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Recent Advances in Thyroid Disorders

*Edited by Ifigenia Kostoglou-Athanassiou,
Panagiotis Athanassiou and Lambros Athanassiou*



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Meet the editors



Dr. Ifigenia Kostoglou-Athanassiou was born in Thessaloniki, Greece. She is an endocrinologist who graduated from the Medical School, Aristotle University of Thessaloniki, Greece. She obtained an MD from the University of Athens Medical School and a Ph.D. from the University of London. Her areas of research include breast cancer, neuroendocrinology, melatonin, thyroid cancer, vitamin D, and autoimmune diseases. She has won several awards for her research. Dr. Kostoglou-Athanassiou has published numerous papers and book chapters. Currently, she works as a consultant endocrinologist and head of the Endocrine Department, Asclepeion Hospital, Voula, Athens, Greece.



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Preface

The science of thyroid physiology and disease has witnessed major advances in recent years. This book discusses recent advances in thyroid disease.

The contribution of iodine and selenium in thyroid physiology and disease. Novel advances in the management of thyroid nodules are discussed. In particular, the contribution of thyroid ultrasonography in the evaluation and management of thyroid nodules is evaluated. The contribution of the TIRAD system, in its various forms, to the evaluation of thyroid nodules by ultrasonography is discussed. The diagnosis of thyroid nodules by fine needle aspiration biopsy is also described. Thyroid nodules are typically treated by thyroid surgery or radioactive iodine therapy. However, the use of thermal ablation for thyroid nodules has recently entered clinical practice. The treatment of thyroid nodules using various thermal ablation methods is extensively discussed in this book.

Thyroid cancer is generally a disease with a good clinical course and prognosis. Despite that, advanced and metastatic thyroid cancer does exist. Thyroidectomy, radioiodine, external radiotherapy, and chemotherapy were traditionally applied in the treatment of advanced and metastatic thyroid cancer. However, recently, multi-targeted kinase and angiogenic inhibitors have been successfully introduced in the treatment of thyroid cancer. The application of multi-targeted kinase and angiogenesis inhibitors in the treatment of thyroid cancer is discussed within this book.

Thyroid function and its relationship with sexual behavior have been widely discussed and are also evaluated within this book. Lastly, the application of computer-assisted diagnosis and treatment has been explored in the context of thyroid disease and is discussed in this book.

This book is the result of the efforts of various authors who specialize in various aspects of thyroid physiology and thyroid disease. The effort of all the authors is gratefully acknowledged. The significant contribution of Dominik Samardzija to the formation of this book is gratefully acknowledged.

Last, but not least, this book is dedicated to my mother, Areti, whose example and efforts have made it possible for me to become the editor of this book.

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Section 1

Aspects of Pathophysiology of Thyroid Disorders

Introductory Chapter: Recent Advances in Thyroid Disorders

Lambros Athanassiou and Ifigenia Kostoglou-Athanassiou

1. Introduction

The thyroid is a large endocrine gland. It is located superficially, which is detectable by palpation. This is a major reason that led to the discovery and in-depth study of thyroid function and any disorders in thyroid size and consistency as well as to the description of thyroid nodules and the study of thyroid cancer.

2. Main text

Early on in history, during the medieval years iodine deficiency was prevalent in Europe in inland mountainous as well as in coastal areas [1–3]. In inland mountainous areas, iodine deficiency was a major problem as there were no means to transfer food rich in iodine in these areas. Consequently, thyroid goiter as well as cretinism was a major health issue in wealthy as well as in poor regions [4, 5]. This led to the discovery that iodine was an important element necessary for the normal function of the thyroid gland. Later on, iodine supplementation of salt, bread, and food led to iodine sufficiency in all areas as well as iodine surplus in some areas and this led to a major change in the epidemiology of thyroid disorders and an increase in the incidence and prevalence of autoimmune thyroid disorders, in particular Hashimoto's thyroiditis [6, 7]. Nowadays, autoimmune Hashimoto's thyroiditis is increasing in incidence and prevalence all over the world in parallel with an increase in the incidence and prevalence of autoimmune disorders [8]. The COVID-19 pandemic led to an increase in the incidence and prevalence of thyroid disease [9], as it led to an increase in the incidence of subacute thyroiditis and later in the incidence of Hashimoto's thyroiditis.

Thyroid surgery began with initial efforts during the eighteenth century [10]. However, with the major advances in anesthesia as well as with the advances in surgical techniques, subtotal thyroidectomy without any major complications became possible in most medical centers all over the world. Nowadays, advances in surgical techniques are taking place with thyroidectomy *via* the maxilla and other novel approaches, in particular robotic surgery [11]. These techniques have to be tested in the test of time to gain the worldwide acceptance.

Thyroid nodules are a problem with major importance as they have a high incidence and prevalence affecting many patients all over the world [12]. Thyroid nodules present with various histological patterns. However, the major challenge faced by the physician is to decide on the malignant or non-malignant nature of the nodule. This was very difficult to accomplish with the traditional methods such as palpation and

the measurement of thyroid hormones as well as the measurement of thyroglobulin and calcitonin. Fine needle aspiration and ultrasonography are now applied with a degree of success in the diagnostic evaluation of thyroid nodules, in particular, in the decision on the malignant or benign nature of the nodule. Ultrasonography is able to describe various characteristics of a nodule, in particular, whether it is a solitary nodule or a nodule detected with other multiple nodules in the thyroid, the echogenicity of the nodule, the presence of microcalcifications as well as the various other characteristics. However, this problem led to the introduction of a system for the evaluation of thyroid nodules on ultrasonography called TIRAD system, which contributes to the characterization of a thyroid nodule as malignant or non-malignant [13, 14]. Fine needle aspiration biopsy is now the major tool, which helps in the identification of the malignant or non-malignant nature of the disorder. The wide application of fine needle aspiration biopsy in the evaluation of thyroid nodules has led to the avoidance of many unnecessary thyroidectomies. Fine needle aspiration biopsy specimens were evaluated in earlier years as malignant or non-malignant as well as with non-conclusive results. However, with the wide application of the Bethesda system for the evaluation of the nature of a thyroid nodule the cytology result is graded with the highest grades compatible with an incident malignancy [15, 16]. Thus, the clinician is called to decide on the malignant or non-malignant nature of the nodule and decide further whether to guide the patient to have a thyroidectomy as well as to the extent of the thyroidectomy.

Thyroid cancer is a malignancy with a relatively good prognosis, with many patients leading a normal life after the diagnosis and treatment of thyroid cancer and the application of various treatment modalities as well as to the prospect of having a normal life span. However, thyroid cancer advanced as well as metastatic does exist [17]. Some forms of thyroid cancer, fortunately rare, such as anaplastic do exist and have a particularly bad prognosis. Fortunately, the incidence of this form of lethal thyroid cancer is becoming even lower now as the surgical treatment of goiter with thyroidectomy is applied early in life. However, advanced and metastatic forms of thyroid cancer do present. This form of thyroid cancer was treated with various treatment modalities, including surgery, the application of therapeutic radioiodine as well as external radiotherapy and chemotherapy. However, in the course of time and very recently it became evident that multi-targeted kinase and angiogenetic inhibitors could be applied in the treatment of advanced thyroid cancer with success and may expand life expectancy and improve quality of life in patients with the advanced and metastatic thyroid cancer [18]. The introduction of multi-targeted kinase and angiogenetic inhibitors in the treatment of advanced thyroid cancer has been a real revolution and has changed the way of thinking and the theory of the application of therapeutic modalities in the treatment of advanced and metastatic thyroid cancer [19, 20]. This evolution led to the discovery and application of various drugs in the treatment of advanced thyroid cancer.

Finally, the evolution of various computer-based methods in the evaluation and treatment of various disorders has led to the introduction of computer based methods in the evaluation and treatment of thyroid disorders.

Thus, slowly and painfully science has entered in the field of the evaluation and treatment of thyroid disease and has brought about various revolutionary changes in the management, diagnostic evaluation, and treatment of thyroid disorders. The historic evaluation of these changes leads us to think that many more scientific discoveries will aid the medical community in the future in the successful diagnosis and treatment of thyroid disorders.

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References

- [1] Delange F, Bürgi H. Iodine deficiency disorders in Europe. *Bulletin of the World Health Organization*. 1989;**67**(3):317-325
- [2] Delange F. Iodine deficiency in Europe and its consequences: An update. *European Journal of Nuclear Medicine and Molecular Imaging*. 2002;**29** (Suppl. 2):S404-S416
- [3] Vanderpump MP. The epidemiology of thyroid disease. *British Medical Bulletin*. 2011;**99**:39-51
- [4] Verheesen RH, Schweitzer CM. Iodine deficiency, more than cretinism and goiter. *Medical Hypotheses*. 2008;**71**(5):645-648
- [5] Doggui R, El Atia J. Iodine deficiency: Physiological, clinical and epidemiological features, and pre-analytical considerations. *Annales d'endocrinologie*. 2015;**76**(1):59-66
- [6] Fragu P, Schlumberger M, Tubiana M. Thyroid iodine content and serum thyroid hormone levels in autoimmune thyroiditis: Effect of iodide supplementation. *Journal of Nuclear Medicine*. 1985;**26**(2):133-139
- [7] Ehlers M, Thiel A, Papewalis C, Domröse A, Stenzel W, Bernecker C, et al. Enhanced iodine supplementation alters the immune process in a transgenic mouse model for autoimmune thyroiditis. *Thyroid*. 2014;**24**(5):888-896
- [8] Miller FW. The increasing prevalence of autoimmunity and autoimmune diseases: An urgent call to action for improved understanding, diagnosis, treatment, and prevention. *Current Opinion in Immunology*. 2023;**80**:102266
- [9] Speer G, Somogyi P. Thyroid complications of SARS and coronavirus disease 2019 (COVID-19). *Endocrine Journal*. 2021;**68**(2):129-136
- [10] Orloff LA, Parangi S. History of thyroid surgery in the last century. *Thyroid*. 2023;**33**(9):1029-1038
- [11] Tae K. Robotic thyroid surgery. *Auris, Nasus, Larynx*. 2021;**48**(3):331-338
- [12] Grani G, Sponziello M, Pecce V, Ramundo V, Durante C. Contemporary thyroid nodule evaluation and management. *The Journal of Clinical Endocrinology and Metabolism*. 2020;**105**(9):2869-2883
- [13] Hussein IH, Altemimi MT, Alidrisi HA, Almomin AMS, Alibrahim NT, Hamza MA, et al. The performance of the American Thyroid Association (ATA) and American College of Radiology (ACR-TIRAD) thyroid nodule risk-stratification systems in determining high-risk nodules, and the correlation of site, size, and autoimmunity with high-risk features. *Indian Journal of Endocrinology and Metabolism*. 2024;**28**(6):622-628
- [14] Parsa AA, Gharib H. Thyroid nodules: Past, present, and future. *Endocrine Practice*. 2025;**31**(1):114-123
- [15] Ali SZ, Baloch ZW, Cochand-Priollet B, Schmitt FC, Vielh P, VanderLaan PA. The 2023 Bethesda system for reporting thyroid cytopathology. *Journal of the American Society of Cytopathology*. 2023;**12**(5):319-325
- [16] Baloch Z, LiVolsi VA. The Bethesda system for reporting thyroid cytology (TBSRTC): From look-backs to

look-ahead. Diagnostic Cytopathology.
2020;**48**(10):862-866

[17] Cabanillas ME, McFadden DG,
Durante C. Thyroid cancer. Lancet.
2016;**388**(10061):2783-2795

[18] Laha D, Nilubol N, Boufraqueh M.
New therapies for advanced thyroid
cancer. Frontiers in Endocrinology
(Lausanne). 2020;**11**:82

[19] Guo T, Ma S. Recent advances in
the discovery of multitargeted tyrosine
kinase inhibitors as anticancer agents.
ChemMedChem. 2021;**16**(4):600-620

[20] Basolo A, Matrone A, Elisei R,
Santini F. Effects of tyrosine kinase
inhibitors on thyroid function and
thyroid hormone metabolism. Seminars
in Cancer Biology. 2022;**79**:197-202

The Importance of Iodine for Thyroid Health

*Şeyma Şimşirgil Kara, Muhittin Yılmaz
and Huriye Demet Cabar*

Abstract

Iodine is a very important trace element involved in the synthesis of thyroid hormones, particularly thyroxine (T₄) and triiodothyronine (T₃). These hormones are essential for various physiological processes, including growth, metabolism and neurodevelopment, especially during fetal and early childhood. The thyroid gland requires iodine to produce these hormones and both deficiency and excess of iodine can lead to significant thyroid dysfunction and disorders. While iodine deficiency can lead to many diseases such as goiter, hypothyroidism and developmental disorders in children, excessive iodine intake can also disrupt thyroid function and lead to conditions such as hyperthyroidism and autoimmune thyroid diseases. Maintaining an appropriate iodine level is critical for preventing thyroid-related disorders and ensuring proper growth and development, especially in vulnerable populations such as children. Given iodine deficiency and the associated health risks, it is clear that public health initiatives such as continuous monitoring and iodization of salt are essential.

Keywords: thyroid gland, trace element, iodine, health, child

1. Introduction

The thyroid gland is an important endocrine organ located in the anterior part of the neck, primarily responsible for regulating metabolism and influencing various physiological functions in the body. It synthesizes and secretes thyroid hormones, particularly thyroxine (T₄) and triiodothyronine (T₃), which are essential for metabolic processes, growth and development [1, 2]. The synthesis of these hormones occurs within thyroid follicles, the functional units of the gland composed of thyrocytes surrounding a colloid matrix filled with thyroglobulin [1, 3, 4].

Thyroid hormones play an important role in the regulation of metabolic rate, heart rate, body temperature and even nerve reflexes [1, 5]. The production of these hormones is primarily stimulated by thyroid stimulating hormone (TSH) secreted by the pituitary gland. This regulatory mechanism is part of the hypothalamic-pituitary-thyroid (HPT) axis, which coordinates the synthesis and release of thyroid hormones in response to the body's metabolic needs [6, 7]. For example, increased TSH levels can increase T₃ and T₄ production, thereby elevating metabolic rate and affecting energy homeostasis. They increase the basal metabolic rate by increasing oxygen

consumption and promoting the metabolism of carbohydrates, fats and proteins. This metabolic effect is mediated by the regulation of genes involved in energy metabolism and thermogenesis [8–10]. In addition, thyroid hormones interact with other hormones, such as growth hormone, to modulate growth and development. For example, thyroid hormones can enhance the anabolic effects of growth hormones and thus influence overall growth patterns [11–13].

In addition to their metabolic function, thyroid hormones are vital for normal growth and development. They influence cellular metabolism and are crucial during prenatal development. This is because maternal thyroid hormone levels can significantly influence fetal growth and thyroid programming. Deficiencies in thyroid hormone production, as in congenital hypothyroidism, can lead to severe developmental problems and metabolic disorders [14]. In contrast, hyperthyroidism, the overproduction of thyroid hormones, can lead to increased metabolic activity, leading to symptoms such as weight loss, increased heart rate and anxiety [5, 9].

The relationship between thyroid hormones and iodine is critical for human health, especially given the essential role iodine plays in the synthesis of thyroid hormones [15, 16]. The synthesis of thyroid hormones is linked to the availability of iodine, which is essential for the production of T4 and T3. The thyroid gland actively absorbs iodine from the bloodstream *via* the sodium/iodide symporter (NIS) and iodine is bound to a carrier protein called thyroglobulin. By incorporating the amino acid tyrosine into its structure, it is transported to thyroid follicular cells for storage [16, 17].

Thyroid hormones exert their effects by binding to thyroid hormone receptors (TRs), nuclear receptors that regulate gene expression. There are two main types of TRs: TR α and TR β , each of which has different roles in various tissues. For example, TR α is predominantly expressed in the heart and skeletal muscle, while TR β is more common in the liver and brain. T3 binding to these receptors initiates a series of transcriptional events that affect cellular metabolism, growth and differentiation [8, 10, 18]. Impairment in the function of these receptors can lead to various disorders, including hypothyroidism and hyperthyroidism, which are characterized by insufficient or excessive levels of thyroid hormone, respectively [12, 19].

2. Iodine and child development

In the human body, the iodide atom (I⁻) exists in various forms such as molecular iodine (I₂), triiodide (I₃), iodine anion (HI₂ O⁻) and iodine-binding molecules (such as iodolipids) [20]. I⁻ is a type of reducing agent that can be oxidized by peroxidase enzymes to produce thyroid hormones (THs) [20]. Iodine is a trace element that is crucial for the production of thyroxine (T4) and triiodothyronine (T3), hormones that regulate metabolism, growth and development [21].

The World Health Organization (WHO) has recognized iodine deficiency as the most preventable cause of brain injury globally and has highlighted the critical need for effective public health interventions to ensure adequate iodine intake [22–24]. Iodine deficiency can lead to a range of health problems, collectively referred to as iodine deficiency disorders (IDDs), including goiter, hypothyroidism and developmental disorders, particularly in children and fetuses [21, 25, 26]. Conversely, excessive iodine intake can also cause thyroid dysfunction. Therefore, it is important to maintain a balanced iodine intake [27].

The impact of environmental factors on thyroid hormone homeostasis is receiving increasing attention, particularly in relation to endocrine disruptors. Compounds

such as bisphenol A (BPA) and polychlorinated biphenyls (PCBs) have been shown to act on thyroid hormone, leading to changes in thyroid hormone levels and function. This effect can cause metabolic, developmental and behavioral disorders and highlights the importance of maintaining thyroid hormone balance in the presence of environmental pollutants. The mechanisms by which these endocrine disruptors exert their effects include competitive binding to thyroid hormone transport proteins and direct interference with thyroid hormone synthesis [10, 28].

In addition to environmental influences, dietary factors also play a critical role in thyroid function. Inadequate dietary iodine intake remains a global health concern as it can lead to goiter and hypothyroidism. For example, vegetarians and vegans may be at higher risk of iodine deficiency due to dietary restrictions that often limit the intake of iodine-rich foods such as fish and dairy products [29]. Furthermore, the bioavailability of iodine may be affected by protein intake; iodine absorption may be reduced and hypothyroidism may be observed in individuals with low-protein diets [29]. The thyroid gland typically has regulatory mechanisms that allow it to adapt to changing iodine levels; however, in the case of inadequate iodine intake, the capacity of these mechanisms may be exceeded, adversely affecting thyroid hormone synthesis and secretion [30]. Excessive iodine intake can also impair thyroid function, leading to hyperthyroidism in susceptible individuals. For example, an increased prevalence of autoimmune thyroiditis and other thyroid disorders has been observed in areas with high iodine intake [31, 32]. Balancing iodine intake is essential to maintain optimal thyroid hormone production and overall endocrine health [33]. Furthermore, micronutrients such as selenium and zinc are vital for the synthesis and metabolism of thyroid hormones, suggesting an interaction between nutrition and thyroid health [32].

Iodine deficiency poses a significant threat to child health and development, with far-reaching consequences on cognitive function. Ensuring adequate iodine intake during critical developmental periods is essential to prevent irreversible disorders and promote optimal health outcomes. Public health strategies need to focus on raising awareness, improving dietary practices and effective supplementation programs to address this preventable cause of brain damage and developmental disorders in children [16, 22, 24, 34, 35].

In addition to its role in thyroid hormone synthesis, iodine is believed to have antioxidant properties and may play a role in the prevention of certain diseases, including cancer and cardiovascular conditions [36, 37]. Adequate iodine intake is very important during critical periods of brain development. Inadequate iodine levels during pregnancy and early childhood can lead to a range of neurocognitive disorders, including low IQ scores and developmental delays. Studies show that even mild to moderate iodine deficiency can adversely affect cognitive outcomes in children and underline the need for adequate iodine nutrition from conception to early childhood [16, 34, 35, 38, 39].

The impact of iodine deficiency goes beyond cognitive impairment and can lead to physical disabilities and growth retardation in children. Iodine deficiency is associated with a range of developmental disorders characterized by severe mental retardation and physical deformities [22, 38, 40]. WHO estimates that approximately 30% of school-aged children worldwide are iodine-deficient and emphasizes the need for targeted interventions to address this public health crisis [41, 42]. Furthermore, iodine deficiency may have long-term consequences on child survival rates as it is linked to increased morbidity and mortality in affected populations [43].

3. Iodine and the fetus

The importance of iodine is particularly evident during pregnancy and breastfeeding, when inadequate iodine levels can adversely affect both maternal and fetal health. Research suggests that inadequate iodine intake during these critical periods can lead to maternal hypothyroidism and impaired fetal neurodevelopment, with severe deficiencies potentially resulting in conditions such as cretinism [44–46]. Cretinism is a severe form of mental and physical disability resulting primarily from iodine deficiency during critical periods of fetal development. It is characterized by two main forms: neurologic cretinism and myxedematous cretinism. Neurologic cretinism manifests as profound mental retardation, deaf mutism, squinting and motor spasticity, while myxedematous cretinism is associated with severe growth retardation and typical features of hypothyroidism, with less severe cognitive impairment [25, 47, 48]. This condition occurs due to inadequate production of thyroid hormones, especially thyroxine, which is crucial for brain and skeletal development. In addition, cretinism is part of a broader spectrum of iodine deficiency disorders (IDDs), including varying degrees of cognitive impairment and developmental delays. Studies have shown that children born in iodine-deficient areas typically exhibit lower IQ levels compared to children born in iodine-sufficient areas, underscoring the critical role of iodine in cognitive development [49–51].

A study from Beijing highlighted the association between iodine nutritional status and adverse pregnancy outcomes, suggesting that both deficiency and excess can have detrimental effects [52]. Furthermore, maternal iodine supplementation has been shown to improve neurodevelopmental outcomes in children born to iodine-deficient mothers, suggesting the need for public health interventions aimed at improving iodine status among pregnant women [53]. The American Thyroid Association recommends that women of reproductive age ensure adequate iodine intake, especially during pregnancy and breastfeeding, to support both their own and their infants' health [54].

Studies have shown that maternal iodine deficiency can lead to neurodevelopmental disorders in children, emphasizing the need for adequate iodine levels during pregnancy [21, 26, 35]. The first trimester is particularly sensitive as the fetal thyroid gland does not become functional until later in pregnancy [19, 35]. The first 1000 days of life, from the beginning of gestation to 2 years of age, are particularly sensitive to iodine levels, as this is the period when the brain undergoes rapid development and maturation [21, 55].

Research suggests that iodine supplementation during pregnancy may improve maternal thyroid function and reduce the risk of adverse pregnancy outcomes [35, 46, 56]. However, the timing and dose of supplementation is critical, as excessive iodine intake can also lead to thyroid dysfunction. For example, the Wolff-Chaikoff effect, which can occur with high iodine intake, can temporarily inhibit thyroid hormone synthesis, leading to potential complications [57, 58]. Therefore, careful monitoring of iodine levels is essential, especially in populations at risk of both deficiency and excess [37, 59].

Studies have shown that severe iodine deficiency in pregnant women is associated with a range of adverse outcomes, including miscarriage, stillbirth and neonatal mortality [34, 35, 38]. Furthermore, children born to iodine-deficient mothers are at risk of developing irreversible cognitive impairments that can manifest as learning disabilities and poor academic performance [39, 43, 60]. Studies have shown that inadequate thyroid hormone levels during pregnancy are associated with an increased risk of neurodevelopmental problems in children, including seizures and cognitive deficits [61, 62].

The global public health response to iodine deficiency has included initiatives such as salt iodization, which has significantly reduced the prevalence of iodine deficiency disorders in many regions. However, despite these efforts, mild to moderate iodine deficiency remains a public health problem in several regions of the world, particularly in Europe and among pregnant women [37, 63]. The World Health Organization recommends that pregnant women consume 220–250 µg of iodine daily to promote fetal development and prevent deficiency-related complications [64].

4. Molecular basis of non-thyroidal effects of iodine

In addition to its role in thyroid hormone synthesis, iodine also exhibits antioxidant properties and may have anti-proliferative effects in various tissues [65]. Approximately 30% of iodine in the body is concentrated in the thyroid, while the remaining iodine is distributed to various tissues [65]. Adequate iodine levels are essential not only for thyroid function but also for cognitive development and general metabolic processes [26, 66, 67].

In addition to its role in the thyroid, iodine has been reported in the literature to function as an antioxidant, immunomodulator and differentiator in various organs and tissues [68]. The sodium iodide symporter (NIS) is the most efficient and specific transporter of I^- expressed in thyroid follicular epithelial cells. Many other organs can also actively accumulate iodine, including the salivary glands, stomach, lactating mammary gland, ovary, prostate and pancreas. In addition to the sodium iodide symporter, the activity of novel iodine transporters such as cystic fibrosis transmembrane conductance regulator (CFTR), anoctamine 1 (ANO1) and sodium multivitamin transporter (SMVT) has recently been discovered in these organs [68]. Thus, iodine itself has non-thyroidal effects on organs that can take it up. Among these, breast and prostate tissue are important. Some epidemiologic studies have shown that moderately high iodine intake is beneficial in reducing the incidence of breast and prostate cancer [69, 70].

4.1 Iodine and lipid metabolism

Iodine plays an important role in lipid metabolism, primarily through its effect on thyroid hormone production and regulation. Thyroid hormones, especially thyroxine (T₄) and triiodothyronine (T₃), are critical regulators of lipid metabolism, affecting various processes such as lipid synthesis, absorption and degradation. For example, it has been reported in the literature that thyroid hormones regulate the synthesis and excretion of bile acids, which are crucial for cholesterol metabolism [71]. In addition, thyroid hormones further contribute to the regulation of serum lipid levels by stimulating lipolysis in adipose tissue [71]. This regulatory effect is important in cases of thyroid dysfunction, where altered hormone levels can lead to dyslipidemia and especially increased cardiovascular risk [72].

Studies have shown that hypothyroidism is associated with increased levels of low-density lipoprotein (LDL) cholesterol and triglycerides, emphasizing the direct impact of thyroid hormone levels on lipid profiles [73, 74]. This relationship highlights the importance of adequate iodine levels to maintain lipid homeostasis. Furthermore, the effect of iodine on lipid metabolism may also vary depending on individual factors such as gender, in addition to being indicated by studies in animal models showing that hormonal interactions play an important role in the effect of

iodine on lipid metabolism [73]. Conversely, adequate iodine intake supports optimal thyroid function, thereby facilitating normal lipid metabolism and reducing the risk of metabolic disorders such as dyslipidemia and metabolic syndrome [75].

Iodine has been implicated in the modulation of several metabolic pathways, including those involved in fatty acid metabolism and regulation of adipocyte function. For example, iodine has been shown to affect the expression of peroxisome proliferator-activated receptors (PPARs), which are critical for lipid metabolism and energy homeostasis [68]. This suggests that iodine not only supports thyroid function but also directly affects lipid metabolism at the cellular level.

Recent studies have also investigated the effect of iodine on lipid metabolism in specific populations, such as patients with thyroid cancer. The literature suggests that lipid metabolism disorders are common in individuals with papillary thyroid cancer and that these disorders may be linked to iodine nutritional status [76]. This further highlights the importance of iodine in metabolic health by emphasizing its potential to affect lipid metabolism in pathological conditions. Ensuring adequate iodine intake may be an important strategy for managing dyslipidemia and associated cardiovascular risks [75]. Another study reported that iodine has antioxidant properties and can modulate immune responses that may indirectly affect metabolic processes [68].

4.2 Iodine and obesity

Obesity is a health condition characterized by excessive accumulation of fat in the body, typically measured using body mass index (BMI), with a BMI of 30 or above classified as obese [77]. The condition is associated with a variety of health risks, including cardiovascular disease, diabetes and some cancers and is becoming a major public health problem globally [78]. The prevalence of obesity has reached high levels around the world, with significant variations observed across different regions and demographics. According to the World Health Organization, the global prevalence of obesity nearly doubled between 1980 and 2008, with nearly one in four adults and one in five children classified as obese by 2019 [77]. In the United States, the prevalence of obesity among children aged 2–19 years was reported to be 17.4%, and this rate is even higher in some regions [79].

The increase in obesity rates is often attributed to a combination of genetic, environmental and behavioral factors, including poor dietary habits, sedentary lifestyles and socioeconomic influences [78]. Deficiency of iodine, one of the trace elements in the diet, has an impact on metabolic health and obesity along with the thyroid. For example, maternal iodine deficiency has been associated with adverse pregnancy outcomes and increased risk of obesity in infants, emphasizing the importance of adequate iodine levels during critical developmental periods [80, 81]. Moreover, obesity itself may contribute to iodine deficiency, as increased adipose tissue may sequester iodine, leading to lower bioavailability for thyroid hormone synthesis [82]. This can worsen metabolic health and increase the risk of further weight gain, creating a vicious cycle in which obesity exacerbates iodine deficiency.

The relationship between obesity and thyroid hormones, particularly thyroid stimulating hormone (TSH), is well established. Studies show that obesity is associated with elevated TSH levels, which can lead to changes in thyroid structure and function [83, 84]. Furthermore, the secretion of leptin, a hormone linked to fat storage and appetite regulation, is synchronized with TSH levels, suggesting a complex interaction between these hormones in obese individuals [84]. This association is of particular concern given that obesity can exacerbate thyroid dysfunction and lead to

conditions such as subclinical hypothyroidism and autoimmune thyroiditis, especially with excessive iodine intake [83, 84].

For example, adequate iodine intake is associated with a lower likelihood of obesity, as shown by studies that found a correlation between iodized salt consumption and lower obesity rates [85, 86]. Conversely, excess iodine intake can lead to thyroid dysfunction, contributing to weight gain and metabolic disturbances [87]. This underscores the need for balanced iodine intake, as both deficiency and excess can have detrimental effects on thyroid health and body weight regulation.

Assessment of iodine status is typically done through urinary iodine concentration (UIC), which serves as a reliable biomarker for recent iodine intake [88]. A cross-sectional study of school-aged children and their parents revealed that elevated UIC is associated with metabolic syndrome [89]. A large epidemiological study (TIDE) conducted in China showed that the prevalence of central obesity was significantly reduced when UIC was 300 $\mu\text{g/L}$ or higher [90]. Among school-aged children in China, overweight children exhibited a lower UIC compared to normal-weight children [91]. In a study by Moleti et al. in iodine-deficient children, median urinary iodine concentration (UIC) was found to be significantly lower in obese children compared to their normal-weight peers, suggesting a potential link between iodine status and obesity [92]. A significantly lower UIC was also found in obese women compared to normal-weight women [93]. In a randomized controlled trial, participants who consumed tablets containing iodine-reduced seaweed powder showed a significant reduction in body fat percentage compared to those taking a placebo [94]. In a 4-week placebo-controlled study, seaweed fucoxanthin supplementation (1 mg/day) was shown to reduce waist circumference (WC) and fat mass in obese Japanese subjects, and in addition, fucoxanthin supplementation (3 mg/day) reduced visceral fat, body mass index (BMI) and weight [95]. Eray et al. also reported a negative correlation between thyroid volume and urinary iodine levels in obese women and suggested that iodine status may affect the hormonal environment associated with obesity [96].

4.3 Iodine and hyperglycemia

Hyperglycemia is defined as a high level of glucose in the blood and is typically characterized by a plasma glucose concentration exceeding 140 mg/dL (7.8 mmol/L) in patients [97]. This condition can occur due to various physiologic stresses such as illness, surgery or the presence of diabetes mellitus and is also affected by iodine metabolism. Hyperglycemia often leads to long-term complications such as cardiovascular disease, neuropathy and retinopathy, and in this respect, it is very important to avoid hyperglycemia [97, 98].

In a cohort study of 71,264 women, Mancini et al. found that individuals with higher iodine intake had a higher risk of developing type 2 diabetes mellitus (T2DM) compared to those with inadequate iodine intake [99]. Ezemaduka et al. reported that lower UIC was associated with an increased risk of elevated fasting plasma glucose (FPG) in women [98]. Kim et al. also reported that patients with T2DM had lower UIC levels compared to healthy individuals [100]. Wang et al. also reported that pregnant and lactating women in the IE region ($\text{mWIC} > 300 \mu\text{g/L}$) had lower blood glucose levels and a lower prevalence of hyperglycemia [101]. Higher iodine status could potentially protect against hyperglycemia during pregnancy. In addition to this study, Neven et al. found that higher iodine concentration in the placenta was associated with a reduced incidence of gestational diabetes mellitus (GDM) among 471 pregnant women [102].

Candido et al. emphasized that mild iodine deficiency may increase the risk of diabetes mellitus, suggesting a complex interaction between iodine levels, thyroid-stimulating hormone (TSH) secretion and insulin resistance, which ultimately leads to hyperglycemia [103]. This association is also supported by Zhuo et al., who noted that thyroid disorders, including those resulting from iodine deficiency, can significantly affect glucose metabolism and hyperthyroidism is a condition known to contribute to hyperglycemia [104].

Both iodine deficiency and excess have been associated with an increased risk of type 2 diabetes mellitus (T2DM), as noted by Barra et al. [105]. This relationship highlights the importance of maintaining adequate iodine levels to support optimal thyroid function and consequently glucose metabolism.

4.4 Iodine and hypertension

Hypertension, defined as high arterial blood pressure, is a major global health problem due to its association with morbidity and mortality from cardiovascular diseases. The World Health Organization (WHO) defines hypertension as having a systolic blood pressure (SBP) of 140 mmHg or higher or a diastolic blood pressure (DBP) of 90 mmHg or higher [106]. The prevalence of hypertension varies considerably between different regions and populations, influenced by numerous factors, including lifestyle, dietary habits and genetic predispositions. Recent studies have reported an increasing trend in the prevalence of hypertension worldwide, affecting approximately 30% of the adult population globally, with variations based on geographic and demographic factors [106, 107].

Menon et al. [108] reported that iodine deficiency is a risk factor for hypertension. This is in line with the findings of Shen et al., who reported that low urinary iodine concentrations are associated with a higher incidence of hypertension, especially in individuals without thyroid disorders [109]. Furthermore, iodine deficiency during pregnancy is of particular concern as it has been linked to hypertensive disorders such as gestational hypertension and pre-eclampsia. Cuellar-Rufino et al. emphasized that iodine deficiency is associated with hypertensive disorders in pregnant women, suggesting that inadequate iodine intake may exacerbate these conditions (similarly, Tadesse et al. emphasized that moderate iodine deficiency in pregnant women can lead to maternal hypothyroidism, which is associated with gestational hypertension and other adverse outcomes [110]). The importance of adequate iodine intake during pregnancy is also supported by Gülaboğlu et al. who recommend iodine supplementation to pregnant women to meet increased requirements and reduce the risks associated with hypertension [111].

Jin et al. observed a U-shaped curve in the relationship between UIC and the prevalence of hypertension, with the lowest point found in the UIC range of 300–499 µg/L [90]. Iodine deficiency has been identified as a risk factor for preeclampsia and hypertensive disease of pregnancy (HPD) [112]. However, a randomized case-control study reported that intake (5 g per day) of wakame (*Undaria pinnatifida*) in brown algae significantly reduced blood pressure in 36 elderly Japanese individuals with hypertension [113].

Thyroid hormones and iodine also have important effects on cardiovascular health. They play a role in blood pressure regulation by influencing heart rate, cardiac output and vascular resistance. Hypothyroidism is often associated with increased cardiovascular risk due to its effects on lipid metabolism and vascular function, while hyperthyroidism can lead to arrhythmias and other cardiac

complications. The relationship between thyroid hormones and cardiovascular health makes regular monitoring of thyroid function important in patients with cardiovascular disease.

5. Sources and safety concentrations of iodine

To eliminate iodine deficiency diseases, most countries have introduced universal salt iodization (USI). However, excess iodine intake from iodized salt consumption, drinking water, iodine-rich animal milk, certain types of seaweed, iodine-containing dietary supplements and a combination of these sources must also be considered. Certain medications (such as Amiodarone), disinfectants and iodine-containing contrast agents may also be common sources of iodine [114]. Under normal conditions, more than 90% of dietary iodine is absorbed. The recommended dietary iodine intake is 150–299 µg/day [27]. The appropriate range of median urinary iodine concentration (mUIC) should be 100–299 µg/L. Biomarkers such as thyroglobulin (Tg) have been identified as effective indicators of iodine status. Elevated Tg levels are usually associated with iodine deficiency, whereas normalization occurs with adequate iodine intake [115, 116]. This correlation emphasizes the importance of monitoring iodine levels in populations at risk of deficiency, especially in areas where iodized salt is not widely used [108].

Du et al. reported that in areas where iodine deficiency is prevalent, such as parts of China and India, public health initiatives have focused on the iodization of salt as the primary strategy to increase iodine intake among the population. However, the effectiveness of these programs should take into account various factors, including dietary habits and geographical differences in iodine levels in water sources [117, 118]. For example, a study in Taiwan revealed significant geographical differences in iodine status, with some areas having adequate levels while others were deficient [118]. This emphasizes the need for continuous monitoring and tailored interventions to address iodine deficiency in specific populations [118].

Excessive iodine intake, while less common, can pose a number of health risks in its own right, particularly in areas with high consumption of iodized salt. The Wolff-Chaikoff effect involves a physiological state in which excess iodine inhibits thyroid hormone synthesis, potentially leading to hypothyroidism in susceptible individuals [119, 120]. Therefore, establishing a balance in iodine intake and ensuring that the population receives adequate amounts of iodine at recommended levels is crucial for maintaining good health. In Turkey, the “Prevention of Iodine Deficiency Diseases and Iodization of Salt Program” was initiated in 1994 in cooperation with the Ministry of Health, General Directorate of Mother Child Health and Family Planning and UNICEF. Within the scope of this program, training activities involving health personnel, provincial directorates of agriculture, laboratory personnel performing iodine analysis, salt producers, public and market authorities, legal amendments on iodization of salt, and monitoring and evaluation activities were organized [121]. According to the Turkish Food Codex Edible Salt Communiqué published in the Official Gazette dated July 9, 1998, and numbered 23,397, iodization of table salt became mandatory. Accordingly, 50–70 mg/kg potassium iodide or 25–40 mg/kg potassium iodate must be added to table salts [122, 123].

In regions where iodine deficiency is endemic, such as parts of Africa and Southeast Asia, the prevalence of iodine deficiency disorders (IDD) has been identified as a problem in a study by Escobar et al. [42]. For example, studies have shown

that school-aged children in these regions often exhibit low urinary iodine concentrations, indicating inadequate iodine intake [39, 124]. Since many people, including pregnant women, may not be consuming enough iodine-rich foods, there is a lack of awareness of dietary sources of iodine [125–127]. Considering that iodine is mainly obtained through diet, iodized salt is an important source in many countries [16, 43].

6. Importance of education in iodized nutrition

In public awareness and education about iodized nutrition, it is important to address the potential for both deficiency and excess of iodized nutrition. Studies have shown that low levels of iodine knowledge among women of childbearing age are associated with higher rates of deficiency, suggesting the need for targeted education campaigns [37, 128]. Furthermore, integrating iodine-rich foods into dietary practices, such as the use of iodized salt and iodine-containing additives in food production, may increase overall iodine intake in the population [129].

Dietary sources of iodine are mainly seafood, dairy products and iodized salt, with iodine content varying depending on geographical location and soil iodine levels [37, 130]. In areas where iodine-rich foods are scarce, public health strategies can focus on education and promotion of iodine-rich diets to reduce deficiency risks [63, 131]. In addition, awareness campaigns, especially targeting women of childbearing age, are crucial against the effects of iodine deficiency, which can have long-term effects on both maternal and child health [56, 132].

Public health approaches aimed at raising awareness of the importance of iodine and promoting dietary sources of iodine are crucial to reduce the prevalence of deficiency [44, 60, 126]. For example, educational initiatives targeting young women of childbearing age can help improve knowledge about iodine-rich foods and the importance of adequate iodine intake during pregnancy [35, 125, 127].

Primary sources of iodine in children include dairy products, fish and iodized salt. Integration of these sources into children's diets is crucial for preventing iodine deficiency and ensuring optimal growth and cognitive development [133]. Dairy products, especially milk, are important sources of iodine for children. One study found that milk accounts for 42% of iodine intake in children [134]. On the other hand, seafood is a very important source of dietary iodine, especially in coastal areas where fish consumption is common. In a study, children who regularly consume fish have lower rates of goiter, suggesting that fish intake may reduce iodine deficiency even in populations using non-iodized salt [133]. Fish is recognized as a rich source of iodine, contributing to the overall iodine status in various populations [135]. Therefore, the importance of dairy products and fish consumption as iodine sources in the diet is increasing, especially in the pediatric age group where salt is restricted [133].

7. Conclusion

Adequate iodine intake is very important for human health. It is an essential trace element that plays a very important role in human health, especially in thyroid function and neurodevelopment, and it is critical for the prevention of iodine deficiency disorders by ensuring adequate iodine intake through dietary sources and supplementation, especially during pregnancy and early childhood, and it is valuable to maintain an optimal balance as excess intake can lead to hyperthyroidism.

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References

- [1] Teimouri K, Pakravan S, Rahmatinia E, Azadbakht K. Evaluation of radiation side effects on thyroid function. *Journal of Parathyroid Disease*. 2022;**10**(1):45-52
- [2] Puri G. Role of thyroid gland in prenatal development – a mini review. *Journal of Dairy & Veterinary Sciences*. 2017;**4**(2):1272-1282. DOI: 10.19080/jdvs.2017.04.555634
- [3] Geven E, Nguyen N, Boogaart M, Spanings F, Flik G, Klaren P. Comparative thyroidology: Thyroid gland location and iodothyronine dynamics in *Mozambique tilapia* (*Oreochromis mossambicus* Peters) and common carp (*Cyprinus carpio* L.). *The Journal of Experimental Biology*. 2007;**210**(22):4005-4015. DOI: 10.1242/jeb.010462
- [4] Torrejón-Moya A, Izquierdo-Gómez K, Pérez-Sayáns M, Jané-Salas E, Roig A, López-López J. Patients with thyroid disorder, a contraindication for dental implants? A systematic review. *Journal of Clinical Medicine*. 2022;**11**(9):2399. DOI: 10.3390/jcm11092399
- [5] Shahid H, Habib A, Saeed S, Saeed N, Gill SA, Sherwani RAK. Functional limitations of hyper and hypothyroid patients in INMOL hospital Lahore, Pakistan. *Journal of Pharmaceutical Research International*. 2021;**33**(18):84-92
- [6] Mondal S, Raja K, Schweizer U, Mugesh G. Chemistry and biology in the biosynthesis and action of thyroid hormones. *Angewandte Chemie*. 2016;**55**(27):7606-7630. DOI: 10.1002/anie.201601116
- [7] Shakeri F, Bibak B, Safdari MR, Keshavarzi Z, Jamialahmadi T, Sathyapalan T, et al. Cellular and molecular mechanisms of curcumin in thyroid gland disorders. *Current Medicinal Chemistry*. 2022;**29**(16):2878-2890
- [8] Yen P. Physiological and molecular basis of thyroid hormone action. *Physiological Reviews*. 2001;**81**(3):1097-1142. DOI: 10.1152/physrev.2001.81.3.1097
- [9] Zeb S, Naz S, Ullah N. Frequency of dyslipidemia in patients having subclinical hypothyroidism. *Journal of Gandhara Medical and Dental Sciences*. 2016;**3**(01):22-26. DOI: 10.37762/jgmds.3-01.44
- [10] Jugan M, Lévi Y, Blondeau J. Endocrine disruptors and thyroid hormone physiology. *Biochemical Pharmacology*. 2010;**79**(7):939-947. DOI: 10.1016/j.bcp.2009.11.006
- [11] Zenebe K, Legesse K, Mandal S, Abdulkader M, Alemu K. Impacts of resistance exercises intervention on thyroid hormone and thyroid stimulating hormone serum concentration level in school children with intellectual disabilities. *Turkish Journal of Kinesiology*. 2020;**6**(2):68-75. DOI: 10.31459/turkjin.730643
- [12] Kim H, Mohan S. Role and mechanisms of actions of thyroid hormone on skeletal development. *Bone Research*. 2013;**1**(2):146-161. DOI: 10.4248/br201302004
- [13] Tapia-Martínez J, Torres-Manzo A, Franco-Colín M, Pineda-Reynoso M, Cano-Europa E. Maternal thyroid hormone deficiency during gestation and lactation alters metabolic and thyroid programming of the offspring in the adult stage. *Hormone and*

- Metabolic Research. 2019;**51**(6):381-388. DOI: 10.1055/a-0896-0968
- [14] Sugihara J, Wong A, Shimizu H, Zhao J, Cho H, Wang Y, et al. Thyroidal transcriptomic profiles of pathoadaptive responses to congenital hypothyroidism in xb130 knockout mice. *Cells*. 2022;**11**(6):975. DOI: 10.3390/cells11060975
- [15] Swanson C, Pearce E. Iodine insufficiency: A global health problem? *Advances in Nutrition*. 2013;**4**(5):533-535. DOI: 10.3945/an.113.004192
- [16] Chung H. Iodine and thyroid function. *Annals of Pediatric Endocrinology & Metabolism*. 2014;**19**(1):8. DOI: 10.6065/apem.2014.19.1.8
- [17] Angell T, Huang S, Alexander E. The thyroid. In: *Thyroid Disease and Hormones*. Cham: Springer. pp. 1-14. DOI: 10.1007/978-3-319-27318-1_14-1
- [18] Jakobsson T, Vedin L, Parini P. Potential role of thyroid receptor β agonists in the treatment of hyperlipidemia. *Drugs*. 2017;**77**(15):1613-1621. DOI: 10.1007/s40265-017-0791-4
- [19] Ahn H, Yi K. Diagnosis and management of thyroid disease during pregnancy and postpartum: 2023 revised Korean Thyroid Association guidelines. *Endocrinology and Metabolism*. 2023;**38**(3):289-294. DOI: 10.3803/enm.2023.1696
- [20] De la Vieja A, Santisteban P. Role of iodide metabolism in physiology and cancer. *Endocrine-Related Cancer*. 2018;**25**(4):R225-R245
- [21] Velasco I, Bath S, Rayman M. Iodine as essential nutrient during the first 1000 days of life. *Nutrients*. 2018;**10**(3):290. DOI: 10.3390/nu10030290
- [22] Zimmermann M. Iodine deficiency. *Endocrine Reviews*. 2009;**30**(4):376-408. DOI: 10.1210/er.2009-0011
- [23] Shawel D, Hagos S, Lachat CK, Kimanya ME, Kolsteren P. Post-production losses in iodine concentration of salt hamper the control of iodine deficiency disorders: A case study in northern Ethiopia. *Journal of Health, Population, and Nutrition*. 2010;**28**(3):238
- [24] Ivanova L. Iodine deficiency disorders and salt iodisation - public health implications. *Journal of Nutritional Health & Food Engineering*. 2015;**2**(1):10.15406/jnhfe.2015.02.00040
- [25] Zimmermann M. The effects of iodine deficiency in pregnancy and infancy. *Paediatric and Perinatal Epidemiology*. 2012;**26**(s1):108-117. DOI: 10.1111/j.1365-3016.2012.01275.x
- [26] Toloza FJ, Motahari H, Maraka S. Consequences of severe iodine deficiency in pregnancy: Evidence in humans. *Frontiers in Endocrinology*. 2020;**11**:409
- [27] Farebrother J, Zimmermann M, Andersson M. Excess iodine intake: Sources, assessment, and effects on thyroid function. *Annals of the New York Academy of Sciences*. 2019;**1446**(1):44-65. DOI: 10.1111/nyas.14041
- [28] Moriyama K, Tagami T, Akamizu T, Usui T, Saijo M, Kanamoto N, et al. Thyroid hormone action is disrupted by bisphenol A as an antagonist. *The Journal of Clinical Endocrinology and Metabolism*. 2002;**87**(11):5185-5190. DOI: 10.1210/jc.2002-020209
- [29] Xu J, Liu S, Ma W, Li X, Guo M, Cao X, et al. Causes of different goiter rates with the same iodine deficiency among the pastoral and agricultural

populations of Tibet: A geographical comparison. *Thyroid Research*. 2022;**15**(1):4

[30] Brotfain E, Koyfman L, Frenkel A, Smolikov A, Zlotnik A, Klein M. Iodine-induced hyperthyroidism—An old clinical entity that is still relevant to daily ICU practice: A case report. *Case Reports in Endocrinology*. 2013;**2013**:792745. DOI: 10.1155/2013/792745

[31] Hwang S, Lee E, Lee W, Shin D, Lee M. Correlation between iodine intake and thyroid function in subjects with normal thyroid function. *Biological Trace Element Research*. 2011;**143**(3):1393-1397. DOI: 10.1007/s12011-011-8997-x

[32] Luo Y, Kawashima A, Ishido Y, Yoshihara A, Oda K, Hiroi N, et al. Iodine excess as an environmental risk factor for autoimmune thyroid disease. *International Journal of Molecular Sciences*. 2014;**15**(7):12895-12912. DOI: 10.3390/ijms150712895

[33] Daniell K, Nucera C. Effect of the micronutrient iodine in thyroid carcinoma angiogenesis. *Aging*. 2016;**8**(12):3180-3184. DOI: 10.18632/aging.101143

[34] Lee SY. Consequences of iodine deficiency in pregnancy. *Frontiers in Endocrinology*. 2021;**12**:740239

[35] Dineva M, Fishpool H, Rayman M, Mendis J, Bath S. Systematic review and meta-analysis of the effects of iodine supplementation on thyroid function and child neurodevelopment in mildly-to-moderately iodine-deficient pregnant women. *The American Journal of Clinical Nutrition*. 2020;**112**(2):389-412. DOI: 10.1093/ajcn/nqaa071

[36] Zava T, Zava D. Assessment of Japanese iodine intake based on seaweed

consumption in Japan: A literature-based analysis. *Thyroid Research*. 2011;**4**(1):14. DOI: 10.1186/1756-6614-4-14

[37] Winder M, Kosztyła Z, Boral A, Kocetlak P, Chudek J. The impact of iodine concentration disorders on health and cancer. *Nutrients*. 2022;**14**(11):2209. DOI: 10.3390/nu14112209

[38] Skeaff S. Iodine deficiency in pregnancy: The effect on neurodevelopment in the child. *Nutrients*. 2011;**3**(2):265-273. DOI: 10.3390/nu3020265

[39] Umenwanne E, Akinyele I. Inadequate salt iodization and poor knowledge, attitudes, and practices regarding iodine-deficiency disorders in an area of endemic goitre in south-eastern Nigeria. *Food and Nutrition Bulletin*. 2000;**21**(3):311-315. DOI: 10.1177/156482650002100311

[40] Zimmermann M, Delange F. Iodine supplementation of pregnant women in Europe: A review and recommendations. *European Journal of Clinical Nutrition*. 2004;**58**(7):979-984. DOI: 10.1038/sj.ejcn.1601933

[41] Watutantrige-Fernando S, Cavedon E, Nacamulli D, Pozza D, Ermolao A, Zaccaria M, et al. Iodine status from childhood to adulthood in females living in north-east Italy: Iodine deficiency is still an issue. *European Journal of Nutrition*. 2015;**55**(1):335-340. DOI: 10.1007/s00394-015-0853-x

[42] Escobar G, Obregón M, Rey F. Iodine deficiency and brain development in the first half of pregnancy. *Public Health Nutrition*. 2007;**10**(12A):1554-1570. DOI: 10.1017/s1368980007360928

[43] Singh V, Joshi A, Gurung C, Banjara M. Determination of urinary iodine excretion to assess iodine

deficiency disorder among pregnant women in district hospital of Sindhupalchowk, Nepal. *Nepal Journal of Science and Technology*. 2020;**19**(1):119-123. DOI: 10.3126/njst.v19i1.29791

[44] Nie J, Zhu Y, Wang C, Qi L, Tayier R, Cai Z, et al. Relationship between iodine knowledge and dietary iodine intake in pregnant and lactating women: A cross-sectional study. *Public Health Nutrition*. 2023;**26**(7):1436-1450. DOI: 10.1017/s1368980023000514

[45] Majumder A, Jaiswal A, Chatterjee S. Prevalence of iodine deficiency among pregnant and lactating women: Experience in Kolkata. *Indian Journal of Endocrinology and Metabolism*. 2014;**18**(4):486. DOI: 10.4103/2230-8210.137491

[46] Censi S, Watutantrige-Fernando S, Groccia G, Manso J, Plebani M, Faggian D, et al. The effects of iodine supplementation in pregnancy on iodine status, thyroglobulin levels, and thyroid function parameters: Results from a randomized controlled clinical trial in a mild-to-moderate iodine deficiency area. *Nutrients*. 2019;**11**(11):2639. DOI: 10.3390/nu11112639

[47] Ghirri P, Lunardi S, Boldrini A. Iodine supplementation in the newborn. *Nutrients*. 2014;**6**(1):382-390. DOI: 10.3390/nu6010382

[48] Zu-pei C, Hetzel B. Cretinism revisited. *Best Practice & Research. Clinical Endocrinology & Metabolism*. 2010;**24**(1):39-50. DOI: 10.1016/j.beem.2009.08.014

[49] Pod P, Buttfield I, Hetzel B. Neurological damage to the fetus resulting from severe iodine deficiency during pregnancy. *International Journal of Epidemiology*. 2012;**41**(3):589-592. DOI: 10.1093/ije/dys070

[50] Yadav K, Pandav C. National iodine deficiency disorders control programme: Current status and future strategy. *The Indian Journal of Medical Research*. 2018;**148**(5):503. DOI: 10.4103/ijmr.ijmr_1717_18

[51] Sharipov A, Boboev Z, Fazliev S, Gulyamov S, Yunuskhodjayev A, Razzokov J. Development of an improved method for the determination of iodine/ β -cyclodextrin by means of HPLC-UV: Validation and the thyroid-stimulating activity revealed by in vivo studies. *Pharmaceutics*. 2021;**13**(7):955. DOI: 10.3390/pharmaceutics13070955

[52] Zhang X, Yuan N, Sun J, Zhao X, Du J, Min N, et al. Association between iodine nutritional status and adverse pregnancy outcomes in Beijing, China: A single-center cohort study. *Biological Trace Element Research*. 2021;**200**(6):2620-2628. DOI: 10.1007/s12011-021-02887-9

[53] Croft C. The role of nutrition in children's neurocognitive development, from pregnancy through childhood. In: *Prenatal and Childhood Nutrition*. Apple Academic Press; 2015. pp. 65-108

[54] Stagnaro-Green A, Dogo-Isonaige E, Pearce E, Spencer C, Gaba N. Marginal iodine status and high rate of subclinical hypothyroidism in Washington DC women planning conception. *Thyroid*. 2015;**25**(10):1151-1154. DOI: 10.1089/thy.2015.0063

[55] Wei W, Wang Y, Dong J, Wang Y, Min H, Song B, et al. Hypothyroxinemia induced by maternal mild iodine deficiency impairs hippocampal myelinated growth in lactational rats. *Environmental Toxicology*. 2014;**30**(11):1264-1274. DOI: 10.1002/tox.21997

[56] Taylor P, Vaidya B. Iodine supplementation in pregnancy – Is

- it time? *Clinical Endocrinology*. 2016;**85**(1):10-14. DOI: 10.1111/cen.13065
- [57] Ak Y, Demirel F, Ermis B, Ie P. Maternal and neonatal urinary iodine status and its effect on neonatal TSH levels in a mildly iodine-deficient area. *Journal of Clinical Research in Pediatric Endocrinology*. 2013;**5**(2):90-94. DOI: 10.4274/jcrpe.997
- [58] Verhagen N, Gowachirapant S, Winichagoon P, Andersson M, Melse-Boonstra A, Zimmermann M. Iodine supplementation in mildly iodine-deficient pregnant women does not improve maternal thyroid function or child development: A secondary analysis of a randomized controlled trial. *Frontiers in Endocrinology*. 2020;**11**:572984. DOI: 10.3389/fendo.2020.572984
- [59] Speeckaert M, Speeckaert R, Wierckx K, Delanghe J, Kaufman J. Value and pitfalls in iodine fortification and supplementation in the 21st century. *The British Journal of Nutrition*. 2011;**106**(7):964-973. DOI: 10.1017/s000711451100273x
- [60] Gordon R, Rose M, Skeaff S, Gray A, Morgan K, Ruffman T. Iodine supplementation improves cognition in mildly iodine-deficient children. *The American Journal of Clinical Nutrition*. 2009;**90**(5):1264-1271. DOI: 10.3945/ajcn.2009.28145
- [61] Pazokian M, Khalandi F. Study of the consequences of mothers' hypothyroidism in children: A systematic review. *International Journal of Medical Reviews*. 2019;**6**(3):101-104. DOI: 10.29252/ijmr-060306
- [62] Andersen S, Laurberg P, Wu C, Olsen J. Maternal thyroid dysfunction and risk of seizure in the child: A Danish nationwide cohort study. *Journal of Pregnancy*. 2013;**2013**:636705. DOI: 10.1155/2013/636705
- [63] Zimmermann M. The remarkable impact of iodisation programmes on global public health. *The Proceedings of the Nutrition Society*. 2022;**82**(2):113-119. DOI: 10.1017/s0029665122002762
- [64] Leung A, Avram A, Brenner A, Duntas L, Ehrenkranz J, Hennessey J, et al. Potential risks of excess iodine ingestion and exposure: Statement by the American Thyroid Association Public Health Committee. *Thyroid*. 2015;**25**(2):145-146. DOI: 10.1089/thy.2014.0331
- [65] Zhao S, Yan Y, Sun F, Tian E, Zu-pei C. The impact of dietary iodine intake on lipid metabolism in mice. *Biological Trace Element Research*. 2010;**142**(3):581-588. DOI: 10.1007/s12011-010-8767-1
- [66] Khandakar M. Factors affecting iodine content of cow milk-a review. *Bangladesh Journal of Animal Science*. 2024;**53**(1):1-12. DOI: 10.3329/bjas.v53i1.72437
- [67] Wang B, He W, Li Q, Jia X, Yao Q, Song R, et al. U-shaped relationship between iodine status and thyroid autoimmunity risk in adults. *Acta Endocrinologica*. 2019;**181**(3):255-266. DOI: 10.1530/eje-19-0212
- [68] Aceves C, Mendieta I, Anguiano B, Delgado-González E. Molecular iodine has extrathyroidal effects as an antioxidant, differentiator, and immunomodulator. *International Journal of Molecular Sciences*. 2021;**22**(3):1228. DOI: 10.3390/ijms22031228
- [69] Cann SA, Van Netten JP, Van Netten C. Hypothesis: Iodine, selenium and the development of breast cancer. *Cancer Causes & Control*. 2000;**11**:121-127

- [70] Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: Defining priorities to reduce cancer disparities in different geographic regions of the world. *Journal of Clinical Oncology*. 2006;**24**(14):2137-2150
- [71] Lee J, Ha J, Jo K, Lim D, Lee J, Chang S, et al. High normal range of free thyroxine is associated with decreased triglycerides and with increased high-density lipoprotein cholesterol based on population representative data. *Journal of Clinical Medicine*. 2019;**8**(6):758. DOI: 10.3390/jcm8060758
- [72] Peppia M, Betsi G, Dimitriadis G. Lipid abnormalities and cardiometabolic risk in patients with overt and subclinical thyroid disease. *Journal of Lipids*. 2011;**2011**:575840. DOI: 10.1155/2011/575840
- [73] Lee K, Shin D, Song W. Low urinary iodine concentrations associated with dyslipidemia in US adults. *Nutrients*. 2016;**8**(3):171. DOI: 10.3390/nu8030171
- [74] Duntas L, Brenta G. A renewed focus on the association between thyroid hormones and lipid metabolism. *Frontiers in Endocrinology*. 2018;**9**:511. DOI: 10.3389/fendo.2018.00511
- [75] Zhang L. The correlation between iodine and metabolism: A review. *Frontiers in Nutrition*. 2024;**11**:1346452. DOI: 10.3389/fnut.2024.1346452
- [76] Zhai Y, Wang X, Luo J, Wang X, Liu Z, Wang J, et al. Lipid metabolism disturbances in papillary thyroid cancer patients and the relationship with iodine nutrition status. *Preprints*. 2023. DOI: 10.21203/rs.3.rs-2915108/v1
- [77] Cotter C, Walsh S. Cutaneous sequelae of a national health crisis: Obesity and the skin. *Skin Health and Disease*. 2021;**1**(1):e7. DOI: 10.1002/ski2.7
- [78] Shu-zhong J, Li W, Zong X, Ruan H, Liu Y. Obesity and hypertension. *Experimental and Therapeutic Medicine*. 2016;**12**(4):2395-2399. DOI: 10.3892/etm.2016.3667
- [79] Okpere AN, Anochie IC, Eke FU. Evaluation of microalbuminuria in obese adolescents. *Nigerian Journal of Paediatrics*. 2012;**39**(3):128-132
- [80] Ovadia Y, Gefel D, Toledano Y, Rosen S, Avrahami-Benyounes Y, Groisman L, et al. Does iodine intake modify the effect of maternal dysglycemia on birth weight in mild-to-moderate iodine-deficient populations? A mother-newborn prospective cohort study. *Nutrients*. 2023;**15**(13):2914. DOI: 10.3390/nu15132914
- [81] Hadid L, Al-Rajabi O, Barmawi M, Al-Sagarat A. The relationship between maternal obesity with pregnancy-associated hypothyroidism, fetal health, and pregnancy outcomes. *Journal of Holistic Nursing and Midwifery*. 2023;**33**(3):183-192. DOI: 10.32598/jhnm.33.3.2400
- [82] Hegazi R. Evolution of the diagnosis of malnutrition in adults: A primer for clinicians. *Frontiers in Nutrition*. 2024;**11**:1169538. DOI: 10.3389/fnut.2024.1169538
- [83] García-Solís P, Solís-S J, García-Gaytán A, Reyes-Mendoza V, Robles-Osorio L, Villarreal-Ríos E, et al. Iodine nutrition in elementary state schools of Querétaro, Mexico: Correlations between urinary iodine concentration with global nutrition status and social gap index. *Arquivos Brasileiros de Endocrinologia e Metabologia*. 2013;**57**(6):473-482. DOI: 10.1590/s0004-27302013000600010

- [84] Grandone A, Santoro N, Coppola F, Calabrò P, Perrone L, Giudice E. Thyroid function derangement and childhood obesity: An Italian experience. *BMC Endocrine Disorders*. 2010;**10**(1):8. DOI: 10.1186/1472-6823-10-8
- [85] Soriguer F, Valdés S, Morcillo S, Esteva I, Almaraz M, Adana M, et al. Thyroid hormone levels predict the change in body weight: A prospective study. *European Journal of Clinical Investigation*. 2011;**41**(11):1202-1209. DOI: 10.1111/j.1365-2362.2011.02526.x
- [86] Association between dietary iodine consumption and body composition in Caucasian females between the ages of 18 to 60: The Pioneer Project. *Endocrinology, Diabetes and Metabolism Journal*. 2018;**2**(3):231. DOI: 10.31038/edmj.2018231
- [87] Yu J, Shan Z, Wang C, Mao J, Geng Y, Zhang C, et al. Vitamin E ameliorates iodine-induced cytotoxicity in thyroid. *The Journal of Endocrinology*. 2011;**209**(3):299-306. DOI: 10.1530/joe-11-0030
- [88] Carvalho A, Meirelles C, Oliveira L, Costa T, Navarro A. Excessive iodine intake in schoolchildren. *European Journal of Nutrition*. 2011;**51**(5):557-562. DOI: 10.1007/s00394-011-0239-7
- [89] Villatoro-Santos CR, Ramirez-Zea M, Villamor E. Urinary sodium, iodine, and volume in relation to metabolic syndrome in Mesoamerican children and their parents. *Nutrition, Metabolism, and Cardiovascular Diseases*. 2022;**32**(7):1774-1783
- [90] Jin M, Zhang Z, Li Y, Teng D, Shi X, Ba J, et al. U-shaped associations between urinary iodine concentration and the prevalence of metabolic disorders: A cross-sectional study. *Thyroid*. 2020;**30**(7):1053-1065. DOI: 10.1089/thy.2020.0005
- [91] Shan X, Liu C, Luo X, Zou Y, Huang L, Zhou W, et al. Iodine nutritional status and related factors among Chinese school-age children in three different areas: A cross-sectional study. *Nutrients*. 2021;**13**(5):1404. DOI: 10.3390/nu13051404
- [92] Moleti M, Di Mauro M, Paola G, Olivieri A, Vermiglio F. Nutritional iodine status and obesity. *Thyroid Research*. 2021;**14**:1-8
- [93] Lecube-Torelló A, Zafon C, Gromaz A, Fort JM, Caubet E, Baena-Fustegueras JA, et al. Iodine deficiency is higher in morbid obesity in comparison with late after bariatric surgery and non-obese women. *The Journal of Clinical Endocrinology and Metabolism*. 2015;**100**(4):1505-1512
- [94] Aoe S, Yamanaka C, Ohtoshi H, Nakamura F, Fujiwara S. Effects of daily kelp (*Laminaria japonica*) intake on body composition, serum lipid levels, and thyroid hormone levels in healthy Japanese adults: A randomized, double-blind study. *Marine Drugs*. 2021;**19**(7):352. DOI: 10.3390/md19070352
- [95] Hito S, Shimoda H. Seaweed fucoxanthin supplementation improves obesity parameters in mild obese Japanese subjects. *Functional Foods in Health and Disease*. 2017;**7**(4):246-262
- [96] Eray E, Sari F, Özdem S, Sari R. Relationship between thyroid volume and iodine, leptin, and adiponectin in obese women before and after weight loss. *Medical Principles and Practice*. 2010;**20**(1):43-46. DOI: 10.1159/000322075
- [97] Lee J, Kim J, Cho H, Lee J, Ryu J, Yum M, et al. Children experiencing

- first-time or prolonged febrile seizure are prone to stress hyperglycemia. *Journal of Child Neurology*. 2015;**31**(4):439-443. DOI: 10.1177/0883073815597757
- [98] Ezemaduka Okoli CB, Woldu HG, Peterson CA. Low urinary iodine concentration is associated with increased risk for elevated plasma glucose in females: An analysis of NHANES 2011-12. *Nutrients*. 2021;**13**(12):4523. DOI: 10.3390/nu13124523
- [99] Mancini FR, Rajaobelina K, Dow C, Habbal T, Affret A, Balkau B, et al. High iodine dietary intake is associated with type 2 diabetes among women of the E3N-EPIC cohort study. *Clinical Nutrition*. 2019;**38**(4):1651-1656. DOI: 10.1016/j.clnu.2018.05.019
- [100] Kim MS, Kim JY, Choi WH, Lee SS. Effects of seaweed supplementation on blood glucose concentration, lipid profile, and antioxidant enzyme activities in patients with type 2 diabetes mellitus. *Nutrition Research and Practice*. 2008;**2**(2):62-67
- [101] Wang D, Wan S, Liu P, Meng F, Zhang X, Ren B, et al. Relationship between excess iodine, thyroid function, blood pressure, and blood glucose level in adults, pregnant women, and lactating women: A cross-sectional study. *Ecotoxicology and Environmental Safety*. 2021;**208**:111706
- [102] Neven KY, Cox B, Cosemans C, Gyselaers W, Penders J, Plusquin M, et al. Lower iodine storage in the placenta is associated with gestational diabetes mellitus. *BMC Medicine*. 2021;**19**:1-10
- [103] Candido A, Azevedo F, Machamba A, Pinto C, Lopes S, Macedo M, et al. Implications of iodine deficiency by gestational trimester: A systematic review. *Archives of Endocrinology and Metabolism*. 2020;**64**(2):123-132. DOI: 10.20945/2359-3997000000289
- [104] Zhuo Y, Lin L, Sun Z, Huang W, Hong Z, Zhang Y, et al. Vitamin D and iodine status was associated with the risk and complication of type 2 diabetes mellitus in China. *Open Life Sciences*. 2021;**16**(1):150-159. DOI: 10.1515/biol-2021-0019
- [105] Barra NG, Anhê FF, Cavallari JF, Singh AM, Chan DY, Schertzer JD. Micronutrients impact the gut microbiota and blood glucose. *Journal of Endocrinology*. 2021;**250**(2):R1-R21
- [106] Hussainy S. Blood pressure in relation to age and gender. *Journal of Drug Delivery and Therapeutics*. 2024;**14**(3):39-43. DOI: 10.22270/jddt.v14i3.6456
- [107] Helelo TP, Gelaw YA, Adane AA. Prevalence and associated factors of hypertension among adults in Durame Town, Southern Ethiopia. *PLoS One*. 2014;**9**(11):e112790
- [108] Menon V, Chellan G, Sundaram K, Murthy S, Kumar H, Unnikrishnan A, et al. Iodine status and its correlations with age, blood pressure, and thyroid volume in South Indian women above 35 years of age (Amrita Thyroid Survey). *Indian Journal of Endocrinology and Metabolism*. 2011;**15**(4):309. DOI: 10.4103/2230-8210.85584
- [109] Shen X, Yang L, Liu Y, Zhang X, Cai P, Huang J, et al. Associations between urinary iodine concentration and the prevalence of metabolic disorders: A cross-sectional study. *Frontiers in Endocrinology*. 2023;**14**:1153462. DOI: 10.3389/fendo.2023.1153462
- [110] Tadesse S, Hymete A, Lieberman M, Gebreyesus SH, Ashenef A. Iodine

status, household salt iodine content, knowledge and practice assessment among pregnant women in Butajira, South Central Ethiopia. *PLoS One*. 2022;**17**(11):e0277208

[111] Gülaboğlu M, Borekci B, Delibaş İ. Urine iodine levels in preeclamptic and normal pregnant women. *Biological Trace Element Research*. 2009;**136**(3): 249-257. DOI: 10.1007/s12011-009-8539-y

[112] Cuellar-Rufino S, Navarro-Meza M, García-Solís P, Irene X, Arroyo-Helguera O. Iodine levels are associated with oxidative stress and antioxidant status in pregnant women with hypertensive disease. *Nutrición Hospitalaria*. 2017;**34**(3):661-669. DOI: 10.20960/nh.460

[113] Hata Y, Nakajima KI, Uchida JI, Hidaka H, Nakano T. Clinical effects of brown seaweed, *Undaria pinnatifida* (wakame), on blood pressure in hypertensive subjects. *Journal of Clinical Biochemistry and Nutrition*. 2001;**30**:43-53

[114] Opazo MC, Coronado-Arrázola I, Vallejos OP, Moreno-Reyes R, Fardella C, Mosso L, et al. The impact of the micronutrient iodine in health and diseases. *Critical Reviews in Food Science and Nutrition*. 2022;**62**(6):1466-1479

[115] Vejbjerg P, Knudsen N, Perrild H, Laurberg P, Carlé A, Pedersen I, et al. Thyroglobulin as a marker of iodine nutrition status in the general population. *Acta Endocrinologica*. 2009;**161**(3):475-481. DOI: 10.1530/eje-09-0262

[116] Ittermann T, Richter A, Junge M, Nauck M, Petersmann A, Jürgens C, et al. Variability of thyroid measurements from ultrasound and laboratory in a repeated measurements study. *European Thyroid Journal*. 2020;**10**(2):140-149. DOI: 10.1159/000507018

[117] Du Y, Gao Y, Meng F, Liu S, Fan Z, Wu J, et al. Iodine deficiency and excess coexist in China and induce thyroid dysfunction and disease: A cross-sectional study. *PLoS One*. 2014;**9**(11):e111937

[118] Wang F, Tang K, Pan W, Won J, Hsieh Y, Huang C. Iodine status of Taiwanese population in 2013: 10 years after changing from mandatory to voluntary salt iodization. *Food and Nutrition Bulletin*. 2017;**39**(1):75-85. DOI: 10.1177/0379572117738883

[119] Wu Y, Yang J, Su Q, Gu H, Li Q. Urinary iodine concentration and its associations with thyroid function in pregnant women of Shanghai. *Frontiers in Endocrinology*. 2023;**14**:1184747. DOI: 10.3389/fendo.2023.1184747

[120] Thapa S, Lamsal M, Chaudhari R, Gelal B, Kunwar S, Baral N. Thyroid dysfunction in region of excess iodine intake of eastern Nepal. *International Journal of Scientific Reports*. 2018;**4**(5):114. DOI: 10.18203/issn.2454-2156.intjsci20181848

[121] Uğurlu G, Aslan D. Bir halk sağlığı sorunu: İyot yetersizliği. *ESTÜDAM Halk Sağlığı Dergisi*. 2023;**8**(3):541-551

[122] Türk Gıda Kodeksi Tuz Tebliği, Resmi Gazete: 28737 (16.08.2013), Tebliğ No: 2013/48, md. 4,5

[123] Türk Gıda Kodeksi Yemeklik Tuz Tebliği (9 Temmuz 1998). Resmi Gazete (Sayı: 23397). Available from: <https://www.resmigazete.gov.tr/arsiv/23398.pdf>

[124] Travers C, Guttikonda K, Norton C, Lewis P, Mollart L, Wiley V, et al. Iodine status in pregnant women and their newborns: Are our babies at risk of iodine deficiency? *The Medical Journal of Australia*. 2006;**184**(12):617-620. DOI: 10.5694/j.1326-5377.2006.tb00417.x

- [125] Lebădă I, Stanciu M, Frum A, Totoian I. Evaluation of iodate status in a group of children with stature delay from Sibiu County. *Acta Medica Transilvanica*. 2019;**24**(4):8-11. DOI: 10.2478/amtsb-2019-0003
- [126] Henjum S, Brantsæter A, Kurniasari A, Dahl L, Aadland E, Gjengedal E, et al. Suboptimal iodine status and low iodine knowledge in young Norwegian women. *Nutrients*. 2018;**10**(7):941. DOI: 10.3390/nu10070941
- [127] Henjum S, Groufh-Jacobsen S, Aakre I, Terragni L. Life-course perspectives of milk consumption among young Norwegian women and their knowledge of milk as a source of iodine: A qualitative study. *Food & Nutrition Research*. 2021;**65**:7758. DOI: 10.29219/fnr.v65.7758
- [128] Adalsteinsdottir S, Tryggvadóttir E, Hrolfsdóttir L, Halldórsson T, Birgisdóttir B, Hreidarsdóttir I, et al. Insufficient iodine status in pregnant women as a consequence of dietary changes. *Food & Nutrition Research*. 2020;**64**:3653. DOI: 10.29219/fnr.v64.3653
- [129] Vinogradov D, Lupova E, Pityurina I. The use of iodine-containing additives in bakery production technology. *IOP Conference Series: Earth and Environmental Science*. 2022;**954**(1):012046. DOI: 10.1088/1755-1315/954/1/012046
- [130] Vasiljev V, Subotić A, Glavić M, Juraga D, Bilajac L, Jelaković B, et al. Overview of iodine intake. *Southeastern European Medical Journal*. 2022;**6**(1):12-20. DOI: 10.26332/seemedj.v6i1.241
- [131] Saeid N, Rami A, Mounach S, Hamrani A, Hamdouchi A, Mouzouni F, et al. Assessment of iodine intake and deficiency in school-age children in Morocco. *Nutrition & Food Science*. 2018;**48**(6):873-885. DOI: 10.1108/nfs-03-2018-0069
- [132] O’Kane SM, Pourshahidi LK, Farren KM, Mulhern MS, Strain JJ, Yeates AJ. Knowledge and awareness of iodine nutrition among women of childbearing age. *Proceedings of the Nutrition Society*. 2015;**74**(OCE4):E260
- [133] Hussein I, Min Y, Ghebremeskel K, Gaffar A. Iodine status and fish intake of Sudanese schoolchildren living in the Red Sea and White Nile regions. *Public Health Nutrition*. 2012;**15**(12):2265-2271. DOI: 10.1017/s1368980012000833
- [134] Bath S, Verkaik-Kloosterman J, Sabatier M, Borg S, Eilander A, Hora K, et al. A systematic review of iodine intake in children, adults, and pregnant women in Europe—Comparison against dietary recommendations and evaluation of dietary iodine sources. *Nutrition Reviews*. 2022;**80**(11):2154-2177. DOI: 10.1093/nutrit/nuac032
- [135] Machado A, Gonçalves C, Moreira P, Pinho O, Padrão P, Silva-Santos T, et al. Iodine intake assessment in the staff of a Porto region university (Portugal): The IMC Salt Trial. *European Journal of Nutrition*. 2023;**62**(5):2245-2256. DOI: 10.1007/s00394-023-03149-1

Chapter 3

The Interplay of Selenium and Human Health

Samy G. Alami, Ahmed Al-Harrasi and Adel Ehab Ibrahim

Abstract

This chapter delves into the intriguing dual nature of selenium (Se), a vital yet paradoxical essential trace element for human health. While indispensable for numerous physiological processes, Se has an extremely narrow margin between its benefits and potential toxicity, making its intake a delicate balancing act. Still, its consumption varies globally due to dietary habits, geographic differences, and environmental conditions. Se's history, sources, biomarkers, nutritional guidelines, and its deficiency and toxicity implications are discussed. It also provides an in-depth look at the pivotal role of selenoproteins, including their synthesis, various types, functions, and the concerns arising from their deficiency or genetic variations. From supporting the brain, fertility, development, and immunity to regulating thyroid function, these proteins illustrate the multifaceted importance of Se in human biology. Notably, Se has also emerged as an environmental contaminant that warrants attention. To address this challenge, the contamination sources, remediation strategies, and analysis methods were summarized.

Keywords: analysis, biomarkers, deficiency, development, essential trace element, history, immunity, mental health, nutritional guidelines, overconsumption, reproduction, selenoproteins, thyroid

1. Introduction

1.1 Chemical properties and nature of selenium

Selenium (Se) is a reactive non-metal or metalloid with an atomic number of 34.0, located in Group 16 (the oxo-acids group) and Period IV of the P-block in the periodic table [1]. With an atomic mass of 78.96, it lies between sulfur and tellurium. Selenium is primarily obtained from sulfide ores, partially replacing sulfur due to their similar physical and chemical properties [2]. It accumulates in plants through the soil and readily combines with elements, such as sulfur, copper, silver, arsenic, nickel, and lead, ranking as the 67th most abundant element in Earth's crust [1]. Selenium exists in both organic forms, like selenocysteine (SeCys) and selenomethionine (SeMet), and inorganic forms, such as selenite (Se(IV)) and selenate (Se(VI)). Se(IV) and Se(VI) ions are classified as toxic elements, with Se(IV) being the more harmful of

the two. Selenide (Se(II)) and elemental Se (Se(0)) are less soluble than the prior two. As an oxo-acid, its chemical properties vary significantly as atomic mass increases [3]. Hence, its six isotopes have a distinct stabilization state, half-life, and decay mode [4]. Furthermore, its amorphous brick-red powder transforms into a black vitreous solid at its melting point [1]. Se is found in the active sites of selenoproteins, which are present in all major domains of life: eukaryotes, archaea, and eubacteria. Additionally, they have also been observed in certain viruses [5, 6].

1.2 The duality of selenium: A lunar exploration

Selenium is now recognized as an essential antioxidant trace element for human development and functions. Still, Se has two faces, bright and dark, much like the moon. The earliest mention of Se dates back to the thirteenth century in Marco Polo's travel notes from the Silk Road. He observed that in some regions of China, the hooves of animals that consumed particular plants, later known as Se hyperaccumulators, became soft and deformed while also suffering nausea and fur loss [7, 8]. Similar cases were documented in Columbia and Fort Randall (South Dakota, USA) in the sixteenth and nineteenth centuries. They reported hair and weight loss, joint diseases, reproductive disorders, lack of vitality, and death. Practitioners of the time referred to this condition as alkali disease due to the high soil salinity in affected areas [7, 9].

In 1817, Swedish chemist Jöns Jacob Berzelius, known for his discoveries of cerium, silicon, and thorium, stumbled upon an element that he initially believed to be tellurium, which Martin Heinrich Klaproth had discovered in 1798. However, after conducting a thorough analysis of the sludge, he revealed the presence of an unknown element. Noticing the similarities between the two elements and their frequent co-occurrence, Berzelius concluded that if tellurium comes from the Greek word "Tellus," meaning Earth, then the symbol of the unknown element should derive from the Greek word "Selene" meaning Moon. Another reason is that when Se cools rapidly after being melted, it gives off a sheen reminiscent of the moon [8, 10, 11].

For nearly 150 years after its discovery and until the first half of the twentieth century, Se was viewed as an undesirable toxic element, primarily harmful to higher organisms and mammals. In addition, the alkali disease was identified as chronic selenosis. It was not until 1957 that Klaus Schwartz and Calvin Foltz revealed its potential benefits by demonstrating that dietary selenium protected rats consuming a vitamin E-deficient diet against muscular dystrophy and liver cirrhosis [8, 12]. Since then, studies have shown that it has significant antioxidant functions and is the key behind selenoproteins. It is as if fate chose the moon to represent this element as Se has the narrowest spectrum between nutritional deficiency and overconsumption, with both extremes leading to adverse health consequences.

1.3 Impact of Se deficiency and overconsumption

Animal deficiency diseases include cataracts, growth depression (ill-thrift), and white muscle disease, which primarily affects lambs' and calves' hearts and skeletal muscles [8, 13, 14]. Furthermore, selenium deficiency is associated with reproductive impairments and early pregnancy loss in sheep, where supplementation has been shown to mitigate this issue [15].

On the one hand, Se deficiency in humans has been linked to various health issues. This includes prostate cancer, nephropathy, respiratory disorders (such as asthma), cardiovascular problems (including impaired circulation, cardiac

arrhythmia, stroke, and heart failure), Keshan disease (endemic cardiomyopathy), and Kashin-Beck disease (deforming arthritis) [10, 13, 14, 16, 17]. Moreover, low selenium levels can worsen the virulence of infections like HIV (human immunodeficiency virus) and accelerate the progression of AIDS (acquired immunodeficiency syndrome) [18]. This is attributed to selenium's immunostimulant effects on innate and adaptive immunity, including enhancing activated T-cell proliferation. Additionally, the lack of selenium can lead to increased accumulation of arsenic in the liver [19]. Selenium deficiency was also found to impair thyroid function, affecting the production and secretion of thyroid hormones. As a result, when selenium and iodine deficiencies coincide, they may intensify the emergence of myxedema and congenital hypothyroidism [20]. In terms of reproductive health, its deficiency can lead to infertility, impaired sperm stability and motility, placental retention, preeclampsia, sudden infant death syndrome, and idiopathic miscarriage [13, 18, 21–23]. Interesting studies have observed significantly lower serum selenium levels in women who have experienced either first-trimester or recurrent miscarriages [21, 24]. Besides that, low plasma selenium concentrations in older adults have been considerably associated with senility, accelerated cognitive decline [25], and increased risk of neurological impairments, including seizures and Parkinson's disease [26, 27]. On top of that, selenium deficiency and the suppression of selenoprotein expression have been linked to elevated levels of inflammatory cytokines in various tissues, such as the gastrointestinal tract (GIT) [28], uterus [29], and mammary glands [30].

On the other hand, overconsumption of Se can lead to oxidative stress and potentially life-threatening conditions. This oxidative stress is caused by the body's redox imbalance, which occurs when there is a mismatch between generating and eliminating reactive oxygen species (ROS) [7], with the latter happening during high consumption. Another hypothesis suggests that Se toxicity may result from its affinity to thiol groups [31]. This affinity could cause non-specific sulfur replacement with selenium in sulfur-containing amino acids, leading to changes in the protein's tertiary structure and disrupting the integrity of proteins responsible for DNA repair [7]. What's more, the toxicity of selenium for plants depends on the capacity to synthesize non-protein amino acids and their volatilization as dimethyl selenide [8]. In animals, the toxicity is influenced by the methylation rate and Se excretion through urine, feces, and breath [8, 32]. Excessive consumption of selenium-rich foods in animals has been linked to diseases, such as alkali disease and "blind staggers" [8], while in humans, it can vary. Acute exposure to high levels of selenium may result in overall weakness and neurological disturbances [33]. Chronic toxicity from selenium can manifest as a condition known as selenosis. Selenosis has characteristic symptoms, including general weakness, fatigue, headaches, hair loss, brittle nails, skin lesions and rashes, an unpleasant garlic odor while exhaling (dimethyl selenide), poor dental health, paralysis, and gastrointestinal disorders, such as vomiting, nausea, and diarrhea [34–36]. Other toxic effects associated with high selenium intake include endocrine disruption, affecting the synthesis of thyroid hormones, growth hormone, and insulin-like growth factor 1 (IGF-1) [33]. These harmful effects of excess selenium are pronounced in regions with alkaline and peaty soils, where selenium levels can reach between 28 and 360 parts per million (ppm) [8]. On the bright side, most symptoms tend to disappear after stopping excess selenium supplementation and some effects, such as fatigue and brittleness of hair and nails, may persist for up to 90 days [37, 38].

1.4 Understanding Se regional dietary differences

Selenium availability and intake vary widely depending on dietary habits, geographic factors, and environmental conditions. These factors include the selenium content in soil and water, the types of plants consumed, climate, fertilizers, humidity, soil pH, and organic matter differences [1, 39, 40]. Regions with volcanic soils, acidic conditions, or high levels of iron and aluminum often exhibit low selenium availability due to chemical complexation [13, 14]. Conversely, selenium hyperaccumulator plants, such as *Astragalus*, *Conopsis*, *Morinda*, *Stanleya*, *Xylorhiza*, and *Neptunia* species, identify regions with seleniferous soils [3, 41]. China is frequently cited as a prime example due to its well-documented geographic regions with extremely low and high selenium status [42]. Additionally, many European countries, such as Germany, report lower mean selenium status than the United States and Mexico [43].

Dietary sources of selenium are diverse, with meat and meat products contributing the largest share (31%), followed by fish and shellfish (20%), pasta and rice (12%), and bread and cereals (11%). Selenium-rich foods also include Brazil nuts, offal, mushrooms, millets, wheat, broccoli, and dairy products [1, 11, 44]. Biofortification efforts, such as selenium-enhanced pork and chicken in Korea and selenium-enriched eggs available in 25 countries, aim to address deficiencies sustainably, as selenium is a non-renewable resource [10, 45]. A report shows that New Zealand improved its selenium intake by importing selenium-rich wheat from Australia [37]. In addition, food processing, such as baking/roasting, boiling, and frying, can substantially reduce selenium content. Refining grains can deplete selenium by 50–75%, while boiling reduces it by 45% [8, 11, 44].

In food, selenium exists primarily as SeCys and SeMet, efficiently absorbed in the small intestine through transcellular diffusion. Inorganic forms like selenite and selenate are present in smaller quantities. The absorption efficiency among Se species is as follows: SeMet > MeSeCys > Selenate > Selenite [46]. Selenium is excreted primarily through urine (60%) and feces (35%), with minor amounts eliminated through exhaling, sweat, and saliva [47]. Lastly, factors, such as smoking, older age, alcohol consumption, and coffee intake, are associated with lower selenium levels [8, 48].

1.5 Dietary guidelines for Se: Balancing benefits and risks

The human body contains approximately 14 mg of Se [20]. Health organizations recommend varying daily selenium intakes based on population needs. The World Health Organization (WHO) suggests a daily intake of 35 µg for men and 26 µg for women [49]. Given the United States Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA), the Recommended Dietary Allowance (RDA) is 55 µg/day for both men and women. The United Kingdom recommendations are slightly higher, with 60 µg/day for women and 75 µg/day for men and lactating women [10, 13, 50]. According to the Food and Nutrition Board of the National Academy of Science, the daily requirement for selenium depends on age and health status. It varies between 40 and 70 µg in men and 45–55 µg in women [18]. The adequate intake is set at 15 µg/day for infants (7 months–3 years) and increases to 70 µg/day for adolescents. For lactating women, an additional intake of 15 µg/day is estimated to cover the amount of selenium secreted in breast milk, so an adequate intake of 85 µg/day has been established [51].

Moreover, according to the European Food Safety Authority, the European population's daily selenium intake is estimated to be between 20 and 70 µg, with specific

countries reporting different levels: Poland at 30–40 µg/day, Spain at 44–50 µg/day, Austria at 48 µg/day, and UK at average 34 µg/day. In the United States, the intake is considerably higher as soils are more prosperous in selenium than in Europe, averaging 93 µg/day for women and 134 µg/day for men [11, 18].

Concerning the foregoing, upper safe limits to prevent Se's toxicity have been set. The U.S. Environmental Protection Agency (US EPA) sets the Reference Dose for Oral Exposure at 5 µg/body weight (kg) per day (350 µg/day for a 70 kg individual) [52]. The WHO's upper limit is 400 µg/day [49], while the European Food Safety Authority suggests a lower limit of 300 µg/day for adults [51]. Experts recommend keeping total selenium intake from all sources below 400–450 µg/day [13].

2. Selenoproteins: The biological agents of selenium function

The human genome contains 25 genes coding for selenoproteins, which contain SeCys at their active site and function as a redox center. SeCys is the 21st proteinogenic amino acid and the only known amino acid in eukaryotes whose biosynthesis occurs on its own transfer RNA (tRNA). Moreover, selenophosphate synthetase is the essential enzyme for incorporating SeCys into selenoproteins [1, 6, 53]. The members of the selenoprotein family are Selenophosphate synthetase, Glutathione peroxidases (GPxs), Iodothyronine deiodinases (DIOs), Thioredoxin reductases (TrxRs), and Methionine-*R*-sulfoxide reductase 1 (MsrB1). Moreover, other members of the selenoprotein family are given a letter after the word selenoprotein, such as selenoprotein K (SelK) and selenoprotein F (SelF). **Table 1** provides an overview of selenoproteins' locations, functions, and health conditions that result from their deficiency or polymorphism. Although glutathione peroxidase 5 (GPx5) (Epididymal Secretory GPx), glutathione peroxidase 7 (GPx7), and glutathione peroxidase 8 (GPx8) are members of the GPx family, they lack SeCys and instead contain a cysteine residue. They are classified within the GPxs, a member of the selenoprotein family, because they share other members' key structural and functional characteristics, particularly antioxidant activity and regulation of peroxides. Notably, a deficiency or polymorphism in GPx7 has been associated with diseases, such as Barrett's esophagus [1, 7, 8, 10, 11, 54–58].

The liver is the main site for synthesizing and distributing selenium throughout the body. What's more, selenoprotein P (SelP), which contains 10 SeCys residues, is the primary transporter of Se from the liver to other tissues. Approximately 60–80% of plasma selenium is bound to SelP [59–61]. Selenium is incorporated into proteins by two pathways, depending on whether SeMet or SeCys is utilized. SeCys, a highly reactive form of selenium, is maintained at low concentrations, while the more abundant and less reactive SeMet is extensively metabolized [62]. In eukaryotes, selenoprotein genes require a Selenocysteine Insertion Sequence (SECIS) element to recode the UGA stop codon in messenger RNA (mRNA) and incorporate SeCys. When the SECIS element is located in the 3'-untranslated region, downstream the UGA codon, it is recognized by SECIS-binding protein 2 (SBP2). SBP2 and SeCys' specific elongation factor (EFSeCys) recruit elongation factors to ensure SeCys' incorporation. Notably, Selenoprotein B conducts SBP2 and EFSeCys functions in prokaryotes. Additional factors, such as ribosomal protein L30, nucleolin, and eukaryotic translation initiation factor eIF3a, contribute to selenoprotein biosynthesis [1, 6, 7, 9, 11, 20, 63].

Without selenium or these factors, the UGA codon, which typically serves as a stop codon in other mRNAs, results in ribosome pausing and premature termination of the protein chain. This is confirmed by studies where selenoprotein synthesis stalls

Selenoproteins (Abbreviation)	Location	Functions	Deficiency or polymorphism
(A) <i>Glutathione peroxidases (GPxs)*</i> : A member of the selenoprotein family. Antioxidants that protect against oxidative stress and regulate antitumor immunity by reducing hydrogen peroxide (H ₂ O ₂), lipid hydroperoxides, phospholipid, and cholesterol hydroperoxides			
Glutathione peroxidase 1 (GPx1) (Cellular GPx)	Cytosol, erythrocytes, liver, lungs, and kidneys	Antioxidative defense protects cell membranes from damage. It reduces hydrogen peroxide and organic peroxides to water and alcohol, respectively. Inactive against lipid hydroperoxides. Decreases retroviral virulence by preventing viral mutations.	Cardiomyopathy (Keshan disease), autism, cardiometabolic effects. Lung, prostate, bladder, and liver cancers
Glutathione peroxidase 2 (GPx2) (Gastrointestinal GPx)	Gastrointestinal tissue and liver	Antioxidative defense reduces free hydroperoxides of fatty acids and hydrogen peroxide. Metabolizing ingested peroxides from fats. Anti-apoptotic function in colon crypts and helps maintain intestinal mucosa integrity.	Free radical accumulation and colon cancer
Glutathione peroxidase 3 (GPx3) (Extracellular GPx)	Extracellular fluid and plasma. Kidney is the source of GPx3 in plasma. Liver, breasts, heart, GIT, placenta, and male reproductive system	Reduces hydrogen peroxide and organic peroxides in extracellular fluids, functioning as an anti-inflammatory and antioxidant agent. It regulates the level of hydrogen peroxide in thyrocytes and the follicular lumen of the thyroid gland, which is crucial for synthesizing thyroid hormones and protecting the gland. Unlike GPx1, it is effective against lipid hydroperoxides.	Stroke, thyroid cancer, and oxidative stress
Glutathione peroxidase 4 (GPx4) (Phospholipid hydroperoxide GPx)	Associated with membrane phospholipids Testis, cytosol, mitochondria, and nucleus	Protects brain membranes, regulates apoptosis, and reduces phospholipid hydroperoxides, thymine hydroperoxides, cholesterol and its esters. Improves immune function by protecting biomembranes from oxidative damage, provided these membranes contain adequate vitamin E. Spermatogenesis, sperm motility and viability.	Breast cancer, adenocarcinoma, and prostate cancer
Glutathione peroxidase 6 (GPx6)	Cytosol, especially olfactory epithelium	Antioxidant reduces hydrogen peroxide.	—

Selenoproteins (Abbreviation)	Location	Functions	Deficiency or polymorphism
(B) <i>Iodothyronine deiodinases (DIOs)</i> : A family that regulates the thyroid gland by catalyzing the conversion of T ₄ to T ₃ , producing the active thyroid hormone T ₃ and reverse T ₃ (rT ₃). It also supports neuron health.			
Iodothyronine deiodinases 1 (DOI 1)	Liver, kidney, thyroid, and brown fat	Production of active T ₃ cell hormones in the thyroid, plasma, and peripheral tissues. Conversion and deactivation of T ₃ and T ₄ , and elimination of rT ₃ from circulation.	Decreased free IGF-1, muscle strength, lean body mass, and appetite
Iodothyronine deiodinases 2 (DOI 2)	Ear, CNS, brown adipose tissue, skeletal muscle, pituitary, and heart	Activation of thyroid hormones and T ₃ synthesis in peripheral tissues. Catalyzes deiodination of T ₄ to T ₃ and of rT ₃ to T ₂ .	Osteoarthritis and reduction in bone mineral density. Type 2 diabetes. Intellectual disabilities in iodine-deficient areas.
Iodothyronine deiodinases 3 (DOI 3)	Skin, cerebral cortex, uterus, placenta, and fetus	Deactivation of thyroid hormones by catalyzing tyrosyl ring deiodination. Prevents overexposure of the fetus to T ₃ by producing rT ₃ .	Osteoarthritis
(C) <i>Thioredoxin reductases (TrxRs)</i> : A family involved in redox signaling with nicotinamide adenine dinucleotide phosphate (NADPH) as a cofactor for a wide range of substrates, notably thioredoxin, which is required for DNA synthesis. It also reduces disulfide bonds, tumor cell apoptosis, oxidative stress, ribonucleotides to deoxyribonucleotides, and maintains intracellular redox potential.			
Thioredoxin reductases 1 (TrxR ₁)	Has at least 6 isoforms. Intracellular content in cytosol and nucleus	Embryogenesis, thioredoxin reduction, regulation of transcription factor activity, apoptosis, and cell proliferation. The main antioxidant defense at the cellular level.	Colorectal adenoma, DNA mutations, and lateral sclerosis
Thioredoxin reductases 2 (TrxR ₂)	Cytosol, mitochondria	Survival of cardiomyocytes, a cell growth factor in DNA synthesis, inhibits apoptosis and regulates cell proliferation. Protection against hydrogen peroxide produced by mitochondrial respiratory chain.	Gastric cancer and ulcers
Thioredoxin reductases 3 (TrxR ₃)	Mitochondria, testicles	Reduces the oxidized forms of mitochondrial thioredoxin and glutaredoxin 2, sperm maturation.	Liver cirrhosis
(D) <i>Miscellaneous selenoproteins</i>			
Selenophosphate synthetase 2 (SEPHS2)	Kidney and liver	Catalyzes the reaction between selenide and adenosine triphosphate (ATP), forming selenophosphate, which is a selenium donor in the biosynthesis of SeCys.	Symptoms of Se deficiency

Selenoproteins (Abbreviation)	Location	Functions	Deficiency or polymorphism
Selenoprotein F (15 kDa selenoprotein)	ER with a thioredoxin-like domain at the C terminus	Glycoprotein folding, thiol-disulfide oxidoreductase, neuroprotective, and immunity	Prostate, lung, and rectal cancers. Glucose metabolism disorders
Selenoprotein H (SelH)	Brain, nucleus, and muscle cells	Gene regulation of glutathione	—
Selenoprotein I (SelI)	Membrane	Phospholipid biosynthesis	Spastic paraplegia
Selenoprotein K (SelK)	Immune cells and spleen	Antioxidants, endoplasmic reticulum-associated degradation, inflammation, and immune response	—
Selenoprotein M (SelM)	ER and neuronal cells	Antioxidant protects neurons	—
Selenoprotein N (SelN)	Transmembrane glycoprotein related to ER	Protein folding, redox signaling, growth and development of muscles. Calcium homeostasis by regulating calcium mobilization in early muscle development. Degradation of H ₂ O ₂ .	Myopathies, multiminicore disease
Selenoprotein O (SelO)	Mitochondria	Antioxidant	—
Selenoprotein P (SelP) (SEPP1)	Contains 10 SeCys residues. Extracellular glycoprotein in plasma, liver, testes, and brain	Serves as a storage, transporter, and reliable indicator of selenium status in the body. Regulates plasma selenium levels. Serves as a chelator for heavy metals such as mercury. Antioxidant, protecting against lipid peroxidation caused by the Hepatitis B virus.	Colorectal and prostate cancers, male infertility with kinked and hypomotile spermatozoa, seizures, selenium status, and selenoproteins' expression
Selenoprotein S (SEPS1)	Transmembrane protein found in endoplasmic reticulum (ER) and plasma membrane	Anti-inflammatory removes misfolded proteins in ER and regulates ER stress-induced apoptosis. Linked to glucose metabolism and insulin sensitivity.	Ischemic stroke, congenital heart disease (CHD), and preeclampsia. Body mass index (BMI) and the waist-hip ratio. Rectal, colorectal, and gastric cancers
Methionine- <i>R</i> -sulfoxide reductase 1 (MsrB1, Selenoprotein R/X)	Kidney and liver cells	Antioxidant, protein repair, and methionine metabolism	Deafness DFNB74
Selenoprotein T (SelT)	ER and Golgi	Calcium mobilization, cell adhesion. Regulate endocrine secretion. Antioxidant protecting dopaminergic neurons	Parkinson
Selenoprotein V (SelV)	Cytosol and testes	Protects ER from reactive oxygen and nitrogen species' oxidative stress	—

Selenoproteins (Abbreviation)	Location	Functions	Deficiency or polymorphism
Selenoprotein W (SelW)	Skeletal muscles, lungs, colon, heart, and prostate	Muscle metabolism, calcium binding in bone remodeling, and antioxidant	—

**GPxs containing SeCys are (GPx 1, 2, 3, 4, and 6), while GPxs (5, 7, and 8) contain cysteine.*

Table 1.
Overview of different selenoproteins.

at the UGA codon under low selenium conditions, leading to mRNA degradation and truncated protein production by nonsense-mediated decay or destruction via C-end degraon mechanisms [64, 65]. Interestingly, under these selenium-deficient conditions, the synthesis of some selenoproteins is prioritized over others, such as glutathione peroxidase (GPx4), and known low-hierarchy selenoproteins include GPX1, SELENOH, SELENOW, and SELENOF [66]. Moreover, some tissues, such as the brain, endocrine glands, and testes, retain selenium more, emphasizing its importance in these systems [12].

The selenoproteins' synthesis pathway utilizing SeCys, also known as Translational Decoding, is a complex multistage process. In an adenosine triphosphate (ATP)-dependent process, selenophosphate synthetase organifies selenium to form activated selenophosphate. This activated selenophosphate then phosphorylates seryl-tRNA synthetase. Next, seryl-tRNA synthetase initially aminoacylates tRNA^(Ser) to form Ser-tRNA^{(Ser)SeCys}. The intermediate, Ser-tRNA^{(Ser)SeCys}, is then phosphorylated by O-phosphoseryl-tRNA kinase, producing phosphoseryl-tRNA^{(Ser)SeCys}. Following that, selenophosphate synthetase 2 (SEPHS2) and selenocysteine synthase (SEPSECS) collaborate to convert phosphoseryl-tRNA^{(Ser)SeCys} into selenocysteinyl-tRNA^{(Ser)SeCys} (SeCys-tRNA^{(Ser)Sec}); SEPHS2 facilitates the phosphorylation of selenide into monoselenophosphate, while SEPSECS catalyzes the critical transformation of phosphoserine into SeCys on the tRNA. This finalized SeCys-tRNA^{(Ser)SeCys} binds to the ribosomal A-site, enabling the cotranslational incorporation of SeCys into the growing polypeptide chain [1, 5–7, 9, 11, 67].

After serving their functions, selenoproteins release SeCys through proteolysis, and SeCys is degraded by SeCys β -lyase producing selenide. This selenide can be metabolized for excretion or undergo the biosynthesis pathway again [68].

The second pathway utilizing SeMet can start when selenium is randomly incorporated in place of regular sulfur during methionine biosynthesis. Later, SeMet can be incorporated into proteins, such as hemoglobin and albumin, based on its abundance. However, SeMet residues are more easily oxidized than sulfur-containing methionine, which can result in a loss of protein function or altered antigenicity, causing side effects. Moreover, long-term consumption of food containing SeMet can be toxic due to the accumulation of selenium in body proteins instead of being excreted, raising the body's apparent selenium levels without providing any biological benefits [69, 70].

SeMet must first be converted into an inorganic precursor to contribute to the available selenium pool. This additional step makes it a less accessible source of selenium than selenite or selenate, which only needs to be reduced to selenide to form selenophosphate, the precursor for SeCys [13]. In conclusion, the term selenoproteins specifically refers to selenocysteine-containing proteins.

3. The comprehensive role of selenium in human health

3.1 Neuroscience of selenium: Implications for mental health

Selenium is crucial in maintaining brain health and supporting cognitive function due to its antioxidant, anti-inflammatory, and neuroprotective properties. This is further emphasized as the brain prioritizes the supply and retention of Se during its deficiency. Not only that, but the brain, which consumes significant oxygen, is also highly susceptible to oxidative damage. However, it lacks catalase, making selenium-dependent enzymes like GPxs vital for eliminating harmful oxidative products, such as hydrogen peroxide and lipid peroxides [13, 26, 71]. Interesting studies revealed that SelP transports Se to brain tissue and has neuroprotective properties that promote neuronal survival and prevent apoptosis [72]. They also showed that SelP deficiency can result in spasticity, abnormal movements, and spontaneous seizures. Furthermore, the lack of selenium was associated with irreversible brain injury, cognitive decline, and alterations in neurotransmitter turnover [27]. It was also linked to various mood and neurological disorders, including Alzheimer's, Parkinson's, depression, anxiety, confusion, and hostility [73]. What makes matters worse is that Se levels decline with age, exacerbating these risks and leading to cognitive impairment in older individuals. A study showcased that selenium-binding protein-1 mRNA is upregulated in cases of schizophrenia [74]. Luckily, selenium supplementation has been shown to alleviate many of these adverse effects. For instance, selenium reduces brain damage in ischemic conditions by lowering inflammatory cytokines, such as interleukin-1 beta (IL-1 β) and tumor necrosis factor-alpha (TNF- α) while increasing neurotrophic factors. Also, histological studies indicate that selenium treatment enhances the density of neurons and reduces edema in affected brain regions [75].

3.2 Selenium and thyroid health

The thyroid gland has the highest selenium content of all endocrine organs, underscoring its significance for thyroid health. The thyroid utilizes GPx and TrxR, antioxidants, to help mitigate inflammation and oxidative damage caused by ROS and reactive nitrogen species (RNS). Excessive ROS and RNS levels rise from hydrogen peroxide and inflammatory processes such as lymphocytic infiltration in Hashimoto's thyroiditis. For instance, GPx3 protects against oxidative damage caused by H₂O₂ during thyroid hormone synthesis. Thyroid peroxidase utilizes H₂O₂ to convert iodide and thyroglobulin into T₃ and T₄, and excess H₂O₂ may remain [20, 76].

Selenium's role goes beyond its antioxidative properties shown by the selenoproteins' iodothyronine deiodinase family (DIO1, DIO2, and DIO3), which regulate thyroid hormone metabolism and activity. DIO1 and DIO2 activate thyroxine (T₄) to triiodothyronine (T₃), while DIO3 inactivates T₄ and T₃ by converting them into reverse T₃ (rT₃) or diiodothyronine (T₂). This fine regulation is essential for maintaining hormonal balance and ensuring optimal functioning. DIO3's widespread distribution across tissues emphasizes its systemic role in hormone inactivation. In contrast, DIO2 is primarily expressed in the central nervous system (CNS), highlighting its importance in the local regulation of thyroid hormones [20, 77–79]. Additionally, studies involving DIO2 knockout mice have shown delayed muscle repair and reduced expression of T₃-dependent genes, suggesting DIO2's role in muscle differentiation and regeneration [80].

While iodine's importance is well recognized globally, public awareness and preventive measures for ensuring adequate Se intake are still in their infancy, specifically for older people and pregnant women. First, unlike iodine, which can be stored in the thyroid gland for months, selenium must be supplied continuously through a balanced diet. Second, a selenium deficiency can reduce the activity of DIOs and GPxs, leading to a decreased conversion of T_4 to T_3 and an increased susceptibility to thyroid diseases, such as Graves, autoimmune thyroid diseases, and goiter [81]. Fortunately, selenium supplementation has been shown to effectively combat autoimmune thyroid disorders like Hashimoto's thyroiditis and Graves' disease. In a study, patients receiving selenium reported improved quality of life, reduced eye involvement, and slower Graves' orbitopathy progression [10, 82]. Additionally, selenium supplementation has been found to lower thyroid peroxidase auto-antibodies' levels in patients with chronic autoimmune thyroiditis [83].

Nonetheless, when iodine intake is insufficient, selenium supplementation may be counterproductive. Restoring adequate iodine levels before administering selenium supplements is crucial to prevent the unintended depletion of iodinated thyroid hormones. Lastly, in cases of mild iodine deficiency, the increased iodine intake can reveal the underlying selenium deficiency [20].

3.3 Selenium's role in reproduction

In males, selenium plays a vital role in testosterone biosynthesis and the formation of healthy spermatozoa. The testes have a unique receptor known as the Sertoli cell apolipoprotein E receptor 2 (ApoER2) to uptake SelP [84]. That said, SelP transports selenium to support GPx4 biosynthesis and was found to be secreted into seminal plasma, suggesting a protective role during sperm storage and transit through the genital tract. In like manner, studies have shown a positive correlation between seminal plasma selenium levels and sperm quality, concentration, motility, and fertility. GPx4 serves a dual purpose in sperm development. In the early stages, it acts as a peroxidase, protecting developing sperm cells from oxidative damage. In mature sperm, GPx4 forms cross-links through intramolecular selenenyl-sulfide bridges with midpiece proteins, becoming a structural component of the mitochondrial sheath surrounding the flagellum and essential for sperm stability and motility [85]. Furthermore, GPx6 was also located on the sperm head, probably to prevent premature capacitation of the sperm [86]. Unfortunately, selenium deficiency can result in structural abnormalities, especially in the midpiece. This hampers motility and increases the risk of tail breakage, reducing fertilization capacity. In a study, supplementation with selenium (100 μ g daily for 3 months) has significantly improved sperm motility, with 11% of participants achieving paternity. However, excessive selenium intake (around 300 μ g per day) has been found to decrease sperm motility [37].

For females, selenium's antioxidative properties are vital during oocyte development and fertilization by combating oxidative stress and environmental pollutants. What's more, selenium regulates the development of granulosa cells during folliculogenesis and promotes the production of 17β -estradiol, an essential female sex hormone [87]. Studies have shown that lower levels of selenium in serum and follicular fluid are associated with increased rates of female infertility. Additionally, selenium supplementation supported oocyte growth and enhanced cell proliferation in both theca and granulosa cells, contributing to overall reproductive health [10].

Over and above that, selenium plays a pivotal role in pregnancy by supporting both maternal and fetal health. Selenium can cross the placental barrier, offering

antioxidant protection to the fetus. Preeclampsia, a complication affecting about 3% of pregnancies, is characterized by maternal oxidative stress and systemic inflammation. It was found that selenoproteins may help alleviate these symptoms by reducing oxidative and endoplasmic reticulum stress, as well as inflammation. Selenoproteins also regulate eicosanoid production and control vascular tone. Selenium deficiency exacerbates preeclampsia as the increased ROS triggers the release of placental factors that promote inflammatory responses, causing placental ischemia-reperfusion injury [23, 88]. A study indicated that SelS, known for its anti-inflammatory properties, mitigates these effects by having a role in managing endoplasmic reticulum and oxidative stress, highlighting its potential to reduce preeclampsia risk [89]. Moreover, lipid peroxidation is implicated in the development of postnatal depression, and as pregnancy progresses, maternal selenium levels naturally decrease, lowering GPxs. This reduction may increase the risk of postnatal depression, and research shows that selenium supplementation reduces this risk. Even more, low selenium levels are reported to cause early pregnancy loss, infertility, miscarriage, and placental retention [8].

During development, Se is delivered to the fetus and infant through the placenta, colostrum, and breast milk [10]. For instance, the role of GPx4 in preventing lipid peroxidation is crucial for early embryo development. In studies with mice, embryonic lethality was observed when the genes encoding GPx4, TrxR1, TrxR2, SelT, and SeCys-tRNA were knocked out [12]. Additionally, the expression of DOI2 reaches its peak in skeletal muscles just after birth and then decreases in the postnatal period. Regardless, DOI2 activity increases in muscles following an injury [80]. Selenium also protects bone mineral density and the nervous and muscular systems. For example, GPx4 protects interneurons from ferroptosis [90], while mutations in the SelN gene have been linked to muscular disorders, such as rigid spine syndrome [91]. On the bright side, some studies have indicated that selenium supplementation helps mice regenerate wasted muscle.

Beyond its essential role in reproduction and development, selenium also mitigates heavy metals' toxicity. This is accomplished by forming insoluble selenides with heavy metals, such as mercury, cadmium, and lead, which can contaminate food and pose risks to human health. Hence, Se provides a protective benefit; some manufacturers are incorporating this advantage into their nutraceuticals [92]. This also calls for reconsidering advices given to pregnant and lactating women to avoid seafood due to heavy metal exposure concerns, despite seafood's valuable source of essential nutrients, including omega-3 fatty acids, high-quality protein, vitamins, and minerals such as selenium, all of which are critical for fetal and neonatal development, especially the brain and eyes. Instead, they should be encouraged to consume safe, low-mercury seafood since Se can potentially mitigate toxicity. Furthermore, an adequate intake of selenium, alongside iodine from seafood, can effectively protect mothers, fetuses, and newborns from potential damage to their brains and thyroids. A study highlighted that deficiencies in both iodine and selenium might worsen myxedematous congenital hypothyroidism [20, 93].

3.4 Selenium and immune function

Innate and adaptive immunity are two fundamental components of the immune system, each with distinct roles in defending the body against pathogens. Innate immunity is the body's first line of defense, providing a rapid, non-specific response that activates immediately or within hours of detecting an antigen. Meanwhile,

adaptive immunity develops more gradually, offering a specific tailored response to the pathogen, ensuring long-lasting protection, and providing immunological memory [94]. Studies indicate that selenium significantly impacts both innate and adaptive immunity. A selenium deficiency can impair innate immunity, leading to increased susceptibility to bacterial infections, such as *Listeria monocytogenes* [95]. In terms of adaptive immunity, selenium enhances immune responses by aiding the activation and function of T- and B cells. Additionally, it promotes the proliferation and differentiation of CD4+ T-helper cells and boosts the production of IgM (immunoglobulin M) and IgG (immunoglobulin G) immunoglobulins [12, 96]. An intriguing study showed that SelK functions as an immunoglobulin gatekeeper, ensuring proper quality control within the endoplasmic reticulum. The knockout studies have demonstrated that selenium-deficient mice are more prone to producing non-functional immunoglobulins [97]. Similarly, research on SelK knockout mice demonstrated a 50% reduction in immune cell functions when their immune system was challenged. The authors attributed this phenomenon to SelK's role as a cofactor that facilitates calcium flux during immune cell activation. SelK performs this function by forming a complex with the enzyme DHHC6 (zinc finger DHHC-type palmitoyltransferase 6), stabilizing the enzyme's acylated intermediate and preventing its hydrolysis [98, 99]. Furthermore, activated T cells exhibit increased activity of selenophosphate synthetase, which is essential for synthesizing SeCys and selenoproteins. As discussed, selenoproteins are vital in managing oxidative stress and ROS. Hence, T cells lacking selenophosphate synthetase struggle to proliferate when stimulated through their T-cell receptors, as they become more vulnerable to oxidative stress. Moreover, suppressor T lymphocytes cannot effectively inhibit interleukin-2 (IL-2) production without selenoproteins. This dysregulation can lead to the activation of autoreactive T lymphocytes, increasing the risk of autoimmunity [79].

Supplementation has notable immunostimulatory effects, even in individuals with adequate selenium levels. Research shows that supplementation leads to a significant increase in cytotoxic lymphocyte-mediated tumor cytotoxicity (up to 118%) and natural killer (NK) cell activity (up to 82%) compared to baseline levels. This enhancement was theorized to occur because selenium increases IL-2 receptor expression on activated lymphocytes and NK cells, thereby facilitating their interaction with IL-2 [13, 100].

Not only that, but selenium deficiency has also been associated with certain viruses' progression, virulence, and occurrence. A study involving 45 adults from the UK with relatively low selenium levels found that supplementation with selenium (50 and 100 µg daily as sodium selenite) led to faster clearance of an oral, live, attenuated poliovirus compared to those receiving a placebo [101]. To add, studies on GPx1 knockout mice have shown that selenium is crucial in preventing oxidative stress in RNA viral genomes. This oxidative damage can lead to coxsackievirus mutations, making it virulent and causing myocardial complications [12, 102]. Furthermore, some viruses exploit the host's selenium supply by incorporating it into their viral selenoproteins, impairing the host's immune response. Examples include poxviruses, HIV-1 and 2 (human immunodeficiency virus types 1 and 2), coxsackievirus, Hepatitis B and C, and measles [13]. Still, maintaining adequate selenium levels can bolster cellular immunity, reduce apoptosis, and enhance the host's resistance to viral replication.

Selenium protects against the progression of Hepatitis B and C to liver cancer. Moreover, HIV progression shimmers Se's impact on immunity as Se can minimize hospitalizations and reduce HIV morbidity. It is well documented that Se inhibits HIV

replication and progression by indirectly increasing cluster of differentiation 4 (CD4) counts. In the same vein, low plasma selenium levels ($\leq 85 \mu\text{g/L}$) are associated with reduced CD4 T-cell counts [12, 37]. A progressive decline in plasma selenium mirrors the continued loss of CD4 T cells during HIV-1 infection. Consequently, low plasma selenium levels pose a greater mortality risk than low helper T-cell counts [103].

Surprisingly, selenium's importance extends to conditions like tuberculosis. It was reported that tuberculosis patients have lower selenium levels than healthy controls, and those with concurrent HIV infection exhibit even greater selenium deficiencies [104]. This deficiency led to heightened wasting and disease severity. Moreover, as discussed before, supplementation reduces thyroid peroxidase auto-antibodies, lowering the risk of autoimmune thyroiditis.

Serendipitously, selenium modulates inflammatory responses. It has been shown to promote the shift of macrophages from a pro-inflammatory (M1) state to an anti-inflammatory (M2) state. This helps parasitic infections' elimination through cyclooxygenase-dependent 15-Deoxy- $\Delta^{-12,14}$ -prostaglandin J2 (15d-PGJ2) generation and M2-mediated clearance [105, 106]. Additionally, studies involving *Staphylococcus aureus* revealed that higher levels of selenium enhance macrophage phagocytic activity, boost nitric oxide production, and improve bacterial killing capacity [107]. Lastly, selenium supplementation has also improved the efficacy of vaccines like the poliovirus vaccine, while others, such as influenza vaccines, had mixed outcomes [12].

4. Biomarkers, environmental contamination, analysis, and remediation

Se nutritional status is evaluated using various biomarkers, including hair, plasma, serum, erythrocytes, and whole blood. Each marker provides different insights, depending on whether the focus is on short-term or long-term intake and their susceptibility to external influences. Serum and plasma Se primarily reflect short-term intake because they respond rapidly to recent dietary changes. However, they saturate early during supplementation, limiting their reliability for assessing long-term status. In contrast, erythrocyte Se is a more dependable long-term marker. Erythrocytes' long lifespan minimizes the influence of external factors and shows a stronger correlation with selenium levels in tissues and organs. Hair Se is also used to evaluate long-term intake due to the ease of sample collection, transport, and storage. Despite this, hair Se has notable limitations: it is susceptible to environmental factors and contamination, lags behind dietary changes due to slow hair growth, and may be impractical when participants hesitate to provide samples. Whole blood Se concentrations offer a more comprehensive assessment, reflecting both short- and long-term Se status, making it a more reliable marker than serum, plasma, or hair alone. Another key indicator is GPxs because GPxs activity decreases during Se deficiency but recovers rapidly following supplementation, making it a reliable marker for Se status and the body's antioxidant capacity. Notably, GPxs levels plateau after approximately 4 weeks of supplementation, signaling the attainment of optimal Se levels and a state of nutritional balance. This plateau highlights the GPxs ability to guide supplementation strategies and ensure appropriate intake [13, 17, 108, 109].

Environmental contamination by selenium (Se) stems from natural and anthropogenic sources, posing significant threats to ecosystems and humans. Natural sources encompass volcanic eruptions and the weathering of rocks. At the same time, human endeavors include metallurgy, mining, coal combustion, oil refineries, agricultural

drainage, and the manufacture of pesticides, electronics, and glass. This discharge of selenium-laden waste has led to deformities and mortality in fish inhabiting nearby lakes [2, 3, 8]. Se overconsumption and tolerable upper intake levels for humans have been discussed previously. Notably, the US EPA has established a maximum contaminant level of 50 µg/L (parts per billion (ppb)) for total selenium in drinking water [110].

Several techniques are employed for its quantitative analysis. These include atomic absorption and atomic fluorescence spectroscopy and various X-ray-based methods, such as X-ray absorption and X-ray fluorescence spectroscopy. Other analytical techniques include inductively coupled plasma spectrometry, neutron activation analysis, gas chromatography, and derivatization coupled with ultraviolet (UV) or fluorescence spectroscopy. Electroanalytical methods, such as stripping and square-wave voltammetry, have also proven efficient. In the environment, toxic species Se(IV) and Se(VI) are of particular concern due to their high mobility, bioavailability, and bioaccumulation. Of these, Se(IV) is considered more hazardous. On the one hand, Se(IV) concentration is usually measured when a sample is analyzed without pretreatment. On the other hand, Se(VI) must first be reduced to Se(IV) to determine the total inorganic selenium content. This reduction is achieved through high-temperature treatment with reducing agents, such as hydrochloric acid (HCl) and sodium borohydride (NaBH₄). NaBH₄ is the most used reducing agent because only Se(IV) can form hydrides among the various selenium species, reducing interference. Furthermore, in the case of samples containing Se(II), oxidation of Se(II) to Se(IV) can be achieved using 0.04 M potassium peroxodisulfate solution in HCl [7, 111].

Soil and groundwater remediation can be broadly classified into two main approaches: ex situ and in situ. Ex situ methods involve removing contaminated areas for treatment at a different location, whereas in situ techniques focus on cleaning the contaminants directly at their source [2]. The in situ approach is generally preferred because it is cost-effective. One notable technique is Bioremediation, which utilizes microorganisms, such as fungi, bacteria, and yeast, to reduce selenium's toxic form, Se(VI) and Se(IV), to less harmful elemental selenium. For example, bacteria like *Pseudomonas aeruginosa* have demonstrated potential for detoxifying Se [112]. In addition to bioremediation, plant-based techniques such as phytoremediation are also employed. Phytoremediation, a green biotechnology approach, relies on specific plant species capable of extracting or neutralizing toxic elements from the soil. Selenium hyperaccumulator plants, such as *Stanleya* species, are particularly effective in this process [113]. Another promising avenue for addressing selenium contamination is using biosynthesized nanoparticles. Nanoscale zero-valent iron (nZVI) has shown significant effectiveness in remediating contaminated soil and groundwater [114]. Recently, researchers have found that coupling nZVI with weak magnetic fields enhances the reactivity of these nanoparticles and improves remediation efficiency [115]. Furthermore, Adsorption techniques using activated carbon and nanomaterials have been extensively studied to remove Se(IV) and Se(VI). These processes are highly dependent on pH levels, where membranes modified with nanomaterials have demonstrated improved water permeability and resistance to contamination, enhancing wastewater treatment. Another emerging technique is Electro-coagulation, which employs electric currents to generate coagulants in situ. Generally, electrokinetic techniques that utilize electric fields and reactive barriers to facilitate Se removal are applied as complementary methods to any mentioned technique, particularly in contaminated soils with low hydraulic conductivity [2].

5. Conclusion

Selenium impacts development, reproduction, human health, and the environment. Initially regarded as a toxic element, its vitality has shone more over the years, highlighting the critical role of selenoproteins. These include antioxidant, anti-inflammatory, neuroprotective, and immunostimulatory effects. However, Se has a narrow intake window, and its intake can vary widely due to multiple factors. Several biomarkers, remediation, and analysis techniques have been developed to tackle any potential circumstances. The chapter provided a comprehensive selenium journey by weaving scientific insights with practical considerations. This approach invites curiosity and paves the way for further research in this enigmatic area.

Conflict of interest

The authors declare no financial or personal conflict of interest.

Abbreviations

GPxs	glutathione peroxidases
HCl	hydrochloric acid
DIOs	iodothyronine deiodinases
IL-2	interleukin-2
nZVI	nanoscale zero-valent iron
NK	natural killer
ROS	reactive oxygen species
Se	selenium
SeCys	selenocysteine
SeMet	selenomethionine
Se(IV)	selenite
Se(VI)	selenate
Se(II)	selenide
SECIS	selenocysteine Insertion Sequence
SBP2	SECIS-binding protein 2
EFSeCys	selenocysteine's specific elongation factor
SEPHS2	selenophosphate synthetase 2
SEPSECS	selenocysteine synthase
NaBH ₄	sodium borohydride
TrxRs	thioredoxin reductases

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References

- [1] Hariharan S, Dharmaraj S. Selenium and selenoproteins: it's role in regulation of inflammation. *Inflammopharmacology*. 2020;**28**(3):667-695
- [2] Ullah H, Lun L, Rashid A, Zada N, Chen B, Shahab A, et al. A critical analysis of sources, pollution, and remediation of selenium, an emerging contaminant. *Environmental Geochemistry and Health*. 2023;**45**(5):1359-1389
- [3] Ullah H, Liu G, Yousaf B, Ali MU, Irshad S, Abbas Q, et al. A comprehensive review on environmental transformation of selenium: Recent advances and research perspectives. *Environmental Geochemistry and Health*. 2019;**41**(2):1003-1035
- [4] Meija J, Coplen TB, Berglund M, Brand WA, De Bièvre P, Gröning M, et al. Isotopic compositions of the elements 2013 (IUPAC technical report). *Pure and Applied Chemistry*. 2016;**88**(3):293-306
- [5] Xu X-M, Carlson BA, Mix H, Zhang Y, Saira K, Glass RS, et al. Biosynthesis of selenocysteine on its tRNA in eukaryotes. *PLoS Biology*. 2007;**5**(1):e4
- [6] Labunsky VM, Hatfield DL, Gladyshev VN. Selenoproteins: Molecular pathways and physiological roles. *Physiological Reviews*. 2014;**94**(3):739-777
- [7] Minich WB. Selenium metabolism and biosynthesis of Selenoproteins in the human body. *Biochemistry (Moscow)*. 2022;**87**(1):S168-SS77
- [8] Bodnar M, Konieczka P, Namiesnik J. The properties, functions, and use of selenium compounds in living organisms. *Journal of Environmental Science and Health, Part C*. 2012;**30**(3):225-252
- [9] Nogueira CW, Rocha JBT. Toxicology and pharmacology of selenium: Emphasis on synthetic organoselenium compounds. *Archives of Toxicology*. 2011;**85**(11):1313-1359
- [10] Kieliszek M, Bano I. Selenium as an important factor in various disease states - A review. *EXCLI Journal*. 2022;**21**:948-966
- [11] Duntas LH, Benvenga S. Selenium: An element for life. *Endocrine*. 2015;**48**(3):756-775
- [12] Avery JC, Hoffmann PR. Selenium, Selenoproteins, and immunity. *Nutrients*. 2018;**10**(9):1203
- [13] Rayman MP. The importance of selenium to human health. *The Lancet*. 2000;**356**(9225):233-241
- [14] Reilly C. *Selenium in Food and Health*. New York, United States: Springer; 1996
- [15] Hidirolou M. Trace element deficiencies and fertility in ruminants: A review. *Journal of Dairy Science*. 1979;**62**(8):1195-1206
- [16] Li C. Selenium deficiency and endemic heart failure in China: A case study of biogeochemistry for human health. *Ambio*. 2007;**36**(1):90-93
- [17] Lv C, Wang R, Zeng Q, Feng C, Li G, Hao S, et al. Erythrocyte selenium as a potential key indicator for selenium supplementation in low-selenium populations: A selenium supplementation study based on Wistar rats. *Nutrients*. 2024;**16**(22):3797

- [18] Kieliszek M, Błażej S. Current knowledge on the importance of selenium in food for living organisms: A review. *Molecules*. 2016;**21**(5):609
- [19] Kolachi NF, Kazi TG, Wadhwa SK, Afridi HI, Baig JA, Khan S, et al. Evaluation of selenium in biological sample of arsenic exposed female skin lesions and skin cancer patients with related to non-exposed skin cancer patients. *Science of the Total Environment*. 2011;**409**(17):3092-3097
- [20] Köhrle J. Selenium, iodine and iron—essential trace elements for thyroid hormone synthesis and metabolism. *International Journal of Molecular Sciences*. 2023;**24**(4):3393
- [21] Barrington J, Lindsay P, James D, Smith S, Roberts A. Selenium deficiency and miscarriage: A possible link? *BJOG: An international. Journal of Obstetrics and Gynaecology*. 1996;**103**(2):130-132
- [22] Stuart L, Oehme F. *Environmental Factors in Bovine and Porcine Abortion*. Manhattan, KS, USA: American College of Veterinary Toxicologists; 1982
- [23] Mistry HD, Broughton Pipkin F, Redman CWG, Poston L. Selenium in reproductive health. *American Journal of Obstetrics and Gynecology*. 2012;**206**(1):21-30
- [24] Barrington JW, Taylor M, Smith S, Bowen-Simpkins P. Selenium and recurrent miscarriage. *Journal of Obstetrics and Gynaecology*. 1997;**17**(2):199-200
- [25] Berr C, Balansard B, Arnaud J, Roussel AM, Alpérovitch A, Group ES. Cognitive decline is associated with systemic oxidative stress: The EVA study. *Journal of the American Geriatrics Society*. 2000;**48**(10):1285-1291
- [26] Ramaekers VT, Calomme M, Berghe DV, Makropoulos W. Selenium deficiency triggering intractable seizures. *Neuropediatrics*. 1994;**25**(04):217-223
- [27] Shayganfard M. Are essential trace elements effective in modulation of mental disorders? Update and perspectives. *Biological Trace Element Research*. 2022;**200**(3):1032-1059
- [28] Nettleford SK, Prabhu KS. Selenium and selenoproteins in gut inflammation—A review. *Antioxidants*. 2018;**7**(3):36
- [29] Zhang Z, Gao X, Cao Y, Jiang H, Wang T, Song X, et al. Selenium deficiency facilitates inflammation through the regulation of TLR4 and TLR4-related signaling pathways in the mice uterus. *Inflammation*. 2015;**38**:1347-1356
- [30] Gao X, Zhang Z, Li Y, Shen P, Hu X, Cao Y, et al. Selenium deficiency facilitates inflammation following *S. Aureus* infection by regulating TLR2-related pathways in the mouse mammary gland. *Biological Trace Element Research*. 2016;**172**:449-457
- [31] Letavayová L, Vlasáková D, Spallholz JE, Brozmanová J, Chovanec M. Toxicity and mutagenicity of selenium compounds in *Saccharomyces cerevisiae*. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*. 2008;**638**(1-2):1-10
- [32] Hassoun BS, Palmer IS, Dwivedi C. Selenium detoxification by methylation. *Research Communications in Molecular Pathology and Pharmacology*. 1995;**90**(1):133-142
- [33] Navarro-Alarcon M, Cabrera-Vique C. Selenium in food and the human body: A review. *Science of the Total Environment*. 2008;**400**(1-3):115-141

- [34] Sutter ME, Thomas JD, Brown J, Morgan B. Selenium toxicity: A case of selenosis caused by a nutritional supplement. *Annals of Internal Medicine*. 2008;**148**(12):970-971
- [35] Nazemi L, Nazmara S, Eshraghy MR, Nasseri S, Djafarian K, Yunesian M, et al. Selenium status in soil, water and essential crops of Iran. *Iranian Journal of Environmental Health Science and Engineering*. 2012;**9**:1-8
- [36] Tinggi U. Essentiality and toxicity of selenium and its status in Australia: A review. *Toxicology Letters*. 2003;**137**(1-2):103-110
- [37] Rayman MP. Selenium and human health. *The Lancet*. 2012;**379**(9822):1256-1268
- [38] MacFarquhar JK, Broussard DL, Melstrom P, Hutchinson R, Wolkin A, Martin C, et al. Acute selenium toxicity associated with a dietary supplement. *Archives of Internal Medicine*. 2010;**170**(3):256-261
- [39] Fordyce F. Selenium geochemistry and health. *Ambio*. 2007;**36**(1):94-97
- [40] Fairweather-Tait SJ, Collings R, Hurst R. Selenium bioavailability: Current knowledge and future research requirements. *The American Journal of Clinical Nutrition*. 2010;**91**(5):1484S-1491S
- [41] Ježek P, Škarpa P, Lošák T, Hlušek J, Jůzl M, Elzner P. Selenium—an important antioxidant in crops biofortification. In: *Antioxidant Enzyme*. London, UK: IntechOpen Limited; 2012. pp. 343-368
- [42] Peters KM, Galinn SE, Tsuji PA. Selenium: Dietary sources, human nutritional requirements and intake across populations. In: Hatfield DL, Schweizer U, Tsuji PA, Gladyshev VN, editors. *Selenium: Its Molecular Biology and Role in Human Health*. Cham: Springer International Publishing; 2016. pp. 295-305
- [43] Combs GF. Selenium in global food systems. *British Journal of Nutrition*. 2001;**85**(5):517-547
- [44] Finley JW. Bioavailability of selenium from foods. *Nutrition Reviews*. 2006;**64**(3):146-151
- [45] Haug A, Graham RD, Christophersen OA, Lyons GH. How to use the world's scarce selenium resources efficiently to increase the selenium concentration in food. *Microbial Ecology in Health and Disease*. 2007;**19**(4):209-228
- [46] Thiry C, Ruttens A, Pussemier L, Schneider Y-J. An in vitro investigation of species-dependent intestinal transport of selenium and the impact of this process on selenium bioavailability. *British Journal of Nutrition*. 2013;**109**(12):2126-2134
- [47] Kobayashi Y, Ogra Y, Ishiwata K, Takayama H, Aimi N, Suzuki KT. Selenosugars are key and urinary metabolites for selenium excretion within the required to low-toxic range. *National Academy of Sciences of the United States of America*. 2002;**99**(25):15932-15936
- [48] Valian N. Putative role of trace elements deficiency in psychiatric disorders including depression. In: Mohamed W, Sandhir R, editors. *Trace Elements in Brain Health and Diseases*. Singapore: Springer Nature Singapore; 2023. pp. 71-93
- [49] (WHO) WHO. Guidelines for Drinking-Water Quality, 4th ed. 2022. Available from: <https://cdn.who.int/media/docs/default-source/>

wash-documents/water-safety-and-quality/chemical-fact-sheets-2022/selenium-fact-sheet-2022.pdf?sfvrsn=5b4dcc7b_2&download=true

[50] Intakes SCotSEoDR, Interpretation So, Intakes UoDR, Nutrients SoURLo, Antioxidants PoD, Compounds R. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington, D.C., United States: National Academies Press; 2000

[51] EFSA Panel on Dietetic Products N, Allergies. Scientific opinion on dietary reference values for selenium. *EFSA Journal*. 2014;**12**(10):3846

[52] Fan AM, Vinceti M. Selenium and its compounds. Hamilton and Hardy's Industrial Toxicology. Hoboken, New Jersey, United States: John Wiley & Sons, Inc.; 2015. pp. 205-228. Print ISBN: 9780470929735 | Online ISBN: 9781118834015

[53] Kryukov GV, Castellano S, Novoselov SV, Lobanov AV, Zehtab O, Guigó R, et al. Characterization of mammalian selenoproteomes. *Science*. 2003;**300**(5624):1439-1443

[54] Kasaikina MV, Hatfield DL, Gladyshev VN. Understanding selenoprotein function and regulation through the use of rodent models. *Biochimica et Biophysica Acta (BBA) – Molecular Cell Research*. 2012;**1823**(9):1633-1642

[55] Zhang X, Xiong W, Chen L-L, Huang J-Q, Lei XG. Selenoprotein V protects against endoplasmic reticulum stress and oxidative injury induced by pro-oxidants. *Free Radical Biology and Medicine*. 2020;**160**:670-679

[56] Consortium U. UniProt: A worldwide hub of protein knowledge. *Nucleic Acids Research*. 2019;**47**(D1):D506-DD15

[57] Gladyshev VN, Arnér ES, Berry MJ, Brigelius-Flohé R, Bruford EA, Burk RF, et al. Selenoprotein Gene Nomenclature *. *Journal of Biological Chemistry*. 2016;**291**(46):24036-24040

[58] Zhao Q, Zhang L, Wang Y, Sun Y, Wang T, Cao J, et al. A bioinformatic analysis: The overexpression and prognostic potential of GPX7 in lower-grade glioma. *International Journal of General Medicine*. 2022;**15**:4321-4337

[59] Schwarz M, Meyer CE, Löser A, Lossow K, Hackler J, Ott C, et al. Excessive copper impairs intrahepatocyte trafficking and secretion of selenoprotein P. *Nature Communications*. 2023;**14**(1):3479

[60] Zachara BA. Mammalian selenoproteins. *Journal of Trace Elements and Electrolytes in Health and Disease*. 1992;**6**(3):137-151

[61] Lamarche J, Ronga L, Szpunar J, Lobinski R. Characterization and quantification of selenoprotein P: Challenges to mass spectrometry. *International Journal of Molecular Sciences*. 2021;**22**(12):6283

[62] Suzuki KT. Metabolomics of selenium: Se metabolites based on speciation studies. *Journal of Health Science*. 2005;**51**(2):107-114

[63] Böck A, Forchhammer K, Heider J, Leinfelder W, Sawers G, Veprek B, et al. Selenocysteine: The 21st amino acid. *Molecular Microbiology*. 1991;**5**(3):515-520

[64] Seyedali A, Berry MJ. Nonsense-mediated decay factors are involved in the regulation of selenoprotein mRNA levels during selenium deficiency. *RNA*. 2014;**20**(8):1248-1256

[65] Lin H-C, Yeh C-W, Chen Y-F, Lee T-T, Hsieh P-Y, Rusnac DV, et al. C-terminal

end-directed protein elimination by CRL2 ubiquitin ligases. *Molecular Cell*. 2018;**70**(4):602-613 e3

[66] Burk RF, Hill KE. Regulation of selenium metabolism and transport. *Annual Review of Nutrition*. 2015;**35**(2015):109-134

[67] Yuan J, Palioura S, Salazar JC, Su D, O'Donoghue P, Hohn MJ, et al. RNA-dependent conversion of phosphoserine forms selenocysteine in eukaryotes and archaea. *National Academy of Sciences of the United States of America*. 2006;**103**(50):18923-18927

[68] Seale LA. Selenocysteine β -lyase: Biochemistry, regulation and physiological role of the selenocysteine decomposition enzyme. *Antioxidants*. 2019;**8**(9):357

[69] Patterson BH, Combs GF Jr, Taylor PR, Patterson KY, Moler JE, Wastney ME. Selenium kinetics in humans change following 2 years of supplementation with selenomethionine. *Frontiers in Endocrinology*. 2021;**12**:621687

[70] Thomson CD, Robinson MF, Butler JA, Whanger PD. Long-term supplementation with selenate and selenomethionine: Selenium and glutathione peroxidase (EC 1.11. 1.9) in blood components of New Zealand women. *British Journal of Nutrition*. 1993;**69**(2):577-588

[71] Halliwell B, Gutteridge JM. Oxygen radicals and the nervous system. *Trends in Neurosciences*. 1985;**8**:22-26

[72] Takemoto AS, Berry MJ, Bellinger FP. Role of selenoprotein P in Alzheimer's disease. *Ethnicity and Disease*. 2010;**20**(1 Suppl 1):S1

[73] Li N, Zhang Z, Shen L, Song G, Tian J, Liu Q, et al. Selenium metabolism

and selenoproteins function in brain and encephalopathy. *Science China Life Sciences*. 2025;**68**:628-656

[74] Chau EJ, Mostaid MS, Cropley V, McGorry P, Pantelis C, Bousman CA, et al. Downregulation of plasma SELENBP1 protein in patients with recent-onset schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2018;**85**:1-6

[75] Ramos P, Santos A, Pinto NR, Mendes R, Magalhães T, Almeida A. Anatomical regional differences in selenium levels in the human brain. *Biological Trace Element Research*. 2015;**163**:89-96

[76] Contempre B, Le Moine O, Dumont JE, Denef J-F, Many M-C. Selenium deficiency and thyroid fibrosis. A key role for macrophages and transforming growth factor β (TGF- β). *Molecular and Cellular Endocrinology*. 1996;**124**(1-2):7-15

[77] Guadaño-Ferraz A, Obregón MJ, Germain DLS, Bernal J. The type 2 iodothyronine deiodinase is expressed primarily in glial cells in the neonatal rat brain. *National Academy of Sciences of the United States of America*. 1997;**94**(19):10391-10396

[78] Köhrle J. Selenium and the control of thyroid hormone metabolism. *Thyroid*. 2005;**15**(8):841-853

[79] Brtko J, Podoba J, Macejova D. Selenium-its role in physiology and endocrinology and as organoselenium compounds in oncology: A minireview. *Endocrine Regulations*. 2024;**58**(4):233-241

[80] Dentice M, Marsili A, Ambrosio R, Guardiola O, Sibilio A, Paik J-H, et al. The FoxO3/type 2 deiodinase pathway is required for normal mouse

myogenesis and muscle regeneration. *The Journal of Clinical Investigation*. 2010;**120**(11):4021-4030

[81] Winther KH, Rayman MP, Bonnema SJ, Hegedüs L. Selenium in thyroid disorders—Essential knowledge for clinicians. *Nature Reviews Endocrinology*. 2020;**16**(3):165-176

[82] Marcocci C, Kahaly GJ, Krassas GE, Bartalena L, Prummel M, Stahl M, et al. Selenium and the course of mild Graves' orbitopathy. *New England Journal of Medicine*. 2011;**364**(20):1920-1931

[83] Triggiani V, Tafaro E, Giagulli VA, Sabbà C, Resta F, Licchelli B, et al. Role of iodine, selenium and other micronutrients in thyroid function and disorders. *Endocrine, Metabolic and Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine and Metabolic Disorders)*. 2009;**9**(3):277-294

[84] Olson GE, Winfrey VP, NagDas SK, Hill KE, Burk RF. Apolipoprotein E receptor-2 (ApoER2) mediates selenium uptake from selenoprotein P by the mouse testis. *Journal of Biological Chemistry*. 2007;**282**(16):12290-12297

[85] Ursini F, Heim S, Kiess M, Maiorino M, Roveri A, Wissing J, et al. Dual function of the selenoprotein PHGPx during sperm maturation. *Science*. 1999;**285**(5432):1393-1396

[86] Chen Y, Wang K, Zhang D, Zhao Z, Huang J, Zhou L, et al. GPx6 is involved in the in vitro induced capacitation and acrosome reaction in porcine sperm. *Theriogenology*. 2020;**156**:107-115

[87] Mojadadi A, Au A, Salah W, Witting P, Ahmad G. Role for selenium in metabolic homeostasis and human reproduction. *Nutrients*. 2021;**13**(9):3256

[88] Rayman MP. Selenium and adverse health conditions of human pregnancy. In: *Selenium: Its Molecular Biology and Role in Human Health*. Guildford, Surrey, England: Springer; 2011. pp. 531-544

[89] Moses EK, Johnson MP, Tømmerdal L, Forsmo S, Curran JE, Abraham LJ, et al. Genetic association of preeclampsia to the inflammatory response gene SEPS1. *American Journal of Obstetrics and Gynecology*. 2008;**198**(3):336.e1.e5

[90] Ingold I, Berndt C, Schmitt S, Doll S, Poschmann G, Buday K, et al. Selenium utilization by GPX4 is required to prevent hydroperoxide-induced ferroptosis. *Cell*. 2018;**172**(3):409-422 e21

[91] Ferreira A, Quijano-Roy S, Pichereau C, Moghadasadeh B, Goemans N, Bönnemann C, et al. Mutations of the selenoprotein N gene, which is implicated in rigid spine muscular dystrophy, cause the classical phenotype of multiminicore disease: Reassessing the nosology of early-onset myopathies. *The American Journal of Human Genetics*. 2002;**71**(4):739-749

[92] Al-Omairi M, Alamir SG, Salman BI, El Deeb S, Alrashdi YBA, Al-Harrasi A, et al. Investigating trace and macro-element composition of herbal and nutraceutical dietary supplements marketed in Oman: Insights into safety and labeling. *Biological Trace Element Research*. 2024. DOI: 10.1007/s12011-024-04343-w

[93] Ralston NVC. Selenium health benefit values as seafood safety criteria. *EcoHealth*. 2008;**5**(4):442-455

[94] Hoebe K, Janssen E, Beutler B. The interface between innate and adaptive immunity. *Nature Immunology*. 2004;**5**(10):971-974

[95] Wang C, Wang H, Luo J, Hu Y, Wei L, Duan M, et al. Selenium

deficiency impairs host innate immune response and induces susceptibility to listeria monocytogenes infection. *BMC Immunology*. 2009;**10**:1-12

[96] Xia X, Zhang X, Liu M, Duan M, Zhang S, Wei X, et al. Toward improved human health: Efficacy of dietary selenium on immunity at the cellular level. *Food and Function*. 2021;**12**(3):976-989

[97] Yim SH, Everley RA, Schildberg FA, Lee S-G, Orsi A, Barbati ZR, et al. Role of Selenof as a gatekeeper of secreted disulfide-rich glycoproteins. *Cell Reports*. 2018;**23**(5):1387-1398

[98] Verma S, Hoffmann FW, Kumar M, Huang Z, Roe K, Nguyen-Wu E, et al. Selenoprotein K knockout mice exhibit deficient calcium flux in immune cells and impaired immune responses. *The Journal of Immunology*. 2011;**186**(4):2127-2137

[99] Fredericks GJ, Hoffmann FW, Hondal RJ, Rozovsky S, Urschitz J, Hoffmann PR. Selenoprotein K increases efficiency of DHHC6 catalyzed protein palmitoylation by stabilizing the acyl-DHHC6 intermediate. *Antioxidants*. 2017;**7**(1):4

[100] Kiremidjian-Schumacher L, Roy M, Wishe HI, Cohen MW, Stotzky G. Supplementation with selenium and human immune cell functions: II. Effect on cytotoxic lymphocytes and natural killer cells. *Biological Trace Element Research*. 1994;**41**:115-127

[101] Broome CS, McArdle F, Kyle JA, Andrews F, Lowe NM, Hart CA, et al. An increase in selenium intake improves immune function and poliovirus handling in adults with marginal selenium status. *The American journal of clinical nutrition*. 2004;**80**(1):154-162

[102] Beck M, Esworthy R, Ho YS, Chu FF. Glutathione peroxidase protects mice from viral-induced myocarditis. *The FASEB Journal*. 1998;**12**(12):1143-1149

[103] Campa A, Shor-Posner G, Indacochea F, Zhang G, Lai H, Asthana D, et al. Mortality risk in selenium-deficient HIV-positive children. *JAIDS Journal of Acquired Immune Deficiency Syndromes*. 1999;**20**(5):508-513

[104] Ramakrishnan K, Shenbagarathai R, Kavitha K, Thirumalaikolundusubramanian P, Rathinasabapati R. Selenium levels in persons with HIV/tuberculosis in India, Madurai City. *Clinical Laboratory*. 2012;**58**(1-2):165-168

[105] Nelson SM, Lei X, Prabhu KS. Selenium levels affect the IL-4–induced expression of alternative activation markers in murine macrophages. *The Journal of Nutrition*. 2011;**141**(9):1754-1761

[106] Nelson SM, Shay AE, James JL, Carlson BA, Urban JF, Prabhu KS. Selenoprotein expression in macrophages is critical for optimal clearance of parasitic helminth *nippostrongylus brasiliensis*. *Journal of Biological Chemistry*. 2016;**291**(6):2787-2798

[107] Aribi M, Meziane W, Habi S, Boulatika Y, Marchandin H, Aymeric J-L. Macrophage bactericidal activities against *Staphylococcus aureus* are enhanced in vivo by selenium supplementation in a dose-dependent manner. *PLoS One*. 2015;**10**(9):e0135515

[108] Sun L, Wang F, Wu Z, Ma L, Baumrucker C, Bu D. Comparison of selenium source in preventing oxidative stress in bovine mammary epithelial cells. *Animals*. 2020;**10**(5):842

[109] Lai C-Y, Cheng S-B, Lee T-Y, Hsiao Y-F, Liu H-T, Huang Y-C. Impact of glutathione and vitamin B-6 in cirrhosis patients: A randomized controlled trial and follow-up study. *Nutrients*. 2020;**12**(7):1978

[110] Singh S, Bashambu L, Devi P, Kansal SK. Chemical methods for removal and treatment of selenium from water. *Selenium Contamination in Water*. Hoboken, New Jersey, United States: John Wiley & Sons Ltd.; 2021. pp. 206-227. Print ISBN: 9781119693451 |Online ISBN: 9781119693567

[111] Pettine M, McDonald TJ, Sohn M, Anquandah GAK, Zboril R, Sharma VK. A critical review of selenium analysis in natural water samples. *Trends in Environmental Analytical Chemistry*. 2015;**5**:1-7

[112] Kora AJ, Rastogi L. Biomimetic synthesis of selenium nanoparticles by *Pseudomonas aeruginosa* ATCC 27853: An approach for conversion of selenite. *Journal of Environmental Management*. 2016;**181**:231-236

[113] Lindblom SD, Fakra SC, Landon J, Schulz P, Tracy B, Pilon-Smits EA. Inoculation of selenium hyperaccumulator *Stanleya pinnata* and related non-accumulator *Stanleya elata* with hyperaccumulator rhizosphere fungi—Investigation of effects on Se accumulation and speciation. *Physiologia Plantarum*. 2014;**150**(1):107-118

[114] Yoon I-H, Kim K-W, Bang S, Kim MG. Reduction and adsorption mechanisms of selenate by zero-valent iron and related iron corrosion. *Applied Catalysis B: Environmental*. 2011;**104**(1-2):185-192

[115] Ullah S, Faiz P, Leng S. Synthesis, mechanism, and performance assessment of zero-valent iron for metal-contaminated water remediation: A review. *Clean—Soil, Air, Water*. 2020;**48**(9):2000080

Section 2

Thyroid Nodules

Recent Advances in the Diagnosis, Pathophysiology, and Management of Thyroid Disorders

Qais Ahmad Naseer and Pan Jianbo

Abstract

Thyroid disorders are among the most prevalent endocrine conditions and have seen significant advances in recent years. Improved diagnostic tools, including high-resolution imaging and molecular assays, now enable more accurate evaluation of thyroid nodules and dysfunction. Refinements in surgical techniques, from minimally invasive procedures to image-guided ablation alongside novel pharmacological therapies, have enhanced treatment outcomes for hyperthyroidism, hypothyroidism, and thyroid cancers. A deeper understanding of the molecular and genetic bases of thyroid diseases is shedding light on pathophysiology, leading to targeted treatments such as kinase inhibitors for advanced thyroid malignancies and biological therapies for autoimmune thyroid conditions. Management approaches for specific disorders have evolved: clinicians now employ risk stratification and even active surveillance for certain low-risk thyroid cancers, individualize therapy for benign thyroid dysfunction, and integrate new drugs for aggressive disease when appropriate. This chapter provides an overview of these recent advances in diagnosis, treatment, and pathophysiological understanding of thyroid disorders and discusses their impact on the clinical management of hyperthyroidism, hypothyroidism, and thyroid cancer. Future directions in research and care, from precision medicine to the role of the microbiome and artificial intelligence, are also explored. These developments promise improved outcomes and more personalized care for patients with thyroid conditions.

Keywords: thyroid disorders, hyperthyroidism, hypothyroidism, thyroid cancer, diagnosis, molecular testing, targeted therapy, pathophysiology

1. Introduction

Thyroid diseases are highly common across the globe, with an increasing clinical impact over the past decades. Thyroid nodules, in particular, are frequently detected; up to an estimated 60% of adults may harbor nodules when examined by high-resolution ultrasound [1]. Fortunately, the vast majority of thyroid nodules are benign; only around 5% are found to be malignant [2]. Despite this low rate of clinically significant disease, the incidence of thyroid cancer diagnosis surged dramatically in recent years

(roughly tripling in many countries) even as mortality remained low and stable [3]. This divergence is largely attributed to overdiagnosis, the detection of very small, slow-growing papillary thyroid carcinomas that might never have caused harm [4]. Widespread use of sensitive imaging has uncovered many subclinical papillary microcarcinomas (often <1 cm), which account for over 60% of the rise in incidence [5]. These epidemiological trends have challenged clinicians to balance the early detection of significant thyroid malignancies with the avoidance of unnecessary interventions for indolent disease. As a result, the management of thyroid disorders has become increasingly nuanced and evidence-based.

Concurrently, thyroid research and clinical practice have advanced on multiple fronts. Diagnostic innovations from improved ultrasound risk stratification systems to molecular cytology tests have bolstered our ability to distinguish benign from malignant thyroid nodules and to detect thyroid dysfunction with greater precision [6]. Therapeutic options for thyroid disorders have expanded beyond traditional surgery and hormone replacement. We have witnessed refinements in surgical techniques (including minimally invasive and scarless approaches), the advent of image-guided ablation therapies for thyroid nodules, and new drugs ranging from second-generation antithyroid medications to targeted kinase inhibitors and immune therapies for aggressive thyroid cancers [7]. Meanwhile, deeper insights into the pathophysiology of thyroid diseases have emerged. Researchers have elucidated key genetic drivers of thyroid cancer, uncovered numerous susceptibility genes for autoimmune thyroid conditions, and even begun to appreciate the role of factors like the gut microbiome in thyroid health [8]. These discoveries pave the way for more tailored and mechanism-based treatments.

This chapter provides a comprehensive overview of these recent advances in thyroid disorders. We first discuss innovations in diagnosis, including state-of-the-art imaging modalities, molecular testing of thyroid nodules, and novel biomarkers. Next, we review improvements in treatment, from surgical and pharmacological advances to novel therapies for benign and malignant thyroid disease. We then describe how new molecular and genetic insights are reshaping our understanding of thyroid pathology. After covering the management updates for specific conditions, hyperthyroidism, hypothyroidism, and thyroid cancer, we consider future perspectives and ongoing research that promise to further transform thyroid care. Through these sections, the chapter aims to inform clinicians and researchers of the cutting-edge developments that are enhancing patient outcomes and guiding the future of thyroid disorder management.

2. Advances in diagnosis

2.1 Imaging innovations for thyroid evaluation

High-resolution ultrasound (US) is the cornerstone of thyroid imaging and has continuously improved in its ability to characterize thyroid lesions. Modern ultrasound devices provide exceptional anatomic detail, allowing detection of nodules only a few millimeters in size. However, the key challenge lies in distinguishing which nodules may be malignant. In this regard, the implementation of standardized risk stratification systems such as the Thyroid Imaging Reporting and Data System (TIRADS) has significantly improved diagnostic accuracy. TIRADS categorization of nodules based on ultrasonographic features (composition, echogenicity, margins,

calcifications, etc.) helps predict malignancy risk and guides the decision for fine-needle aspiration biopsy [9]. Studies have confirmed that using TIRADS or similar scoring systems increases the specificity of ultrasound and reduces unnecessary biopsies while maintaining sensitivity for thyroid cancer detection [10, 11].

Beyond conventional gray-scale and Doppler ultrasound, several novel ultrasound-based techniques have been introduced. One such advance is ultrasound elastography, which measures tissue stiffness [12]. Thyroid cancers are often firmer than benign tissue; elastography (either strain or shear-wave) provides a quantitative stiffness assessment that complements visual ultrasound findings. The addition of elastography has been shown to improve sensitivity and specificity for malignancy when combined with standard ultrasound [13]. Another enhancement is superb microvascular imaging (SMI), an advanced Doppler technique that can depict minute blood flow without needing contrast, thus highlighting the vascular pattern of nodules with greater clarity than conventional Doppler [14]. Similarly, contrast-enhanced ultrasound (CEUS) involves injecting microbubble contrast agents to evaluate nodule perfusion: malignant nodules often show chaotic or rapid contrast uptake and washout patterns distinct from benign lesions [15]. CEUS can thereby improve characterization of indeterminate nodules' vascularity. Researchers have also combined multiple ultrasound modalities (B-mode, Doppler, elastography, etc.) in multiparametric ultrasound (MPUS) approaches to expand the diagnostic spectrum [16]. By synthesizing information on nodule appearance, stiffness, and vascularity, MPUS may provide a more holistic and accurate risk assessment than any single technique alone.

Perhaps one of the most cutting-edge developments in thyroid imaging is the application of artificial intelligence (AI) and machine learning to ultrasound interpretation. Computer-aided diagnostic algorithms have been trained on large ultrasound image datasets to identify patterns associated with malignancy. Early results are promising in some studies, and AI models have matched or even modestly exceeded expert radiologists in diagnostic performance for nodule classification [9]. AI tools can provide real-time decision support by automatically assigning TIRADS categories or malignancy risk scores to scanned nodules. Such systems aim to reduce observer variability and improve accuracy, especially in resource-limited settings or for less experienced operators. While AI in thyroid ultrasound is still being refined, it represents a major future direction for enhancing diagnosis.

In addition to ultrasound, nuclear medicine imaging plays a role in thyroid evaluation, particularly for assessing function and detecting metastatic disease. Established techniques include radioactive iodine uptake scans and scintigraphy (which can differentiate Graves' disease from thyroiditis or identify autonomously functioning nodules). Recent advances in nuclear imaging involve positron emission tomography (PET) and novel tracers. ^{18}F -fluorodeoxyglucose (FDG) PET can incidentally detect hypermetabolic thyroid lesions (so-called "thyroid PET incidentalomas"), some of which prove to be malignant [17]. Investigators are now applying radiomic analysis and machine learning to PET images to improve characterization of these findings [18]. In one systematic review, radiomics/ML methods were applied in 17 studies across various thyroid scenarios, from distinguishing benign versus malignant PET incidentalomas to evaluating indeterminate nodules and even classifying different thyroid diseases on imaging [19, 20]. These advanced computational approaches to nuclear imaging are expanding diagnostic possibilities beyond the human eye. Moreover, new molecular imaging tracers have emerged for specific thyroid cancers. For example, in medullary thyroid carcinoma (a neuroendocrine tumor), PET tracers

like ^{68}Ga -DOTATATE can target somatostatin receptors expressed by the tumor, revealing otherwise occult metastatic foci [21]. Such tracers not only improve the sensitivity of detection but also enable theranostic use (paired diagnostic and therapeutic targeting, discussed later). In summary, imaging advances from enhanced ultrasound techniques and AI integration to sophisticated functional and molecular imaging are markedly improving our ability to diagnose and stratify thyroid disorders.

2.2 Molecular testing and biomarkers in thyroid nodule diagnosis

While imaging is indispensable, definitive diagnosis of thyroid nodules often requires cytological evaluation via fine-needle aspiration (FNA). A significant proportion of FNAs, however, yield indeterminate results (approximately 20–30% fall into Bethesda class III or IV, atypia or follicular lesion of undetermined significance, or follicular neoplasm) [1]. Historically, most patients with indeterminate cytology were referred for diagnostic surgery, yet only a minority (typically 20% or less) proved malignant on final histology [22]. This meant many patients underwent unnecessary thyroidectomies for an ultimately benign disease. A major advance to address this dilemma has been the development of molecular testing for thyroid nodule FNA samples. Over the past decade, molecular diagnostic platforms have emerged as powerful tools to risk-stratify indeterminate thyroid nodules by detecting genetic alterations or expression patterns associated with cancer [23].

Two broad categories of molecular tests are in use. Gene expression classifiers (GEC) analyze the mRNA expression profile of dozens of genes in the FNA specimen to distinguish benign from suspicious nodules. The first such test, a 167-gene classifier, demonstrated high sensitivity and negative predictive value, effectively ruling out malignancy in indeterminate nodules so that surgery could be avoided [23, 24]. In a landmark study, this genomic classifier correctly identified benign nodules with about 90% sensitivity, sparing patients from diagnostic lobectomy in cases where the test called the nodule “benign” [25]. More recent iterations of expression assays have improved specificity as well. On the other hand, mutation panels and sequencing-based tests focus on detecting specific gene mutations, fusions, or other alterations known to drive thyroid cancer (such as point mutations in BRAF or RAS, RET/PTC and PAX8/PPAR γ fusions, and TERT promoter mutations) [26]. Early multi-gene panels tested for a handful of common mutations, whereas newer comprehensive tests (e.g., ThyroSeq v3) use next-generation sequencing to interrogate dozens of genes and hundreds of mutation types [27]. These tests can “rule-in” malignancy by identifying a known oncogenic mutation in an FNA sample, prompting definitive surgery. They can also provide prognostic information; for instance, identifying an aggressive mutation like BRAF $^{\text{V600E}}$ or TERT mutation may influence the extent of surgery and subsequent therapy [28].

Molecular testing has quickly moved from research into routine clinical practice. It is now considered an integral part of thyroid nodule management in many centers. When faced with an indeterminate FNA, clinicians can incorporate molecular test results into decision making: a benign gene expression signature strongly suggests observation is appropriate, whereas detection of a mutation associated with carcinoma favors surgical removal. By avoiding diagnostic surgeries for benign nodules, these tests reduce patient exposure to operative risks and lifelong thyroid hormone dependence, while still correctly triaging those nodules that require intervention. It should be noted that molecular tests are not 100% accurate; there remains a small false-negative rate and occasional false positives. Therefore, results are interpreted in

conjunction with clinical and sonographic factors. Nevertheless, the overall impact of molecular diagnostics has been to make the management of indeterminate thyroid nodules more precise and personalized, sparing many patients unnecessary surgery. Ongoing refinements, including tests that combine mutational analysis with expression profiling, continue to improve performance. **Figure 1** outlines the integration of molecular diagnostics, including gene expression classifiers and mutation panels, into clinical decision-making for indeterminate thyroid nodules.

In addition to molecular assays on cytology, biochemical biomarkers play important roles in thyroid disorder diagnosis. For hyperthyroid and hypothyroid conditions, sensitive assays for thyroid-stimulating hormone (TSH), free T₄, and free T₃ remain fundamental and have become even more accurate over time [29]. An area of advance in autoimmune thyroid disease is the measurement of TSH receptor antibodies. In Graves' disease, TSH receptor autoantibodies (TRAb) cause hyperthyroidism; modern immunoassays for TRAb are highly sensitive and specific. TRAb testing can confirm Graves' disease without needing a radioiodine uptake scan, and quantitative levels may predict the likelihood of remission or recurrence after antithyroid drug therapy. For instance, patients whose TRAb levels become undetectable during therapy have a higher chance of lasting remission, whereas those with persistently elevated TRAb are at greater risk of relapse. This information can inform the decision to continue medical therapy versus consider definitive treatment [30].

Another important biomarker is serum calcitonin, used in the context of medullary thyroid carcinoma (MTC). Calcitonin is a hormone produced by the thyroid's C-cells (from which MTC arises), and it is a highly specific tumor marker for medullary cancer. Elevated basal or stimulated calcitonin in a patient with a thyroid nodule strongly suggests MTC, even when cytology is nondiagnostic. Recent literature has re-emphasized the value of routine calcitonin screening in patients with nodules, a practice more common in Europe than in North America. Given that MTC is infrequent (~1–2% of thyroid nodules) but can be cured if caught early, some experts advocate measuring calcitonin in all indeterminate nodules prior to surgery [31]. A 2024

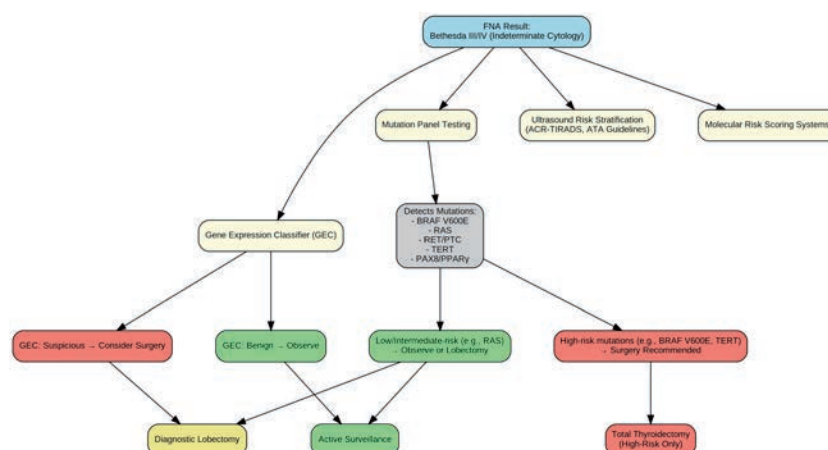


Figure 1. Molecular diagnostic pathway for indeterminate thyroid cytology (Bethesda III/IV). This schematic illustrates the role of gene expression classifiers (GEC) and mutation panels in stratifying indeterminate thyroid nodules. Depending on test results, patients may be observed, undergo active surveillance, or proceed to diagnostic lobectomy or total thyroidectomy. High-risk mutations such as BRAF^{V600E} and TERT support surgical intervention, while benign profiles allow for conservative management.

international white paper critically reviewed this issue, noting that while ultrasound and FNA often miss medullary carcinoma, calcitonin is the most reliable preoperative test for early detection [32]. The authors provided an easy-to-use guide for when to consider serum calcitonin measurement, aiming to ensure that occult MTC is diagnosed before surgery whenever possible. Wider adoption of calcitonin testing could lead to timely total thyroidectomy for MTC and improved patient outcomes.

For thyroid cancer follow-up, the main biomarker is thyroglobulin (Tg), measured after thyroidectomy and radioiodine ablation to monitor for residual or recurrent differentiated cancer. Advances here include the development of highly sensitive Tg assays that can detect very low levels of Tg, potentially obviating the need for routine diagnostic whole-body iodine scans in low-risk patients. There is also recognition of the significance of anti-thyroglobulin antibodies (TgAb), which can interfere with Tg measurement; trends in TgAb levels themselves are now used as a surrogate marker for disease activity in TgAb-positive patients. Recent research in pediatric thyroid cancer suggests that even preoperative or pre-ablation thyroglobulin levels might have prognostic value [33]. In one review, elevated thyroglobulin measured after surgery but before radioiodine (“pre-ablative Tg”) was correlated with a higher risk of persistent or recurrent disease in children, and specific cutoff values were proposed to stratify risk [34]. **Figure 2** presents a flowchart that integrates thyroid-stimulating hormone (TSH), free/total thyroid hormone levels, and antibody testing to assist in the differential diagnosis of thyroid dysfunction. In summary, modern diagnosis of thyroid disorders has been markedly enhanced by molecular and biomarker developments. The integration of molecular cytology for indeterminate nodules is preventing unnecessary surgeries while identifying cancers earlier. Improved autoantibody and hormone assays allow more confident etiological diagnosis of thyrotoxicosis and hypothyroidism. And for thyroid cancer, serum markers like calcitonin and thyroglobulin enable both early detection and long-term surveillance. Together with

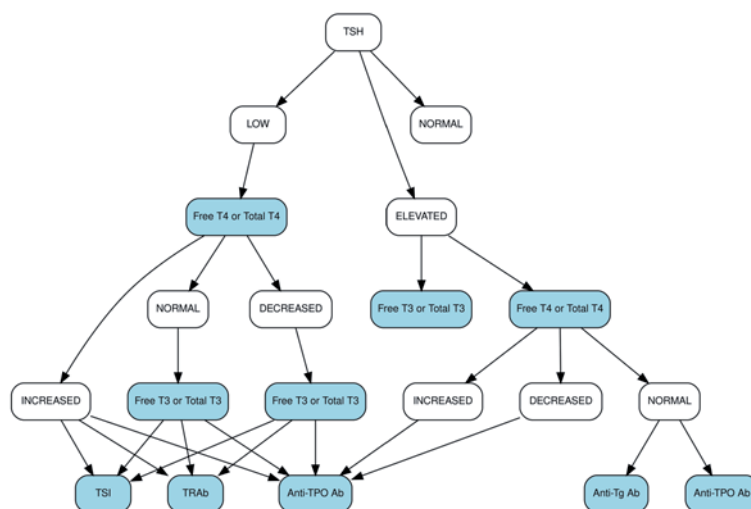


Figure 2.

Diagnostic algorithm for thyroid dysfunction based on hormonal and antibody evaluation. This flowchart guides the interpretation of thyroid-stimulating hormone (TSH), free or total T₃ and T₄ levels, and thyroid-specific antibodies including thyroid-stimulating immunoglobulin (TSI), TSH receptor antibody (TRAb), antithyroid peroxidase antibody (anti-TPO Ab), and anti-thyroglobulin antibody (anti-Tg Ab), aiding in the diagnosis of hyperthyroidism, hypothyroidism, and autoimmune thyroid diseases.

imaging innovations, these diagnostic advances enable a more informed, patient-specific approach to thyroid disease management.

3. Advances in treatment

3.1 Surgical and locoregional treatment advances

Surgery has long been the definitive treatment for many thyroid disorders, from total thyroidectomy for thyroid cancers to partial thyroidectomy for symptomatic goiter or hyperthyroid nodules. Over the past decade, thyroid surgery has evolved to become safer and less invasive, improving patient outcomes and satisfaction. A key trend has been the development of minimally invasive and remote-access thyroidectomy techniques designed to avoid a visible neck scar. One such approach is the transoral endoscopic thyroidectomy vestibular approach (TOETVA), in which surgeons remove the thyroid through small incisions on the inner lower lip (oral vestibule). This totally endoscopic “scarless” thyroidectomy approach was pioneered in Asia and has since spread globally for carefully selected patients. According to a recent systematic review and meta-analysis, TOETVA achieves comparable safety and efficacy to conventional open thyroidectomy [35]. In pooled analyses of over a thousand patients, transoral thyroid surgery showed complication rates comparable to conventional surgery, with slightly longer operative times and reduced postoperative pain. Its scarless outcome makes it an appealing option, especially for younger patients or those prone to keloids. Other remote-access approaches, such as axillo-breast and retroauricular techniques, similarly aim to improve cosmetic outcomes while maintaining oncologic safety, though they require careful patient selection and surgical expertise [35].

Even in conventional open thyroidectomy, there have been notable advances. The routine use of intraoperative nerve monitoring is now common to help identify and protect the recurrent laryngeal nerves during thyroidectomy, potentially reducing the risk of vocal cord paralysis. Improved energy devices (advanced bipolar and ultrasonic shears) allow precise hemostasis and dissection, reducing operative time and blood loss. For large goiters or difficult reoperative cases, surgeons have refined techniques to minimize morbidity [36]. Enhanced recovery after surgery (ERAS) protocols are being applied to thyroid surgery, enabling many patients to be discharged the same day as the operation with appropriate analgesia and calcium monitoring. A major advance in thyroid nodule treatment is the emergence of nonsurgical locoregional therapies, particularly thermal ablation. Techniques like radiofrequency ablation (RFA) and laser ablation offer minimally invasive options for symptomatic benign nodules and are being investigated for small cancers. Under ultrasound guidance, thermal energy is delivered to induce coagulative necrosis, leading to nodule shrinkage and symptom relief. Studies show RFA can reduce nodule volume by 50–80% within 6–12 months, with minimal complications [37]. These procedures are typically done under local anesthesia and conscious sedation, with patients resuming normal activities by the next day, a stark contrast to surgical lobectomy, which requires general anesthesia and carries the risks of hospitalization, scarring, and potential hypothyroidism if the remaining thyroid cannot meet demands [9]. Given these advantages, international guidelines now endorse thermal ablation as an effective treatment option for benign thyroid nodules in patients who prefer to avoid surgery.

However, these remote-access techniques introduce distinct limitations. Transaxillary thyroidectomy requires creating an extensive subplatysmal working

space from the axilla to the anterior neck, which significantly prolongs operative time—reports indicate mean operative durations of 150–200 minutes compared with 60–90 minutes for open surgery. The large flap dissection often results in increased postoperative pain and shoulder discomfort, with some series reporting transient brachial plexus irritation or sensory changes in up to 15% of patients due to retraction and positioning of the arm [36]. Indirect access to the contralateral lobe limits visualization of the central compartment, making comprehensive lymph node dissection challenging; studies have documented that inadvertent nodal tissue can be left behind in as many as 10–20% of cases when preoperative imaging underestimates metastatic burden. Additionally, the need to tunnel beneath the pectoralis muscle and sternocleidomastoid increases the risk of chest wall sensory nerve injuries, leading to transient paresthesia of the anterior chest or upper medial arm in approximately 10–25% of patients. For large goiters (over 5 cm) or thyroid cancers with extrathyroidal extension, the narrow working corridor frequently necessitates conversion to an open procedure, which carries higher complication rates and longer anesthesia times.

The transoral endoscopic thyroidectomy vestibular approach (TOETVA) also has specific drawbacks. Creating a subplatysmal space via CO₂ insufflation at pressures of 6–8 mm Hg can lead to subcutaneous emphysema in the neck and chest in up to 10% of cases, with rare reports of CO₂ embolism. Because the access incisions are intraoral, bacterial contamination risk is higher; postoperative surgical-site infection rates can reach 2–3%, compared with <0.5% in open thyroidectomy. Mental nerve injury occurs in 1–5% of patients, manifesting as numbness or paresthesia of the lower lip and chin due to the proximity of the lateral port sites to the mental foramen. The working space is more confined than in the transaxillary route, so identifying and preserving the recurrent laryngeal nerve and parathyroid glands is technically demanding; inexperienced surgeons can face transient vocal cord paresis rates of 3–5% and temporary hypoparathyroidism in up to 8% of cases during their learning curve [36]. Both TOETVA and transaxillary approaches require specialized endoscopic instruments, and extensive training centers usually need to exceed 50 procedures before complication rates approximate those of open surgery, which limits their availability to high-volume institutions and increases overall costs.

Thermal ablation is being actively explored for autonomously functioning thyroid nodules and primary microcarcinomas in patients who are poor surgical candidates or decline surgery. Early results show that RFA can restore euthyroidism in many patients with solitary toxic nodules by ablating hyperactive tissue. For papillary microcarcinomas, particularly in elderly or high-risk patients, ablation has demonstrated encouraging local control, and clinical trials are comparing RFA to thyroidectomy for small, low-risk cancers. The prospect of curing thyroid cancer with a needle rather than a scalpel is promising, though long-term data are pending. High-intensity focused ultrasound (HIFU), a noninvasive method that ablates tissue externally, is also under investigation [38]. In advanced, unresectable, or recurrent thyroid cancers, locoregional therapies like percutaneous ethanol injection (PEI) and arterial embolization may be used selectively. PEI, which involves injecting ethanol into metastatic lymph nodes or cystic lesions, induces necrosis and remains a valuable option, especially for cervical nodal metastases in inoperable patients. Though not new, PEI techniques have been refined and continue to play a role in minimally invasive management.

For advanced, unresectable, or recurrent thyroid cancers, locoregional therapies like percutaneous ethanol injection (PEI) and arterial embolization offer minimally invasive options in select cases. PEI, which induces necrosis by injecting ethanol into

metastatic lymph nodes or cystic lesions, has been particularly useful for treating cervical nodal metastases in patients unfit for further surgery. Though established, its techniques have been refined for improved outcomes. In summary, thyroid surgeons now have a broader range of options, from scarless endoscopic procedures to percutaneous ablation, allowing personalized treatment based on patient needs and preferences. These innovations have reduced the invasiveness of thyroid care; for instance, a symptomatic benign nodule may now be managed with outpatient ablation instead of surgery. Even surgical patients benefit from enhanced safety and recovery. As clinical experience expands, these advancements are expected to become more accessible and further improve thyroid disorder management.

3.2 Pharmacological advances in hyperthyroidism and hypothyroidism

Medical management of thyroid disorders has advanced through both optimization of existing therapies and the introduction of new drugs. In hyperthyroidism, antithyroid medications, primarily methimazole and propylthiouracil, remain the mainstay. Methimazole is now the preferred first-line agent for Graves' disease due to its superior efficacy and safety, except during the first trimester of pregnancy or in thyroid storm, where propylthiouracil is favored. A notable shift in practice is the use of long-term, low-dose methimazole for maintenance in patients who relapse after initial therapy but wish to avoid definitive treatment. This strategy, increasingly adopted in Europe and Asia, has shown good tolerability with minimal side effects and effective disease control under regular monitoring. Remission prediction has also improved with the use of TSH receptor antibody (TRAb) testing. Declining or cleared TRAb titers correlate with higher remission rates, while persistently high levels suggest continued therapy or definitive intervention may be needed. Another major advance is the use of teprotumumab, a biologic targeting the insulin-like growth factor-1 receptor, for Graves' ophthalmopathy. Approved in 2020, it is the first effective targeted therapy for moderate to severe active thyroid eye disease, significantly reducing proptosis and improving diplopia and inflammation in clinical trials [39]. This has been a game-changer for patients, offering a medical alternative to extensive orbital surgeries. Teprotumumab's success also provides proof of the principle that immunotherapy can modify the autoimmune process in Graves' disease. Although its use is presently limited to orbitopathy, it raises the question of whether future biologics could treat the hyperthyroidism of Graves directly by targeting immune pathways (for instance, therapies aimed at TSH receptor antibodies or B cells). Indeed, rituximab (an anti-B cell antibody) has been investigated in Graves' with mixed results, and novel antagonists of the TSH receptor are under early study.

In hypothyroidism, levothyroxine (LT4) remains the standard treatment, but recent advances aim to improve its effectiveness and patient experience. New formulations, including liquid LT4 and soft-gel capsules, offer better absorption, especially in patients with gastrointestinal issues such as coeliac disease, gastric bypass, or atrophic gastritis. Unlike tablets, liquid LT4 bypasses the need for gastric dissolution, achieving faster absorption and more stable thyroid hormone levels [40]. This has proven particularly beneficial in patients with poor response to tablets, and even in those without malabsorption, liquid LT4 offers greater dosing flexibility and consistency [41]. A key debate in hypothyroid care is the use of liothyronine (LT3) alongside LT4 in patients who remain symptomatic despite normalized thyroid-stimulating hormone (TSH). About 15% of LT4-treated patients have lower serum T3 than healthy individuals, possibly due to impaired peripheral conversion from

T4, often influenced by genetic variations in deiodinase enzymes [42]. While most randomized trials show no significant benefit of combination LT4 + LT3 therapy over LT4 alone [43], select patients with persistent symptoms may experience improvement. Many report a strong preference for combination therapy, even when objective measures show little difference. Accordingly, professional societies, including the European Thyroid Association, now support individualized trials of LT4 + LT3 for select patients. This shift is reflected in the increasing use of combination therapy and desiccated thyroid extract [44].

To make combination therapy safer and more physiological, there are ongoing efforts to develop better T3 formulations. The traditional liothyronine tablets are rapid-acting and can cause transient high T3 peaks and hyperthyroid symptoms in some patients. In response, researchers have explored slow-release T3 preparations that could provide a smoother T3 curve. Early prototypes using slow-release compounding matrices showed modest success in blunting peak levels [45], and a particularly innovative approach has been testing T3 analogs like triac (triiodothyroacetic acid) or T3 sulfate that act as prodrugs; these compounds can be converted to T3 gradually in the body, offering a sustained T3 supply. A recent human trial of oral T3 sulfate demonstrated that it is absorbed and then slowly metabolized to active T3, maintaining stable serum T3 for up to 48 hours with minimal peaks [46]. While not yet commercially available, these developments may improve safety and efficacy in the future. In the meantime, clinicians using combination therapy often prescribe small LT3 doses (5–10 µg once or twice daily) with LT4, targeting a normal TSH and modest T3 increase within range. In severe hypothyroidism and myxoedema coma, protocolized treatment with intravenous LT4 and LT3 has improved outcomes, restoring tissue T3 levels more effectively. Advances in intensive care support have also enhanced survival in this once-fatal condition.

Finally, thyroid hormone analogs are being explored beyond traditional hypothyroidism. Compounds like eprotirome and resmetirom, selective for specific thyroid hormone receptor subtypes, are under investigation for treating hypercholesterolemia and nonalcoholic fatty liver disease. A liver-targeted T3 analog has shown promise in reducing hepatic fat without systemic thyrotoxicosis [47]. While these are not treatments for primary thyroid disorders, they reflect the broader pharmacological advances stemming from thyroid science and may indirectly benefit patients (e.g., hypothyroid patients who also have liver disease might 1 day receive combination therapy that includes such analogs).

In summary, the pharmacologic management of thyroid diseases is moving toward greater individualization and new horizons. In hyperthyroidism, fine-tuning antithyroid drug use and introducing targeted immunotherapies are improving outcomes. In hypothyroidism, new formulations and combination approaches are addressing the needs of those who were not fully served by traditional therapy. **Figure 3** summarizes the major pharmacological milestones that have shaped the modern management of hyperthyroidism, hypothyroidism, and related thyroid conditions. Patients are increasingly maintained in the euthyroid state with minimal symptoms, and emerging therapies promise to further reduce the burden of both overactive and underactive thyroid conditions.

3.3 Novel and targeted therapies for thyroid cancer

Perhaps the most significant therapeutic advances in thyroid disorders have occurred in thyroid cancer, particularly in advanced cases that previously lacked

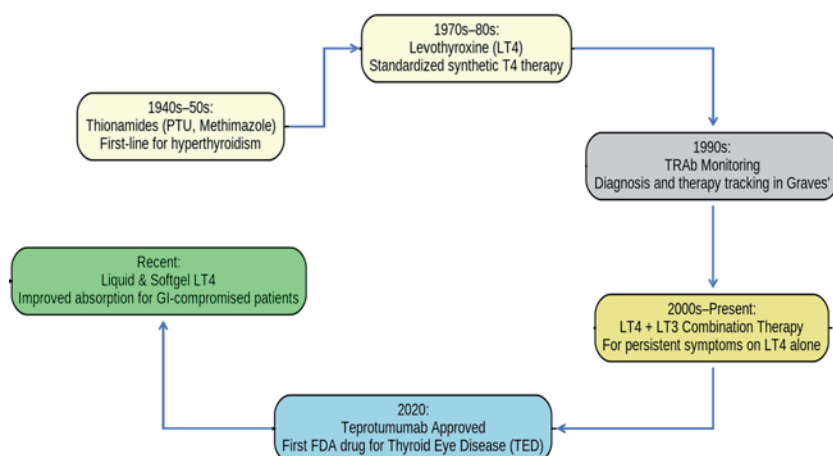


Figure 3.
 Timeline of key pharmacological advances in thyroid disorder management. A historical overview showing the evolution from thionamide use for hyperthyroidism, the standardization of levothyroxine (LT₄) therapy, the advent of TSH receptor antibody (TRAb) monitoring, the introduction of combination LT₄ + LT₃ therapy, and the recent approval of teprotumumab for thyroid eye disease (TED) alongside novel LT₄ formulations for improved absorption.

effective treatments. A deeper understanding of tumor genetics has led to the development of targeted therapies that have transformed outcomes for patients with aggressive or metastatic disease. In differentiated thyroid carcinoma (DTC), including papillary and follicular types, the standard treatment remains thyroidectomy followed by radioactive iodine (RAI) ablation when indicated. However, some DTCs become RAI-refractory or progress despite standard therapy. Before 2010, systemic options were limited, with cytotoxic chemotherapy offering poor outcomes. The approval of multi-kinase inhibitors (MKIs) sorafenib and lenvatinib marked a turning point [48]. These oral agents inhibit multiple tyrosine kinases involved in tumor proliferation and angiogenesis. In phase III trials, lenvatinib achieved a 65% response rate and extended progression-free survival (PFS) to ~18 months versus <4 months on placebo [49]. Though not curative, MKIs provide long-term disease control and improved quality of life, albeit with manageable side effects such as hypertension and fatigue.

Subsequent therapies have become increasingly mutation-specific. About 60% of papillary thyroid cancers harbor BRAF^{V600E} mutations, with others exhibiting RAS mutations or RET fusions. Targeted BRAF and MEK inhibitors (e.g., dabrafenib + trametinib) demonstrated a 69% response rate in BRAF-mutant anaplastic thyroid carcinoma (ATC), leading to FDA approval [50]. Many of these responses were rapid and dramatic, with some patients' tumors shrinking enough to allow surgical resection or significantly prolonging survival in a disease that often kills within months. This result was unprecedented in ATC therapy and has made molecular testing for BRAF mutation standard in all ATC cases. For BRAF-mutated papillary cancers that are aggressive or RAI-refractory, BRAF/MEK inhibition is also being explored, though lenvatinib remains the front-line in DTC, and the role of BRAF inhibitors in DTC is not yet fully defined outside of clinical trials [51].

Another success story is in medullary thyroid carcinoma (MTC). MTC is driven by mutations in the RET proto-oncogene in about 50% of sporadic cases and nearly all hereditary cases (MEN2 syndrome). Earlier MKIs like vandetanib and cabozantinib had some efficacy in advanced MTC by targeting RET among other kinases, and

were approved in the early 2010s [52]. More recently, RET-specific inhibitors such as selpercatinib and pralsetinib have shown superior outcomes, with ~69% response rates and better tolerability, making selpercatinib a preferred first-line therapy for metastatic RET-mutant MTC [53]. Selpercatinib extends progression-free survival in RET-mutant thyroid cancers with fewer side effects than older multi-kinase inhibitors (MKIs), such as mild hypertension or liver enzyme elevations. As a targeted therapy matched to RET alterations, it exemplifies precision oncology and is also effective in RET fusion—positive papillary thyroid carcinomas.

Another emerging approach is immune checkpoint inhibition. While most differentiated thyroid cancers are poorly immunogenic, anaplastic thyroid carcinoma often exhibits high PD-L1 expression and mutational burden, making it more responsive. However, trials of PD-1 inhibitors like pembrolizumab have shown modest response rates (~10–20%) in anaplastic thyroid cancer [54], but a French registry did record a 25% response in ATC patients treated with pembrolizumab, indicating a subset derive benefit [55]. Combining immunotherapy with targeted therapy appears more promising. Multi-kinase inhibitors (MKIs) like lenvatinib can enhance the tumor microenvironment's responsiveness to immune attack. In a recent study, lenvatinib plus pembrolizumab achieved an 80% disease control rate in anaplastic and poorly differentiated thyroid carcinoma, including some complete remissions [56]. In one report, 4 of 6 ATC patients had a complete response to the combination, far exceeding historical outcomes [57].

Finally, the concept of theragnostic radioisotopes has extended beyond iodine in thyroid cancer. In MTC, for example, the use of a radioactive somatostatin analog therapy (Lutetium-177 DOTATATE) is being studied after imaging with Gallium-68 DOTATATE PET confirmed uptake in metastases [58]. This strategy has shown success in other neuroendocrine tumors and may offer a targeted radiation option for metastatic medullary thyroid carcinoma (MTC). Similarly, redifferentiation agents like MAPK inhibitors are being tested to restore radioiodine uptake in refractory thyroid cancers. **Figure 4** outlines a structured approach to managing iodine-refractory disease, integrating molecular profiling, suppression therapy, targeted drugs, and redifferentiation strategies.

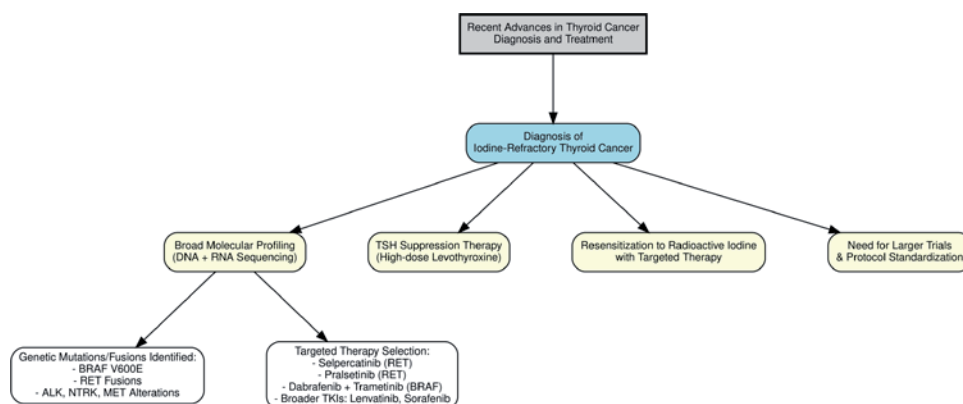


Figure 4.

A visual representation outlining the recent advances in diagnosing and treating iodine-refractory thyroid cancer. The diagram integrates molecular diagnostics (including identification of BRAF, RET, ALK, NTRK, and MET alterations), selection of corresponding targeted therapies (e.g., selpercatinib and dabrafenib + trametinib), TSH suppression strategies, and the role of redifferentiation therapies, while also highlighting the need for further clinical standardization.

These emerging therapies have significantly broadened options for advanced thyroid cancer, transforming some once-terminal cases into manageable chronic conditions. Based on molecular profiling, treatments now include multi-kinase inhibitors, mutation-specific agents, immunotherapy, and investigational radiopharmaceuticals.

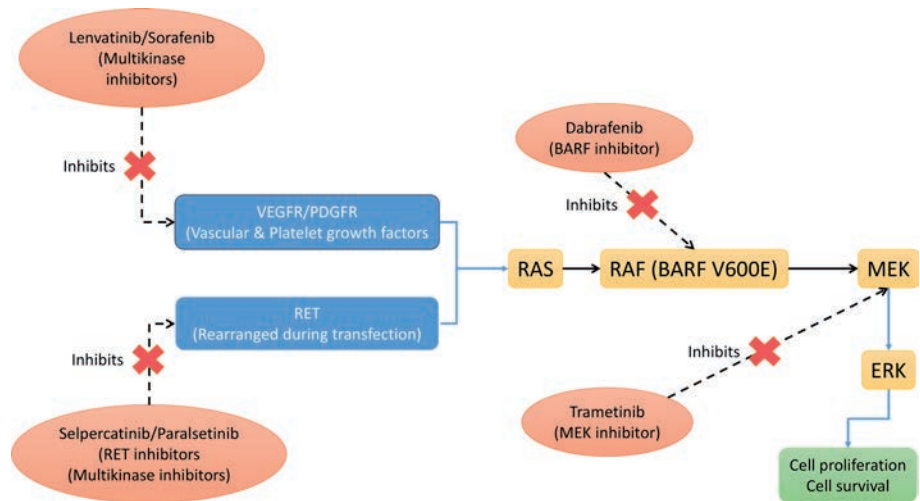


Figure 5. Targeted inhibition of oncogenic pathways in thyroid cancer. The diagram shows common molecular alterations in thyroid cancer, including mutations in RET, BRAF^{V600E}, and activation of VEGFR/PDGFR pathways. Targeted therapies such as selpercatinib and pralsetinib (RET inhibitors), dabrafenib (BRAF inhibitor), trametinib (MEK inhibitor), and multi-kinase inhibitors like lenvatinib and sorafenib interrupt these signaling cascades, ultimately suppressing tumor cell proliferation and survival.

Domain	Traditional approach	Recent advances
Diagnosis	Ultrasound imaging and FNA biopsy; limited use of molecular diagnostics; reliance on clinical and basic laboratory tests.	High-resolution multiparametric ultrasound; AI-assisted imaging interpretation; molecular cytology testing (gene expression classifiers and mutation panels); advanced biomarker assays (calcitonin and thyroglobulin).
Treatment of hyperthyroidism	Fixed duration of antithyroid drug therapy (12–18 months), routine use of radioactive iodine or surgery, limited monitoring of antibody levels.	Prolonged low-dose antithyroid therapy for Graves'; TRAb level monitoring; introduction of teprotumumab for Graves' orbitopathy; minimally invasive thermal ablation (RFA) for toxic nodules.
Treatment of hypothyroidism	Levothyroxine tablets as standard treatment; minimal consideration for persistent symptoms; uniform TSH-targeted dosing.	Availability of liquid and soft-gel LT4 formulations; consideration of combination LT4 + LT3 therapy for symptomatic patients; personalized dosing considering absorption issues and genetic differences in deiodination.
Thyroid cancer management	Total thyroidectomy for most cancers; routine radioactive iodine ablation; little differentiation based on cancer risk profiles.	Risk-adapted surgery (lobectomy vs. total thyroidectomy); active surveillance for low-risk papillary microcarcinomas; selective use of radioactive iodine; targeted therapies for advanced/metastatic cases (e.g., BRAF inhibitors, RET inhibitors, and immunotherapy combinations).

Table 1. Recent advances in thyroid disorder management: a comparison between traditional approaches and recent innovations.

Figure 5 illustrates key molecular pathways and the mechanisms of targeted therapies, exemplifying precision medicine. Ongoing research aims to overcome resistance, enhance combination strategies, and improve outcomes. **Table 1** summarizes the shift from traditional to modern approaches across key domains of thyroid disorder management.

As evident from the comparison, the field is moving decisively toward greater precision, individualized care, and improved patient outcomes, paving the way for the future directions discussed next.

4. Advances in understanding pathophysiology

4.1 Molecular and genetic insights into thyroid cancer

Over the past decade, major advances have clarified the molecular pathogenesis of thyroid cancer. The Cancer Genome Atlas (TCGA) study of papillary thyroid carcinoma (2014) revealed that ~97% of cases are driven by a limited set of mutations, categorizing them into BRAF^{V600E}-like and RAS-like subtypes [59]. BRAF^{V600E} mutations (~60% of papillary cancers) are linked to classic histology, extrathyroidal extension, and reduced radioiodine uptake. RAS mutations (NRAS, HRAS, and KRAS) are common in follicular-pattern tumors and predict more indolent behavior. RET gene fusions (e.g., RET/PTC1 and RET/PTC3) are seen in younger or radiation-exposed patients [60]. This improved molecular classification has practical implications: it refines prognosis and is beginning to guide therapy (as targeted drugs against BRAF, RET, etc., become available, as discussed earlier).

Additional driver alterations have been identified, such as NTRK1/3 gene fusions, which, though rare, are actionable with TRK inhibitors. TERT promoter mutations, found in aggressive papillary and follicular cancers, help explain unexpectedly poor outcomes in some low-grade tumors, especially when co-occurring with BRAF or RAS mutations—prompting some centers to include TERT testing in risk assessment. Genomic studies of Hürthle cell carcinoma have revealed distinct features, including widespread mitochondrial DNA mutations and copy number alterations, suggesting unique metabolic drivers [61]. Pediatric thyroid cancers, predominantly papillary, differ genetically from adult cases. They more often carry RET or ALK fusions and less frequently BRAF or RAS mutations. Despite often presenting at an advanced stage, they respond well to treatment and rarely become radioiodine-refractory [62]. This suggests a distinct biology where fusion oncogenes contribute to radioiodine sensitivity and favorable outcomes, underscoring the importance of avoiding overtreatment in children. Another milestone in thyroid tumor classification was the 2016 redefinition of the encapsulated follicular variant of papillary carcinoma. If noninvasive, it was renamed “noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)” [63]. This change, based on its benign behavior and frequent RAS mutations, prevents overdiagnosis and overtreatment.

These insights have enhanced risk stratification and therapeutic precision. Molecular testing now informs surgical extent and adjunct therapy decisions; for instance, tumors with BRAF+TERT mutations may warrant total thyroidectomy and radioiodine, while low-risk RAS-mutant tumors may be managed with lobectomy [64]. The tumor immune microenvironment is also under investigation. An intriguing link exists between Hashimoto’s thyroiditis and papillary carcinoma, with shared

immune features like PD-L1 overexpression. While chronic inflammation may foster tumorigenesis, tumor-infiltrating lymphocytes may also restrain progression [65]. The PD-1/PD-L1 axis is a shared pathway in thyroid autoimmunity and cancer, supporting trials of immune checkpoint inhibitors in thyroid malignancies [66]. In summary, molecular advances have redefined thyroid carcinoma as a group of genetically distinct diseases. Molecular profiling now informs diagnosis, prognosis, and treatment, enabling targeted therapies for aggressive cancers and avoiding overtreatment of indolent lesions. This shift from morphology to molecular precision is reshaping thyroid cancer care.

4.2 Autoimmune thyroid disease and immune mechanisms

Autoimmune disorders of the thyroid Graves' disease (autoimmune hyperthyroidism) and Hashimoto's thyroiditis (autoimmune hypothyroidism) are among the most common autoimmune conditions. Advances in genetics and immunology have deepened our understanding of their pathogenesis. In Graves' disease, familial clustering implies genetic predisposition, and GWAS has identified over 80 susceptibility loci in European and Asian populations [67]. These include immune-regulatory genes (HLA class II, CTLA4, PTPN22, cytokine, and T-cell-regulation genes) as well as thyroid-specific genes (TSH receptor, thyroglobulin) [68]. Individually, these variants confer small risks but collectively explain much of the heritability; for example, certain HLA-DR alleles and CTLA4 polymorphisms are prominent. Thus, Graves' is a polygenic disease with no single "Graves' gene," and twin studies estimate 60–80% concordance from genetic factors [69].

Genetic insights have clinical correlates: specific HLA variants are associated with ophthalmopathy and disease severity, and genetic profiling is being explored to predict relapse risk [69]. Pathway identification also suggests therapeutic targets: since the TSH receptor is the primary autoantigen and interacts with IGF-1R on orbital fibroblasts, IGF-1R became the target of teprotumumab. Other interventions aim to reduce autoantibody production by targeting CD20 on B cells (rituximab) or CD40.

In Hashimoto's thyroiditis, many loci overlap with Graves' (HLA-DR, CTLA4, and PTPN22), but certain HLA variants preferentially predispose to Hashimoto's. Variants in the TSH receptor gene can also favor Hashimoto by altering receptor expression and immune recognition. Additionally, FOXP3 variants, important for regulatory T cells, have been implicated [70]. As a multifactorial disease, genetic predisposition leads to faulty tolerance to thyroglobulin and thyroid peroxidase, driving inflammatory destruction. Environmental factors include iodine intake, while necessary to prevent goiter, excess iodine can trigger thyroiditis in susceptible individuals, and smoking, which exacerbates Graves' (especially eye disease) but appears protective against Hashimoto's [71]. Although stress and infections (e.g., *Yersinia enterocolitica*) have been proposed as triggers, evidence remains inconclusive. Emerging research into gut microbiota differences in patients versus controls suggests a "gut-thyroid axis" in which microbial metabolites influence systemic immunity; probiotic interventions are still experimental [72]. At the cellular level, diminished regulatory T cell (Treg) function in both Graves' and Hashimoto's contributes to loss of tolerance; therapies enhancing Tregs may be beneficial. Checkpoint molecules such as PD-1/PD-L1 are also critical: thyroid follicular cells in Hashimoto's can express PD-L1 to attenuate immune attack, and PD-1 inhibitors used in cancer immunotherapy can induce thyroiditis, mimicking Hashimoto's and underscoring the pathway's role. In Graves' ophthalmopathy, PD-1/PD-L1 is active in inflamed orbital tissues [73].

These insights have practical implications. Some countries have refined iodine supplementation programs to avoid excess intake, reducing the risk of precipitating thyroiditis in genetically susceptible populations. Selenium supplementation has shown modest benefits, lowering thyroid peroxidase antibody levels and improving ultrasound markers of inflammation in Hashimoto's, though effects are limited. Looking ahead, the goal is antigen-specific immunotherapy or tolerance induction. Research into vaccines or peptides designed to re-educate the immune system, targeting the TSH receptor in Graves' or thyroid peroxidase in Hashimoto's continues. Trials of a TSH receptor peptide tolerogen have been conducted with mixed results, but this strategy remains under investigation [74].

Advances have shown that autoimmune thyroid diseases arise from a blend of genetic risk, environmental triggers, and immune-regulatory breakdown. With dozens of contributing genes and key inflammatory pathways now identified, patient care is becoming more precise, enabling risk prediction and tailored Graves' therapies and paving the way for treatments that target the immune system directly rather than relying solely on lifelong hormone replacement or broad immunosuppression.

5. Advances in the management of specific thyroid disorders

5.1 Hyperthyroidism

Management of hyperthyroidism focuses on restoring euthyroidism and treating the underlying cause, with Graves' disease being the most common, followed by toxic nodular goiter in older adults [75]. In Graves', decisions among antithyroid drugs, radioactive iodine (RAI), or surgery are now guided by TRAb levels and disease severity: high TRAb titers predict low remission with short-course drugs, favoring definitive therapy, while low or declining TRAb may support extended medical therapy (≥ 18 –36 months) to increase remission odds [76]. Long-term low-dose methimazole (2.5–5 mg daily) can maintain euthyroidism in relapsed patients who decline definitive treatment [77]. RAI remains highly effective but can transiently worsen Graves' ophthalmopathy (GO); thus, patients with active moderate or severe GO often undergo surgery or receive prophylactic glucocorticoids if RAI is needed [78]. Dosing now considers gland volume and uptake to minimize the need for repeat treatments. For toxic nodular hyperthyroidism, RAI or surgery are standard, but percutaneous ethanol injection or radiofrequency ablation of solitary adenomas offer alternatives in select cases [79]. Teprotumumab's approval for thyroid eye disease has lowered thresholds for definitive hyperthyroidism treatment, knowing GO can be managed if it worsens [80]. Subclinical hyperthyroidism (TSH < 0.1 mU/L) in patients over 65, postmenopausal women at risk of osteoporosis, or those with heart disease is now often treated rather than observed due to risks of atrial fibrillation and bone loss [81, 82]. Thyroid storm management has improved via standardized protocols combining beta-blockers, high-dose antithyroid drugs, inorganic iodine, glucocorticoids, supportive care, and, in refractory cases, therapeutic plasma exchange [83, 84].

In short, while the therapeutic arsenal for hyperthyroidism is familiar, its deployment is now more nuanced. Personalized treatment plans consider disease severity, antibody levels, patient age and comorbidities, and even patient preference in ways that reflect evidence-based probabilities of remission or complications. The integration of novel therapies like teprotumumab for Graves' eye disease and techniques like nodular ablation further contributes to the comprehensive management of

hyperthyroid patients. The result is that patients with hyperthyroidism today are more likely to receive a treatment approach optimized for their individual scenario, with improved safety and efficacy.

5.2 Hypothyroidism

Levothyroxine (LT4) remains the cornerstone of hypothyroidism treatment, but awareness of persistent symptoms despite normal TSH has led to reconsidering combination LT4 + LT3 therapy in select patients after counseling; guidelines now permit a trial of combination therapy, especially when DIO2 polymorphisms suggest potential benefit [85]. New LT4 formulations (liquid or soft-gel) improve TSH stability and symptom control in patients with absorption issues or interfering medications since they are less affected by gastric pH and can be taken with minimal fasting requirements [86]. Management of subclinical hypothyroidism is more evidence-driven: treatment is recommended when TSH > 10 mU/L to prevent progression and cardiovascular effects, while for TSH, 4–10 mU/L decisions are individualized [87, 88]. Trials like TRUST (adults >65) show no clear benefit in mild cases, supporting a conservative approach in asymptomatic elderly patients [89]. In pregnancy or women trying to conceive, lower TSH thresholds (usually >2.5–4 mU/L) prompt treatment due to risks of miscarriage and impaired fetal neurodevelopment; new obstetric guidelines emphasize strict TSH targets and adequate iodine/levothyroxine supplementation [90]. Long-term follow-up typically involves annual TSH checks, with proactive re-evaluation when weight changes, new medications, or gastrointestinal surgeries may alter LT4 needs. Telemedicine and at-home TSH testing devices enhance convenience [91, 92]. Research into tissue-specific hypothyroidism (e.g., in nonalcoholic fatty liver disease) has spurred trials of TRIAC and liver-targeted T3 analogs, suggesting future therapies may aim for tissue-level euthyroidism beyond normalizing serum TSH [93].

In central (secondary) hypothyroidism, advances in pituitary imaging have improved diagnosis, but LT4 dosing relies on free T4 levels rather than TSH; it remains critical to address adrenal insufficiency first to avoid adrenal crisis [94]. Overall, hypothyroidism management is more patient-centered: recognizing that “one size does not fit all,” clinicians now tailor LT4 preparations, consider combination therapy, and apply nuanced treatment thresholds, integrating patient-reported outcomes alongside laboratory results.

5.3 Thyroid cancer

The management of thyroid cancer now emphasizes risk-adapted, individualized care, treating aggressive disease vigorously while avoiding overtreatment of indolent tumors [95, 96]. Very small papillary cancers (<1 cm) can often be managed with active surveillance instead of immediate surgery; long-term studies show that most subcentimeter lesions remain stable, and only 5–15% require delayed intervention without compromising survival [97]. Consequently, guidelines endorse active surveillance for low-risk tumors (no invasion or metastasis) in compliant patients, and dedicated “watch and wait” programs are expanding globally [98]. When surgery is necessary for low-risk cases, lobectomy is favored for solitary, unifocal papillary carcinomas ≤4 cm without high-risk features; outcomes match total thyroidectomy, but many patients avoid lifelong hormone replacement and unilateral surgical risks [99]. Prophylactic central neck dissection is now reserved for clinically or radiologically

evident nodal metastases, sparing patients unnecessary morbidity when microscopic spread is unlikely [100]. Postoperative radioactive iodine (RAI) has been de-escalated: low-risk differentiated thyroid cancers (<2 cm, intrathyroidal, completely resected) typically forego RAI, while higher-risk cases receive tailored RAI doses (e.g., 30 mCi vs. 100 mCi) to minimize side effects without reducing efficacy [101]. Dynamic risk stratification reevaluating response (excellent, indeterminate, biochemical incomplete, and structural incomplete) using thyroglobulin and imaging allows for the reclassification of a patient's risk over time, so those with excellent responses can follow minimal surveillance akin to low-risk patients [102, 103]. Intermediate-risk differentiated thyroid carcinoma (e.g., minor extrathyroidal extension, limited nodal metastases) is managed variably; recent reviews highlight heterogeneous practices, and trials like ESTIMABL2 are investigating whether certain patients with low-volume nodal disease can safely avoid RAI [104]. The trend, however, is toward tailoring RAI decisions to specific risk factors within this heterogeneous group; for example, a patient with a tall-cell variant papillary carcinoma might be more likely to benefit from RAI than one with a conventional papillary carcinoma of similar size. Clinical trials like ESTIMABL2 are attempting to clarify this by comparing outcomes with or without RAI in lower-volume nodal disease [105].

For metastatic or RAI-refractory disease, management is multidisciplinary: isolated lesions may undergo surgery, ethanol ablation, or radiotherapy, whereas widespread or progressive disease warrants tyrosine kinase inhibitors (e.g., lenvatinib and sorafenib) initiated when significant progression or symptoms emerge [106]. Anaplastic thyroid carcinoma (ATC) requires urgent, aggressive multimodal care. Rapid molecular testing (e.g., BRAF V600E) guides targeted therapy (dabrafenib + trametinib) that can downstage tumors for surgery; BRAF-negative cases are referred to trials of immunotherapy or novel agents, with combined surgery, radiation, and systemic therapy as needed [107]. Survivorship and follow-up are stratified by initial risk and dynamic response: patients with excellent response and years of disease-free status may require only annual or less frequent imaging, whereas those with biochemical or structural persistence undergo closer monitoring and tailored therapies [108]. Overall, modern thyroid cancer care de-escalates intervention for low-risk tumors utilizing surveillance, limited surgery, and selective RAI, while escalating multidisciplinary, targeted treatments for high-risk and advanced disease. As outcomes data and molecular markers evolve, management algorithms will continue to refine therapy to individual patient risk.

6. Future perspectives and research directions

The future of thyroidology will depend on increasingly personalized approaches as molecular and genetic data become integral to decision-making. For thyroid nodules, enhanced molecular classifiers or even whole-genome sequencing of fine-needle aspirates could more accurately predict behavior; cancer patients may benefit from broader genomic profiling, for example, identifying ALK or NTRK fusions to guide targeted therapies. Polygenic risk scores for autoimmune thyroid disease could emerge, enabling pre-emptive screening or preventive strategies for individuals at high risk of Graves' or Hashimoto's before clinical disease manifests.

Numerous novel agents are in early trials. In Graves' disease, pharmacological approaches such as TSH receptor antagonists or monoclonal antibodies that block

stimulating autoantibodies could provide a “medical thyroidectomy” without surgery or RAI; vaccines designed to induce immune tolerance to the TSH receptor are also under investigation. In Hashimoto’s thyroiditis, immune modulators, such as low-dose naltrexone, may 1 day arrest autoimmune destruction once pathogenic mechanisms are better understood. In thyroid cancer, second- and third-generation inhibitors (e.g., next-generation RET inhibitors overcoming selpercatinib resistance or more potent MEK inhibitors in RAS-mutant tumors) and combination regimens (tyrosine kinase inhibitor plus immunotherapy) hold promise for converting metastatic disease into a manageable chronic condition or even achieving remission in cases currently regarded as incurable. In anaplastic carcinoma, neoadjuvant approaches combining dabrafenib, trametinib, and pembrolizumab before surgery show that some inoperable tumors can be downstaged, offering meaningful survival extension. Looking further ahead, oncolytic virotherapy or gene therapy targeted to thyroid-specific proteins could offer entirely new strategies.

Regenerative medicine may revolutionize hypothyroidism management. Laboratory-grown thyroid organoids derived from stem cells have already restored euthyroidism in animal models, suggesting that bioengineered thyroid grafts could ultimately replace lifelong hormone replacement. Gene editing, for instance using CRISPR to correct congenital defects or to delete autoreactive immune clones, offers a theoretical path to curing certain forms of hypothyroidism or preventing autoimmunity altogether.

Artificial intelligence is poised to inform diagnostics and treatment selection. AI-driven ultrasound may not only detect nodules but also predict molecular profiles, triaging which lesions require biopsy and perhaps guiding robotic-assisted sampling. In pathology, machine learning could help distinguish indeterminate lesions, such as noninvasive follicular thyroid neoplasm with papillary-like nuclear features, from true carcinoma. Clinical decision support tools that synthesize patient-specific data (demographics, laboratory values, imaging, and genomics) will yield individualized follow-up schedules and treatment recommendations based on large outcome datasets.

Advances in understanding subclinical or tissue-specific thyroid dysfunction may broaden therapeutic indications. Recognizing that certain patients experience organ-level hypothyroidism despite normal serum markers, for example, in nonalcoholic fatty liver disease, has prompted trials of liver-targeted T3 analogs. Similarly, clarifying how mild thyroid dysfunction affects cognitive aging could lead to more nuanced targets, potentially treating subclinical abnormalities to preserve brain health. The gut-thyroid axis represents another emerging frontier: if microbiome alterations prove causal in autoimmune thyroid disease, future management of Hashimoto’s might include probiotics or dietary interventions alongside conventional therapy. Although speculative at present, such adjunctive treatments could modulate immunity and reduce autoantibody production.

Global disparities must also be addressed. Many regions still struggle with iodine deficiency, and access to molecular testing or novel drugs remains uneven. International collaborations and policy reforms will be necessary to ensure that genomic diagnostics, targeted therapies such as RET inhibitors, and innovative treatments reach underserved populations. Repurposing affordable drugs, for example, metformin, which preliminary data suggest could slow thyroid cancer progression, may offer cost-effective options. Equitable delivery of these advances will be essential to ensure that personalized, cutting-edge thyroid care benefits patients worldwide (**Figure 6**).

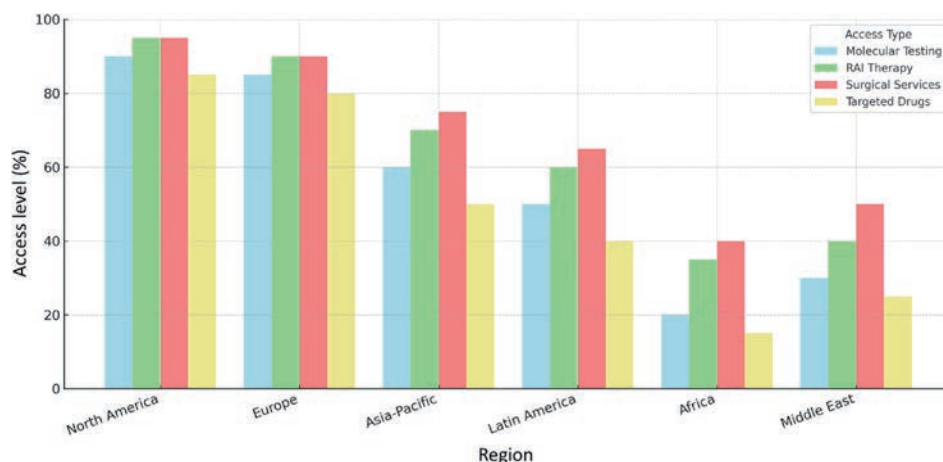


Figure 6.

Global disparities in access to thyroid cancer diagnostics and treatment. The bar chart compares access levels (%) to molecular testing, radioactive iodine (RAI) therapy, surgical services, and targeted drug therapies across major global regions. Lower access in Latin America, Africa, and the Middle East underscores the need for investment in infrastructure and equitable therapeutic availability [109–111].

In essence, the future of thyroid disorder management is moving toward more precise, less invasive, and more comprehensive care. Patients will likely benefit from earlier detection (through genetic or biomarker screening), more targeted treatments (drugs or interventions tailored exactly to their condition's drivers), and potentially even preventive strategies if we can identify those at risk (for example, prophylactic measures in high-risk carriers of thyroid cancer genes, or immunomodulation in early thyroid autoimmunity). Interdisciplinary research combining endocrinology, molecular biology, immunology, bioengineering, and data science is particularly rich in the thyroid field and will continue to yield novel solutions. The hope is that diseases like thyroid cancer become consistently curable or chronically manageable and that hypothyroid and hyperthyroid patients achieve symptom-free, normal lives with minimal burden of treatment.

7. Conclusions

Thyroid disorders encompass benign nodules, hormone imbalances, and aggressive cancers. Improved imaging and molecular diagnostics now allow precise nodule assessment, distinguishing lesions needing surgery from those suitable for observation. Treatments have advanced: less invasive surgery; novel thyroid hormone formulations; and targeted kinase inhibitors or immunotherapies for advanced cancers. A deeper understanding of molecular and genetic factors enables personalized management, minimizing overtreatment in low-risk cases and intensifying therapy in high-risk situations. In hyperthyroidism, especially Graves' disease, autoantibody measurement, and new ophthalmopathy treatments have refined care. In hypothyroidism, alternative hormone-delivery options and focus on patient-reported outcomes guide therapy. Thyroid cancer management now favors active surveillance for very low-risk lesions while using targeted systemic agents for refractory disease. Most differentiated thyroid cancer patients maintain excellent prognoses, and those with advanced disease experience improved survival and quality of life.

Future advances will likely include broader molecular profiling to inform decisions, AI-enhanced diagnostics and novel therapies, next-generation targeted drugs, immunotherapies, and regenerative approaches that may eventually offer cures. Integrating these innovations in a patient-centered, evidence-based manner and ensuring global access will be essential. Overall, precision and innovation now define thyroid care, yielding better outcomes, fewer side effects, and higher quality of life, with continued research promising even more refined management and, ultimately, prevention or cure.

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Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

AI	artificial intelligence
FNA	fine-needle aspiration
US	ultrasound
TIRADS	Thyroid Imaging Reporting and Data System
CEUS	contrast-enhanced ultrasound
MPUS	multiparametric ultrasound
PET	positron emission tomography
FDG	fluorodeoxyglucose
ML	machine learning
TRAb	thyroid-stimulating hormone receptor antibodies
TSH	thyroid-stimulating hormone
T3	triiodothyronine
T4	thyroxine
MTC	medullary thyroid carcinoma
Tg	thyroglobulin
TgAb	anti-thyroglobulin antibodies
LT4	levothyroxine
LT3	liothyronine
RFA	radiofrequency ablation
TOETVA	transoral endoscopic thyroidectomy vestibular approach
ERAS	enhanced recovery after surgery
RAI	radioactive iodine
DTC	differentiated thyroid carcinoma
MKI	multi-kinase inhibitor
ATC	anaplastic thyroid carcinoma
FDA	Food and Drug Administration
RET	rearranged during transfection
PD-1	programmed death-1

PD-L1	programmed death-ligand 1
MEN2	multiple endocrine neoplasia type 2
ALK	anaplastic lymphoma kinase
NTRK	neurotrophic tyrosine receptor kinase
NIFTP	noninvasive follicular thyroid neoplasm with papillary-like nuclear features
HIFU	high-intensity focused ultrasound
GWAS	genome-wide association study
FOXP3	Forkhead box P3
ICU	intensive care unit
LDL	low-density lipoprotein
ESTIMABL	Evaluation of the Utility of Recombinant Human TSH in Management of Differentiated Thyroid Cancer
BTA	British Thyroid Association
TKI	tyrosine kinase inhibitor
Thyroid-stimulating hormone TSH	Nomenclature a hormone produced by the pituitary gland that regulates the production of thyroid hormones (T3 and T4) by the thyroid gland
Triiodothyronine T3	an active thyroid hormone that regulates metabolism, heart rate, and body temperature
Thyroxine T4	the primary hormone produced by the thyroid gland, converted into the more active T3 in tissues
Thyroid-stimulating hormone receptor antibodies TRAb	autoantibodies that stimulate or block the TSH receptor, implicated in Graves' disease
Thyroglobulin Tg	a protein produced by thyroid follicular cells, used as a tumor marker in thyroid cancer follow-up
Anti-thyroglobulin antibodies TgAb	autoantibodies that interfere with the measurement of thyroglobulin levels
Radioactive iodine RAI	a form of iodine used in diagnostic imaging and treatment of hyperthyroidism and thyroid cancer
Radiofrequency ablation RFA	a minimally invasive technique using thermal energy to destroy thyroid nodules
Multi-kinase inhibitor MKI	a type of targeted cancer therapy that blocks multiple pathways involved in tumor growth and angiogenesis
Tyrosine kinase inhibitor TKI	a specific inhibitor that targets tyrosine kinase enzymes involved in cancer progression

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References

- [1] Pitoia F, Trimboli P. New insights in thyroid diagnosis and treatment. *Reviews in Endocrine and Metabolic Disorders*. 2024;**25**(1):1-3
- [2] Durante C, Grani G, Lamartina L, Filetti S, Mandel SJ, Cooper DS. The diagnosis and management of thyroid nodules: A review. *Journal of the American Medical Association*. 2018;**319**(9):914-924
- [3] Davies L, Welch HG. Current thyroid cancer trends in the United States. *JAMA Otolaryngology–Head & Neck Surgery*. 2014;**140**(4):317-322
- [4] Krajewska J, Kukulska A, Oczko-Wojciechowska M, Kotecka-Blicharz A, Drosik-Rutowicz K, Haras-Gil M, et al. Early diagnosis of low-risk papillary thyroid cancer results rather in overtreatment than a better survival. *Frontiers in Endocrinology*. 2020;**11**:571421
- [5] Sugitani I. Active surveillance of low-risk papillary thyroid microcarcinoma. *Best Practice & Research Clinical Endocrinology & Metabolism*. 2023;**37**(1):101630
- [6] Yazdaan HE, Jaya F, Sanjna F, Junaid M, Rasool S, Baig A, et al. Advances in thyroid function tests: Precision diagnostics and clinical implications. *Cureus*. 2023;**15**(11):e48961
- [7] Fallahi P, Ferrari SM, Elia G, Ragusa F, Paparo SR, Camastra S, et al. Therapy of endocrine disease: Endocrine-metabolic effects of treatment with multikinase inhibitors. *European Journal of Endocrinology*. 2021;**184**(1):R29-R40
- [8] Tomer Y. Genetic susceptibility to autoimmune thyroid disease: Past, present, and future. *Thyroid*. 2010;**20**(7):715-725
- [9] Bojunga J, Trimboli P. Thyroid ultrasound and its ancillary techniques. *Reviews in Endocrine and Metabolic Disorders*. 2024;**25**(1):161-173
- [10] Grani G, Lamartina L, Ascoli V, Bosco D, Biffoni M, Giacomelli L, et al. Reducing the number of unnecessary thyroid biopsies while improving diagnostic accuracy: Toward the “right” TIRADS. *The Journal of Clinical Endocrinology & Metabolism*. 2019;**104**(1):95-102
- [11] Russ G, Trimboli P, Buffet C. The new era of TIRADSs to stratify the risk of malignancy of thyroid nodules: Strengths, weaknesses and pitfalls. *Cancers*. 2021;**13**(17):4316
- [12] DeJong HM, Abbott S, Zelesco M, Kennedy BF, Ziman MR, Wood FM. The validity and reliability of using ultrasound elastography to measure cutaneous stiffness, a systematic review. *International Journal of Burns and Trauma*. 2017;**7**(7):124
- [13] Huang R, Jiang L, Xu Y, Gong Y, Ran H, Wang Z, et al. Comparative diagnostic accuracy of contrast-enhanced ultrasound and shear wave elastography in differentiating benign and malignant lesions: A network meta-analysis. *Frontiers in Oncology*. 2019;**9**:102
- [14] Jiang L, Zhang D, Chen Y-N, Yu X-J, Pan M-F, Lian L. The value of conventional ultrasound combined with superb microvascular imaging and color Doppler flow imaging in the diagnosis of thyroid malignant nodules: A systematic review and meta-analysis. *Frontiers in Endocrinology*. 2023;**14**:1182259

- [15] Papini E, Bizzarri G, Bianchini A, Guglielmi R, Graziano F, Lonerio F, et al. Contrast-Enhanced Ultrasound in the Management of Thyroid Nodules. *Thyroid Ultrasound and Ultrasound-Guided FNA*. 2nd ed. Boston, Massachusetts, USA: Springer; 2008. pp. 151-171
- [16] Kloth C, Kratzer W, Schmidberger J, Beer M, Clevert DA, Graeter T. Ultrasound 2020—diagnostics & therapy: On the way to multimodal ultrasound: Contrast-enhanced ultrasound (ceus), microvascular doppler techniques, fusion imaging, sonoelastography, interventional sonography. In: *RöFo-Fortschritte auf dem Gebiet der Röntgenstrahlen und der bildgebenden Verfahren*. Stuttgart, Germany: Georg Thieme Verlag KG; 2021
- [17] Le Bars D. Fluorine-18 and medical imaging: Radiopharmaceuticals for positron emission tomography. *Journal of Fluorine Chemistry*. 2006;**127**(11):1488-1493
- [18] Zhu J, Pan F, Cai H, Pan L, Li Y, Li L, et al. Positron emission tomography imaging of lung cancer: An overview of alternative positron emission tomography tracers beyond F18 fluorodeoxyglucose. *Frontiers in Medicine*. 2022;**9**:945602
- [19] Rizzo A, Albano D, Dondi F, Cioffi M, Muoio B, Annunziata S, et al. Diagnostic yield of FAP-guided positron emission tomography in thyroid cancer: A systematic review. *Frontiers in Medicine*. 2024;**11**:1381863
- [20] Imperiale A, Berti V, Burgy M, Cazzato RL, Piccardo A, Treglia G. Molecular imaging and related therapeutic options for medullary thyroid carcinoma: State of the art and future opportunities. *Reviews in Endocrine and Metabolic Disorders*. 2024;**25**(1):187-202
- [21] Treglia G, Tamburello A, Giovanella L. Detection rate of somatostatin receptor PET in patients with recurrent medullary thyroid carcinoma: A systematic review and a meta-analysis. *Hormones*. 2017;**16**(4):362-372
- [22] Pitoia F, Trimboli P. New insights in thyroid diagnosis and treatment. *Reviews in Endocrine & Metabolic Disorders*. 2023;**25**
- [23] Alzumaili B, Sadow PM. Update on molecular diagnostics in thyroid pathology: A review. *Genes*. 2023;**14**(7):1314
- [24] Agrawal N, Akbani R, Aksoy BA, Ally A, Arachchi H, Asa SL, et al. Integrated genomic characterization of papillary thyroid carcinoma. *Cell*. 2014;**159**(3):676-690
- [25] Alzumaili BA, Krumeich LN, Collins R, Kravchenko T, Ababneh EI, Fisch AS, et al. A comprehensive study on the diagnosis and management of noninvasive follicular thyroid neoplasm with papillary-like nuclear features. *Thyroid*. 2023;**33**(5):566-577
- [26] Nikiforov YE, Steward DL, Robinson-Smith TM, Haugen BR, Klopper JP, Zhu Z, et al. Molecular testing for mutations in improving the fine-needle aspiration diagnosis of thyroid nodules. *The Journal of Clinical Endocrinology & Metabolism*. 2009;**94**(6):2092-2098
- [27] Nikiforova MN, Mercurio S, Wald AI, Barbi de Moura M, Callenberg K, Santana-Santos L, et al. Analytical performance of the ThyroSeq v3 genomic classifier for cancer diagnosis in thyroid nodules. *Cancer*. 2018;**124**(8):1682-1690

- [28] Jackson S, Kumar G, Banizs AB, Toney N, Silverman JF, Narick CM, et al. Incremental utility of expanded mutation panel when used in combination with microRNA classification in indeterminate thyroid nodules. *Diagnostic Cytopathology*. 2020;**48**(1):43-52
- [29] Spencer CA. Laboratory thyroid tests: A historical perspective. *Thyroid*. 2023;**33**(4):407-419
- [30] Schott M, Morgenthaler N, Fritzen R, Feldkamp J, Willenberg H, Scherbaum W, et al. Levels of autoantibodies against human TSH receptor predict relapse of hyperthyroidism in Graves' disease. *Hormone and Metabolic Research*. 2004;**36**(02):92-96
- [31] Piticchio T, Frasca F, Trimboli P. Prevalence and significance of indeterminate calcitonin values in patients with thyroid nodules: A systematic review and meta-analysis. *Reviews in Endocrine and Metabolic Disorders*. 2023;**24**(4):685-694
- [32] Trimboli P, Valderrabano P, Pitoia F, Piccardo A, Bojunga J. Appropriate and mindful measurement of serum calcitonin in patients with thyroid nodules. *A White Paper. Endocrine*. 2024;**83**(1):60-64
- [33] Li S, Ren C, Gong Y, Ye F, Tang Y, Xu J, et al. The role of thyroglobulin in preoperative and postoperative evaluation of patients with differentiated thyroid cancer. *Frontiers in Endocrinology*. 2022;**13**:872527
- [34] Chou R, Dana T, Brent GA, Goldner W, Haymart M, Leung AM, et al. Serum thyroglobulin measurement following surgery without radioactive iodine for differentiated thyroid cancer: A systematic review. *Thyroid*. 2022;**32**(6):613-639
- [35] Oh MY, Chai YJ, Yu HW, Kim S-J, Choi JY, Lee KE. Transoral endoscopic thyroidectomy vestibular approach as a safe and feasible alternative to open thyroidectomy: A systematic review and meta-analysis. *International Journal of Surgery*. 2023;**109**(8):2467-2477
- [36] Liu Z, Li Y, Wang Y, Xiang C, Yu X, Zhang M, et al. Comparison of the transoral endoscopic thyroidectomy vestibular approach and open thyroidectomy: A propensity score-matched analysis of surgical outcomes and safety in the treatment of papillary thyroid carcinoma. *Surgery*. 2021;**170**(6):1680-1686
- [37] Deandrea M, Trimboli P, Garino F, Mormile A, Magliona G, Ramunni MJ, et al. Long-term efficacy of a single session of RFA for benign thyroid nodules: A longitudinal 5-year observational study. *The Journal of Clinical Endocrinology & Metabolism*. 2019;**104**(9):3751-3756
- [38] Ntelis S, Linos D. Efficacy and safety of radiofrequency ablation in the treatment of low-risk papillary thyroid carcinoma: A review. *Hormones*. 2021;**20**(2):269-277
- [39] Couch SM. Teprotumumab (Tepezza) for thyroid eye disease. *Missouri Medicine*. 2022;**119**(1):36
- [40] Vandse S, Psarrakis Y, Washington K, Baron MA. Comparative bioavailability of a novel solution and a tablet formulation of levothyroxine. *Clinical Pharmacology in Drug Development*. 2023;**12**(5):502-508
- [41] Antonelli A, Elia G, Ragusa F, Paparo SR, Cavallini G, Benvenega S, et al. The stability of TSH, and thyroid hormones, in patients treated with tablet, or liquid levo-thyroxine. *Frontiers in Endocrinology*. 2021;**12**:633587

- [42] Bianco AC. Emerging therapies in hypothyroidism. *Annual Review of Medicine*. 2024;**75**:307-319
- [43] Tariq A, Wert Y, Cheriya P, Joshi R. Effects of long-term combination LT4 and LT3 therapy for improving hypothyroidism and overall quality of life. *Southern Medical Journal*. 2018;**111**(6):363
- [44] Vargas-Uricoechea H, Wartofsky L. LT4/LT3 combination therapy vs. monotherapy with LT4 for persistent symptoms of hypothyroidism: A systematic review. *International Journal of Molecular Sciences*. 2024;**25**(17):9218
- [45] Idrees T, Price JD, Piccariello T, Bianco AC. Sustained release T3 therapy: Animal models and translational applications. *Frontiers in Endocrinology*. 2019;**10**:544
- [46] Santini F, Giannetti M, Ricco I, Querci G, Saponati G, Bokor D, et al. Steady-state serum T3 concentrations for 48 hours following the oral administration of a single dose of 3, 5, 3'-triiodothyronine sulfate (T3S). *Endocrine Practice*. 2014;**20**(7):680-689
- [47] Zhao M, Xie H, Shan H, Zheng Z, Li G, Li M, et al. Development of thyroid hormones and synthetic thyromimetics in non-alcoholic fatty liver disease. *International Journal of Molecular Sciences*. 2022;**23**(3):1102
- [48] Ancker OV, Krüger M, Wehland M, Infanger M, Grimm D. Multikinase inhibitor treatment in thyroid cancer. *International Journal of Molecular Sciences*. 2019;**21**(1):10
- [49] De Leo S, Di Stefano M, Persani L, Fugazzola L, Colombo C. Lenvatinib as first-line treatment for advanced thyroid cancer: Long progression-free survival. *Endocrine*. 2021;**72**:462-469
- [50] Subbiah V, Kreitman RJ, Wainberg ZA, Cho JY, Schellens JH, Soria JC, et al. Dabrafenib and trametinib treatment in patients with locally advanced or metastatic BRAF V600-mutant anaplastic thyroid cancer. *Journal of Clinical Oncology*. 2018;**36**(1):7-13
- [51] Lieberman L, Worden F. Novel therapeutics for advanced differentiated thyroid cancer. *Endocrinology and Metabolism Clinics of North America*. 2022;**51**(2):367-378
- [52] Vodopivec DM, Hu MI. RET kinase inhibitors for RET-altered thyroid cancers. *Therapeutic Advances in Medical Oncology*. 2022;**14**:17588359221101691
- [53] Wirth LJ, Sherman E, Robinson B, Solomon B, Kang H, Lorch J, et al. Efficacy of selpercatinib in RET-altered thyroid cancers. *New England Journal of Medicine*. 2020;**383**(9):825-835
- [54] Jannin A, Escande A, Al Ghuzlan A, Blanchard P, Hartl D, Chevalier B, et al. Anaplastic thyroid carcinoma: An update. *Cancers*. 2022;**14**(4):1061
- [55] Rousseau A, Michiels S, Bonastre J, Lolivier A, Planchard D, Barlesi F, et al. Overall Survival Impact of Pembrolizumab Duration and Comorbidities on Advanced NSCLC: A Nationwide Cohort Study. Boston, Massachusetts, USA: Massachusetts Medical Society; 2020
- [56] Nervo A, Retta F, Ragni A, Piovesan A, Gallo M, Arvat E. Management of progressive radioiodine-refractory thyroid carcinoma: Current perspective. *Cancer Management and Research*. 2022;**14**(4):1061
- [57] Derbel O, Limem S, Ségura-Ferlay C, Lifante J-C, Carrie C, Peix J-L, et al. Results of combined

treatment of anaplastic thyroid carcinoma (ATC). *BMC Cancer*. 2011;**11**:1-8

[58] Pishdad R, Treglia G, Mehta A, Santhanam P. Somatostatin receptor imaging of thyroid tissue and differentiated thyroid cancer using gallium-68-labeled radiotracers—A review of clinical studies. *Endocrine*. 2024;**85**(2):566-575

[59] Alzumaili B, Sadow PM. Update on molecular diagnostics in thyroid pathology: A review. *Genes*. 2023;**14**(7):1-8

[60] Romei C, Elisei R. RET/PTC translocations and clinico-pathological features in human papillary thyroid carcinoma. *Frontiers in Endocrinology*. 2012;**3**:54

[61] Ganly I, McFadden DG. Short review: Genomic alterations in Hürthle cell carcinoma. *Thyroid*. 2019;**29**(4):471-479

[62] Gruber JJ, Colevas AD. Differentiated thyroid cancer: Focus on emerging treatments for radioactive iodine-refractory patients. *The Oncologist*. 2015;**20**(2):113-126

[63] Grixti L, Lane LC, Pearce SH. The genetics of Graves' disease. *Reviews in Endocrine and Metabolic Disorders*. 2024;**25**(1):203-214

[64] Lubitz CC, Sadow PM, Daniels GH, Wirth LJ. Progress in treating advanced thyroid cancers in the era of targeted therapy. *Thyroid*. 2021;**31**(10):1451-1462

[65] Menicali E, Guzzetti M, Morelli S, Moretti S, Puxeddu E. Immune landscape of thyroid cancers: New insights. *Frontiers in Endocrinology*. 2021;**11**:637826

[66] D'Andréa G, Lassalle S, Guevara N, Mograbi B, Hofman P. From biomarkers to therapeutic targets: The promise of PD-L1 in thyroid autoimmunity and cancer. *Theranostics*. 2021;**11**(3):1310

[67] Tomer Y, Barbesino G, Greenberg DA, Concepcion E, Davies TF. Mapping the major susceptibility loci for familial Graves' and Hashimoto's diseases: Evidence for genetic heterogeneity and gene interactions. *The Journal of Clinical Endocrinology & Metabolism*. 1999;**84**(12):4656-4664

[68] Allison JP, Krummel MF. The Yin and Yang of T cell costimulation. *Science*. 1995;**270**(5238):932

[69] Eliana F, Suwondo P, Asmarinah A, Harahap A, Djauzi S, Prihartono J, et al. The role of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) gene, thyroid stimulating hormone receptor (TSHR) gene and regulatory T-cells as risk factors for relapse in patients with Graves disease. *Acta Medica Indonesiana*. 2017;**49**(3):195-204

[70] Mokoagow MI, Manthovani AZ, Epriliawati M. Outcome of Graves' disease and associated genetic predisposition: A systematic review of literature. *medRxiv*. 2024;**270**:932-932. 2024.09.27.24314519

[71] Stramazzo I, Capriello S, Filardo S, Centanni M, Virili C. Microbiota and thyroid disease: An updated systematic review. In: Donelli G, editor. *Advances in Microbiology, Infectious Diseases and Public Health*. Vol. 17. Cham: Springer International Publishing; 2023. pp. 125-144

[72] Liu Q, Sun W, Zhang H. Interaction of gut microbiota with endocrine homeostasis and thyroid cancer. *Cancers*. 2022;**14**(11):2656

- [73] Giancchetti E, Delfino DV, Fierabracci A. Recent insights into the role of the PD-1/PD-L1 pathway in immunological tolerance and autoimmunity. *Autoimmunity Reviews*. 2013;**12**(11):1091-1100
- [74] Pearce SHS, Dayan C, Wraith DC, Barrell K, Olive N, Jansson L, et al. Antigen-specific immunotherapy with thyrotropin receptor peptides in Graves' hyperthyroidism: A phase I study. *Thyroid®*. 2019;**29**(7):1003-1011
- [75] Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid®*. 2016;**26**(10):1343-1421
- [76] Giancchetti E, Delfino DV, Fierabracci A. Erratum notice for duplicate publications. *Endocrine Reviews*. 2020;**41**(6):886
- [77] Villagelin D, Romaldini JH, Santos RB, Milkos ABBP, Ward LS. Outcomes in relapsed Graves' disease patients following radioiodine or prolonged low dose of methimazole treatment. *Thyroid®*. 2015;**25**(12):1282-1290
- [78] Bartalena L, Baldeschi L, Dickinson A, Eckstein A, Kendall-Taylor P, Marcocci C, et al. Consensus statement of the European Group on Graves' orbitopathy (EUGOGO) on management of GO. *European Journal of Endocrinology*. 2008;**158**(3):273-285
- [79] Gharib H, Papini E, Paschke R, Duick DS, Valcavi R, Hegedüs L, et al. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European thyroid association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules: Executive summary of recommendations. *Endocrine Practice*. 2010;**16**(3):468-475
- [80] Smith TJ, Kahaly GJ, Ezra DG, Fleming JC, Dailey RA, Tang RA, et al. Teprotumumab for thyroid-associated ophthalmopathy. *The New England Journal of Medicine*. 2017;**376**(18):1748-1761
- [81] Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. *Endocrine Reviews*. 2008;**29**(1):76-131
- [82] Fadel BM, Ellahham S, Ringel MD, Lindsay J Jr, Wartofsky L, Burman KD. Hyperthyroid heart disease. *Clinical Cardiology*. 2000;**23**(6):402-408
- [83] Akamizu T, Satoh T, Isozaki O, Suzuki A, Wakino S, Iburi T, et al. Diagnostic criteria, clinical features, and incidence of thyroid storm based on nationwide surveys. *Thyroid*. 2012;**22**(7):661-679
- [84] Chiha M, Samarasinghe S, Kabaker AS. Thyroid storm: An updated review. *Journal of Intensive Care Medicine*. 2015;**30**(3):131-140
- [85] Wiersinga WM. T4+T3 combination therapy: An unsolved problem of increasing magnitude and complexity. *Endocrinology and Metabolism (Seoul)*. 2021;**36**(5):938-951
- [86] Henderson BB, Smith SP, Mengelkamp ME, Rhymer EK, Gray KN, Jackson AG, et al. Liquid thyroxine improves outcomes in hypothyroid patients with small intestinal bacterial overgrowth and irritable bowel syndrome. *Endocrine Practice*. 2024;**30**(6):505-512

- [87] Gencer B, Collet T-H, Virgini V, Bauer DC, Gussekloo J, Cappola AR, et al. Subclinical thyroid dysfunction and the risk of heart failure events. *Circulation*. 2012;**126**(9):1040-1049
- [88] Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, et al. Guidelines for the treatment of hypothyroidism: Prepared by the american thyroid association task force on thyroid hormone replacement. *Thyroid*. 2014;**24**(12):1670-1751
- [89] Stott DJ, Rodondi N, Kearney PM, Ford I, Westendorp RGJ, Mooijaart SP, et al. Thyroid hormone therapy for older adults with subclinical hypothyroidism. *The New England Journal of Medicine*. 2017;**376**(26):2534-2544
- [90] Korevaar TIM, Medici M, Visser TJ, Peeters RP. Thyroid disease in pregnancy: New insights in diagnosis and clinical management. *Nature Reviews Endocrinology*. 2017;**13**(10):610-622
- [91] Patrizio A, Ferrari SM, Elia G, Ragusa F, Balestri E, Botrini C, et al. Hypothyroidism and metabolic cardiovascular disease. *Frontiers in Endocrinology (Lausanne)*. 2024;**15**:1408684
- [92] Nuguru SP, Rachakonda S, Sripathi S, Khan MI, Patel N, Meda RT. Hypothyroidism and depression: A narrative review. *Cureus*. 2022;**14**(8):e28201
- [93] Mullur R, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. *Physiological Reviews*. 2014;**94**(2):355-382
- [94] Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Murad MH, Salvatori R, et al. Hormonal replacement in hypopituitarism in adults: An endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism*. 2016;**101**(11):3888-3921
- [95] Haugen BR. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: What is new and what has changed? *Cancer*. 2017;**123**(3):372-381
- [96] Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. *Journal of the American Medical Association*. 2006;**295**(18):2164-2167
- [97] Ito Y, Miyauchi A, Inoue H, Fukushima M, Kihara M, Higashiyama T, et al. An observational trial for papillary thyroid microcarcinoma in Japanese patients. *World Journal of Surgery*. 2010;**34**(1):28-35
- [98] Tuttle RM, Fagin JA, Minkowitz G, Wong RJ, Roman B, Patel S, et al. Natural history and tumor volume kinetics of papillary thyroid cancers during active surveillance. *JAMA Otolaryngology–Head & Neck Surgery*. 2017;**143**(10):1015-1020
- [99] Nixon IJ, Ganly I, Patel SG, Palmer FL, Whitcher MM, Tuttle RM, et al. Thyroid lobectomy for treatment of well differentiated intrathyroid malignancy. *Surgery*. 2012;**151**(4):571-579
- [100] Randolph GW, Duh QY, Heller KS, LiVolsi VA, Mandel SJ, Steward DL, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. *Thyroid*. 2012;**22**(11):1144-1152
- [101] Schlumberger M, Leboulleux S. Current practice in patients with

- differentiated thyroid cancer. *Nature Reviews Endocrinology*. 2021;**17**(3):176-188
- [102] Fu H, Ma C, Tang L, Wu F, Liu B, Wang H. Recombinant human thyrotropin versus thyroid hormone withdrawal in radioiodine remnant ablation for differentiated thyroid cancer: A meta-analysis. *The Quarterly Journal of Nuclear Medicine and Molecular Imaging*. 2015;**59**(1):121-128
- [103] Tuttle RM, Haugen B, Perrier ND. Updated American Joint Committee on cancer/tumor-node-metastasis staging system for differentiated and anaplastic thyroid cancer (eighth edition): What changed and why? *Thyroid*. 2017;**27**(6):751-756
- [104] Leboulleux S, Bornaud C, Chougnet CN, Zerdoud S, Al Ghuzlan A, Catargi B, et al. Thyroidectomy without radioiodine in patients with low-risk thyroid cancer. *The New England Journal of Medicine*. 2022;**386**(10):923-932
- [105] Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: A randomised, double-blind, phase 3 trial. *Lancet*. 2014;**384**(9940):319-328
- [106] Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *The New England Journal of Medicine*. 2015;**372**(7):621-630
- [107] Wells SA Jr, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: A randomized, double-blind phase III trial. *Journal of Clinical Oncology*. 2012;**30**(2):134-141
- [108] Bible KC, Kebebew E, Brierley J, Brito JP, Cabanillas ME, Clark TJ Jr, et al. 2021 American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. *Thyroid*. 2021;**31**(3):337-386
- [109] Pitoia F, Scheffel RS, Califano I, Gauna A, Tala H, Vaisman F, et al. Management of radioiodine refractory differentiated thyroid cancer: The Latin American perspective. *Reviews in Endocrine & Metabolic Disorders*. 2024;**25**(1):109-121. DOI: 10.1007/s11154-023-09818-0
- [110] Lyu Z, Zhang Y, Sheng C, Huang Y, Zhang Q, Chen K. Global burden of thyroid cancer in 2022: Incidence and mortality estimates from GLOBOCAN. *Chinese Medical Journal*. 2024;**137**(21):2567-2576. DOI: 10.1097/CM9.0000000000003284
- [111] Yang ZM et al. Geographic disparities in thyroid cancer staging at presentation: Insights from an Australian context. *World Journal of Surgery*. 2024;**48**(6):1440-1447

Local Ablation of Thyroid Nodules

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Abstract

Numerous treatment modalities are available for thyroid nodules. Besides conventional surgery, local-ablative therapies play an increasing role for various entities. Now mentioned in most national and international guidelines, minimal-invasive techniques, such as radiofrequency ablation, microwave ablation, laser-induced thermotherapy, high-intensity focused ultrasound and in the future maybe also electroporation, histotripsy or others, have been explored and partly established as valuable tools for interventions on thyroid nodules. The techniques, indications, technical prerequisites and results of them are described in this article. The goal is to provide an overview to describe existing technology and practical use of local ablation for thyroid nodules.

Keywords: benign thyroid nodules, radiofrequency ablation, thermoablation, microwave ablation, local-ablative treatment, guidelines, high-intensive focused ultrasound

1. Introduction

Whereas conventional treatment strategies for thyroid nodules like resection and radioiodine therapy treat at least part of non-nodular, otherwise healthy thyroid tissue as well, either by surgically removing it or by distributing irradiation into the whole gland though heterogeneously, in local ablation exclusively the nodule is treated and functional thyroid tissue remains untangled.

In most cases, local ablation involves the insertion of a needle under image guidance (**Figure 1**), most popular being ultrasound. Either alternating current or other energy sources (laser, ultrasound (US)) lead to tissue destruction; a common mechanism is the generation of heat. Thus, only the nodule volume is treated as long as the area where energy is applied is predictable.

The obvious advantages consist in using a minimal-invasive technique with minimal—if ever—cosmetic constraints due to scar formation, outpatient treatment under local anesthesia and absence of functional impairment due to exclusive nodule treatment without collateral tissue destruction. Local ablation of thyroid nodules is therefore believed to be particularly cost-effective.

The following chapter is meant to give an overview displaying the various technologies available at date and recommendations on the basis of existing evidence. Besides, the reader finds explanations for common questions and some practical

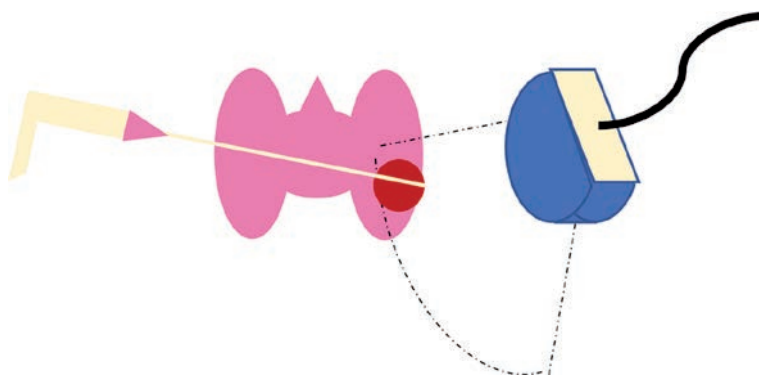


Figure 1.
Schematic principle of local ablation. The yellow applicator enters the pink thyroid gland to reach the red nodule under ultrasound (blue probe) control.

issues. Abundant illustrations will serve as supplement where words are insufficient to describe the whole topic.

2. Monopolar radiofrequency ablation

2.1 Mechanism of action and procedural review

Monopolar radiofrequency ablation (MRFA) is a widely implemented thermal ablation technique used to treat symptomatic benign nodules causing compressive or cosmetic symptoms, autonomously functioning thyroid nodules (AFTNs) and low-risk small papillary thyroid cancers (PTCs).

The decision to treat with MRFA is usually taken by radiologists, thyroid surgeons and endocrinologists, ideally in a multidisciplinary team setting. The cellular nature of benign and malignant nodules should be confirmed with fine needle aspiration (FNA).

Radiofrequency ablation (RFA) generates thermal energy by passing electrical current through the body; focal impedance in the target tissue, in this case the ablation zone in the thyroid nodule, causes heat generation, which in turn results in coagulative necrosis of the ablated tissue. RFA can be delivered using a monopolar or bipolar system. MRFA requires two electrodes, an interstitial electrode placed into the thyroid tissue under ultrasound (US) guidance and a ground electrode (dispersive electrode), usually stuck on the thigh to complete the electrical circuit. Both electrodes transmit current through the patient but the current passing through the interstitial electrode occurs over a small surface area of the probe tip, resulting in heat generation in the surrounding tissue. The current delivered through the grounding pad/dispersive electrode is delivered over a larger surface area, causing dispersal of the generated heat, which is seldom felt. For MRFA of the thyroid, the probes are typically 18 gauge or 19 gauge with an active tip of 7–10 mm in size. Saline passes through the needle continuously to cool it and prevent carbonization of the ablating tissues. For patients with implantable devices such as pacemakers, MRFA may be contraindicated and other minimally invasive modalities such as bipolar RFA (BRFA) or microwave ablation (MWA) may be more appropriate.

The procedure is normally performed using local anesthetic infiltrated down to the thyroid capsule. Sedation can be given, if patients are nervous. If the nodule lies

close to the thyroid capsule, hydrodissection, for example with 0.5% dextrose, can be performed. A general anesthetic is not typically required.

MRFA is performed under direct US guidance, usually as a day case procedure. The transisthmoid approach is used, whereby the probe is inserted at the paramedian anterior midline of the neck, approaching from the side opposite to the side of the nodule. The probe traverses the isthmus to enter the nodule. As a result of the movement of the needle from medial to lateral, the critical anatomical structures of the recurrent laryngeal nerve sited within the 'danger triangle' of the tracheoesophageal groove and the esophagus should be spared, minimizing the risk of recurrent laryngeal nerve injury/voice change and esophageal injury (**Figure 2**). Once the probe has safely been placed into the nodule, the 'moving shot' technique is implemented, whereby in a fixed superoinferior plane, the tip of the probe is placed in the most lateral portion of the target ablation zone and once ablation has been achieved, the tip is moved in-plane from lateral to medial to achieve ablation in the entire mediolateral trajectory of the probe, as shown diagrammatically in **Figure 3** [1, 2].

Three modes of feedback can be observed during ablation to confirm the tissue is adequately ablated, usually in the following order:

- The visual feedback of gas forming in and around the ablation zone.
- A popping sound that is sometimes felt and heard by the patient and operator.
- Drop in power caused by increased resistance/impedance of the ablated tissue. Once there is increased resistance in the ablation zone, the probe tip can be moved according to the 'moving shot' technique described above.

Once ablation has been achieved in a single superoinferior plane, the RFA probe is repositioned under direct US guidance without repeating the puncture into the next superoinferior plane until complete ablation has been achieved. For larger nodules, two puncture sites may be required.

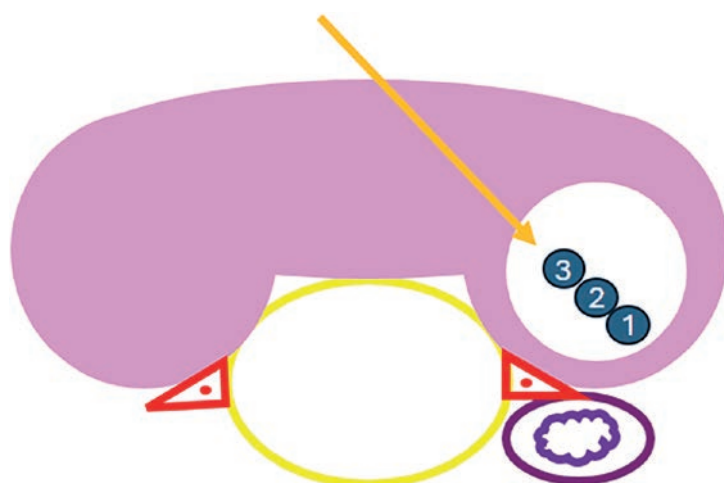


Figure 2.
 Diagram illustrating the 'moving shot' and 'trans-isthmoid approach'. Numbers 1, 2 and 3 are the ablation zones in a single superoinferior plane.

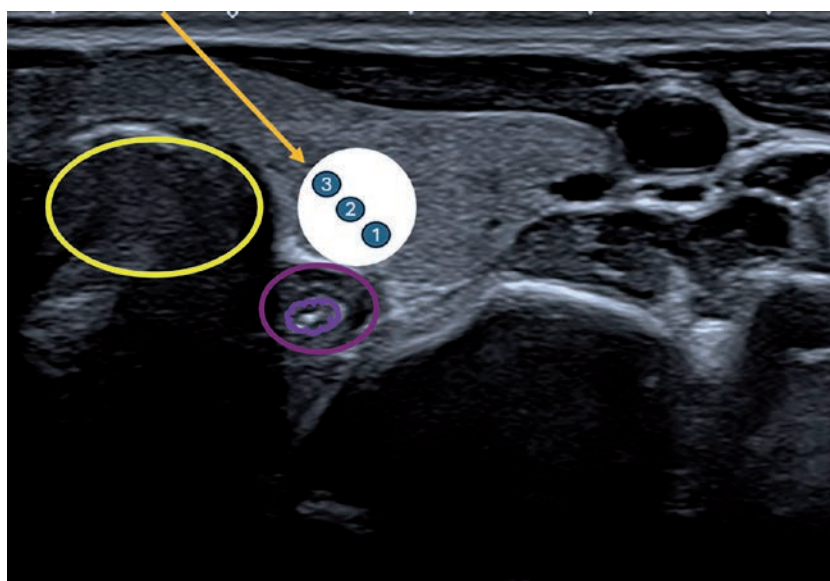


Figure 3.

The 'moving shot' and 'transisthmoid approach' illustrated on real life sonographic anatomy.

A cool pack should be placed directly on the skin once the procedure is over and the wound should be appropriately dressed. Patients usually make a rapid recovery and are typically discharged home in the hours after the procedure. Follow-up with US should be between 1 and 6 months initially, with further follow-up at 12 months as a minimum in order to calculate the volume reduction rate (VRR) and to assess the symptomatic state of the patient and any quality-of-life measures. Repeat treatment may be required if adequate volume reduction to relieve symptoms has not been achieved, especially if viable residual tissue is seen on post-procedure follow-up US; **Figure 4** illustrates the appearances of a nodule after two episodes of MRFA treatment. Retreatment may also be required longer term after the procedure, if there is regrowth from the nidus volume of greater than 50% [3].

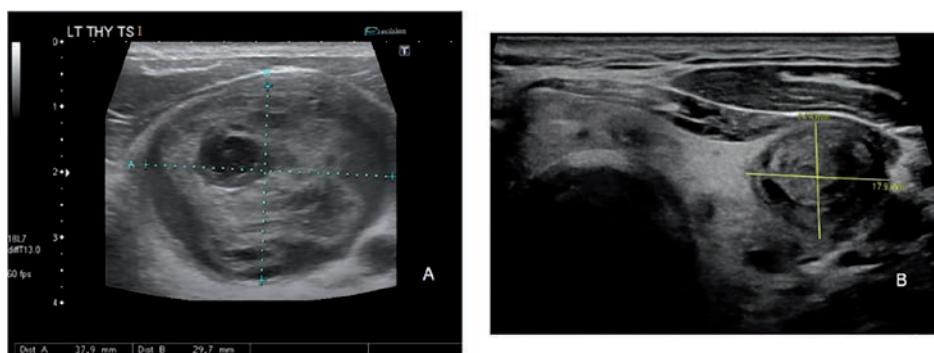


Figure 4.

(A) A symptomatic left-sided nodule prior to monopolar radiofrequency ablation (MRFA). (B) The same nodule as in (A) two post- MRFA treatments. The volume reduction rate of this nodule was 76%.

2.2 Results and efficacy

MRFA has proven to be a safe and effective mode of reducing the volume of symptomatic benign thyroid nodules. Short- and medium-term VRRs representing the difference between the pre- and post-treatment volumes divided by the pretreatment initial volume [1] of 70–90% have been reported [3–7].

A meta-analysis reported rapid reduction in volume is usually achieved by 12 months post-treatment, with a plateau in volume reduction at 12–36 months and further reduction in volume after 36 months, consistent with efficacy over a medium time period [6]. In recent years, longer-term data on the efficacy of MRFA are becoming available, for example, a 10-year follow-up review showed high average VRR of 98.8% at 10.9 years post-treatment [8].

Nodular regrowth can occur after MRFA, possibly because of incomplete ablation, resulting in regrowth of the non-ablated component and this may necessitate further MRFA treatment or surgical excision [3, 9].

2.3 Complications

MRFA is a safe procedure with a low complication rate of 0–16.7% for all complications and 3.8% for serious complications [6, 10–12]. Multiple complications can occur, and these can be classified as immediate/early and delayed as follows.

- Immediate/early complications

- Skin burn
- Voice change
- Tracheal injury
- Hemorrhage

- Late complications

- Hypothyroidism
- Nodule rupture
- Infection

Nerve injury, tracheal injury and nodule rupture, which may require further radiological or surgical interventions, are major complications [13–16].

While nerve injury/voice change and tracheal injury may manifest rapidly, nodule rupture is a delayed complication that occurs in the weeks after thyroid MRFA and occurs when there is loss of integrity of the thyroid capsule, with resultant extravasation of the treated nodule contents in the soft tissues surrounding the thyroid (**Figure 5**), which mainly presents as sudden onset of swelling and occasionally pain and redness in the anterior neck. More rarely, the ruptured contents can cause compression on the trachea, necessitating urgent surgical intervention. The

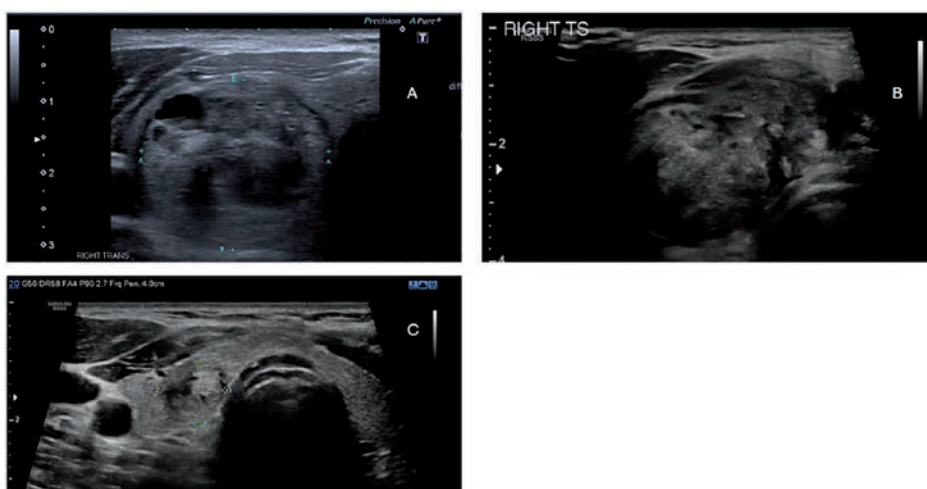


Figure 5.
(A) A right-sided thyroid nodule, prior to monopolar radiofrequency ablation (MRFA) treatment. (B) Nodule rupture 5 weeks post-MRFA treatment, note the extruded ablated nodular tissue lying in an extracapsular location deep to the strap muscles. (C) The same nodule 6 months post-nodule rupture; the patient was treated with expectant treatment and oral antibiotics alone.

incidence of nodule rupture is 0.2–2.5% [17, 18]. The pathophysiology of nodule rupture is not yet understood, hypotheses for it include intranodular hemorrhage [10, 19], low-grade infection, overpalpation by the patient and breakdown of the capsule secondary to mechanical forces at the fulcrum of the RFA probe combined with thermal disruption of the capsule [20]. Management strategies include conservative treatment (a watch and wait approach with serial imaging and clinical review), medical treatment with intravenous antibiotics and surgical management with incision and drainage or lobectomy.

2.4 Pros & cons

- + Most experience among all local-ablative treatment strategies.
- + Overwhelming data support.
- Inherent limitations due to technical conditions (heat sink).
- Contraindications in patients with cardiac pacemaker systems.

2.5 Conclusions

MRFA of thyroid nodules is an effective and safe treatment. It has revolutionized the way that patients with certain thyroid nodules are managed, offering an alternative to more invasive thyroid surgery. It is however not without complications, one of the more serious being nodule rupture, which may cause tracheal compromise necessitating surgical intervention. Appropriate patient selection for MRFA is vital, ideally with input from the multidisciplinary clinical team, including surgeons, endocrinologists and radiologists.

3. Bipolar radiofrequency ablation (BRFA)

3.1 Mechanism of action and procedural overview

RFA uses a high-frequency generator that generates a field with frequencies of 200–1200 kHz. The electric field is applied via a special usually cooled probe. Cooling takes place by means of isotonic saline solution via a microcapillary system within the probe using a separate pump system. Frictional heat of 60–100°C is generated at the approx. 2 mm wide probe tip (active tip) due to an induced ion oscillation in the tissue, which leads to coagulation necrosis of the tissue. Both bipolar and monopolar ablation systems are widely used. The latter require a surface grounding electrode (usually applied to the thigh). In the vast majority of cases, the trans-isthmus approach is chosen to treat a thyroid nodule. The first RFA on a thyroid nodule was performed in 2006 using the monopolar technique in South Korea [21]. Bipolar technology is also known for years, more popular in Germany and characterized by special applicators incorporating both electrodes required for a closed current circuit in one needle with one electrode at the tip of the needle and the other one nearby at the shaft. Depending on the distance from one to the other, the length of the active tip is determined and accordingly the field where radiometer long waves are emitted.

For the treatment, the patient is positioned with the neck reclined (**Figure 6**) and with the practitioner in an overhead position, sometimes also in a lateral position. During application, the ultrasound probe is held in one hand and the radiofrequency probe in the other (**Figure 7**).

Radiofrequency ablation should be performed under local anesthesia. Approx. 5–10 mL each of 1–2% lidocaine (mepivacaine, procaine) is applied subcutaneously and between the infrahyoid fascia and thyroid capsule, respectively (**Figure 8**).

Depending on the sharpness of the probe tip, the actual application continues with a scalpel incision (2–3 mm) in the area of the isthmus (trans-isthmus approach, **Figure 2**) or, more rarely, between the sternocleidomastoid and sternohyoid muscles (lateral approach), through which the radiofrequency probe is inserted into the lump or cyst (**Figure 9**). Some tips do not need a scalpel incision and the operator can place the probe directly through the skin into the desired target location, where heat is applied.

Depending on the user's preference, the nodule is now processed with the Moving Shot Technique or Multiple Overlapping Shot Technique (MOST) [22]. The grape-like ablation zones along the tip of the probe are lined up in overlapping rows within the nodule volume, until the entire volume has been 'filled' or treated. Particular attention must be paid to the treatment of the peripheral zones, because there is the vascularization (arterial and venous) of the nodule, which has a significant influence on the success of the treatment (final, permanent volume reduction of the nodule vs. regrowth of the incompletely treated nodule, persistence of hyperthyroidism/'hyperthyroid' symptoms or risk of recurrence in autonomous adenomas) [23]. In general, two techniques are distinguished: (1) Artery-first ablation, in which the nodal artery is closed upfront in order to reduce the heat sink effect (undesired removal of energy at the tip of the probe through large vessels) and to cut off the arterial supply to the nodule (particularly important in autonomous nodules and cysts). (2) Marginal vein ablation is used to destroy the marginal veins; this technique accelerates shrinkage and minimizes regrowth of the nodule [2].



Figure 6.
Setup for bipolar radiofrequency ablation with patient.

Hydrodissection has been described as a further technique for protecting critical structures [24]: The slow injection of cooled, isotonic saline solution or 5% glucose solution forms a heat barrier between the target nodule and the critical cervical structures, thus protecting them from heat damage.

Temperatures of 60–100°C are generated around the active tip leading to immediate tissue coagulation. In the ultrasound image, echo-dense areas around the probe tip ('microbubbles') can be demarcated within the hypoechoic nodule (compared to the echogenicity of the thyroid gland); the surrounding tissue dries out. By continuously measuring the impedance between the tissue and the probe, the energy transfer is reduced, while the local dehydration causes an impedance increase. Once the area is



Figure 7.
Trans-isthmus approach. Left hand: RFA probe, right hand: ultrasound probe.



Figure 8.
Pericapsular infiltration of local anesthesia.

sufficiently treated, the next area within the nodule volume can be treated. This is an important feedback loop that can be used to determine the end point for application within this area.

Figure 10 shows a completely treated nodule with immediate reduction of volume due to loss of liquid (destroyed cystic chambers) and a significant reduction of perfusion of the marginal vessels (complete white rim of microbubbles surrounding the nodule).

3.2 Clinical outcomes and efficacy

RFA has demonstrated high efficacy in reducing nodule volume and alleviating symptoms. Studies report:

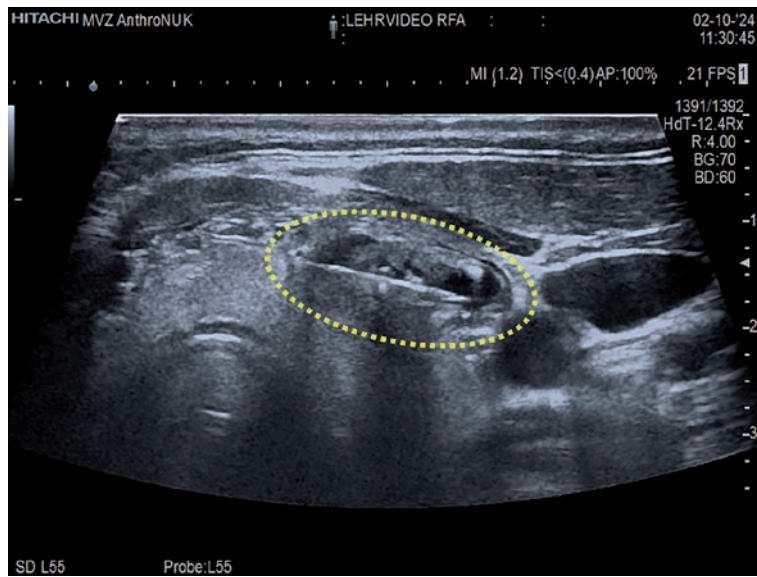


Figure 9.
RFA probe inside of a thyroid nodule.

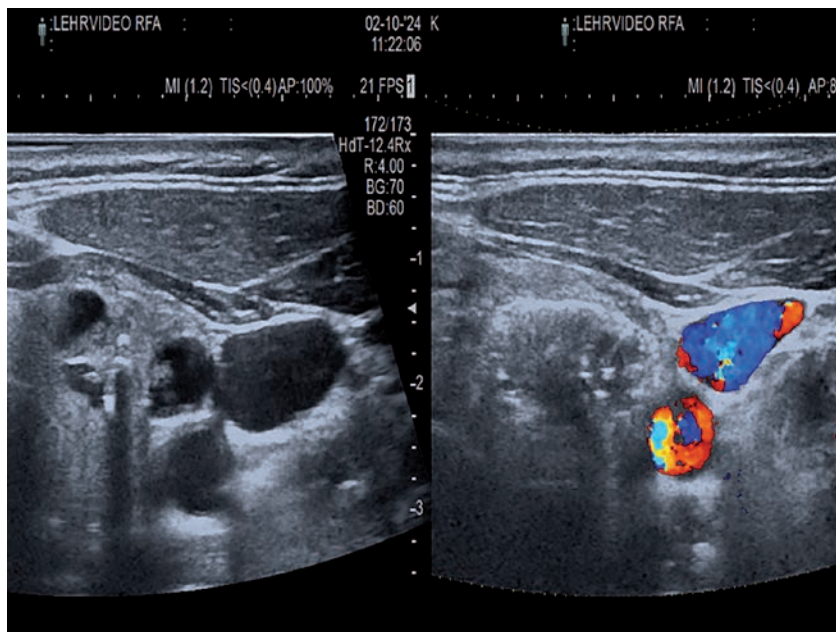


Figure 10.
Thyroid nodule before (left) and after treatment (right).

- Mean volume reduction rates of 80–90% were found for RFA at 12-month follow-up [25]. Over 90% of patients with treated autonomous adenomas were still euthyroid after 12 months and longer periods. In longer follow-up studies of up to 10 years, significant and stable volume reduction rates of >90% were demonstrated [26].

- Significant improvement in compressive symptoms, including dysphagia, globus sensation and cosmetic concerns [25].
- Treatment of autonomously functioning thyroid nodules (AFTNs) with RFA is superior to radioiodine therapy (RAI) regarding safety profile (no hypothyroidism vs. 10% with RAI, no radiation vs. radioactive iodine) offering a similar success rate > 90% (stable euthyroidism) [own data].
- Low regrowth rates 5 years post-treatment comparable to microwave ablation (MWA) (<5%), superior to laser ablation (LA, 13–28%) [27].
- Lowest rates of minor and major complications compared to all other thermoablative techniques [28].

3.3 Complications

Radiofrequency ablation is considered a safe and well-tolerated procedure. The majority of complications is minor. They normally resolve on their own with no need of medical or any therapeutic intervention.

We distinguish intratherapeutic and post-therapeutic complications.

Intratherapeutic complications can include bleeding (subcutaneous and prethyroidal), hypertonic crisis, vasovagal reflex, hypoglycemia, neural discomfort and pain due to the proximity of the nodule to anatomical structures, a transient paresis of the recurrent laryngeal nerve (RLN) or a nodule rupture due to an insufficiency of the thyroid capsule. Most of these complications can be avoided by carefully informing the patient in advance (e.g. discontinuation of anticoagulants, not fasting before the procedure) and by using certain techniques to protect vulnerable anatomical structures (e.g. hydrodissection).

Among the more or less frequent post-therapeutic complications are post-operative bleeding due to cervical pressure (sport, lifting heavy objects, etc.). Patients are requested to countervail by consistently adhering to behavioral rules.

Complications, such as infections, irreversible recurrent paresis and Horner's syndrome, are extremely rare.

3.4 Pros & cons

- + Technology well known for years.
- + No grounding pads required, no contraindications in patients with electronic devices.
- Inherent limitations due to technical conditions (heat sink).
- Technical complexity is comparably expensive.

3.5 Conclusion

Radiofrequency ablation (RFA) nowadays plays a significant role in the treatment portfolio of surgeons and interventionalists. It is a minimally invasive and highly effective alternative to classical surgery, which preserves the thyroid being one of the most important organs of well-being, stress management and whole body energy administration. RFA offers the highest safety and the lowest risk profile compared to all other thermoablative techniques [28].

RFA shows the lowest post-treatment rates of hoarseness, vocal cord palsy and regrowth. Skin burn is not a common complication at all, and no hypothyroidism or hypoparathyroidism is caused.

Reduction of volume, symptom and cosmetic scores of ablated nodules are comparable to microwave ablation (MWA) [28, 29], while RFA is the safer method for learning an initial thermoablative procedure.

Future research and investigation should focus on optimizing the efficacy and safety of minimally invasive thermoablative techniques and should raise the awareness of both, patients and users alike, RFA and MWA being a sensible addition to thyroid treatment options and an organ-preserving alternative to conventional surgery.

4. Microwave ablation (MWA)

4.1 Mechanism of action and procedural overview

MWA is a thermal ablation technique that utilizes electromagnetic waves to generate heat within biological tissues. The oscillating microwave field, typically set at 915 MHz or 2.45 GHz, induces rapid molecular rotation of water molecules, generating intense frictional heat [30]. This leads to protein denaturation, cellular apoptosis and irreversible coagulative necrosis, effectively destroying the targeted tissue.

An example for the setup of equipment for interventional thyroid treatments including microwave ablation is displayed in **Figure 11**. Compared to other thermal ablation methods, MWA offers several key advantages:

- It reaches higher intratumoral temperatures (100–150°C), ensuring complete tissue necrosis, whereas RFA typically reaches only 60–100°C [29].
- It delivers energy more rapidly and uniformly, reducing the risk of incomplete ablation [30].
- It is less affected by the heat sink effect, making it more effective in treating highly vascularized nodules [31].
- It creates wider ablation zones, decreasing the need for multiple needle insertions and reducing procedure time [32].

During the procedure, the patient is positioned supine with the neck hyperextended to optimize thyroid gland access (**Figure 12**). Local anesthesia (1% lidocaine) is injected along the needle trajectory to minimize discomfort. In cases of large nodules or nodules close to critical structures, a hydrodissection technique is used, where sterile water or 5% glucose solution is injected to create a protective barrier around the thyroid capsule, separating it from the trachea, esophagus and recurrent laryngeal nerve [32].

Under ultrasound guidance, the MWA antenna (typically 18-17G) is inserted percutaneously into the nodule using a transisthmoid approach, which helps stabilize the probe and reduce the risk of thermal damage to surrounding structures.

A widely used energy delivery technique is the moving shot method, where the probe is repositioned within the nodule to ensure complete and uniform necrosis [30]. Once the generator is activated, energy is delivered for 5–10 minutes, depending



Figure 11.

Tower with three generators earmarked for thyroid ablation. The yellow arrow points at the Laser generator (Leonardo® Dual 45, biolitec® biomedical technology GmbH, Jena, Germany), the orange one at a microwave generator (AveCure®, MedWaves, Inc., San Diego, CA, USA) and the blue one at a monopolar radiofrequency generator (RF ablation system V-1000 with 140 W output, RF Medical Co., Inc., Seoul, South Korea).

on the nodule's size and vascularization. The temperature in the ablation zone rises above 100°C, leading to instant coagulative necrosis.

Throughout the procedure, continuous ultrasound monitoring is crucial. The presence of gas bubbles within the treated nodule is a key indicator of successful vaporization and necrosis [29].

After ablation, contrast-enhanced ultrasound (CEUS) is often performed to confirm that the treated area is non-vascularized, ensuring complete nodule destruction.

Recently, a new technique has been described for thyroid MWA, the “fluid motion technique” [33]. With this technique, the MWA antenna is inserted into the nodule,



Figure 12. Whereas microwave ablation might be performed under sterile conditions in a fully equipped operation theater (left side) or in the general practitioner's office (right side), it is recommended to observe general rules of hygienics and patients' safety as outlined by the World Health Organization, among others.

and then continuously moved within it, in order to achieve both mechanical and thermal destruction, with reported faster ablation and excellent results. Patients are monitored for immediate complications, including hematoma, transient voice changes or localized pain [31].

4.2 Clinical outcomes and efficacy

MWA has demonstrated high efficacy in reducing nodule size and alleviating symptoms (**Figure 13**). Studies report:

- A 65–85% reduction in nodule volume within 6–12 months [29–31].
- Significant improvement in compressive symptoms, including dysphagia, globus sensation and cosmetic concerns [30].
- Lower recurrence rates (<5%), superior to laser ablation (LA) [31].

One of the major advantages of MWA over surgery is the preservation of thyroid function. Unlike thyroidectomy, which often results in hypothyroidism, MWA selectively ablates the target nodule while preserving healthy thyroid tissue [31, 32]. Studies indicate that post-ablation hypothyroidism occurs in less than 1% of cases, making MWA an excellent alternative for patients wishing to avoid lifelong hormone replacement therapy [31].

4.3 Complications

While microwave ablation is considered a safe and well-tolerated procedure, it is not entirely free from risks. Fortunately, the majority of complications are minor and



Figure 13.
 Patient with a visible thyroid nodule. A. Before treatment. B. Immediately prior to ablation, local anesthesia and incision have already been performed. C. One week following microwave ablation. The protruding aspect is already vanished.

resolve on their own with minimal medical intervention. However, in rare cases, more significant issues can arise that require prompt medical attention. Understanding these potential complications allows for better preparation and risk mitigation.

Most patients undergoing MWA will experience some degree of discomfort or transient side effects, which are usually short-lived. Since MWA involves thermal energy deposition, it is common for patients to feel mild to moderate neck pain or a burning sensation during and after the procedure. This typically resolves within a few days and can be managed with over-the-counter pain relievers like NSAIDs (nonsteroidal anti-inflammatory drugs) or acetaminophen. Some patients may notice slight swelling or bruising around the treatment area due to minor vascular irritation. This is generally harmless and fades within a week or two without requiring specific treatment. Because the thyroid is close to the trachea and esophagus, temporary coughing or mild swallowing difficulties may occur. This is often due to minor irritation of nearby structures rather than actual tissue damage and usually resolves within a few days.

Although rare, some complications may require medical intervention, one of the more concerning yet uncommon risks is temporary hoarseness due to thermal irritation of the recurrent laryngeal nerve (RLN). Most cases improve within weeks to months, but in extremely rare instances, nerve damage may be permanent. The use of hydrodissection techniques significantly reduces this risk. While uncommon, some patients may develop a hematoma (localized bleeding) due to vascular injury during the procedure. If the hematoma is small, it typically resolves on its own, but larger ones may need drainage or surgical intervention. Because MWA involves high temperatures, there is a minimal risk of superficial burns if the energy is not properly distributed. This can be prevented by proper probe placement and monitoring during the procedure. Excessive heating or improper probe placement could, in rare cases, lead to damage to the trachea or esophagus. Hydrodissection and careful ultrasound guidance help prevent this [34]. A very rare complication that occurs if thermal damage creates an abnormal connection between the thyroid and adjacent structures,

such as the trachea or esophagus (Fistula). This is exceedingly uncommon and typically only occurs in cases of excessive energy application [35].

4.4 Pros & cons

- + Powerful technology also for larger target volumes.
- + Sound database.
- + No grounding pads required, pacemaker resembles no contraindication.
- Requires some experience with thermoablation.
- Success depends on dielectric properties of the nodule (difficult to predict).

4.5 Conclusion

Microwave ablation (MWA) represents a major advancement in the treatment of thyroid nodules, offering a minimally invasive, highly effective and safe alternative to surgery. With its superior thermal efficiency, larger ablation zones and lower recurrence rates, MWA has become a preferred option for experienced interventional radiologists.

Compared to other percutaneous techniques, MWA demonstrates faster energy delivery, larger treatment areas and better resistance to heat sink effects, making it particularly effective for large or highly vascularized nodules.

Future research should focus on refining patient selection criteria and optimizing procedural techniques to further enhance the efficacy and safety of this innovative approach [29–32].

5. Laser ablation

5.1 Mechanism of action and procedural overview

The word “Laser” is the abbreviation of Light Amplification by Stimulated Emission of Radiation. Laser light has unique physical properties, including coherence (the light waves are phase-locked and travel in a uniform direction), monochromaticity (it consists of a single wavelength or color) and collimation (the light beams remain narrow and do not spread out). These properties allow laser light to be highly focused and to precisely deliver the thermal energy, which is absorbed by the targeted tissue, causing rapid heating. This heat leads to thermal denaturation, coagulation or vaporization of the tissue. For the application in the body, very thin optical fibers can be used (0.3 mm) into the tissue to be treated in order to deliver high-intensity laser energy [36].

For application in the thyroid, laser fibers are inserted through exceptionally thin needles under US guidance, in a very precise way. **Figure 14** shows the content of a set earmarked for thyroid ablation. During the procedure, the patient is positioned supine with the neck extended to facilitate access to the thyroid gland. Local anesthesia is administered to ensure patient comfort [37]. Under real-time ultrasound guidance, a 21G or 19G needle is inserted into the nodule, through which an optical fiber is advanced into the targeted tissue [36, 38].

Laser ablation (LA) typically employs wavelengths of 1064 nm or 980 nm, with energy settings ranging from 3 to 5 W and a total energy delivery between 1200 and



Figure 14.
Content of a set earmarked for Laser ablation of the thyroid. The needle (left margin) is separately inserted before placement of the coiled up glass fiber applicator (right).

3600 J per session [36]. A typical generator is illustrated in **Figure 11**. Throughout the procedure, continuous ultrasound monitoring is essential to ensure precise fiber placement and adequate thermal coverage. The ablation process is considered complete when the desired coagulation zone is achieved [39].

Laser provides excellent precision, thus minimizing the risk of damage to surrounding structures, making it a particularly safe and effective option in selected cases [1]. However, the success of LA is highly operator-dependent, requiring experience in ultrasound-guided interventions to achieve optimal results while minimizing complications [36].

According to the nodule size and shape, single and multiple optical fibers can be used. Single-fiber techniques are preferred for smaller nodules, while multiple fibers may be necessary for larger nodules exceeding 30 mL [40].

5.2 Results and efficacy

Meta-analyses have reported that LA achieves a 48–52% volume reduction within 6–12 months, with a sustained reduction of 44% at 36 months (**Figure 15**) [40]. In very large nodules, long-term follow-up studies indicate a volume reduction rate (VRR) of 80–81% at 4 years [37].

Studies have shown that up to 85% of patients experience significant symptom relief and esthetic improvement following LA treatment (**Figure 16**) [40, 41].

Follow-up data suggest that LA provides stable results over 3–5 years, with only a small percentage of patients requiring additional treatment due to nodule regrowth [37].

5.3 Complications

Laser ablation is considered a well-tolerated procedure with a low complication rate [42]. Reported complications include:

- Transient pain or swelling (3–6%)—Typically mild and self-limiting [37].
- Hematoma formation (1–2%)—Usually resolves without intervention [42].
- Voice changes (temporary recurrent laryngeal nerve injury, <1%)—A rare occurrence due to thermal injury, which generally resolves within weeks [36].

5.4 Pros & cons

- + Inexpensive consumables.
- + Good visualization in real-time ultrasound.
- Only for small nodules (< 12 mL volume) recommended.
- Bipartite access system needs getting used to.

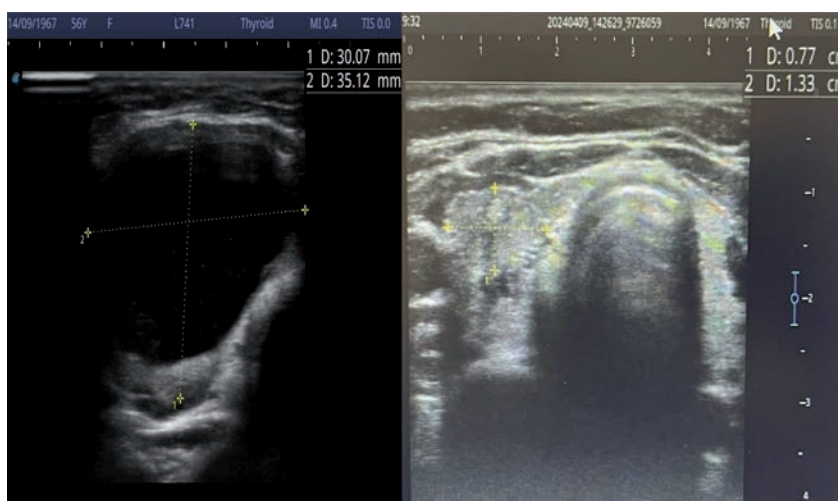


Figure 15.
Ultrasound view of a predominantly cystic thyroid nodule before (left) and 7 months after (right) Laser ablation.



Figure 16.
Patient before (left) and 4 months after Laser ablation (right) of a thyroid nodule.

5.5 Conclusion

Laser ablation represents a valuable minimally invasive option for the treatment of thyroid nodules, offering high precision, low complication rates and significant volume reduction [36]. It is particularly beneficial for patients who seek an alternative to surgery or have contraindications to other treatment modalities [42].

When compared to other percutaneous methods, LA provides superior precision and a lower complication rate, making it a good option for specific clinical scenarios [2]. However, nodule regrowth remains a challenge, and further studies are needed to refine patient selection criteria and optimize procedural techniques [40].

6. High-intensity focused ultrasound

6.1 Mechanism of action and procedural overview

ECHOPULSE® is the first robotic and completely non-invasive solution for echo-therapy treatment (High-Intensity Focused Ultrasound = HIFU) of thyroid nodules. It does not require surgery and can be performed without damaging surrounding tissue.

The treatment can be conducted on an outpatient basis without a hospital stay and takes an average of approximately 1 hour.

The ECHOPULSE® system uses High-Intensity Focused Ultrasound (HIFU) to deliver thermal energy to a specific area for ablation. It combines a therapeutic ultrasound probe with a standard linear ultrasound probe, allowing for targeted heat delivery while simultaneously providing real-time imaging.

The concentrated thermal energy delivered by the HIFU beam causes the targeted tissue to heat up to 85°C, leading to tissue destruction through coagulation, necrosis and protein denaturation.

6.2 How I do it

To determine the possible option of HIFU treatment of a thyroid nodule, a detailed diagnostic work-up is performed in our practice with sonography, scintigraphy and methoxy-isobutyl-isonitrile (MIBI) scintigraphy for dignity clarification. Only nodules classified as benign are eligible for treatment with HIFU.

If echotherapy of the thyroid node is conducted under local anesthesia, it is usually not painless, particularly in case of larger nodules and longer treatment periods. In most cases, mild sedation or application of intravenous analgetic medication is considered, while general anesthesia or deep sedation is not required. **Figure 17** provides an impression of the general assembly in our interventional suite.

We therefore perform the treatment in our practice with the support of an anesthesiologist using a laryngeal mask, which guarantees not only freedom from pain but also a reliable immobilization of the patient and thus a trouble-free course of treatment. This can also significantly reduce the duration of treatment time



Figure 17.
High-intensity focused ultrasound in an interventional suite of a private office as a day-surgical procedure. Overview of the arrangement of the ECHOPULSE® system.

in most cases, however, the induction of and the recovery from anesthesiological treatment take its time, too. In addition, the treatment of nodules with larger volume and thus longer treatment duration can also be performed without any problems.

6.3 Indications

Based on the authors' experience, HIFU of thyroid nodules is promising in about 70% of cases, especially in benign, non-functional and scintigraphically "cold" nodules. An average volume reduction of 30–50% can be achieved here. Complete ablation is only possible in individual cases with very small nodules up to a maximum of 0.5 mL.

Significantly limited prospects of success can be seen in the case of decompensated autonomic adenoma. In most cases, a euthyroid metabolic state can only be achieved for a few months. In about 80–90% of the cases, the patients had to be presented for conservative ablative therapy by surgery or radioiodine therapy.

In our opinion, HIFU therapy is not suitable for the reduction of large goiters or for the ablative treatment of Graves' disease.

6.4 Clinical outcomes and efficacy

Volume reduction rates (VRRs) vary throughout the literature. A systematic review published by Lang and Wu in 2017 reports on VRR of 45–68% in 95 patients [43]. The authors criticize a maximal treatment depth of 2.8 cm and a treatment duration of up to 60–80 minutes. In another review article published in 2020, an analysis of 292 patients is reported and VRR is specified with 48–70% [44]. A multi-institutional retrospective study published in 2020 with 56 patients achieves a VRR of 32% after a follow-up of 3 years [45]. A bi-institutional study from Germany reveals 50–64% VRR in 58 patients with a complication rate of 5.2% [46]. The most recent systematic review includes nine papers with 346 patients and found 47% VRR after 2 years [47]. In summary, the reported VRR ranges from 32 to 70%, with a majority of data centering on 50–60%, thus hardly meeting the criteria for successful local ablation, which is thought to be confirmed if 50% volume reduction is achieved.

6.5 Complications

The possible range of complications resembles the general pattern thermoablative therapies have in common, except for bleeding and scar formation. Remarkable is the comparably high incidence of 1–2% vocal cord palsy [44] and the occurrence of Horner's syndrome in up to 0.5% of cases [47]. The reason is the formation of edema leading to an irritation of the recurrent laryngeal nerve (RLN), which is reversible in most cases and can be relieved by speech therapy.

If no general anesthesia is applied, the pain levels are comparably high with a peri-procedural range from 1 to 7 and a mean of 4.85 during and 1.54 following the procedure using the 10° visual analogue scale [47]. This leads to a more generous choice of anesthesia for HIFU. Hypnosis has also been suggested [48].

Severe complications like external tissue damage and persistent RLN paresis are rare cases due to the gradual improvement of the treatment software with higher control and safety standards.

6.6 Pros & cons

- + Completely non-invasive modality.
- Expensive hardware.
- Inferior VRR.

6.7 Conclusion

HIFU therapy is an efficient alternative to conservative therapy methods such as surgery or radioiodine therapy for benign thyroid nodules that are suitable for this purpose. A complete ablation of the nodule is usually not successful; however, a significant reduction in volume of the treated node is frequently achieved, increasing acceptance as well as satisfaction of the patient.

The non-invasive treatment procedure does not require incisions or scars, the complication rate is minimal and the pain occurring during the treatment is usually well controlled by administered co-medication. Treatment can be conducted on an outpatient basis; an inpatient stay is not necessary. The function of the thyroid gland is usually preserved, and a substitution of thyroid hormones not necessary.

However, enthusiasm for HIFU has decreased over the recent years due to the mentioned disadvantages of treatment duration (RFA/MWA 30–40% faster [43, 47]), limitation in the maximal treatable nodule size, need for sufficient analgesia and high initial cost for the generator (approximately 400.000 US\$, 12 times more than a microwave or radiofrequency generator [43, 47]), in addition to inferior volume reduction rates. The theoretical advance is clearly a truly non-invasive treatment, however, for intraprocedural pain relief either administering intravenous drugs or mild sedation has to be considered.

7. Other modalities

7.1 Ignored and omitted treatments

Various treatment modalities have never found the way into the treatment of thyroid nodules, but the combination of therapies like embolization and ablation [49], ablation and radioiodine therapy [50] or embolization and radioiodine therapy [51] might become a promising approach to the treatment of particularly large goiters in near future. These combinations are however beyond the scope of this chapter encompassing single session ablations only.

Whereas cryotherapy currently plays no role in the treatment of benign thyroid nodules in Europe, the search for non-thermal treatment modalities is still ongoing, since the major drawbacks of thermoablative treatments are the limitations to treat nodules completely even if their borders are abutting crucial structures in the neighborhood, namely vessels, nerves, esophagus and trachea.

7.2 Histotripsy

Regarding the results of HIFU, research calls for an advancement of the by nature non-invasive ultrasound-induced cell destruction and found—instead of the heat induced by ultrasound—a way to mechanically destroy cell walls by cavitation induced by gaseous bubbles formed by ultrasound pulses, a technique called histotripsy [52]. Initial potential was found in treating cancer of the liver, prostate, renal,

breast, pancreas and musculoskeletal organs, in treating disorders of the brain such as tumors and intracerebral hemorrhage, and finally in the treatment of vessels like in neonatal heart disease, calcified aortic stenosis or deep vein thrombosis [53]. A first proof of concept for thyroid ablation has been published using a porcine model [54].

Apart from that, clinical experience centers on the local-ablative treatment of liver cancer [55]. The first case of histotripsy for hepatocellular carcinoma in a candidate for liver transplantation was recently published revealing complete necrosis of the tumor in the explanted liver following the liver transplantation [56]. The THERESA trial as a first-in-man feasibility study including eight patients was published in 2022 [57], whereas in 2025, already 230 cases of hepatic histotripsy were published [58]. From 2021 to 2022, patients were recruited for the HOPE4LIVER trial. Meanwhile, the promising preliminary 1-year results have been published [59].

For thyroid nodules, it remains at date unclear whether histotripsy might play a greater role in the future, since the procedure is time-consuming with approximately 2 to 4 hours duration and requires general anesthesia to ensure minimal movement of the target area [55].

7.3 Electroporation

Another non-thermal ablation is electroporation utilizing high-voltage electrical fields with field strengths exceeding 1 kV/cm. Eisele et al. explain the consequences: “At a molecular level, such a field induces the opening of nanometer-sized pores in the cell membrane. According to the field strength, this event may be reversible, and the cells survive. In case of a voltage exceeding 1000 V/cm and more, the pores do not close again. Subsequently, cell content ... pours out of the cell. ... Afterwards – within 16 to 18 hours – the cells undergo apoptosis.” [60].

This mechanism of action offers two options for treatment: Either comparably low voltage is applied, and additional application of a chemotherapeutic agent is required (electrochemotherapy, ECT) [61], or even higher voltage leads to irreversible electroporation (IRE) and immediately rendering the target cells out of function. An initial proof-of-concept study in rodent thyroids was able to show complete follicle destruction while preserving structures like trachea and larger vessels [62].

One case report describes percutaneous IRE in a patient suffering from repeated recurrence of thyroid carcinoma [63]. Within 7 months of follow-up, IRE was successful without evidence of recurrent cancer. To the best of the authors’ knowledge, no further cases have been published to date. A possible reason might be the need for general anesthesia including muscle relaxation and the cost for the treatment. ECT is less common at least for benign thyroid disease due to reluctance to administer chemotherapy in benign diseases.

7.4 Pros & cons

- + Non-invasive or non-thermal alternatives.
- No outcome data in the thyroid available so far.

7.5 Conclusion

Despite the availability of alternative local-ablative treatment modalities with non-thermal or even non-invasive attributes, thermoablations remain at date most popular and resemble a standard, whose more recent developments will have to be

compared due to the excellent results obtained in combination with a favorable complication profile and the hitherto superior cost efficiency of thermoablative treatment modalities.

8. Guidelines

8.1 Present status of representation of local ablation of thyroid nodules in the guidelines

Presently, numerous guidelines have incorporated recommendations for thermoablation of thyroid nodules, namely national societies from the United States of America [64], South Korea [65], United Kingdom [66, 67], Austria [68], Italy [69], Germany [70] and China [71]. In addition, joint publications of consensus statements are available from North American, Asia Pacific, Latin American and European societies [72], Europe [73] and USA/Italy [74]. In summary, the unequivocal conclusion is that local-ablative therapies of thyroid nodules represent “a less expensive and less invasive alternative to thyroid surgery, without the risks of subsequent cutaneous scar or hypothyroidism” [74].

Accepted indications are symptomatic solid benign nodules, symptomatic cystic benign nodules, autonomously functioning thyroid nodules (AFTNs), papillary thyroid microcarcinoma and recurrent malignancy [68, 72]. In 2018, standard operation procedures have been published for the use of ultrasound in guiding diagnostic and therapeutic thyroid interventions [34]. At least in German-speaking countries, also action recommendations regarding the handling of local anesthesia are available [75].

8.2 Standards for follow-up examinations

Only four guidelines set criteria for the follow-up of patients after thyroid thermal ablations: The American Thyroid Association recommends performing ultrasound and recording symptoms after 1–3, 6 and 12 months [64] and laboratory parameters only in case of AFTN treatment; the European Thyroid Association clinical, biochemical and ultrasound examinations after 1–3, 6 and 12 months [73]; the Chinese expert consensus workshop report relies on imaging (CEUS is preferred), including volumetry, interrogation, thyroid function indicators including tumor markers where appropriate, and even biopsy sampling where available, after 1–3, 6 and 12 months [71]. The Austrian Good Clinical Practice recommendations provide minimal requirements for a follow-up [68], with only two time points within the first year after 3 and 12 months, where ultrasound including volume assessment, vocal cord function and thyroid-specific laboratory parameters are recorded, whereas in case of AFTN, additional scintigraphy after 3 months is demanded.

8.3 Conclusions

Establishing standards for local ablation of thyroid nodules until 2020 was important for the development of this technology [65–71], but the incorporation of thermoablations into treatment recommendations from 2020 on was a

game-changer not only in Europe [73], but also in other regions of the world [64, 72]. Future directions of action are aiming at increasing the adherence to the guidelines. This goal makes it necessary to spread the knowledge of the potential of local ablation of thyroid nodules to obtain favorable clinical results with great patient satisfaction.

9. Outlook

Local ablation of thyroid nodules nowadays belongs as a matter of fact into the toolbox of physicians treating thyroid disorders. International guidelines unequivocally recommend such modalities for symptomatic benign thyroid nodules, autonomously functional thyroid nodules and oligonodular recurrent thyroid cancer. Presently, papillary thyroid microcarcinoma is under investigation as an indication for local ablation. Most popular are Radiofrequency as well as Microwave ablation. Slightly different physical heat generation does not impair clinical success rates, with the exception that Laser might be reserved for the treatment of smaller nodules, whereas high-intensity focused ultrasound seems to be widely abandoned. Whether more recently introduced modalities like irreversible electroporation or histotripsy might play a significant role in near future remains at date a subject of debate.

10. Conclusion

Ultrasound-guided thyroid interventions are in widespread use now and are offered in numerous specialized centers all over the world. Not only in selected cases, they can be considered valid alternatives to standard therapies. More and more data are available, confirming success rates and long-lasting effects. Thermoablations will be an element of the routine care, and at least for benign symptomatic thyroid nodules, it is all but one already. Reluctance to face up to the competition seems to impede prospective randomized trials in Western countries so far; the currently published safety and quality-of-life parameters are favoring these minimally invasive techniques. Two major questions have to be addressed within the near future: (1) How are the future specialists trained, which content of training should be imparted, how is knowledge to be transferred best? (2) Reimbursement is an issue, which remains widely unresolved. Whereas there are solutions in some countries (Austria, India), some others (Germany, United States) are lagging behind. It is incumbent on us to counteract such a geographic disparity.

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References

- [1] Kim JH, Baek JH, Lim HK, et al. Thyroid radiofrequency ablation guideline: Korean Society of Thyroid Radiology. *Korean Journal of Radiology*. 2018;**19**:632-655
- [2] Park HS, Baek JH, Park AW, et al. Thyroid radiofrequency ablation: Updates on innovative devices and techniques. *Korean Journal of Radiology*. 2017;**18**:615-623
- [3] Kim HJ, Baek JH, Cho W, et al. Long-term follow-up of the radiofrequency ablation of benign thyroid nodules: The value of additional treatment. *Ultrasonography*. 2022;**41**:661-669
- [4] Monpeyssen H, Alamri A, Ben HA. Long-term results of ultrasound-guided radiofrequency ablation of benign thyroid nodules: State of the art and future perspectives—A systematic review. *Frontiers in Endocrinology (Lausanne)*. 2021;**12**:622996
- [5] Lui MS, Patel KN. Current guidelines for the application of radiofrequency ablation for thyroid nodules: A narrative review. *Gland Surgery*. 2024;**13**:59-69
- [6] Cho SJ, Baek JH, Chung SR, et al. Long-term results of thermal ablation of benign thyroid nodules: A systematic review and meta-analysis. *Endocrinology and Metabolism (Seoul)*. 2020;**35**:339-350
- [7] Lim JY, Kuo JH. Thyroid nodule radiofrequency ablation: Complications and clinical follow up. *Techniques in Vascular and Interventional Radiology*. 2022;**25**:100824
- [8] Shin JH, Seo M, Lee MK, et al. Radiofrequency ablation of benign thyroid nodules: 10-year follow-up results from a single center. *Korean Journal of Radiology*. 2025;**26**:193-203
- [9] Sim JS, Baek JH. Unresolved clinical issues in thermal ablation of benign thyroid nodules: Regrowth at long-term follow-up. *Korean Journal of Radiology*. 2021;**22**:1436-1440
- [10] Baek JH, Lee JH, Sung JY, et al. Complications encountered in the treatment of benign thyroid nodules with US-guided radiofrequency ablation: A multicenter study. *Radiology*. 2012;**262**:335-342
- [11] Jeong WK, Baek JH, Rhim H, et al. Radiofrequency ablation of benign thyroid nodules: Safety and imaging follow-up in 236 patients. *European Radiology*. 2008;**18**:1244-1250
- [12] Muhammad H, Santhanam P, Russell JO, et al. RFA and benign thyroid nodules: Review of the current literature. *Laryngoscope Investigative Otolaryngology*. 2021;**6**:155-165
- [13] van Baardewijk LJ, Plaisier ML, van den Broek FJC, et al. Tracheal necrosis following radiofrequency ablation of a benign thyroid nodule. *Cardiovascular and Interventional Radiology*. 2021;**44**:170-171
- [14] Morvan JB, Maso V, Pascaud D, et al. Tracheal necrosis following thyroid radiofrequency ablation. *European Annals of Otorhinolaryngology, Head and Neck Diseases*. 2021;**139**(1):29-32
- [15] Ben Hamou A, Ghanassia E, Espiard S, et al. Safety and efficacy of thermal ablation (radiofrequency and laser): Should we treat all types of thyroid nodules? *International Journal of Hyperthermia*. 2019;**36**:666-676

- [16] Wang JF, Wu T, Hu KP, et al. Complications following radiofrequency ablation of benign thyroid nodules: A systematic review. *Chinese Medical Journal*. 2017;**130**:1361-1370
- [17] Chen WC, Luo SD, Chen WC, et al. The importance of nodule size in the management of ruptured thyroid nodule after radiofrequency ablation: A retrospective study and literature review. *Frontiers in Endocrinology*. 2021;**12**:776919
- [18] Valcavi R, Tsimatropoulos P. Health-related quality of life after percutaneous radiofrequency ablation of cold, solid, benign thyroid nodules: A 2-year follow-up study in 40 patients. *Endocrine Practice*. 2015;**21**:887-896
- [19] Shin JH, Jung SL, Baek JH, et al. Rupture of benign thyroid tumors after radio-frequency ablation. *American Journal of Neuroradiology*. 2011;**32**:2165-2169
- [20] Austerlitz J, Mann DS, Noel JE, et al. Thyroid nodule rupture following radiofrequency ablation for benign thyroid nodules. *JAMA Otolaryngology. Head and Neck Surgery*. 2024;**150**:651-657
- [21] Kim Y-S, Rhim H, Tae K, et al. Radiofrequency ablation of benign cold thyroid nodules: Initial clinical experience. *Thyroid*. 2006;**16**:361-367
- [22] Kohlhasse KD, Korkusuz Y, Gröner D, et al. Bipolar radiofrequency ablation of benign thyroid nodules using a multiple overlapping shot technique in a 3-month follow-up. *International Journal of Hyperthermia*. 2016;**32**:1-6
- [23] Sim JS, Baek JH, Lee J, et al. Radiofrequency ablation of benign thyroid nodules: Depicting early sign of regrowth by calculating vital volume. *International Journal of Hyperthermia*. 2017;**33**:1-17
- [24] Xiaoyin T, Ping L, Dan C, et al. Risk assessment and hydrodissection technique for radiofrequency ablation of thyroid benign nodules. *Journal of Cancer*. 2018;**9**:3058-3066
- [25] Dobnig H, Amrein K. Monopolar radiofrequency ablation of thyroid nodules: A prospective Austrian single center study. *Thyroid*. 2018;**28**(4):472-480
- [26] Park SI, Baek JH, Lee DH, et al. Radiofrequency ablation for the treatment of benign thyroid nodules: 10-year experience. *Thyroid*. 2024;**34**(8):990-998
- [27] Xu X, Peng Y, Han G. Comparative efficacy of different thermal ablation and conventional surgery for the treatment of papillary thyroid microcarcinoma: Systematic review including traditional pooling and Bayesian network meta-analysis. *American Journal of Otolaryngology*. 2024;**45**(6):104479
- [28] Chorti A, Bontinis V, Tzikos G, et al. Minimally invasive treatments of benign thyroid nodules: A network meta-analysis of short-term outcomes. *Thyroid*. 2023;**33**(8):950-964
- [29] Lim H, Cho SJ, Baek JH. Comparative efficacy and safety of radiofrequency ablation and microwave ablation in benign thyroid nodule treatment: A systematic review and meta-analysis. *European Radiology*. 2025;**35**(2):612-623
- [30] Morelli F, Sacchini A, Pompili G, et al. Microwave ablation for thyroid nodules: A new string to the bow for percutaneous treatments? *Gland Surgery*. 2016;**5**(6):553-558
- [31] Yue W, Wang S, Yu S, Wang B. Ultrasound-guided percutaneous

microwave ablation of solitary T1N0M0 papillary thyroid microcarcinoma: Initial experience. *International Journal of Hyperthermia*. 2014;**30**(2):150-157

[32] Han R, Gao X, Ji Z, Chen Y. Comparison of ultrasound-guided percutaneous microwave ablation and conventional thyroidectomy in the treatment of papillary thyroid microcarcinoma: Meta-analysis. *Ear, Nose, & Throat Journal*. 2024. DOI: 10.1177/01455613241272476. Online ahead of print

[33] Aliberti C, Impellizzeri H, Inama M, et al. Microwave ablation for large benign thyroid nodules: A proposal for a new approach: 'The fluid-motion technique'. *Updates in Surgery*. 2024;**76**(1):239-244

[34] Dietrich CF, Müller T, Bojunga J, et al. Statement and recommendations on interventional ultrasound as a thyroid diagnostic and treatment procedure. *Ultrasound in Medicine and Biology*. 2018;**44**(1):14-36

[35] Di Rienzo G, Surrente C, Lopez C, Quercia R. Tracheal laceration after laser ablation of nodular goitre. *Interactive CardioVascular and Thoracic Surgery*. 2012;**14**(1):115-116

[36] Mauri G, Gennaro N, Lee MK, Baek JH. Laser and radiofrequency ablations for benign and malignant thyroid tumors. *International Journal of Hyperthermia*. 2019;**36**(2):13-20

[37] Gambelunghe G, Ristagno S, Stefanetti E, Avenia N, De Feo P. Ultrasound-guided laser ablation of very large benign thyroid nodules: 4-year, retrospective follow-up in 24 patients. *International Journal of Hyperthermia*. 2022;**39**(1):217-221

[38] Pescatori LC, Torcia P, Nicosia L, Mauri G, Rossi UG, Cariati M.

Which needle in the treatment of thyroid nodules? *Gland Surgery*. 2018;**7**(2):111-116

[39] Gendvilaite N, Zidonis Z, Zidonyte Z, Beisa A, Poskus T, Strupas K. Ultrasound-guided percutaneous laser ablation for papillary thyroid microcarcinoma: A literature review. *Endokrynologia Polska*. 2023;**74**(2):128-134

[40] Trimboli P, Castellana M, Sconfienza LM, et al. Efficacy of thermal ablation in benign non-functioning solid thyroid nodule: A systematic review and meta-analysis. *Endocrine*. 2020;**67**(1):35-43

[41] Mainini AP, Monaco C, Pescatori LC, et al. Image-guided thermal ablation of benign thyroid nodules. *Journal of Ultrasound*. 2016;**20**(1):11-20

[42] Mauri G, Nicosia L, Della Vigna P, et al. Percutaneous laser ablation for benign and malignant thyroid diseases. *Ultrasonography*. 2019;**38**(1):25-36

[43] Lang BHH, Wu ALH. High-intensity focused ultrasound (HIFU) ablation of benign thyroid nodules – A systematic review. *Journal of Therapeutic Ultrasound*. 2017;**5**:11

[44] Palyga I, Palyga R, Mlynarczik J, Kopczynski J, Gozdz S, Kowalska A. The current state and future perspectives of high intensity focused ultrasound (HIFU) ablation for benign thyroid nodules. *Gland Surgery*. 2020;**9**(Suppl 2):S95-S104

[45] Monpeyssen H, Hamou AB, Hegedüs L, et al. High-intensity focused ultrasound (HIFU) therapy for benign thyroid nodules: A 3-year retrospective multicenter follow-up study. *International Journal of Hyperthermia*. 2020;**37**:1301-1309

- [46] Fischer A, Korkusuz H, Vorländer C. Effectiveness of high-intensity focused ultrasound (HIFU) therapy of solid and complex benign thyroid nodules – A long-term follow-up two center study. *Experimental and Clinical Endocrinology and Diabetes*. 2022;**130**:374-380
- [47] Cheong CWS, Au JXY, Lim MY, Fu EW, Li H, Gan JY. The efficacy and safety of high-intensity focused ultrasound in the treatment of benign thyroid nodules: A systematic review and meta-analysis from 1990 to 2021. *Annals of the Academy of Medicine, Singapore*. 2022;**51**:101-108
- [48] Oung C, Tesoro R, Marti V, Mavromati M, Lahoud MJ. Hypnosis in high-intensity focused ultrasound for thyroid nodule ablation. *The American Journal of Clinical Case Reports*. 2023;**24**:e941524
- [49] Cheng KL, Liang KW, Lee HL, Wang HY, Shen CY. Thyroid artery embolization of large solitary symptomatic benign thyroid nodules through transradial approach. *Quantitative Imaging in Medicine and Surgery*. 2023;**13**(8):5355-5361
- [50] Korkusuz H, Happel C, Koch DA, Gruenwald F. Combination of ultrasound-guided percutaneous microwave ablation and radioiodine therapy in benign thyroid disease: A 3-month follow-up study. *Rofo*. 2016;**188**(1):60-68
- [51] Van Tol KM, Hew JM, Jager PL, Vermey A, Dullaart RP, Links TP. Embolization in combination with radioiodine therapy for bone metastases from differentiated thyroid carcinoma. *Clinical Endocrinology*. 2000;**52**(5):653-659
- [52] WilliamsRP, SimonJC, KhokhlovaVA, Sapozhnikov OA, Khokhlova TD. The histotripsy spectrum: Differences and similarities in techniques and instrumentation. *International Journal of Hyperthermia*. 2023;**40**(1):2233720
- [53] Xu Z, Hall TL, Vlaisavljevich E, Lee FT Jr. Histotripsy: The first non-invasive, non-ionizing, non-thermal ablation technique based on ultrasound. *International Journal of Hyperthermia*. 2021;**38**(1):561-575
- [54] Swietlik JF, Mauch SC, Knott EA, et al. Noninvasive thyroid histotripsy treatment: Proof of concept study in a porcine model. *International Journal of Hyperthermia*. 2021;**38**(1):798-804
- [55] Uysal M, Wehrle CJ, Satish S, et al. Histotripsy of liver tumors: Patient selection, ethical discussions and how we do it. *Cancers*. 2025;**17**:1100
- [56] Uysal M, Wehrle CJ, Coppa C, et al. Bridging therapy with histotripsy prior to liver transplantation for hepatocellular carcinoma: A first case report. *Experimental Hematology and Oncology*. 2025;**14**:20
- [57] Vidal-Jove J, Serres X, Vlaisavljevich E, et al. First-in-man histotripsy of hepatic tumors: The THERESA trial, a feasibility study. *International Journal of Hyperthermia*. 2022;**39**(1):1115-1123
- [58] Wehrle CJ, Burns K, Ong E, et al. The first international experience with histotripsy: A safety analysis of 230 cases. *Journal of Gastrointestinal Surgery*. 2025;**29**:102000
- [59] Ziemlewicz TJ, Critchfield JJ, Mendiratta-Lala M, et al. The #HOPE4LIVER single-arm pivotal trial for histotripsy of primary and metastatic LIVER tumors: 1-year update of clinical outcomes. *Annals of Surgery*. 2025.

DOI: 10.1097/SLA.00000000000006720.
 Online ahead of print

[60] Eisele RM, Chopra SS, Glanemann M, Gebauer B. Risk of local failure after ultrasound guided irreversible electroporation of malignant liver tumors. *Interventional Medicine and Applied Science*. 2014;**6**(4):147-153

[61] Spiliotis AE, Holländer S, Wagenpfeil E, et al. Electrochemotherapy with intravenous, intratumoral, or combined administration of bleomycin in the treatment of colorectal hepatic metastases in a rat model. *Scientific Reports*. 2024;**14**:17361

[62] Lv Y, Zhang Y, Huang J, Wang Y, Rubinsky B. A study on nonthermal irreversible electroporation of the thyroid. *Technology in Cancer Research and Treatment*. 2019;**18**:1533033819876307

[63] Meijerink MR, Scheffer HJ, deBree R, Sedee RJ. Percutaneous irreversible electroporation for recurrent thyroid cancer – A case report. *The Journal of Vascular and Interventional Radiology*. 2015;**26**(8):P1180-P1182

[64] Sinclair CF, Baek JH, Hands KE, et al. General principles for the safe performance, training and adoption of ablation techniques for benign thyroid nodules: An American thyroid association statement. *Thyroid*. 2023;**33**(10):1150-1170

[65] Kim JH, Baek JH, Lim HK, Ahn HS, Baek SM, Choi YJ, et al. 2017 thyroid radiofrequency ablation guideline: Korean society of thyroid radiology. *Korean Journal of Radiology*. 2018;**19**:632-655

[66] National Institute for Health and Care Excellence. Ultrasound-Guided Percutaneous Radiofrequency

Ablation for Benign Thyroid Nodules. *Interventional Procedure Guidance IPG562*. 2016. Available from: <https://www.nice.org.uk/guidance/ipg562/resources/ultrasoundguided-percutaneous-radiofrequency-ablation-for-benign-thyroid-nodules-pdf-1899872044366021> [Accessed: May 10, 2025]

[67] National Institute for Health and Care Excellence. Percutaneous Ultrasound-Guided Microwave Ablation for Symptomatic Benign Thyroid Nodules. *Interventional Procedure Guidance IPG743*. 2022. Available from: <https://www.nice.org.uk/guidance/ipg743/resources/ultrasoundguided-microwave-ablation-for-symptomatic-benign-thyroid-nodules-pdf-1899876278677957> [Accessed: May 10, 2025]

[68] Dobnig H, Zechmann W, Hermann M, Lehner M, Heute D, Mirzaei S, et al. Radiofrequency ablation of thyroid nodules: Good clinical practice recommendations. *Journal für klinische Endokrinologie und Stoffwechsel*. 2018;**11**:73-80

[69] Papini E, Crescenzi A, D'Amore A, et al. Italian guidelines for the management of non-functioning benign and locally symptomatic thyroid nodules. *Endocrine, Metabolic and Immune Disorders Drug Targets*. 2023;**23**(6):876-885

[70] Feldkamp J, Grünwald F, Luster M, Lorenz K, Vorländer C, Führer D. Non-surgical and non-radioiodine techniques for ablation of benign thyroid nodules: Consensus statement and recommendation. *Experimental and Clinical Endocrinology and Diabetes*. 2020;**128**:687-692

[71] Xu D, Ge M, Yang A, et al. Expert consensus workshop report: Guidelines

for thermal ablation of thyroid tumors (2019 edition). *Journal of Cancer Research and Therapeutics*. 2020;**16**:960-966

[72] Orloff LA, Noel JE, Stack BC Jr, et al. Radiofrequency ablation and related ultrasound-guided ablation technologies for treatment of benign and malignant thyroid disease: An international multidisciplinary consensus statement of the American head and neck society endocrine surgery section with the Asia Pacific Society of Thyroid Surgery, Associazione Medici Endocrinologi, British Association of Endocrine and Thyroid Surgeons, European thyroid association, Italian Society of Endocrine Surgery Units, Korean Society of Thyroid Radiology, Latin American thyroid society, and thyroid nodules therapies association. *Head and Neck*. 2022;**44**(3):633-660

[73] Papini E, Monpeyssen H, Frasoldati A, Hegedüs L. 2020 European thyroid association clinical practice guideline for the use of image-guided ablation in benign thyroid nodules. *European Thyroid Journal*. 2020;**9**:172-185

[74] Gharib H, Papini E, Garber JR, et al. American association of clinical endocrinologists, American college of endocrinology, and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules--2016 update. *Endocrine Practice*. 2016;**22**(5):622-639

[75] Wiesmann T, Schubert AK, Volk T, et al. Prevention and therapy of local anaesthetic systemic toxicity (LAST). *Anesthesiologie und Intensivmedizin*. 2020;**61**:225-238

Heat over Surgery: The Rise of Thermal Ablation in Thyroid Nodules Treatment

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Abstract

Thyroid nodules (TNs) are a common endocrine condition, typically benign, though some may cause symptoms that require clinical management. While thyroidectomy has traditionally been the standard treatment, its invasive nature and associated risks—such as vocal changes, hypocalcemia, and visible scarring—have led to increasing interest in less invasive approaches. In this context, ultrasound-guided thermal ablation (UG-TA) has emerged as a promising, minimally invasive alternative for treating benign and selected malignant thyroid nodules (TNs). This chapter provides an overview of four key thermal ablation (TA) techniques: radiofrequency ablation (RFA), microwave ablation (MWA), laser ablation (LA), and high-intensity focused ultrasound (HIFU). It explores their underlying mechanisms, clinical indications, and comparative effectiveness. Evidence from recent meta-analyses and long-term studies suggests that these techniques can achieve significant volume reduction with fewer complications and faster recovery times compared to surgery. Although thyroidectomy may still offer the most substantial volume reduction in some instances, UG-TA procedures present notable advantages, including improved safety profiles, shorter hospital stays, and more favorable cosmetic outcomes. Although TA has demonstrated promising results, concerns persist regarding procedural standardization, operator dependency, and long-term oncologic outcomes. This chapter reviews current evidence, compares various thermal ablation modalities with each other and with surgery, and highlights key directions for future research and clinical practice.

Keywords: thermal ablation, thyroidectomy, thyroid, surgical resection, thyroid nodules, ablation

1. Introduction

The thyroid gland regulates body metabolism, growth, and development through thyroid hormones [1]. Thyroid nodules (TN) caused by a localized proliferation of

thyroid cells are one of the most common endocrinological disorders [2]. They are more common in older adults and are commonly associated with metabolic diseases [3]. According to the American Thyroid Association, benign thyroid nodules (BTNs) have a low risk of malignancy. Like all tumors, they can lead to clinical symptoms, such as difficulty swallowing and breathing, even if they are benign [4]. In contrast, malignant nodules may exhibit more alarming symptoms, such as neck pain and edema [5].

With the advancement in imaging techniques, particularly ultrasound (US), TNs can now be detected in up to 68% of the general population [6]. In addition, ultrasound is now also used for therapeutic purposes, providing a less invasive alternative for managing BTNs.

Over the past few decades, the management of BTNs has shifted toward minimally invasive approaches, given the low likelihood of malignant transformation. Even though traditional surgical interventions (thyroidectomy, hemithyroidectomy, lobectomy) can be effective in removing TNs, it is often more aggressive than necessary [4]. These interventions are frequently associated with post-operative complications and adverse effects, including hoarseness, hypocalcemia, infection, and cosmetic concerns, that may significantly affect patients' quality of life [7, 8]. Instead, ultrasound-guided thermal ablation (UG-TA) is a minimally invasive technique that has emerged as a viable alternative that offers effective treatment while preserving thyroid function with lower postoperative complications rate. Various thermal ablation (TA) techniques, including microwave ablation (MWA), radiofrequency ablation (RFA), high intensity focused ultrasound (HIFU), and laser ablation (LA), have gained widespread acceptance as safe and efficient procedures to reduce nodule size and alleviate symptoms [9, 10]. In cases of malignant thyroid nodules, TA is primarily employed for treating recurrent thyroid cancer and solitary low-risk papillary thyroid microcarcinoma (PTMC) [10–14]. As research continues to refine these modalities, their significance in managing TAs has become increasingly evident. However, there are still concerns about the long-term effects and safety of ablation, especially regarding the potential for tumor recurrence. In this review, we critically examine the role of TA in the management of TNs, highlighting its efficacy, safety, and advantages over conventional surgical approaches. Additionally, we discuss recent advancements, clinical outcomes, and future directions in minimally invasive thyroid nodule treatment.

2. Pathophysiology and classification of thyroid nodules (TNs)

2.1 Pathophysiology of thyroid nodules (TNs)

TN development stems from a complex interplay of genetic mutations, hormonal influences, autoimmune processes, and environmental factors [15]. BTNs often arise from polyclonal hyperplasia driven by thyroid-stimulating hormone (TSH) or inflammation, while malignant changes require specific genetic alterations that enhance cell proliferation and invasiveness. Understanding these mechanisms supports risk assessment and informs targeted treatment strategies for thyroid nodular disease.

TNs arise due to:

- Clonal proliferation (neoplastic)
- Polyclonal hyperplasia (non-neoplastic)

2.1.1 Neoplastic thyroid nodules

2.1.1.1 Genetic mutations

Thyroid cancers can arise from the accumulation of genetic mutations in parafollicular or follicular cells, with each type associated with specific genes (For example, activating mutations in the MAPK pathway, such as those found in the BRAF gene, are common in papillary thyroid carcinoma) [16]. As mutations occur in lesions with follicular patterns and in follicular thyroid carcinoma (FTC), activating both the PI3K/AKT and MAPK pathways, the PAX8-PPAR γ rearrangement is linked to follicular thyroid cancer, while RET mutations are associated with medullary thyroid carcinoma (MTC), particularly in cases related to radiation exposure [17]. Collectively, mutations in the BRAF, RAS, or RET genes are identified in nearly 70% of papillary thyroid cancer cases [18].

2.1.1.2 Growth factors

Growth factor signaling is also critical in the context of thyroid cancer development. The activation of the TSH receptor promotes the growth of nodules, with TSH playing an essential role in nodule formation [19]. Elevated TSH levels stimulate the proliferation of follicular cells, thereby increasing the risk of nodule development [20]. Additionally, both iodine deficiency and excessive iodine intake can lead to nodule formation through dysregulated hormone synthesis [21]. Insulin-like growth factor 1 (IGF-1) further enhances thyroid cell proliferation, and elevated levels of circulating IGF-1 have been linked to an increased risk of various cancer types and more rapid disease progression [22]. This indicates that IGF-1 significantly contributes to the growth of thyroid cells and may play a role in the pathogenesis of thyroid-related diseases. Moreover, vascular endothelial growth factor (VEGF) promotes angiogenesis, which supports the enlargement of nodules [19].

2.1.2 Non-neoplastic thyroid nodules

2.1.2.1 Iodine deficiency and excessive iodine intake

Iodine is essential for thyroid function; deficiency and excess can lead to nodule formation. Chronic iodine deficiency reduces thyroid hormone synthesis, increasing TSH secretion, which stimulates follicular cell hyperplasia [23]. This can result in multinodular goiter due to uneven cellular growth [23, 24]. Conversely, excessive iodine intake, particularly in those with thyroid dysfunction, can lead to hyperthyroidism and promote nodular changes [24].

2.1.2.2 Autoimmune thyroid disease

Autoimmune conditions like Hashimoto's thyroiditis and Graves' disease significantly impact thyroid architecture and contribute to nodules [25]. In Hashimoto's, chronic inflammation causes follicle destruction and compensatory hyperplasia, forming pseudonodules or true hyperplastic nodules [26]. With Graves' disease, increased thyroid activity may result in heterogeneous nodular transformation [27]. These processes promote structural nodular changes and affect thyroid function.

2.1.2.3 Environmental factors

Environmental factors such as radiation and endocrine disruptors contribute to thyroid nodules' development [28]. Ionizing radiation, especially in childhood, is a known risk factor. The Chernobyl disaster highlighted this link, increasing thyroid neoplasia incidence [28]. Endocrine disruptors like bisphenol A can interfere with hormone synthesis and contribute to nodule formation, emphasizing the need for regulatory measures to reduce exposure [29].

2.1.2.4 Molecular and cellular mechanisms

2.1.2.4.1 Thyroid follicular cell proliferation

Uncontrolled proliferation of thyroid follicular cells is driven by dysregulated cell cycle progression and growth factor signaling [30]. Overexpression of cyclin D1 accelerates cell division, while the PI3K/AKT/mTOR pathway promotes survival and growth [30]. These molecular alterations create an environment conducive to nodule growth, with some lesions acquiring mutations that can lead to malignancy.

2.1.2.4.2 Apoptosis resistance

Resistance to programmed cell death is crucial for the persistence of TNs. Overexpression of the anti-apoptotic protein Bcl-2 is common in adenomas and carcinomas [31]. Loss of function in the tumor suppressor p53 allows genetically unstable cells to proliferate [32]. This dysregulation of apoptotic factors facilitates the formation and expansion of TNs.

2.1.2.4.3 Angiogenesis and nodule vascularization

The growth of TNs relies on a sufficient blood supply facilitated by angiogenesis. VEGF and fibroblast growth factor (FGF), secreted by thyroid cells, promote the migration of endothelial cells to form new blood vessels [31]. Hypoxia-inducible factor-1 α (HIF-1 α) is upregulated in enlarged nodules, enhancing VEGF production and creating a feedback loop that boosts vascular growth [31]. This process is particularly active in rapidly growing or malignant nodules, where higher micro-vessel density indicates more aggressive behavior. Consequently, inhibiting angiogenesis has become a key therapeutic strategy in advanced thyroid cancer.

2.1.2.4.4 Extracellular matrix remodeling and fibrosis

The growth and structural integrity of TNs depend on the remodeling of the extracellular matrix (ECM). Matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, break down collagen and ECM components, allowing tissue expansion [32]. Chronic inflammation, as seen in Hashimoto's thyroiditis, can lead to fibrosis, which increases collagen deposition and disrupts normal thyroid architecture [33]. This stiffness may also complicate fine-needle aspiration (FNA) diagnostics. The balance between ECM degradation and fibrosis shapes the properties of thyroid nodules, affecting clinical presentation and management.

2.2 Classification of thyroid nodules (TNs)

2.2.1 First: Based on imaging characteristics (ultrasound classifications)

High-resolution US is a widely used, cost-effective, and highly sensitive technique for identifying TNs, even their small and nonpalpable nodules. It is the imaging modality of choice and the standard of care for evaluating such nodules. However, due to its high sensitivity, it often detects incidental small solid or cystic nodules that are typically inconsequential.

The use of the US for the evaluation of TNs dates back to the 1960s. In 1967, Fujimoto et al. published their research involving 184 patients and identified four primary patterns of TNs: cystic, sparsely spotted, increased attenuation without internal echoes, and malignant [34].

At the time, the US was capable of identifying nodules but lacked the resolution required to differentiate between benign and malignant nodules effectively. Realizing that the sensitivity and specificity of US features were inadequate for predicting the nature of TNs, researchers developed risk stratification systems that integrate multiple ultrasound features. Many of these systems are referred to as the Thyroid Imaging Reporting and Data System (TI-RADS). One of the earliest versions was introduced by Horvath and colleagues in 2009. Since then, numerous research groups and professional societies have created various versions of TI-RADS [35].

2.2.2 US classification systems for thyroid nodules

2.2.2.1 Different TI-RADS (thyroid imaging reporting and data system)

2.2.2.1.1 The American College of Radiology (ACR) TI-RADS (TR1-TR5)

The ACR TI-RADS is an US-based risk stratification system for TNs published in 2017 [36]. The ACR TI-RADS assigns points based on specific ultrasound features of thyroid nodules, with the total score determining the risk category; a higher score indicates a greater risk of cancer. The five US features assessed in TI-RADS include composition, echogenicity, shape, margin, and punctate echogenic foci. Each feature is allocated a specific number of points. The points from all categories are then aggregated to establish the TI-RADS level, each of which is accompanied by recommendations for management as illustrated in **Figure 1**.

In the recommendations, the nodules smaller than 5 mm do not require follow-up, even if they are classified as TI-RADS 5. This is due to the extremely low likelihood of such small nodules developing into clinically significant malignancies [36].

The 2.5 cm threshold for fine needle aspiration (FNA) in mildly suspicious TR3 lesions is based on studies showing that thyroid carcinomas do not decline in survival rates until they reach this size (3).

The risk of malignancy is: TR1: 0.3%, TR2: 1.5%, TR3: 4.8%, TR4: 9.1%, and TR5: 35%.

2.2.2.1.2 EU-TI-RADS (EU-TI-RADS 1–5)

The European Thyroid Association (EU-TI-RADS) classification system was first introduced by Russ et al. in 2011 and has since been refined into a more user-friendly version, validated numerous times, and ultimately published as a European guideline

ACR TI-RADS

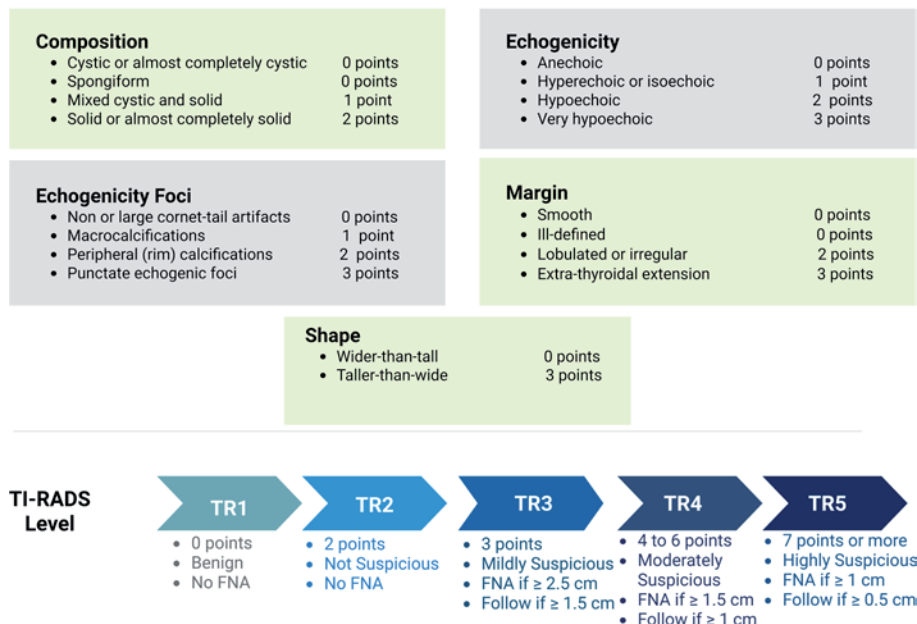


Figure 1.

ACR TI-RADS classification system for thyroid nodules based on ultrasound features. Points are assigned for composition, echogenicity, shape, margin, and echogenic foci to determine malignancy risk and guide management.

in 2017 [37]. The latest version of EU-TI-RADS comprises five categories, each assigned a score based on features identified during US examination: EU-TI-RADS 1 indicates that no TN is present, while the remaining four categories represent nodules that are benign or classified with low, intermediate, and high risks of malignancy.

In the EU-TI-RADS framework, unlike the ACR classification, which relies on a point system, a single definitive characteristic can determine a nodule's classification. This approach eliminates the need for point summation and streamlines the classification process, making it less time-consuming. A nodule can be classified as high risk for malignancy (category 5) if it exhibits features such as non-oval morphology, irregular margins, microcalcifications, or marked hypoechoogenicity [37]. However, the focus on simplicity means that some potentially relevant features, including the presence of macrocalcifications, are not considered [37].

2.2.2.1.3 Korean (K)-TI-RADS

The Korean Society of Thyroid Radiology (KSThR) published its initial guidelines for the US-based diagnosis and management of TNs in 2011 [38]. Recently, there has been a greater emphasis on utilizing US for the personalized management of patients with TNs. In response, the KSThR has revised its guidelines to improve the US diagnosis and imaging-based management of these nodules.

In 2016, the K-TI-RADS classification system was introduced by Shin et al. [39], with the latest revised version of the guideline released in 2021 [40]. In this system, the estimated risk of malignancy is derived from a combination of US findings rather than a single indicator. The 2021 K-TIRADS algorithm stratifies malignancy risk based

on nodule composition and echogenicity, and suspicious US features, such as punctate echogenic foci (microcalcifications), non-parallel orientation (taller than wide shape), and irregular margins.

The K-TIRADS classification has five categories: high suspicion (K-TIRADS 5), intermediate suspicion (K-TIRADS 4), low suspicion (K-TIRADS 3), and benign categories (K-TIRADS 2). K-TIRADS 1 indicates no nodules in the thyroid gland [39].

2.2.2.2 BTA “U” the British Thyroid Association (BTA) (U1-U5)

An alternative classification system for TNs in the United States is the British Thyroid Association (BTA) ultrasound classification, as outlined in their 2014 guidelines on the management of thyroid cancer [41]. This system consists of five categories: normal (U1), benign (U2), equivocal/indeterminate (U3), suspicious (U4), and malignant (U5).

The BTA classification evaluates various US characteristics that may suggest malignancy. These include the eccentric positioning of the solid portion in partially cystic nodules, irregular margins, hypoechogenicity of the solid component, microcalcifications, and a taller-than-wide shape [41].

2.2.2.3 ATA guidelines (ATA (American Thyroid Association))

The American Thyroid Association (ATA) guidelines on TNs and differentiated thyroid cancer were initially published in 2006 and later updated in 2009 [42, 43]. Unlike other classification systems, the ATA employs pattern recognition to evaluate the risk of malignancy in thyroid nodules [4].

In its clinical management guidelines, the ATA focuses solely on US characteristics, intentionally excluding Color Doppler or elastography parameters from its assessment. The ATA classification system considers several criteria: echostructure, echogenicity, margins, the presence or absence of microcalcifications, and shape [4].

This system categorizes nodules into five distinct patterns, each associated with a specific level of malignancy risk, ranging from benign to high suspicion patterns. During ultrasound examinations, each nodule is classified into one of these five categories to facilitate clinical decision-making [4].

2.2.2.4 American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE), and Associazione Medici Endocrinologi (AME) classification

The initial edition of the AAACE /ACE/AME Guidelines for the Diagnosis and Management of TNs was released in 2006 and has been updated in 2010 and 2016 [44].

ACE/ACE/AME employed information from US examinations to classify nodules into a three-tier system based on their risk of malignancy (low, intermediate, and high). This system combined ultrasound features of thyroid nodules—such as composition, echogenicity, margins, vascularity, and calcifications—with nodule size and the patient’s clinical history [44].

These guidelines are more focused on management rather than purely on imaging classifications. It has specific recommendations for FNS, indicating if the patient has high-risk thyroid lesions on US measuring 10 mm or larger,

intermediate-risk thyroid lesions on US exceeding 20 mm, low-risk thyroid lesions on US only if they are larger than 20 mm, and either show growth or are associated with a history of risk prior to thyroid surgery or minimally invasive ablation. Besides that, FNS is an indication of whether the patient has any specific characteristics, such as a family history of thyroid cancer.

2.2.3 Second: Based on cytological and histopathological features (the Bethesda system for reporting thyroid cytopathology (TBSRTC))

Since its initial publication in 2010 [45], the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) has provided cytopathologists with a standardized, category-based framework for reporting thyroid fine needle aspirations. TBSRTC upgraded and ended with a third edition in 2023 [46].

The third edition builds on the successes of the two prior editions and introduces several notable updates. The most significant enhancement is the assignment of a single name to each of the six diagnostic categories: (i) nondiagnostic; (ii) benign; (iii) atypia of undetermined significance; (iv) follicular neoplasm; (v) suspicious for malignancy; and (vi) malignant [46]. Each category carries an implied risk of malignancy; the risk of malignancy for each category is 1–4%, 0–3%, 5–15%, 15–30%, 60–75%, and 97–99%, respectively. Six major categories of results are obtained from fine-needle aspiration (FNA), each of which indicates different subsequent management.

2.2.4 Third: Based on functional activity

These classifications depend on thyroid scans (radioiodine scans) and the nodules' relative uptake of the radioactive isotopes. The appearance of the nodules indicates their function; they may appear as hot spots (hot nodules), darks (cold nodules), or as the thyroid tissue (warm nodules) [47].

2.2.4.1 Cold nodule

A cold nodule refers to a thyroid nodule that does not produce thyroid hormones and appears darker on a radioactive iodine thyroid scan. Although most of the cold thyroid nodules are benign, approximately 15–20% can still be malignant, emphasizing the necessity for careful evaluation [48].

2.2.4.2 Hot nodule

Conversely, a hot TN is recognized as a hot spot on a thyroid scan. Hot nodules are rarely malignant; however, they do produce excess thyroid hormones, which can result in hyperthyroidism. Nevertheless, hyperthyroidism may present symptoms such as a rapid heartbeat, weight loss, and even anxiety.

2.2.4.3 Warm nodule

They act as normal thyroid cells and appear like thyroid tissue in the thyroid scan. About 5–8% of warm nodules are malignant [49].

2.2.5 Fourth: Based on Etiology

2.2.5.1 Benign

BTNs are the most prevalent type, accounting for over 95% of TNs (**Figure 2**) [50]. These nodules typically arise from the excessive proliferation of normal thyroid tissue. The most common types are colloid cysts, multinodular goiter, and thyroid adenoma. Surgical intervention is typically not recommended, and a benign nodule can be monitored over time with ultrasound. If there is an increase in size, a follow-up biopsy or surgical intervention may be advised. Some surgeons suggest excising nodules that exceed 4 cm in size. Additionally, large benign thyroid nodules may be treated through radiofrequency ablation.

2.2.5.2 Malignant

Approximately 5 percent of TNs are malignant. The different types of thyroid cancer include papillary, follicular, medullary, anaplastic, lymphoma, and metastatic thyroid cancer [16]. Fortunately, a majority of individuals diagnosed with thyroid cancer have an excellent prognosis for recovery and long-term survival.

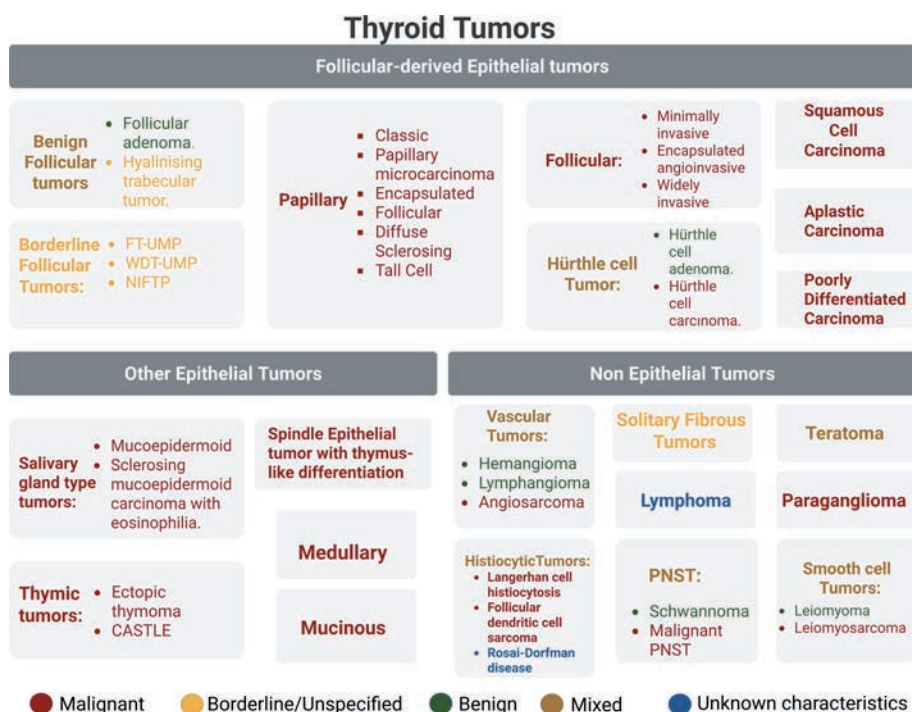


Figure 2.

Overview of thyroid tumor classification. The diagram highlights key categories, including follicular-derived epithelial tumors, other epithelial tumors, and non-epithelial tumors. Among papillary thyroid carcinoma variants, six commonly recognized types are depicted. Abbreviations: FT-UMP – Follicular tumor of uncertain malignant potential; WDT-UMP – Well-differentiated tumor of uncertain malignant potential; NIFTP – Non-invasive follicular thyroid neoplasm with papillary nuclear features; CASTLE – Carcinoma showing thymus-like differentiation; PNST – Peripheral nerve sheath tumor.

The specific treatment approach will depend on the type and size of the cancer. Typically, thyroid cancers require the surgical removal of part or all of the thyroid gland, and sometimes one or more treatments with radioiodine, followed by thyroid hormone (T4) therapy. Patients who undergo total thyroidectomy will require lifelong thyroid hormone replacement therapy to maintain normal metabolic function.

3. Thermal ablation techniques for thyroid nodules

Over the past few decades, several non-surgical ablative methods have been developed. Two key options include chemical ablation with ethanol, which involves exposing the TN to a high concentration of ethanol and UG-TA techniques such as MWA, RFA, HIFU, and LA that are based on the principle of delivering high levels of energy to the tissue, causing its destruction (**Figure 3**). These techniques are widely used alternatives to surgery for the treatment of tumors in various organs, including the thyroid gland. All these techniques are minimally invasive and achieve tissue destruction through heat application.

UG-TA offers several benefits over traditional surgical treatment. These include quicker recovery times, fewer complications, and a lower mortality risk. UG-TA is also less costly, can be performed on a daycare basis, and often results in a shorter hospital stay [51, 52]. Furthermore, with the help of US or CT guidance, tumors can be

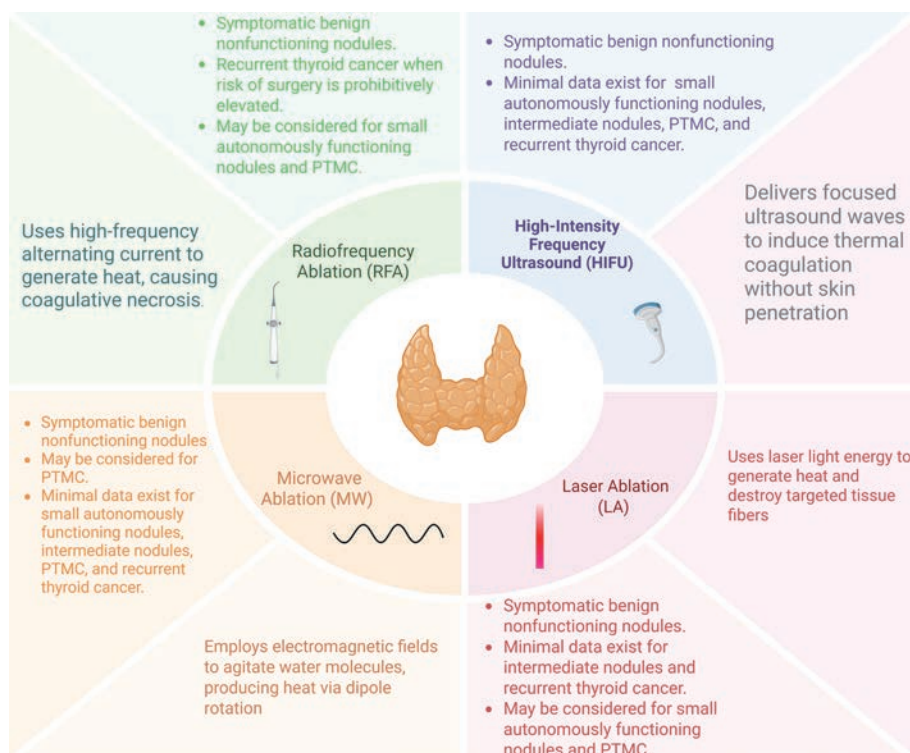


Figure 3. Comparison of four thermal ablation techniques for thyroid nodules—RFA, MWA, HIFU, and LA—highlighting their mechanisms and key indications.

precisely targeted, and the treatment is easily repeatable in cases where the residual disease remains [53].

RFA is a minimally invasive technique that uses high-frequency alternating current—typically between 200 and 1200 kHz—to generate localized thermal energy [54, 55]. This energy is delivered through an electrode needle connected to an external radiofrequency generator, which produces an electric field that agitates ions within the surrounding tissue [56]. This ionic movement results in resistive (frictional) heating, raising the local tissue temperature to between 50°C and 100°C. The heat induces coagulative necrosis in the targeted tissue, effectively destroying it [56].

To ensure safety and protect adjacent critical structures—including the vagus nerve, cervical ganglia, esophagus, trachea, and surrounding blood vessels—a protective buffer of either normal thyroid tissue or injected fluids such as normal saline or lactated ringers's solution is maintained [11, 55, 57]. Ablation is considered complete upon observing hyperechogenicity on US (indicating coagulated tissue) along with a sudden rise in electrical impedance as detected by the generator [11, 55, 57].

Complications associated with RFA are similar to those seen in other interventional procedures. Despite the thyroid's proximity to critical structures—including the recurrent laryngeal and vagus nerves, cervical ganglia, esophagus, trachea, and major blood vessels—there have been no documented cases of injury to the esophagus, trachea, or major vessels [56]. The most significant complication is transient voice change, resulting from irritation or thermal injury to the laryngeal or vagus nerves, with most cases resolving within 3 months. Rare events include brachial plexus injury, nodule rupture, and temporary thyroid dysfunction [58]. Minor complications—more frequently observed—include pain, hematoma, skin burns, with most being self-limited [58, 59].

MWA is another minimally invasive technique used in the treatment of TNs. Although relatively new and not yet extensively documented in the literature, MWA shows promising therapeutic potential. Unlike RFA, which generates heat by sending electrical currents through body tissues, MWA uses electromagnetic fields to heat the tissue directly. This energy is delivered via an antenna, generating heat by agitating water molecules within the tissue. The primary mechanism behind this is the dipole rotation theory, where water molecules—due to their polar nature—continuously realign and oscillate in response to the applied electromagnetic field. This agitation creates frictional heat, leading to a rapid rise in local temperature and subsequent destruction of the target tissue through coagulative necrosis [60, 61]. A secondary mechanism, called ionic polarization, occurs when the electromagnetic field causes ions in the tissue to move and collide with each other, thereby contributing to additional heat production [60–62]. Together, these processes result in effective ablation of thyroid tissue, making MWA a promising alternative to more established techniques like RFA.

MWA is performed using a generator, a cooled antenna, and a coaxial cable. The generator delivers 30–50 watts of energy at 2450 MHz, causing water molecules in the tissue to heat up and destroy the targeted nodule [56, 63]. The antenna, guided by ultrasound, is inserted into the nodule, and the ablated area appears hyperechoic on imaging [56]. Hydrodissection may be used to protect nearby structures. Complications are similar to other ablation methods and include pain, voice changes, hematoma, and temporary thyroid dysfunction [56, 64].

LA works by delivering laser energy—typically from neodymium: yttrium aluminum garnet (Nd:YAG) or diode lasers—directly into the nodule, where the light is converted into heat. This localized heating increases tissue temperature beyond

60°C, causing cellular denaturation, necrosis, and eventually fibrosis [56, 65]. It is performed under US guidance using one to four 21-gauge needles inserted into the TN after administering local anesthesia. Through each needle, a 300 µm optical fiber is introduced, with the tip placed in direct contact with the tissue. Energy output typically ranges from 2 to 5 watts and is delivered over 5 to 15 minutes. As the procedure progresses, US monitoring shows the formation of a hyperechoic zone that expands over time, corresponding to the treated area [65, 66].

LA is generally well tolerated, with most patients experiencing only mild discomfort. Common minor side effects include cervical pain, swelling, bruising, hematoma, or low-grade fever. Major complications such as thyroid dysfunction, vocal cord palsy, or injury to surrounding neck structures are rare and typically transient. Clinical trials and observational studies have consistently shown that LA leads to a significant and sustained reduction in nodule volume and improvement in both cosmetic and pressure-related symptoms [65, 67]. Overall, LA is considered a safe, effective, and minimally invasive treatment option, with consistent outcomes when performed by experienced practitioners [65, 67].

However, LA is primarily indicated for benign, non-functioning thyroid nodules and is not recommended for malignant or autonomously functioning nodules. Large or deeply located nodules may require multiple sessions, and potential complications include transient voice changes, hematoma, or thermal injury to adjacent structures [68]. The procedure's success is highly dependent on the operator's skill, and access to specialized equipment may limit its widespread use [69].

HIFU is a non-invasive TA technique used to treat TNs by delivering precisely focused US energy to the target tissue. The concentrated US waves raise the tissue temperature above 56°C for at least 1 second, resulting in coagulative necrosis through protein denaturation. Unlike other TA methods, HIFU does not require skin penetration, making it a minimally invasive alternative for patients seeking non-surgical options [70].

The principle behind HIFU lies in the mechanical oscillation of particles induced by high-frequency ultrasound waves (>20 kHz), which transmit energy through tissue via compression and rarefaction. When these waves reach the targeted area, energy is absorbed and converted into heat through friction between particles, causing localized cell death. To achieve effective treatment, multiple sonications are required, as each delivers only a small volume of ablation. The depth and precision of tissue penetration depend on factors such as wave frequency, lesion size, and the definition of the focus point—lower frequencies penetrate deeper but with less precision [56, 70].

The procedure is typically performed under conscious sedation with the patient lying supine and the neck extended. Treatment is monitored continuously, with the focal point displayed as a hyperechoic zone on imaging. The lesion is divided into voxel areas, each treated with short sonications lasting 4–8 seconds, followed by cooling intervals of 20–40 seconds to prevent overheating [56, 70]. HIFU treatment times can be lengthy due to the small ablation volume per sonication [56].

However, HIFU is currently indicated only for benign, cytologically confirmed thyroid nodules. It is not recommended for malignant or indeterminate lesions due to insufficient evidence of oncologic safety [71]. Some patients may experience transient pain or skin burns during or shortly after the procedure [72]. Efficacy may also be reduced in large or deeply located nodules due to physical limitations in ultrasound energy penetration [73]. Furthermore, the availability of HIFU technology is limited in many regions, and its high cost, coupled with inconsistent insurance reimbursement, poses barriers to access [74]. In some cases, repeat sessions may be necessary to achieve satisfactory results [72].

4. Clinical indications, nodule-specific selection, and post-ablation follow-up

4.1 Indications for thermal ablation (TA)

TA is increasingly accepted as a safe and effective alternative to surgery in selected TN cases (**Table 1**). The primary indications include:

- Symptomatic benign nonfunctioning nodules, particularly those causing compressive symptoms or cosmetic concerns;
- Autonomously functioning nodules (AFNs) in patients with subclinical or overt hyperthyroidism who are poor candidates for surgery or radioactive iodine (RAI);
- Recurrent thyroid cancer, especially in patients with prior neck surgeries or increased surgical risk;
- Papillary thyroid microcarcinoma (PTMC) as an alternative to surgery or active surveillance in low-risk patients [75].

TA is not indicated for nodules with indeterminate cytology or suspected aggressive malignancy, as histologic evaluation remains essential for these cases. Additionally, special consideration should be given to cases of bilateral nodules, tracheal compression, Pemberton's sign, or dyspnea at rest, which may favor surgical management [75].

Nodule type	Preferred technique(s)	Clinical notes
Cystic nodules	EA (initial), Repeat EA or TA (recurrence)	EA is first-line for initial management. TA or surgery may be considered if cysts recur or are symptomatic.
Solid benign nodules	RFA, MWA, LA, HIFU	Patient preference guides choice. HIFU is suitable for those avoiding puncture; RFA and MWA preferred for large or highly vascular nodules.
AFNs (Toxic nodules)	RFA, MWA (small <30 mL) Surgery or RAI (large >30 mL)	MWA and RFA offer favorable outcomes in small-volume toxic nodules. Surgery or RAI are preferred for larger nodules.
Highly vascular nodules	MWA > RFA/LA	MWA's higher energy output can improve efficacy in vascular environments.
Nodules near critical structures	RFA > MWA	RFA offers more controlled energy delivery, reducing risk near nerves or trachea.
PTMC	RFA, MWA, LA	An option for low-risk microcarcinomas in patients refusing surgery or unsuitable for active surveillance.
Recurrent thyroid cancer	RFA (preferred)	Especially useful in surgically challenging areas post-thyroidectomy.

Table 1.
Thermal ablation selection based on nodule type.

4.2 Post-procedural follow-up

Following thyroid TA, a structured follow-up protocol is essential to assess treatment success, detect early recurrence, and support long-term thyroid health. Immediate post-procedural monitoring is brief, focused on identifying acute complications like hematoma or localized pain. Mild swelling, bruising, or discomfort at the ablation site may occur but typically resolves with conservative care [76, 77]. The first follow-up, usually within 1–2 weeks, evaluates healing and addresses patient concerns [76]. Long-term surveillance includes neck ultrasounds at 3 and 6 months, then annually, to assess nodule shrinkage, reduced vascularity, and any new growth. Thyroid function tests (TSH, free T4, total T3) are also checked at similar intervals, particularly for previously hyperfunctioning nodules, to ensure stable thyroid function [11]. If regrowth or new symptoms such as dysphagia or a palpable mass appear, repeat ablation or alternative treatments like surgery or radioiodine may be needed. Patient education is key—recognizing symptoms, maintaining a healthy lifestyle, and attending regular follow-ups are critical [78]. Consistent monitoring, patient engagement, and tailored care plans are central to successful long-term outcomes.

5. Evidence-based outcomes and comparative studies

Numerous studies have recently been conducted to assess the effectiveness and safety of TA compared with conventional surgery and to compare various TA modalities for treating TNs. The primary outcomes evaluated included nodule volume reduction, symptom and cosmetic improvements, complication rates, nodule regrowth, and additional treatment. The application of TA has expanded beyond BTNs, with recent advancements highlighting its potential role in the management of PTMC as well. Several retrospective cohort studies and meta-analyses have examined TA as a possible alternative to surgery in patients with low-risk PTMC, focusing on outcomes such as tumor disappearance, local recurrence, lymph node metastasis, long-term complications, and the need for further intervention.

5.1 Thermal ablation vs. surgery: Clinical outcomes and safety

Several systematic reviews and meta-analyses have shown substantial evidence for direct comparison of TA with traditional surgical approaches emphasizing both short- and long-term clinical outcomes, safety, and efficacy profiles. In the treatment of BTNs, a recent meta-analysis by Qafesha et al., which included seven randomized controlled trials and 19 cohort studies, reported that UG-TA significantly decreased nodule volume at 3, 6, and 12 months of follow-up. In addition to efficacy, TA was correlated with improved perioperative outcomes such as decreased lengths of hospitalization, shorter operative times, lower intraoperative blood loss, and better cosmetic outcomes than surgical intervention. TA was further associated with lower incidence of postoperative complications (postoperative pain, hoarseness, hypothyroidism, parathyroid injury) and was associated with significantly milder postoperative inflammatory response than surgery [79]. These findings are supported by a network meta-analysis (NMA) conducted by Chorti et al. which found that both RFA and MWA were linked to lower rates of vocal cord complications and laryngeal nerve injury than surgery [80].

Thyroid function preservation represents another critical advantage of TA. Che et al. reported that 71.5% of patients required hormone replacement after surgery, while 93% of those treated with RFA maintained normal thyroid levels. Only 7% in the RFA group had a temporary, asymptomatic TSH decrease that resolved within a month [81]. These findings highlight RFA's role in reducing post-treatment hypothyroidism. Additionally, Chorti et al. identified a higher risk of nodule regrowth in patients who underwent surgery, suggesting an additional long-term advantage of TA [80]. Meanwhile, another study found no significant differences in terms of recurrence, wound infections, or hematomas between the two approaches [80]. Meanwhile, HIFU did not show significant benefits regarding procedure time or post-operative hoarseness over surgery, unlike RFA and MWA—a finding likely influenced by the limited number of HIFU studies (n = 2) included [80].

Regrowth is a recognized concern following TA in BTNs, particularly when ablation is incomplete or limited by proximity to critical structures. Marginal regrowth, originating from undertreated peripheral zones of the nodule, is the most common cause [82]. Regrowth definitions vary across studies, including a > 20% increase in volume from the 1-year baseline or recurrence beyond the pre-ablation size [83]. In a retrospective study of 120 patients treated with RFA, a 13.3% recurrence rate was observed, with solitary nodules, larger initial diameter, and high-risk anatomical locations identified as independent predictors [84]. Nodules larger than 20 mL and incompletely ablated lesions may require staged or repeat RFA sessions to ensure durable control [82, 83]. Additional RFA has been shown to improve volume reduction and symptom relief in residual or recurrent nodules [85, 86]. For recurrent, predominantly cystic nodules, EA remains the first-line option, particularly when recurrent fluid accumulation leads to compressive symptoms [87]. According to American Thyroid Association AACA/ATA guidelines, percutaneous ethanol injection (PEI) or surgery should be considered for recurrent symptomatic cystic nodules, with PEI achieving success rates of 75–85% [87]. Surgery, generally via hemithyroidectomy, is indicated for benign nodules larger than 4 cm that continue to enlarge, cause compressive symptoms, or raise clinical concern despite repeat benign cytology [87].

In PTC management, TA has demonstrated comparable oncologic control to surgery. Yu et al. found no significant difference between TA and surgery regarding tumor progression or recurrence-free survival [88]. After a three-year follow-up period, Nguyen et al. found that the tumor VRR and complete resolution rate were consistently high (99% and 93–95%, respectively). Further evidence from Xue et al.'s meta-analysis reinforced these outcomes, reporting a pooled three-year volume reduction rate (VRR) of 98.9% and a complete disappearance rate of 83% post-ablation. Recurrence rates remained low and comparable across both treatment strategies, averaging approximately 2–3% [89].

Further comparative studies strengthen the evidence base in favor of TA. In terms of oncologic control, both Kim et al. and Yan et al. demonstrated comparable recurrence-free survival between TA and surgery (97% vs. 98.2%, respectively). Importantly, TA also resulted in fewer persistent lesions and reduced need for additional procedures, suggesting its effectiveness in disease control [90, 91]. The incidence of micro-PTC or lymph node metastasis was extremely low following TA (0.3% and 0.0%, respectively), confirming TA's long-term safety and efficacy in appropriately selected patients with PTC [92]. In terms of procedural efficiency, TA was associated with fewer complications, shorter hospital stays, shorter operation times, reduced blood loss, lower costs, and better quality of life outcomes than surgery [88–90, 93].

When evaluating complications and procedural safety, TA consistently outperformed surgery. Kim et al. reported a significantly lower complication rate with TA compared to surgery (3.3% vs. 7.8%, $p = 0.03$) [94]. Furthermore, evidence from multi-arm meta-analyses (Li et al.) confirmed that RFA ranked highest for safety (SUCRA 88.8%), lowest for complication rates (RR 0.12, 95% CI: 0.05–0.29 vs. surgery), and showed superior rankings in reducing operative time, blood loss, and hospital stay compared to surgery and other TA methods [93].

RFA is an increasingly utilized alternative to surgery in selected patients with recurrent thyroid cancers (RTCs), particularly when lesions are ≤ 2 cm and surgery is contraindicated or declined. In a retrospective comparison, RFA demonstrated recurrence-free survival rates comparable to reoperation at both 1 and 3 years (96.0% vs. 92.2%), with fewer complications such as hypocalcemia [90]. According to The Korean Society of Thyroid Radiology (KSThR) 2025 guideline, curative-intent RFA is indicated for ≤ 3 localized recurrent tumors measuring ≤ 2 cm when complete ablation is feasible, while palliative RFA can be used to reduce symptoms and improve quality of life in cases of unresectable or symptomatic disease [95]. A recent meta-analysis of six studies reported a 95.03% pooled volume reduction rate and a 92% complete disappearance rate after RFA, with only a 6% recurrence rate and 5% complication rate over a 2-year follow-up [96]. Case reports also support the safety and effectiveness of RFA in anatomically challenging lesions, including metastatic lymph nodes with dense macrocalcification when combined with RAI ablation [97].

Although MWA and LA have been explored in limited series, RFA remains the most evidence-supported TA modality for RTCs and is endorsed by current international guidelines [95, 98]. Complete peripheral ablation and inclusion of a 2 mm safety margin are crucial to avoid residual tumor and late recurrence [98]. Surgery remains the standard of care when complete resection is feasible, especially for tumors > 2 cm, aggressive histology, or incomplete ablation. Multidisciplinary assessment is essential for patient selection, ensuring that RFA is reserved for localized, small-volume disease in patients unsuitable for surgery or with high operative risk.

5.2 Comparative effectiveness of different TA modalities

Volume reduction rate (VRR) is the primary efficacy endpoint in the evaluation of ablation methods for the treatment of TNs. A recent NMA published in 2023 included 4112 patients, compared efficacy and safety of various TA modalities with surgery being the control group for treating BTNs. Interestingly, there were no statistically significant differences in VRR outcomes between surgery and any of the thermal methods. However, the surface under the cumulative ranking (SUCRA) analysis indicated that surgery (SUCRA 98.49), MWA (SUCRA 57.0), and LA (SUCRA 51.58) were the most likely to achieve the greatest VRR at the 12-month follow-up [80]. However, this finding contrasts with several other studies. For instance, a recent NMA by Yuan et al. found that RFA demonstrated the highest VRR at both 1 and 12 months among the four treatment modalities (RFA, MWA, LA, EA), while LA ranked the highest at 6 months [99]. Additional meta-analyses consistently reported superior VRR outcomes with RFA compared to MWA at both 6- and 12-month follow-ups [100, 101]. Moreover, studies focusing on elderly populations reported that LA was more effective than MWA in reducing nodule volume at 6 months, with no significant difference observed between LA and RFA [102].

Moreover, a meta-analysis of randomized controlled trials (RCTs) by He et al. highlighted that two sessions of RFA had the highest probability (SUCRA 77.9) of

being the most effective treatment for solid or predominantly solid BTNs [103]. These variations may reflect intrinsic technical differences between modalities: while MWA generates higher central temperatures and larger ablation zones, it may be more prone to early carbonization, limiting effective heat diffusion. In contrast, RFA achieves lower temperatures (up to 110°C) and allows controlled ablation at the nodule margins, enhancing dissolution and sustained volume reduction. Notably, even in the 2023 NMA where MWA ranked highest among TAs, the differences did not reach statistical significance, and the authors acknowledged potential heterogeneity in technique and energy protocols [80]. Taken together, while MWA may show promising SUCRA-based rankings in select analyses, the overall body of evidence—including consistent significant findings—supports RFA as the most effective TA method for sustained nodule shrinkage.

Longitudinal data are critical in evaluating the durability of TA in BTNs. One long-term study examining MWA over a 3-year period showed continued volume reduction, with a plateau phase between 12 and 36 months, followed by further volume shrinkage. This supports the sustained effectiveness of MWA over time. In subgroup analysis, RFA demonstrated superior outcomes compared to LA in terms of lower rates of regrowth, less need for delayed surgery, and better cosmetic results [8]. In another larger cohort, Xidong et al. evaluated the 5-year outcomes of TA in 939 patients. The pooled final VRR was 74.48% (95% CI: 70.05–78.91%), with the majority of patients requiring no additional intervention (**Figure 4**). Nodule regrowth occurred in 10.6% of cases, and 9.6% required retreatment, which included surgical or additional non-surgical options [104].

Symptomatic and cosmetic outcomes significantly improved following TA, particularly with RFA and MWA, as pooled analyses demonstrated notable reductions in symptom and cosmetic scores as early as 1 and 3 months post-treatment,

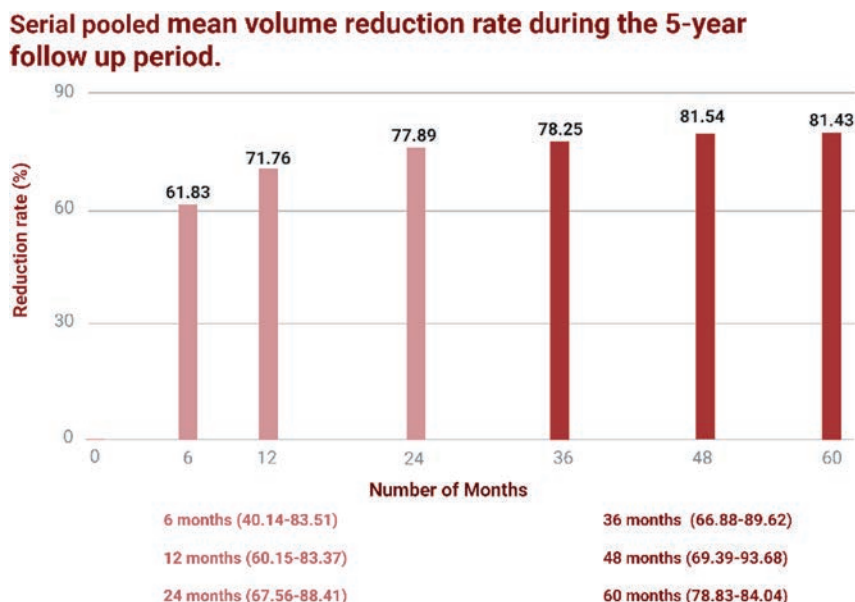


Figure 4. Serial pooled mean volume reduction rate (VRR) of thyroid nodules during 5-year follow-up after thermal ablation in Xidong et al. study [104], showing progressive and sustained reduction over time—from 61.83% at 6 months to 81.43% at 60 months.

with sustained improvement observed up to 12 months [100]. Several meta-analyses, including those by Chorti et al. and Yuan et al., consistently reported no statistically significant differences among TA techniques—RFA, MWA, and LA—in terms of symptomatic or cosmetic outcomes [101]. Additionally, both studies utilized SUCRA ranking to explore relative effectiveness, revealing that RFA was most likely to achieve the greatest reduction in symptom scores. Chorti et al. also reported that MWA showed the highest probability of cosmetic improvement [80, 99]. These findings suggest comparable clinical efficacy across modalities, with a slight advantage for RFA in symptom relief and MWA in esthetic outcomes.

Regarding safety outcomes, transient voice change is the most common complication reported after TA, usually due to thermal or mechanical injury to the recurrent laryngeal nerve during the ablation of large nodules [105]. Techniques like hydrodissection and the moving-shot method help reduce this risk [106]. Most cases are mild and resolve within weeks without intervention [107]. Overall, complication rates were low and comparable across TA modalities, with no significant differences [86, 99, 101, 103]. Among all TA modalities, RFA consistently ranked as the safest, with Chorti et al. reporting the lowest regrowth rate (RR 0.09; 95% CI: 0.00–0.85) and minimal risk of hypothyroidism. In the same study, LA demonstrated higher regrowth rates, while HIFU was linked to more frequent voice disturbances [80]. Conversely, in He et al.'s NMA, HIFU had the lowest complication probability (SUCRA 79.5), followed by RFA with one or two sessions, ethanol ablation, and LA [103]. In elderly populations, MWA was associated with relatively higher rates of major complications, including hypothyroidism and brachial plexus injury [102]. Despite these concerns, all methods are generally considered safe; however, cases of Horner's syndrome have been reported with MWA and HIFU, likely due to injury to the sympathetic trunk near the carotid sheath [108, 109].

While TA is mainly employed for BTNs, it is increasingly being utilized in select cases of low-risk PTMC. In a pooled analysis by Tong et al., RFA achieved a complete disappearance rate of 76.2% (95% CI: 50.0%–95.4%), which further increased to 91.6% (95% CI: 83.6%–97.4%) when studies with shorter follow-up durations were excluded. In comparison, MWA and laser LA achieved complete resolution in 62.9% (95% CI: 19.7%–96.6%) and 57.3% (95% CI: 13.0%–95.4%) of cases, respectively [110]. Volume reduction was also substantial across modalities, with SMD of -1.35 for RFA, -3.82 for MWA, and -1.80 for LA, indicating significant tumor shrinkage post-ablation [110]. These outcomes are further supported by long-term follow-up data, such as the study by Tuttle et al. [111], where 98.5% of lesions treated with TA completely resolved over a five-year period [112].

Complication rates associated with TA for PTMC remain low and are generally minor. According to Tong et al., the pooled complication rates were 1.7% for RFA, 6.0% for MWA, and 0.92% for LA [110]. Reported adverse events typically included transient voice changes, mild pain, or minor bleeding, all of which resolved without intervention. Permanent hypothyroidism—a concern in surgical cohorts—was virtually absent. Supporting this, Tuttle et al. reported transient hoarseness in only 1.4% of over 5000 patients, all of whom recovered fully within 1–6 months. No severe or life-threatening complications were documented, reinforcing the safety of TA in appropriately selected cases [111].

Despite not removing surrounding thyroid tissue or lymph nodes, TA demonstrated excellent local control. The five-year recurrence rate reported by Cho et al. was only 2.7% (95% CI: 1.0%–6.5%) [112]. Tong et al.'s pooled data revealed extremely low rates of local recurrence within the ablation zone: 0% for RFA (pooled

rate 0.01%), 0.5% for MWA, and 0% for LA. Additional low-risk recurrences occurred in other parts of the thyroid (1.1% for RFA, 0.3% for MWA) or in regional lymph nodes (0.6% RFA, 1.3% MWA, 2.0% LA). Importantly, distant metastases were not reported in any of the thermal ablation studies analyzed [110]. This suggests that, when used in low-risk cases, TA offers high local control with minimal systemic spread. A network meta-analysis by Li et al. further supported these conclusions, indicating that MWA had the lowest recurrence probability (SUCRA 64.4%), followed by LA (60.9%) and RFA (19.9%). For minimizing lymph node metastases, RFA was ranked highest (SUCRA 67.8%), followed by MWA (60.0%). These findings suggest both high efficacy and a strong safety profile across the available modalities [93].

Thermal ablation demonstrates excellent durability in long-term follow-up. In a study included in Tuttle et al.'s analysis, 65 of 5268 nodules (1.2%) showed regrowth within the ablated zone over an average of 3.3 years [111]. Only 32 patients (0.6%) developed cervical lymph node metastases, and these were successfully managed without mortality. Cho et al. reported similar results, with a five-year recurrence rate of 2.7% and complete disappearance in nearly all patients (98.5%) [112].

6. Conclusion and future recommendations

Future research on TA for BTN should prioritize long-term follow-up to better assess delayed complications and recurrence rates, which remain underexplored in the current literature. There is a pressing need for large-scale, prospective studies across diverse geographic regions to validate the long-term efficacy and safety of TA, particularly in managing cases like medullary thyroid carcinoma. Comparative studies evaluating TA against conventional surgery, as well as head-to-head trials comparing various ablation modalities such as ethanol and laser ablation, are essential to identify the most effective and practical approaches. Additionally, given that current data often stem from small, single-center studies, future multicenter trials with larger sample sizes are necessary to account for operator-dependent variability and to ensure broader applicability of findings in clinical practice.

For BTNs, the Society of Interventional Radiology (SIR) recently highlighted the limitations of ablation in treating large functional nodules, due to the relatively modest rates of biochemical and clinical improvement observed post-ablation [113]. The panel also emphasized the importance of research comparing the safety, quality of life improvements, and cost-effectiveness of TA versus surgery for multinodular goiter, as well as assessing the long-term risks of nodule regrowth and malignant transformation following percutaneous ablation. Additionally, more studies are needed to refine patient selection criteria, define the indications for TA, and clarify the role of combination therapies in clinical practice.

When comparing long-term outcomes of TA versus surgery for papillary thyroid microcarcinoma (PTMC), the absence of prospective randomized controlled trials (RCTs) is a significant challenge. A large multi-center retrospective study by Yan et al. involving 1021 patients with single PTMC demonstrated a 95.5% disease-free survival rate at 8 years for the TA group, compared to 97.1% for the surgery group [114]. The cox regression analysis showed that age younger than 55, male sex, tumor location, tumor volume, Hashimoto thyroiditis diagnosis, treatment with ablation, and duration of follow-up period were not significantly associated with disease progression. Despite this, prospective RCTs are urgently needed to further classify key issues such as optimal patient selection, patient perspectives on TA versus surgery, and

tumor characteristics that predict the best outcomes. Addressing these gaps through future research will be pivotal in expanding the role of TA in clinical practice [113]. Additionally, the SIR panel stressed the need for further evaluation of locoregional therapies for papillary thyroid carcinomas larger than 1 cm but less than 2 cm, as well as long-term outcomes for TA in PTMC, to determine the safety and efficacy for larger lesions.

Conflict of interest

The authors declare no conflict of interest.

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References

- [1] Mullur R, Liu Y-Y, Brent GA. Thyroid hormone regulation of metabolism. *Physiological Reviews*. 2014;**94**(2):355-382. DOI: 10.1152/physrev.00030.2013
- [2] Cesareo R et al. Efficacy of radiofrequency and laser thermal ablation in solving thyroid nodule-related symptoms and cosmetic concerns. A systematic review and meta-analysis. *Reviews in Endocrine & Metabolic Disorders*. 2022;**23**(5):1051-1061. DOI: 10.1007/s11154-022-09743-8
- [3] Moon JH et al. Prevalence of thyroid nodules and their associated clinical parameters: A large-scale, multicenter-based health checkup study. *The Korean Journal of Internal Medicine*. 2018;**33**(4):753-762. DOI: 10.3904/kjim.2015.273
- [4] Haugen BR et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2016;**26**(1):1-133. DOI: 10.1089/thy.2015.0020
- [5] Alexander LF, Patel NJ, Caserta MP, Robbin ML. Thyroid ultrasound: Diffuse and nodular disease. *Radiologic Clinics of North America*. 2020;**58**(6):1041-1057. DOI: 10.1016/j.rcl.2020.07.003
- [6] Guth S, Theune U, Aberle J, Galach A, Bamberger CM. Very high prevalence of thyroid nodules detected by high frequency (13 MHz) ultrasound examination. DOI: 10.1111/j.1365-2362.2009.02162.x
- [7] Jin H, Lin W, Lu L, Cui M. Conventional thyroidectomy vs thyroid thermal ablation on postoperative quality of life and satisfaction for patients with benign thyroid nodules. *European Journal of Endocrinology*. 2021;**184**(1):131-141. DOI: 10.1530/EJE-20-0562
- [8] Cho SJ, Baek JH, Chung SR, Choi YJ, Lee JH. Long-term results of thermal ablation of benign thyroid nodules: A systematic review and meta-analysis. *Endocrinology and Metabolism*. 2020;**35**(2):339-350. DOI: 10.3803/EnM.2020.35.2.339
- [9] Bo X-W et al. Comparison of efficacy, safety, and patient satisfaction between thermal ablation, conventional/open thyroidectomy, and endoscopic thyroidectomy for symptomatic benign thyroid nodules. *International Journal of Hyperthermia :The Official Journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group*. 2022;**39**(1):379-389. DOI: 10.1080/02656736.2022.2040608
- [10] Durante C et al. 2023 European thyroid association clinical practice guidelines for thyroid nodule management. *European Thyroid Journal*. 2023;**12**(5):e230067. DOI: 10.1530/ETJ-23-0067
- [11] Kim J et al. 2017 thyroid radiofrequency ablation guideline: Korean Society of Thyroid Radiology. *Korean Journal of Radiology*. 2018;**19**(4):632-655. DOI: 10.3348/kjr.2018.19.4.632
- [12] Xu D et al. Expert consensus workshop report: Guidelines for thermal ablation of thyroid tumors (2019 edition). *Journal of Cancer Research and Therapeutics*. 2020;**16**(5):960-966. DOI: 10.4103/jcrt.JCRT_558_19

- [13] Mauri G et al. European thyroid association and cardiovascular and interventional radiological Society of Europe 2021 clinical practice guideline for the use of minimally invasive treatments in malignant thyroid lesions. *European Thyroid Journal*. 2021;**10**(3):185-197. DOI: 10.1159/000516469
- [14] Orloff LA et al. Radiofrequency ablation and related ultrasound-guided ablation technologies for treatment of benign and malignant thyroid disease: An international multidisciplinary consensus statement of the American head and neck society endocrine surgery section with the Asia Pacific Society of Thyroid Surgery, Associazione Medici Endocrinologi, British Association of Endocrine and Thyroid Surgeons, European thyroid association, Italian Society of Endocrine Surgery Units, Korean Society of Thyroid Radiology, Latin American thyroid society, and thyroid nodules therapies association. *Head & Neck*. 2022;**44**(3):633-660. DOI: 10.1002/hed.26960
- [15] Salabè GB. Pathogenesis of thyroid nodules: Histological classification? *Biomedicine and Pharmacotherapy*. 2001;**55**(1):39-53. DOI: 10.1016/s0753-3322(00)00010-x
- [16] Abdullah MI, Junit SM, Ng KL, Jayapalan JJ, Karikalan B, Hashim OH. Papillary thyroid cancer: Genetic alterations and molecular biomarker investigations. *International Journal of Medical Sciences*. 2019;**16**(3):450-460. DOI: 10.7150/ijms.29935
- [17] Kamani T, Charkhchi P, Zahedi A, Akbari MR. Genetic susceptibility to hereditary non-medullary thyroid cancer. *Hereditary Cancer in Clinical Practice*. 2022;**20**:9. DOI: 10.1186/s13053-022-00215-3
- [18] Nikiforova MN, Tseng GC, Steward D, Diorio D, Nikiforov YE. MicroRNA expression profiling of thyroid tumors: Biological significance and diagnostic utility. *The Journal of Clinical Endocrinology and Metabolism*. 2008;**93**(5):1600-1608. DOI: 10.1210/jc.2007-2696
- [19] van Staveren WCG et al. Gene expression in human thyrocytes and autonomous adenomas reveals suppression of negative feedbacks in tumorigenesis. *Proceedings of the National Academy of Sciences of the United States of America*. 2006;**103**(2):413-418. DOI: 10.1073/pnas.0507354102
- [20] Fighera TM et al. TSH levels are associated with increased risk of thyroid carcinoma in patients with nodular disease. *Endokrynologia Polska*. 2015;**66**(6):480-485. DOI: 10.5603/EP.a2015.0059
- [21] Belfiore A et al. Cancer risk in patients with cold thyroid nodules: Relevance of iodine intake, sex, age, and multinodularity. *The American Journal of Medicine*. 1992;**93**(4):363-369. DOI: 10.1016/0002-9343(92)90164-7
- [22] Liu Y-J, Qiang W, Shi J, Lv S-Q, Ji M-J, Shi B-Y. Expression and significance of IGF-1 and IGF-1R in thyroid nodules. *Endocrine*. 2013;**44**(1):158-164. DOI: 10.1007/s12020-012-9864-z
- [23] Wang F et al. Strong association of high urinary iodine with thyroid nodule and papillary thyroid cancer. *Tumour Biology: The Journal of the International Society for Oncodevelopmental Biology and Medicine Journal*. 2014;**35**(11):11375-11379. DOI: 10.1007/s13277-014-2397-8
- [24] Santos JEC, Kalk WJ, Freitas M, Marques Carreira I, Castelo Branco M. Iodine deficiency and thyroid nodular

pathology - epidemiological and cancer characteristics in different populations: Portugal and South Africa. *BMC Research Notes*. 2015;**8**:284. DOI: 10.1186/s13104-015-1155-3

[25] Kassi GN, Evangelopoulou CC, Papapostolou KD, Karga HJ. Benign and malignant thyroid nodules with autoimmune thyroiditis. *The Archives of Endocrinology and Metabolism*. 2022;**66**(4):446-451. DOI: 10.20945/2359-3997000000483

[26] Azizi G et al. Association of Hashimoto's thyroiditis with thyroid cancer. *Endocrine-Related Cancer*. 2014;**21**(6):845-852. DOI: 10.1530/ERC-14-0258

[27] Carnell NE, Valente WA. Thyroid nodules in graves' disease: Classification, characterization, and response to treatment. *Thyroid*. 1998;**8**(7):571-576. DOI: 10.1089/thy.1998.8.571

[28] Drozdovitch V. Radiation exposure to the thyroid after the Chernobyl accident. *Frontiers in Endocrinology*. 2021;**11**. DOI: 10.3389/fendo.2020.569041

[29] Milczarek-Banach J, Miśkiewicz P. The role of bisphenol a and its analogues as endocrine disruptors influencing the thyroid gland: A short review. *Journal of Medical Sciences*. 2020;**89**(3) Art. no. 3. DOI: 10.20883/medical.e441

[30] Robbins HL, Hague A. The PI3K/Akt pathway in Tumors of endocrine tissues. *Frontiers in Endocrinology*. 2016;**6**. DOI: 10.3389/fendo.2015.00188

[31] Bassyoni OY, Soliman AE, El Sayed LK, Roshdy RG. Significance of expression of VEGF, BCL-2, p63 and β -hCG in gestational trophoblastic diseases. *Benha Medical Journal*. 2025;**42**(4):594-607. DOI: 10.21608/bmfj.2025.344396.2287

[32] Xing M. Molecular pathogenesis and mechanisms of thyroid cancer. *Nature Reviews. Cancer*. 2013;**13**(3):184-199. DOI: 10.1038/nrc3431

[33] Brent GA. Environmental exposures and autoimmune thyroid disease. *Thyroid*. 2010;**20**(7):755-761. DOI: 10.1089/thy.2010.1636

[34] Fujimoto Y, Oka A, Omoto R, Hirose M. Ultrasound scanning of the thyroid gland as a new diagnostic approach. *Ultrasonics*. 1967;**5**:177-180. DOI: 10.1016/s0041-624x(67)80065-9

[35] Horvath E et al. An ultrasonogram reporting system for thyroid nodules stratifying cancer risk for clinical management. *The Journal of Clinical Endocrinology and Metabolism*. 2009;**94**(5):1748-1751. DOI: 10.1210/jc.2008-1724

[36] Tessler FN et al. ACR thyroid imaging, reporting and data system (TI-RADS): White paper of the ACR TI-RADS Committee. *Journal of the American College of Radiology*. 2017;**14**(5):587-595. DOI: 10.1016/j.jacr.2017.01.046

[37] Russ G, Bonnema SJ, Erdogan MF, Durante C, Ngu R, Leenhardt L. European thyroid association guidelines for ultrasound malignancy risk stratification of thyroid nodules in adults: The EU-TIRADS. *European Thyroid Journal*. 2017;**6**(5):225-237. DOI: 10.1159/000478927

[38] Moon W-J et al. Ultrasonography and the ultrasound-based Management of Thyroid Nodules: Consensus statement and recommendations. *Korean Journal of Radiology*. 2011;**12**(1):1-14. DOI: 10.3348/kjr.2011.12.1.1

[39] Shin JH et al. Ultrasonography diagnosis and imaging-based

Management of Thyroid Nodules: Revised Korean Society of Thyroid Radiology Consensus Statement and Recommendations. *Korean Journal of Radiology*. 2016;**17**(3):370-395. DOI: 10.3348/kjr.2016.17.3.370

[40] Ha EJ et al. 2021 Korean thyroid imaging reporting and data system and imaging-based Management of Thyroid Nodules: Korean Society of Thyroid Radiology Consensus Statement and Recommendations. *Korean Journal of Radiology*. 2021;**22**(12):2094-2123. DOI: 10.3348/kjr.2021.0713

[41] Perros P et al. Guidelines for the management of thyroid cancer. *Clinical Endocrinology*. 2014;**81**(Suppl 1):1-122. DOI: 10.1111/cen.12515

[42] American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2009;**19**(11):1167-1214. DOI: 10.1089/thy.2009.0110

[43] Cooper DS et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. The American Thyroid Association Guidelines Taskforce. *Thyroid*. 2006;**16**(2):109-142. DOI: 10.1089/thy.2006.16.109

[44] Gharib H et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of Thyroid Nodules - 2016 update appendix. *Endocrine Practice*. 2016;**22**:1-60. DOI: 10.4158/EP161208.GL

[45] Cibas ES, Ali SZ, NCI Thyroid FNA State of the Science Conference.

The Bethesda system for reporting thyroid cytopathology. *American Journal of Clinical Pathology*. 2009;**132**(5):658-665. DOI: 10.1309/AJCPHLWMI3JV4LA

[46] Ali SZ, Baloch ZW, Cochand-Priollet B, Schmitt FC, Vielh P, Vander Laan PA. The 2023 Bethesda system for reporting thyroid cytopathology. *Thyroid®*. 2023;**33**(9):1039-1044. DOI: 10.1089/thy.2023.0141

[47] Iqbal A, Rehman A. Thyroid uptake and scan. In: StatPearls. StatPearls Publishing; 2022. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK555978/> [Accessed: April 16, 2025]

[48] Alzahrani HA. Malignancy in a solitary thyroid nodule: A retrospective histopathological evaluation. *International Journal of General Medicine*. 2024;**17**:135-140. DOI: 10.2147/IJGM.S445734

[49] David E et al. Thyroid nodule characterization: Overview and state of the art of diagnosis with recent developments, from imaging to molecular diagnosis and artificial intelligence. *Biomedicine*. 2024;**12**(8):1676. DOI: 10.3390/biomedicines12081676

[50] Giovanella L, Campennì A, Tuncel M, Petranović Oščariček P. Integrated diagnostics of thyroid nodules. *Cancers*. 2024;**16**(2):311. DOI: 10.3390/cancers16020311

[51] Goldberg SN, Gazelle GS, Mueller PR. Thermal ablation therapy for focal malignancy. *American Journal of Roentgenology*. 2000;**174**(2):323-331. DOI: 10.2214/ajr.174.2.1740323

[52] Dupuy DE, Goldberg SN. Image-guided radiofrequency tumor ablation: Challenges and opportunities—Part II.

Journal of Vascular and Interventional Radiology. 2001;**12**(10):1135-1148.
 DOI: 10.1016/S1051-0443(07)61670-4

[53] Gala KB, Shetty NS, Patel P, Kulkarni SS. Microwave ablation: How we do it? Indian Journal of Radiology And Imaging. 2021;**30**(2):206-213.
 DOI: 10.4103/ijri.IJRI_240_19

[54] Rhim H et al. Essential techniques for successful radio-frequency thermal ablation of malignant hepatic tumors. Radiographics. 2001;**21**:S17-S35.
 DOI: 10.1148/radiographics.21.suppl_1.g01oc11s17

[55] Muhammad H, Santhanam P, Russell JO. Radiofrequency ablation and thyroid nodules: Updated systematic review. Endocrine. 2021;**72**(3):619-632.
 DOI: 10.1007/s12020-020-02598-6

[56] Barile A et al. Interventional radiology of the thyroid gland: Critical review and state of the art. Gland Surgery. 2018;**7**(2) Art. no. 2.
 DOI: 10.21037/gs.2017.11.17

[57] Lee J, Shin JH, Hahn SY, Park KW, Choi JS. Feasibility of adjustable electrodes for radiofrequency ablation of benign thyroid nodules. Korean Journal of Radiology. 2020;**21**(3):377-383.
 DOI: 10.3348/kjr.2019.0724

[58] De Bernardi IC et al. Vascular and interventional radiology radiofrequency ablation of benign thyroid nodules and recurrent thyroid cancers: Literature review. La Radiologia Medica. 2014;**119**(7):512-520. DOI: 10.1007/s11547-014-0411-2

[59] Shibata T et al. Small hepatocellular carcinoma: Comparison of radio-frequency ablation and percutaneous microwave coagulation therapy. Radiology. 2002;**223**(2):331-337.
 DOI: 10.1148/radiol.2232010775

[60] Gala KB, Shetty NS, Patel P, Kulkarni SS. Microwave ablation: How we do it? Indian Journal Of Radiology And Imaging. 2020;**30**(2):206-213.
 DOI: 10.4103/ijri.IJRI_240_19

[61] Sun Y et al. Comparison of ablation zone between 915- and 2,450-MHz cooled-shaft microwave antenna: Results in in vivo porcine livers. AJR. American Journal of Roentgenology. 2009;**192**(2):511-514. DOI: 10.2214/AJR.07.3828

[62] Skinner MG, Iizuka MN, Kolios MC, Sherar MD. A theoretical comparison of energy sources--microwave, ultrasound and laser--for interstitial thermal therapy. Physics in Medicine and Biology. 1998;**43**(12):3535-3547.
 DOI: 10.1088/0031-9155/43/12/011

[63] Liu Y-J, Qian L-X, Liu D, Zhao J-F. Ultrasound-guided microwave ablation in the treatment of benign thyroid nodules in 435 patients. Experimental Biology and Medicine (Maywood, NJ). 2017;**242**(15):1515-1523.
 DOI: 10.1177/1535370217727477

[64] Feng B et al. Ultrasound-guided percutaneous microwave ablation of benign thyroid nodules: Experimental and clinical studies. European Journal of Endocrinology. 2012;**166**(6):1031-1037.
 DOI: 10.1530/EJE-11-0966

[65] Gharib H et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of Thyroid Nodules--2016 update. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2016;**22**(5):622-639. DOI: 10.4158/EP161208.GL

- [66] Papini E, Bizzarri G, Pacella CM. Percutaneous laser ablation of benign and malignant thyroid nodules. *Current Opinion in Endocrinology, Diabetes, and Obesity*. 2008;**15**(5):434-439. DOI: 10.1097/MED.0b013e32830eb89a
- [67] Papini E et al. Long-term efficacy of ultrasound-guided laser ablation for benign solid thyroid nodules. Results of a three-year multicenter prospective randomized trial. *The Journal of Clinical Endocrinology and Metabolism*. 2014;**99**(10):3653-3659. DOI: 10.1210/jc.2014-1826
- [68] Døssing H, Bennedbæk FN, Hegedüs L. Long-term outcome following interstitial laser photocoagulation of benign cold thyroid nodules. *European Journal of Endocrinology*. 2011;**165**(1):123-128. DOI: 10.1530/EJE-11-0220
- [69] Pacella CM et al. Outcomes and risk factors for complications of laser ablation for thyroid nodules: A multicenter study on 1531 patients. *The Journal of Clinical Endocrinology and Metabolism*. 2015;**100**(10):3903-3910. DOI: 10.1210/jc.2015-1964
- [70] Masciocchi C, Conchiglia A, Gregori LM, Arrigoni F, Zugaro L, Barile A. Critical role of HIFU in musculoskeletal interventions. *La Radiologia Medica*. 2014;**119**(7):470-475. DOI: 10.1007/s11547-014-0414-z
- [71] Lang BH-H, Woo Y-C, Wong CKH. High-intensity focused ultrasound for treatment of symptomatic benign thyroid nodules: A prospective study. *Radiology*. 2017;**284**(3):897-906. DOI: 10.1148/radiol.2017161640
- [72] Trimboli P, Pelloni F, Bini F, Marinozzi F, Giovanella L. High-intensity focused ultrasound (HIFU) for benign thyroid nodules: 2-year follow-up results. *Endocrine*. 2019;**65**(2):312-317. DOI: 10.1007/s12020-019-01909-w
- [73] Lang BH-H, Wu ALH. High intensity focused ultrasound (HIFU) ablation of benign thyroid nodules – A systematic review. *Journal of Therapeutic Ultrasound*. 2017;**5**:11. DOI: 10.1186/s40349-017-0091-1
- [74] Mauri G, Bernardi S, Palermo A, Cesareo R. Minimally-invasive treatments for benign thyroid nodules: Recommendations for information to patients and referring physicians by the Italian minimally-invasive treatments of the thyroid group. *Endocrine*. 2022;**76**(1):1-8. DOI: 10.1007/s12020-022-03005-y
- [75] Hu QL, Kuo JH. Choice in ablative therapies for thyroid nodules. *Journal of the Endocrine Society*. 2023;**7**(7):bvad078. DOI: 10.1210/jendso/bvad078
- [76] Yang Z et al. Value of radiofrequency ablation for treating locally recurrent thyroid cancer: A systematic review and meta-analysis for 2-year follow-up. *Endocrine*. 2024;**85**(3):1066-1074. DOI: 10.1007/s12020-023-03660-9
- [77] Na DG et al. Radiofrequency ablation of benign thyroid nodules and recurrent thyroid cancers: Consensus statement and recommendations. *Korean Journal of Radiology*. 2012;**13**(2):117-125. DOI: 10.3348/kjr.2012.13.2.117
- [78] McCann B, Hughes D. In: Batell B, editor. *Thyroid Nodule Ablation: Post Procedure Patient Instructions*. Medical Procedures Unit, Michigan Medicine. Chevy Chase, MD, USA: The Endocrine Society; 2023. Available from: <https://www.med.umich.edu/1libr/MPU/ThyroidNoduleAblationPostProcedure.pdf>
- [79] Qafesha RM et al. Ultrasound-guided thermal ablation versus thyroidectomy in

the treatment of benign thyroid nodules: Systematic review and meta analysis. *Journal of Ultrasound in Medicine*. 2025;**44**(4):605-635. DOI: 10.1002/jum.16630

[80] Chorti A et al. Minimally invasive treatments of benign thyroid nodules: A network meta-analysis of short-term outcomes. *Thyroid®*. 2023;**33**(8):950-964. DOI: 10.1089/thy.2022.0671

[81] Che Y et al. Treatment of benign thyroid nodules: Comparison of surgery with radiofrequency ablation. *American Journal of Neuroradiology*. 2015;**36**(7):1321-1325. DOI: 10.3174/ajnr.A4276

[82] Sim JS, Baek JH. Unresolved clinical issues in thermal ablation of benign thyroid nodules: Regrowth at long-term follow-up. *Korean Journal of Radiology*. 2021;**22**(8):1436-1440. DOI: 10.3348/kjr.2021.0093

[83] Sim JS, Baek JH. Long-term outcomes following thermal ablation of benign thyroid nodules as an alternative to surgery: The importance of controlling regrowth. *Endocrinology and Metabolism*. 2019;**34**(2):117-123. DOI: 10.3803/EnM.2019.34.2.117

[84] Xia Y, Fu Y, Qian M, Cui Y. Risk factors of recurrent thyroid nodules after radiofrequency ablation. *African Health Sciences*. 2023;**23**(3):584-592. DOI: 10.4314/ahs.v23i3.68

[85] Huh JY, Baek JH, Choi H, Kim JK, Lee JH. Symptomatic benign thyroid nodules: Efficacy of additional radiofrequency ablation treatment session--prospective randomized study. *Radiology*. 2012;**263**(3):909-916. DOI: 10.1148/radiol.12111300

[86] Baek JH, Ha EJ, Choi YJ, Sung JY, Kim JK, Shong YK. Radiofrequency

versus ethanol ablation for treating predominantly cystic thyroid nodules: A randomized clinical trial. *Korean Journal of Radiology*. 2015;**16**(6):1332-1340. DOI: 10.3348/kjr.2015.16.6.1332

[87] Haugen BR. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: What is new and what has changed? *Cancer*. 2017;**123**(3):372-381. DOI: 10.1002/cncr.30360

[88] Yu N, Zhao Z-l, Wei Y, Cao S-l, Wu J, Yu M. Comparison of US-guided thermal ablation and surgery for papillary thyroid cancer: A systematic review and meta-analysis. *International Journal of Hyperthermia*. 2025;**42**(1):2464206. DOI: 10.1080/02656736.2025.2464206

[89] Nguyen VC, Park JS, Song CM, Ji YB, Jeong JH, Tae K. Efficacy and oncologic outcomes of thermal ablation techniques in the treatment of primary low-risk papillary thyroid carcinoma: A systematic review and network meta-analysis. *Head & Neck*. 2025;**47**(2):759-775. DOI: 10.1002/hed.28029

[90] Kim J et al. Efficacy and safety of radiofrequency ablation for treatment of locally recurrent thyroid cancers smaller than 2 cm. *Radiology*. 2015;**276**(3):909-918. DOI: 10.1148/radiol.15140079

[91] Yan L, Zhang M, Song Q, Luo Y. Ultrasound-guided radiofrequency ablation versus thyroid lobectomy for low-risk papillary thyroid microcarcinoma: A propensity-matched cohort study of 884 patients. *Thyroid®*. 2021;**31**(11):1662-1672. DOI: 10.1089/thy.2021.0100

[92] Xue J, Teng D, Wang H. Over than three-year follow-up results of thermal ablation for papillary thyroid carcinoma: A systematic review and meta-analysis.

Frontiers in Endocrinology. 2022;**13**. DOI: 10.3389/fendo.2022.971038

[93] Li B, Qian Y, Huang Y, Li Z. Efficacy and safety of thermal ablation modalities for the treatment of papillary thyroid microcarcinoma: Systematic review and network meta-analysis. *Heliyon*. 2024;**10**(3). DOI: 10.1016/j.heliyon.2024.e25536

[94] Kim HJ, Cho SJ, Baek JH. Comparison of thermal ablation and surgery for low-risk papillary thyroid microcarcinoma: A systematic review and meta-analysis. *Korean Journal of Radiology*. 2021;**22**(10):1730-1741. DOI: 10.3348/kjr.2020.1308

[95] Ha EJ et al. Radiofrequency ablation for recurrent thyroid cancers: 2025 Korean Society of Thyroid Radiology Guideline. *Korean Journal of Radiology*. 2025;**26**(1):10-28. DOI: 10.3348/kjr.2024.0963

[96] My LT, My TTT, Tu NTT, Anh TTH, Hiep PV. Radiofrequency ablation for recurrent papillary thyroid carcinoma at the central compartment node: A case report. *Indian Journal of Radiology And Imaging*. 2024. DOI: 10.1055/s-0044-1800862

[97] Yoo R-E, Kim J-H, Paeng JC, Park YJ. Radiofrequency ablation for treatment of locally recurrent thyroid cancer presenting as a metastatic lymph node with dense macrocalcification: A case report and literature review. *Medicine (Baltimore)*. 2018;**97**(9):e0003. DOI: 10.1097/MD.00000000000010003

[98] de los Santos GP et al. Brazilian consensus on the application of thermal ablation for treatment of thyroid nodules: A task force statement by the Brazilian Society of Interventional Radiology and

Endovascular Surgery (SOBRICE), Brazilian Society of Head and Neck Surgery (SBCCP), and Brazilian Society of Endocrinology and Metabolism (SBEM). *The Archives of Endocrinology and Metabolism*. 2024;**68**:e230263. DOI: 10.20945/2359-4292-2023-0263

[99] Yuan W, Di L, Yu X, Li J. Comparison of efficacy and safety of different minimally invasive therapies for thyroid nodules: A network meta-analysis. *Endocrine*. 2024;**85**(3):979-987. DOI: 10.1007/s12020-024-03782-8

[100] Lim H, Cho SJ, Baek JH. Comparative efficacy and safety of radiofrequency ablation and microwave ablation in benign thyroid nodule treatment: A systematic review and meta-analysis. *European Radiology*. 2025;**35**(2):612-623. DOI: 10.1007/s00330-024-10881-7

[101] Zufry H, Hariyanto TI. Comparative efficacy and safety of radiofrequency ablation and microwave ablation in the treatment of benign thyroid nodules: A systematic review and meta-analysis. *Korean Journal of Radiology*. 2024;**25**(3):301-313. DOI: 10.3348/kjr.2023.1004

[102] Qian Y, Li Z, Fan C, Huang Y. Comparison of ultrasound-guided microwave ablation, laser ablation, and radiofrequency ablation for the treatment of elderly patients with benign thyroid nodules: A meta-analysis. *Experimental Gerontology*. 2024;**191**:112425. DOI: 10.1016/j.exger.2024.112425

[103] He L, Zhao W, Xia Z, Su A, Li Z, Zhu J. Comparative efficacy of different ultrasound-guided ablation for the treatment of benign thyroid nodules: Systematic review and network meta-analysis of randomized controlled trials. *PLoS One*. 2021;**16**(1):e0243864. DOI: 10.1371/journal.pone.0243864

- [104] Xu X, Peng Y, Han G. Five-year follow-up results of thermal ablation for benign thyroid nodules: Systematic review and meta-analysis. *American Journal of Otolaryngology*. 2024;**45**(1):104025. DOI: 10.1016/j.amjoto.2023.104025
- [105] Jeong WK et al. Radiofrequency ablation of benign thyroid nodules: Safety and imaging follow-up in 236 patients. *European Radiology*. 2008;**18**(6):1244-1250. DOI: 10.1007/s00330-008-0880-6
- [106] Lim HK et al. Efficacy and safety of radiofrequency ablation for treating locoregional recurrence from papillary thyroid cancer. *European Radiology*. 2015;**25**(1):163-170. DOI: 10.1007/s00330-014-3405-5
- [107] Jin H, Fan J, Liao K, He Z, Li W, Cui M. A propensity score matching study between ultrasound-guided percutaneous microwave ablation and conventional thyroidectomy for benign thyroid nodules treatment. *International Journal of Hyperthermia*. 2018;**35**(1):232-238. DOI: 10.1080/02656736.2018.1492028
- [108] Lang BHH, Wong CKH, Ma EPM, Woo Y-C, Chiu KW-H. A propensity-matched analysis of clinical outcomes between open thyroid lobectomy and high-intensity focused ultrasound (HIFU) ablation of benign thyroid nodules. *Surgery*. 2019;**165**(1):85-91. DOI: 10.1016/j.surg.2018.05.080
- [109] Cheng Z et al. US-guided percutaneous radiofrequency versus microwave ablation for benign thyroid nodules: A prospective Multicenter study. *Scientific Reports*. 2017;**7**(1):9554. DOI: 10.1038/s41598-017-09930-7
- [110] Tong M, Li S, Li Y, Li Y, Feng Y, Che Y. Efficacy and safety of radiofrequency, microwave and laser ablation for treating papillary thyroid microcarcinoma: A systematic review and meta-analysis. *International Journal of Hyperthermia*. 2019;**36**(1):1277-1285. DOI: 10.1080/02656736.2019.1700559
- [111] Tuttle RM, Li D, Ridouani F. *Percutaneous Ablation of Low-Risk Papillary Thyroid Cancer*. Amsterdam, Netherlands: Elsevier Ltd.; 2023. DOI: 10.1530/ERC-22-0244
- [112] Cho SJ, Baek SM, Na DG, Lee KD, Shong YK, Baek JH. Five-year follow-up results of thermal ablation for low-risk papillary thyroid microcarcinomas: Systematic review and meta-analysis. *European Radiology*. 2021;**31**(9):6446-6456. DOI: 10.1007/s00330-021-07808-x
- [113] Lam AH et al. Role of Locoregional therapies in the treatment of thyroid pathology: Proceedings from the Society of Interventional Radiology Foundation Research Consensus Panel. *Journal of Vascular and Interventional Radiology*. 2024;**35**(12):1752-1759. DOI: 10.1016/j.jvir.2024.08.008
- [114] Yan L et al. Long-term comparison of image-guided thermal ablation vs. lobectomy for solitary papillary thyroid microcarcinoma: A multi-center retrospective cohort study. *International Journal of Surgery*. 2024;**110**(8):4867. DOI: 10.1097/JS9.0000000000001595

Section 3

Recent Advances in Thyroid Cancer

Advances in Diagnosis and Treatment of Radioactive Iodine Refractory Differentiated Thyroid Cancer

Yongji Jiang, Chao Ma, Renfei Wang and Zhongwei Lv

Abstract

Differentiated thyroid cancer (DTC) often has a good prognosis, but some patients have progressive disease after radioiodine-131 (^{131}I) treatment and become radioactive iodine refractory differentiated thyroid cancer (RAIR-DTC). At present, the concept of precision diagnosis and treatment of thyroid cancer based on molecular characteristics has gradually been known, and a variety of molecular targeted drugs have demonstrated good efficacy and safety. Multi-kinase inhibitors and selective kinase inhibitors significantly prolong the progression-free survival and overall survival time of RAIR-DTC patients. Local treatment is beneficial for relieving local symptoms and reducing tumor burden. This chapter will introduce the recent advances in molecular mechanism, diagnosis, and treatment of RAIR-DTC.

Keywords: differentiated thyroid cancer, radioiodine refractory, RAIR-DTC, diagnosis, treatment

1. Introduction

Thyroid cancer is the most common endocrine malignancy in head and neck, and DTC is the most frequent subtype of thyroid cancer, accounting for more than 95%. Most DTC patients have a good prognosis and can achieve a clinically tumor-free state after standardized and comprehensive treatment. Intermediate- and high-risk DTC patients routinely require ^{131}I treatment to ablate residual thyroid or recurrent/metastatic lesions. Even so, about 5–23% of patients will develop distant metastases and about 1/3–2/3 of this subset will develop RAIR-DTC [1–3]. The 10-year survival rate of RAIR-DTC patients will drop to less than 20%, and the average life expectancy will drop to 3–5 years [4–6]. RAIR-DTC has rapid progression, poor prognosis, and inappropriate diagnosis and treatment, which has always been the focus of clinical attention. With the development of next-generation sequencing technology, the concept of precise diagnosis and treatment of thyroid cancer based on molecular characteristics has gradually formed [7]. The emergence of new radionuclide molecular probes is helpful for the discovery and treatment of DTC recurrence or metastases [8]. The results of

many clinical trials have demonstrated great efficacy and safety of multiple molecular targeted drugs in RAIR-DTC, and the combination of multiple drugs shows its good application prospects [9, 10].

2. Definition of RAIR-DTC

The definition of RAIR-DTC requires comprehensive judgment from multiple disciplines such as nuclear medicine, radiology, oncology, and endocrinology departments. In the absence of interference from exogenous iodine load, if one of the following situations occurs during thyroid-stimulating hormone (TSH) stimulation, it can be considered as RAIR-DTC: (1) metastases that are radioiodine-nonavid on the initial posttreatment whole body scan (WBS); (2) functional metastases that originally are radioiodine-avid gradually lose their iodine uptake ability; (3) some metastases are radioiodine-avid, while others are radioiodine-nonavid, which can be detected by other imaging methods such as ^{18}F -FDG PET/CT, CT, or MRI; (4) radioiodine-avid metastases maintain the iodine uptake ability, but the disease progress within 1 year after ^{131}I treatment, including gradual growth of the lesions, the appearance of new lesions, or a continuous increase of thyroglobulin (Tg) or Tg-antibody (TgAb) levels; and (5) cumulative ^{131}I treatment dose >600 mCi [2, 3]. The above indicates the patients will benefit little from subsequent ^{131}I treatment.

3. Molecular mechanism of RAIR-DTC

RAIR-DTC is characterized by dedifferentiation, which shows a significantly decreased expression of thyroid-specific molecules, such as sodium-iodine symporter (NIS), Tg, TSH receptor (TSHR), and thyroid peroxidase (TPO). The decreased expression or abnormal function of NIS is the most important. In addition, thyroid-specific transcription factors such as paired-box gene 8 (Pax-8) and thyroid transcription factor-1 (TTF-1) can affect the iodine avidity of thyroid cells. The abnormal expression of thyroid-specific genes and thyroid transcription factors leads to a decrease of NIS expression and/or a weakening of NIS membrane targeting, thereby causing the loss of iodine avidity of thyroid cancer cells.

Gene mutations may be observed in DTC such as B-Raf proto-oncogene, serine/threonine kinase (BRAF), telomerase reverse transcriptase (TERT), rat sarcoma oncogene (RAS), anaplastic lymphoma kinase (ALK), or rearranged in transformation (RET)/papillary thyroid cancer (PTC), neurotrophin receptor tyrosine kinase (NTRK) rearrangement, leading to abnormal activation of mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K), and anaplastic lymphoma kinase (APK) signaling pathways and downregulation of NIS expression, which is the main mechanism of RAIR. In addition, multiple signaling pathways such as TSHR, Wnt/ β -catenin, transforming growth factor (TGF)- β /Smad homologous 3 (Smad3), nuclear factor kappa-B (NF- κ B), Notch, have also been reported to affect the transcription level of NIS [7, 9, 11–16]. About 70–80% of human PTC are associated with BRAF, RAS mutations, or RET/PTC rearrangement, which lead to abnormal activation of the MAPK signaling pathway, causing the progression of thyroid cancer, and are essential for regulating cell proliferation, growth, survival, and dedifferentiation.

At the epigenetic level, a variety of oncogenic signals lead to gene promoter's excessive methylation such as NIS and TSHR, or modify histones through histone

deacetylases, inhibiting the expression of NIS [17]. At the post-transcriptional level, microRNA regulation can affect the expression of thyroid cancer differentiation genes, while the activation of the PI3K signaling pathway and the decreased expression of phosphatidylinositol glycosyl anchor biosynthesis class U (PIGU) will inhibit NIS glycosylation and affect its normal cell membrane localization [18].

In summary, RAIR may be the result of the combined effects of multiple gene mutations and signaling pathways activation, involving multiple mechanisms such as gene transcription, epigenetics, and post-transcriptional modification. However, it should be noted that current studies on genetic and molecular characteristics are mainly focused on primary lesions, and little is known about the paired molecular characteristics of primary tumors and their metastases and whether they have the same genetic abnormalities [19]. Future studies should also pay attention to the heterogeneity of primary lesions and metastases, as it is important for guiding targeted treatment.

4. Prediction and diagnosis of RAIR-DTC

RAIR is a state that the lesion is resistant to ^{131}I treatment and there is no clear histopathological definition of RAIR-DTC. Thus, the diagnosis of RAIR-DTC requires a comprehensive evaluation of ^{131}I treatment efficacy and other examinations. If it is possible to diagnose or predict whether DTC is RAIR earlier, it will be beneficial for these patients to receive early intervention treatment and prolong progression-free survival (PFS) or overall survival time (OS).

4.1 Molecular genetic testing

As mentioned above, RAIR-DTC is associated with gene mutations, among which BRAF and RAS mutations are the most common, and both are early driving events in the carcinogenesis process [20]. The fifth edition of the WHO classification of thyroid cancer combines tumor morphological characteristics, mutations, and transcriptomic characteristics, and proposes RAS-like, BRAF-like, and non-BRAF/non-RAS-like tumors. BRAF-like tumors are more prone to dedifferentiation than RAS-like tumors and more related to RAIR [21]. RAIR-DTC often manifests as secondary invasive mutations based on early driver gene mutations such as BRAF, RAS, or a few gene fusions (usually RET or NTRK3), and the most common are late molecular events such as TERT promoter, TP53, and phosphatidylinositol-4,5-bisphosphate3-kinase-catalytic subunit α isoform (PIK3CA) [22]. Double-gene mutations of BRAF and TERT are currently relatively clear molecular alternations with potential invasiveness and poor prognosis [23].

4.2 Imaging examination

^{131}I -WBS + SPECT/CT can evaluate the lesion ^{131}I -avidity and is an important method for pre-evaluation, efficacy evaluation, lesion detection, restaging, treatment guidance, and prognosis judgment for DTC ^{131}I treatment. ^{18}F -FDG PET/CT is performed to detect the lesions when the Tg level is abnormally elevated or the lesions are ^{131}I -nonavid (negative ^{131}I -WBS). The poorer the degree of lesion differentiation, the more metabolically active and aggressive it is and the worse the prognosis. The iodine uptake ability and ^{18}F -FDG avidity often show a “flip-flop” phenomenon.

Regardless of ^{131}I -avidity, if lesions are ^{18}F -FDG avid, it indicates the patients benefit little from ^{131}I treatment [24]. ^{18}F -FDG PET/CT combined with ^{131}I -WBS + SPECT/CT can comprehensively evaluate the tumor burden.

In addition to ^{18}F -FDG PET/CT, new tumor radionuclide probes are gradually being applied for detecting RAI-DTC lesions. For some patients with negative ^{18}F -FDG imaging, prostate-specific membrane antigen (PSMA) PET/CT can help identify RAI-DTC lesions and display a potential additional diagnostic role [25]. PSMA assessment might be useful to timely identify DTC patients at higher risk of recurrence [26]. Small sample studies showed that radionuclide-labeled fibroblast activation protein inhibitor (FAPI), ^{68}Ga -FAPI, has a higher detection ability for RAI-DTC lesions than ^{18}F -FDG, especially in lymph nodes and pulmonary metastases [27]. Another study reported that FAPI accumulates in recurrent and metastatic lesions of RAI-DTC patients at least as well as FDG with particular privileges such as lower injected activity and lower background [28]. Two RAI-DTC patients who accepted ^{18}F -FDG and ^{18}F -FAPI or ^{18}F -PSMA PET/CT are shown in **Figure 1**.

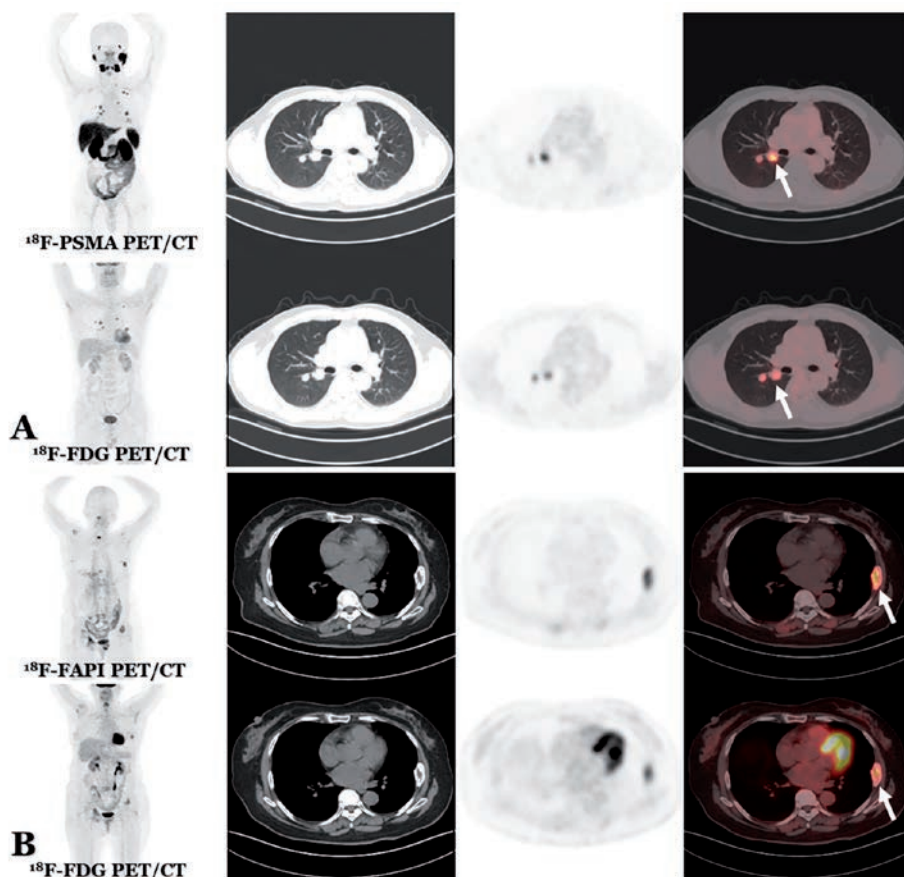


Figure 1. Two RAI-DTC patients underwent multimodal imaging examinations. (A) A 61-year-old male, PET/CT showed multiple PSMA-avid and FDG-avid metastases in both lungs. The patient is now receiving targeted treatment with anlotinib. (B) A 72-year-old female, PET/CT showed multiple FDG-avid and FAP-avid bone metastases throughout the body. The patient had received external beam radiotherapy, ^{125}I seed implantation treatment, targeted anlotinib therapy, and zoledronic acid treatment.

4.3 Clinicopathological feature

Studies reported that suppressive Tg level decreases by less than 25.3% after ^{131}I treatment compared with before treatment in DTC patients with distant metastases indicating it is difficult to achieve biochemical benefit from the next ^{131}I treatment [29]. If the stimulated Tg before the second ^{131}I treatment does not decrease significantly compared with the first, it may progress to RAIR-DTC [30]. Preoperative thyroglobulin can also be served as an independent predictor of RAIR-DTC [31]. Besides, other clinicopathological features such as TgAb level, age, extraglandular invasion, high-risk histological subtype, maximum tumor diameter, lactate dehydrogenase A are associated with RAIR to a certain extent [32–34].

5. Treatment for RAIR-DTC

The natural course of RAIR-DTC varies greatly, and comprehensive evaluations should be performed periodically to make individualized treatment decisions based on specific conditions, ensuring patients can receive effective interventions timely when symptoms or progression occur and avoiding overtreatment to patients with stable or slowly progressive conditions.

5.1 Pre-treatment assessment

Clinical evaluation mainly includes [35]: (1) Tumor burden: For maximum tumor diameter ≤ 1 cm, active monitoring under TSH suppression treatment can be selected; for large tumor burden, a single lesion maximum diameter $> 1\text{--}2$ cm or the sum of diameters of target lesions ≥ 4 cm, individualized treatment is recommended based on multiple considerations [36]. (2) Tumor progression rate: For evaluable or measurable lesions, tumor volume doubling time can assess the progression rate from a three-dimensional perspective [37]. Active intervention therapy is recommended for patients with RAIR-DTC progression within 1 year, and when the disease is stable and has no progression, regular follow-up and lesion monitoring should be considered. For patients with no evaluable or measurable lesions, serum Tg doubling time can indirectly assess tumor progression [38]. (3) Tumor location and number: For few metastatic lesions or they are concentrated in one organ (oligometastasis), local treatment can be recommended; for those with multiple lesions or are involved in multiple organs, systemic treatment and/or local treatment can be considered; in some special cases, such as bone metastasis in weight-bearing sites or isolated brain metastasis, local treatment is recommended as a priority. (4) Concomitant symptoms: Active systemic treatment is recommended when tumor-related clinical symptoms occur.

5.2 TSH suppression treatment

For RAIR-DTC patients with stable or slowly progressive lesions and low tumor burden, an active observation strategy under TSH suppression therapy can be adopted. TSH level should be below 0.1 mU/L under suppression treatment (especially for patients still with iodine-avid lesions), but it should also be appropriately adjusted in combination with the risk assessment of adverse reactions to TSH suppression treatment. A retrospective study showed that Tg change rate was $0.03\text{ }\mu\text{g/L}$

per month during TSH suppression treatment alone in DTC patients with iodine-nonavid lung metastases and the median PFS was as long as 54.4 months [39].

Most tyrosine kinase inhibitors (TKIs) may affect the efficacy of thyroid hormones, and possible mechanisms include TKI-related diarrhea causing thyroid hormone malabsorption and inhibition of monocarboxylate transporter 8-dependent thyroid hormone uptake resulting in its suppression to pituitary [40]. Therefore, the thyroid hormone dose should be adjusted on time to control TSH level.

5.3 Local treatment

Local treatments aim to relieve local symptoms, improve patient's quality of life, and prolong survival. Indications mainly include the following situations: (1) lesions invading or compressing the central nervous system; (2) single distant metastasis; (3) symptomatic bone metastasis or asymptomatic patients with lesions in weight-bearing sites; (4) respiratory obstruction; (5) recurrence or metastasis causing gastrointestinal obstruction or bleeding; and (6) other obvious clinical symptoms or invasion of key sites that may cause significant risks [35].

5.3.1 Surgery

When deciding on surgical treatment for RAI-DTC, two situations should be noted: for regional or distant metastases losing ^{131}I -avidity at the initial radioiodine scan and the indication for surgery is available, surgery should be actively considered; while for patients who have received multiple ^{131}I treatments and other treatments, lesions can be surgically removed and what kind of surgical method should be performed requires multidisciplinary discussion. A study reported that surgical treatment for RAI FDG-avid cervical recurrence led to 40% of study patients achieving a biochemical and radiological cure [41]. For some RAI-DTC patients who cannot obtain immediate surgical remission and the lesions seriously threaten them, targeted treatment may be a beneficial attempt. In 18 advanced DTC patients, after a median of 6 months of treatment with sorafenib or lenvatinib, the median reduction in primary tumor diameter was 25%. Surgical treatment was performed in 10/18 of the patients, and 6/10 of them achieved R0/R1 resection status [42].

5.3.2 ^{125}I seed implantation treatment

As a radionuclide, ^{125}I seed has low energy (27.4–35.5 KeV) and long half-life (59.5 days), and it can deliver a lethal radiation dose to the tumor cells while causing little damage to surrounding normal tissues (the tissue penetration is 17 mm). ^{125}I seed is mainly used for RAI-DTC with cervical recurrence or metastatic lymph nodes, soft tissue metastases, and bone metastases that affect function, which cannot be surgically removed. In the short term, it can effectively reduce the tumor volume, significantly improve local compression symptoms, relieve local pain, reduce Tg level, and even prolong OS [43, 44].

Before implantation treatment, the physicians should jointly discuss and decide the treatment plan, and then delineate the target area and determine the prescription dose. One study reported that ^{125}I seed implantation treating locally recurrent refractory thyroid cancer, with a dose of 100–140 Gy (median prescription dose: 120 Gy), can effectively control local lesions without serious adverse events [45].

For target lesion with small size, poor differentiation, and close distance to the organ at risk, ^{125}I seed activity should be reduced. When the tumor diameter is ≥ 5 cm, higher activity seeds can be implanted into the target area in batches [46].

5.3.3 External beam radiotherapy

External beam radiotherapy (EBRT) is mainly suitable for RAIR-DTC patients with recurrence or metastases that cannot be surgically removed or macroscopic or microscopic residual lesions after surgery. For brain metastases, bone metastases, etc., especially accompanied by local pain or compression symptoms, EBRT is the preferred local treatment method [47, 48]. For patients with RAIR-DTC, postoperative EBRT is associated with long-lasting locoregional control (LRC) and OS with acceptable toxicity. About 1-, 5-, and 10-year LRC rates after EBRT were 91.2, 71.0, and 59.2%, respectively; OS rates were 87.8, 56.7, and 25.3%, respectively [49]. A retrospective cohort suggested that definitive radiotherapy can impart excellent control rates with minimal toxicities for oligometastatic and oligoprogressive thyroid cancer, with OS at 3 and 5 years of 81.5 and 70%, respectively [50]. However, some studies argued that EBRT cannot improve the OS, distant metastasis rate, or biochemical and radiological cure rate [41, 51, 52].

5.3.4 Ablation

Physical ablation can be divided into radiofrequency ablation, microwave ablation, and cryoablation according to the treatment principle, as well as the relatively new nano-knife, laser ablation, and HIFU treatment. Ablation therapy is mainly applied to the following situations: RAIR-DTC recurrent or metastatic lesions that cannot be completely resected; lesions that invade important structures such as the trachea, esophagus, blood vessels, and nerves; patients who cannot tolerate the surgery [35].

A meta-analysis of the safety and efficacy of radiofrequency ablation (RFA) for treating locally recurrent thyroid cancer reported a therapeutic success (volume reduction rate $> 50\%$) of 89.5–100%, with 68.8% of lesions completely disappearing after RFA [53]. Recently, a study indicated that RAF can be used as a palliative treatment to relieve the symptoms caused by metastases; however, it has a limited value in improving the overall prognosis of thyroid cancer patients with distant metastasis [54]. Imaging guide laser ablation is also a safe and effective debulking treatment and can significantly relieve the pain suffering from DTC metastases that are not responsive to standard treatments [55].

5.4 Systemic treatment

Systemic treatments for RAIR-DTC include targeted treatment against specific mutant proteins, immunotherapy, and cytotoxic chemotherapy. Although the efficacy of immune checkpoint inhibitor monotherapy is limited, there have been many clinical trials combining it with the targeted treatment or chemoradiotherapy. Cytotoxic chemotherapy is only used as a complementary treatment to the abovementioned for its limited clinical benefits. Systemic treatment is recommended for RAIR-DTC patients with symptomatic or rapidly progressive diseases who are unable to receive local treatment and/or with multiple organ involvement. Partial targeted drugs for thyroid cancer are summarized in **Table 1**.

Drug	Target	Adverse events	Efficacy (median PFS or 1-year PFS rate, ORR, Reference)
Multi-kinase inhibitors			
Sorafenib	VEGFR1/2/3, PDGFR, c-KIT, RET, FLT, RAF, etc.	Hand-foot skin reactions, hypertension, hypocalcemia, diarrhea, etc.	a. 10.8 months, 12.2%, [56] b. 17.6 months, 21.7%, [57] c. 13.3 months, 24.0%, [58]
Lenvatinib	VEGFR, FGFR, PDGFR α , RET, KIT, etc.	Hypertension, proteinuria, hand-foot skin reactions, diarrhea, weight decrease, fatigue or asthenia, etc.	a. 18.3 months, 64.8%, [59] b. 12.9 months, 69.9%, [60] c. 35.3 months, 59.0%, [58]
Cabozantinib	VEGFR-2, AXL, RET, MET, etc.	Palmar-plantar erythrodysesthesia, hypertension, fatigue, etc.	median not reached (96% CI 5.7-not estimable), 15.0%, [61]
Selective kinase inhibitors			
Selpercatinib	RET	Hypertension, increased alanine and aspartate aminotransferase level, hyponatremia, hyponatremia	79, 64%, [62]
Pralsetinib	RET	Hypertension, neutropenia, lymphopenia, anemia	Median not reached (95% CI not estimable), 89%, [63]
Larotrectinib	NTRK	Myalgia, fatigue, nausea, constipation, cough, dizziness, peripheral edema	81, 71%, [64]
Vemurafenib	BRAF	Rash, fatigue, alopecia, dysgeusia, blood creatinine increase, weight decrease, arthralgia, etc.	18.2 months, 38.5% (cohort 1); 8.9 months, 27.3% (cohort 2), [65]
Selumetinib	MEK1/2	Rash, fatigue, hepatic enzymes increased, diarrhea, nausea, mucositis oral, etc.	7.5 months, 3%, [66]

ORR: objective response rate, PFS: progression-free survival.

Table 1.
Targeted drugs for thyroid cancer.

5.4.1 Targeted treatment

5.4.1.1 Multi-kinase inhibitors (MKIs)

Among MKIs, sorafenib and lenvatinib are currently recommended as standard treatments for RAIR-DTC. Sorafenib is an oral MKI that targets VEGFR1/2/3, PDGFR, c-KIT, RET, FLT, RAF, etc. In a phase 3 clinical trial [56], a total of 417 patients with RAIR locally advanced or metastatic lesions were randomly treated with sorafenib (400 mg, twice daily) or placebo until disease progression, intolerable adverse reactions, or patient non-compliance occurred. The median PFS and objective response rate (ORR) of the sorafenib group were significantly higher than placebo group (10.8 vs. 5.8 months, 12.2 vs. 0.5%), but there was no statistically significant difference in the median OS between the two groups. Based on it, sorafenib became the world's first TKI approved for the treatment of RAIR-DTC in 2013. A real-world

study showed that the ORR of 72 patients with progressive RAIR-DTC treated with sorafenib (200 mg, twice daily) was 21.7%, and the median PFS and OS were 17.6 and 28.9 months [57]. Another multicenter retrospective cohort study showed that 80 progressive RAIR-DTC patients were treated with sorafenib, the partial response (PR) rate was 24%, and the median PFS was 13.3 months [58].

Lenvatinib targets VEGFR, FGFR, PDGFR α , RET, KIT, etc. The results of a phase 3 clinical trial [59] showed that 392 RAIR-DTC patients were randomly assigned to receive lenvatinib (24 mg/d in 28-day cycles) or placebo. The median PFS and total response rate of the lenvatinib group were significantly better than placebo (18.3 vs. 3.6 months, 64.8 vs. 1.5%). Lenvatinib was approved in 2015 for the treatment of RAIR-DTC by U.S. Food and Drug Administration (FDA). Another phase 3 SELECT study showed that median PFS was significantly longer with lenvatinib treatment versus placebo (12.9 vs. 3.7 months), and the ORR was 69.9 and 0%, respectively [60]. Lenvatinib is more effective than sorafenib in improving PFS, but it is more likely to cause severe hypertension and proteinuria. There are currently no head-to-head trials of lenvatinib versus sorafenib, but guidelines published by the National Comprehensive Cancer Network (NCCN) have designated lenvatinib as the preferred systemic treatment for patients with progressive or symptomatic RAIR-DTC [67].

Cabozantinib mainly targets VEGFR-2, AXL, RET, and MET, and has been approved by the FDA for the treatment of metastatic medullary thyroid cancer (MTC). Cabozantinib showed its effectiveness as a first-line drug and a salvage drug when VEGFR-TKI treatment is ineffective in phase 1/2 clinical trials for the treatment of RAIR-DTC [68]. A phase 3 clinical trial (COSMIC-311 trial) [61] included 187 RAIR-DTC patients with progressive disease after previous treatment with sorafenib and/or lenvatinib. The patients were randomly assigned to receive cabozantinib (60 mg/d) or placebo, and the interim analysis showed that the median PFS of the cabozantinib group was significantly longer than placebo group. Cabozantinib can be used as a second-line treatment for RAIR-DTC that has progressed after lenvatinib and sorafenib treatment.

Other targeted drugs, such as vandetanib, pazopanib, anlotinib, and apatinib, have shown good efficacy in different phase 2 clinical trials [9, 10, 69–71], prolonging the PFS and OS of RAIR-DTC patients and providing more treatment options for drug-resistant patients.

5.4.1.2 Selective kinase inhibitors

Since MKIs mainly exert the antitumor effect through anti-angiogenesis, their common adverse reactions include hypertension, proteinuria, hand-foot syndrome, diarrhea, etc. Some patients cannot tolerate it and inevitably reduce or withdraw drugs, and their life quality is also greatly affected. For RAIR-DTC patients with detected specific genetic mutations, selective kinase inhibitors may have better specificity and safety.

- a. *RET inhibitor*. Selpercatinib is a highly selective and potent RET inhibitor with central nervous system activity. Selpercatinib (phase 2 trial dose of 160 mg, twice daily) showed good efficacy and safety in patients with RET fusion-positive DTC treated by MKIs previously, among the 19 patients, the ORR was 79% and the 1-year PFS rate was 64% [62]. Pralsetinib is also a RET inhibitor, in a phase 1/2 multicenter clinical trial involving 142 thyroid cancer patients with RET mutation or RET fusion positivity, and it also showed highly effective antitumor activity and safety [63].

- b. *TRK inhibitor*. The protein encoded by NTRK gene fusion activates the downstream MAPK and PI3K pathway, promoting tumor proliferation and spread. Larotrectinib is a highly selective TRK inhibitor that has previously demonstrated great efficacy in phase 1/2 clinical trials in adult or pediatric DTC patients [64]. In addition, one study reported that larotrectinib may promote the redifferentiation of RAIR-DTC tumor cells and restore their iodine uptake ability [72].
- c. *MAPK pathway inhibitor*. BRAF mutation occurs in approximately 45% of PTC patients, and continuous activation of the MAPK signaling pathway promotes PTC tumor cell proliferation, metastasis, and recurrence. It can also reduce the NIS expression and cause tumor cell dedifferentiation. Vemurafenib and dabrafenib are BRAF inhibitors that were approved by the FDA for the treatment of melanoma. In a phase 2 clinical trial of BRAF mutation-positive RAIR-DTC patients, 26 patients who had not previously received MKIs were treated with vemurafenib, achieving an ORR of 38.5% and a median PFS of 18.2 months [65]. Studies showed that BRAF inhibitors plus downstream MEK inhibitor trametinib may achieve dual inhibition of MAPK pathway and can delay or prevent the MAPK pathway secondary activation caused by BRAF inhibitors, thereby enhancing its antitumor activity compared with BRAF inhibitors alone [73, 74]. Selumetinib is a selective MEK-1/2 inhibitor, a previous study found that selumetinib is not effective in treating RAIR-DTC patients, but it can enhance their uptake of radioiodine [66].
- d. *Mammalian target of rapamycin (mTOR) inhibitor*. The dysregulation of the PI3K signaling pathway is closely related to the occurrence and progress of thyroid cancer. mTOR inhibitors such as everolimus and temsirolimus inhibit the downstream key signaling molecule mTOR in PI3K pathway, thereby inhibiting tumor growth. A phase 2 clinical study of the combination of temsirolimus (25 mg weekly) and sorafenib (200 mg, twice daily) for RAIR-DTC patients showed that the ORR of 36 RAIR-DTC patients was 22%, which was higher than the ORR (12.2%) of the sorafenib group in the DECISION trial, and the safety was similar [56, 75].

5.4.2 Immunotherapy

As a “cold tumor,” the immunotherapy efficacy of DTC is relatively limited except for a few patients with high tumor mutation load [76]. The results of a phase 2 clinical trial of pembrolizumab (200 mg every 3 weeks) for the treatment of advanced thyroid cancer showed that pembrolizumab had a certain and relatively long-lasting efficacy regardless of the extent of programmed cell death receptor-1 (PD-L1) expression [77]. The overall response rate of pembrolizumab plus lenvatinib in a multicenter phase 2 study for RAIR-DTC reached 62%, and the 1-year PFS rate was 74% [78].

5.5 Other treatment

5.5.1 Redifferentiation treatment

Currently, BRAF inhibitors dabrafenib and vemurafenib, MEK inhibitor trametinib, RET inhibitor selpercatinib, and NTRK rearrangement inhibitor larotrectinib that were reported can restore iodine uptake ability and then accept ¹³¹I treatment [65, 72, 79–81]. Among them, the combination of dabrafenib and

trametinib has been studied the most, and the related phase 2 clinical studies have shown good benefits, and 38% of patients achieved partial remission 6 months after ^{131}I treatment and after redifferentiation induction, suggesting a broad prospect for combined ^{131}I treatment after drug-induced differentiation [74]. However, existing researches vary in terms of drug selection, iodine uptake evaluation, efficacy evaluation nodes, and clinical characteristics of included patients, and long-term benefits still need to be further studied.

5.5.2 Radionuclide therapy

Gradually, more and more studies focused on targeted radionuclide therapy. ^{177}Lu -labeled somatostatin analogues, PSMA, and FAPI showed a certain efficacy [27, 82–84], but adequately powered phase 2/3 trials are now required to generate further data on their safety and efficacy, including long-term outcomes.

6. Follow-up and monitoring

6.1 Efficacy

After receiving local or systemic treatment, RAIR-DTC patients should achieve regular serological and imaging efficacy monitoring and evaluation. Serum Tg level can reflect the overall tumor burden to a certain extent and is a convenient means for monitoring the efficacy and managing the follow-up. The response evaluation criteria in solid tumors (RECIST) 1.1 are also applicable to evaluate the therapeutic efficacy of RAIR-DTC [85]. Molecular imaging showed its certain advantages in early evaluation of efficacy. The PET response criteria in solid tumors (PERCIST) based on ^{18}F -FDG PET/CT can quantitatively compare the glucose metabolism changes in RAIR-DTC lesions and evaluate the metabolic response after targeted therapy, which is related to PFS [86–88].

6.2 Treatment-related adverse effects

Clinical trial data showed that the probability of adverse effects related to targeted therapy was nearly 100%. The incidence of adverse effects greater than grade 3, the proportion of dose reduction, interruption, and discontinuation due to severe adverse reactions can reach 87.4, 80.6, 76.0, and 18.8%, respectively, and the treatment-related mortality rate is about 1.0–2.3% [35]. The occurrence of adverse effects to targeted therapy varies significantly between individuals. Treatment of underlying diseases before targeted treatment and close monitoring during medication in RAIR-DTC patients can reduce the probability of adverse effects. Strictly implementing the graded treatment of adverse effects is necessary. If adverse effects greater than grade 3 or vital organ damage are observed, the drug should be discontinued or reduced in time. A treatment strategy is recommended to be formulated after a multidisciplinary evaluation, and a strategy of prevention, monitoring, and treatment should be implemented in parallel [89].

7. Conclusion

RAIR-DTC is becoming more and more common in clinical practice and the survival of it is generally short, so it is very important to identify RAIR-DTC and treat it

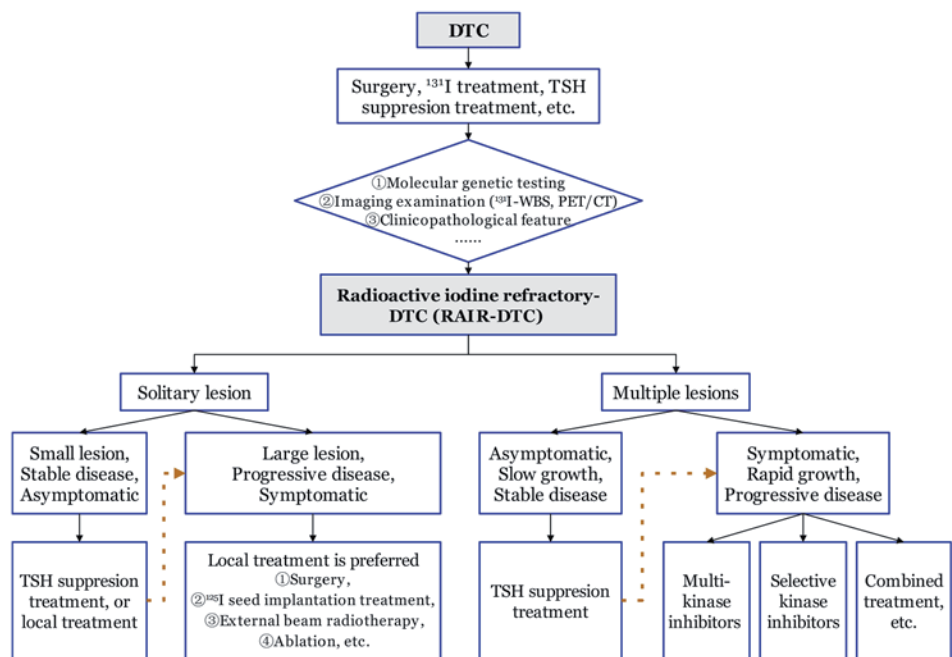


Figure 2.
Suggested flowchart for the management of RAIR-DTC.

early. Detection of gene mutations, imaging and serological examinations, and evaluation of clinicopathological features are helpful in diagnosing RAIR-DTC as early as possible, but the current treatment methods for RAIR-DTC are still very limited. The drug-targeting gene mutations and signaling pathways and multidisciplinary treatments have significantly improved the PFS and OS of RAIR-DTC patients, but the resistance to targeted drugs and treatment-related adverse effects limit their application to a certain extent. **Figure 2** shows the suggested flowchart for the management of RAIR-DTC.

Conflict of interest

The authors declare no conflict of interest.

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References

- [1] Fugazzola L, Elisei R, Fuhrer D, Jarzab B, Leboulleux S, Newbold K, et al. 2019 European thyroid association guidelines for the treatment and follow-up of advanced radioiodine-refractory thyroid cancer. *European Thyroid Journal*. 2019;**8**(5):227-245
- [2] Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2016;**26**(1):1-133
- [3] Chinese Society of Nuclear Medicine. Guidelines for radioiodine therapy of differentiated cancer (2021 edition). *Chinese Journal of Nuclear Medicine and Molecular Imaging*. 2021;**41**(04):218-241
- [4] Liu J, Liu Y, Lin Y, Liang J. Radioactive iodine-refractory differentiated thyroid cancer and redifferentiation therapy. *Endocrinology and Metabolism*. 2019;**34**(3):215-225
- [5] Jin Y, Van Nostrand D, Cheng L, Liu M, Chen L. Radioiodine refractory differentiated thyroid cancer. *Critical Reviews in Oncology/Hematology*. 2018;**125**:111-120
- [6] Durante C, Haddy N, Baudin E, Leboulleux S, Hartl D, Travagli J, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: Benefits and limits of radioiodine therapy. *The Journal of Clinical Endocrinology & Metabolism*. 2006;**91**(8):2892-2899
- [7] Yu Q, Zhang X, Li L, Zhang C, Huang J, Huang W. Molecular basis and targeted therapies for radioiodine refractory thyroid cancer. *Asia-Pacific Journal of Clinical Oncology*. 2023;**19**(3):279-289
- [8] Satapathy S, Bal C. Theranostic options for radioiodine-refractory differentiated thyroid carcinoma: Recent advances, challenges, and road ahead. *Frontiers in Endocrinology*. 2022;**13**:924841
- [9] Voinea I-A, Petrova E, Dumitru N, Cocoloş A, Ioachim D, Goldstein AL, et al. Pathogenesis and management strategies in radioiodine-refractory differentiated thyroid cancer: From molecular mechanisms toward therapeutic approaches: A comprehensive review. *Journal of Clinical Medicine*. 2024;**13**(23):7161
- [10] Chen P, Yao Y, Tan H, Li J. Systemic treatments for radioiodine-refractory thyroid cancers. *Frontiers in Endocrinology*. 2024;**15**:1346476
- [11] Shen H, Zhu R, Liu Y, Hong Y, Ge J, Xuan J, et al. Radioiodine-refractory differentiated thyroid cancer: Molecular mechanisms and therapeutic strategies for radioiodine resistance. *Drug Resistance Updates*. 2024;**72**:101013
- [12] Zou M, Baitei EY, Alzahrani AS, BinHumaid FS, Alkhafaji D, Al-Rijjal RA, et al. Concomitant RAS, RET/PTC, or BRAF mutations in advanced stage of papillary thyroid carcinoma. *Thyroid®*. 2014;**24**(8):1256-1266
- [13] Lee H, Krishnan V, Wirth LJ, Nucera C, Venturina M, Sadow PM, et al. Case report of CCDC149–ALK fusion: A novel genetic alteration and a clinically relevant target in metastatic papillary thyroid carcinoma. *Thyroid®*. 2022;**32**(12):1580-1585

- [14] Subbiah V, Yang D, Velcheti V, Drilon A, Meric-Bernstam F. State-of-the-art strategies for targeting RET-dependent cancers. *Journal of Clinical Oncology*. 2020;**38**(11):1209-1221
- [15] Zhang W, Ruan X, Li Y, Zhi J, Hu L, Hou X, et al. KDM1A promotes thyroid cancer progression and maintains stemness through the Wnt/ β -catenin signaling pathway. *Theranostics*. 2022;**12**(4):1500-1517
- [16] Jiang Y, Huo Y, Lv Z, Ma C. Clinical advances of 18F-FDG PET/CT in the evaluating differentiation of recurrent or metastatic differentiated thyroid carcinoma and guiding 131I therapy. *Chinese Journal of Nuclear Medicine and Molecular Imaging*. 2022;**09**:559-562
- [17] Fu H, Cheng L, Jin Y, Cheng L, Liu M, Chen L. MAPK inhibitors enhance HDAC inhibitor-induced redifferentiation in papillary thyroid cancer cells harboring BRAF V600E: An In vitro study. *Molecular Therapy - Oncolytics*. 2019;**12**:235-245
- [18] Cai X, Wang R, Tan J, Meng Z, Li N. Mechanisms of regulating NIS transport to the cell membrane and redifferentiation therapy in thyroid cancer. *Clinical and Translational Oncology*. 2021;**23**(12):2403-2414
- [19] Gomes-Lima CJ, Shobab L, Wu D, Ylli D, Bikas A, McCoy M, et al. Do molecular profiles of primary versus metastatic radioiodine refractory differentiated thyroid cancer differ? *Frontiers in Endocrinology (Lausanne)*. 2021;**12**:623182
- [20] Ding Z, Tao X, Deng X, Guo B, Kang J, Wu B, et al. Genetic analysis and clinicopathologic features of locally advanced papillary thyroid cancers: A prospective observational study. *Journal of Cancer Research and Clinical Oncology*. 2023;**149**(9):6303-6313
- [21] Baloch ZW, Asa SL, Barletta JA, Ghossein RA, Juhlin CC, Jung CK, et al. Overview of the 2022 WHO classification of thyroid neoplasms. *Endocrine Pathology*. 2022;**33**(1):27-63
- [22] Singh A, Ham J, Po JW, Niles N, Roberts T, Lee CS. The genomic landscape of thyroid cancer tumorigenesis and implications for immunotherapy. *Cells [Internet]*. 2021;**10**(5):1082
- [23] Mu Z, Zhang X, Liang D, Fang J, Chen G, Guo W, et al. Risk stratification for radioactive iodine refractoriness using molecular alterations in distant metastatic differentiated thyroid cancer. *Chinese Journal of Cancer Research*. 2024;**36**(1):25-35
- [24] Jiang Y, Liu S, Huo Y, Tong J, Lv Z, Ma C. Correlation of postoperative PET/CT findings of residual/metastatic lymph nodes with efficacy of 131I treatment and clinicopathological features of patients with differential thyroid carcinoma. *Journal of Tongji University (Medical Science)*. 2023;**44**(03):387-393
- [25] Van den Broeck B, Debacker JM, Bauters W, Creytens D, Ferdinande L, Huvenne W, et al. Potential application of [(18)F]AlF-PSMA-11 PET/CT in radioiodine refractory thyroid carcinoma. *EJNMMI Research*. 2024;**14**(1):82
- [26] Sollini M, Kirienko M, di Tommaso L, Pini C, Gelardi F, Ariano S, et al. The complementary role of PSMA expression and [(18)F]FDG PET/CT in predicting thyroid cancer outcome: From black and white to shades of gray, in the era of precision oncology. *EJNMMI Research*. 2023;**13**(1):54

- [27] Fu H, Wu J, Huang J, Sun L, Wu H, Guo W, et al. 68Ga fibroblast activation protein inhibitor PET/CT in the detection of metastatic thyroid cancer: Comparison with 18F-FDG PET/CT. *Radiology*. 2022;**304**(2):397-405
- [28] Nourbakhsh S, Salehi Y, Farzanehfar S, Ghaletaki R, Bakhshi Kashi M, Abbasi M. FAPI PET/CT provides higher uptake and better target to back ground in recurrent and metastatic tumors of patients with iodine refractory papillary thyroid cancer compared with FDG PET CT. *Nuklearmedizin*. 2024
- [29] Sa R, Cheng L, Jin Y, Fu H, Shen Y, Chen L. Distinguishing patients with distant metastatic differentiated thyroid cancer who biochemically benefit from next radioiodine treatment. *Frontiers in Endocrinology*. 2020;**11**:587315
- [30] Meng C, Song J, Long W, Mu Z, Sun Y, Liang J, et al. A user-friendly nomogram for predicting radioiodine refractory differentiated thyroid cancer. *Frontiers in Endocrinology*. 2023;**14**:1109439
- [31] Cheng X, Xu S, Zhu Y, Wu J, Bao J, Yu H, et al. Markedly elevated serum preoperative thyroglobulin predicts radioiodine-refractory thyroid cancer. *European Journal of Clinical Investigation*. 2022;**52**(4):e13721
- [32] Chai J, Zhang R, Zheng W, Zhang G, Jia Q, Tan J, et al. Predictive value of clinical and pathological characteristics for metastatic radioactive iodine-refractory differentiated thyroid carcinoma: A 16-year retrospective study. *Frontiers in Endocrinology (Lausanne)*. 2022;**13**:930180
- [33] Liu W, Jiang B, Xue J, Liu R, Wei Y, Li P. Clinicopathological features of differentiated thyroid carcinoma as predictors of the effects of radioactive iodine therapy. *Annals of Diagnostic Pathology*. 2024;**69**:152243
- [34] Tian T, Dai H, Zhang M, Su M, Chen X, Huang R. Lactate dehydrogenase a is associated with elevated FDG metabolism, radioiodine non-avidity, and poor prognosis in differentiated thyroid cancer. *Academic Radiology*. 2024;**31**(10):4011-4020
- [35] Nuclear Medicine Expert Committee of Chinese Society of Clinical Oncology, Thyroid Cancer Expert Committee of Chinese Society of Clinical Oncology, Chinese Society of Nuclear Medicine, Thyroid Disease Professional Committee of Chinese Research Hospital Association, Thyroid Disease Branch of China International Exchange and Promotive Association for Medical and Health Care, Thyroid Oncology Committee of China Anti-Cancer Association, Thyroid Disease Prevention and Treatment Committee of China Population Culture Promotion Association. Management guidelines for radioactive iodine-refractory differentiated thyroid cancer (2024 edition). *Chinese Journal of Nuclear Medicine and Molecular Imaging*. 2024;**44**(06):359-372
- [36] Fukuda N, Toda K, Ohmoto A, Wang X, Hayashi N, Urasaki T, et al. Baseline tumour size as a prognostic factor for radioiodine-refractory differentiated thyroid cancer treated with lenvatinib. *Anticancer Research*. 2021;**41**(3):1683-1691
- [37] Song E, Ahn J, Jeon MJ, Lee SM, Lee JH, Kim TY, et al. Estimating the growth rate of lung metastases in differentiated thyroid carcinoma: Response evaluation criteria in solid tumors or doubling time? *Thyroid*. 2019;**30**(3):418-424
- [38] Giovanella L, Garo ML, Albano D, Görges R, Ceriani L. The role of

thyroglobulin doubling time in differentiated thyroid cancer: A meta-analysis. *Endocrine Connections*. 2022;**11**(4):e210648

[39] Mu Z, Li Z, Zhang X, Lin Y. The effect of empiric ¹³¹I therapy in papillary thyroid cancer patients with pulmonary metastasis. *China Oncology*. 2020;**30**(12):991-995

[40] Braun D, Kim TD, le Coutre P, Köhrle J, Hershman JM, Schweizer U. Tyrosine kinase inhibitors noncompetitively inhibit MCT8-mediated iodothyronine transport. *The Journal of Clinical Endocrinology & Metabolism*. 2012;**97**(1):E100-E105

[41] Chiapponi C, Alakus H, Faust M, Schultheis AM, Rosenbrock J, Schmidt M. Salvage surgery for cervical radioiodine refractory ¹⁸F-FDG-PET positive recurrence of papillary thyroid cancer. *Endocrine Connections*. 2021;**10**(9):1180-1188

[42] Pitoia F, Abelleira E, Román-González A, Danilovic DL, Scheffel RS, Maia AL, et al. Neoadjuvant treatment of locally advanced thyroid cancer: A preliminary Latin American experience. *Thyroid*. 2024;**34**(7):949-952

[43] Wan Q, Tan L, Tang X, Wang W, Su Y, Wu Z, et al. The clinical value of iodine-125 seed implantation in the treatment of iodine-refractory differentiated thyroid carcinoma. *Frontiers in Endocrinology (Lausanne)*. 2024;**15**:1327766

[44] Zhang W, Hao S, Wang Z, Ding T, Zhang G. (125)I seed implantation for lymph node metastasis from radioactive iodine-refractory differentiated thyroid carcinoma: A study on short-term efficacy and dosimetry. *Frontiers in Oncology*. 2024;**14**:1325987

[45] Yu H, Zhang H, Gao Z, Liu X, Zhang L, Di X, et al. ¹²⁵I seed

brachytherapy for refractory loco-regional recurrence of non-anaplastic thyroid cancer. *Frontiers in Oncology*. 2022;**12**:773708

[46] Committee of Minimally Invasive Therapy in Oncology, Committee of Experts on Radioactive Particle Implantation. Chinese expert consensus on iodine-125 seed implantation for locally advanced differentiated thyroid cancer(2023 edition). *National Medical Journal of China*. 2023;**103**(03):149-157

[47] Blomain E, Berta S, Hug N, Giau D, Meola A, Binkley M, et al. Radiotherapy for brain metastases from thyroid cancer: An institutional and national retrospective cohort study. *Thyroid*. 2022;**32**(7):781-788

[48] Iñiguez-Ariza NM, Bible KC, Clarke BL. Bone metastases in thyroid cancer. *Journal of Bone Oncology*. 2020;**21**:100282

[49] Groen AH, van Dijk D, Sluiter W, Links TP, Bijl HP, Plukker JT. Postoperative external beam radiotherapy for locoregional control in iodine refractory differentiated thyroid cancer. *European Thyroid Journal*. 2022;**11**(1):e210033

[50] Dudzinski SO, Cabanillas ME, Hamidi S, Marczyk VR, Busaidy NL, Dadu R, et al. Definitive radiotherapy for oligometastatic and oligoprogressive thyroid cancer: A potential strategy for systemic therapy deferral. *Journal of the National Comprehensive Cancer Network*. 2024;**23**(1):e247072

[51] Jacomina LE, Jacinto JKM, Co LBA, Yu KKL, Agas RAF, Co JL, et al. The role of postoperative external beam radiotherapy for differentiated thyroid carcinoma: A systematic review and meta-analysis. *Head & Neck*. 2020;**42**(8):2181-2193

- [52] Chiapponi C, Hartmann MJ, Schmidt M, Faust M, Schultheis AM, Bruns CJ, et al. Radioiodine refractory follicular thyroid cancer and surgery for cervical relapse. *Cancers*. 2021;**13**(24):6230
- [53] Suh CH, Baek JH, Choi YJ, Lee JH. Efficacy and safety of radiofrequency and ethanol ablation for treating locally recurrent thyroid cancer: A systematic review and meta-analysis. *Thyroid®*. 2016;**26**(3):420-428
- [54] Lee JH, Chung SR, Baek JH, Song DE, Kim WG, Kim TY, et al. Role of radiofrequency ablation in the treatment of symptomatic distant metastasis of thyroid cancer. *Skeletal Radiology*. 2025:1-8
- [55] Pacella CM, Di Stasio E, Guglielmi R, Baroli A, Pedrazzini L, Misicchi I, et al. Role of laser ablation in multimodal treatment of radioiodine-refractory bone metastases of thyroid cancer: A retrospective study. *Endocrine*. 2020;**70**(2):338-347
- [56] Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: A randomised, double-blind, phase 3 trial. *The Lancet*. 2014;**384**(9940):319-328
- [57] Cheng L, Fu H, Jin Y, Sa R, Chen L. Clinicopathological features predict outcomes in patients with radioiodine-refractory differentiated thyroid cancer treated with sorafenib: A real-world study. *The Oncologist*. 2020;**25**(4):e668-e678
- [58] Kim M, Jin M, Jeon MJ, Kim EY, Shin DY, Lim DJ, et al. Lenvatinib compared with sorafenib as a first-line treatment for radioactive iodine-refractory, progressive, differentiated thyroid carcinoma: Real-world outcomes in a multicenter retrospective cohort study. *Thyroid®*. 2023;**33**(1):91-99
- [59] Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *New England Journal of Medicine*. 2015;**372**(7):621-630
- [60] Zheng X, Xu Z, Ji Q, Ge M, Shi F, Qin J, et al. A randomized, phase III study of Lenvatinib in Chinese patients with radioiodine-refractory differentiated thyroid cancer. *Clinical Cancer Research*. 2021;**27**(20):5502-5509
- [61] Brose MS, Robinson B, Sherman SI, Krajewska J, Lin C-C, Vaisman F, et al. Cabozantinib for radioiodine-refractory differentiated thyroid cancer (COSMIC-311): A randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology*. 2021;**22**(8):1126-1138
- [62] Wirth LJ, Sherman E, Robinson B, Solomon B, Kang H, Lorch J, et al. Efficacy of selpercatinib in RET-altered thyroid cancers. *New England Journal of Medicine*. 2020;**383**(9):825-835
- [63] Subbiah V, Hu MI, Wirth LJ, Schuler M, Mansfield AS, Curigliano G, et al. Pralsetinib for patients with advanced or metastatic RET-altered thyroid cancer (ARROW): A multi-cohort, open-label, registrational, phase 1/2 study. *The Lancet Diabetes & Endocrinology*. 2021;**9**(8):491-501
- [64] Waguespack SG, Drilon A, Lin JJ, Brose MS, McDermott R, Almubarak M, et al. Efficacy and safety of larotrectinib in patients with TRK fusion-positive thyroid carcinoma. *European Journal of Endocrinology*. 2022;**186**(6):631-643

- [65] Brose MS, Cabanillas ME, Cohen EEW, Wirth LJ, Riehl T, Yue H, et al. Vemurafenib in patients with BRAF V600E-positive metastatic or unresectable papillary thyroid cancer refractory to radioactive iodine: A non-randomised, multicentre, open-label, phase 2 trial. *The Lancet Oncology*. 2016;**17**(9):1272-1282
- [66] Ho AL, Grewal RK, Leboeuf R, Sherman EJ, Pfister DG, Deandreis D, et al. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. *New England Journal of Medicine*. 2013;**368**(7):623-632
- [67] Wirth LJ, Durante C, Topliss DJ, Winkquist E, Robenshtok E, Iwasaki H, et al. Lenvatinib for the treatment of radioiodine-refractory differentiated thyroid cancer: Treatment optimization for maximum clinical benefit. *The Oncologist*. 2022;**27**(7):565-572
- [68] Maroto P, Porta C, Capdevila J, Apolo AB, Viteri S, Rodriguez-Antona C, et al. Cabozantinib for the treatment of solid tumors: A systematic review. *Therapeutic Advances in Medical Oncology*. 2022;**14**:17588359221107112
- [69] Ji X, Liang W, Lv G, Ding C, Lai H, Li L, et al. Efficacy and safety of targeted therapeutics for patients with radioiodine-refractory differentiated thyroid cancer: Systematic review and network meta-analysis. *Frontiers in Pharmacology*. 2022;**13**:933648
- [70] Chi Y, Gao M, Zhang Y, Shi F, Cheng Y, Guo Z, et al. 2650 Anlotinib in locally advanced or metastatic radioiodine-refractory differentiated thyroid carcinoma: A randomized, double-blind, multicenter phase II trial. *Annals of Oncology*. 2020;**31**:S1347
- [71] Lin Y-S, Zhang X, Wang C, Liu Y-Q, Guan W-M, Liang J. Long-term results of a phase II trial of apatinib for progressive radioiodine refractory differentiated thyroid cancer. *The Journal of Clinical Endocrinology & Metabolism*. 2021;**106**(8):e3027-e3036
- [72] Groussin L, Theodon H, Bessiere L, Bricaire L, Bonnet-Serrano F, Cochand-Priollet B, et al. Redifferentiating effect of larotrectinib in NTRK-rearranged advanced radioactive-iodine refractory thyroid cancer. *Thyroid®*. 2022;**32**(5):594-598
- [73] Subbiah V, Kreitman RJ, Wainberg ZA, Cho JY, Schellens JHM, Soria JC, et al. Dabrafenib plus trametinib in patients with BRAF V600E-mutant anaplastic thyroid cancer: Updated analysis from the phase II ROAR basket study. *Annals of Oncology*. 2022;**33**(4):406-415
- [74] Leboulleux S, Do Cao C, Zerdoud S, Attard M, Bournaud C, Lacroix L, et al. A phase II redifferentiation trial with dabrafenib-trametinib and 131I in metastatic radioactive iodine refractory BRAF p.V600E-mutated differentiated thyroid cancer. *Clinical Cancer Research*. 2023;**29**(13):2401-2409
- [75] Sherman EJ, Dunn LA, Ho AL, Baxi SS, Ghossein RA, Fury MG, et al. Phase 2 study evaluating the combination of sorafenib and temsirolimus in the treatment of radioactive iodine-refractory thyroid cancer. *Cancer*. 2017;**123**(21):4114-4121
- [76] Mehnert JM, Varga A, Brose MS, Aggarwal RR, Lin C-C, Prawira A, et al. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with advanced, PD-L1-positive papillary or follicular thyroid cancer. *BMC Cancer*. 2019;**19**(1):196
- [77] Oh D-Y, Algazi A, Capdevila J, Longo F, Miller W Jr, Chun Bing JT, et al.

Efficacy and safety of pembrolizumab monotherapy in patients with advanced thyroid cancer in the phase 2 KEYNOTE-158 study. *Cancer*. 2023;**129**(8):1195-1204

[78] Haugen B, French J, Worden FP, Konda B, Sherman EJ, Dadu R, et al. Lenvatinib plus pembrolizumab combination therapy in patients with radioiodine-refractory (RAIR), progressive differentiated thyroid cancer (DTC): Results of a multicenter phase II international thyroid oncology group trial. *Journal of Clinical Oncology*. 2020;**38**(Suppl. 15):6512-6512

[79] Rothenberg SM, Daniels GH, Wirth LJ. Redifferentiation of iodine-refractory BRAF V600E-mutant metastatic papillary thyroid cancer with dabrafenib—Response. *Clinical Cancer Research*. 2015;**21**(24):5640-5641

[80] Irvani A, Solomon B, Pattison DA, Jackson P, Ravi Kumar A, Kong G, et al. Mitogen-activated protein kinase pathway inhibition for redifferentiation of radioiodine refractory differentiated thyroid cancer: An evolving protocol. *Thyroid®*. 2019;**29**(11):1634-1645

[81] Falchook GS, Millward M, Hong D, Naing A, Piha-Paul S, Waguespack SG, et al. BRAF inhibitor dabrafenib in patients with metastatic BRAF-mutant thyroid cancer. *Thyroid®*. 2015;**25**(1):71-77

[82] Roll W, Riemann B, Schäfers M, Stegger L, Vrachimis A. ¹⁷⁷Lu-DOTATATE therapy in radioiodine-refractory differentiated thyroid cancer: A single center experience. *Clinical Nuclear Medicine*. 2018;**43**(10):e346-e351

[83] de Vries LH, Lodewijk L, Braat AJAT, Krijger GC, Valk GD, Lam MGEH, et al. ⁶⁸Ga-PSMA PET/CT in radioactive

iodine-refractory differentiated thyroid cancer and first treatment results with ¹⁷⁷Lu-PSMA-617. *EJNMMI Research*. 2020;**10**(1):18

[84] Ballal S, Yadav MP, Moon ES, Roesch F, Kumari S, Agarwal S, et al. Novel fibroblast activation protein inhibitor-based targeted theranostics for radioiodine-refractory differentiated thyroid cancer patients: A pilot study. *Thyroid*. 2022;**32**(1):65-77

[85] Ruan M, Shen Y, Chen L, Li M. RECIST 1.1 and serum thyroglobulin measurements in the evaluation of responses to sorafenib in patients with radioactive iodine-refractory differentiated thyroid carcinoma. *Oncology Letters*. 2013;**6**(2):480-486

[86] Ferrari C, Santo G, Ruta R, Lavelli V, Rubini D, Mammucci P, et al. Early predictive response to multi-tyrosine kinase inhibitors in advanced refractory radioactive-iodine differentiated thyroid cancer: A new challenge for [¹⁸F]FDG PET/CT. *Diagnostics*. 2021;**11**(8):1417

[87] Valerio L, Guidoccio F, Giani C, Tardelli E, Puccini G, Puleo L, et al. [¹⁸F]-FDG-PET/CT correlates with the response of radiorefractory thyroid cancer to lenvatinib and patient survival. *The Journal of Clinical Endocrinology & Metabolism*. 2021;**106**(8):2355-2366

[88] Ahmaddy F, Burgard C, Beyer L, Koehler VF, Bartenstein P, Fabritius MP, et al. ¹⁸F-FDG-PET/CT in patients with advanced, radioiodine refractory thyroid cancer treated with lenvatinib. *Cancers*. 2021;**13**(2):317

[89] Reed N, Glen H, Gerrard G, Good J, Lei M, Lyon AR, et al. Expert consensus on the management of adverse events during treatment with lenvatinib for thyroid cancer. *Clinical Oncology*. 2020;**32**(5):e145-e153

Recent Advances in Thyroid Surgery

Sudharsanan Sundaramurthi and G.S. Dharanya

Abstract

Thyroid surgery has seen significant advancements in recent years, driven by the quest for improved patient outcomes, enhanced recovery, reduced morbidity, and enhanced cosmetic results. Among these innovations, robotic thyroidectomy has emerged as a promising technique, particularly for patients seeking a scar-free alternative to conventional open thyroid surgery. Robotic thyroidectomy provides high precision and better visualization, enabling surgeons to perform intricate maneuvers with minimal tissue trauma. This method not only minimizes visible scarring but also reduces postoperative pain, accelerates recovery, and improves cosmetic satisfaction. Despite some limitations, such as higher costs and longer operative times, robotic thyroidectomy represents a crucial step forward in the field of endocrine surgery. This presentation will review the latest developments in thyroid surgical techniques, focusing on robotic thyroidectomy's efficacy, safety, patient selection criteria, and potential future directions in minimally invasive thyroid surgery.

Keywords: papillary carcinoma of thyroid, Da Vinci robot, robotic thyroidectomy, minimally invasive thyroid surgeries, bilateral axillary and breast approach, thyroid malignancy

1. Introduction

1.1 Historical perspective on thyroid surgery

Thyroid surgery has seen remarkable advancements over the years, transforming from crude and often fatal operations to highly sophisticated and minimally invasive procedures. The earliest thyroidectomy recorded in history was performed by Albucasis in 952 AD, but these thyroid surgeries were associated with significant morbidity and mortality due to significant hemorrhage and infections. In the mid-nineteenth century, the mortality rate of thyroid surgery was as high as 40%, and the French Academy of Medicine imposed a ban on the procedure in 1850.

It was in the nineteenth century when Theodor Billroth and Theodor Kocher revolutionized thyroid surgery when they introduced antiseptic use and performed meticulous surgical dissection resulting in a dramatic reduction in the mortality rates. Kocher demonstrated the extra-capsular dissection of the thyroid with mortality rates

as low as 0.18% by 1917. He was recognized with a Nobel Prize in 1909 and was also regarded as the father of modern thyroid surgery [1–3].

By the twentieth century, considerable advancements had happened in the diagnosis and management of thyroid pathologies including fine needle aspiration cytology (FNAC), radioactive iodine therapy, and thyroid hormone replacement therapy making thyroid surgeries safer and effective with improved patient outcomes.

1.2 Overview of recent advancements

In recent decades, there has been a paradigm shift in the field of thyroid surgery with the advent of minimally invasive techniques and robotic surgeries. Minimally Invasive Video-Assisted Thyroidectomy (MIVAT), introduced by Miccoli in 2000, has significantly improved patient outcomes by reducing postoperative pain, recovery time, and wound cosmesis. Subsequently, robotic-assisted transaxillary thyroidectomy (RATT) was introduced by Kang in 2009, which provided an alternative to traditional open surgery, benefiting patients who were concerned about scars in the neck [4, 5].

The past decade witnessed the development of the Transoral Endoscopic Thyroidectomy Vestibular Approach (TOETVA), one of the most revolutionary surgical techniques for thyroid surgery in 2011. The TOETVA technique eliminates external scarring while maintaining oncological safety, making it a preferred option in select cases of thyroid cancer [6]. Additionally, the introduction of intraoperative neuromonitoring (IONM) has significantly reduced the risk of recurrent laryngeal nerve injury, enhancing surgical precision and patient safety [7].

Advancements like ultrasound-guided FNAC and molecular marker analysis have enhanced diagnostic accuracy, thereby refining patient selection for surgery and avoiding unnecessary thyroidectomies. Also, innovations in ablative techniques like radiofrequency ablation (RFA) have provided options for non-surgical management of thyroid nodules, reducing the need for invasive procedures in selected patients. Newer imaging techniques like autofluorescence and indocyanine green fluorescence have aided in the accurate real-time identification of parathyroid glands during thyroid surgery, preventing their injury and enhancing surgical precision [8].

2. Innovations in surgical techniques

2.1 Robotic thyroidectomy

2.1.1 Introduction

Robotic thyroidectomy has rapidly gained popularity as a cutting-edge technique for thyroid surgery, offering patients and surgeons alike an innovative alternative to traditional open procedures. With its promise of superior cosmetic outcomes, as it negates the need for anterior neck incision and minimally invasive features, this technique has gained attention from both medical professionals and patients seeking advanced, less invasive options for thyroid removal. The evolution of robotic thyroidectomy began with the first endoscopic thyroidectomy performed in 1997, which paved the way for minimally invasive and remote-access surgical approaches.

The introduction of the *Da Vinci robotic system* marked a turning point, with its first application in transaxillary thyroidectomy by Chung in 2007. Since then, this

technique has gained global recognition, with thousands of successfully performed cases demonstrating its safety and feasibility [9–13].

Robotic systems help address some of the limitations faced by earlier endoscopic techniques, such as limited range of motion and impaired eye-hand coordination due to reliance on two-dimensional views [14–16]. This has contributed to the growing acceptance of robotic thyroidectomy, which is now recognized for its improved precision, reduced complication rates, and faster recovery times. Numerous studies have confirmed that robotic thyroidectomy provides comparable oncologic outcomes to conventional open thyroidectomy while offering significant advantages in terms of cosmetic results [17–20].

Several robotic approaches have been developed over time, including transaxillary, retroauricular (facelift), and transoral techniques, each offering distinct advantages and challenges. These methods aim to provide comparable oncologic outcomes while enhancing cosmetic benefits and patient satisfaction. Although robotic thyroidectomy has demonstrated safety and efficacy, certain limitations such as longer operative times and higher costs remain challenging.

The American Thyroid Association has acknowledged the role of remote-access robotic thyroidectomy in high-volume centers and stressed the importance of strict patient selection criteria for optimal results [21].

With continuous technological progress, the future of robotic thyroidectomy is expected to evolve further and gain further traction. Innovations such as tele-surgery, single-port access, and Artificial Intelligence (AI) integration may refine surgical precision and optimize patient outcomes. As the field advances, appropriate patient selection and high-volume center expertise will play crucial roles in ensuring the widespread adoption and success of robotic thyroidectomy in thyroid cancer management [13].

2.1.2 Transaxillary approach

2.1.2.1 Position

The transaxillary approach (TA) avoids visible neck scars by accessing the thyroid through an incision in the axilla. Under general anesthesia, the patient is positioned supine with the neck extended using a pillow. The ipsilateral arm is abducted, rotated cephalad, and secured to minimize the distance between the axilla and the neck while preventing brachial plexus injury [22–24].

2.1.2.2 Working space creation

A 5–6 cm axillary incision is made, concealed within the natural crease. A subplatysmal flap is raised from the axilla to the anterior neck over the pectoralis major, dissecting through the avascular plane between the two heads of the sternocleidomastoid (SCM). Care is taken to preserve the internal jugular vein, carotid artery, and surrounding soft tissues. The omohyoid is elevated, and dissection continues between the strap muscles and thyroid gland, ensuring exposure of the superior pole and partial contralateral lobe. A retractor is placed to maintain the working field.

2.1.2.3 Robot docking and instrumentation

All four robotic arms are inserted through the axillary incision. The 12 mm trocar for the camera is centrally positioned, while the 8 mm ProGrasp forceps trocar is

placed laterally, ensuring parallel alignment with the suction tube to prevent instrument collision. The Maryland dissector and Harmonic scalpel are positioned on either side, facilitating precise dissection (**Figure 1**).

2.1.2.4 Surgical procedure

The superior thyroid vessels are divided first, with ProGrasp forceps retracting the gland caudally. Maryland forceps isolate the vessels, which are divided near the gland using a Harmonic scalpel. The superior parathyroid gland is identified and preserved. Dissection proceeds inferiorly, carefully tracing and preserving the recurrent laryngeal nerve (RLN) up to its entry into the larynx. The thyroid is then separated from the trachea, completing the thyroidectomy [26–30].

2.1.3 Variations in TART techniques

- *Single-Port (SP) TART*: Uses a smaller 3–3.5 cm incision, reducing docking time. However, the SP system lacks Harmonic scalpel compatibility, necessitating alternative dissection tools like the Maryland dissector with bipolar forceps or a monopolar blade.
- *Gas-Insufflation One-Step Single-Port Transaxillary (GOSTA) Approach*: Utilizes CO₂ insufflation at 8 mmHg, allowing robotic creation of the skin flap. The SP endoscope is positioned at 12 o'clock, with robotic arms assigned specific roles—Maryland bipolar forceps (arm 1), monopolar cautery (arm 2), and Cadiere forceps (arm 3) [30, 31].

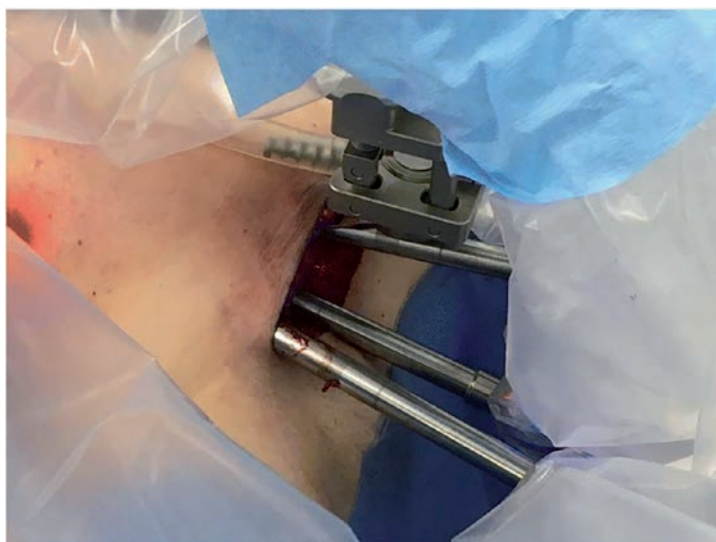


Figure 1.

Detail of dissection using three robotic arms through the axillary incision (camera and instruments are ideally located at the three sides of an equilateral pyramid). Image from Prete FP et al., BMC Surgery, 2019. Licensed under CC BY 4.0 (<http://creativecommons.org/licenses/by/4.0/>) [25].

2.1.4 Transoral approach

2.1.4.1 Approach and positioning

Transoral robotic thyroidectomy (TORT) is a minimally invasive technique that provides a completely scar-free neck by accessing the thyroid gland through the oral cavity. The patient is positioned in lithotomy with the neck extended. The surgical field, including the lower lip, axillae, and upper chest, is disinfected with povidone-iodine solution.

2.1.4.2 Working space creation

A 2 cm U-shaped incision is made in the midline of the lower lip following local injection of diluted epinephrine for hydrodissection. Blunt tunneling expands the working space, and a 12 mm trocar is placed at the midline with two 5 mm lateral ports at the lip junctions. CO² insufflation is maintained at 5–7 mmHg to facilitate visualization. A 10 mm videoscope is used to create a clear working space extending down to the sternal notch and laterally to the sternocleidomastoid (SCM) muscles.

2.1.4.3 Robot docking and instrumentation

A 30-degree endoscope is positioned centrally, while Maryland dissectors and a Harmonic scalpel are inserted through the lateral ports. An additional 8 mm port is placed in the right axillary region before docking the robotic system (**Figure 2**).

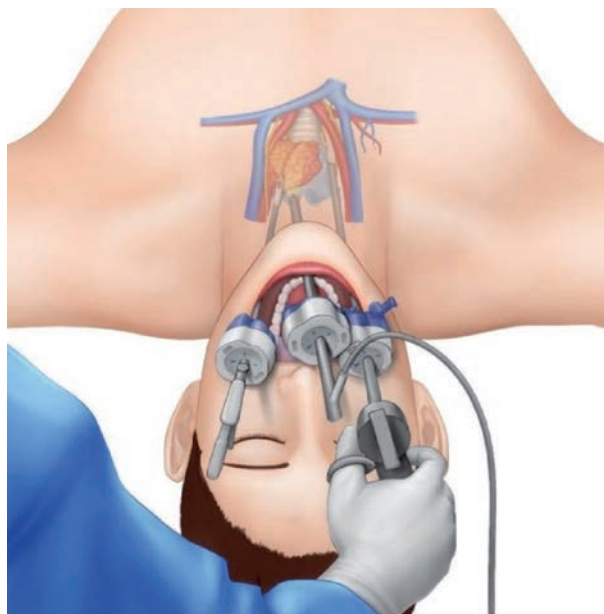


Figure 2.
Transoral endoscopic thyroidectomy. Illustrated by the author. Image from Park [32].

2.1.4.4 Surgical procedure

The midline of the strap muscles is separated using monopolar cautery, and the isthmus is divided with a Harmonic scalpel. Dissection proceeds laterally to detach the thyroid from the SCM. The superior pole is dissected along an avascular plane, and its vessels are divided while preserving the upper parathyroid gland. The thyroid is then retracted upward, allowing careful identification and preservation of the recurrent laryngeal nerve (RLN) near Berry's ligament. Finally, the thyroid gland is detached from the trachea, ensuring the lower parathyroid gland remains intact.

This technique offers excellent cosmetic outcomes while maintaining oncologic safety, but requires expertise due to its complex anatomical approach [33, 34].

2.1.5 Retroauricular (facelift) approach for robotic thyroidectomy

2.1.5.1 Working space formation

Under general anesthesia, the patient is positioned supine with the head turned contralaterally to expose the posterior auricular sulcus and the lateral neck. The incision is placed along the posterior auricular sulcus, extending over the mastoid and parallel to the occipital hairline, ensuring optimal cosmetic concealment. After skin preparation and draping, a subcutaneous retroauricular flap is elevated anteriorly, exposing the parotid tail and sternocleidomastoid (SCM) muscle. Care is taken to preserve the greater auricular and marginal mandibular nerves. A subplatysmal flap is dissected toward the midline, exposing the mandibular border, strap muscles, and thyroid gland. A modified Chung retractor is inserted beneath the strap muscles to maintain the working space.

2.1.5.2 Docking stage

Once adequate exposure is achieved, the robotic system is docked, ideally using all three robotic arms—a 30-degree endoscope and two instrument arms. If space is limited, the procedure can still be performed with two arms, though it presents technical challenges. The Maryland dissector and Harmonic scalpel are controlled by the surgeon's left and right hands, respectively, following a docking technique similar to the transaxillary approach (**Figure 3**).

2.1.5.3 Console stage and surgical steps

The procedure begins with superior pole dissection, which is then retracted upward while ligating its vessels individually. The superior parathyroid gland is identified and preserved, avoiding thermal injury. After mobilizing the superior pole and exposing the cricothyroid muscle, an isthmusectomy is performed to facilitate recurrent laryngeal nerve (RLN) identification. The nerve is traced within the tracheoesophageal groove near the cricothyroid joint and confirmed using intraoperative nerve monitoring (IONM). Once the RLN is secured, the thyroid gland is carefully dissected and separated from surrounding tissues, completing the procedure.

This approach provides an excellent cosmetic outcome while ensuring precise nerve preservation. However, it requires advanced robotic expertise due to its complex anatomical dissection [13].

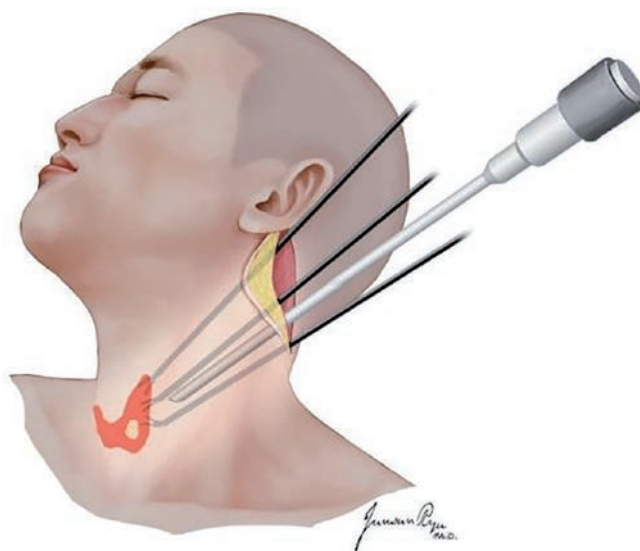


Figure 3.
 The postauricular facelift approach. A 30-degree face-down endoscope and three robotic instruments, namely Maryland dissectors, Prograsp forceps, and Harmonic curved shears, are inserted through the postauricular incision. Image from Tae et al. [35].

2.1.6 Bilateral axillo-breast approach (BABA)

2.1.6.1 Approach and positioning

The Bilateral Axillo-Breast Approach (BABA) utilizes four small incisions—two in the axilla and two around the areola—providing a symmetrical and comprehensive view of the thyroid. The patient is positioned supine with a pillow under the shoulders for neck extension, while both arms are slightly abducted.

2.1.6.2 Working space creation

A subcutaneous flap is elevated using a tunneler, with ports (8–12 mm) placed in the axillary and circumareolar regions. The flap extends superiorly to the thyroid cartilage, inferiorly 2–3 cm below the clavicle, and laterally to the SCM muscle margins. CO₂ insufflation at 5–6 mmHg maintains the working space. The midline is identified and divided to expose the thyroid gland.

2.1.6.3 Robot docking and instrumentation

The camera is inserted *via* the right breast port, while the Harmonic scalpel enters through the left breast port. The grasper and retractors are positioned through the right and left axillary ports (**Figure 4**).

2.1.6.4 Surgical procedure

The isthmus is first divided to enhance lateral and posterior dissection, improving access to the superior thyroid pedicle. The thyroidectomy is performed with clear

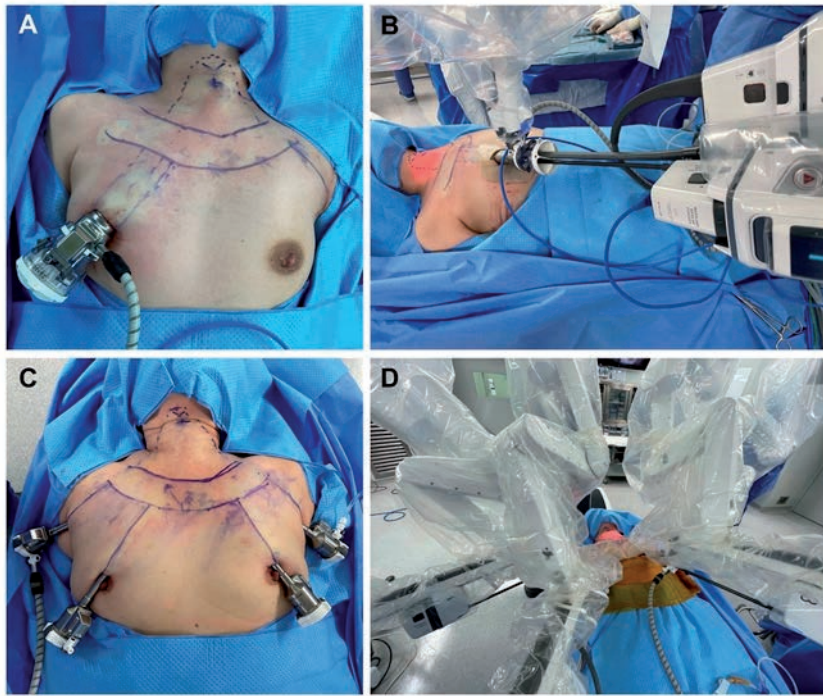


Figure 4. Robotic trocar positioning and robot docking in SPRA and BABA surgery. (A) Trocar placement for SPRA, (B) da Vinci SP docking in SPRA (C) Trocar placement for BABA, (D) da Vinci Xi docking in BABA). Image from Lee et al. [36].

visualization of the middle and inferior thyroid pedicles, the recurrent laryngeal nerve (RLN), and the superior and inferior parathyroid glands, ensuring safe and effective gland removal.

This technique provides excellent exposure with a hidden scar approach, making it an esthetically favorable option for patients [37, 38].

Contraindications to robotic thyroidectomy in thyroid malignancy:

1. previous head and neck surgery or irradiation;
2. definite tumor invasion to an adjacent organ (RLN, esophagus, or trachea);
3. multiple lateral neck node metastases or perinodal metastatic lymph node infiltration; and
4. distant metastasis [22].

2.1.7 Single-port robotic areolar approach

The single-port robotic areolar thyroidectomy (SPRA) is a novel, minimally invasive thyroid surgery developed as an evolution of the bilateral axillo-breast approach (BABA). Unlike BABA, SPRA eliminates the need for bilateral axillary access, reducing flap dissection and enhancing patient recovery while maintaining superior cosmetic outcomes.

2.1.7.1 Surgical technique

Under general anesthesia with neuromonitoring, a 3-cm circumareolar incision is made on the right breast for *Da Vinci SP system docking*, with an additional 8-mm incision for suction and air circulation. Hydrodissection with epinephrine facilitates flap elevation, extending from the breast to the thyroid cartilage. A vascular tunneler and advanced bipolar device are used for blunt dissection before inserting the SP trocar (**Figure 4**).

Once docked, the procedure follows a systematic approach:

1. Strap muscle midline division and isthmusectomy to improve gland exposure.
2. Lateral thyroid retraction for separation from the strap muscles.
3. Identification and preservation of the recurrent laryngeal nerve (RLN) and parathyroid glands.
4. Thyroid mobilization and dissection at Berry's ligament, followed by superior thyroid vessel division.
5. Central lymph node dissection (Level 6) while safeguarding the RLN.
6. Specimen retrieval *via* the 3-cm trocar, followed by muscle and skin closure with a drain placement [39].

2.2 Minimally invasive video-assisted thyroidectomy (MIVAT)

2.2.1 Introduction

Minimally invasive video-assisted thyroidectomy (MIVAT) is a widely practiced minimally invasive surgical technique for thyroidectomy, offering advantages in cosmetic outcomes, reduced postoperative pain, and quicker recovery compared to conventional open surgery. Introduced by Miccoli et al. in 1999, MIVAT eliminates the need for CO² insufflation, thereby avoiding gas-related complications [40].

2.2.2 Patient selection and indications

MIVAT is primarily recommended for small thyroid nodules (≤ 30 mm), normal-sized thyroid glands (≤ 20 cm³), and benign conditions such as toxic adenomas, follicular tumors, and small goiters with indeterminate cytology. While initially limited to benign diseases, recent applications extend to low-risk thyroid malignancies, including small papillary thyroid carcinomas and RET gene mutation carriers where central compartment lymphadenectomy is not required. However, strict selection criteria are essential to ensure safety and efficacy.

2.2.3 Surgical approach

The cervical approach for MIVAT involves three to four small ports, including a 12-mm endoscopic port and two to three instrument ports placed in the anterior or lateral neck. Unlike other minimally invasive techniques, MIVAT employs direct central access with a 1.5–2 cm incision, allowing for symmetrical exposure of both

thyroid lobes. This makes it more suitable for bilateral thyroid conditions compared to lateral approaches, which are more suited for single-lobe procedures [9, 41, 42].

2.2.4 Efficacy and limitations

MIVAT has demonstrated comparable safety and complication rates to conventional thyroidectomy while offering better cosmetic results and reduced postoperative discomfort. Although some studies suggest that MIVAT can achieve similar oncologic radicality as open surgery for low-risk cancers, concerns remain regarding long-term oncologic outcomes and its ability to perform comprehensive lymph node dissections. Current literature still supports benign thyroid disease as the primary indication for MIVAT, with malignancy cases requiring careful patient selection.

As surgical techniques evolve, MIVAT remains a safe and effective minimally invasive alternative, particularly for well-selected benign thyroid conditions and select low-risk malignancies. Future advancements may further refine its role in endocrine surgery [35, 40].

3. Technological enhancements in thyroid surgery

3.1 Intraoperative neuromonitoring (IONM)

The fundamental goals of thyroid surgery are the preservation of the recurrent laryngeal nerve (RLN) and the external branch of the superior laryngeal nerve (EBSLN), ensuring the maintenance of normal voice function. However, advancements in neurophysiology have shown that maintaining anatomical integrity does not always equate to functional preservation. Despite careful dissection techniques, nerve injuries can still occur unpredictably and may not always be visually identifiable during surgery.

Intraoperative nerve monitoring (IONM) has been introduced to enhance nerve identification and detect early signs of functional impairment. Initially, intermittent monitoring was widely practiced, but the evolution of surgical technology has paved the way for continuous IONM, allowing real-time functional assessment throughout the procedure. However, despite its widespread adoption, ongoing debate persists regarding its overall effectiveness and cost-benefit ratio, as studies have yet to establish definitive clinical superiority over conventional visual identification.

The RLN and EBSLN have long been considered critical yet vulnerable structures in thyroid surgery. A well-documented case highlighting the clinical significance of these nerves is that of Amelita Galli-Curci, an opera singer who lost her ability to produce high-pitched notes following an EBSLN injury. Depending on the extent of nerve damage, postoperative outcomes can range from mild vocal changes to severe airway complications requiring prolonged interventions, including tracheostomy.

Historically, thyroid surgeons were cautious about exposing these nerves, believing that avoidance reduced the risk of injury. This approach shifted dramatically when Lahey advocated for direct RLN identification, revolutionizing surgical techniques. Today, thyroid surgery has evolved beyond mere visualization, incorporating functional assessment methods such as IONM to enhance precision and minimize complications [43, 44].

3.1.1 Neurophysiology of IONM

Principle: Electrical stimulation of the recurrent laryngeal nerve (RLN) elicits a response in the vocalis muscle, leading to its contraction, a principle akin to electromyography (EMG).

Components of IONM: (Figure 5).

Stimulation Unit:

The stimulator probe, essential for nerve stimulation, is available in monopolar and bipolar forms. A reference electrode is positioned distally, typically on the shoulder or sternum, to minimize stimulus artifacts. The stimulating-side ground electrode is placed at least 10 mm away from the reference electrode to reduce interference from other devices.

Recording Unit:

This includes an endotracheal tube embedded with four pre-configured surface laryngeal EMG electrodes—two for each vocalis muscle. A recording-side ground electrode is placed near the surgical field to ensure signal clarity. Inadequate grounding can introduce noise artifacts.

Electro-Neurophysiological (ENP) Unit:

Proper setup involves connecting the ET tube electrodes, ground and reference electrodes, and the stimulator probe to the interface box, which links to the EMG monitor. These components collectively facilitate effective intraoperative nerve monitoring [46].

3.1.2 Indications for intraoperative nerve monitoring (IONM)

IONM is particularly beneficial in high-risk thyroid surgeries where nerve identification and preservation are challenging. It is indicated in the following scenarios:

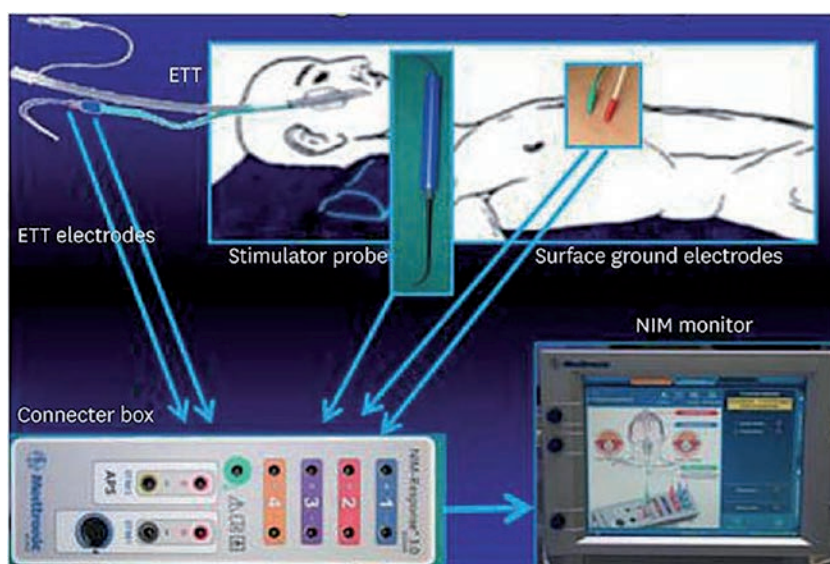


Figure 5. Patient and EMG ETT scheme for IONM. EMG = electromyographic; ETT = endotracheal tube; IONM = intraoperative neuromonitoring; NIM = nerve integrity monitor. Image from Kim et al. [45].

- Revision thyroid surgery: Helps in identifying and safeguarding nerves that may be altered due to fibrosis.
- Thyrotoxicosis: Useful in cases with excessive vascularity and inflammation, where nerve visualization is difficult.
- Extensive central compartment lymphadenopathy: Aids in nerve localization when lymph nodes obscure surgical landmarks.
- Locally advanced thyroid cancer: Enhances nerve protection in cases with tumor infiltration or fibrotic tissue.
- Large goiter with retrosternal extension: Assists in nerve mapping when the goiter extends into the mediastinum, limiting visibility.
- Rare anatomical variations: Crucial for detecting uncommon nerve courses such as extra-laryngeal branching or a non-recurrent laryngeal nerve (<1% occurrence).
- Enhanced nerve preservation: Proven to reduce both temporary and permanent RLN palsy rates, especially when visual identification alone is insufficient [47–55].

Advantages:

- Enhances identification and preservation of the recurrent laryngeal nerve (RLN) during surgery.
- Provides real-time feedback on nerve function, aiding in intraoperative decision-making.
- Reduces nerve injury rates, improving surgical safety and patient outcomes.
- Assesses nerve integrity at the end of the surgery, allowing immediate corrective measures if needed.
- Has a high negative predictive value (NPV), making it particularly useful in high-risk procedures.

Disadvantages:

- Limited benefit in routine cases, leading to ongoing debate regarding its universal application.
- Increased costs and the need for specialized equipment may limit widespread use.
- Requires proper training and experience along with a neurophysiologist for optimal interpretation and application [46].

3.1.3 Future directions in IONM

The future of intraoperative neuromonitoring (IONM) lies in harnessing predictive analytics and adaptive algorithms to enhance surgical precision and patient safety. Predictive analytics, leveraging vast datasets and machine learning models, can identify subtle electrophysiological patterns that precede nerve injury, allowing for proactive interventions before irreversible damage occurs. Adaptive algorithms further refine this approach by dynamically adjusting neuromonitoring parameters in real time, tailoring responses based on intraoperative conditions. These AI-driven advancements promise not only to reduce postoperative neurological deficits but also to revolutionize decision-making by providing surgeons with intelligent, data-driven insights. As these technologies evolve, the integration of real-time neurophysiological modeling and autonomous response systems may redefine the gold standard in nerve preservation, paving the way for safer, more effective surgical outcomes.

3.2 Advanced hemostatic devices

Achieving hemostasis in thyroid surgery is critical due to the gland's vascular nature and its close proximity to important structures like the recurrent laryngeal nerve (RLN), and the parathyroid glands. Bleeding during thyroid surgery can obscure the surgical field, increase the operative time, and heighten the risk of injury to these vital structures. Bleeding in the postoperative period can lead to hematoma formation, airway obstruction, and hypoxic complications; therefore, ensuring hemostasis becomes a priority.

3.2.1 Energy-based hemostatic devices

Energy-based devices (EBDs) are replacing the traditionally used techniques of suture ligation, monopolar and bipolar electrocautery, and vessel clips due to their ability to efficiently seal the vessels, reduce intraoperative blood loss, and shorten the operating duration.

- Ultrasonic coagulating shear (Harmonic) operates at 55 kHz and can effectively seal vessels up to 5 mm in diameter with minimal lateral thermal spread. The tissue charring is minimal and therefore, results in less postoperative inflammation and early recovery.
- Bipolar radiofrequency devices (LigaSure) use mechanical pressure and electrical energy to degrade collagen and elastin, thereby ensuring a strong seal without the formation of intravascular thrombi. They can seal vessels even up to 7 mm in diameter.
- Hybrid devices (Thunderbeat) combine the principle of ultrasonic and bipolar technologies and allow for simultaneous vessel sealing and tissue cutting, thereby enhancing surgical efficiency. Studies have shown shorter coagulation and resection times compared to monopolar and bipolar electrocautery in thyroid surgeries [56–58].

The use of EBDs in thyroid surgeries is still evolving, and therefore, practicing surgeons should be cautious of the possible complications in using them. The thermal

effect on adjacent tissues, though minimal, is a matter of concern when the device is used too close to the recurrent laryngeal nerve without giving adequate cooling time. Optimal surgical outcomes can be achieved when a 3–5 mm safety margin can be adhered to while operating close to critical structures.

3.2.2 Topical hemostatic agents

Hemostatic agents can be used as adjuncts to EBDs in promoting intraoperative hemostasis and reducing seroma formation in the postoperative period.

They can be categorized into five types based on their mechanism of action.

1. Topical hemostats are procoagulants and enhance clot formation by mimicking natural hemostasis. Some of the topical hemostats include fibrin sealants (Tisseel, Evicel) and thrombin-based agents (FloSeal, Recothrom).
2. Mechanical hemostats are passive hemostats and work by providing a scaffold for clotting and platelet aggregation. Oxidized regenerated cellulose (Surgicel, Tabotamp), collagen-based agents (Helistat, Instat), and gelatin-based sponges (Gelfoam, Surgifoam) can be classified as mechanical hemostats.
3. Sealants are hemostatic barriers and work by creating a physical barrier to prevent blood and fluid leakage. These collagen-fibrinogen-thrombin patches (CFTP) and synthetic polyethylene glycol (PEG) sealants (CoSeal).
4. Polysaccharide-based hemostats, such as microporous polysaccharide hemospheres (Arista AH) and chitosan-based agents (Celox), rapidly absorb plasma to concentrate clotting factors.
5. Adhesives (tissue bonding agents), including cyanoacrylate-based adhesives (Dermabond, Glubran 2), act as synthetic glue to bond tissues and seal small vessels [59].

Oxidized cellulose like Surgicel and Fibrin sealants are widely used to minimize intraoperative bleeding in thyroid surgeries. Collagen-based hemostats like Gelfoam are effective in highly vascularized tissues like the thyroid. Hemostatic patches like CFTP and oxidized regenerated cellulose reduce postoperative drainage and seroma formation, particularly in high-risk cases. The choice of agent depends on the severity of bleeding, surgical technique, and patient-specific factors to optimize hemostasis and recovery.

A meta-analysis of 941 patients comparing conventional hemostasis to hemostatic gels (71%) and oxidized cellulose patches (29%) found that while hemostatic agents significantly reduced postoperative drain output (40.75 ± 35.6 mL vs. 66.26 ± 31.2 mL, $p < 0.05$) and shortened hospital stays, they did not significantly reduce the incidence of hematoma, seroma, RLN injury, or transient hypocalcemia. Another study evaluating four different hemostatic agents, including collagen-fibrinogen-thrombin patches (CFTP), polysaccharide particles, and oxidized cellulose gauze, showed that only the larger CFTP (9.5×4.8 cm) significantly decreased postoperative drainage volume compared to controls ($p < 0.05$) [60, 61].

Despite these benefits, hemostatic agents remain controversial due to their high cost, with most experts recommending selective use in high-risk patients, such as

those on anticoagulant therapy. Additionally, hemostatic agents should not replace meticulous surgical techniques, as studies have shown that surgeon experience is the most critical factor in minimizing perioperative bleeding complications.

3.3 Imaging modalities

The traditional methods of identification of parathyroid glands (PGs) during thyroid surgery rely on the visual inspection of the gland and the surgeon's expertise. The introduction of fluorescence-based imaging enhances accuracy in the visualization of PGs and lymphatic drainage during thyroid surgery. The near-infrared fluorescence imaging (NIFI) technique utilizes autofluorescence (AF) and indocyanine green fluorescence (ICGF) in the identification and preservation of PGs.

3.3.1 Autofluorescence imaging

AF imaging is based on the principle that parathyroid glands naturally emit fluorescence under near-infrared light without requiring contrast agents. This allows real-time intraoperative detection of PGs before surgical dissection. However, AF does not provide adequate information on the perfusion of the gland, therefore, preservation of the gland may not always ensure function.

3.3.2 Indocyanine green fluorescence

ICGF imaging has been widely used in various fields of surgery. It involves the administration of indocyanine green dye intravenously, which binds to plasma proteins and fluoresces under near-infrared light. The real-time visualization of the PG vascularization can be made intra-operatively (**Figure 6**). ICGF, in addition to its efficiency in identifying the PGs, also accurately predicts the perfusion status, thereby correlating well with postoperative function of the PGs [63–65].

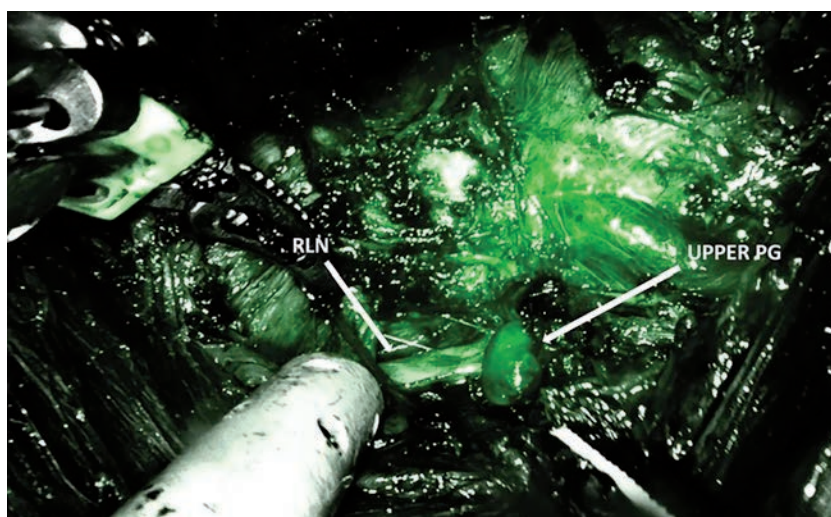


Figure 6.
Identification of the upper parathyroid gland (PG) with indocyanine green fluorescence (RLN, recurrent laryngeal nerve). Image from Materazzi and Rossi [62].

Combined use of AF and ICGF can improve PG Identification, guide the assessment of perfusion status, and thereby lower the incidence of postoperative hypocalcemia. It also aids in the need for auto-transplantation of PGs when there is a compromise in blood supply. One of the challenges in the use of AF and ICGF is the need for standardization of interpretation criteria to optimize widespread clinical adoption.

4. Non-surgical ablative therapies

The standard treatment options for thyroid nodules include surgery or radioactive iodine (RAI), both of which carry risks such as hypothyroidism, scarring, dysphonia, and complications related to anesthesia. An emerging therapeutic option for these patients is minimally invasive ablative therapy, which has the advantage of preserving the organ function while at the same time avoiding the risks of surgery or RAI treatment [66].

4.1 Types of ablative therapies

- *Percutaneous ethanol injection (PEI)*: Effective for recurrent thyroid cysts and select cases of papillary thyroid microcarcinoma (PTMC). It works by causing cellular dehydration, protein denaturation, and ischemia [67].
- *Thermal ablation*: Includes radiofrequency ablation (RFA), laser ablation (LA), microwave ablation (MWA), and high-intensity focused ultrasound (HIFU). The most widely used technique is the RFA with significant efficiency in reducing the nodule volume and in improving the patient's symptoms [68].

4.2 Indications

- Benign thyroid nodules with pressure symptoms like dysphagia or dyspnea, with cosmetic concerns, and in patients who prefer to avoid surgery or RAI for their complications.
- Toxic thyroid nodules when patients wish to preserve the thyroid function and to avoid RAI-induced hypothyroidism.
- Recurrent symptomatic thyroid cysts not responding to aspiration.
- Low-risk papillary thyroid microcarcinoma (PTMC) when the patient wants to avoid surgery and when the option for active surveillance is available.
- Recurrent thyroid cancers occur when the patient is unfit for surgery [69].

RFA is preferred in solid or predominantly solid benign nodules and about 70–80% reduction in volume can be achieved over 6–12 months. Multiple sessions may be needed in larger nodules. Complications with RFA therapy are rare with less than 5% of the patients experiencing mild local pain or a transient voice change [70].

5. Future directions in thyroid surgery

5.1 Integration of artificial intelligence and robotics

Artificial Intelligence (AI) is a major boon in development and advancements in the field of surgery and has revolutionizing thyroid surgery by assisting in diagnosis, surgical planning, and intraoperative decision-making. AI-powered machine learning and deep learning models enhance ultrasound interpretation, nodule classification, and risk stratification, thereby reducing interobserver variability and improving diagnostic accuracy [71]. AI-integrated robotic systems provide enhanced visualization of the surgical field, reduces tremor at the tissue level and minimizes intraoperative complications by aiding in better identification of critical structures like recurrent laryngeal nerve and parathyroids [31]. In addition, certain AI models can also aid in the real-time identification of parathyroid glands by the application of AI-driven fluorescence imaging aids.

The cosmetic benefits, improved dexterity, and decreased postoperative pain have resulted in making robotic surgery a popular option for thyroid surgeries. Approaches such as transaxillary, transoral, and bilateral axillo-breast (BABA) techniques allow for scarless thyroidectomy with comparable oncologic outcomes. However, challenges like higher costs, longer operative times, and the steep learning curve limit their widespread adoption. Future advancements include miniaturized robotic systems, augmented reality-assisted navigation, and AI-powered intraoperative guidance, which could further refine robotic thyroid surgery [31].

5.2 Tele-surgery and remote consultations

The concept of tele-surgery and remote robotic-assisted thyroidectomy is gaining attention, allowing experienced thyroid surgeons to perform or guide procedures from distant locations. Telemedicine has already enhanced preoperative consultations and postoperative follow-ups, improving accessibility and continuity of care. Future developments in 5G-enabled robotic platforms and AI-driven real-time assistance could facilitate long-distance thyroid surgeries, expanding specialized care to underserved regions [72].

5.3 Personalized medicine approaches

AI also plays a critical role in personalized medicine, tailoring treatment plans based on genomic, molecular, and clinical data. AI-driven models help predict lymph node metastasis, recurrence risks, and patient-specific treatment outcomes, guiding individualized surgical decisions such as lobectomy versus total thyroidectomy. The integration of genomic profiling and AI-based decision support systems will enable targeted therapies for thyroid cancer, reducing overtreatment and improving patient outcomes [73].

6. Limitations and criticisms of modern techniques

Despite the growing enthusiasm surrounding the novel minimally invasive and robotic thyroid surgeries, their widespread use has been affected by a handful of limitations and critical evaluations.

The transaxillary approach claimed to be cosmetically beneficial by avoiding a cervical scar, including concerns related to the complexity of the surgical technique,

longer operative times, higher costs, risk of brachial plexus injury, and difficulty in accessing bilateral thyroid lobes, particularly in large or retrosternal goiters. These challenges nearly led to the withdrawal of the transaxillary approach in several centers, especially where surgeon experience or patient selection criteria were sub-optimal. Over time, refinements such as gasless techniques and robotic assistance have improved outcomes, but the approach remains largely restricted to high-volume specialized centers with expertise in robotic surgery.

Over the past two decades, various remote-access techniques including retroauricular (facelift), transoral vestibular, and bilateral axillo-breast approaches were explored. While each of these techniques offered unique cosmetic advantages, accumulated evidence suggests that they confer only a few significant advantages over conventional open thyroidectomy in terms of oncologic safety, complication rates, and long-term outcomes. The primary benefit remains mainly cosmetic, and the steep learning curve, longer operative times, potential risks, and higher costs have limited their routine application.

As a result, the current emphasis is on strict patient selection, surgeon expertise, and individualized decision-making when considering remote-access thyroidectomy. Classic open thyroidectomy continues to remain the gold standard, especially in complex, malignant, or revision cases where ensuring patient safety and complete oncologic clearance remains the highest priority.

7. Conclusion

The field of thyroid surgery has seen significant progress over the past few decades with a focus on achieving better oncological outcomes, surgical safety, decreased morbidity, and improved cosmetic results. The introduction of minimally invasive and robotic techniques, including transoral, transaxillary, retroauricular, and bilateral axillo-breast approaches, has revolutionized this field by providing scar-free alternatives while maintaining surgical efficacy.

However, critical evaluations over time have shown that these modern approaches, while cosmetically advantageous, often offer limited functional or oncological superiority over conventional open thyroidectomy. Although refinements such as gasless and robotic-assisted techniques have enhanced feasibility, these procedures remain best suited for highly selected patients and experienced high-volume centers.

Technological innovations such as intraoperative neuromonitoring (IONM), advanced hemostatic devices, fluorescence-guided imaging, and non-surgical ablative therapies have further enhanced the safety and precision of thyroid surgery. Moving forward, the need for better patient selection criteria, cost-effectiveness, and surgeon expertise in adopting newer techniques are some of the challenges to be faced while adopting these advancements. Future directions in thyroid surgery will likely be shaped by the integration of artificial intelligence, augmented reality, and tele-surgery, allowing for greater precision, real-time decision-making, and expanded access to specialized care. As science evolves, continued ongoing research, validation of long-term results, and technical refinement to optimize patient safety and cost will decide their widespread adoption.

The future of thyroid surgery lies in a multidisciplinary approach that combines cutting-edge technology with evidence-based surgical principles. Surgeons should adapt to the changes and use these advancements as leverage to enhance patient care, ensuring safer, more effective, and esthetically favorable outcomes for patients undergoing thyroid surgery.

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References

- [1] Sarkar S, Banerjee S, Sarkar R, Sikder B. A review on the history of 'thyroid surgery'. *Indian Journal of Surgery*. 2016;**78**:32-36
- [2] Dorairajan N, Pradeep PV. Thyroid surgery: A glimpse into its history. *International Surgery*. 2013;**98**:70-75
- [3] Gasparri G. History of thyroid surgery. In: *Thyroid Surgery*. Cham: Springer International Publishing; 2023. pp. 3-9
- [4] Miccoli P, Berti P, Materazzi G, Minuto MN, Barellini L. Minimally invasive video-assisted thyroidectomy: Five years of experience. *Journal of the American College of Surgeons*. 2004;**199**(2):243-248
- [5] Kang SW, Jeong JJ, Yun JS, Sung TY, Lee SC, Lee YS, et al. Robot-assisted endoscopic thyroidectomy for thyroid malignancies using a gasless transaxillary approach. *Journal of the American College of Surgeons*. 2009;**209**(2):e1-e7
- [6] Anuwong A. Transoral endoscopic thyroidectomy vestibular approach: A series of the first 60 human cases. *World Journal of Surgery*. 2016;**40**(3):491-497
- [7] Dionigi G, Boni L, Rovera F, Rauseri S, Castelnovo P, Tanda ML. Neuromonitoring and video-assisted thyroidectomy: A prospective, randomized case-control evaluation. *Surgical Endoscopy*. 2009;**23**(5):996-1003
- [8] Haugen BR. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2016;**26**(1):1-133
- [9] Hüscher CS, Chiodini S, Napolitano C, et al. Endoscopic right thyroid lobectomy. *Surgical Endoscopy*. 1997;**11**:877
- [10] Chung WY. The evolution of robotic thyroidectomy: From inception to neck dissection. *Journal of Robotic Surgery*. 2011;**5**:17-23
- [11] Axente DD, Silaghi H, Silaghi CA, et al. Operative outcomes of robot-assisted transaxillary thyroid surgery for benign thyroid disease: Early experience in 50 patients. *Langenbeck's Archives of Surgery*. 2013;**398**:887-894
- [12] Sung ES, Ji YB, Song CM, et al. Robotic thyroidectomy: Comparison of a postauricular facelift approach with a gasless unilateral axillary approach. *Otolaryngology and Head and Neck Surgery*. 2016;**154**:997-1004
- [13] Chang EH, Kim HY, Koh YW, Chung WY. Overview of robotic thyroidectomy. *Gland Surgery*. 2017;**6**(3):218-228. DOI: 10.21037/g.2017.03.18
- [14] Ban EJ, Yoo JY, Kim WW, et al. Surgical complications after robotic thyroidectomy for thyroid carcinoma: A single center experience with 3000 patients. *Surgical Endoscopy*. 2014;**28**:2555-2563
- [15] Lee J, Chung WY. Robotic surgery for thyroid disease. *European Thyroid Journal*. 2013;**2**:93-101
- [16] Lee J, Chung WY. Robotic thyroidectomy and neck dissection: Past, present and future. *Cancer Journal*. 2013;**19**:151-161
- [17] Lang BH, Wong CK, Tsang JS, et al. A systematic review and meta-analysis

comparing surgically-related complications between robotic-assisted thyroidectomy and conventional open thyroidectomy. *Annals of Surgical Oncology*. 2014;**21**:850-861

[18] Lee S, Lee CR, Lee SC, et al. Surgical completeness of robotic thyroidectomy: A prospective comparison with conventional open thyroidectomy in papillary thyroid carcinoma patients. *Surgical Endoscopy*. 2014;**28**:1068-1075

[19] Adam MA, Speicher P, Pura J, et al. Robotic thyroidectomy for cancer in the US: Patterns of use and short-term outcomes. *Annals of Surgical Oncology*. 2014;**21**:3859-3864

[20] Tae K, Song CM, Ji YB, et al. Comparison of surgical completeness between robotic total thyroidectomy versus open thyroidectomy. *Laryngoscope*. 2014;**124**:1042-1047

[21] Berber E, Bernet V, Fahey TJ 3rd, et al. American Thyroid Association statement on remote-access thyroid surgery. *Thyroid*. 2016;**26**:331-337

[22] Kim JK, Lee CR, Kang SW, Jeong JJ, Nam KH, Chung WY. Expansion of thyroid surgical territory through 10,000 cases under the da Vinci robotic knife. *Scientific Reports*. 2024;**14**(1):7555

[23] Holsinger FC, Chung WY. Robotic thyroidectomy. *Otolaryngologic Clinics of North America*. 2014;**47**:373-378

[24] Kang SW, Lee SC, Lee SH, et al. Robotic thyroid surgery using a gasless, transaxillary approach and the da Vinci S system: The operative outcomes of 338 consecutive patients. *Surgery*. 2009;**146**:1048-1055

[25] Prete FP, Marzaioli R, Lattarulo S, et al. Transaxillary robotic-assisted thyroid surgery: Technique and results of

a preliminary experience on the Da Vinci Xi platform. *BMC Surgery*. 2019;**18**:1-11. Licensed under CC BY 4.0. Available from: <http://creativecommons.org/licenses/by/4.0/>

[26] Park J, Kang LK, Kim K, Bae JS, Kim JS. The learning curve for single-port transaxillary robotic thyroidectomy (SP-TART): Experience through initial 50 cases of lobectomy. *Updates in Surgery*. 2023;**75**:691-700

[27] Kim JK, Choi SH, Choi SM, Choi HR, Lee CR, Kang S-W, et al. Single-port transaxillary robotic thyroidectomy (START): 200-cases with two-step retraction method. *Surgical Endoscopy*. 2022;**36**:2688-2696

[28] An S, Park J, Kim K, Bae JS, Kim JS. Safety and surgical outcomes of single-port trans-axillary robot-assisted thyroidectomy: Experience from a consecutive series of 300 patients. *Journal of Robotic Surgery*. 2024;**18**:13

[29] Ryu CH, Seok J, Jung Y-S, Ryu J. Novel robot-assisted thyroidectomy by a transaxillary gas-insufflation approach (TAGA): A preliminary report. *Gland Surgery*. 2020;**9**:1267

[30] Yu DY, Chang YW, Ku D, Ko SY, Lee HY, Son GS. Robotic thyroidectomy using gas-insufflation one-step single-port transaxillary (GOSTA) approach. *Surgical Endoscopy*. 2023;**37**:8861-8870

[31] Park J, Kim K. Current and future of robotic surgery in thyroid cancer treatment. *Cancers*. 2024;**16**:2470. DOI: 10.3390/cancers16132470

[32] Park JO. Current concepts in thyroid gland surgery: Transoral endoscopic and robotic surgical procedures. *Journal of the Korean Medical Association*. 2021;**64**(3). Licensed under CC BY-NC 3.0. Available from:

<http://creativecommons.org/licenses/by-nc/3.0/>

[33] Kim HY, Chai YJ, Dionigi G, Anuwong A, Richmon JD. Transoral robotic thyroidectomy: Lessons learned from an initial consecutive series of 24 patients. *Surgical Endoscopy*. 2018;**32**:688-694

[34] Richmon JD, Kim HY. Transoral robotic thyroidectomy (TORT): Procedures and outcomes. *Gland Surgery*. 2017;**6**:285

[35] Tae K, Ji YB, Song CM, Ryu J. Robotic and endoscopic thyroid surgery: Evolution and advances. *Clinical and Experimental Otorhinolaryngology*. 2019;**12**(1):1-11. Licensed under CC BY-NC 4.0. Available from: <http://creativecommons.org/licenses/by-nc/4.0/>

[36] Lee SM, Hwang H, Shin MH, Yi JW. One-year clinical experience of single-port and multi-port robotic thyroid surgery in a single institution. *Journal of Clinical Medicine*. 2024;**13**(18):5486. Licensed under CC BY 4.0. Available from: <https://creativecommons.org/licenses/by/4.0/>

[37] Lee KE, Choi JY, Youn Y-K. Bilateral axillo-breast approach robotic thyroidectomy. *Surgical Laparoscopy Endoscopy & Percutaneous Techniques*. 2011;**21**:230-236

[38] Kwak HY, Kim HY, Lee HY, Jung SP, Woo SU, Son GS, et al. Robotic thyroidectomy using bilateral axillo-breast approach: Comparison of surgical results with open conventional thyroidectomy. *Journal of Surgical Oncology*. 2015;**111**:141-145

[39] Choi YS, Choi JH, Jeon MS, Yu MJ, Lee HM, Shin AY, et al. First experience of single-port robotic areolar

approach thyroidectomy. *Clinical and Experimental Otorhinolaryngology*. 2023;**16**(3):275-281

[40] Miccoli P, Minuto MN, Ugolini C, Pisano R, Fosso A, Berti P. Minimally invasive video-assisted thyroidectomy for benign thyroid disease: An evidence-based review. *World Journal of Surgery*. 2008;**32**(7):1333-1340

[41] Miccoli P, Berti P, Conte M, Bendinelli C, Marcocci C. Minimally invasive surgery for thyroid small nodules: Preliminary report. *Journal of Endocrinological Investigation*. 1999;**22**(11):849-851

[42] Gagner M, Inabnet WB 3rd. Endoscopic thyroidectomy for solitary thyroid nodules. *Thyroid*. 2001;**11**(2):161-163

[43] Lahey FH, Hoover WB. Injuries to the recurrent laryngeal nerve in thyroid operations: Their management and avoidance. *Annals of Surgery*. 1938;**108**(4):545-562. DOI: 10.1097/00000658-193810000-00006

[44] Deshmukh A, Thomas AE, Dhar H, Velayutham P, Pantvaidya G, Pai P, et al. Seeing is not believing: Intraoperative nerve monitoring (IONM) in the thyroid surgery. *Indian Journal of Surgical Oncology*. 2022;**13**(1):121-132. DOI: 10.1007/s13193-021-01348-y. Epub 2021 May 17

[45] Kim HY, Liu X, Chai YJ, Tufano R, Dralle H, Dionigi G. Standards for intraoperative neuromonitoring in thyroid operations. *Journal of Endocrine Surgery*. 2017;**17**(3):1-2. Licensed under CC BY-NC 4.0. Available from: <https://creativecommons.org/licenses/by-nc/4.0/>

[46] Barczyński M, Konturek A, Pragacz K, Papier A, Stopa M, Nowak W.

- Intraoperative nerve monitoring can reduce prevalence of recurrent laryngeal nerve injuries in thyroid reoperations: Results of a retrospective cohort study. *World Journal of Surgery*. 2014;**38**(3):599-606. DOI: 10.1007/s00268-013-2260-x
- [47] Chan WF, Lang BH, Lo CY. The role of intraoperative neuromonitoring of recurrent laryngeal nerve during thyroidectomy: A comparative study on 1000 nerves at risk. *Surgery*. 2006;**140**:866-872; discussion 872-863. DOI: 10.1016/j.surg.2006.07.017
- [48] Dralle H, Sekulla C, Haerting J, Timmermann W, Neumann HJ, Kruse E, et al. Risk factors of paralysis and functional outcome after recurrent laryngeal nerve monitoring in thyroid surgery. *Surgery*. 2004;**136**(6):1310-1322. DOI: 10.1016/j.surg.2004.07.018
- [49] Ling Y, Zhao J, Zhao Y, Li K, Wang Y, Kang H. Role of intraoperative neuromonitoring of recurrent laryngeal nerve in thyroid and parathyroid surgery. *The Journal of International Medical Research*. 2020;**48**(9):300060520952646. DOI: 10.1177/0300060520952646
- [50] Chiang FY, Wang LF, Huang YF, Lee KW, Kuo WR. Recurrent laryngeal nerve palsy after thyroidectomy with routine identification of the recurrent laryngeal nerve. *Surgery*. 2005;**137**:342-347. DOI: 10.1016/j.surg.2004.09.008
- [51] Sun W, Liu J, Zhang H, Zhang P, Wang Z, Dong W, et al. A meta-analysis of intraoperative neuromonitoring of recurrent laryngeal nerve palsy during thyroid reoperations. *Clinical Endocrinology*. 2017;**87**(5):572-580. DOI: 10.1111/cen.13379
- [52] Wong KP, Mak KL, Wong CK, Lang BH. Systematic review and meta-analysis on intra-operative neuro-monitoring in high-risk thyroidectomy. *International Journal of Surgery*. 2017;**38**:21-30. DOI: 10.1016/j.ijssu.2016.12.039
- [53] Yang S, Zhou L, Lu Z, Ma B, Ji Q, Wang Y. Systematic review with meta-analysis of intraoperative neuromonitoring during thyroidectomy. *International Journal of Surgery*. 2017;**39**:104-113. DOI: 10.1016/j.ijssu.2017.01.086
- [54] Wu CW, Dionigi G, Barczynski M, Chiang FY, Dralle H, Schneider R, et al. International neuromonitoring study group guidelines 2018: Part II: Optimal recurrent laryngeal nerve management for invasive thyroid cancer-incorporation of surgical, laryngeal, and neural electrophysiologic data. *Laryngoscope*. 2018;**128**(Suppl. 3):S18-S27
- [55] Bai B, Chen W. Protective effects of intraoperative nerve monitoring (IONM) for recurrent laryngeal nerve injury in thyroidectomy: Meta-analysis. *Scientific Reports*. 2018;**8**(1):7761. DOI: 10.1038/s41598-018-26219-5
- [56] Bakkar S, Papavramidis TS, Aljarrah Q, Materazzi G, Miccoli P. Energy-based devices in thyroid surgery—An overview. *Gland Surgery*. 2020;**9**(Suppl. 1):S14-S17. DOI: 10.21037/gs.2019.08.05
- [57] Konturek A, Szpyra B, Stopa-Barczyńska M, Barczyński M. Energy-based devices for hemostasis in thyroid surgery. *Gland Surgery*. 2020;**9**(Suppl. 2):S153-S158. DOI: 10.21037/gs.2019.10.17
- [58] Pacilli M, Tartaglia N, Gerundo A, Pavone G, Fersini A, Ambrosi A. Energy-based vessel sealing devices in thyroid surgery: A systematic review to clarify the relationship with recurrent laryngeal nerve injuries. *Medicina*. 2020;**56**(12):651. DOI: 10.3390/medicina56120651

- [59] Romano RM, Pignatelli MF, Ferrandes S, Docimo G. Energy devices, hemostatic agents, and optical magnification in thyroid surgery. In: Testini M, Gurrado A, editors. *Thyroid Surgery: Recent Advances*. Cham: Springer Nature Switzerland; 2024. pp. 131-136
- [60] Khadra H, Bakeer M, Hauch A, Hu T, Kandil E. Hemostatic agent use in thyroid surgery: A meta-analysis. *Gland Surgery*. 2018;7(Suppl. 1):S34-S41. DOI: 10.21037/gs.2018.03.02
- [61] von Ahnen T, von Ahnen M, Militz-Müller S, Süß A, Schardey J, Schopf S, et al. Efficacy of four different hemostatic agents in thyroid surgery in reducing the amount of post-operative fluid collection. *BMC Surgery*. 2023;23:303. DOI: 10.1186/s12893-023-02172-7
- [62] Materazzi G, Rossi L. Robot-assisted transaxillary thyroidectomy. In: *Thyroid Surgery*. Cham: Springer International Publishing; 2023. pp. 83-91. Licensed under CC BY-NC-ND 4.0. Available from: <http://creativecommons.org/licenses/by-nc-nd/4.0/>
- [63] Yin S, Pan B, Yang Z, Tang M, Mo H, Li Y, et al. Combined use of autofluorescence and indocyanine green fluorescence imaging in the identification and evaluation of parathyroid glands during total thyroidectomy: A randomized controlled trial. *Frontiers in Endocrinology (Lausanne)*. 2022;13:897797. DOI: 10.3389/fendo.2022.897797
- [64] Hauck A, Pons A, Abdel-Aziz T. On indocyanine green fluorescence and autofluorescence in thyroid and parathyroid surgery: A scoping systematic review. *Health Sciences Review*. 2022;5:100064. DOI: 10.1016/j.hsr.2022.100064
- [65] Dip F, Alesina PF, Anuwong A, et al. Use of fluorescence imaging and indocyanine green during thyroid and parathyroid surgery: Results of an intercontinental, multidisciplinary Delphi survey. *Surgery*. 2022;172:S6-S13. DOI: 10.1016/j.surg.2022.09.004
- [66] Hu QL, Kuo JH. Choice in ablative therapies for thyroid nodules. *Journal of the Endocrine Society*. 2023;7(7):bvad078
- [67] Clark RD, Luo X, Issa PP, Tufano RP, Kandil E. A clinical practice review of percutaneous ethanol injection for thyroid nodules: State of the art for benign, cystic lesions. *Gland Surgery*. 2023;13(1):108
- [68] Korkusuz Y, Gröner D, Raczynski N, Relin O, Kingeter Y, Grünwald F, et al. Thermal ablation of thyroid nodules: Are radiofrequency ablation, microwave ablation and high intensity focused ultrasound equally safe and effective methods? *European Radiology*. 2018;28:929-935
- [69] Stan MN, Papaleontiou M, Schmitz JJ, Castro MR. Nonsurgical management of thyroid nodules: The role of ablative therapies. *The Journal of Clinical Endocrinology & Metabolism*. 2022;107(5):1417-1430
- [70] Bernardi S, Dobrinja C, Fabris B, Bazzocchi G, Sabato N, Ulcigrai V, et al. Radiofrequency ablation compared to surgery for the treatment of benign thyroid nodules. *International Journal of Endocrinology*. 2014;2014(1):934595
- [71] Taha A, Saad B, Taha-Mehlitz S, Ochs V, El-Awar J, Mourad MM, et al. Analysis of artificial intelligence in thyroid diagnostics and surgery: A scoping review. *American Journal of Surgery*. 2024;229:57-64. DOI: 10.1016/j.amjsurg.2023.11.019

[72] Bhatia P, Mohamed HE, Kadi A, Kandil E, Walvekar RR. Remote access thyroid surgery. *Gland Surgery*. 2015;**4**(5):376

[73] Habchi Y, Himeur Y, Kheddar H, Boukabou A, Atalla S, Chouchane A, et al. Ai in thyroid cancer diagnosis: Techniques, trends, and future directions. *Systems*. 2023;**11**(10):519

Section 4

Evolution in the Management of Thyroid Disease

Intersections between Autoimmune Thyroid Disease, Sexual Dysfunction, and Mental Health in Women

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Abstract

This chapter provides a comprehensive narrative review exploring the complex relationships between autoimmune thyroid disease (AITD), sexual dysfunction, and mental health disturbances in women. A systematic search of the recent literature was conducted, focusing on recent studies. The chapter discusses the multidimensional impact of thyroid autoimmunity, emphasizing how hormonal dysregulation, chronic inflammation, and neurotransmitter imbalances contribute to impaired sexual function and increased risk of depression and anxiety. Particular attention is given to the role of psychological stress and major life events in the development and exacerbation of AITD, especially Graves' disease. An integrated, multidisciplinary management approach is proposed, combining endocrine therapy, psychological support, and sexual health interventions, to optimize the quality of life and emotional well-being of affected women.

Keywords: autoimmune thyroid disease, AITD, female sexual dysfunction, FSD, mental health

1. Introduction

Autoimmune thyroid diseases (AITD) are among the most common endocrine disorders affecting women, with conditions such as Hashimoto's thyroiditis and Graves' disease having a significant impact on overall health. The thyroid gland plays a central role in regulating metabolism, hormonal balance, and multiple physiological functions, including those related to sexual and mental well-being. Despite their high prevalence, the effects of thyroid autoimmunity on female sexual dysfunction and mental health remain underexplored in both clinical practice and research. Many women with AITD report low libido, arousal difficulties, and an overall decline in

sexual satisfaction, often accompanied by psychiatric symptoms such as depression and anxiety. These manifestations are frequently dismissed or attributed to other causes, leading to inadequate diagnosis and management.

Emerging evidence suggests that psychological stress and depression may not only be consequences of autoimmune thyroid diseases but also be significant contributors to their onset and progression. Chronic stress is known to dysregulate the hypothalamic-pituitary-adrenal (HPA) axis and impair immune tolerance, potentially triggering autoimmune responses against thyroid tissue. In particular, major life stressors have been associated with an increased risk of developing Graves' disease, highlighting the complex interplay between emotional well-being and thyroid autoimmunity. Understanding these psychoneuroimmunological mechanisms is essential for a comprehensive approach to the prevention and management of AITD.

The bidirectional relationship between thyroid disorders and psychological well-being is complex, with thyroid hormone imbalances influencing neurotransmitter pathways that regulate mood, cognitive function, and emotional resilience. Thyroid dysfunction can lead to hormonal deficiencies that further contribute to sexual dysfunction, amplifying the psychological distress experienced by affected individuals. Women with AITD frequently struggle with fatigue, brain fog, and mood instability, all of which can negatively impact intimate relationships and sexual confidence. Furthermore, the societal stigma associated with thyroid disease symptoms, such as weight gain, hair loss, and skin changes, may lead to body image issues, further reducing sexual motivation and satisfaction.

This chapter aims to delve into the intricate connections between AITD, sexual dysfunction, and mental health disturbances, emphasizing the bidirectional influences that exist between these domains. The discussion will explore the pathophysiological mechanisms underlying these relationships, highlighting how thyroid hormones, autoimmunity, and neuroinflammation contribute to changes in libido, sexual response, and mood. Additionally, the chapter will provide insights into the clinical implications of these findings and discuss management strategies that integrate endocrinology, psychiatry, and sexual medicine. Recognizing and addressing these interrelated issues is crucial for improving the quality of life in women with thyroid disorders.

2. Methodology

This chapter is based on a narrative review of the current literature exploring the interrelationships between autoimmune thyroid disease, sexual dysfunction, and mental health in women. Relevant articles were identified through a comprehensive search of peer-reviewed journals, using keywords such as "autoimmune thyroid disease," "female sexual dysfunction," "mental health," "depression," and "Graves' disease." Priority was given to studies providing insights into pathophysiological mechanisms, clinical outcomes, and interdisciplinary management strategies. Only articles published in English were considered. The selected literature informed the synthesis of findings and the development of the integrated clinical approach proposed in this chapter.

3. Pathophysiological mechanisms involved

Thyroid hormones are critical regulators of multiple physiological processes, influencing not only metabolism but also reproductive and neurological

functions. Their role in sexual function extends beyond traditional metabolic effects, directly affecting blood flow to genital tissues, neurotransmitter activity, and hormonal equilibrium. Thyroid-stimulating hormone (TSH) and anti-thyroid antibodies have been implicated in sexual dysfunction through both direct and indirect pathways. Elevated TSH levels in hypothyroidism can disrupt the hypothalamic–pituitary–gonadal axis, leading to reduced estrogen and testosterone levels, which are essential for maintaining libido and normal sexual function. Conversely, hyperthyroidism, marked by excessive thyroid hormone production, is associated with increased sympathetic nervous system activity, which may lead to sexual performance issues, including arousal and orgasm difficulties. This bidirectional hormonal influence underscores the complex interplay between thyroid function and sexual health [1].

Beyond hormonal disruptions, dopamine and serotonin—key neurotransmitters involved in both sexual function and mental health—are also affected by thyroid dysfunction. Dopamine, often referred to as the “pleasure neurotransmitter,” is crucial for sexual arousal and motivation, while serotonin plays a central role in mood stabilization and emotional regulation. In individuals with AITD, dysregulated thyroid hormone levels have been shown to alter both dopamine and serotonin transmission, leading to profound effects on both sexual function and mental well-being. Research indicates that hypothyroidism is associated with lower dopamine activity, which contributes to reduced libido, anhedonia, and a general lack of sexual motivation. In contrast, hyperthyroidism is linked to overstimulation of serotonin pathways, potentially triggering heightened anxiety, emotional instability, and difficulties with sexual performance. These disruptions illustrate how thyroid-related neurotransmitter imbalances can contribute to both mood disorders and sexual dysfunction, highlighting the need for an integrative approach to treatment [2, 3].

Expanding on this neurochemical interaction, thyroid hormones (T3 and T4) directly regulate serotonin, dopamine, and glutamate systems, which are essential for mood stability and cognitive function. Reduced serotonin availability in hypothyroidism has been strongly associated with depressive symptoms, emotional instability, and diminished sexual desire, while dopamine impairment exacerbates anhedonia and motivational deficits, further reducing arousal. Meanwhile, hyperthyroidism can overstimulate serotonin pathways, leading to emotional dysregulation, anxiety, and restlessness, all of which can negatively affect sexual interest and satisfaction. In addition to these hormonal and neurotransmitter changes, chronic inflammation and thyroid autoantibodies have been identified as potential aggravating factors, further worsening mood symptoms and sexual dysfunction in AITD patients [4].

The autoimmune component of AITD plays a crucial role in its neurological and sexual health consequences, as chronic inflammation disrupts neurotransmitter balance and contributes to psychiatric symptoms. Elevated levels of pro-inflammatory cytokines have been shown to modulate dopamine and serotonin activity, affecting both libido and mood stability. Furthermore, the presence of anti-thyroid antibodies, particularly thyroid peroxidase antibodies (TPOAb), has been linked to increased rates of depression and anxiety, suggesting that the neuroimmune interaction extends beyond thyroid hormone levels alone. This evidence underscores the importance of addressing both immune regulation and endocrine balance in the management of sexual dysfunction and mental health disturbances in AITD (**Figure 1**) [3, 5].

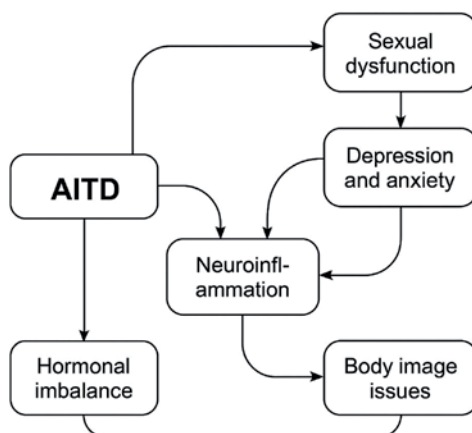


Figure 1.

Impact pathways of autoimmune thyroid disease on sexual and mental health in women.

4. Sexual dysfunction in women with AITD

Sexual dysfunction in women with autoimmune thyroid disease (AITD) can present in various forms, including decreased libido, difficulty with arousal and lubrication, and impaired orgasmic response. Studies utilizing the Female Sexual Function Index (FSFI) have consistently shown that women with hypothyroidism and Hashimoto's thyroiditis score significantly lower in all domains of sexual function compared to healthy controls. These impairments tend to be more severe in overt hypothyroidism, where hormonal deficiencies lead to vascular and neurological impairments that directly affect sexual response. Conversely, hyperthyroidism is frequently associated with heightened anxiety and restlessness, which can disrupt sexual performance, satisfaction, and overall relationship dynamics [1, 2, 6].

The burden of female sexual dysfunction (FSD) is notably higher among women with thyroid disorders compared to the general population, affecting up to 46.1% of patients versus 20.7% of healthy women. Among the different thyroid conditions, nodular goiter was linked to the highest prevalence of FSD (68.4%), suggesting that even euthyroid structural thyroid abnormalities can influence sexual health. Studies have further revealed that desire, arousal, lubrication, and orgasmic function are the most affected aspects in thyroid disease patients, while pain during intercourse (dyspareunia) does not appear to differ significantly from that observed in healthy women. These findings emphasize the broad impact of thyroid dysfunction on multiple dimensions of female sexual health, reinforcing the need for thorough assessment and targeted intervention [7].

One crucial factor in AITD-related sexual dysfunction is the distinction between subclinical and clinical stages of the disease. Women with subclinical hypothyroidism, characterized by elevated TSH levels but normal thyroid hormone levels, frequently report mild to moderate sexual impairments that are subtle enough to be overlooked in routine evaluations. These may include slight reductions in libido, difficulty with arousal, and inconsistent lubrication. In contrast, women with overt hypothyroidism are more likely to experience severe sexual impairments, such as pronounced lubrication difficulties, reduced orgasmic capacity, and heightened sexual distress. Similarly, hyperthyroid patients in the subclinical stage may develop

anxiety-related sexual difficulties, whereas those with clinical hyperthyroidism often suffer from fatigue and metabolic hyperactivity, both of which exacerbate sexual dysfunction [1, 3, 8, 9].

The severity of sexual dysfunction in thyroid disease appears to be directly correlated with TSH levels, underscoring the critical role of hormonal dysregulation. Studies have identified a strong inverse correlation between TSH levels and FSFI scores, particularly in women with nodular goiter, indicating that higher TSH levels are predictive of worse sexual function outcomes. Interestingly, even euthyroid patients with Hashimoto's thyroiditis exhibit significant declines in desire, arousal, and lubrication, suggesting that autoimmune mechanisms may contribute to sexual dysfunction independent of thyroid hormone levels. While hypothyroidism predominantly leads to reduced sexual desire, hyperthyroidism is more often associated with anxiety-driven sexual dysfunction, highlighting the multifaceted nature of thyroid-related FSD, which involves hormonal, neurological, and immune-mediated factors [7, 10].

Moreover, a TSH threshold of 2.75 mIU/L has been identified as a significant predictor of increased FSD risk, with women exceeding this level showing marked impairments across multiple domains of sexual function, including desire, arousal, lubrication, and orgasmic response. These findings suggest that even mild TSH elevations, which were traditionally considered within the normal range, can negatively impact sexual health. As a result, maintaining TSH levels below this threshold may be a critical strategy for mitigating thyroid-related sexual dysfunction. A combination of hormonal regulation, psychological support, and targeted sexual health interventions should be considered for women with AITD experiencing these difficulties [5].

Additionally, hypothyroidism is frequently linked to metabolic syndrome, a condition that raises the risk of cardiovascular disease and type 2 diabetes, both of which are independent contributors to sexual dysfunction. The overlap of hypothyroid symptoms with perimenopause further compounds the problem, as hormonal fluctuations and metabolic changes during this phase exacerbate FSD. This highlights the importance of comprehensive, individualized management strategies that consider both endocrine and reproductive health factors when addressing sexual dysfunction in women with AITD [11, 12].

5. Mental health disorders associated with AITD

Beyond its impact on sexual function, thyroid dysfunction also exerts profound effects on mental health, contributing to conditions such as depression and anxiety. Given the interdependence of sexual well-being and emotional stability, it is essential to explore the psychiatric manifestations of AITD and their underlying pathophysiological mechanisms.

Depression is among the most frequently reported mental health concerns in women with autoimmune thyroid disease (AITD), reflecting the complex bidirectional relationship between thyroid function and mood disorders. Hypothyroidism has been shown to alter neurochemical pathways, predisposing individuals to depressive symptoms, while anti-thyroid antibodies are independently associated with depression, even in euthyroid individuals. Conversely, hyperthyroidism often manifests as heightened anxiety, as excessive thyroid hormone levels stimulate the sympathetic nervous system, leading to restlessness, nervousness, and panic-like symptoms. This intricate link between thyroid imbalances and mental health disturbances highlights the need for early identification and targeted psychiatric interventions to mitigate the impact of AITD on emotional well-being [1, 3, 13].

Among the thyroid disorders, Graves' disease is particularly associated with a high prevalence of neuropsychiatric symptoms, significantly affecting patients' quality of life. Studies have reported that up to 72% of individuals with Graves' disease experience anxiety, while 78% report irritability, and symptoms such as insomnia (66.4%), frequent crying (55.1%), and anger outbursts (55.9%) are also common. These emotional disturbances often contribute to social and marital stress, as well as frustration with healthcare providers, particularly when symptoms are misdiagnosed as primary psychiatric conditions. Alarming, these neuropsychiatric symptoms frequently persist even after achieving euthyroidism, suggesting that Graves' disease may induce long-term alterations in the central nervous system. The high prevalence of panic attacks and emotional reactivity in hyperthyroid patients further underscores the need for early psychiatric evaluation and intervention, ensuring that the psychological burden of AITD is addressed alongside its endocrine manifestations [14].

Beyond the direct hormonal imbalances observed in thyroid dysfunction, the link between AITD and neuropsychiatric symptoms extends to neuroinflammation and autoimmunity. Studies have demonstrated that up to 52% of patients with treatment-resistant depression exhibit subclinical thyroid dysfunction, indicating that thyroid abnormalities may contribute to persistent mood disturbances even when hormone levels appear normal. Furthermore, anti-thyroid antibodies have been independently linked to mood disorders, reinforcing the notion that autoimmune activity may disrupt brain function through chronic inflammation and immune-mediated neurotransmitter dysregulation. Patients with Graves' disease or Hashimoto's thyroiditis frequently experience depression, emotional instability, and cognitive impairments, which are often overlooked in clinical settings. Additionally, hyperthyroidism may exacerbate psychiatric symptoms, leading to anxiety, panic attacks, and, in extreme cases, psychotic episodes, complicating the overall management of these patients. These findings highlight the importance of routine thyroid screening in psychiatric populations, particularly among individuals with treatment-resistant mood disorders [4].

In addition to hormonal imbalances and autoimmune processes, psychosomatic factors play a significant role in AITD-related mental and sexual health issues. Women with thyroid disease often continue to experience impaired sexual function despite achieving normal thyroid hormone levels, suggesting that underlying psychological distress, body image concerns, and autoimmune inflammation contribute to persistent dysfunction. Moreover, research has shown that BMI correlates negatively with FSFI scores, indicating that obesity, which is more prevalent in hypothyroid patients, further exacerbates sexual dysfunction. This interplay between metabolic, psychological, and autoimmune mechanisms reinforces the necessity of a holistic treatment approach, integrating psychological counseling, lifestyle interventions, and endocrine management to optimize both mental and sexual well-being in women with AITD [7].

An increasing body of research has established that women with AITD face a significantly elevated risk of developing mood disorders compared to the general population. Large-scale cohort studies have found that even euthyroid women with Hashimoto's thyroiditis exhibit higher rates of depression, underscoring the role of autoimmunity itself, rather than just hormonal fluctuations, in mental health deterioration. This reinforces the need for proactive psychiatric screening in women diagnosed with AITD, particularly since mood disorders often precede more overt endocrine symptoms, making early intervention critical for improving long-term outcomes [2, 3].

Emerging evidence suggests that psychological stress and depression are not only consequences but also significant risk factors for the development of autoimmune

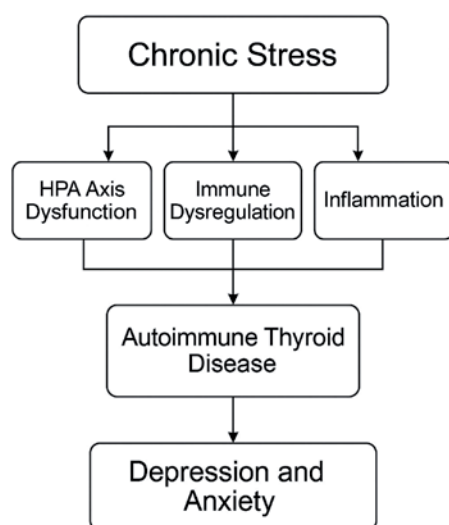


Figure 2.
 Proposed pathways linking psychological stress to autoimmune thyroid disease.

thyroid diseases (AITD), particularly Graves' disease. Chronic exposure to stress is known to dysregulate the hypothalamic–pituitary–adrenal (HPA) axis, leading to impaired immune regulation and a predisposition toward autoimmunity. Stress-induced alterations in cortisol levels can disturb the balance between pro-inflammatory and anti-inflammatory cytokines, promoting the activation of autoreactive lymphocytes and the production of thyroid autoantibodies [15].

Several studies have identified major life events, such as bereavement, job loss, or severe interpersonal conflicts, as triggers for the onset of Graves' disease. Moreover, depression itself, through its association with systemic inflammation and immune dysregulation, may contribute to the pathogenesis of thyroid autoimmunity. This bidirectional relationship between mental health and autoimmune processes underscores the importance of early psychological intervention in individuals at risk for AITD [16, 17].

The relationship between hormonal changes and mental health in AITD is further complicated by reproductive factors, particularly pregnancy and postpartum thyroid dysfunction. Research suggests that pregnancy can act as a trigger for hyperthyroidism, with affected women experiencing heightened anxiety, emotional instability, and pronounced mood swings. Given the overlap between pregnancy-related hormonal shifts, postpartum depression, and thyroid dysfunction, clinicians must be particularly vigilant in identifying psychiatric symptoms in postpartum women with a genetic predisposition to AITD. Furthermore, estrogen's protective effect against hyperthyroidism has been hypothesized to play a role in stabilizing mood and preventing excessive activation of the sympathetic nervous system, suggesting a potential avenue for hormonal interventions in managing thyroid-related mental health disturbances (Figure 2) [16].

6. Clinical implications and integrated management

Given the multifaceted impact of AITD on both sexual and mental health, an integrated, multidisciplinary approach is crucial for effective management. Collaboration between endocrinologists, psychiatrists, gynecologists, and sexual health specialists

can ensure that the diverse and interconnected challenges faced by affected patients are adequately addressed. Routine thyroid function screening should be a key consideration for women presenting with sexual dysfunction, particularly when accompanied by fatigue, mood disturbances, or unexplained weight gain. Treatment strategies should focus on hormonal therapy to restore thyroid function, while psychological interventions, such as cognitive-behavioral therapy (CBT) and sex therapy, can support mental and emotional well-being. Additionally, lifestyle modifications, including weight management and regular exercise, may enhance mood stability and improve overall metabolic health. Targeted therapies for sexual dysfunction—such as pelvic floor exercises, lubricants, and personalized counseling—can further aid in symptom relief. Moreover, emerging research suggests that medications targeting serotonin and dopamine pathways may offer therapeutic potential, addressing both sexual and psychiatric symptoms in AITD patients [1, 3, 11].

Given the strong association between thyroid dysfunction and psychiatric disorders, thyroid screening should also be considered in patients with unexplained depression, anxiety, or cognitive impairment. Clinical guidelines recommend that thyroid function tests, including TSH, T3, T4, and anti-thyroid antibody screening, be incorporated into the diagnostic workup for mood disorders, particularly in cases that are treatment-resistant or atypical in presentation. When hypothyroidism is identified as a contributing factor to persistent depression, levothyroxine (LT4) therapy has been shown to alleviate mood symptoms. Additionally, triiodothyronine (T3) supplementation has demonstrated potential in augmenting antidepressant response, particularly in treatment-resistant depression (TRD). Some studies indicate that T3 enhances serotonin neurotransmission, thereby improving mood stability, motivation, and overall emotional resilience. These findings reinforce the importance of early thyroid assessment in psychiatric care, ensuring that hormonal imbalances contributing to mental health disturbances are not overlooked [4].

In the context of sexual dysfunction associated with AITD, it is crucial to recognize that thyroid hormone imbalances alone do not always fully explain persistent impairments in sexual function. Thus, routine FSFI (Female Sexual Function Index) screening should be integrated into thyroid disease assessments to ensure a more comprehensive evaluation of sexual health. Research suggests that thyroid hormone therapy alone may not always restore normal sexual function, as many women continue to experience arousal and orgasmic difficulties despite achieving euthyroidism. This underscores the need for additional therapeutic interventions, such as sex therapy, cognitive-behavioral therapy (CBT), and structured lifestyle modifications, to address both the physiological and psychological components of sexual dysfunction. Furthermore, obesity and metabolic disturbances—which are more prevalent in hypothyroid patients—have been identified as significant contributors to sexual dysfunction, reinforcing the importance of targeted weight management strategies as part of the broader treatment plan. Addressing the psychosomatic aspects of sexual dysfunction through patient education and counseling can further support women in navigating the emotional and psychological burdens associated with AITD-related sexual dysfunction, ultimately improving their long-term quality of life and sexual satisfaction [7].

Building on these considerations, an effective approach to managing sexual dysfunction in women with AITD must be multidimensional, extending beyond FSFI screening and general lifestyle modifications. While thyroid hormone replacement remains the cornerstone of endocrine management, the persistence of sexual dysfunction despite achieving euthyroidism suggests that additional, targeted

interventions are necessary. Pharmacological strategies should be carefully evaluated, particularly for patients with concurrent sexual dysfunction and mood disorders. In such cases, switching from SSRIs to antidepressants with a lower risk of sexual side effects, such as bupropion or vortioxetine, may enhance both mood stability and sexual function. Additionally, hormonal supplementation with testosterone or estrogen may be beneficial for certain women, especially those in perimenopause or those experiencing persistent arousal difficulties. Beyond pharmacological approaches, cognitive-behavioral interventions, including mindfulness-based therapy, have shown efficacy in reducing sexual distress and improving intimacy in women with chronic illnesses. Given the multifaceted nature of sexual dysfunction in AITD, an individualized, integrative treatment plan that incorporates hormonal, psychological, and pharmacological strategies is essential for optimizing outcomes and enhancing overall quality of life [18].

7. Recent research and future directions

Despite the growing recognition of the interplay between AITD, sexual dysfunction, and mental health, significant gaps in research remain, particularly regarding the long-term psychiatric consequences of subclinical thyroid disorders. While progress has been made in understanding the neuropsychiatric impact of thyroid dysfunction, there is still much to learn about genetic markers and inflammatory pathways that contribute to mood disturbances in AITD patients. Emerging evidence suggests that early thyroid screening in high-risk populations could help detect and manage thyroid-related psychiatric and sexual dysfunction before symptoms become severe. Future research should explore preventive interventions, such as modulating estrogen levels, closer postpartum monitoring, and targeted hormonal therapies, to determine whether these approaches can reduce the incidence of AITD in genetically predisposed women. Additionally, a deeper understanding of the genetic overlap between Graves' disease and Hashimoto's thyroiditis may provide insights into personalized treatment strategies, helping to identify patients at higher risk of developing both endocrine and neuropsychiatric complications [16].

In light of these findings, personalized treatment approaches are emerging as a promising avenue for improving both mental health and endocrine outcomes in AITD patients. Strategies such as tailored T3 supplementation, novel anti-inflammatory interventions, and individualized hormonal balancing could enhance treatment efficacy, particularly for patients experiencing persistent depressive or anxiety symptoms despite achieving euthyroidism. Given the strong connection between thyroid hormones and neurotransmitter function, further investigation into thyroid-based augmentation strategies for psychiatric disorders is warranted. Longitudinal studies are particularly needed to establish causative relationships and evaluate the long-term effectiveness of combined endocrine and psychiatric treatment approaches. Additionally, the discovery of emerging biomarkers for thyroid-related sexual dysfunction could pave the way for targeted therapies that address the complex hormonal, neurological, and psychological components of AITD-associated sexual disorders [2, 4].

While the association between AITD and psychiatric disorders is well-documented, the precise mechanisms linking thyroid autoimmunity to depression and anxiety remain unclear. The persistence of psychiatric symptoms even after achieving euthyroidism suggests that chronic inflammation, neuroimmune dysfunction, and

autoantibody activity may play critical roles in the pathophysiology of thyroid-related mood disturbances. This raises important questions about whether standard thyroid hormone replacement therapy alone is sufficient or if additional anti-inflammatory and immunomodulatory treatments should be integrated into management plans. Future research should focus on tracking neuropsychiatric symptoms in AITD patients across different stages of treatment, assessing whether autoimmune activity contributes to long-term neurotransmitter dysregulation. Investigating the roles of cytokines, oxidative stress, and gut microbiota in modulating serotonin and dopamine pathways may provide novel therapeutic targets for treating thyroid-related psychiatric conditions. Additionally, integrating endocrinology and psychiatry through personalized treatment plans—combining levothyroxine therapy, selective serotonin reuptake inhibitors (SSRIs), cognitive-behavioral therapy (CBT), and lifestyle interventions—may be essential for improving both mental health and overall well-being in AITD patients. As thyroid dysfunction remains one of the most underrecognized contributors to psychiatric illness, advancing interdisciplinary research will be key in refining diagnostic criteria and developing tailored interventions that address the complex interplay between immune dysregulation, thyroid hormone metabolism, and mental health [19].

In addition, accumulating evidence indicates that chronic psychological stress can significantly contribute to immune dysregulation and the development of autoimmune conditions, including autoimmune thyroid diseases. Stress-induced alterations in neuroendocrine-immune interactions may promote persistent inflammation and autoantibody production, providing a potential pathway linking emotional distress with thyroid autoimmunity [20].

While current research has provided valuable insights into the impact of AITD on sexual and mental health, critical gaps remain in the long-term management of these conditions. Future studies should prioritize personalized treatment approaches, interdisciplinary interventions, and novel biomarkers that can predict which patients are most at risk for persistent symptoms despite achieving euthyroidism. Addressing these gaps will be essential in refining clinical guidelines and improving patient outcomes.

8. Conclusion

Autoimmune thyroid diseases (AITD) exert a profound and multifaceted impact on women's sexual and mental health, affecting not only biological functions but also psychological well-being and intimate relationships. Despite increasing recognition of the systemic effects of thyroid dysfunction, sexual dysfunction and psychiatric symptoms remain significantly underdiagnosed and undertreated in clinical practice. Women with AITD often report low libido, arousal difficulties, and orgasmic dysfunction, yet these concerns are frequently overlooked in endocrinological evaluations, with treatment focusing primarily on metabolic and hormonal balance. Similarly, depression, anxiety, and cognitive disturbances—which are often the earliest signs of thyroid dysfunction—are commonly misattributed to primary psychiatric disorders, delaying appropriate thyroid-specific interventions.

The complex interplay between hormonal imbalances, autoimmune inflammation, neurotransmitter dysregulation, and psychosocial factors necessitates a holistic, patient-centered approach. An effective management strategy must extend beyond thyroid hormone replacement therapy to include mental health support, sexual health

counseling, and lifestyle interventions. Routine screening for sexual dysfunction and psychiatric disorders in AITD patients should be incorporated into standard clinical assessments to ensure early identification and timely intervention. Likewise, multidisciplinary collaboration between endocrinologists, psychiatrists, gynecologists, and sexual health specialists is essential to provide comprehensive care tailored to the unique challenges faced by women with thyroid disease.

As research continues to uncover the intricate relationships between thyroid autoimmunity, mood disorders, and reproductive health, future therapeutic strategies must integrate endocrine, neurological, and psychotherapeutic modalities. Personalized medicine approaches, including hormonal optimization, immune modulation, and targeted psychopharmacology, may offer new avenues for improving long-term outcomes. Additionally, patient education and advocacy are crucial in empowering women to recognize the connection between thyroid health and their overall well-being, enabling them to seek appropriate care.

Ultimately, shifting the clinical paradigm to a broader interdisciplinary perspective will be key to improving the quality of life, emotional resilience, and intimate well-being of women affected by AITD. Addressing these gaps in research and clinical care is not only a medical necessity but also an essential step toward comprehensive, gender-sensitive healthcare.

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Conflict of interest

The authors declare no conflict of interest.

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References

- [1] Gabrielson AT, Sartor RA, Hellstrom WJG. The impact of thyroid disease on sexual dysfunction in men and women. *Sexual Medicine Reviews*. 2019;7:57-70
- [2] Krysiak R, Drosdzol-Cop A, Skrzypulec-Plinta V, Okopien B. Sexual function and depressive symptoms in young women with thyroid autoimmunity and subclinical hypothyroidism. *Clinical Endocrinology*. 2016;84(6):925-931
- [3] Bunevicius R, Prange AJ Jr. Psychiatric manifestations of Graves' hyperthyroidism: Pathophysiology and treatment options. *CNS Drugs*. 2006;20(11):897-909. DOI: 10.2165/00023210-200620110-00003
- [4] Feldman AZ, Shrestha RT, Hennessey JV. Neuropsychiatric manifestations of thyroid disease. *Endocrinology and Metabolism Clinics of North America*. Sep 2013;42(3):453-476. DOI: 10.1016/j.ecl.2013.05.005
- [5] Bortun AMC, Ivan V, Navolan DB, Dehelean L, Borlea A, Stoian D. Thyroid autoimmune disease—Impact on sexual function in young women. *Journal of Clinical Medicine*. 2021;10(2):1-14
- [6] Bhasin S, Enzlin P, Coviello A, Basson R. Sexual dysfunction in men and women with endocrine disorders. *Lancet*. 17 Feb 2007;369(9561):597-611. DOI: 10.1016/S0140-6736(07)60280-3
- [7] Pasquali D, Maiorino MI, Renzullo A, Bellastella G, Accardo G, Esposito D, et al. Female sexual dysfunction in women with thyroid disorders. *Journal of Endocrinological Investigation*. 2013;36(9):729-733
- [8] Krysiak R, Kowalcze K, Okopień B. Sexual function and depressive symptoms in young women with overt hyperthyroidism. *European Journal of Obstetrics and Gynecology and Reproductive Biology*. 2019;234:43-48
- [9] Atis G, Dalkilinc A, Altuntas Y, Atis A, Caskurlu T, Ergenekon E. Sexual dysfunction in women with clinical hypothyroidism and subclinical hypothyroidism. *Journal of Sexual Medicine*. 2010;7(7):2583-2590
- [10] Atis G, Dalkilinc A, Altuntas Y, Atis A, Gurbuz C, Ofluoglu Y, et al. Hyperthyroidism: A risk factor for female sexual dysfunction. *Journal of Sexual Medicine*. 2011;8(8):2327-2333
- [11] Wang Y, Wang H. Effects of hypothyroidism and subclinical hypothyroidism on sexual function: A meta-analysis of studies using the female sexual function index. *Sexual Medicine*. 2020;8:156-167
- [12] Maseroli E, Fanni E, Cipriani S, Scavello I, Pampaloni F, Battaglia C, et al. 003 Cardiometabolic risk and female sexuality: Focus on clitoral vascular resistance. *The Journal of Sexual Medicine*. 2017;14(Suppl. 5):e351-e352
- [13] Placidi GP, Boldrini M, Patronelli A, Fiore E, Chiovato L, Perugi G, Marazziti D. Prevalence of psychiatric disorders in thyroid diseased patients. *Neuropsychobiology*. Nov 1998;38(4):222-225. DOI: 10.1159/000026545
- [14] Stern RA, Robinson B, Thorner AR, Arruda JE, Prohaska ML, Prange AJ Jr. A survey study of neuropsychiatric complaints in patients with Graves' disease. *The Journal of Neuropsychiatry*

and Clinical Neurosciences. Spring;
1996;**8**(2):181-185. DOI: 10.1176/
jnp.8.2.181

[15] Segerstrom SC, Miller GE.
Psychological stress and the human
immune system: A meta-analytic study
of 30 years of inquiry. *Psychological
Bulletin*. 2004;**130**(4):601-630

[16] Strieder TG, Prummel MF,
Tijssen JG, Endert E, Wiersinga WM.
Risk factors for and prevalence of
thyroid disorders in a cross-sectional
study among healthy female relatives
of patients with autoimmune thyroid
disease. *Clinical Endocrinology
(Oxf)*. Sep 2003;**59**(3):396-401.
DOI: 10.1046/j.1365-2265.2003.01862.x

[17] Dantzer R, O'Connor JC, Freund GG,
Johnson RW, Kelley KW. From
inflammation to sickness and depression:
When the immune system subjugates
the brain. *Nature Reviews Neuroscience*.
2008;**9**:46-56

[18] Clayton AH, El Haddad S,
Iluonakhamhe JP, Ponce Martinez C,
Schuck AE. Sexual dysfunction
associated with major depressive
disorder and antidepressant treatment.
Expert Opinion on Drug Safety.
2014;**13**(10):1361-1374

[19] Siegmann EM, Müller HHO,
Luecke C, Philipsen A, Kornhuber J,
Grömer TW. Association of depression
and anxiety disorders with autoimmune
thyroiditis: A systematic review and
meta-analysis. *JAMA Psychiatry*. 1 Jun
2018;**75**(6):577-584. DOI: 10.1001/
jamapsychiatry.2018.0190. Erratum in:
JAMA Psychiatry. 1 Aug 2019;**76**(8):872.
DOI: 10.1001/jamapsychiatry.2019.1643

[20] Dhabhar FS. Effects of Stress on
Immune Function: The Good, the
Bad, and the Beautiful. *Immunologic
Research*. 2014;**58**:193-210

Role of Artificial Intelligence in Thyroid Disorders

Qaviullah Mian and Nebiyou Bayleyegn

Abstract

Artificial intelligence (AI), in its simplest form, uses computers to interpret or solve a simple or complex task, making our lives easier and better. Machine learning and deep learning are two fields of AI in medicine. Neural networks that resemble the neurons of the human nervous system are being used to enhance the processing of text, images, and clinical records for improved diagnostic efficiency, achieving high accuracy. With recurrent neural networks (RNNs), thyroid samples can be classified as cancerous or goiter, enhancing diagnostic capabilities for pathologists. There is a need for improved models to better understand hypothyroidism, hyperthyroidism, and thyroid cancer and facilitate novel therapeutic developments. Computer vision aids in the precise identification of vital structures during open and Minimal Access Surgery, reducing morbidity and fatal complications. As part of personalized medicine, pre-operative imaging data are analyzed for adequate pre-surgical planning and intraoperative real-time guidance during robotic-assisted thyroid surgery. Medical education has touched new horizons by using AI to provide automatic evaluation metrics while training for surgical skills. Holograms are being used to dissect the different layers of the thyroid gland to understand the peculiar anatomy of each patient. The use of virtual reality has revolutionized undergraduate and postgraduate education, allowing several students to be mentored and assessed simultaneously.

Keywords: artificial intelligence, machine learning, deep learning, neural network, thyroid disorders, thyroid dysfunction, thyroid cancer, thyroidectomy, computer vision

1. Introduction

The thyroid gland plays a central role in maintaining homeostasis in the human body through its hormones, specifically T3 and T4. These hormones are involved in various functions, including, but not limited to, the regulation of metabolism, thermogenesis, and growth and development. Although anatomically impalpable in normal conditions, its dysfunction may result in the most pronounced imbalance in the human body, even leading to vital compromise [1]. The thyroid gland is regulated by a feedback mechanism completed by the hypothalamus and the pituitary gland, which release thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH).

Physicians in the modern era face certain undeniable challenges in patient care related to the thyroid gland. Subjective interpretations of imaging, ambiguous biopsy results, and delays in thyroid function test analysis are some of the difficulties that traditional diagnostic and treatment approaches for thyroid disorders, including hypothyroidism and hyperthyroidism, encounter. These restrictions may result in incorrect diagnosis, postponed start of treatment, and challenges in providing patients with the best possible, individualized care.

Since its inception in 1956, artificial intelligence (AI) in medicine has shown visible progress in the 2000s, when patient electronic medical records and other electronic resources were analyzed to develop evidence-based responses in medicine [2]. This, along with technological advances in computer hardware and software, enabled humans to utilize natural language processing (NLP), a branch of AI, to create computer interfaces that facilitate conversations ranging from superficial to meaningful communication; Eliza, Siri, and Alexa, to name a few. Pharmabot was developed to educate patients on medication related to pediatrics, and similarly, Mandy was made to assist in primary practice. Machine learning (ML) entails analyzing extensive datasets to identify unique patterns and generate predictions, often termed supervised learning. Other techniques employ the use of unlabeled data, which is called unsupervised learning, and reinforcement learning, where a “rewards/punishments” system is used to provide feedback to the machine to improve its algorithm, whereas deep learning (DL), an enhanced form of ML, comprises algorithms to develop artificial neural networks, mimicking some aspects of the human brain, allowing the computer to make decisions independently [3].

AI has the potential to revolutionize patient care by enhancing screening for diseases, patient-doctor encounters, diagnostic workups, treatment modalities, rehabilitation medicine, and healthcare delivery.

This chapter systematically reviews the evidence for AI applications in thyroid disorder management while maintaining a critical perspective on implementation challenges. The discussion is organized according to the clinical workflow: diagnosis, treatment planning, and outcome monitoring, with special attention to thyroid cancer as a distinct domain where AI shows particular promise. Ethical and legal challenges have been addressed. Lastly, the impact of computer vision and augmented reality in medical education at both undergraduate and postgraduate levels is expanded upon as well.

2. Current challenges in thyroid disorder diagnosis and management

Clinicians face significant diagnostic and management challenges of thyroid disorders, encompassing conditions such as hypothyroidism, hyperthyroidism, and thyroid cancers. Traditionally, diagnostic modalities and treatment strategies have certain limitations that can impede better patient outcomes.

This section dives deep into the challenges mentioned previously to emphasize the need for innovative solutions to enhance patient care.

2.1 Limitations of traditional diagnostic methods

2.1.1 Subjectivity in interpretation

Ultrasound imaging is a cornerstone in evaluating thyroid nodules. However, since it is operator-dependent, this inter-observer variation often compromises its efficacy.

The interpretation of ultrasound images of pathology in one patient need not always coincide, which could lead to an inconsistent assessment of the characteristics of the thyroid nodules, and a malignancy might be overlooked. This subjectivity can result in either overdiagnosis or underdiagnosis, affecting subsequent clinical decisions [4].

2.1.1.1 False positives and negatives in fine-needle aspiration biopsies

Fine-needle aspiration (FNA) biopsy is a standard procedure for evaluating thyroid nodules. Despite its widespread use, FNA has a notable rate of inconclusive results, ranging from 15% to 30%. Such indeterminate findings often necessitate repeat biopsies or additional diagnostic procedures, leading to patient anxiety, increased healthcare costs, and potential delays in definitive diagnosis [5].

2.1.1.2 Delayed diagnosis due to manual analysis of thyroid function tests

Thyroid function tests (TFTs), including measurements of serum thyroid-stimulating hormone (TSH) and thyroid hormones (T3 and T4), are essential for diagnosing thyroid dysfunctions. However, the manual interpretation of these tests can be time-consuming and is susceptible to human error. Delays in analyzing TFTs can postpone the initiation of appropriate treatment, potentially exacerbating patient conditions [6].

2.2 Challenges in treatment planning and monitoring

2.2.1 Personalized treatment needs

The management of hypothyroidism typically involves levothyroxine replacement therapy. Determining the optimal dosage is complex and influenced by patient age, weight, residual thyroid function, and comorbidities. Standard dosing guidelines recommend 1.6–1.8 µg/kg for overt hypothyroidism and 0.8–1 µg/kg for subclinical cases. However, individual responses vary, necessitating frequent monitoring and dose adjustments to achieve euthyroidism [7].

2.2.2 Monitoring disease progression

Post-treatment surveillance, especially in thyroid cancer patients, is critical for early detection of recurrence. Traditional monitoring methods, including periodic imaging and serum thyroglobulin measurements, may not always detect recurrence promptly. Deep learning models have been developed that analyze comprehensive data on the clinicopathological features of differentiated thyroid cancer to monitor disease progression and recurrence with high accuracy. This approach has enabled personalized treatment, allowing the surgeon to intervene promptly, improving patient care and outcomes significantly in thyroid cancer management [8].

2.3 Need for innovative solutions

The limitations of conventional diagnostic and treatment approaches in thyroid disorders highlight the necessity for innovative solutions. Artificial intelligence (AI) and machine learning (ML) technologies offer promising avenues to address these challenges. AI-driven tools can automate image analysis, reducing inter-observer variability in ultrasound interpretations. Predictive analytics can assist

in risk stratification, identifying patients at higher risk of malignancy or recurrence. Furthermore, AI algorithms can optimize levothyroxine dosing by analyzing patient-specific data, leading to more personalized and effective treatment plans. By integrating these technologies into clinical practice, healthcare providers can enhance diagnostic accuracy, streamline treatment planning, and improve patient outcomes in thyroid disorder management.

3. AI techniques in thyroid disorder diagnosis

Artificial intelligence (AI) has revolutionized the field of thyroid disorder diagnosis by enhancing accuracy, reducing subjectivity, and streamlining clinical workflows. This section explores the key AI techniques employed in thyroid diagnostics, including machine-learning approaches, multimodal diagnostic integration, and real-world clinical implementation case studies.

3.1 Machine learning approaches

Machine learning (ML), a subset of AI, has been instrumental in automating the classification and diagnosis of thyroid disorders. Algorithms such as decision trees, support vector machines (SVMs), random forests, and deep learning models like convolutional neural networks (CNNs) have accurately differentiated benign and malignant thyroid nodules. For instance, a study reported that random forest classifiers achieved an accuracy of 99.81% in predicting hypothyroidism, outperforming other algorithms like k-nearest neighbors (KNN) and SVM [8].

Deep learning models, particularly CNNs, have shown remarkable performance in analyzing ultrasound images of thyroid nodules as shown in **Figure 1**. These models can automatically extract relevant features from imaging data, reducing the reliance on manual interpretation and minimizing inter-observer variability. In one study, a deep learning algorithm achieved an area under the curve (AUC) of 0.69, comparable to experienced radiologists, in classifying thyroid nodules on ultrasound images [9]. Deep learning models have been developed that have successfully identified lymph nodes involved in thyroid cancers.

The data standards of the clinical characteristics used to train these models are of ample significance. They undergo data cleaning, for example, removal of duplicate values and missing variables. The datasets are then divided into testing, training, and validation sets. The training set is used to teach the model, the testing set checks how well the model learned, and the validation set helps adjust the model's settings.

3.2 Multimodal diagnostic integration

Integrating data from multiple diagnostic modalities enhances the accuracy and reliability of thyroid disorder diagnosis. AI systems can combine information from ultrasound imaging, fine-needle aspiration (FNA) cytology, thyroid function tests (TFTs), and patient clinical data to provide a comprehensive assessment. This multimodal approach allows for more precise risk stratification and personalized treatment planning.

For example, AI-based computer-aided diagnosis (CAD) systems have been created to interpret ultrasound features, which has resulted in a decrease in unnecessary FNAs. Additionally, AI algorithms can analyze electronic medical records and other clinical data, including but not limited to US features, such as composition, shape,

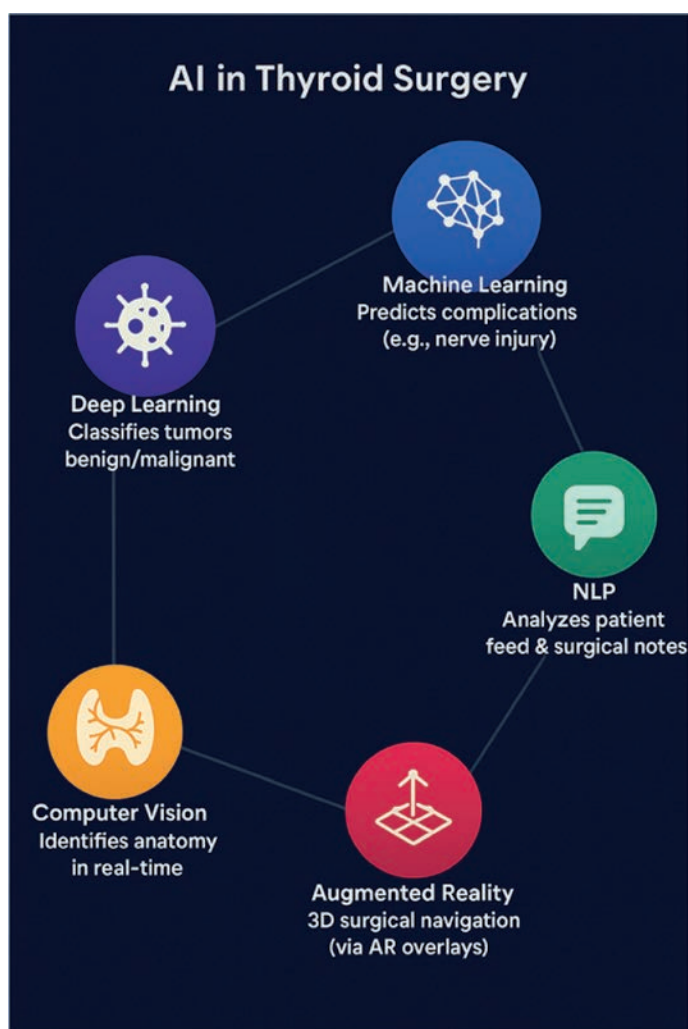


Figure 1.
 Application of artificial intelligence in thyroid surgery.

margin, echogenicity, and calcifications, to identify patterns and risk factors for thyroid disorders, facilitating earlier detection and intervention [8].

However, their specificities in ruling out malignancies are lower than those of experienced radiologists. Researchers analyzing the methodology of these models for diagnostic purposes have pointed out some points that may have led to the low specificity and accuracy of the results using machine learning and deep learning techniques.

- *The studies had limited comparability and reproducibility due to different imaging protocols, segmentation methods, and scanners/vendors.*
- *Their studies had variations in feature type, selection, and classifiers.*
- *Most studies lacked adequate test and validation datasets and were developed using relatively small sample sizes.*

Nonetheless, this still underscores the usefulness of the current CADs as they could be better used as screening tools for the objective [10].

3.3 Clinical implementation case studies

Several clinical studies have demonstrated the successful implementation of AI techniques in thyroid disorder diagnosis. In one case, a deep learning-based AI model called ThyNet was developed to differentiate between malignant tumors and benign thyroid nodules, showing promising results in assisting radiologists [11].

Another study focused on enhancing thyroid volumetry used by nuclear medicine specialists to determine the dosage of radioactive iodine for monitoring and treating various thyroid diseases, particularly for radioiodine therapy in hyperthyroidism. This was achieved by combining tracked 3D ultrasound with a deep neural network-based model for automatic segmentation. This approach significantly reduced inter-observer variability and increased the accuracy of thyroid volume measurements, leading to more consistent assessments; however, this model was also trained using a low number of volunteers [12]. The improved performance can be attributed to the nature of the 3D acquisition and the automatic segmentation. The study's small, healthy participant group and equipment specificity limit generalizability.

These case studies demonstrate AI's potential to enhance diagnostic accuracy, reduce variability, and improve clinical outcomes in managing thyroid disorders. Larger, diverse samples and long-term studies are needed to validate and integrate the technique into clinical practice.

4. AI in treatment planning and management

4.1 Risk stratification and prognostication

Determining the best course of treatment for thyroid disorders requires accurate risk assessment. Artificial intelligence (AI) models, especially machine learning algorithms, have proven their worth in successfully classifying patients according to the probability of disease progression or recurrence. To help identify patients who might benefit from more aggressive interventions or closer surveillance, predictive models that use clinicopathological features, for example, have demonstrated high accuracy in predicting the recurrence of differentiated thyroid cancer.

4.2 Personalized therapeutic decision-making

AI facilitates the development of individualized treatment plans by integrating diverse data sources, including genetic profiles, imaging studies, and laboratory results. In thyroid cancer, AI algorithms assist in tailoring the most appropriate therapeutic modalities like surgery, radioactive iodine therapy, or active surveillance based on tumor characteristics and patient preferences. Moreover, achieving clinical and biochemical euthyroidism is difficult, and movement beyond traditional weight-based dosing strategies becomes necessary to achieve more personalized and precise medical treatment.

AI-driven tools can optimize levothyroxine dosing in hypothyroid patients by analyzing diverse clinical factors such as age, weight, comorbidities, and response to previous treatments, enhancing therapeutic efficacy and minimizing adverse effects.

Machine learning models (Extra Trees Regressor) demonstrated the highest accuracy (R^2 of 87.37%) and the lowest mean absolute error (MAE of 9.4 mcg) in predicting dosing requirements. BMI emerged as the strongest predictor of levothyroxine replacement therapy. These findings of a retrospective study indicate that using models in clinical systems could help personalize dosing for hypothyroidism; however, the study's design and missing adherence data are major drawbacks, so future studies should focus on improving dosing strategies and treatment outcomes [13].

4.3 Monitoring and follow-up

Digital therapeutics (DTx) and Remote Continuous Data Monitoring (RCDM) are essential for managing chronic thyroid conditions and detecting potential complications. AI-powered applications and AI-assisted wearable devices enable real-time tracking of physiological parameters, such as heart rate, sleep patterns, and weight fluctuations, providing valuable insights into a patient's response to therapy. These technologies support proactive adjustments to treatment regimens and facilitate timely interventions, ultimately improving patient adherence and outcomes.

4.4 Enhancing treatment planning and outcomes

AI contributes to preoperative planning in surgical management by analyzing imaging data to delineate anatomical structures and identify potential challenges. Advanced AI models, such as the E2E-Swin-Unet++, have been developed to enhance the precision of procedures like radiofrequency ablation by providing real-time segmentation of thyroid tumors, thereby improving targeting accuracy and reducing the risk of complications. In a world of precision medicine, imaging investigations are evaluated to facilitate surgical planning more efficiently. Real-time AI-assisted intraoperative guidance can prospectively transform robotic-assisted thyroid surgery. AI models have been devised based on endoscopic thyroid surgery datasets to identify the Recurrent Laryngeal Nerve (RLN), giving rise to promising results as in **Table 1**.

S. no	AI technology	Function in thyroid surgery	Key applications	Potential benefits
1.	Machine learning	Predicts post-operative complications	Risk modeling for nerve injury, hypocalcemia, and vocal cord issues	Improved surgical planning, reduced complications
2.	Deep learning	Classifies thyroid tumors as benign or malignant	Histopathology image analysis, cytology interpretation	Faster and more accurate diagnosis, aiding treatment decisions
3.	Natural language processing (NLP)	Analyzes patient feedback and surgical notes	Extracts insights from EHRs, follow-up notes, and patient reports	Identifies care gaps, and improves documentation and outcomes
4.	Augmented reality (AR)	Provides 3D surgical navigation through AR overlays	Visualizes critical structures (e.g., nerves, vessels) during surgery	Enhances precision, reduces errors during operations
5.	Computer vision	Identifies anatomical structures in real-time during surgery	Real-time recognition of glands, nerves, blood vessels	Supports intraoperative decision-making

Table 1.
AI in thyroid disorders.

Future research should concentrate on continuous learning mechanisms for AI models, utilizing periodically updated data and feedback from clinical use to improve the accuracy and relevance of these models over time. Exploring hybrid models that combine convolutional neural networks with transformers and integrating multi-modal learning approaches that utilize different forms of clinical data may further enhance the model's accuracy and robustness [14].

Ultrasound-guided thoracoscopic surgery based on an artificial intelligence algorithm has significantly better outcomes in terms of postoperative pain and reduced surgical time, as it offers better image resolution compared to conventional methods. This approach also maintains high safety standards and provides substantial clinical benefits, although further research is needed to confirm long-term efficacy [15].

4.5 AI innovations in robotic thyroid surgery

AI enhances robotic thyroid surgery by optimizing preoperative planning, real-time decision support, and post-operative tracking, improving precision, safety, and patient outcomes. This revolutionizes the preoperative planning process by allowing precise mapping of the vital structures related to the thyroid gland. Additionally, AI assists in robotic-assisted thyroid surgery, optimizing instrument movements, predicting potential complications, and minimizing tissue damage. Machine learning algorithms analyze surgical videos to identify best practices and offer an adequate assessment of resident training [16]. Furthermore, AI-driven simulation platforms provide immersive training environments, allowing surgeons to practice procedures in virtual reality before performing them on patients aiding in skill development and procedural efficiency.

4.6 Integration into multidisciplinary care

AI systems can streamline multidisciplinary team (MDT) meetings by aggregating and presenting relevant patient data, facilitating collaborative decision-making. By offering evidence-based recommendations and highlighting critical information, AI fosters efficient and effective discussions among endocrinologists, surgeons, radiologists, and other healthcare professionals involved in thyroid disorder management. Studies have proven enhanced concordance rates of LLM-produced results with guidelines and MDT recommendations; however, large prospective multi-center data must be analyzed, and nevertheless, the importance of counterchecking the AI-generated response by experienced clinicians cannot be undermined. Transcription software can be utilized during MDT meetings to avoid missing important recommendations.

5. AI in thyroid cancer detection and treatment

Artificial intelligence (AI) has emerged as a transformative force in the detection and treatment of thyroid cancer, offering enhanced diagnostic accuracy, personalized treatment planning, and improved postoperative care. This section delves into the multifaceted applications of AI in thyroid oncology, highlighting its role in early detection, surgical planning, and postoperative management.

5.1 Early detection

Early and accurate detection of thyroid cancer is crucial for effective treatment and improved patient outcomes. AI technologies, particularly machine learning (ML) and deep learning (DL) algorithms, have shown remarkable proficiency in analyzing complex datasets to identify malignancies at an early stage.

5.1.1 Ultrasound imaging analysis

Ultrasound is a primary modality for evaluating thyroid nodules. AI-enhanced ultrasound analysis utilizes DL algorithms, such as convolutional neural networks (CNNs), to assess sonographic features like echogenicity, margins, and calcifications. These models have demonstrated diagnostic accuracies comparable to experienced radiologists, thereby aiding in the differentiation between benign and malignant nodules.

5.1.2 Cytopathological assessment

Fine-needle aspiration biopsy (FNAB) is a standard procedure for evaluating thyroid nodules. AI applications in cytopathology involve the use of DL models to analyze digitized cytological slides, enhancing the detection of malignant cells and reducing inter-observer variability. This approach streamlines the diagnostic process and assists pathologists in making more accurate assessments.

5.1.3 Molecular marker integration

AI models can integrate molecular and genetic data, such as BRAF and RAS mutations, to assess the risk of malignancy in thyroid nodules. By combining imaging findings with molecular profiles, AI facilitates a more comprehensive risk stratification, guiding clinicians in decision-making regarding the necessity of surgical intervention.

5.2 Surgical planning and postoperative care

AI's role extends beyond diagnosis to encompass surgical planning and postoperative management, ensuring precision and personalized care.

5.2.1 Preoperative planning

Accurate delineation of tumor boundaries and identification of critical anatomical structures are paramount for successful thyroid surgery. AI-driven image segmentation tools, employing architectures like U-Net, assist surgeons in visualizing the tumor extent and planning the surgical approach, thereby minimizing complications and preserving vital structures. U-Net is a CNN structure widely used in deep learning, mainly for image segmentation [17].

5.2.2 Postoperative monitoring

Monitoring for recurrence is a critical aspect of postoperative care. AI algorithms can analyze serial ultrasound images to detect subtle changes indicative of recurrent

disease. Additionally, AI models can predict recurrence risk by evaluating postoperative histopathological data and patient-specific factors, enabling timely interventions.

5.3 Case studies

The Mayo Clinic has pioneered the development of a novel class of AI, termed hypothesis-driven AI, which integrates existing medical knowledge with data-driven approaches. This AI model has demonstrated a 15% improvement in thyroid cancer detection rates, underscoring its potential to enhance diagnostic accuracy and inform treatment strategies.

In another instance, researchers at the Mayo Clinic developed high-resolution ultrasound imaging software compatible with existing ultrasound machines. This technology, termed quantitative high-definition microvessel imaging (q-HDMI), albeit investigative, captures high-resolution 2D and 3D images combined with AI algorithms, thus allowing the visualization of microvessels to the size of human hair within tumors, studying their distinct morphological feature called biomarkers that are out of the scope of this chapter, facilitating earlier and more accurate detection of malignancies [18].

These case studies exemplify the transformative impact of AI in thyroid cancer care, highlighting its capacity to augment clinical decision-making and improve patient outcomes.

6. Ethical and legal considerations

The integration of artificial intelligence (AI) into the diagnosis and management of thyroid disorders presents significant ethical and legal challenges. These challenges range across algorithmic bias, data privacy, and evolving regulatory frameworks. Addressing these issues is crucial to ensure equitable, safe, and compliant AI applications in thyroid care.

6.1 Bias and fairness

AI systems in healthcare are susceptible to biases that carry the potential to worsen existing health disparities. Non-diverse training datasets lead to misdiagnoses or suboptimal treatment recommendations for underrepresented groups. For instance, studies have shown that AI models may misdiagnose patients of color due to underrepresentation in training data. Hallucination or confabulation is another term given to the phenomenon where an AI model might hallucinate to make a response of its own if it is not trained on the relevant data.

Some of the measures to mitigate these biases are:

- Ensure diverse training data: Incorporate data from varied demographic groups to enhance model generalizability.
- Implement bias audits: Regularly assess AI systems for discriminatory outcomes and rectify identified issues.
- Promote transparency: Maintain openness in AI development processes to facilitate accountability and trust.

By proactively addressing bias, AI can be harnessed to improve thyroid disorder management across diverse populations [19].

6.2 Data privacy and security

The deployment of AI in healthcare warrants rigorous data privacy and security procedures. Compliance with regulations such as the Health Insurance Portability and Accountability Act (HIPAA) in the U.S. and the General Data Protection Regulation (GDPR) in the EU is crucial.

Key considerations include:

- **Data encryption:** Protect patient data through encryption during storage and transmission.
- **Access controls:** Implement strict access protocols to ensure that only authorized personnel can access sensitive information.
- **Consent management:** Explicit patient consent should be signed for data usage, aligning with GDPR's emphasis on informed consent.

Adhering to these practices not only ensures legal compliance but also fosters patient trust in AI-driven healthcare solutions.

6.3 Regulatory frameworks

Regulatory bodies are evolving to address the unique challenges posed by AI in medical devices. In the United States, the Food and Drug Administration (FDA) has issued draft guidance emphasizing a total product lifecycle approach for AI-enabled medical devices.

6.3.1 Key aspects of the FDA's approach include

- **Premarket evaluation:** Assessing AI devices through pathways like premarket clearance (510(k)), De Novo classification, or premarket approval, depending on risk levels put forward by the United States Food and Drug Administration
- **Postmarket monitoring:** Continuous oversight to ensure ongoing safety and effectiveness of AI systems.
- **Transparency requirements:** Mandating clear documentation of AI algorithms' functionality and decision-making processes.

These regulatory measures aim to balance innovation with patient safety, ensuring that AI applications in thyroid disorder management are both effective and trustworthy.

7. Conclusion

We are standing at a fascinating crossroads in thyroid medicine. The arrival of AI is not just changing our tools—it is reshaping how we think about patient care altogether. Imagine a world where diagnoses are sharper, treatments fit like custom-tailored suits, and healthcare resources flow exactly where they are needed most. That's the promise AI is already starting to deliver in thyroid clinics worldwide.

Bringing these futuristic tools into real exam rooms is not as simple as flipping a switch. Doctors and patients alike face real questions: How do these algorithms reach their conclusions? Can we trust them with sensitive health data? Will they work as well for a grandmother in rural Africa as they do for a young executive in New York or Tokyo? Training in AI is a requirement of the modern world for endocrinologists, surgeons, and radiologists alike.

The road ahead has some clear signposts. We need AI systems that can explain their thinking in plain language, not just spit out recommendations. The development of reasoning models in recent times is a step toward that. They must prove their worth across all communities, not just in high-tech research hospitals. And perhaps most importantly, they need to slide effortlessly into the existing rhythms of healthcare, not force doctors to learn entirely new ways of working.

It is exciting to watch AI grow from a helpful assistant to a true partner in care. It is not about replacing the doctor's intuition, but about combining human wisdom with machine precision. Here comes the "human-in-the-loop feedback," which implies human involvement in the form of reinforcement learning to give results that are enhanced and more toward artificial general intelligence than AI alone. The thyroid patients of tomorrow may never know about the complex algorithms working behind the scenes—they will just experience care that's more accurate, more personal, and more responsive than we ever thought possible [20].

This transformation would not happen overnight, but each month brings breakthroughs. As someone who has witnessed both the frustrations of traditional thyroid care and the potential of these new technologies, I cannot help but feel optimistic. The future of thyroid medicine is not cold and computerized—it is warmer, smarter, and more human than ever before.

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References

- [1] Atighi F, Yazdanpanahi P, Keshtkar A, Karimi A, Naseri A, Dabbaghmanesh MH. Illuminating the path to thyroid disorder management using artificial intelligence: A narrative review. *Shiraz E-Medical Journal*. 2024;**26**(2):1-12. DOI: 10.5812/semj-e151031
- [2] Kaul V, Enslin S, Gross SA. History of artificial intelligence in medicine. *Gastrointestinal Endoscopy*. 2020;**92**(4):807-812. DOI: 10.1016/j.gie.2020.06.040. Epub 2020 Jun 18
- [3] Toro-Tobon D, Loor-Torres R, Duran M, et al. Artificial intelligence in thyroidology: A narrative review of the current applications, associated challenges, and future directions. *Thyroid*. 2023;**33**(8):903-917. DOI: 10.1089/thy.2023.0132
- [4] Alyami J, Almutairi FF, Aldoassary S, et al. Interobserver variability in ultrasound assessment of thyroid nodules. *Medicine (Baltimore)*. 2022;**101**(41):e31106. DOI: 10.1097/MD.00000000000031106
- [5] de Jong MC, McNamara J, Winter L, Roskell D, Khan S, Mihai R. Risk of malignancy in thyroid nodules with indeterminate (THY3f) cytology. *Annals of the Royal College of Surgeons of England*. 2022;**104**(9):703-709. DOI: 10.1308/rcsann.2021.0358
- [6] Meyer AND, Murphy DR, Al-Mutairi A, et al. Electronic detection of delayed test result follow-up in patients with hypothyroidism. *Journal of General Internal Medicine*. 2017;**32**(7):753-759. DOI: 10.1007/s11606-017-3988-z
- [7] Gupta P, Rustam F, Kanwal K, et al. Detecting thyroid disease using an optimized machine learning model based on differential evolution. *International Journal of Computational Intelligence Systems*. 2024;**17**(3):1-19. DOI: 10.1007/s44196-023-00388-2
- [8] Weng J, Wildman-Tobriner B, Buda M, et al. Deep learning for classification of thyroid nodules on ultrasound: Validation on an independent dataset. *Clinical Imaging*. 2023;**99**:60-66. DOI: 10.1016/j.clinimag.2023.04.010
- [9] Ahmad MA-S, Haddad J. An explainable AI model for predicting the recurrence of differentiated thyroid cancer. In: *Second Jordanian International Biomedical Engineering Conference (JIBEC)*; Amman, Jordan. Vol. 2024. New Jersey, USA: IEEE; 2024. pp. 84-89. DOI: 10.1109/JIBEC63210.2024.10932125
- [10] Ha EJ, Baek JH. Applications of machine learning and deep learning to thyroid imaging: Where do we stand? *Ultrasonography*. 2021;**40**(1):23-29. DOI: 10.14366/usg.20068
- [11] Nagendra L, Pappachan JM, Fernandez CJ. Artificial intelligence in the diagnosis of thyroid cancer: Recent advances and future directions. *Artificial Intelligence in Cancer*. 2023;**4**(1):1-10. DOI: 10.35713/aic.v4.i1.1
- [12] Krönke M, Eilers C, Dimova D, et al. Tracked 3D ultrasound and deep neural network-based thyroid segmentation reduce interobserver variability in thyroid volumetry. *PLoS ONE*. 2022;**17**(7):e0268550. DOI: 10.1371/journal.pone.0268550
- [13] Ngan TT, Tra DH, Mai NTQ, Dung HV, Khai NV, Linh PV, et al. Developing a machine learning-based

predictive model for levothyroxine dosage estimation in hypothyroid patients: A retrospective study. *Frontiers in Endocrinology*. 2025;**16**:1-14. DOI: 10.3389/fendo.2025.1415206

[14] Dialameh M, Rajabzadeh H, Sadeghi-Goughari M, Sim JS, Kwon HJ. E2E-Swin-Unet++: An enhanced end-to-end Swin-Unet architecture with dual decoders For PTMC segmentation [preprint]. arXiv. 2024. Available from: <https://arxiv.org/abs/2410.18239>

[15] Shen X, Yuan A, Zhang K. Ultrasound image under artificial intelligence algorithm in thoracoscopic surgery for papillary thyroid carcinoma. *Scientific Programming*. 2022;**2022**(1):2646094

[16] Park J, Kim K. Current and future of robotic surgery in thyroid cancer treatment. *Cancers*. 2024;**16**(13):2470. DOI: 10.3390/cancers16132470

[17] Yang L, Wang X, Zhang S, Cao K, Yang J. Research progress on artificial intelligence technology-assisted diagnosis of thyroid diseases. *Frontiers in Oncology*. 2025;**15**:1536039. DOI: 10.3389/fonc.2025.1536039

[18] Kurti M, Sabeti S, Robinson KA, Scalise L, Larson NB, Fatemi M, et al. Quantitative biomarkers derived from a novel contrast-free ultrasound high-definition microvessel imaging for distinguishing thyroid nodules. *Cancers*. 2023;**15**(6):1888. DOI: 10.3390/cancers15061888

[19] Chang T, Nuppnau M, He Y, Kocher KE, Valley TS, Sjoding MW, et al. Racial differences in laboratory testing as a potential mechanism for bias in AI: A matched cohort analysis in emergency department visits. *PLOS Global Public Health*. 2024;**4**(10):e0003555. DOI: 10.1371/journal.pgph.0003555

[20] Mosqueira-Rey E, Hernández-Pereira E, Alonso-Ríos D, et al. Human-in-the-loop machine learning: A state of the art. *Artificial Intelligence Review*. 2023;**56**:3005-3054. DOI: 10.1007/s10462-022-10246-w

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The medical evaluation of thyroid disease has undergone significant advances in recent years. Within this book, the contributions of iodine and selenium to the physiology and pathophysiology of thyroid disorders are discussed. The diagnosis of thyroid nodules by ultrasound and fine-needle aspiration biopsy is evaluated. Recent advances in the treatment of thyroid nodules by thermal ablation are extensively discussed. The novel paradigm of the treatment of advanced and metastatic thyroid cancer by multi-targeted kinase and angiogenesis inhibitors is also presented. Lastly, the application of computer-assisted diagnosis and treatment in thyroid disease is presented.

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