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ABSTRACT

of the dissertation for the degree of Doctor of Sciences

WAYS TO IMPROVE THE DIAGNOSIS AND SURGICAL TREATMENT OUTCOMES OF ENDEMIC NODULAR GOITER (CLINICAL-EXPERIMENTAL STUDY)

Specialty: 3213.01 - Surgery

Science field: Medicine

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Rəsad Şəmsəddin oğlu Talışınskiy
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GENERAL CHARACTERISTICS OF THE RESEARCH

Relevance of the topic and degree of completion. Nodular thyroid diseases are among the most common disorders worldwide[1]. This increase is primarily associated with the risk of thyroid disease development in iodine-deficient regions, the deterioration of the ecological situation leading to a higher radiation burden on the population, and the widespread use of visualization methods[2]. The identification and treatment of patients with nodular goiter remains a relevant issue to this day[3]. The prevalence of nodular goiter is significantly higher in iodine-deficient regions[3]. Certain mountainous and foothill areas of our country (Nakhchivan Autonomous Republic, Sheki, Gakh, Oghuz, Gabala, Guba, Gusar, Zagatala, Balakan districts, etc.) have been identified as iodine-deficient regions, and efforts such as universal salt iodization have been undertaken to address this problem. However, regional disparities and persisting risks still remain[3,4].

One of the key challenges faced by the practicing physician in patients diagnosed with nodular goiter is determining whether the nodule is benign or malignant[5]. Only a small proportion of nodules are malignant.

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[1] Качко, В.А. Диагностика новообразований щитовидной железы / В.А. Качко, Ч.В. Семкина, Н.М. Платонова [и др] // Эндокринная Хирургия, - 2018, 12(3). – с. 109-127.

[2] Tovkai, A. İodine deficiency and prevalence of nodular goitre in Ukraine // İnternational journal of endocrinology (Ukraine), – 2022,18(4), – p. 226-230.

[3] Turcan, L. Progress in Iodine Deficiency Disorders (IDD) Control and Elimination in Europe and Central Asia Region (ECAR) in 2010–2020 / L. Turcan, A. Gregory, A.Gerasimov [et al.] // Clinical and experimental thyroidology, – 2021, 17(4), – p. 4-16.

[4] Markou, K.B. Iodine Deficiency in Azerbaijan After the Discontinuation of an Iodine Prophylaxis Program / K.B.Markou, A.G. Neoklis, M. Maria [et al.] // Reassessment of Iodine Intake and Goiter Prevalence in Schoolchildren Thyroid, – 2001, 11(12), – p. 1141-1146.

[5] Sajisevi, M. Evaluating the rising incidence of thyroid cancer and thyroid nodule detection modes: A multinational, multi-institutional analysis / M. Sajisevi, L. Caulley, A. Eskander [et al.] // JAMA Otolaryngol Head Neck Surg. – 2022. 148(9). – p. 811–818.

However, their diagnosis at early stages presents considerable difficulties, since the existing methods sometimes yield inconclusive results. Therefore, the application of multimodal approaches and new technologies is essential to improve diagnostic accuracy[5].

In our country, an increase in the incidence of thyroid cancer among women in the 50–59 age group has also been identified[6].

The use of fine-needle aspiration biopsy (FNAB) in the diagnosis of nodular goiter has led to a reduction of surgical interventions by 50%, while the detection rate of thyroid cancer has doubled[7,8]. Despite its diagnostic accuracy, in many cases, significant difficulties arise in the interpretation of morphological examination results obtained through FNAB, and false-negative results are reported in 20% of cases. Therefore, the proportion of diagnostic surgeries continues to increase[8]. Although diagnostic technologies and methods have advanced, substantial progress has not yet been achieved in the differential diagnosis of follicular and Hürthle cell tumors, and it has been reported that 80% of patients with follicular neoplasia undergo unnecessary thyroidectomy[9].

The TIRADS (Thyroid Imaging Reporting and Data System) classification, based on ultrasound findings, is considered sufficiently effective in predicting the malignant potential of thyroid nodules.

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[6] Марданлы, Ф.А. Эпидемиологические аспекты заболеваемости раком щитовидной железы в Азербайджанской Республике за период 2009-2015 гг. / Ф.А. Марданлы, А.Д. Алиев, Н.А. Гулиев [и др]. // Российский Онкологический журнал. – 2016. 21 (5). – с. 271-274.

[7] Alçı, E., Şahin, G.A. Tiroid Nodüllerinin Yönetiminde İnce İğne Aspirasyon Biyopsisine Ne Zaman ve Ne Kadar Güvenmeliyiz? // Van Sag. Bil. Derg. –2023, 16(2), – s.168-175.

[8] Pusztaszeri, M. The Bethesda System for Reporting Thyroid Cytopathology: Proposed Modifications and Updates for the Second Edition from an International Panel. / M. Pusztaszeri, ED. Rossi, M. Auger [et al.] // Acta Cytol., – 2016, 60(5), – p. 399-405.

[9] Yamamoto, M. Active Surveillance Outcomes of Patients with Low-Risk Papillary Thyroid Microcarcinoma According to Levothyroxine Treatment Status / M. Yamamoto, Miyauchi, A, İto, Y // Thyroid. – 2023. 33 (10). – p. 1182-1189.

According to various authors, the use of this unified system facilitates patient evaluation and assists physicians in selecting the optimal management strategy (biopsy, surgery, or observation) for thyroid nodules[10,11].However, certain limitations must be taken into account, such as low sensitivity in follicular carcinomas, operator dependency, and uncertainty in some types of nodules. For optimal results, TIRADS should be used in combination with other diagnostic methods[11]. In fact, no single ultrasound feature or examination method alone allows for a reliable distinction between benign and malignant nodules.

Some authors have highlighted the role of thyroid elastography, a method that noninvasively assesses tissue stiffness and increases the sensitivity and specificity of ultrasound in detecting malignant nodules, in the diagnosis of nodular goiter, particularly in cases with intermediate or non-diagnostic cytology[12,13]. Although ultrasound elastography results are considered useful only when applied in addition to B-mode ultrasound findings, due to technical and clinical limitations, its combined use with other diagnostic methods is recommended for optimal outcomes. However, guidelines defining its indications for FNAB have not yet been fully established. The treatment of nodular goiter encompasses a range of surgical options, from traditional thyroidectomy to minimally invasive techniques.

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[10] Тимофеева, Л.А. Мультипараметрическое ультразвуковое исследование с применением классификации TIRADS в определении диагностической тактики при тиреоидных узловых образованиях / Л.А. Тимофеева, А.Н. Сенча - Практическая медицина. Современные вопросы диагностике, – 2018. 1(120). – с. 134-139.

[11] Chaigneau, E. TIRADS score is of limited clinical value for risk stratification of indeterminate cytological results / E. Chaigneau, G. Russ, B. Royer [et al.] // Eur. J. Endocrinol. – 2018, 179(1), – p. 13–20.

[12] Hussein, HO. Role of elastography strain ratio and TIRADS score in predicting malignant thyroid nodule / H.O. Hussein , M. Mona , S. Nermine [et al.] // Arch Endocrinol Metab. – 2020. 64 (6). – p. 735–742.

[13] Hairu, L. Elastography for the diagnosis of high-suspicion thyroid nodules based on the 2015 American Thyroid Association guidelines: a multicenter study /L.Hauri, P. Yulan, W. Yan [et/al] // BMC Endocrine Disorders. – 2020. Apr 3. – p. 20-43.

The choice of method depends on the characteristics of the nodule and clinical indications. In general surgical clinics, the frequency of thyroid surgeries is particularly high, especially in countries with endemic regions[14]. As a functionally important organ, surgical interventions on the thyroid require special skills, proficiency, technical expertise, and extensive experience[14]. Over the past decade, total thyroidectomy has been increasingly performed, and during its course, clinically significant complications such as bleeding, injury to the laryngeal nerves, and damage to the parathyroid glands may occur. These complications not only prolong hospital stay and increase the need for biochemical testing but also negatively impact quality of life[15,16]. Nowadays, most surgeons use the extracapsular total thyroidectomy technique to carefully visualize and preserve critical anatomical structures (laryngeal nerves, parathyroid glands, etc.), aiming to significantly reduce the incidence of the aforementioned complications and improve patients' quality of life[14,15]. However, according to various authors and the results of scientific studies, the rates of complications are as follows: hemorrhage 0.25–2.3%, permanent hypoparathyroidism 0.6–3.8%, transient hypoparathyroidism 20–70%, transient recurrent laryngeal nerve palsy 0.4–12%, and permanent paralysis 1–5%[14-16].

In most cases, the choice of surgical technique depends on the surgeon's experience and the characteristics of the disease. Numerous useful maneuvers have been proposed to facilitate the surgeon's work.

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[14] Jin, Sh., Sugitani İ. Narrative review of management of thyroid surgery complicarions // Gland Surgery. – 2021, 10(3), – p.1135-1146

[15] Emre, F.Y. Evaluation of Thyroidectomy Results Performed at a Tertiary Academic Center/ F.Y. Emre, E. Doğan, P. Keskinoğlu [et al.] // Turk Arch Otorhinolaryngol. – 2023. 61 (3). – p. 118-123

[16] Mejia MG1 , Gonzalez-Devia D, Fierro F , Tapiero M , Rojas L and Cadena E. Hypocalcemia posthyroidectomy: prevention, diagnosis and management // J Transl Sci. – 2018. 4(2). – p.1-7.

However, although the thyroidectomy technique is well described, differences in the sequence of applied methods remain. To date, no optimal approach has been established that could significantly reduce complications and operative time.The use of minimally invasive, organ-preserving techniques remains relevant in the treatment of cystic and benign solid thyroid nodules[17,18]. However, among surgeons, a unified approach has not yet been developed regarding the management strategy for this category of patients, as well as the indications and contraindications for minimally invasive interventions.

Many issues related to hormone replacement therapy with levothyroxine (LT4) after thyroidectomy remain unresolved. Levothyroxine, the hormone of the thyroid gland, performs essential physiological functions in the body, and its circulating concentration must be maintained within a precise range. The selection of an adequate LT4 dose depends on numerous critical factors, including age, sex, body weight, menopausal status, concomitant medications, the nature of food and beverages, coexisting gastrointestinal disorders, and metabolic diseases (such as diabetes mellitus, obesity, etc.). The duration of LT4 action and its half-life decrease in the second half of the day, which can reduce patients' work capacity. As a result, in some cases, an increase in the daily dose of the medication becomes necessary, which may raise the risk of adverse effects (such as angina, atrial arrhythmias, osteoporosis, and bone fractures). The only practical factor affecting patients' quality of life is the necessity of daily levothyroxine intake[19]. bloodstream.

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[17] Catherine, F.S. General Principles for the Safe Performance, Training, and Adoption of Ablation Techniques for Benign Thyroid Nodules / F.S. Catherine, H.B. Jung, E.H. Kathleen [et al.] // An American Thyroid Association Statement Thyroid, - 2023. 33 (10), – p. 1150-1170.

[18] Hahn, S.Y. Ethanol ablation of the thyroid nodules: 2018 Consensus statement by the Korean Society of Thyroid Radiology / S.Y.Hahn, J.H. Shin, D.G. Na, E.J.Ha[et al.] // Korean J Radiol. – 2019. 20 (4). – p. 609–620.

[19] Liu, H. Levothyroxine: Conventional and Novel Drug Delivery Formulations / H. Liu, W. Li, W. Zhang [et al.] // Endocrine Reviews, – 2023. 44. – p. 393-416.

[20] Ghazi, R.F. Levothyroxine sodium loaded dissolving microneedle arrays for transdermal delivery / R.F. Ghazi, M.H. Al-Mayahy // ADMET and DMPK, – 2022. 10 (3), –p. 213-230.

Chemical polymer carriers are capable of controlling the kinetics of drugs in the body, ensuring their gradual increase in plasma and the long-term maintenance of concentration levels, thereby enhancing therapeutic efficacy.

Therefore, there is a need for new drug formulations that can maintain a long-term effective concentration of LT4 in the The use of biopolymer carriers allows for a reduction in the drug dose and frequency of administration, while improving its absorption[19].

Thus, the absence of a universally accepted doctrine for selecting indications for FNAB in the diagnosis of thyroid nodules, the incomplete development of techniques and reliable technical skills for the safe preservation of the laryngeal nerve and surrounding thyroid glands during thyroidectomy, the lack of standardized treatment principles for physical and chemical ablation, and the inability to maintain long-term stable concentrations of replacement levothyroxine after surgery have highlighted the necessity of conducting new research in these areas.

Object and Subject of the Research

The epidemiological object of this research was the ultrasound examination of the thyroid gland and iodine intake data of 273 schoolchildren aged 14–17 years, conducted in 2018 in the same geographic zone of the Azerbaijan Republic (Gabala, Guba, and Sheki).

The clinical object of this study consisted of data from 713 patients with nodular goiter who underwent diagnostic and treatment management at the Educational-Surgical Clinic of Azerbaijan Medical University and Real Hospital from 2015 to 2024. The patients included in the study were divided into two groups based on diagnostic methods. Group I (comparison group) comprised 200 patients who sought care between 2015 and 2018. Examination of these patients was carried out according to a standard protocol: nodules were evaluated using the TIRADS classification, FNAB samples were obtained from “suspicious” nodules, and an appropriate management strategy—dynamic monitoring by ultrasound, minimally invasive, or

surgical treatment—was selected based on nodule size and cytological results.

Group II (main group) included 513 patients during the period from 2019 to 2024. The patients of this group were further divided into two subgroups: in Subgroup II^a (n = 140), in addition to conventional examinations, nodules were evaluated by ultrasound using the TIRADS classification, followed by the application of compression elastography (CSE). Based on the results of these diagnostic methods, appropriate management strategies—dynamic monitoring by ultrasound, minimally invasive, or open surgical treatment—were selected. In Subgroup II^b (n = 373), in addition to conventional examinations, nodules were assessed using the TIRADS classification, and CSE was performed. Under CSE guidance, FNAB was applied to the stiff areas of the nodules, after which appropriate management strategies—dynamic monitoring, minimally invasive, or open surgical treatment—were selected.

The outcomes of 38 patients aged 26–64 years (31 women, 7 men) who underwent invasive treatment were analyzed. Sclerotherapy was performed in 28 patients with cystic-colloid nodules, while intranodular laser ablation was carried out in 10 patients with benign solid nodules. The patients who underwent sclerotherapy were divided into two groups: in Group I, 15 patients with cystic-colloid nodules received standard sclerotherapy with a 95% ethanol solution; in Group II, 13 patients with cystic-colloid nodules underwent improved single-session sclerotherapy with multiple re-aspirations using a 95% ethanol solution.

The results of 361 patients included in our study who underwent surgical intervention were analyzed. Among them, 143 patients who underwent total thyroidectomy were divided into two subgroups. Among the 143 patients who underwent total thyroidectomy, two subgroups were distinguished: Subgroup I consisted of 67 patients who underwent conventional total thyroidectomy, while Subgroup II included 76 patients who underwent modified extrafascial thyroidectomy. Both subgroups were comparatively evaluated through prospective studies in terms of

intraoperative and postoperative complications, as well as operation duration.

The experimental part of the research was conducted at the laboratory of the Institute of Catalysis and Inorganic Chemistry named after Acad. M. Nagiyev of Ministry of Science and Education of the Azerbaijan Republic. The object of the study was the newly synthesized levothyroxine/biopolymer complex. The acute toxicity of this compound was evaluated in 80 white mice, while chronic toxicity was assessed in 30 laboratory white rats. The absorption of the levothyroxine/biopolymer complex in the small intestine, its effect on TSH and free T4 hormones, as well as the quantitative analysis of the active substance in the blood, were investigated in six white rabbits of the "Chinchilla" breed with experimentally induced hypothyroidism.

Research Purpose: To determine the prevalence of thyroid gland pathologies in endemic regions after the introduction of iodized salt prophylaxis, to optimize treatment approaches through the improvement of diagnostic methods for various clinical and morphological forms of nodular goiter, and to conduct experimental studies on a novel long-acting form of levothyroxine for hypothyroidism correction.

Research Tasks:

1. To investigate the prevalence of thyroid gland pathologies by ultrasonography against the background of iodized table salt consumption in certain endemic regions of the Azerbaijan Republic (Gabala, Sheki, Guba);
2. To assess the degrees of iodine deficiency by determining urinary iodine levels against the background of iodized table salt consumption in certain endemic regions of the Azerbaijan Republic (Gabala, Sheki, Guba);
3. Comparative evaluation of the results in patients with thyroid nodular lesions assessed by the TIRADS classification using US-guided FNAB, FNAB under compression elastography guidance, and CSE alone;
4. Comparative analysis of outcomes in patients with cystic-colloid thyroid nodules selected for minimally invasive organ-preserving

intervention, following traditional sclerotherapy and modified single-session multiple reaspiration sclerotherapy, based on diagnostic criteria;

5. Development of a modified technique of extrafascial total thyroidectomy for the surgical management of various forms of nodular goiter, and comparative evaluation of its outcomes with conventional total thyroidectomy in terms of operation duration and complication rates;
6. Investigation of the dynamics of levothyroxine release from experimentally prepared chitosan/arabinogalactan-based levothyroxine-Na pentahydrate samples using a spectrophotometric method;
7. Investigation of the toxicity of chitosan/arabinogalactan-based levothyroxine-Na pentahydrate biopolymer in experimental studies on mice;
8. Investigation of the quantitative analysis of the active substance using high-performance liquid chromatography (HPLC) after administration of the new levothyroxine-biopolymer complex in rabbits with experimentally induced hypothyroidism created by total thyroidectomy.

Research methods: The dissertation was carried out in several stages. The main focus of the first stage was the epidemiological study of thyroid gland diseases among schoolchildren in the endemic northern regions of Azerbaijan (Gabala, Guba, and Sheki districts) following prophylactic intake of iodized table salt, along with the assessment of urinary iodine levels. In the second stage, a long-acting levothyroxine-chitosan/arabinogalactan biopolymer/levothyroxine complex was developed in the laboratory of the Institute of Catalysis and Inorganic Chemistry named after Acad. M. Nagiyev of the Ministry of Science and Education of the Republic of Azerbaijan (MSE AR). Its primary indicators of acute and chronic toxicity were evaluated in white mice at the Scientific Research Center of Azerbaijan Medical University.

In the laboratory of the Department of Pharmaceutical Chemistry at AMU, an experimental hypothyroidism model was

established in rabbits, and the amount of levothyroxine in their blood samples was analyzed using HPLC. The release time of levothyroxine sodium pentahydrate from a chitosan/arabogalactan-based levothyroxine-Na pentahydrate biocomplex nanogel was evaluated spectrophotometrically, and its effect on thyroid hormone levels was investigated.

In the third phase of the study, the examination and treatment outcomes of 713 patients aged 16–91 years from both sexes were analyzed. The patients' examination algorithm included traditional general-clinical (objective) assessments, evaluation of hormonal status, classification of detected thyroid nodules according to the TIRADS system, assessment by compression elastography, and fine-needle aspiration biopsy of "suspicious" nodules.

When evaluating the short- and long-term outcomes of minimally invasive methods and surgical operations, parameters such as nodule size reduction dynamics, recurrence, duration of surgery, bleeding, injury to the recurrent laryngeal nerve, hypocalcemia, etc., were investigated.

Main points submitted for defense:

– In the endemic regions of the Azerbaijan Republic (Gabala, Sheki, Guba), under the condition of iodized salt intake, the early identification of the severity of iodine deficiency in schoolchildren based on urinary iodine levels provides broad opportunities for implementing corrective and preventive measures for the detected disorders.

– The combined use of FNAB and compression elastography in thyroid nodules evaluated according to the TIRADS classification can provide more accurate and reliable results in terms of malignancy.

– In the treatment of cystic-colloid multinodular goiter, the clinical application of the improved single-session multiple reaspiration sclerotherapy method, compared to traditional sclerotherapy, has led to a significant reduction in recurrence and can be used with great success.

– In the surgical treatment of various forms of nodular goiter, the proposed modification of the extracapsular total thyroidectomy

technique provides the basis for reducing operation time and minimizing complications related to the recurrent laryngeal nerves and parathyroid glands by allowing manipulations to be performed comfortably, safely, and reliably. This method offers broad opportunities for clinical application.

– After preparing solutions for the measurement of optical density, it was proven by spectrophotometry and high-performance liquid chromatography methods in rabbits, in which a hypothyroidism model was created by total thyroidectomy, that it is possible to ensure long-term concentration of levothyroxine in the blood by applying its immobilized compound on a new biocidal nanogel carrier containing chitosan arabinogalactan.

Scientific novelty of the research:

1. For the first time in the endemic regions of the Azerbaijan Republic (Gabala, Sheki, Guba), the prevalence of thyroid pathologies in schoolchildren was determined using ultrasonography against the background of iodized salt intake. At the same time, the severity of iodine deficiency in this population was assessed based on urinary iodine levels, and measures for the correction of the detected disorders were developed and proposed.
2. Based on diagnostic criteria, an improved single-session multiple reaspiration sclerotherapy technique has been developed for minimally invasive, organ-preserving intervention in patients with cystic-colloid nodules.
3. An improved modification of the total thyroidectomy technique (Eurasian Patent No. 048306, 18.11.2024) for the surgical treatment of various forms of nodular goiter has been developed, and its impact on operation duration as well as complications related to the laryngeal nerves and parathyroid glands has been investigated.
4. A new chitosan/arabogalactan-based compound of levothyroxine with prolonged action has been developed (Eurasian Patent No. 046579, 27.03.2024), and experimental studies have been conducted on animals with an induced hypothyroidism model.

Theoretical and practical significance of the research:

– In the endemic regions of the Azerbaijan Republic (Gabala, Sheki, Guba), the severity of iodine deficiency in schoolchildren was determined based on urinary iodine levels under the condition of iodized salt intake, and preventive measures for the correction of the identified disorders were developed and proposed.

– To improve the early diagnosis of thyroid nodules evaluated by the TIRADS classification, puncture points were specified in the stiffer areas of the nodule under compression elastography, which resulted in an increased detection rate of malignant nodules and a reduction in false-negative results.

– An improved single-session multiple reaspiration sclerotherapy method has been developed and recommended for clinical practice in order to reduce the incidence of recurrences in the treatment of cystic-colloid nodular goiter.

– In order to reduce the incidence of complications related to the laryngeal nerves and parathyroid glands, the technique of extrafascial total thyroidectomy has been improved and implemented in clinical practice.

– A chitosan/arabogalactan-based biocidal nanogel with prolonged action of levothyroxine, applicable in the treatment of patients with hypothyroidism, has been developed. In experimental studies, its acute and chronic toxicity was investigated in mice, and its positive effect on TSH and T4 hormone levels was evaluated in hypothyroid rabbits. Furthermore, using HPLC, the prolonged presence of levothyroxine sodium pentahydrate in the blood was confirmed, and spectrophotometric analysis demonstrated that its concentration remained at a high level for 72 hours.

– The results of the study can be applied in the practical work of surgical, endocrinological, and radiological units and departments of polyclinics and hospitals. At the same time, the study materials can be incorporated into relevant sections of teaching aids, tutorials,

and monographs, and thus be widely used in the educational process.

Approbation of the research

The scientific findings of the study have been presented at the University, Republican, and international scientific-practical conferences:

The 100th Anniversary Conference of the Azerbaijan Democratic Republic dedicated to "Current Issues in Medicine" (Baku, 2018); 8th Turkish Thyroid Diseases Congress (Ankara, Turkiye, 2018); 21st National Surgery Congress (Antalya, Turkiye, 2018); 17th Postgraduate Medical Surgical Endocrinology Training Course (November 1–4, Antalya, Turkiye, 2018); International Scientific-Practical Internet Conference "Advances in Surgery" (November 1, 2019 – Baku-Minsk); Abstracts of the XVIII International Euroasion Congress of Surgery and Hepatogastroenterology (11-14 sentyabr 2019, Baku); Congress on "Current Issues in Medicine" dedicated to the 90th Anniversary of Azerbaijan Medical University (December 19–20, 2020, Baku); Congress on "Current Issues in Medicine" dedicated to the 100th Anniversary of Honored Scientist, Professor Tamerlan Aziz oglu Aliyev (October 6–8, 2021, Baku); International Scientific-Practical Conference on "New Methods in the Diagnosis and Treatment of Surgical Diseases" dedicated to the 100th Anniversary of the 3rd Department of Surgical Diseases (December 16–17, 2022, Baku); 1st International Medical Forum (June 18–21, 2022, Nakhchivan); International Thyroidology Conference on "Thyroid Problems: Scientific Perspectives and Modern Approaches" (February 12, 2022, Baku); International Scientific-Practical Conference dedicated to the 100th Anniversary of Honored Scientist, Professor H. A. Sultanov (2022, Baku); 22nd National Surgery Congress (March 23–27, 2022, Antalya, Turkiye); International Scientific-Practical Conference on "Contemporary Medicine: Innovations and Modern Approaches" dedicated to the 100th Anniversary of National Leader Heydar Aliyev (2023, Baku); Seminar on "Modern Approaches in the Diagnosis of Thyroid Nodules" (March 10, 2023, Baku); 11th National Endocrine

Surgery Congress (March 16–19, 2023, Antalya, Turkiye). American Thyroid Association Annual Meeting (September 27 – October 1, 2023, Washington, USA); 1st National Endocrinology Conference (May 24–26, 2024, Baku); 12th National Endocrine Surgery Congress (February 13–16, 2025, Antalya, Turkiye); Medical Festival dedicated to the 102nd Anniversary of National Leader Heydar Aliyev and the 95th Anniversary of Azerbaijan Medical University (May 6–8, 2025, Baku); 11th European Society of Endocrine Surgeons Congress (ESESMIR) (May 22–24, 2025, Izmir, Turkiye); 7th Regional Conference of the Azerbaijan Society of Minimally Invasive Surgeons (June 21, 2025, Ganja).

- An interdepartmental discussion was held at the 1st Department of Surgical Diseases of Azerbaijan Medical University (April 23, 2025, Protocol No. 09);
- It was discussed at the Scientific Seminar of the ED 2.06 Dissertation Council operating under Azerbaijan Medical University (June 3, 2025, Protocol No. 8).

Application of the research results. The main provisions and findings of the dissertation have been implemented in the practical activities at the 1st Department of Surgical Diseases of the Azerbaijan Medical University and Real Hospital.

Organization where the dissertation work was conducted. The dissertation work was carried out at the "Nanostructured Processed Polymer Catalysts" Laboratory of the Institute of Catalysis and Inorganic Chemistry named after Acad. M. Nagiev of the Ministry of Science and Education of the Republic of Azerbaijan, at the laboratories of the Scientific-Research Center and the Department of Pharmaceutical Chemistry of Azerbaijan Medical University, as well as at the Educational-Surgical Clinic of Azerbaijan Medical University and Real Hospital (Baku).

Publications. A total of 27 journal articles and 30 theses related to the topic of the dissertation have been published in periodical scientific publications. Two international patents (Eurasian Patent No. 046579, March 27, 2024; Eurasian Patent No. 048306, November 18, 2024, Moscow) and two certificate (Azerbaijan

Republic Intellectual Property Agency, Baku, No. 13528; No.15201) have been obtained.

Volume and Structure of the Work: The dissertation is written in Azerbaijani on A4 paper, using "Times New Roman" font, size 14, with 1.5 line spacing. It consists of the following sections: Table of Contents (10,792 characters), Introduction (25,411 characters), Literature Review (74,458 characters), Chapter II on Materials and Methods of the Research (69,290 characters), Chapters III, IV, V, VI, VII (23,673 + 51,609 + 45,778 + 44,022 + 17,240 characters), Conclusion (50,161 characters), Results (3,548 characters), and Practical Recommendations (1,345 characters), totaling 329 pages with 417,327 characters. The References list includes 38 national and 300 foreign sources (338 in total). The research work is illustrated with 79 tables, 13 graphs, and 66 figures.

MATERIALS AND METHODS

The epidemiological material of the scientific research consisted of 273 students in grades 9–11 in 2018. The clinical material included 713 patients diagnosed with nodular goiter who were examined and treated between 2015 and 2024 at the Educational-Surgical Clinic based at the 1st Department of Surgical Diseases of Azerbaijan Medical University and at Real Hospital in Baku.

The experimental material consisted of 80 outbred white mice of both sexes weighing 18–22 g and 6 white rabbits of the "Chinchilla" breed with an average weight of 3.5±0.5 kg, all housed at the Central Scientific-Research Laboratory of Azerbaijan Medical University. Inter-institutional agreements and ethical committee approval were obtained for conducting the medical research.

The epidemiological subjects of the study consisted of examination data from 273 schoolchildren (144 girls, 129 boys) aged 14–17 years, residing in the same geographical zone of the Azerbaijan Republic (the districts of Gabala, Guba, and Sheki). After measuring

and recording the students' anthropometric indicators (height, weight) at the school medical office, an initial thyroid examination and ultrasound were performed using the palpation method recommended by the WHO. To determine the prevalence and severity of iodine deficiency, the level of iodine excretion in urine was studied. The method for determining iodine in urine is based on a color reaction involving the iodide ion, which acts as a catalyst in the reaction between a non-toxic amine (tetramethylbenzidine) and an acid containing active peroxide (peracetic acid). As a result of the reaction, the urine samples changed color depending on the amount of iodine present, ranging from yellow to blue, thereby allowing the quantification of iodine in the urine.

The clinical subjects of the study consisted of examination and treatment data from 713 patients with nodular goiter who had undergone various treatment methods. FNAB was performed in 558 patients, 38 patients received minimally invasive treatments, 361 patients underwent surgical operations, and 314 patients were managed with dynamic monitoring and conservative treatment methods. The patients' laboratory examination algorithm included standard tests: complete blood count and biochemical analyses, TSH, free T3, free T4 hormones, calcium, antibodies against thyroid tissue (anti-Tg, anti-TPO), hemocoagulogram, etc.

In all patients, ultrasound examination was performed to assess the characteristics of the nodules and their relationship with surrounding anatomical structures, using the "Toshiba Aplio 650" (Japan) and "Sonoscape S9 Pro2" (China) ultrasound devices equipped with a linear transducer operating at a frequency of 12–14 MHz. The detected nodules were evaluated according to the TIRADS (Russ.G.) classification.

To assess the elasticity of nodules detected in the thyroid gland, CSE was performed using an ultrasound transducer, and the findings were evaluated according to the Rago T. and Asteria C. scoring systems.

FNAB was performed under ultrasound guidance in aseptic conditions using 22-gauge, 5 ml syringes. The material obtained from

the aspiration was evenly spread on a glass slide, air-dried at 18–22 °C, and subsequently stained with Hematoxylin-Eosin. Cytological and histopathological examinations were performed in the Pathomorphology laboratory of the Oncology Clinic of the Medical University and the Scientific Surgery Center named after Acad. M.A. Topchubashov.

For histological examination, multiple tissue samples were primarily taken from the pathological nodules and their tissues, including the nodule capsule and surgical margins. The tissue samples were fixed in 0.1% neutral formalin solution, then processed through a series of specific fixatives, and paraffin blocks were prepared from them. Histological sections 5–8 μm thick were obtained from the paraffin blocks using an ultramicrotome and subsequently stained with Hematoxylin-Eosin and Picrosirius (Van Gieson method). The purpose of staining the preparations with Picrosirius was to determine the ratio of fibrotic changes (fibrous tissue) to the parenchyma in the thyroid gland in cases of chronic thyroiditis.

In patients with nodular cystic goiter, standard and single-session multiple reaspiration sclerotherapy using 95% ethanol solution was performed on an outpatient basis. For the laser ablation of benign solid nodules, a Biolitec device (Germany) was used, employing diode lasers with Nd:YAG or Nd:$Y_3Al_5O_{12}$ crystals. The laser radiation had a wavelength of 980 nm; the device output power was approximately 4–5 W; the diameter of the laser fiber was 0.40 mm, and the energy delivered per milliliter of tissue was at least 500–600 J/mL, with a maximum of 1200 J.

In 143 patients who underwent total thyroidectomy, intraoperative monitoring of the recurrent laryngeal nerve was performed using a Dr. LANGER AVALANCHE device (Germany). In cases where postoperative vocal cord paralysis (VCP) developed, the diagnosis was confirmed by an otorhinolaryngologist through laryngoscopic examination. Patients who developed postoperative hypocalcemia were kept under observation, and both hypocalcemia symptoms and laboratory findings were dynamically evaluated.

In our study, the synthesis of hydrogel and the immobilization of levothyroxine-Na through processing mixtures of chitosan with arabinogalactan (AG) at different mass ratios under low temperatures were carried out at Laboratory No. 9, Nanostructured Metal Polymer Catalysts, of the Institute of Catalysis and Inorganic Chemistry named after Academician M.F. Naghiyev (MS AR).

The release time of levothyroxine-Na pentahydrate from the prepared chitosan/arabinogalactan-based nanogel biocomplex containing levothyroxine-Na pentahydrate was determined by a spectrophotometric method ("Agilent Technologies Cary 60 UV-Vis," USA spectrophotometer) and studied in the laboratory of the Department of Pharmaceutical Chemistry at Azerbaijan Medical University.

The acute and chronic toxicity of the newly synthesized levothyroxine/biopolymer complex was studied on mice and rats in the laboratory of the Scientific Research Center of Azerbaijan Medical University.

The absorption of the newly synthesized levothyroxine/biopolymer complex from the small intestine and its effects on TSH and free T4 hormones were studied in white rabbits of the "Chinchilla" breed with an induced "hypothyroidism" model. On days 3, 5, and 7, fasting blood samples were collected, and the plasma levels of TSH and free T4 hormones were measured using the immunoenzymatic (ELISA) method on a "BioScreen MS-500" (USA) device with a test system from the company "XEMA" (Germany). In addition, to study the long-term activity and concentration of levothyroxine in the blood, quantitative analysis of the same blood samples was carried out using HPLC with a UV detector on an "HPLC-Agilent 1260" chromatograph (USA) in the laboratory of the Department of Pharmaceutical Chemistry at Azerbaijan Medical University.

For statistical processing (calculations) of the obtained results, Statistica 8.0 and SPSS 16.0 software were used. Before starting the statistical analysis, the distribution law of quantitative variables was examined using the Shapiro–Wilk test and distribution histograms. In most groups, the variables were found not to follow a normal distribution. The comparison of quantitative variables between two independent

groups was performed using the nonparametric Mann–Whitney test. For related groups, in other words, to analyze changes in the same patients before and after treatment, the paired Wilcoxon test was used. For the interpretation of quantitative variables, descriptive statistics – mean and standard deviation (M ± s) – were calculated. Analysis of tables of close relatives (parents, siblings) was performed by calculating the χ^2 (Pearson test) statistic for qualitative features (e.g., US appearance, number of lesions, etc.).When the size of the tables of close relatives was 2×2, Yates' continuity correction was applied. For the interpretation of qualitative variables, absolute values and their percentages were calculated as descriptive statistics. To characterize the diagnostic performance of ultrasound features, their sensitivity, specificity, positive and negative predictive values, and accuracy were calculated using the corresponding formulas in accordance with the principles of evidence-based medicine. A significance level of $p < 0.05$ was considered statistically significant.

Analysis of Obtained Results

In accordance with the objectives of the study, the epidemiological structure of iodine deficiency and thyroid diseases was investigated in three pilot districts (Gabala, Guba, and Sheki) located in the same geographic zone of the Republic of Azerbaijan. The study population included 273 school-aged children (14–17 years), both boys and girls.

In the Gabala district, 90 schoolchildren (32.9%) were examined, including 35 boys (38.9%) and 55 girls (61.1%). In the Guba district, 82 schoolchildren (30.0%) were studied, of whom 27 were boys (32.9%) and 55 were girls (67.1%). In the Sheki district, 101 schoolchildren (37.0%) participated in the examination, including 67 boys (66.3%) and 34 girls (33.7%). Overall, across these districts, a total of 144 girls (52.7%) and 129 boys (47.3%) were examined for thyroid pathology. The number of schoolchildren by sex differed significantly across districts ($\chi^2 = 24.036$, $p = 0.000$).

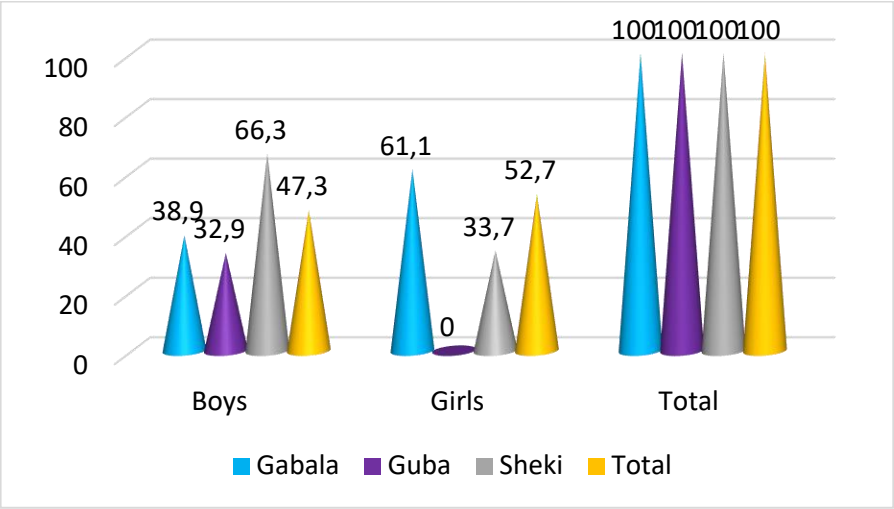


Figure 1. Overall distribution of schoolchildren examined for thyroid gland pathologies in the northern districts of the Azerbaijan Republic

In the Gabala district, thyroid ultrasound (US) revealed a normal thyroid structure in 58 students (64.4%). In the Guba district, 50 students (61.0%) and in the Sheki district, 83 students (82.2%) showed no organic thyroid pathology on US. In general, in 191 students (70%) who underwent US across these districts, the thyroid gland demonstrated a normal structure. In total, 82 students (30%) exhibited various pathological changes in the thyroid during the US examination.

The prevalence of different forms of thyroid pathology identified by US was also studied by districts. The frequency of nodular colloid goiter was 24.4% (n = 22) among students in Gabala, 12.2% (n = 10) in Guba, and 9.9% (n = 10) in Sheki. That is, the prevalence of thyroid pathologies among schoolchildren in the Gabala district was twice as high compared to the two neighboring districts. Exographic signs of thyroiditis were observed in 8 students (8.9%) in Gabala, 17 students (20.7%) in Guba, and 5 students (5.0%) in Sheki.

Solid nodules were detected in 2 students (2.4%) in Guba and 1 student (1.0%) in Sheki. Thyroid hyperplasia was found in 2 students (2.2%) in Gabala, and in 1 student each in Guba (1.2%) and Sheki (1.0%). Thyroid hypoplasia was identified in 2 students (2.4%) in Guba and 1 student (1.0%) in Sheki. A statistically significant difference in the prevalence of thyroid pathologies among students from the Guba, Sheki, and Gabala districts was observed ($\chi^2 = 26.827$, $p \leq 0.05$) (Table 1).

Table 1. Structure and prevalence of thyroid gland pathologies based on ultrasound findings

Exostructure of the thyroid gland		Gabala	Guba	Sheki	Total
Normal TG	Absolute	58	50	83	191
	%	64.4	61.0	82.2	70.0
Colloid goiter	Absolute	22	10	10	42
	%	24.4	12.2	9.9	15.4
Thyroiditis	Absolute	8	17	5	30
	%	8.9	20.7	5.0	11.0
Solid nodule	Absolute	-	2	1	3
	%	-	2.4	1.0	1.1
Thyroid hyperplasia	Absolute	2	1	1	4
	%	2.2	1.2	1.0	1.5
Thyroid hypoplasia	Absolute	-	2	1	3
	%	-	2.4	1.0	1.1
Total	Absolute	90	82	101	273
	%	100.0	100.0	100.0	100.0

To determine the dependence of thyroid pathologies on hereditary and genetic factors, the prevalence of certain thyroid disorders among family members and close relatives of the examined schoolchildren was studied. In the Gabala district, 79 schoolchildren

(87.8%) had no family history of EG. This pathology was identified only in the family members and close relatives of 11 students (12.2%). In the Guba district, 58 schoolchildren (70.7%) had no family history of EG, while the family members and close relatives of 24 students (29.3%) had undergone treatment for EG. Among the Sheki district schoolchildren, 80 (79.2%) had no family history of EG, whereas in 21 (20.8%) cases, family members and close relatives had EG. According to anamnesis, among the families and close relatives of 217 schoolchildren (79.5%), the absence of thyroid pathology - endemic goiter (EG) was reported, whereas in 56 cases (20.5%) it was confirmed. A statistically significant difference was found between the number of schoolchildren with EG in their family (or close relatives) and the prevalence rates in the respective districts ($\chi^2 = 7.654$, $p \leq 0.05$).

To assess the functional and metabolic status of the thyroid gland under the prophylaxis of iodized table salt, urinary iodine excretion was measured in the examined schoolchildren. For this purpose, the iodine content in the urine of 189 schoolchildren from the region was determined in the laboratory. Normal urinary iodine levels (100–300 μg/L) were found in 17 students (29.8%) in the Guba district, 43 students (64.2%) in the Sheki district, and 34 students (52.3%) in the Gabala district. Overall, a total of 94 schoolchildren (49.7%) across the districts had no iodine deficiency. Among 95 schoolchildren from the region (50.3%), varying degrees of iodine deficiency were detected. Severe iodine deficiency (urinary iodine < 70 μg/L) was observed in 12.2% overall: 15.4% in Gabala, 21.1% in Guba, and 1.5% in Sheki. Mild iodine deficiency (urinary iodine 70–99 μg/L) was found in 21.2% overall: 10.8% in Gabala, 42.1% in Guba, and 13.4% in Sheki. Excess urinary iodine (>300 μg/L) was identified in 16.9% of students. A statistically significant difference was observed between the epidemiological status of urinary iodine excretion and the number of students across the districts ($\chi^2 = 39.732$, $p \leq 0.05$) (Table 2).

Table 2

Urinary iodine excretion levels in schoolchildren

Level of ioduria		Gabala	Guba	Sheki	Total
Normal (100-300 m kg/L)	Absolute	34	17	43	94
	%	52.3	29.8	64.2	49.7
Severe iodine deficiency (<70 m kg/L)	Absolute	10	12	1	23
	%	15.4	21.1	1.5	12.2
Mild iodine deficiency (70-99 m kg/L)	Absolute	7	24	9	40
	%	10.8	42.1	13.4	21.2
Excess iodine concentration (>300 m kg/L)	Absolute	14	4	14	32
	%	21.5	7.0	20.9	16.9
Total	Absolute	65	57	67	189
	%	100.0	100.0	100.0	100.0

A statistically significant difference was observed between the number of students in relation to sex and the characteristics of thyroid ultrasound (exostructure) findings ($\chi^2 = 11.951$; $p = 0.035$). On ultrasound examination, no pathological changes of the thyroid gland were detected in 191 schoolchildren (70.0%) (105 boys (55.0%), 86 girls (45.0%)) from the study cohort. This examination revealed nodular colloid goiter in 42 schoolchildren (28 girls (19.4%) and 14 boys (10.9%)). That is, nodular colloid goiter was found to be twice as common among girls compared to boys.

The presence or absence of EG in family history—among family members and close relatives—was examined according to the sex of the schoolchildren. In 217 schoolchildren (79.5%), there was no family (lifetime) history of EG. Among boys, EG was not observed in the family members and close relatives of 110 students (40.3% of all schoolchildren, 85.3% of the 129 boys examined in the region). In 107 schoolgirls (74.3%), EG was not observed in their family members and close relatives. A family (lifetime) history of EG was reported in 56 schoolchildren (20.5%) in total: Among girls, 25.7%, and among boys, 14.7% had no EG detected in their family members or close relatives. A statistically significant difference was observed between

the prevalence of EG in family members/relatives and the sex of the students ($\chi 2 = 5.02$, $p \leq 0.05$).

The urinary iodine excretion status was also analyzed according to sex, and no statistically significant differences were observed between these values and the number of students ($p = 0.107$).

In the dissertation, the studies concerning the analysis of correlations between the number of schoolchildren with structural changes on ultrasound examination and the levels of urinary iodine excretion have been extensively discussed.

Correlations between urinary iodine excretion levels and the number of students with structural changes detected on ultrasound were analyzed. No statistically significant differences in ioduria levels were found among students depending on the sonographic structural changes.

Table 3

Sex-specific prevalence of endemic goiter in family members and close relatives

Endemic goiter in family embers and close relatives	Frequency of occurrence	Boys	Girls	Total
Absent	Absolute	110	107	217
	%	85.3	74.3	79.5
Present	Absolute	19	37	56
	%	14.7	25.7	20.5
Total	Absolute	129	144	273

$\chi^2 = 5.018$, $p=0.025$.

In addition to studying the epidemiological status of EG in family history, iodine metabolism was also assessed in the examined schoolchildren. Among students whose family members and close relatives had no EG, severe iodine deficiency was observed in 12.8%, mild iodine deficiency in 19.9%, and excessive urinary iodine excretion in 17.0%. No statistically significant difference was found

in ioduria levels between students with and without EG in their family members or close relatives ($\chi^2 = 0.655$, $p = 0.884$) (Table 3).

In the clinical stage of the study, our main objective was to improve the differential diagnosis of thyroid nodules (TN) and optimize treatment outcomes by comparatively evaluating the diagnostic capabilities and results of various examination methods, including B-mode US, TIRADS classification, compression sonoelastography (CSE), and fine-needle aspiration biopsy (FNAB).

In the study group, women (629; 87.9%) were significantly more represented than men (84; 12.1%). In Group I, 89.0% were women and 11.0% were men; in Subgroup II^a, 90.0% were women; in Subgroup II^b, 87.1% were women.

Ultrasound features of thyroid nodules were evaluated comparatively and jointly with TIRADS classification, CSE indicators, cytological, and pathomorphological results.

Between 2015 and 2018, in Group I (control), the echographic signs (criteria) of thyroid nodules were retrospectively assessed in 200 patients according to the TIRADS criteria, and the results were evaluated as follows: TIRADS II in 1 patient (0.5%), TIRADS III in 165 patients (82.5%), TIRADS IV^a in 16 patients (8.0%), TIRADS IV^b in 17 patients (8.5%), and TIRADS V in 1 patient (0.5%). In this group, nodules were most frequently classified as TIRADS III.

FNAB was performed on 185 nodules, and the cytological examination results were analyzed according to the Bethesda classification. The cytological characteristics of the nodular lesions were as follows: Bethesda I in 10 samples (5.4%), Bethesda II in 120 samples (64.9%), Bethesda III in 19 samples (10.3%), Bethesda IV in 19 samples (13.3%), Bethesda V in 14 samples (7.6%), and Bethesda VI in 3 samples (1.6%).

Based on the data presented in Table 4, a total of 151 nodules classified as TIRADS III were biopsied. Among them, 10 (6.6%) were categorized as Bethesda I, 115 (76.2%) as Bethesda II, 15 (9.9%) as Bethesda IV, 7 (4.6%) as Bethesda IV, 3 (2.0%) as Bethesda V, and 1 (0.7%) as Bethesda VI.

Among the 15 nodules classified as TIRADS IV[a], 3 (20%) were categorized as Bethesda II, 1 (6.7%) as Bethesda III, 10 (66.7%) as Bethesda IV, and 1 (6.7%) as Bethesda V. Among the 17 nodules classified as TIRADS IV[b], 2 (11.8%) were categorized as Bethesda II, 2 (11.8%) as Bethesda III, 2 (11.8%) as Bethesda IV, 10 (58.8%) as Bethesda V, and 1 (5.9%) as Bethesda VI. The single nodule classified as TIRADS V was diagnosed as Bethesda VI. In the comparison group, a statistically significant difference was identified between the number of patients examined using both the TIRADS and Bethesda classifications ($\chi^2 = 206.213$; $p < 0.001$).

Table 4

Exosonographic and cytological characteristics of nodular neoplasms according to the TIRADS system and Bethesda classification (comparison group)

Bethesda		TIRADS				
		II	III	IVa	IVb	V
I	Absolute	0	10	0	0	0
	%	0.0	6.6	0.0	0.0	0.0
II	Absolute	0	115	3	2	0
	%	0.0	76.2	20.0	11.8	0.0
III	Absolute	1	15	1	2	0
	%	100.0	9.9	6.7	11.8	0.0
IV	Absolute	0	7	10	2	0
	%	0.0	4.6	66.7	11.8	0.0
V	Absolute	0	3	1	10	0
	%	0.0	2.0	6.7	58.8	0.0
VI	Absolute	0	1	0	1	1
	%	0.0	0.7	0.0	5.9	100

In Group I, the histological outcomes of surgical patients (n=79) were analyzed in relation to the malignancy risk according to the TIRADS classification system of echographic criteria. Based on

the TIRADS classification, 62 patients (78.5%) had benign and 17 patients (21.5%) had malignant pathohistological results. Among nodules classified as TIRADS II, III, IV[a], IV[b], and V, the rates of benign results were 100%, 92.5%, 90.0%, 21.4%, and 0.0%, respectively. Malignant histopathological results were detected in nodules classified as TIRADS II, III, IV[a], IV[b], and V in 0.0%, 7.5%, 10.0%, 78.6%, and 100% of cases, respectively. A statistically significant difference was observed between TIRADS criteria and benign/malignant histopathological outcomes ($\chi^2 = 37.816$; $p < 0.001$).

To evaluate the predictive potential of the TIRADS classification in patients of Group I, a ROC curve analysis was performed. Based on the analysis of data from 79 patients, a model was obtained. During the ROC analysis, the AUC (area under the curve) was calculated as 0.839 ± 0.067; 95% CI (0.708–0.969), p = 0.000. According to preliminary calculations, in the stratification of malignant nodules of the thyroid gland, in cases where TIRADS was greater than III, the sensitivity of TIRADS was 76.5 ± 10.3%, specificity 80.6 ± 5.0%, positive predictive value 52.0 ± 10.0%, and negative predictive value 92.6 ± 3.6%. The overall diagnostic accuracy (ODA) was 79.7 ± 4.5%, with a likelihood ratio for a positive result (LR+) of 3.95 (adequate) and a likelihood ratio for a negative result (LR–) of 0.29 (adequate) (Table 4.2.5). In cases with TIRADS greater than IV, the sensitivity of TIRADS was 70.6 ± 11.1%, specificity 95.2 ± 2.7%, positive predictive value 80.0 ± 10.3%, and negative predictive value 92.2 ± 3.4%. The ODA was 89.9 ± 3.4%, with LR+ of 14.6 and LR– of 0.31.

Considering that the area under the ROC curve is an integral measure of diagnostic performance, it can be stated that TIRADS demonstrated adequate predictive potential in thyroid cancer. The quality of the diagnostic test is high (AUC = 0.839).

In the comparison group, 79 patients underwent surgical intervention, and preoperative FNAB was performed in 69 of them. Among those operated, histopathological results were malignant in 16 cases (23.2%) and benign in 53 cases (76.3%). According to the data presented in Figure 2, histopathological results were benign in 2

(100%) patients with Bethesda I, 31 (93.9%) patients with Bethesda II, 7 (87.5%) patients with Bethesda III, 8 (66.7%) patients with Bethesda IV, 4 (36.4%) patients with Bethesda V, and 1 (33.3%) patient with Bethesda VI. Malignant histopathological results were identified in 0.0%, 6.1%, 12.5%, 33.3%, 63.6%, and 66.7% of these categories, respectively. A statistically significant difference was observed between the number of patients with Bethesda category II and those with Bethesda categories IV–VI in terms of benign and malignant histopathological outcomes ($\chi^2_{emp} = 20.533$, $p \leq 0.001$).

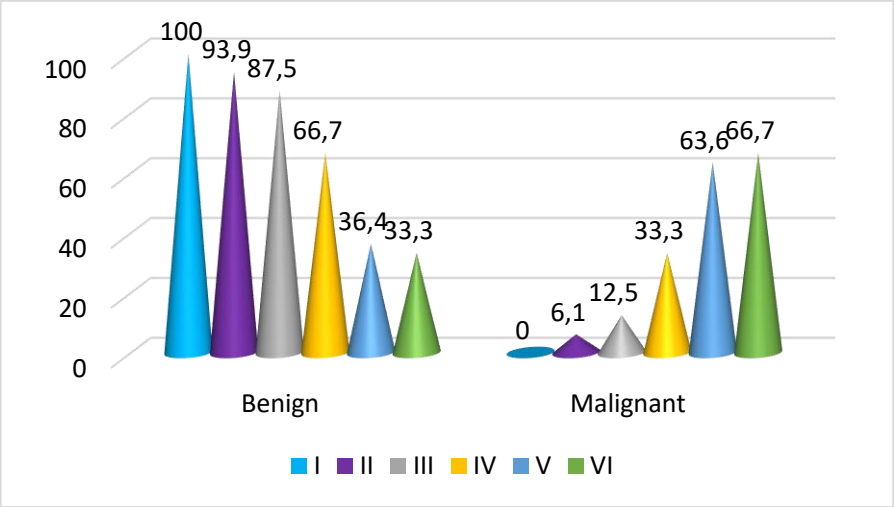
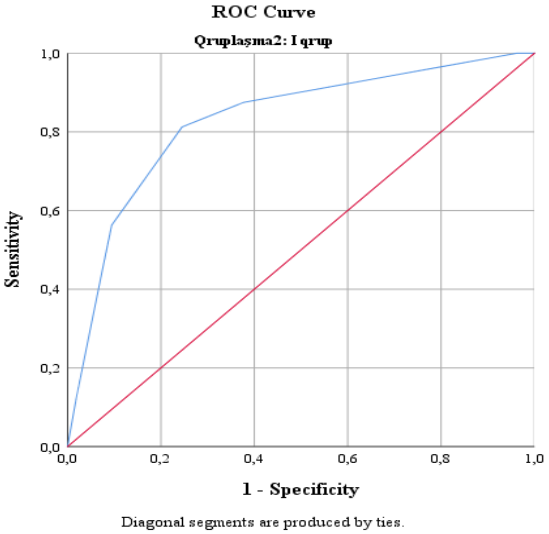


Figure 2. Distribution of patients by Bethesda classification according to histopathological results (comparison group)

In the comparison group, ROC analysis of FNAB yielded an AUC = 0.828 ± 0.061; 95% CI (0.709–0.948), p = 0.000. According to the results from our control group, in cases with Bethesda category greater than III, the sensitivity of FNAB, i.e., the ability to detect malignant nodules, was 81.3 ± 9.8%, and the specificity, i.e., the ability to identify benign nodules, was 75.5 ± 5.9%. The overall diagnostic accuracy, i.e., the ability to distinguish patients from healthy individuals, was 76.8 ± 5.1%. The likelihood ratio for a positive result (LR+) was 3.31 (adequate), and for a negative result

(LR–) it was 0.25 (adequate). The probability of nodules being malignant, i.e., the positive predictive value (PPV), was 50.0 ± 9.8%, whereas the probability of nodules being benign, i.e., the negative predictive value (NPV), was relatively high at 93.0%. In cases with Bethesda category greater than IV, the PPV of FNAB was 64.3% and the NPV was 87.3%. Based on the scale of AUC values, which reflect the quality of the diagnostic test, it is important to note that ultrasound in B-mode represents a highly reliable test for identifying whether nodules requiring FNAB are benign or malignant (AUC = 0.828). Considering that the area under the ROC curve is an integral measure of diagnostic performance, FNAB demonstrated high informativeness for the diagnosis of thyroid nodules in this group of patients with a Bethesda category greater than III (p = 0.000) (Figure 3).



Area	Std.error	P	95% confidence interval	
			Lower bound	Upper bound
0.828	0.061	0.000	0.709	0.948

Figure 3. ROC curve reflecting the diagnostic potential of FNAB (comparison group)

In both subgroups of the main group (II^a n=140; II^b n=373), the ultrasonographic features (criteria) of thyroid nodules (TNs) according to the TIRADS classification were characterized as follows. In subgroup II^a: TIRADS II – 50 (37.8%), TIRADS III – 75 (53.6%), TIRADS IV^a – 11 (7.9%), TIRADS IV^b – 4 (2.9%), TIRADS V – 0 (0.0%). In subgroup IIb: TIRADS II – 20 (5.4%), TIRADS III – 218 (58.4%), TIRADS IV^a – 61 (16.4%), TIRADS IV^b – 52 (13.9%), TIRADS V – 22 patients (5.9%). A statistically significant difference was observed between the two subgroups (IIa and IIb) in terms of the distribution of patients according to TIRADS criteria (χ^2=174.573, p≤0.001).

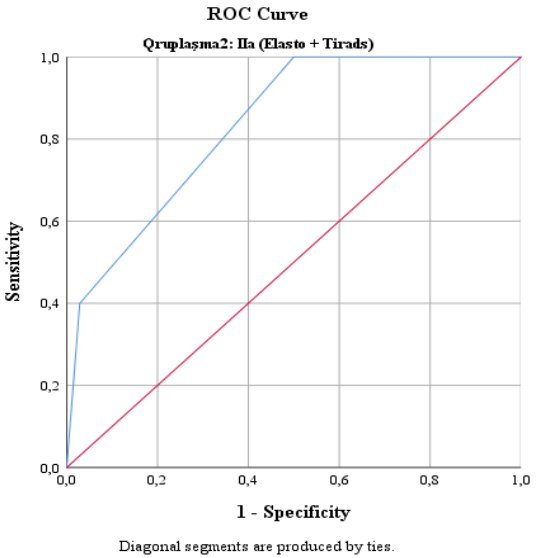
In patients of the main group, the elasticity index (EI) of the nodules was evaluated: in subgroup II^a, 64.1% of nodules had an EI of 2, 19.1% had an EI of 3, and 8.3% had an EI of 4; in subgroup II^b, the corresponding values were 35.9%, 80.9%, 91.7%, and 100%, respectively. In subgroup II^a, the majority of nodules were characterized by EI 2 (soft–benign) (64.1%), whereas in subgroup II^b, nodules with EI 4 and 5 (hard, with a high probability of malignancy) predominated, accounting for 91.7% and 22.8%, respectively. A statistically significant difference was found between the two subgroups (II^a and II^b) in terms of CSE (χ^2=107.864, p≤0.001).

In patients of subgroup II^a of the main group, the results of the combined evaluation of nodules according to TIRADS and EI were analyzed. Based on this analysis, among 45 nodules with EI score 2, TIRADS II was observed in 90.0%, TIRADS III in 38.7%, and TIRADS IVa in 9.1%, while no cases of TIRADS IV^b or TIRADS V were detected. Among 5 nodules with EI score 3, TIRADS II was identified in 10.0%, TIRADS III in 60.0%, TIRADS IV^a in 54.5%, and TIRADS IV^b in 25.0% of cases. In nodules with an EI score of 4, TIRADS II was observed in 0.0%, TIRADS III in 1.3%, TIRADS IV^a in 36.4%, and TIRADS IV^b in 75.0% of cases. In subgroup IIa, the difference between the number of patients whose thyroid nodules were evaluated by compression elastography indices and the TIRADS classification was statistically significant (χ^2=97.960, p≤0.001).

In subgroup II[a], after diagnostic evaluation of thyroid nodules by TIRADS and CSE, the results of histopathological examination of surgically resected nodules were analyzed. According to the data, benign histopathological outcomes were observed in 100% of patients with an EI score of 2, in 89.1% of those with an EI score of 3, and in 42.6% of those with an EI score of 4; malignant histopathological outcomes were identified in 0.0%, 10.9%, and 57.1% of cases, respectively, according to elastography scores. In this subgroup, the number of patients with benign histopathological results and EI score of 2 differed statistically significantly from those with EI scores of 3 and 4 (χ^2=25.780, p≤0.001).

In patients of subgroup IIa, ROC curve analysis was performed to evaluate the prognostic value of combining CSE with TIRADS. A model was developed by analyzing the data of 114 patients. The ROC analysis showed an AUC of 0.836 ± 0.056; 95% CI (0.726–0.945), p = 0.000. According to the initial calculations, in the stratification of malignant thyroid nodules, when the EI score was greater than 3 points, the sensitivity of the examination was 40.0 ± 15.5%, specificity – 97.1 ± 1.6%, accuracy – 92.1 ± 2.3%, positive likelihood ratio (LR+) – 13.87, and negative likelihood ratio (LR–) – 0.62 (Figure 4).

In patients of subgroup II[a], a ROC curve analysis was performed to assess the predictive value of CSE in combination with TIRADS. A model was obtained by analyzing the data of 114 patients. ROC analysis yielded an AUC of 0.836 ± 0.056; 95% CI (0.726–0.945), p=0.000. According to the initial calculations, in the stratification of malignant thyroid nodules, when EI scores greater than 3 were considered, the sensitivity of the method was 40.0 ± 15.5%, specificity – 97.1 ± 1.6%, accuracy – 92.1 ± 2.3%; the positive likelihood ratio (LR+) was 13.87, while the negative likelihood ratio (LR–) was 0.62. The PPV was 57.1%, and the NPV was relatively high at 94.4%.



Area	Std. error	P	95% confidence interval	
			Lower bound	Upper bound
0.836	0.056	0.000	0.726	0.945

Figure 4 ROC curve reflecting the diagnostic potential of compression elastography (subgroup IIa)

Considering that the area under the ROC curve is an integral measure of diagnostic performance, the combined application of CSE with TIRADS demonstrates high predictive value for benign thyroid nodules and shows good diagnostic performance. The quality of the diagnostic test is high (AUC = 0.836).

In subgroup II^{b} of the main group, a comparative analysis of 373 patients with biopsy material was performed according to TIRADS and Bethesda classifications. According to the data, among 20 nodules classified as TIRADS II, 18 (90.0%) corresponded to Bethesda II and 2 (10.0%) to Bethesda IV. Among 218 nodules classified as TIRADS III, 3 (1.4%) were Bethesda I, 127 (58.3%) were Bethesda II, 15 (6.9%) were Bethesda III, 63 (28.9%) were Bethesda IV, 9 (4.1%) were Bethesda V, and 1 (0.5%) was Bethesda VI. Among

56 nodules classified as TIRADS IV[a], 23 (37.1%) were Bethesda II, 1 (1.6%) was Bethesda III, 25 (41.0%) were Bethesda IV, 5 (8.2%) were Bethesda V, and 7 (11.5%) were Bethesda VI. Among 52 nodules classified as TIRADS IV[b], 5 (9.6%) corresponded to Bethesda II, 3 (5.8%) to Bethesda III, 13 (25.0%) to Bethesda IV, 20 (38.5%) to Bethesda V, and 11 (21.2%) to Bethesda VI. Among 27 nodules classified as TIRADS V, 2 (9.1%) were Bethesda II, and 4 (18.2%) were Bethesda VI. In subgroup II[b], a statistically significant difference was observed between the number of patients evaluated according to both TIRADS and Bethesda classifications (χ^2=172.706; p<0.001). Based on the combined application of TIRADS classification, CSE, and FNAB, histopathological results were obtained from 168 surgically treated patients: 123 (73.2%) showed benign and 45 (26.8%) showed malignant outcomes. Among nodules classified as TIRADS II, III, IVa, IVb, and V, benign outcomes were observed in 100%, 97.7%, 69.2%, 28.2%, and 16.7% of cases, respectively. Malignant histopathological outcomes were found in 0.0%, 2.3%, 30.8%, 71.4%, and 83.3%, respectively. Notably, nodules classified as TIRADS IV[a] and V showed higher concordance between TIRADS assessment and cytological results. A statistically significant difference was observed between benign and malignant histopathological outcomes and TIRADS categories (χ^2=84.870, p<0.001). In histological examinations of nodules from patients classified as TIRADS III, thyroid cancer was detected in 3.7% of cases (TIRADS ≤5%); in the TIRADS IVa group, 31.4% (TIRADS 5–10%); in the TIRADS IV[b] group, 71.8% (TIRADS 10–80%); and in the TIRADS V group, 83.3% (TIRADS >80%). Against the background of increasing awareness of thyroid disease, FNAB plays a crucial role in stratifying patients into surgical and non-surgical groups.

In subgroup II[b] (n=373), the firm portion of nodules (dark blue area) was identified under CSE and subjected to FNAB, and a comparative analysis of cytological and elastography results was performed. Among 242 nodules with an EI score of 3, Bethesda outcomes were as follows: II – 73.1%, III – 75.0%, IV – 77.1%, V – 27.7%, VI – 8.7%. In nodules with an EI score of 4, the corresponding

values were 7.4%, 25.0%, 15.2%, 70.2%, and 91.3%, respectively. In a single patient with an EI score of 5, Bethesda V was detected. Overall, in 117 nodules (31.4%), the cytological result was classified as "intermediate–suspicious," corresponding to Bethesda III and IV. Malignant cytological outcomes were more frequently observed in patients whose nodules were evaluated as EI 4 under CSE and underwent FNAB from the firmer "dark blue" regions, compared with nodules biopsied from softer "light blue" areas with EI scores of 2 and 3. A statistically significant difference was found between the cytological results obtained from FNAB of the firm nodule regions under CSE guidance and the corresponding Bethesda classification (χ^2=166.61, p≤0.001).

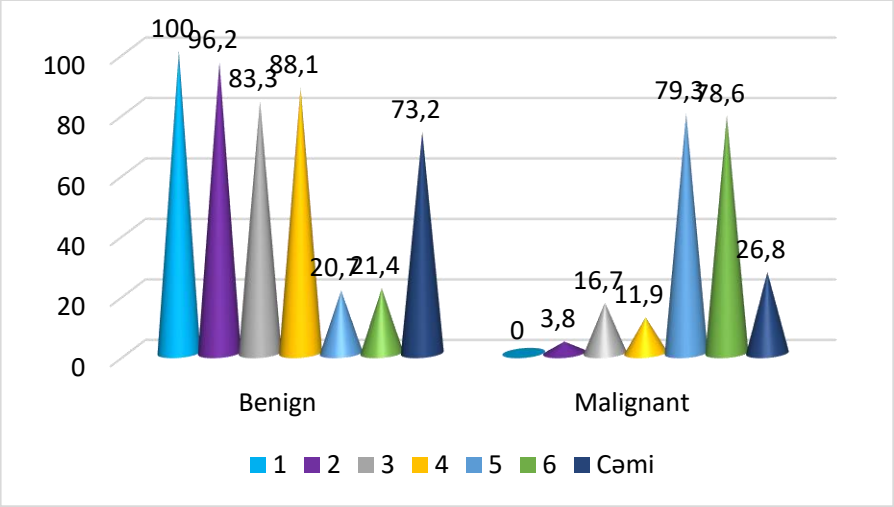


Figure 5. Distribution of patients according to histopathological outcomes based on the Bethesda classification (main group)

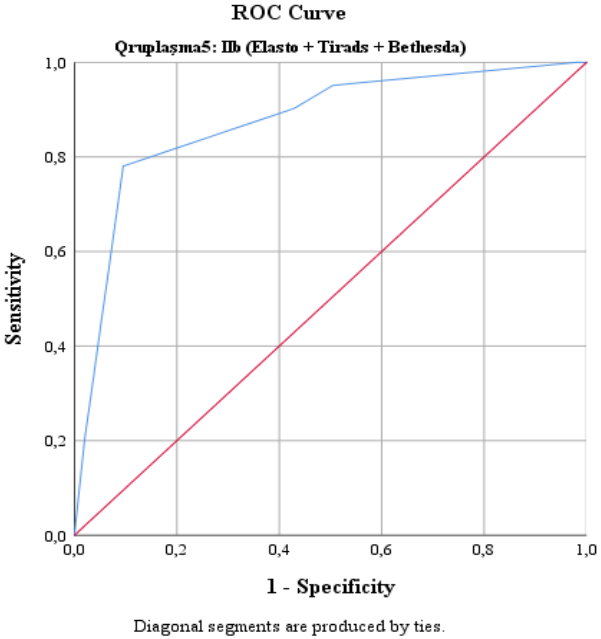
In subgroup II[b], following combined evaluation of thyroid nodules using TIRADS, CSE, and FNAB, benign histopathological outcomes were observed in nodules with EI scores of 2 – 100%, EI 3 – 89.1%, and EI 4 – 31.3%; malignant histopathological outcomes were detected in 0.0%, 10.9%, and 68.8% of cases, respectively. In a

single patient with an EI score of 5, the nodule was found to be malignant (100%). A statistically significant difference was observed between the number of patients with EI scores of 3 and 4 in terms of histopathological results (χ^2=65.433, p≤0.001).A combined analysis of histopathological results and Bethesda classification was performed in 168 surgically treated patients belonging to subgroup II^b. Nodules in 123 patients (73.2%) were histopathologically benign, while 45 (26.8%) were malignant. Benign histopathological outcomes were observed in 2 patients (100%) with Bethesda I cytology, 50 patients (96.2%) with Bethesda II, 10 patients (83.3%) with Bethesda III, 52 patients (88.1%) with Bethesda IV, 6 patients (20.7%) with Bethesda V, and 3 patients (21.4%) with Bethesda VI. Correspondingly, malignant histopathological outcomes were 0.0%, 3.8%, 16.7%, 11.9%, 79.3%, and 78.6%, respectively. In the main group, the correlation between Bethesda classification and histopathological results was statistically significant (χ^2=78.86, p<0.001). (Figure 5).

In subgroup II^b, ROC analysis of FNAB performed from CSE-targeted areas yielded an AUC of 0.865 ± 0.034; 95% CI (0.799–0.932), p<0.001 (Figure 6). The prognostic potential of FNAB for diagnosing thyroid cancer was assessed based on the combined results of Bethesda V and VI categories. In this subgroup, for FNAB performed in cases above Bethesda III, the sensitivity was 91.1 ± 4.2%, specificity 49.6 ± 4.5%, accuracy 60.7 ± 3.8%, PPV 39.8 ± 4.8%, and NPV was 93.8 ± 3.0%. For cases above Bethesda IV, FNAB sensitivity was 75.6 ± 6.4%, specificity 91.9 ± 2.5%, accuracy 87.5 ± 2.6%, positive likelihood ratio (LR+) 9.29 (good), negative likelihood ratio (LR–) 0.27 (satisfactory), PPV 77.3 ± 6.3%, and NPV 91.1 ± 2.6%.

Thus, in the main group, based on the scale of the AUC reflecting the diagnostic performance of the test, FNAB after combined application of TIRADS and CSE is a statistically significant and more reliable marker (p<0.001) for diagnosing thyroid cancer in nodules above Bethesda III. FNAB also demonstrates good prognostic performance across different thyroid nodules.

According to the results obtained at the beginning of our study (2015–2018), in the comparison group, FNAB demonstrated a sensitivity of 81.3% and specificity of 75.5% for cases above Bethesda III. In the main group (2019–2024), the corresponding values were 91.1% and 49.6%, respectively. Under the combined application of TIRADS classification and CSE in thyroid nodules, target points for FNAB were selected based on the intensity of color shades, providing a more accurate and reliable assessment of malignancy.



Area	Std. error	p	95% confidence interval	
			Lower bound	Upper bound
0.865	0.034	0.000	0.799	0.932

Figure 6. ROC curve illustrating the diagnostic performance of the combined application of TIRADS, CSE, and FNAB.

After the application of the selected diagnostic methods for thyroid nodules, FNAB was performed in 185 of 200 patients (92.5%) in the comparison group, and surgical operations were carried out in 79 patients (39.5%). In the main group, FNAB was performed in 373 of 513 patients (72.7%), and 282 patients (55.0%) underwent surgical intervention. Among those who underwent FNAB, 168 patients (45.0%) subsequently had surgery. Based on a comparative analysis of these data, the use of FNAB in the comparison group and subgroup II^b led to a reduction of more than 50% in the number of surgical operations. In subgroup II^a, among 140 patients, FNAB was performed in 114 (84.4%) and corresponding surgical procedures were carried out. In subgroup II^b of the main group, during the comparative analysis of FNAB results, CSE proved to be a useful "indicator" for selecting the puncture zone of the firm part of the nodule (dark blue areas) and allowed us to determine the part of the node from which more punctate (biopsy) should be taken. As a result, in selected patients of subgroup II^b, FNAB contributed to a more than twofold reduction in the number of surgical operations. According to histopathological examination of surgical materials, nodules were malignant in 21.5% of cases in the comparison group, 8.8% in subgroup II^a, and 26.8% in subgroup IIb ($p<0.001$). In subgroup IIb, favorable outcomes and a higher detection rate of malignant thyroid nodules can be explained by the improved diagnosis of thyroid nodular lesions achieved through the combined application of TIRADS, CSE, and FNAB.

In our study, the correlation between preoperative thyroid ultrasound reports and the TIRADS system with postoperative histopathological findings was analyzed to assess the diagnosis of malignancy in patients with endemic and non-endemic nodular goiter. During study design, the criteria developed by Horwath and G. Russ were examined. Patients were divided into two subgroups: subgroup II^a – 139 patients with endemic nodular goiter, and subgroup II^b – 222 patients with non-endemic nodular goiter.

Among patients from endemic regions, nodules were classified as TIRADS II in 13.7%, TIRADS III in 61.2%, TIRADS IVa in 7.9%, TIRADS IVb in 13.7%, and TIRADS V in 3.6% of cases. In patients from non-endemic regions, the corresponding percentages were TIRADS II –

8.1%, TIRADS III – 57.7%, TIRADS IVa – 15.3%, TIRADS IVb – 15.3%, and TIRADS V – 3.6%. No statistically significant difference was observed in the diagnostic outcomes according to the TIRADS scale between the regions (χ^2=6.620, p≥0.05) (Figure 7).

The results of the pathohistological examinations of surgical samples showed that among patients with endemic nodular goiter, 114 cases (82.0%) were benign and 25 cases (18.0%) were malignant; whereas among patients with non-endemic nodular goiter, 175 cases (78.8%) were benign and 47 cases (21.2%) were malignant. No statistically significant difference was found between the pathohistological results across the regions (χ2=0.912, p≥0.05).

In the endemic subgroup, a significant and statistically strong positive correlation was observed between TIRADS scale scores and postoperative histopathological outcomes (p<0.001). In the non-endemic subgroup, a moderate but statistically significant positive correlation was found between TIRADS scores and postoperative histopathological findings (p<0.001).

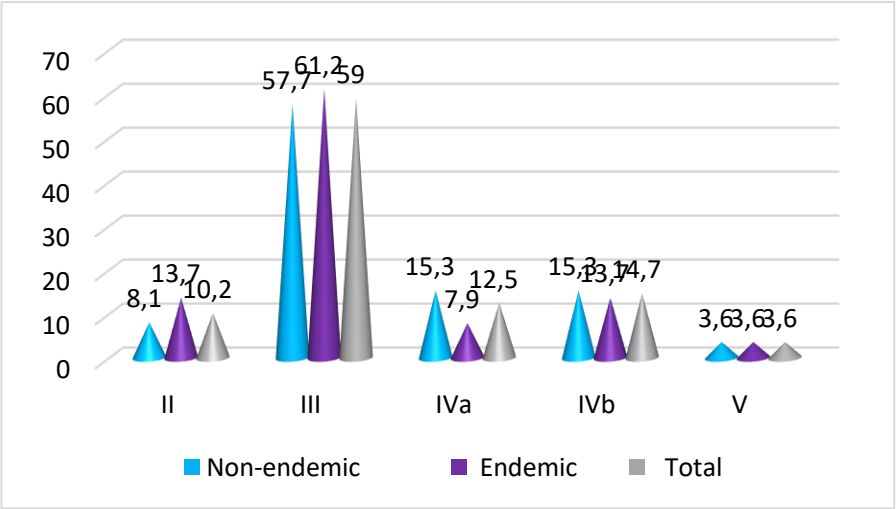


Figure 7. Evaluation of endemic and non-endemic nodular goiter according to TIRADS classification

For the diagnosis of endemic nodular goiter, the area under the ROC curve for TIRADS was 0.916 ± 0.036; 95% CI (0.845–0.988); p=0.000. TIRADS classification proved to be a statistically significant indicator for the diagnosis of thyroid nodules in endemic regions.

For the diagnosis of nodular goiter in non-endemic regions, the area under the ROC curve for TIRADS was 0.875 ± 0.031; 95% CI (0.814–0.936); p=0.000. In these regions, the TIRADS scale also proved to be a significant indicator for the diagnosis of thyroid nodules.

In the endemic subgroup, the parameters of TIRADS classification were favorable: sensitivity 93.8%, specificity 94.0%, and accuracy (i.e., the ability to correctly identify nodules among healthy individuals) 93.9%. For nodules classified as TIRADS IV–VI, the PPV was 75.0%, whereas for TIRADS II–III, the probability of benign nodules was 98.7%. In the non-endemic group, the values were 78.1%, 82.9%, 82.0%, 53.2%, and 93.9%, respectively.

Based on diagnostic indicators, the outcomes of different minimally invasive treatment methods were analyzed in 38 patients aged 26–64 years (mean age: 42.3 ± 3.7 years; 31 women, 7 men). The predominant complaints of the patients were a sensation of compression/strangulation in the anterior region of the neck and/or swelling (visible, sometimes excessively large, and even deforming). The patients were divided into two groups. Group I – 28 patients with cystic-colloid nodules (CCN) underwent sclerotherapy (ST); Group II – 10 patients with benign solid nodules (BSN) underwent intranodular laser ablation (LA).

The patients who underwent sclerotherapy were followed up by us with ultrasound monitoring (after 1, 3, and 6 months). During these periods, the changes in size and volume of the thyroid nodules with fluid components were evaluated, and the results were analyzed. The patients were divided into two subgroups: the main subgroup – 13 patients, and the comparison subgroup – 15 patients. In the main subgroup, the initial mean volume of cystic nodules was 4.1 ± 3.5 cm^3, whereas in the comparison subgroup the initial mean volume of cystic nodules was 3.7 ± 1.5 cm^3.

A statistically significant difference was observed between the number of patients before and after the procedure in terms of nodule

volume reduction ($p \leq 0.05$). The mean volume of cystic nodules prior to the procedure was 3.9 ± 0.4 cm³, whereas immediately after completion of the procedure, it decreased to 1.1 ± 0.2 cm³; at 1 month to 0.9 ± 0.1 cm³; at 3 months to 0.5 ± 0.1 cm³; and at 6 months to 0.4 ± 0.1 cm³. In both subgroups, a marked reduction in the size of larger cystic nodules was noted after the procedure. In both subgroups, the outcomes of sclerotherapy were statistically evaluated using the Wilcoxon and Mann–Whitney tests. Immediately after completion of the procedure, ultrasound demonstrated a reduction in nodule volume and size in the main subgroup, with a median of 1.3 cm³ and interquartile range (IQR) 0.4–1.8 cm³ (PW = 0.002). At 1 month, the median volume was 0.9 cm³, IQR 0.4–1.3 cm³ (PW = 0.002); at 3 months, 0.3 cm³, IQR 0.2–0.6 cm³ (PW = 0.002); and at 6 months, 0.3 cm³, IQR 0.2–0.6 cm³ (PW = 0.002). The same examinations were performed in the comparison subgroup. Immediately after completion of the procedure, the median nodule volume was 0.9 cm³, IQR 0.5–1.2 cm³ (PW = 0.005); at 1 month, median 0.6 cm³, IQR 0.2–1.0 cm³ (PW = 0.002); at 3 months, median 0.3 cm³, IQR 0.2–0.8 cm³ (PW = 0.001); and at 6 months, median 0.3 cm³, IQR 0.2–0.8 cm³ (PW = 0.001). No statistically significant difference was detected between the groups regarding the reduction in cystic nodule volume after sclerotherapy ($p \geq 0.05$).

In both subgroups, a significant reduction in nodule volume was observed (Figure 9). The volume of larger nodules decreased more markedly, leading to the resolution of choking symptoms in patients and an improvement in aesthetic outcomes.

In the comparison subgroup, a significant reduction was observed in cystic lesions with an initial mean volume of 3.2 ± 1.5 cm³ (12 patients). In these patients, the nodule volume decreased by more than 68.8%. The volume reduction ratio (VRR) reached 75.6% within the first month (mean 0.9 ± 0.2 cm³), 86.5% at 3 months (mean 0.5 ± 0.2 cm³), and 89.2% at 6 months (mean 0.4 ± 0.2 cm³). Following standard sclerotherapy in the comparison subgroup, a decrease in nodule size was recorded in 12 patients after 1 month, whereas in 2 patients, an increase was noted, and in 1 patient, the nodule volume remained unchanged. Recurrence occurred in the last 3 patients (20%). In two patients, no

reduction in cystic nodule volume was observed at the 3-month follow-up, and therefore, single-session multiple reaspiration sclerotherapy was performed. The procedure was repeated once in all three patients; however, in one of them, increasing intracystic hemorrhage (hematoma) developed, and a hemithyroidectomy was performed one week after the procedure.

In two other patients, the results of ethanol injection were favorable. In 80.0% of patients treated with standard sclerotherapy, compressive and aesthetic symptoms were resolved.

In 13 patients who underwent single-session multiple reaspiration sclerotherapy, a significant reduction was observed in cystic nodules with a mean volume of 4.1 ± 3.5 cm^3. In 12 patients, a volume reduction of more than 68.3% was recorded after the procedure. The VRR reached 78.0% within the first month (mean 0.9 ± 0.4 cm^3); 87.8% after 3 months (mean 0.5 ± 0.4 cm^3); and 90.2% after 6 months (mean 0.4 ± 0.2 cm^3). In one patient (7.7%) of this subgroup, recurrence occurred one month later, and a repeated staged sclerotherapy session was performed. At the one-month follow-up, the outcomes of staged ethanol injection in this patient were favorable.

Ten patients with solid nodular goiter who underwent laser ablation (2018–2024) were included. Formally, these nodules did not present direct surgical indications; however, as they reached larger sizes, the patients faced the prospect of surgical intervention. In this group of patients, further evaluation of the method's effectiveness allowed substantiation of this indication for LA.

The mean volume of solid nodules before the procedure was 4.2 ± 2.8 cm^3. In 9 patients, a single session of LA was performed, whereas 2 sessions were required in 1 patient. The procedures were carried out according to the standard protocol. Each patient underwent laser irradiation in 1–2 sessions with an average power of 4W, a median exposure time of 900 seconds, and an energy of 1300 J.

When analyzing the dynamics of solid thyroid nodule volume changes over a period of 1–2.5 years, the mean nodule volume was 2.7 ± 1.7 cm^3 at 1 month after the procedure, 2.0 ± 0.6 cm^3 at 3 months, and 2.0 ± 0.4 cm^3 at 6 months. The most pronounced reduction was observed 3–

6 months after LA sessions in nodules with a diameter of less than 25 mm ($p<0.01$) (at 3 months after the initial ablation session, $p<0.01$; at 6 months, $p<0.001$).

In the dissertation, the studies related to the complications of operated patients by groups, the selected types of surgery, and the pathohistological findings have been extensively discussed. The patients included in the study who underwent surgical treatment (n=361) were divided into two subgroups according to region: non-endemic (n=222; 61.5%) and endemic (n=139; 38.5%). The outcomes of their surgical management were comparatively assessed and analyzed.

Among patients aged 30–39 years, the proportion was 17.1% in non-endemic regions and 21.6% in endemic regions; among those aged 40–49 years, 25.7% and 23.7%, respectively; among patients aged 50–59 years, 27.9% and 29.5%, respectively; and among those aged 60–69 years, 11.3% and 14.4%, respectively. No statistically significant difference in age distribution was observed between the regions ($\chi^2=5.153$, $p\geq0.05$).

The scope of surgical interventions for nodular goiter differed between non-endemic and endemic regions. In non-endemic regions, the following procedures were performed: right lobectomy with isthmusectomy – 6.8% (n=15), left lobectomy with isthmusectomy – 0.9% (n=2), total thyroidectomy (TT) – 75.7% (n=168), near-total thyroidectomy (TyTE) – 9.0% (n=20), completion thyroidectomy (TE) – 3.2% (n=7), subtotal thyroidectomy – 0.5% (n=1), TT with central and right selective lateral lymph node dissection – 2.7% (n=6), TT with central and left selective lateral lymph node dissection – 0.9% (n=2), and TT combined with laparoscopic cholecystectomy – 0.5% (n=1). In endemic regions, the distribution was as follows: right lobectomy with isthmusectomy – 2.2% (n=3), left lobectomy with isthmusectomy – 2.7% (n=3), TT – 77.7% (n=108), TyTE – 10.8% (n=15), completion TE – 2.2% (n=3), TT with central and right selective lateral lymph node dissection – 2.9% (n=10), TT with central and left selective lateral lymph node dissection – 0.7% (n=1), and TT combined with laparoscopic cholecystectomy – 0.7% (n=1). No statistically significant differences

were observed between the regions in terms of surgical approaches and the extent of interventions (χ^2=7.610, p≥0.05).

According to postoperative histopathological findings, thyroid cancer was diagnosed in 47 patients (21.2%) and benign nodules in 175 patients (78.8%) from non-endemic regions; in endemic regions, the respective numbers were 25 (18.0%) and 114 (82.0%). No statistically significant difference was observed between the regions in terms of benign versus malignant histopathological outcomes (χ^2=0.912, p≥0.05). In non-endemic regions, the histopathological diagnoses were distributed as follows: macro-microfollicular nodular colloid adenomatous goiter – 159 cases (71.6%); macro-microfollicular nodular colloid adenomatous goiter on the background of autoimmune thyroiditis – 1 case (0.5%); macro-microfollicular nodular colloid adenomatous goiter on the background of Hashimoto's thyroiditis – 10 cases (4.5%); Hürthle cell (oncocytic) adenoma – 1 case (0.5%); follicular adenoma – 4 cases (1.8%); follicular carcinoma – 1 case (0.5%); papillary microcarcinoma – 1 case (0.5%); and classic variant of papillary carcinoma – 45 cases (20.3%). In endemic regions, the histopathological diagnoses were as follows: macro-microfollicular nodular colloid adenomatous goiter – 101 cases (72.7%); macro-microfollicular nodular colloid adenomatous goiter on the background of autoimmune thyroiditis – 1 case (0.7%); macro-microfollicular nodular colloid adenomatous goiter on the background of Hashimoto's thyroiditis – 5 cases (3.6%); follicular adenoma – 7 cases (5.0%); and classic variant of papillary carcinoma – 25 cases (18.0%). Based on histopathological results, no statistically significant difference was found between the two regions (χ^2=1.016, p≥0.05).

A comparative analysis of early postoperative complications was conducted in patients from both regions. Early postoperative complications were observed in 29 patients (8.0%): voice disorders in 13 cases (3.6%), hypocalcemia in 14 cases (3.9%), seroma in 5 cases (1.4%), and postoperative bleeding in 1 case (0.3%). In non-endemic regions, complications occurred in 19 patients (8.6%), while in endemic regions they were recorded in 10 patients (7.2%). In non-endemic regions, transient voice hoarseness occurred in 7 patients (3.2%), hypocalcemia in 11 patients (5.0%), seroma in 3 patients (1.4%), and early postoperative

bleeding in 1 patient (0.5%). The patient with bleeding underwent reopening of the wound, and the bleeding vessel was re-ligated. In endemic regions, transient voice hoarseness was observed in 6 patients (4.3%), hypocalcemia in 3 patients (2.2%), and seroma in 2 patients (1.4%). No statistically significant difference was found between the two regions regarding the incidence of early complications ($p \geq 0.05$). In the long-term follow-up, one patient (0.5%) from the non-endemic region developed a persistent complication: despite undergoing voice therapy, hoarseness remained unresolved.

The purpose of our modified thyroidectomy technique (inferior–superior thyroidectomy) is to perform the surgical steps in a defined sequential order, allowing maneuvers to be carried out more easily, safely, and securely, thereby reducing operative time as well as complications related to the laryngeal nerves and parathyroid glands.

In our study, the outcomes of 143 patients who underwent total thyroidectomy were analyzed. The age range was 16–77 years (130 women – 91%; 13 men – 9%). The diagnosis of "multinodular goiter" was confirmed in 132 patients, while "autoimmune thyroiditis, diffuse nodular form" was confirmed in 11 patients. The patients were divided into two groups: Group I included 67 patients who underwent standard total thyroidectomy (TT), and Group II included 76 patients who underwent an inferior-to-superior thyroidectomy modified by us. A comparative analysis was performed in both subgroups regarding operation time, intraoperative, and postoperative complications.

Of the 143 patients, 81 (56.6%) were young and middle-aged patients between 30 and 60 years of age. No statistically significant differences were found between the two subgroups regarding the number of patients by age ($\chi^2=8.573$, $p=0.266$, $p>0.05$). Likewise, no statistically significant differences were detected between the subgroups in terms of nodule localization and size ($\chi^2_{loc.}=4.193$, $p=0.123$; $\chi^2_{size}=2.769$, $p=0.429$).

No statistically significant difference was observed between the two subgroups in terms of patients' pathohistological diagnoses following TT surgery ($\chi^2=0.126$, $p=0.722$). The pathohistological findings were as follows: macro-microfollicular nodular colloid

adenomatoid goiter – 100 cases (70.0%); macro-microfollicular nodular colloid adenomatoid goiter on the background of autoimmune thyroiditis – 1 case (0.7%); macro-microfollicular nodular colloid adenomatoid goiter on the background of Hashimoto's thyroiditis – 10 cases (7.0%); Hürthle cell (oncocytic) adenoma – 1 case (0.7%); follicular adenoma – 5 cases (3.5%); follicular carcinoma – 1 case (0.5%); classic variant of papillary carcinoma – 25 cases (17.4%). The number of patients by pathohistological diagnosis did not differ statistically significantly between those who underwent TT and those who underwent IST (χ^2=4.993, p=0.552, p≥0.05).

The duration parameters of both TT and IST surgeries were investigated. In our study, the outcomes of 143 patients who underwent total thyroidectomy were analyzed. The age range was 16–77 years (130 women – 91%; 13 men – 9%). A diagnosis of multinodular goiter was confirmed in 132 patients, while 11 patients were diagnosed with autoimmune thyroiditis in its diffuse nodular form. The patients were divided into two groups: Group I included 67 patients who underwent standard total thyroidectomy (TT), and Group II included 76 patients who underwent our modified TT procedure. Comparative analysis of operative time, intraoperative complications, and postoperative complications was performed for both subgroups.

A statistically significant difference was observed between the traditional group (TTE) and the inferior-to-superior thyroidectomy (IST) group in terms of operation duration. In the TTE group, the mean duration of operations was 80 minutes, whereas in the IST group, it was 67.5 minutes. The difference in operation duration between the two subgroups was statistically significant (p=0.000). We believe that the surgeon's skill, experience, the sequence of the procedure, and comfortable execution play a decisive role in the correct performance of IST. Operation times are shortened, and both the doses of anesthetic agents used during surgery and the overall drug consumption are reduced. In patients of Subgroup I, early postoperative complications were more frequently observed—6.0% (n=4); in Subgroup II, this indicator was more than twice lower—2.6% (n=2). Thus, among wound complications, a hematoma was recorded in one patient in Group I, and a seroma was observed in one patient in Group

II. The seroma was evacuated using puncture, while the patient with the hematoma underwent wound revision through repeat surgery. On the first postoperative day in Subgroup I, voice disturbances occurred in 3 patients (4.5%) (multinodular toxic goiter – 1, papillary carcinoma – 1, Hashimoto's thyroiditis with diffuse nodular form – 1), and transient hypocalcemia was observed in 2 patients (3.0%). In Subgroup II, transient voice disturbance was observed in 1 patient (1.3%) with diffuse nodular form of autoimmune thyroiditis (Hashimoto's disease).

In Subgroup II, transient voice disturbance was observed in 1 patient (1.3%) with diffuse nodular form of autoimmune thyroiditis (Hashimoto's disease). No cases of hypocalcemia (0%) occurred in this subgroup. In this subgroup, no cases of hypocalcemia (0%) were observed. The proposed technique allows more reliable protection of the superior and inferior laryngeal nerves from tension, as well as safe identification of the parathyroid glands, thereby reducing the risk of potential complications. Moreover, the simplicity of the technical procedure enables its use even without neuromonitoring, and its application in training young surgeons makes the mastering of thyroid surgery more accessible to them. In our study, preference was given to a new pharmacological formulation due to its more controllable composition and the potential to reduce side effects. A chitosan/arabinogalactan-based bioside hydrophilic nanogel with prolonged action of levothyroxine was developed for the treatment of patients with hypothyroidism. Its acute and chronic toxicity was studied experimentally in mice, and the effects on TSH and T4 hormone levels were evaluated in rabbits with experimentally induced hypothyroidism. At the same time, the prolonged presence of levothyroxine-Na pentahydrate in the blood was confirmed using high-performance liquid chromatography.

The absorption spectra of standard levothyroxine and the nanocarrier-based solutions were obtaine, and their optical densities were determined in the laboratory. In both solutions, the maximum absorption spectrum was identified at 330 nm.

The release time of levothyroxine-Na pentahydrate from the nanocarrier was determined by measuring the optical density of the

solutions immediately after preparation and at 5 min, 10 min, 15 min, 30 min, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 24 h, 48 h, and 72 h (average of 3 measurements). It was found that, as a result of levothyroxine release from the nanocarrier into the solution, the level reached 93.8% after 30 minutes, attained its maximum (98.9%) after 1 hour, decreased between 2–6 hours (97.5–95.2%), increased again at 24 hours (97.9%), and remained at a high level at 48 and 72 hours (98.1–98.3%) (Figure 8). Analysis of the obtained results shows that levothyroxine in the nanocarrier reaches maximum concentration within 1 hour in an alkaline medium and maintains a high concentration level for 72 hours.

To study the acute toxicity of the levothyroxine/biopolymer complex, the levothyroxine/biopolymer compound was administered intraperitoneally to mice at a dose of 5 mg/kg. The experiments were divided into the following series: in Series I (control), mice received an average of 0.2 mL of 0.9% NaCl solution, in Series II, animals received 0.2 mL of the levothyroxine/biopolymer complex (0.0001 mg), in Series III, animals received 0.4 mL of the levothyroxine/biopolymer compound (0.0002 mg), in Series IV, animals received 0.8 mL of the levothyroxine/biopolymer solution (0.0004 mg), and in Series V, animals received 1 mL of the levothyroxine/biopolymer solution (0.0005 mg) intraperitoneally in increasing doses.

During the experiment, the condition, behavior, locomotion, and grooming reactions of the mice were monitored. They were provided with food and water throughout the 24-hour period. After administration of the newly synthesized levothyroxine/biopolymer complex, no severe reactions were observed in the first hours. After 1–2 hours, the animals exhibited sedation, huddling, and grooming behaviors. Following free access to food and water, the mice remained in normal condition throughout the 24-hour period, with no disturbances in behavior, locomotion, or grooming. No mortality was observed in any series within 24 hours after administration of the levothyroxine/biopolymer compound at a dose of 5 mg/kg.

After determining that the levothyroxine/biopolymer compound at a dose of 5 mg/kg did not exhibit toxic effects in mice, it became necessary to study the potential toxic effects of a higher dose—10 μg/kg.

For this purpose, the experimental animals were divided into four series. In Series I (control), animals received 0.4 mL of 0.9% NaCl solution. In Series II, mice were administered 0.4 mL of the levothyroxine/biopolymer complex dissolved in gastric juice (0.0004 mg) intraperitoneally. During the experiment, no severe adverse reactions or mortality were observed in the animals. The test substance was administered to the animals in Series III at a dose of 0.6 mL (0.0006 mg) and in Series IV at 0.8 mL (0.0008 mg) in increasing doses. Within 5–10 minutes, no severe adverse reactions occurred in the mice; however, signs of sedation, huddling, and reduced locomotion were noted. After 1–2 hours, the animals returned to normal condition, began consuming food and water, and no lethal events were observed within 24 hours at the tested doses. Thus, the levothyroxine/biopolymer complex at doses of 5 and 10 mg/kg did not induce toxic reactions in mice within 24 hours.

The intestinal absorption of the newly synthesized levothyroxine/biopolymer complex and its effects on TSH and free T_4 hormones were studied in white rabbits of the "Chinchilla" breed using a "hypothyroidism" model. The rabbits were divided into two groups: Series I (comparison group) received levothyroxine at a dose of 12.5 μg, while Series II (main group) received the newly prepared levothyroxine (10 μg)/polymer complex in 3 rabbits. In both series, the preparations were administered orally to the rabbits in a single morning dose on an empty stomach, followed by water, and the administration was discontinued on subsequent days. The effects on thyroid hormone levels in blood samples taken on days 3, 5, and 7, as well as the quantitative determination of levothyroxine sodium pentahydrate in plasma using the HPLC method, were extensively discussed in the dissertation.

The acute and chronic toxicity of the levothyroxine/biopolymer complex under investigation, its effect on thyroid hormone levels in the plasma of rabbits with experimentally induced hypothyroidism, as well as the quantitative analysis of levothyroxine-Na pentahydrate in plasma using HPLC, are extensively discussed in the dissertation.

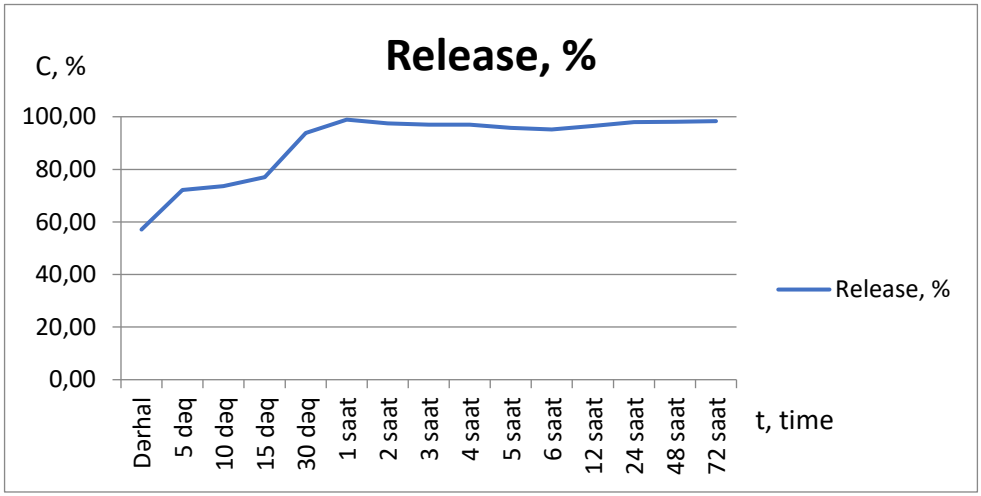


Figure 8. Release time of L-thyroxine from the nanocarrier

CONCLUSIONS

1. Against the background of iodized table salt consumption, thyroid pathologies were detected in 82 schoolchildren (30%) during ultrasound screening of students (n=273) from Gabala, Sheki, and Guba districts of the Azerbaijan Republic. These pathologies were identified in 32 out of 90 students in Gabala (35.6%), 18 out of 101 students in Sheki (17.8%), and 32 out of 82 students in Guba (39%). A statistically significant difference was found in the prevalence rates among the regions (χ^2=26.827, p=0.001) [32].
2. Against the background of iodized table salt consumption, assessment of urinary iodine levels among schoolchildren (n=189) from Gabala, Sheki, and Guba districts of the Azerbaijan Republic revealed iodine deficiency in 63 children (33.4%) and iodine excess in 32 children (16.9%). The prevalence of iodine deficiency was 26.2% in Gabala (mild – 10.8%, severe – 15.4%), 14.9% in Sheki (mild – 13.4%, severe – 1.5%), and 63.2% in Guba (mild – 42.1%, severe – 21.1%). A statistically significant difference was observed between the epidemiological status of urinary iodine excretion and the number of students across the districts (χ^2=39.732, p=0.001).

Cases of excessive urinary iodine concentration were recorded in 20.5% of students in Gabala, 20.9% in Sheki, and 7% in Guba [35].

3. In the patients who underwent FNAB under ultrasound guidance evaluated by the TIRADS classification, the malignancy rate of nodules was 20.3% with a sensitivity of 81.3%. In those assessed only by compression elastography, the malignancy rate was 8.8% with a sensitivity of 40.0%. In patients who underwent FNAB under compression elastography guidance, the malignancy rate was 26.8% with a sensitivity of 91.1% ($\chi^2_{emp.}$=40.92, p<0.001). Thus, FNAB performed under the guidance of compression elastography from more precise and reliable areas yielded highly effective results [26].
4. In patients with thyroid cystic-colloid nodules, the recurrence rate after conventional sclerotherapy was 20%, whereas after the improved single-session multiple reaspiration sclerotherapy, it was 8.3%. This corresponds to more than a twofold increase in treatment effectiveness (χ^2=4.381, p=0.037) [25,59].
5. In the surgical treatment of various forms of nodular goiter, the incidence of recurrent laryngeal nerve paresis and transient hypoparathyroidism after conventional total thyroidectomy was 4.5% and 3.0%, respectively, whereas after improved extrafascial total thyroidectomy these rates were 1.3% (χ^2=4.057, p=0.044) and 0.0%, respectively. The mean duration of surgery was 80 minutes in conventional total thyroidectomy and 67.5 minutes in improved total thyroidectomy, resulting in a reduction of up to 13 minutes in the average operation time (p=0.000). Thus, the application of the improved total thyroidectomy modification led to a significant reduction in operation time and allowed for safer and more reliable dissection of anatomical structures, resulting in more than a twofold decrease in the incidence of complications [29,43,57].
6. Biocomplexes of levothyroxine-Na pentahydrate were prepared with chitosan/arabinogalactan-based bioside nanogel samples. After preparing solutions for spectrophotometric analysis, it was found that the release of levothyroxine from the nanocarrier reached 93.8% after 30 minutes, attained a maximum of 98.9% after 1 hour, decreased to

97.5–95.2% between 2–6 hours, increased to 97.9% at 24 hours, and remained at a high level of 98.1–98.3% at 48 and 72 hours.

7. In the experiment, levothyroxine/biopolymer complex at doses of 5 and 10 mg/kg in mice did not produce any detectable lethality. The LD_{50}, as well as other lethality indicators (LD_{10}, LD_{16}, and LD_{84}), were not observed [20,30].
8. In the treatment of experimental hypothyroidism, the new levothyroxine/polymer compound demonstrated high efficacy. Analysis of levothyroxine-Na pentahydrate levels in the blood using liquid chromatography showed 60% on day 3, 10% on day 5, and 1% on day 7, indicating that the administered dose decreased from 60% to 1% over the 7-day period.

PRACTICAL RECOMMENDATIONS

1. Regular thyroid ultrasound screening and urinary iodine assessment are recommended to be conducted by specialists at district polyclinics and family health centers for the early detection of thyroid pathologies and correction of iodine deficiency in schoolchildren from endemic regions of the Azerbaijan Republic.
2. For thyroid nodules evaluated using the TIRADS classification, the combined use of FNAB and compression elastography is necessary to obtain more accurate and reliable results regarding malignancy.
3. To reduce the recurrence rate in the treatment of cystic-colloid nodular goiter, the application of the improved single-session multiple reaspiration sclerotherapy technique is recommended.
4. In the surgical treatment of various forms of nodular goiter, the use of the improved extrafascial total thyroidectomy technique is recommended to reduce complications related to the laryngeal nerves and parathyroid glands.
5. The chitosan/arabinogalactan-based bioside nanogel immobilizing levothyroxine-Na pentahydrate is recommended for use as a medicinal formulation in the treatment of hypothyroidism, administered every three days, with studies conducted in accordance with pharmacopeial requirements.

6. Thus, the gradual release of the active substance from the biopolymer carrier indicates that this nanocarrier could potentially be proposed in the future as a long-acting medicine.

List of Publications

1. Hümmətov, A.F., Abbasov, A.H., Şirinova, X.N. Düyünlü urun müalicəsində total və subtotal tiroidektomiyanın müqayisəli öyrənilməsi //– Bakı: Sağlamlıq, – 2015. №3, – s. 95-102.
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Abbreviations

MSE AR -Ministry of Science and Education of the Republic of Azerbaijan

anti-TPO – Antibodies against thyroid peroxidase

SSMRS – birmomentli çoxsaylı reaspirasiyalı skleroterapiya

NL – Nodular lesion

NG – Nodular goiter

EG – Endemic goiter

EC – Elasticity coefficient

FNAB-Fine-needle aspiration biopsy

IST – inferior-to-superior thyroidectomy

CSE – compression sonoelastography

TG – Thyroid gland

RLN-recurrent laryngeal nerve

LA – Laser Ablation

fT4 – Free thyroxine

fT3 – Free triiodothyronine

TA – Thermal Ablation

TE – Thyroidectomy

TT – Total Thyroidectomy

TSH – Thyroid-Stimulating Hormone

TIRADS – thyroid imaging report data system

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