Med Pregl 2025; LXXVIII (9-12): 265-269. Novi Sad: septembar-decembar.

REVIEW ARTICLES
PREGLEDNI ČLANCI

MINIMALLY INVASIVE AND NON-INVASIVE TREATMENT OF BENIGN THYROID NODULES

MINIMALNO INVAZIVNO I NEINVAZIVNO LEČENJE BENIGNIH ČVOROVA ŠTITASTE ŽLEZDE

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Review article
Pregledni članak
UDK 616.441-08
https://doi.org/10.2298/MPNS2512265P

Abstract

Introduction. The thyroid gland is a bilobed endocrine organ connected by a thin isthmus and may also present with a pyramidal lobe. **A thyroid nodule** is defined as a localized structural alternation of the thyroid tissue. **Laser thermal ablation** represents a novel minimally invasive intervention, with contemporary guidelines and evidence from randomized trials, observational studies, and multicenter retrospective analyses consistently demonstrating its safety and clinical efficacy in the treatment of symptomatic cold thyroid nodules. **Radiofrequency ablation** is increasingly employed in the management of papillary thyroid microcarcinoma and offers a valuable alternative for patients with medullary thyroid carcinoma who are not suitable surgical candidates. It is also particularly effective in treating recurrent cystic nodules following ethanol ablation and clinically significant lesions with large residual non-cystic components. **Microwave ablation** is a newer technique that has shown substantial improvements in symptom relief and in cosmetic outcomes while preserving thyroid function; however, it has been associated with a relatively higher rate of procedure-related complications. **High-intensity focused ultrasound** is with a non-invasive, computer-guided technique that enables precise targeting while preserving surrounding thyroid tissue. Owing to its lower overall efficacy, higher cost, and limited scientific validation, interventionist use should be restricted to carefully selected patients who are not eligible for other treatment options. For benign thyroid nodules with a significant cystic component, particularly recurrent or symptomatic lesions, current guidelines recommend **percutaneous ethanol injection** as the preferred treatment. **Conclusion**. Whereas surgical intervention was historically the standard approach for thyroid nodules, advances in minimally invasive techniques now provide effective, thyroid-preserving alternatives for appropriately selected patients.

Key words: Thyroid Nodule; Minimally Invasive Surgical Procedures; Ablation Techniques; Laser Therapy; Ethanol; High-Intensity Focused Ultrasound Ablation; Microwaves; Radiofrequency Ablation

Sažetak

Uvod. Štitasta žlezda je endokrini organ leptirastog oblika sačinjen od dva režnja spojena istmusom u blizini kog se nalazi nestalni piramidalni režanj. **Tiroidni nodus** predstavlja lokalizovanu promenu arhitektonike tkiva štitaste žlezde, koja se razlikuje od okolnog žlezdanog parenhima. **Laserska termalna ablacija** je nova minimalno invazivna tehnika. Novi vodiči kao i brojne nerandomizovane, randomizovane i multicentrične retrospektivne studije potvrđuju efikasnost i sigurnost u lečenju simptomatskih nefunkcionalnih nodusa. **Radiofrekvetna ablacija** predstavlja sve prisutniju metodu u lečenju papilarnog mikrokarcinoma. Može se koristiti za zbrinjavanje medularnog karcinoma ukoliko je hirurški pristup kontraindikovan. Takođe je jedan od modaliteta lečenja rekurentnih cističnih lezija nakon tretmana etanolom ili simptomatskih nodusa sa velikom cističnom komponentom**. Mikrotalasna ablacija** je metoda u razvoju kod koje je zapaženo signifikantno povlačenje simptoma i korekcija estetskih problema bez narušavanja funkcije štitaste žlezde, međutim povezuje se sa većim rizikom od komplikacija**. Fokusirani ultra-zvuk visokog intenziteta** se izvodi kompjuterskim navođenjem i planiranjem, što dovodi do poštede okolnog zdravog tkiva štitaste žlezde. Zbog nedovoljne efikasnosti preporučuje se samo u slučaju kada nema drugih terapijskih opcija. **Perkutano apli- kovanje etanola** prema novim smernicama, predstvalja metodu izbora za relapsne i simptomatske benigne cistične lezije i za čvorove sa tečnom komponentom. **Zaključak**. Do skoro je lečenje čvorova štitaste žlezde podrazumevalo hirurišku intervenciju dok danas postoje superiornije minimalno invazivne tehnike.

Ključne reči: tiroidni nodusi; minimalno invazivne hirurške procedure; tehnike ablacije; laserska terapija; etanol; fokusirani ultrazvuk visokog intenziteta; mikrotalasi; radiofrekventna ablacija

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Abbreviations

T4	– thyroxine
TSH	– Thyroid Stimulating Hormone
T3	– triiodothyronine
TBG	– thyroid-binding globulin
AITD	– autoimmune thyroid diseases
US	– ultrasonography
MRI	– magnetic resonance imaging
CT	– computerized tomography
FDG	– fluorodeoxyglucose
FNA	– fine needle aspiration
LTA	– laser thermal ablation
RFA	– radiofrequency ablation
HIFU	– high-intensity focused ultrasound
MWA	– microwave ablation
PEI	– percutaneous ethanol injection
TI-RADS	– Thyroid Imaging Reporting and Data Systems

Introduction

The thyroid gland is a bilobed endocrine organ connected by a thin isthmus and enclosed by two capsules [1,2]. Posterior to the gland lie the recurrent laryngeal nerves and the parathyroid glands. Iatrogenic injury to the recurrent laryngeal nerve may result in voice disturbances, whereas damage to the parathyroid glands can lead to hypocalcemia and tetanic symptoms. Despite its superficial anatomical position, the thyroid gland is physiologically non-palpable owing to its soft consistency. Thyroid enlargement typically progresses posteriorly or retrosternally due to resistance from the infrahyoid muscles, whereas large goiters may extend anteriorly and become visibly apparent. Structurally and functionally, the gland consists of numerous secretory follicles responsible for the synthesis of thyroxine (T4) and triiodothyronine (T3).

Thyroid hormone production is regulated by a feedback mechanism involving T3, T4, and thyroid stimulating hormone (TSH). Thyroxine-binding globulin (TBG) is the primary transport protein for T4 in circulation, and its concentration may vary under different physiological and pathological conditions, such as pregnancy. Thyroid hormones are essential for normal tissue development and metabolic regulation. They stimulate cell division and differentiation, regulate lipid, carbohydrate, and electrolyte metabolism, influence enzyme and protein synthesis and activity, promote the expression of catecholamine receptors, support mammary gland development and function , and inhibit the secretion of TSH and prolactin from the anterior pituitary gland [3,4]. Adequate hormone synthesis required a minimum iodine intake of approximately 1 mg per week. Disorders of the thyroid gland arise from dysfunction of the hypothalamic-pituitary-thyroid axis and manifest clinically as hypothyroidism or hyperthyroidism. These conditions are classified as primary, secondary, or tertiary depending on whether the underlying defect originates in the thyroid gland, pituitary gland, or hypothalamus, respectively [5].

Thyroid nodule

On ultrasonographic examination, a thyroid nodule is defined as a focal lesion that is clearly distinguishable from the surrounding tissue [6]. Nodular thyroid disease can be categorized into three main entities: solitary thyroid nodules, multinodular goiter, and thyroid nodules associated with autoimmune thyroid disease (AITD). Autoimmune thyroid disorders are primarily represented by Graves–Basedow disease and Hashimoto's thyroiditis, which differ substantially in their pathophysiology [7]. Thyroid nodules occur more frequently in older individuals, females, patients with iron deficiency, and those with a history of thyroid irradiation [8].

From a clinico-pathological perspective, thyroid nodules are classified into three principal groups: pseudonodules (hyperplastic and inflammatory lesions, including acute and subacute thyroiditis and Hashimoto's thyroiditis), benign neoplasms (afunctional cold nodules – solid and cystic – and functional hot nodules, such as adenomas), and malignant neoplasms. Malignant lesions include primary thyroid cancers – papillary, follicular, anaplastic, and medullary carcinomas – as well as lymphomas and metastatic tumors [9]. Functionally, nodules are classified as "hot" or "cold" based on radionuclide uptake. Hot nodules demonstrate increased isotope uptake and autonomous hormone production, whereas cold nodules, which account for more than 80% of all thyroid nodules, exhibit reduced uptake [10].

Thyroid nodules can be detected through patient self-examination, clinical palpations, or incidentally during imaging studies such as ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) of the neck. Ultrasound represents the primary diagnostic modality for nodule detection and characterization, allowing detailed assessment of size, margins, contours, echogenicity, homogeneity, presence of a peripheral halo, calcifications, extracapsular extension, echo signal amplification, edge artifacts, and reverberation phenomena. Additionally, ultrasound guidance is essential for fine needle aspiration (FNA) and for percutaneous treatment of selected lesions [6].

Thyroid scintigraphy is performed using various radiopharmaceuticals, most commonly radioactive iodine isotopes or technetium-99m pertechnetate. Based on radionuclide uptake relative to normal thyroid tissue, nodules are classified as "hot", "warm", or "cold." Hot nodules exhibit increased uptake, warm

nodules show uptake comparable to surrounding tissue, and cold nodules demonstrate reduced uptake.

Scintigraphy provides valuable functional information that assists in diagnostic stratification and therapeutic decision-making. Hot nodules are generally considered benign, and management depends on nodule size and the presence of clinical or biochemical thyrotoxicosis. In contrast, hypofunctioning cystic nodules are typically evaluated using FNA cytology, which may also have a therapeutic effect. For solid or partially cystic cold nodules, treatment decisions are guided primarily by cytological findings.

Fine-needle aspiration cytology is a cornerstone of thyroid nodule evaluation and is recommended for nodules larger than 1 cm. Interpretation should be performed exclusively by experienced cytopathologists. Surgical management is determined based on cytological results, whereas advanced imaging modalities are reserved for selected cases. Although more than 85% of thyroid nodules are cold, only approximately 20% of these lesions are malignant. The risk of malignancy in hypofunctioning nodules is higher in individuals younger than 30 or older than 60 years, in males, and in populations from iodine-deficient regions. Hot nodules account for approximately 5% of all thyroid nodules, with prevalence varying according to regional iodine intake, and carry a very low risk of malignancy. The remaining 15% of nodules are isoactive and demonstrate minimal malignant potential [11].

Fine-needle aspiration biopsy (FNAB) represents the cornerstone of preoperative assessment for thyroid nodules due to its reliability, simplicity, and favorable safety profile. Cytological evaluation obtained through FNAB forms the basis of Thyroid Imaging Reporting and Data Systems (TI-RADS) classification and plays a pivotal role in determining optimal management strategies, ranging from surgical intervention to nonoperative surveillance [12]. Each thyroid nodule should be independently assessed to determine the indication for FNAB. Cytological samples are processed and categorized according to the Bethesda System into six diagnostic groups: nondiagnostic (5-10% malignancy risk), benign (0-3% risk), atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS) (10-30% risk), follicular neoplasm (FN) or suspicious for follicular neoplasm (SFN) (25-40% risk), suspicious for malignancy (50-75% risk), and malignant (97-99% risk) [6].

Minimally invasive approaches for the management of benign thyroid nodules

Laser thermal ablation (LTA) is a minimally invasive technique that utilizes laser-generated heat to induce coagulation necrosis within targeted thyroid tissue. This approach results in significant nodule volume reduction, symptom relief, and improved cosmetic outcomes while minimizing patient discomfort. Contemporary guidelines, provide strong evidence for the safety, efficacy, and high tolerability of LTA as an alternative to surgery. LTA has emerged as a low-risk and effective treatment for clinically manifest cold nodules, achieving sustained volume reduction and symptomatic improvement. The procedure is generally well tolerated, with most adverse events being mild and transient, including cervical swelling, localized discomfort, minor bleeding, hematoma formation, or low-grade fever. Rare but more serious complications include thyroid dysfunction, autoimmune reactions, laryngeal impairment, vocal cord paralysis, and damage to adjacent cervical structures. Although LTA is not considered first-line therapy for hot nodules or multinodular goiter, conditions for which radioactive iodine therapy or surgery remain superior, it may be considered in selected cases, such as solitary modest-sized hot nodules in patients unfit for standard treatments or as adjunctive therapy in recurrent or residual papillary thyroid carcinoma [6,13].

Radiofrequency ablation (RFA) has gained widespread acceptance as a minimally invasive modality for treating benign thyroid nodules, offering favorable cosmetic results and a lower incidence of postprocedural hypothyroidism compared with thyroidectomy [14]. RFA operates by generating an alternating electric field that causes ionic oscillation, resulting in localized thermal injury and tissue necrosis. It is primarily indicated for nodules producing compressive symptoms or cosmetic concerns and may be employed in patients with recurrent thyroid carcinoma who are unsuitable for surgery. Due to limited long-term oncological data, RFA is not recommended as primary therapy for thyroid malignancies. The procedure is performed under continuous ultrasound guidance using either the moving-shot technique – particularly effective for the treatment of oval-shaped nodules – or the trans-isthmic approach, which enhances needle stability and reduces the risk of displacement during movement, phonation, or coughing. Real-time ultrasound visualization of critical neck structures, including the recurrent laryngeal nerve, further improves procedural safety [13]. Beyond benign disease, RFA has demonstrated utility in selected cases of papillary thyroid microcarcinoma and in medullary thyroid carcinoma when surgery is contraindicated [15,16]. Additionally, it is effective for treating recurrent cystic nodules after ethanol ablation and nodules with persistent solid components that continue to cause symptoms [17].

Microwave ablation (MWA) is a relatively novel minimally invasive technique, although clinical experience and available evidence remain limited. Preliminary data suggest a potentially higher incidence of unexpected adverse events compared with LTA and RFA, likely due to less precise energy control and the larger caliber of applications. Currently, robust studies evaluating the efficacy and safety of MWA in autonomously functioning thyroid nodules are lacking, underscoring the need for further investigation [17].

High intensity focused ultrasound (HIFU) is a noninvasive technique that induces coagulative necrosis through the focused delivery of ultrasound energy while reserving skin integrity. Due to the limited volume treated per application, multiple sessions are often required to achieve adequate ablation, resulting in prolonged procedural times. Advanced computer-assisted planning allows precise delineation of treatment boundaries, minimizing damage to the surrounding tissues [13]. Compared with RFA and LTA, HIFU demonstrates lower therapeutic efficacy, higher costs, and a more limited evidence base. Consequently, its use is generally restricted to carefully selected patients who are not candidates for other treatment modalities or with structured clinical research protocols [17]. Although HIFU is associated with a relatively low complication rate, the extent of nodule volume reduction remains modest [13].

Percutaneous ethanol injection (PEI) is a targeted ablative therapy involving direct injection of ethanol into thyroid nodules, leading to coagulative necrosis, endothelial injury, and vascular occlusion. This results in ischemia and definitive ablation of the lesion. PEI is considered the first-line treatment for recurrent or clinically significant benign cystic nodules and for nodules with a predominant cystic component, owing to its favorable safety profile, good tolerability, cost-effectiveness and low recurrence rate. It may also be considered when other therapeutic options are contraindicated or unavailable. However, repeated treatment sessions can cause perinodular fibrosis due to ethanol leakage, potentially complicating future surgical interventions. Therefore, PEI is generally reserved for solid benign nodules only when more advanced ablative techniques are unsuitable [17].

Conclusion

Historically, the management of thyroid nodules relied predominantly on surgical intervention. Advances in minimally invasive technologies have introduced effective alternatives with reduced morbidity and improved patient acceptance. Percutaneous ethanol injection is primarily indicated for cystic or predominantly cystic thyroid nodules, whereas laser thermal ablation and radiofrequency ablation are effective options for benign nodules irrespective of functional status, particularly in patients who are poor surgical candidates, ineligible for radioactive iodine therapy, or who decline these treatments. In cases of recurrent papillary thyroid carcinoma, laser thermal ablation, percutaneous ethanol injection, and radiofrequency ablation may represent feasible nonsurgical options for patients unsuitable for repeat surgery. Although microwave ablation and high-intensity focused ultrasound currently lack sufficient high-quality evidence to support widespread use, early results appear promising. Further well-designed studies are necessary to establish the long-term efficacy and optimal role of high-intensity focused ultrasound, despite its lower complication rate, is associated with relatively limited nodule volume reduction.

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Rad je primljen 5. XI 2025.
Recenziran 16. XII 2025.
Prihvaćen za štampu 5. I 2026.
BIBLID.0025-8105:(2025):LXXVIII:9-12:265-269.