

- For patients with a structural incomplete response to treatment during the follow-up, TSH level should be maintained ≤0.1 mU/L in the absence of contraindications [5]. The risk of therapeutically induced subclinical hyperthyroidism affects the cardiovascular system (rhythm disorders, atrial fibrillation) and the bones (osteopenia, osteoporosis) [62].
- For patients with a biochemical incomplete treatment response, the serum TSH should be maintained between 0.1 and 0.5 mU/L, taking into account the initial ATA risk, Tg level, Tg dynamics over time and the risk of TSH suppression [5, 62].
- For high-risk cancer patients who have an excellent (clinically and biochemically disease free) or indeterminate response to therapy, serum TSH may be maintained between 0.1 and 0.5 mU/L for up to 5 years after which the degree of TSH suppression can by reduced with continued surveillance for recurrence [5].
- Patients with excellent therapeutic response (clinically and biochemically disease free), patients with an initial low-risk and intermediate response and those who did not carry out remnant ablation may maintain their TSH in the lower half of the reference range (from 0.5 to 2 mU/L) [67].

6. Conclusion

The cornerstones of the preoperative diagnosis of thyroid cancer are the careful US examination, FNAB and cytology assessment of the suspicious thyroid nodules. An interdisciplinary team comprising endocrinologists, surgeons, pathologists, radiologists and oncologists should guide the patient through the diagnostic and treatment process. Strict criteria have been introduced for treatment options and follow-up on the base of initial and ongoing risk assessment in order to minimize the potential harm of over-treatment of low-risk patients and to provide adequate therapy to patients at high risk.

Conflict of interest

I declare no conflict of interest.

Author details

Mira Siderova[1,2]*

*Address all correspondence to: mirasiderova@abv.bg

1 Medical University of Varna, Bulgaria

2 University Hospital "St. Marina" Varna, Clinic of endocrinology and metabolic diseases, Bulgaria

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This is a small book containing various aspects of thyroid gland disorders. Congenital hypothyroidism chapter emphasizes early diagnosis in prevention of irreparable damage to growth and brain of infants. Role of nuclear medicine in diagnosis and treatment is outlined. Last few chapters deal with congenital hypothyroidism, thyroid carcinoma, its diagnosis, treatment and preservation of posterior parathyroid gland during thyroid surgery. The purpose of the book is to disseminate knowledge on thyroid diseases. It will be a good reference book both for students of medicine and general practitioners.

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