Doctoral School in Medical Sciences

With manuscript title
U.D.C: 616.441-006-07-089(043.2)

COJOCARU Cristina

OPTIMIZATION OF DIAGNOSTIC METHODS AND SURGICAL TREATMENT OF PATIENTS WITH THYROID NODULES

321.13 SURGERY

Summary of doctoral thesis in medical sciences

Chisinau, 2023

The thesis was pursued within the Department of Surgery no. 5, Dentistry Faculty of "Nicolae Testemitanu" State University of Medicine and Pharmacy, Republic of Moldova.

PhD supervisor:
Bour Alin,
Habilitated Doctor of Medical Sciences, University Professor

Members of the supervision team:
Vudu Lorina,
Doctor of Medical Sciences, Associate Professor

Botoşanu Valerian,
Doctor of Medical Sciences, Associate Professor

Gugava Vahtang, Surgeon

Doctoral thesis defense will take place on *December 7, 2023, at 14:00*, "Nicolae Testemițanu" State University of Medicine and Pharmacy, 165, Stefan cel Mare si Sfant Ave., room 204, at the meeting of the Commission for public defense of the doctoral thesis, approved by the decision of the Scientific Council of the Consortium no. 17 from June 28, 2023.

The Commission for public defense of the doctoral thesis:
Chairman:
Guțu Evghenii,
Habilitated Doctor of Medical Sciences, University Professor

Members:
Bour Alin,
Habilitated Doctor of Medical Sciences, University Professor

Hotineanu Adrian,
Habilitated Doctor of Medical Sciences, University Professor

Cazacov Vladimir,
Habilitated Doctor of Medical Sciences, University Professor

Melnic Eugen,
Habilitated Doctor of Medical Sciences, Associate Professor

Official reference members:
Târcoveanu Eugen,
Doctor of Medical Sciences, University Professor

Vudu Lorina,
Doctor of Medical Sciences, Associate Professor

Sclifos Ina, Doctor of Medical Sciences, Oncologist

Author
Cojocaru Cristina

TABLE OF CONTENTS

CONCEPTUAL FRAMEWORK OF THE RESEARCH

Actuality and importance of the researched problem

Thyroid gland pathology is the most common in the structure of endocrine disorders with an increasing trend in recent years related to endemic iodine deficiency, lack of mass prophylaxis and radioactive contamination [1,2].

The nosological entity, which has currently become the cause of multidisciplinary discussions, represents the thyroid nodule (TN) [3]. The incidence of thyroid nodules increases annually by 0.1% [4,5]. Literature data record a prevalence of over 50% in the world population, being estimated that every second person is a carrier of at least one thyroid nodule, and the most exposed (50 - 90%) to this pathology are women aged 45-50 and over [1,3,6]. In the Republic of Moldova, the morbidity index in nodular pathologies of the thyroid gland is quantified at values of 2.7‰ for men and 6.7‰ for women [1,7,8]. Thyroid nodules (TNs) are detected palpatory in 3 - 7% of cases, in 20 - 70% of cases - by USG, and 50% of cases - at autopsy [9,10].

Solitary or multiple TNs have a clinical variety because they hide a wide range of diseases: colloid goiter, cysts, hypertrophic form of autoimmune thyroiditis, follicular adenoma and thyroid carcinomas [11]. Although the rate of thyroid neoplasms is 7 - 15%, the major clinical importance of thyroid nodules is limited to the exclusion of thyroid carcinoma (TC) regarding the age and sex of patients, history of radiation exposure, family history, and the presence of other risk factors [3,11,12,13,14]. Thyroid carcinoma ranks third among the most common malignant neoplasms affecting women [15,16]. Some Russian authors note that the rate of development of thyroid carcinoma is about 55% on the background of a multinodular goiter and 30% on the background of the solitary nodule [17,18]. It is not excluded that benign tumors can generate cancer of the thyroid gland, an event studied by Arora et al. in a review of 10 years of experience, through which they noted the malignant transformation of 2% of previously confirmed benign nodules [19].

Beside the malignant potential of thyroid nodules, the compression on neighboring organs due to the size and number of thyroid nodules is important, including the thyroid dysfunction by the nodules functional autonomy [3,7,9,12].

The modern diagnosis of thyroid nodules, mainly with the purpose of differentiating malignant nodules from benign ones, is performed by combining serum tests, imaging, nuclear, genetic methods, preoperative cytological and intraoperative histological examinations, systematized according to local experiences and studies in the ATA 2015 Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer; AACE/ACE/AME for clinical practice of diagnosis and management of thyroid nodules updated in 2016; ACR Thyroid Imaging Data and Reporting System (TI-RADS): Report of the ACR TI-RADS Committee and European Thyroid Association Guidelines for stratification of ultrasonographic risk of malignancy in adults: EU-TIRADS [3,20,21,22]. Over time, the recommendations of these guidelines have led to controversial data, with the overstated use of diagnostic methods and the provision of insufficient treatment options in some cases [23].

At the moment, the problem of diagnosis and differential medical-surgical treatment of patients with thyroid nodules is a difficult task in endocrine surgery, since there is no well-established, unified, and unanimously accepted algorithm. Despite multiple laboratory investigations, the diagnosis of thyroid nodules and the type of appropriate treatment for each individual case remain questionable [24,25].

The aim of the study is to optimize the diagnostic methods in patients with thyroid nodules for improving surgical care.

Research objectives:

1. Clinical, hormonal, immunological, imaging, pre- and intraoperative morphological exploration of patients with thyroid nodules and assessment of the correlation between morphological changes and clinical evolution parameters of thyroid nodules.
2. Estimation of sensitivity and specificity of the diagnostic tests for thyroid nodules.
3. Establishment of indications and contraindications for surgical treatment of patients with thyroid nodule and selection of the appropriate extent of surgery.
4. Study of the results of surgical treatment at different postoperative terms (1 month, 3 months, 6 months, 12 months, and 24 months) in accordance with individual clinical-morphological peculiarities.
5. Development of a rational algorithm for diagnosis and treatment of patients with thyroid nodules.

The research methodology. This study represents a clinical trial that was conducted in a series of stages, with retro- and prospective analysis, focused on the evaluation of clinical parameters, results of instrumental diagnostic methods, establishment of optimal treatment and postoperative outcomes of 124 patients with thyroid nodules. The evaluation of patients with TNs included standard methods of examination - serological and urine tests, EKG, chest X-ray; immunological tests – determination of thyroid hormones, TSH, tumor and autoimmune markers; imaging methods, including nuclear imaging – USG, color Doppler, Sonoelastography, Scintigraphy; cytological and histological methods. In order as indications for surgical treatment were estimated, surgery was performed, but the type of thyroidectomy was determined individually. The duration of postoperative surveillance of patients was 24 months, with a view to possible complications and recurrences, and postoperative visits were scheduled after1 month (clinical and hormonal evaluation), 3 months (clinical, hormonal and imaging evaluation), 6 months (clinical, hormonal and imaging evaluation), 12 months (clinical, hormonal and imaging evaluation) and 24 months (clinical, hormonal and imaging evaluation). The research methods used in the study included historical, comparison, descriptive, analytical, observational, biostatistical methods.

The research protocol was approved by the Research Ethics Committee of "Nicolae Testemitanu" State University of Medicine and Pharmacy (minutes no. 84 from June 7, 2017).

The scientific novelty and originality of the research. For the first time in the Republic of Moldova was conducted an interdisciplinary clinical, hormonal, immunological, imaging, morphological pre- and intraoperative study of patients with thyroid nodules, in an effort to estimate the role of various diagnostic methods in determining the management of the patients with thyroid nodules.

The first approach in the complex evaluation of patients with thyroid nodules was the implementation of dopplerography, sonoelastography and intraoperative frozen section (IFS).

For the first time were assessed the sensitivity and specificity of diagnostic methods of patients with thyroid nodules: hormonal study, ultrasonography, color Doppler, sonoelastography, scintigraphy, fine needle aspiration (FNA), intraoperative frozen section.

First time was developed a rational algorithm of diagnosis and differentiated treatment for patients with solitary and multiple thyroid nodules, based on the research findings and scientific arguments.

Unique to the field of thyroid nodules research in our country was the study of the results of surgical treatment of patients in the postoperative period at terms of 1 month, 3 months, 6 months, 12 months and 24 months.

The solved scientific problem in the research is the development of the rational algorithm of diagnosis and differentiated treatment for patients with solitary and multiple thyroid nodules based on the informativeness of the evaluation methods of thyroid nodules in various clinical situations and the selection of optimal thyroidectomy for each case.

Theoretical importance and the applicative value of the research. The results obtained highlighted the clinical, functional, imaging, cytological, and histological peculiarities of thyroid nodules and their interrelations, which are relevant in the diagnosis and treatment of these patients. The diagnostic value of thyroid nodule evaluation methods quantified in the study is essential in assessing the medical-surgical tactics of patients with thyroid nodules, well as a starting point for other studies in this field. The interdisciplinary study led to the elaboration of a rational diagnosis and treatment algorithm for patients with solitary and multiple thyroid nodules, in the absence of such an algorithm in the existing literature and guidelines. The observation of the postoperative results of the patients studied over a period of 24 months provides notable data on the evolution and prognosis of thyroid nodular disease.

The practical importance of the study is given by the implementation of the developed algorithm and practical recommendations in the diagnostic and curative care of patients with thyroid nodules managed by family doctors, endocrinologists, radiologists, surgeons and oncologists.

The scientific-practical results obtained during the study were integrated into the didactic, scientific and clinical activity of the Department of Surgery no. 5, "Nicolae Testemitanu" State University of Medicine and Pharmacy. The algorithm of diagnosis and treatment of patients with thyroid nodules and the use of dopplerography, sonoelastography, intraoperative frozen section in the evaluation of patients with thyroid nodules were implemented in the General Surgery Department of Clinical Hospital "Saint Archangel Michael".

Approval of scientific results. The scientific results obtained during the study were presented, discussed and published in national and international scientific forums: Conference "Nicolae Anestiadi - eternal name of Bessarabian surgery" (Chisinau, Republic of Moldova, 2016); The 7th International Congress for Students and Young Doctors MedEspera (Chisinau, Republic of Moldova, 2018); Annual Scientific Conference of the "Nicolae Testemitanu" State University of Medicine and Pharmacy (Chisinau, Republic of Moldova, 2018); The XIII Congress of the Association of Surgeons "Nicolae Anestiadi" and the III Congress of the Society of Endoscopy, Minimally Invasive Surgery and Ultrasonography "V.M. Gutu" of the Republic of Moldova (with international participation) (Chisinau, 2019); The 8th International Congress for Students and Young Doctors MedEspera (Chisinau, Republic of Moldova, 2020); The V National Congress of Oncology of the Republic of Moldova with international participation "Cancer prevention and control – a continuous challenge!" (Chisinau, 2020); Congress dedicated to the 75th anniversary of "Nicolae Testemitanu" State University of Medicine and Pharmacy (Chisinau, Republic of Moldova, 2020); CONFER 2020. Conferences of the Regional Institute of Oncology Iasi (Iasi, Romania, 2020); Meeting of the Association of Surgeons "Nicolae Anestiadi" of the Republic of Moldova (Chisinau, 2021); Annual Scientific Conference "Research in Biomedicine and Health: Quality, Excellence and Performance" (Chisinau, Republic of Moldova, 2021); Southeastern European Club of Endocrine and Breast Tumors (SECEBT) (Iasi, Romania, 2022); The 9th

International Congress for Students and Young Doctors MedEspera (Chisinau, Republic of Moldova, 2022); National Congress of Surgery (Sinaia, Romania, 2022); Annual Scientific Conference "Research in Biomedicine and Health: Quality, Excellence and Performance" Chisinau, Republic of Moldova, 2022); Medical Days of the Clinical Hospital "Saint Archangel Michael" (Chisinau, Republic of Moldova, 2022); CONFER 2022. Conferences of the Regional Institute of Oncology Iasi (Iasi, Romania, 2022).

The results of the thesis were discussed and approved during the Meeting of the Department of Surgery nr. 5 of the "Nicolae Testemitanu" State University of Medicine and Pharmacy (minutes no. 9 from May 26, 2023) and the Scientific Seminar "Surgery" of the "Nicolae Testemitanu" State University of Medicine and Pharmacy (minutes no. 4 from June 21, 2023).

Publications on the topic of the thesis. On the topic of the thesis were published 23 scientific papers, of which: articles in international journals indexed in Web of Science - 1; articles in journals from the National Register of profile journals of category B - 4; materials / theses at conferences: international (abroad) - 4, international (Republic of Moldova) - 4; national with international participation - 2; national - 3, and posters (from abroad) - 2; posters (from the country) - 3. Oral communications were reported at 7 scientific forums. 3 innovation certificates were registered.

Summary of thesis chapters. The thesis includes the list of abbreviations, introduction, 4 chapters, synthesis of the obtained results, general conclusions and recommendations, a bibliography with 211 literary sources on the topic of the thesis, annexes, declaration of responsibility and CV of the candidate.

Keywords: thyroid nodules, thyroid carcinoma, intraoperative frozen section, algorithm, surgical treatment.

THESIS CONTENT

1. THYROID NODULES – THE CURRENT ADVANCES IN DIAGNOSIS AND SURGICAL TREATMENT

This chapter includes extensive study of literature information by retrieving data from accredited databases, international guidelines, clinical trials, reviews and meta-analyses on thyroid nodules. The historical, anatomical, epidemiological, etiopathogenetic, clinical, diagnostic and curative attributes of thyroid nodules were described. Has been noted the controversies and unsolved problems existing at the moment in the management of thyroid nodules.

2. DESCRIPTIVE ANALYSIS OF STUDY MATERIAL AND RESEARCH METHODS

Within the Department of Surgery no. 5 of the "Nicolae Testemitanu" State University of Medicine and Pharmacy an interdisciplinary serial clinical trial was conducted, with the accumulation of the material during 2012 – 2022.

Inclusion criteria:

1. Discerning persons.
2. Men and women aged between 18 and 75 years.
3. Patients with the diagnosis of thyroid nodule established by clinical and imaging methods.
4. Human subjects who voluntarily and consciously signed the informed consent.

5. Persons who are fit and able to complete the study according to protocol.

Exclusion criteria:

a. Human subjects who have not signed the informed consent.
b. Patients who for various reasons are not fit and unable to complete the study according to protocol.
c. Patients with other pathologies of the thyroid gland that do not fit into the nosological entity of nodular formation.
d. People with various health conditions that may compromise the results of the study or be withdrawn from the study.
e. Patients with serious concomitant pathologies that pose a major risk in the occurrence of pre, intra- and postoperative complications.
f. Human subjects participating or wishing to participate concomitantly in another study.

After applying selection and exclusion criteria, a group of 124 patients with clinically and/or imaging confirmed solitary or multiple thyroid nodules were integrated into the study.

The patients included in the research were identified by family doctors, endocrinologists, radiologists or independently addressed to the research team.

Gender division of 124 participants in the research, revealed 104 (83.87%) (95% CI 77.4 - 90.3) women, and 20 (16.13%) (95% CI 9.7 - 22.6) men. The age of the patients ranged from 19 to 71 years. The average age was 46.79 years among women it was 47.55 years, and 42.85 years among men.

According to anamnestic information, patients indicated the duration of the disease from 1 month to 10 years (240 months) with an average duration of pathology of 47.13 months, which means about 4 years. Although patients were followed up by an endocrinologist or complete an endocrinological examination, 104 (83.9%) (95% CI 77.4 - 90.3) patients did not achieve disease remission despite drug treatment, 17 (13.7%) (95% CI 8.1 - 19.4) patients due to high suspicion of malignancy and obvious increase in TN size in a short time did not follow conservative treatment, and 2 (1.6%) (95% CI 0.0 - 4.0) patients developed contralateral relapse of disease after hemithyroidectomy and 1 (0.8%) (95% CI 0.0 - 2.4) - ipsilateral relapse after subtotal lobectomy. Patients, who had previously undergone surgical treatment, performed the interventions in other surgical clinics.

The initial clinical diagnosis in 75 (60.49%) (95% CI 52.4 - 69.4) patients was solitary NT and 49 (39.51%) (95% CI 30.6 - 47.6) patients presented with multinodular goiter.

In the first stage, patients with TNs were examined clinically, by standard laboratory and by instrumental investigations, to detect nodules suspected of malignancy. In the next stage, in order to increase the informativeness of the results obtained, a number of patients were additionally investigated by Dopplerography, sonoelastography, preoperative cytological (ultrasound-guided fine needle aspiration - FNA) and intraoperative (frozen section - IFS) investigation, thus increasing the success of detecting suspicious for malignancy TNs and confirmation of the diagnosis, and determination of the appropriate extent of surgery.

The duration of active monitoring of patients was 24 months and was divided into 5 visits - at 1 month, 3 months, 6 months, 12 months and 24 months.

The design of the research is shown in Figure 1.

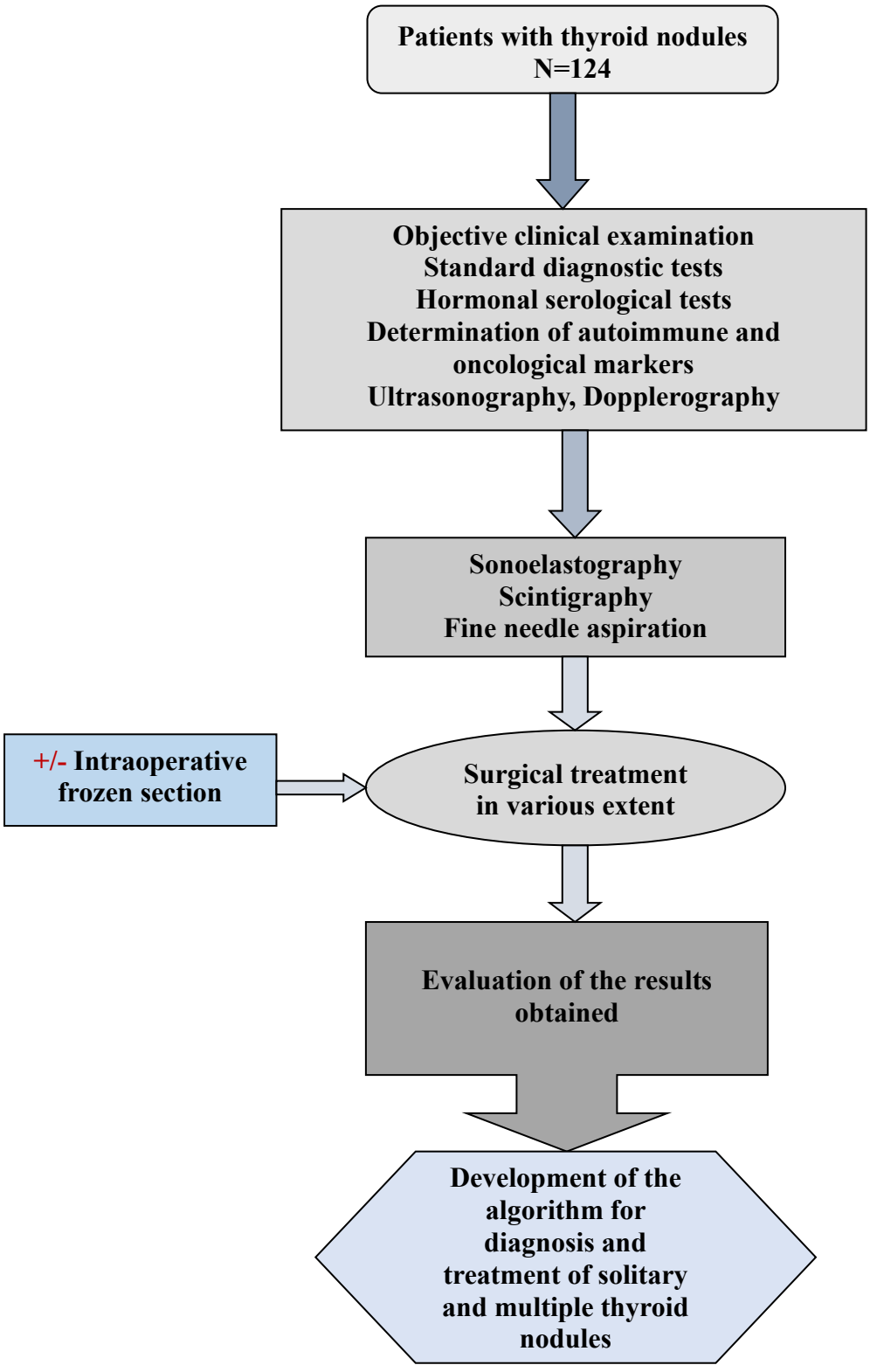

Figure 1. **The design of the study**

The thyroidectomy technique we tackled in research comprised several steps:

I. Under the general anesthesia with orotracheal intubation, after preparing and delimitation of the operating field, the incision was sketched by pressing with a suture on the skin, located about 2.5 cm above the jugular incision of the sternal manubrium,

bilaterally extended towards to the anterior edge of the sternocleidomastoid muscles with incision of the skin, subcutaneous tissue, and platysma – inferior cervicotomy.

II. Detachment of the upper flap to the upper edge of the thyroid cartilage, and the lower flap to the sternal manubrium with the exposition of the subhyoid muscles, sternohyoid muscle, and anterior jugular veins (ligation), with subsequent incision of the "linea alba" of the neck.

III. Finger or instrument assisted mobilization of sternohyoid and sternothyroid muscles, with their lateral spacing without incision and exposition of the anterior surface and external edges of the thyroid gland.

IV. Release of the affected lobe from adhesions with adjacent tissues for inspection of the posterior face of the gland and identification of parathyroid glands and recurrent nerves.

V. Incision of the thyroid isthmus between two ligatures, after it has been detached from the anterior surface of the trachea.

VI. Cautious mobilization of the thyroid lobe from the trachea, neurovascular bundle and parathyroid glands with separate ligation of the upper, middle and lower thyroid arteries and veins – lobectomy with or without dissection of the capsule. The current method of mobilization applied in this study provides for the use of a minimal number of hemostatic forceps (1-3), which differs from the classical Kocher method, where numerous hemostatic forceps are used, which reduce the tissue visibility and operating comfort.

VII. In case of extent for total thyroidectomy - contralateral lobectomy is performed in the same manner.

VIII. In subtotal thyroidectomy, each lobe is partially resected subcapsular and keeping a glandular stump at the level of the inferior thyroid artery.

IX. Control of hemostasis, drainage of the thyroid lodge(s) and suturing by anatomical planes. Finishing the intervention by applying intradermal suture.

3. CLINICAL ASSESSMENT AND PARACLINICAL RESULTS OF PATIENTS WITH THYROID NODULES

3.1. Clinical manifestations of thyroid nodules

The clinical picture of the patients included in the study alternates from modest signs to obvious signs of compression on adjacent structures and thyroid dysfunction. Clinical manifestations are systematized in table 1.

Personal pathological history was recorded in 58 (46.77%) (95% CI, 47.1 - 66.0) patients represented by thyroid and non-thyroid disorders. The frequency and interpolation of concomitant pathologies in patients with TNs are shown in figure 2.

The objective clinical examination included the two important steps: inspection and palpation. At the inspection of the cervical region, we followed the shape of the neck, the color of the skin, the presence and dimensions of the lump in the TG projection, the mobility in the act of swallowing. At the palpation were appreciated the consistency of TG and TNs, dimensions, elasticity and mobility of TNs, the presence of the cervical lymphadenopathy.

Table 1. **Clinical manifestations of patients with thyroid nodules**

Clinical signs		Frequency no. (%)	95% CI
Discomfort/pain in anterior cervical region	Absent	5 (4.0)	0.8 - 8.1
	Present	**119 (96.0)**	**91.9 - 99.2**
Globus sensation	Absent	18 (14.5)	8.9 - 21.0
	Present	**106 (85.5)**	**79.0 - 91.1**
Fatigue	Absent	34 (27.4)	19.4 - 34.7
	Present	**90 (72.6)**	**65.3 - 80.6**
Visible cervical lump	Absent	49 (39.5)	30.7 - 48.4
	Present	**75 (60.5)**	**51.6 - 69.3**
Emotional lability and/or irritability	Absent	69 (55.6)	47.6 -64.5
	Present	**55 (44.4)**	**35.5 - 52.4**
Heart palpitations	Absent	81 (65.3)	57.3 - 74.2
	Present	**43 (34.7)**	**25.8 - 42.7**
Dyspnea	Absent	104 (83.9)	77.4 - 90.3
	Present	**20 (16.1)**	**9.7 - 22.6**
Tremor	Absent	109 (87.9)	81.5 - 93.5
	Present	**15 (12.1)**	**6.5 - 18.5**
Sweating	Absent	113 (91.1)	85.5 - 95.2
	Present	**11 (8.9)**	**4.8 - 14.5**
Weight loss	Absent	119 (96.0)	91.9 - 99.2
	Present	**5 (4.0)**	**0.8 -8.1**
Dysphonia	Absent	120 (96.8)	92.7 - 99.2
	Present	**4 (3.2)**	**0.8 - 7.3**

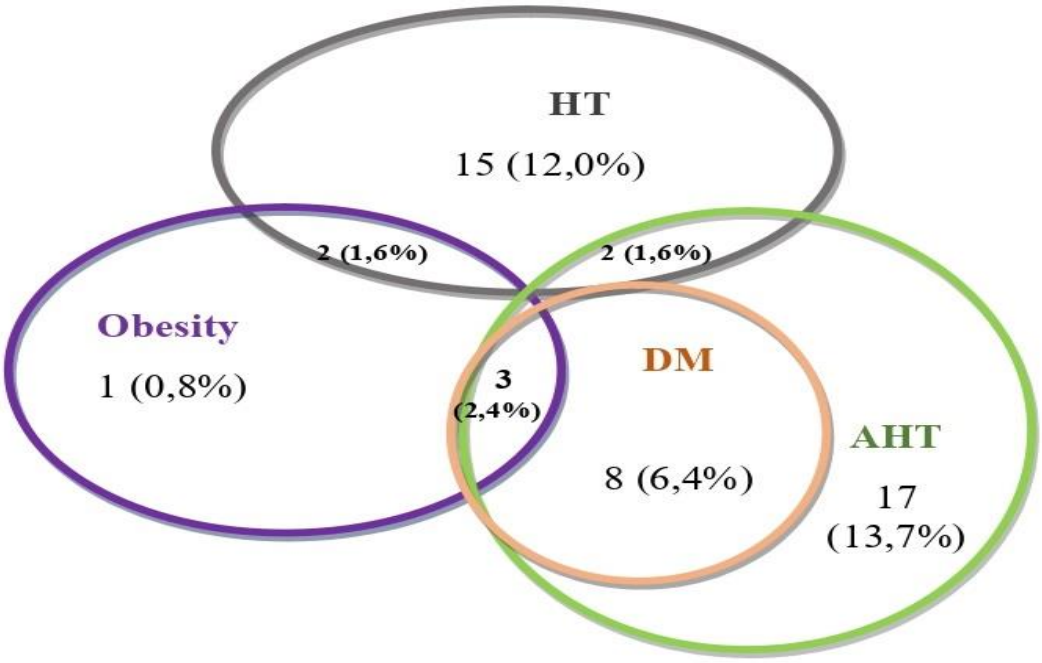

Figure 2. **Frequency and interpolation of concomitant pathologies in patients with TNs**

TNs were located predominantly in the right thyroid lobe 44 (35.5%) (95% CI 27.4 - 44.4) (figure 3). Bilateral TNs were determined in 37 (29.8%) (95% CI 21.8 - 37.9) patients, and nodules in the left thyroid lobe were appreciated in 36 (29.0%) (95% CI 21.8 - 37.9) patients. Nodules

located in the isthmus were recorded in 5 (4.0%) (95% CI 0.8 - 8.1) patients and only in 2 (1.6%) (95% CI 0.0 - 4.0) cases, TNs were appreciated in the isthmus and a part of one lobe.

Figure 3. **Image of the a female patient with a right sided thyroid nodule (II degree, WHO): A – anterior image; B- profile image**

Unlike women, in men TNs was mostly established in one anatomical part of TG (lobe or isthmus) and only in 2 (1.6%) cases TNs were appreciated in both lobes (figure 4).

Cervical adenopathy was detected palpatory in compartment III on the right side only in one patient.

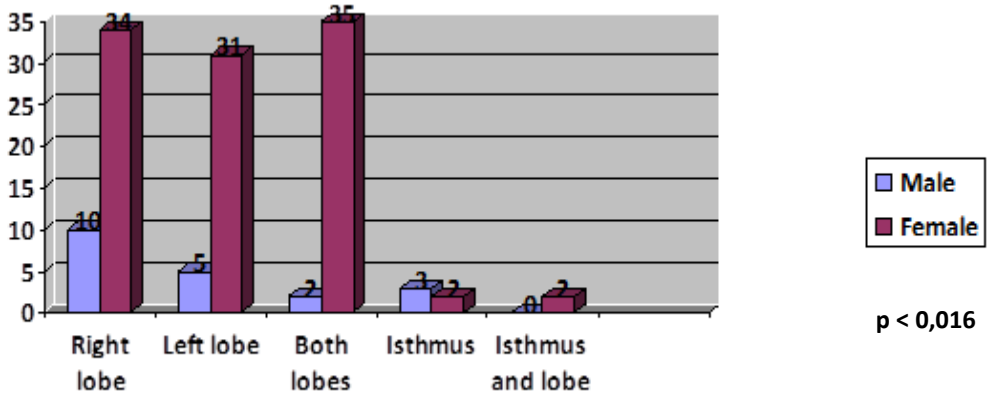

Figure 4. **Localization of TNs according to gender**

3.2. Function diagnosis of thyroid nodules and results of standard tests

The assessment of the functional status of TNs was based on the values of T_3/FT $_3$, T_4/FT_4 and TSH. Triiodthyronine values below the lower limit of the reference range were identified in 4 (3.2%) patients, and exceeding the upper limit was found in 2 (1.6%) patients. Thyroxine levels were below the norm in 1 (0.8%) patient, with high values determined in 4 (3.2%) patients. A decreased TSH was found in 9 (7.2%) cases, while an increased TSH was observed in 2 (1.6%) patients.

Markers of autoimmune processes Anti-TPO and Anti-Tg showed high elevations in 2 (1.6%) (95% CI 0.0 - 4.0) patients. Independently, Anti-TPO was increased in 7 (5.6%) (95% CI 1.6 - 9.7) patients, and Anti-Tg in 2 (1.6%) (95% CI 0.0 - 4.0) patients. The presence of these

antibodies demonstrates the occurrence of TNs on the background of Hashimoto's autoimmune thyroiditis, Anti-TPO being associated to a greater degree with this condition than Anti-Tg.

Testing for calcitonin revealed values above normal range in 3 (2.4%) (95% CI 0.8 - 7.3) patients, and Tg obtained values were elevated in 7 (5.6%) (95% CI 1.6 - 9.7) patients. Synchronous elevation of both tumor markers was not detected in any patient.

TG scintigraphy was performed in 115 patients and tracked function autonomy estimation of TNs. Most TNs were hypofunctional, occurring in 92 (74.2%) (95% CI 66.9 - 81.5) patients (figure 5).

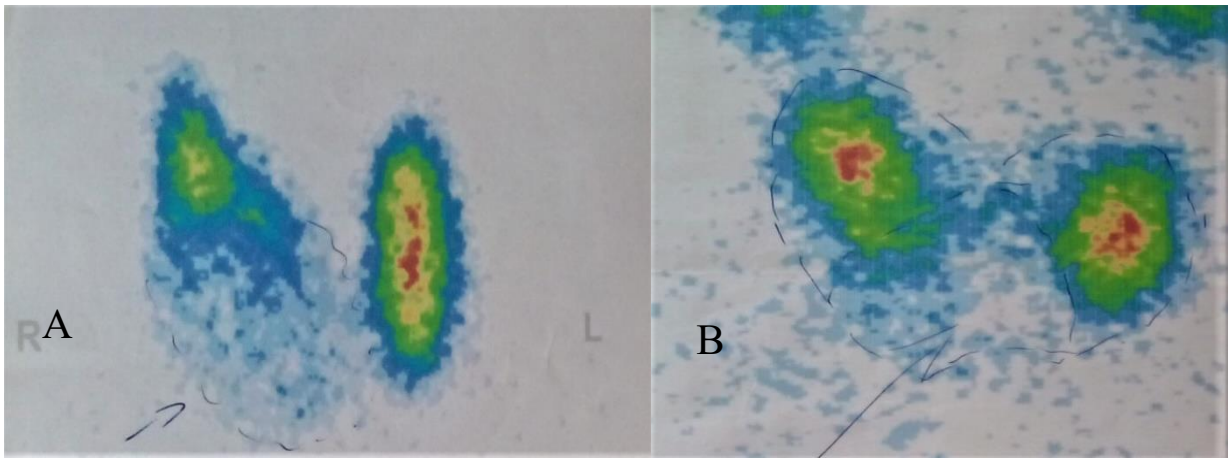

Figure 5. **"Cold" scintigraphic thyroid nodules: A - right lobe nodule; B – nodule in the lower pole of the right lobe and the isthmus**

Hyperfunctional nodules were detected in 11 (8.9%) (95% CI 4.0 - 14.5) patients and in 8 (6.5%), (95% CI 2.4 - 11.3) cases were "warm". In 4 (3.2%) (95% CI 0.8 - 7.3) patients, TNs were not detected at scintigraphy because of the posterior location that cannot afford adequate images. Also, TNs size in multinodular goiter < 1.0 cm was not detected in all cases.

Indices of standard blood samples – general and biochemical analysis of blood, coagulogram showed no deviations. After the ABO blood type system, patients with blood type A(II) predominantly developed TNs - 64 (51.6%) (95% CI 42.7 - 60.5) cases, followed by patients with blood type O(I) - 33 (26.6%) (95% CI 19.4 - 34.7) and B (III) - 21 (16.9%) (95% CI 10.5 - 24.2), and patients with blood type AB (IV) were affected in a smaller number - 6 (4.8%) (95% CI 1.6 - 8.9). A prevalence of TNs was also found in patients with Rh positive factor 106 (85.5%) (95% CI 79.0 - 91.1), as opposed to patients with Rh negative factor - 18 (14.5%) (95% CI 8.9 - 21.0).

The urinalysis in studied patients revealed no changes. At the chest X-ray there were no peculiarities. In the ECG of the studied patients, changes occurred in 18 (14.5%) (95% CI 8.9 - 21.0) cases, which were manifested by rhythm disturbances - 5 (4.0%) (95% CI 0.8 - 8.1), conduction abnormalities - 4 (3.2%) (95% CI 0.8 - 7.3), left ventral hypertrophies - 2 (1.6%) (95% CI 0.0 - 4.0) and combined changes - 7 (5.6%) (95% CI 1.6 - 9.7) cases, related to the cardiotropic effect of thyroid hormones and more to concomitant pathologies.

3.3. Diagnostic value of ultrasonography in thyroid nodules

The dimensions of the evaluated TNs ranged from 0.8 to 6.0 cm. According to the distribution by dimensional groups (table 2), most patients had TNs with size ≥ 0.8 and ≤ 1.9 cm, with the number of patients decreasing in the next dimensional groups.

Table 2. **Distribution of patients with thyroid nodules by nodule sizes**

Nodule sizes (cm)	Frequency no. (%)	95% CI
0.8-1.9	56 (45.2)	35.5 - 54.0
2.0-2.9	32 (25.8)	18.5 - 33.9
3.0-3.9	20 (16.1)	9.7 - 22.6
4.0-4.9	11 (8.9)	4.0 - 14.5
5.0-6.0	5 (4.0)	0.8 - 8.1
Total	124 (100.0)	100.0 - 100.0

The composition of TNs in more than half of patients 80 (64.5%) (95% CI 55.6 - 72.6) was combined, solid nodules were appreciated in 38 (30.6%) (95% CI 22.6 - 37.9) cases and in 6 (4.8%) (95% CI 1.6 - 8.9) cases were revealed cystic nodules. The content of TNs is also reflected on their echogenicity. Ordinary echogenicity (isoechogenicity) of TNs was recorded in 52 (41.9%) (95% CI 33.9 - 51.6) patients, hypoechogenicity - in 46 (37.1%) (95% CI 28.2 - 45.9) patients, and hyperechoic and anechoic TNs were determined in 24 (19.4%) (95% CI 1.9 - 25.8) and 2 (1.6%) (95% CI 0.0 - 4.0) patients, respectively.

By shape, "wider than tall" TNs predominated, "taller than wide" constituting only 11 (8.9%) (95% CI 4.0 - 1 3.7) cases. And the edges of nodules were most often clearly visualized, being smooth in 106 (85.5%) (95% CI 79.0 - 91.1) cases. Extrathyroid extension was not found among the evaluated nodules. Echogenic foci as macrocalcifications and punctate foci were appreciated in 10 (8.1%) (95% CI 3.2 - 13.7) and correspondingly in 9 (7.3%) (95% CI 3.2 - 12.1) cases (figure 6).

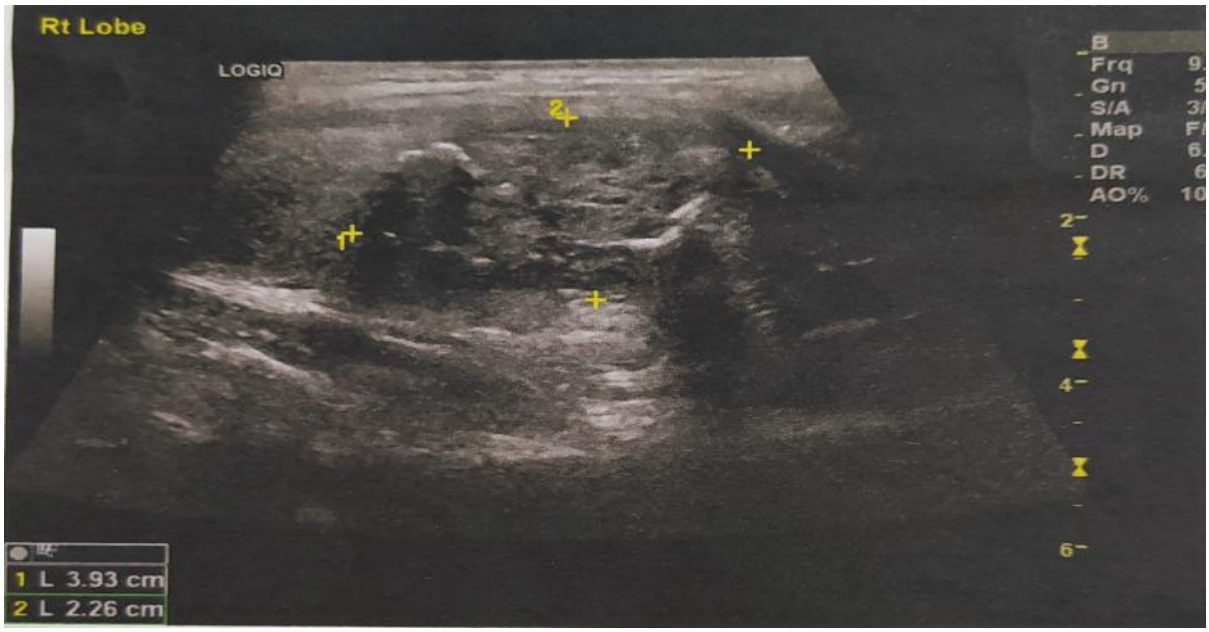

Figure 6. **Ultrasound aspect of TN of inhomogeneous structure with liquid inclusions, hypoechoic, irregular margins, peripheral and central point calcifications (TI-RADS 5)**

When exploring the cervical region, except for the assessment of TNs according to TI-RADS criteria, regional cervical ganglia were also examined. Cervical adenopathy was detected by

ultrasound in 10 (8.1%) (95% CI 3.2 - 1 2.9) patients. In one case, adenopathy showed suspected ultrasound signs of malignancy, while in the rest of the cases reactive changes were reported.

The most common type of TNs vascularity, estimated by *Color Doppler*, was mixed, which signifies intra- and perinodular vascularization, followed by peripheral, intranodular vascularization, and in a lower percentage TNs were avascular (figure 7).

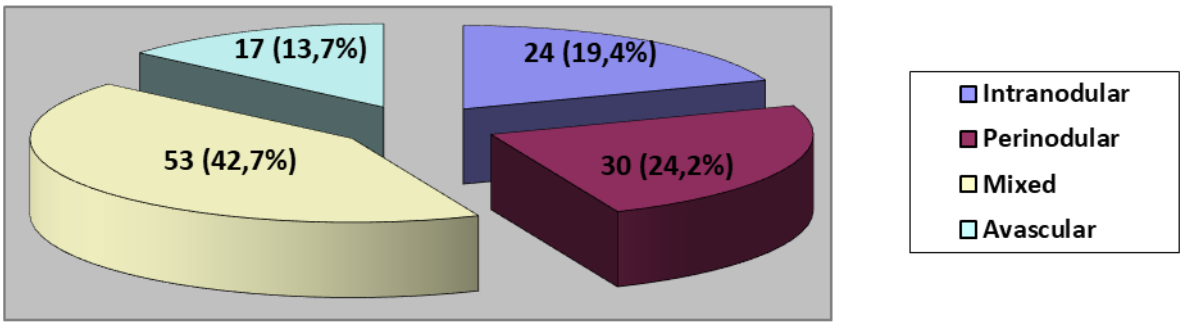

Figure 7. **Vascularization types of thyroid nodules**

Sonoelastography was possible to perform in 114 patients. Sonoelastographic TNs were manifested by elastic tissues in 93 (74.4%) (95% CI 66.9 - 81.5) patients, and with stiff tissues were noted in 21 (16.9%) (95% CI 10.5 - 23.4) cases.

Combining 2D ultrasound image with sonoelastography and dopplerography increases the quality of the TNs image by clearly delimiting from adjacent tissues, especially isoechogenic nodules, identifying solid areas with increased stiffness and intense peri- and/or intranodular vascularization. In our research, no nodules were found, integrating all of highly suspicious ultrasound signs - solid, highly hypoechogenic content, "taller than wide", with extra thyroid extension and microcalcifications.

3.4. Cytological and histological findings and peculiarities of thyroid nodules

After TIRADS evaluation, 53 patients underwent FNA. According to the cytogram, patient distribution was performed by TBSRTC categories (table 3).

Table 3. **Distribution of patients with thyroid nodules according to cytological result**

Bethesda Category	Frequancy no. (%)	95% CI
Nondiagnostic	2 (1.6)	0,0 – 4,0
Benign	17 (13.7)	8.1- 20.2
Atipia of undetermined significance	14 (11.3)	5.6 - 16.9
Follicular/oncocytic neoplasm	11 (8.9)	4.0 - 14.5
Suspicion of malignancy	8 (6.5)	2.4 - 11.3
Malignant	1 (0.8)	0.0 - 2.4

Is noted that benign TNs was the category in which the largest number of patients were included. An impressive number of patients were diagnosed with Atipia of undetermined

significance and follicular or oncocytic neoplasm, these Bethesda categories are considered indetermined, which require confirmation of malignancy by using other methods.

We used IFS to exclude the malignant process, certify undetermined cytological diagnosis and guide in the need to extend thyroidectomy and performed 83 procedures. Benign lesions such as hyperplastic, thyroid, colloid or adenomatous nodules constituted 69 (55.6%) (95% CI 46.8 - 63.7) cases. Frozen section with malignant result were found in 14 (11.3%) (95% CI 5.6 - 16.9) cases.

Differentiating benign follicular lesions from malignant ones involves visualizing the nodule capsule, whose invasion signifies a malignant process and can only be detected by histological examination, cytograms not being conclusive in these situations.

Benign results obtained on IFS determined the finishing thyroidectomy in the initial scheduled volume. In the case of reporting malignant results we extended to total thyroidectomy. The patient informative consent about type of thyroidectomy was obtained preoperatively, after information, explanations and consensual discussions.

Postoperative removed material in all patients were subjected to histopathological investigation by which the final diagnosis was established (table 4).

Table 4. **Distribution of TNs patients according to histopathological result**

Histopathological result	Frequency no. (%)	95% CI
Goiter	43 (34.7)	26.6 – 43.5
Papillary carcinoma	8 (6.5)	2.4 - 11.3
Papillary carcinoma, follicular variant	3 (2.4)	0.0 - 5.6
Follicular carcinoma	10 (8.1)	4.0 - 12.9
Hürthle cell carcinoma	1 (0.8)	0.0 - 2.4
Follicular adenoma	57 (46.0)	36.3 - 54.0
Oncocytoma	2 (1.6)	0.0 – 4.0
Total	124 (100.0)	100.0 - 100.0

The majority of TNs were of benign etiology, represented essentially by follicular adenoma in 46.0% and goiter in 34.7%. Malignant tumors were detected in 22 (17.74%) (95% CI 10.4 - 24.6) cases, being represented by differentiated carcinomas. Compared to literature data, the frequency of malignant TNs in our study exceeds the reported data of 5-15% [3,12,20,24].

At the examination of the tissue samples, we did not find complete invasion of the tumor capsule and of the thyroid capsule, respectively, which means the absence of extrathyroidal extension and intact surgical resection margin.

3.5. Clinical features of malignant thyroid nodules and accuracy of diagnostic methods

According to age groups, TC affected the majority of patients aged 25 to 34 years in 8 (36.4%) (CI 15.8 - 57.9 years) cases, in a smaller number the patients aged 55 to 64 years, and in other groups showing a constant frequency (table 5).

Table 5. **Distribution of patients with malignant thyroid nodules by age groups**

Age group (years)	Frequency no. (%)	95%CI
25-34	8 (36.4)	15.8 - 57.9
35-44	4 (18.2)	4.3 - 35.0
45-54	4 (18.2)	4.0 - 36.4
55-64	2 (9.1)	0.0 - 23.5
65-74	4 (18.2)	3.8 - 35.0
Total	22 (100.0)	100.0 - 100.0

In male patients, malignant TNs were detected in 5 (25%) (95% CI 4.3 - 39.1) cases and predominantly confirmed as papillary carcinoma, in an equal proportion of conventional and follicular variants, and follicular carcinoma was found in only one case. Most FTC cases were found among women, including one case of HTC, followed by classic and follicular PTC (figure 8). Consequently, women are more prone to thyroid tumors with risk of invasiveness and distant metastasis.

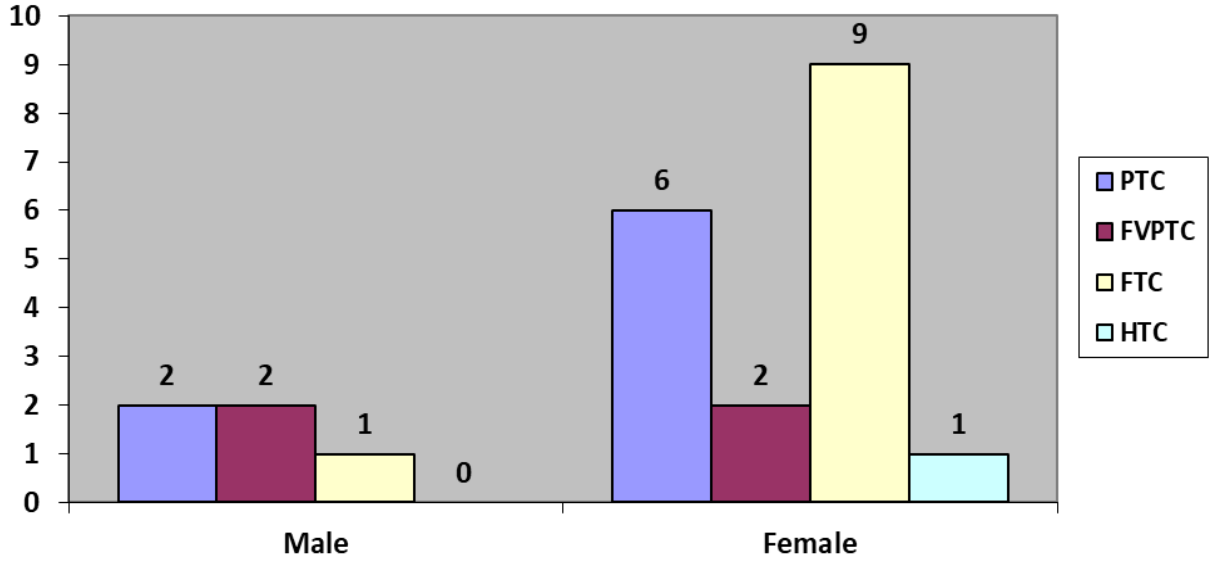

Figure 8. **Distribution of patients with malignant thyroid nodules by gender**

It should be mentioned that malignant TNs by size integrated mainly into the group of 1.0 - 1.9 cm and did not exceed the diameter of 4.0 cm.

The functional status of malignant TNs was primarily euthyroid, in euthyroidism were 19 (86.4%) patients. The patient diagnosed with oncocytic carcinoma had hypothyroidism, and 2 (9.1%) patients, confirmed with PTC, manifested hyperthyroidism. When estimating the statistical indicators, we obtained the values shown in table 6.

High Tg values were found in 3 FTC patients and one PTC patient, but also in 3 patients with follicular adenoma, which implies a reduced preoperative information as a tumor marker, but indirectly orients us to a degenerative process in thyroid follicles.

Table 6. **Statistical indicators of diagnostic accuracy of hormonal tests**

Indicator	Value	95%CI
Sensibility	13.64%	2.91% - 34.91%
Specificity	94.12%	87.64% - 97.81%
FPR	2.32	0.63 - 8.57
TPR	0.92	0.77 - 1.09
PPV	33.33%	11.92% - 64.88%
NPV	83.48%	80.95% - 85.73%
Accuracy	79.84%	71.69% - 86.51%

As mentioned, no case of MTC was detected histopathologically, so elevated preoperative calcitonin levels were irrelevant, being associated with follicular adenoma, Hürthle cell carcinoma and papillary carcinoma.

According to scintigraphy results in 17 (89.5%) patients with malignancy TNs were hypofunctional, in 2 (10.5%) were hyperfunctional, last ones being confirmed as FTC. The diagnostic value of scintigraphy is shown in table 7.

Table 7. **Statistical indicators of diagnostic accuracy of TNs scintigraphy**

Indicator	Value	95%CI
Sensibility	10.53%	1.30% - 33.14%
Specificity	89.29%	80.63% - 94.98%
FPR	0.98	0.23 - 4.18
TPR	1.00	0.84 - 1.19
PPV	18.18%	4.96% - 48.62%
NPV	81.52%	78.80% - 83.96%
Accuracy	74.76%	65.24% - 82.80%

The high percentage of specificity and NPV means that scintigraphy correctly determines subjects who do not show TC.

In order to estimate the diagnostic value of USG in the evaluation and detection of malignant TNs, statistical parameters were calculated for each ultrasound features (table 8).

Table 8. **Statistical indicators of diagnostic accuracy of TNs ultrasonography**

Indicator	Composition	
	Value	**95% CI**
Sensibility	100.00%	84.56% - 100.00%
Specificity	5.88%	2.19% - 12.36%
FPR	1.06	1.01 - 1.12
TPR	0.00	

PPV	18.64%	17.92% - 19.39%
NPV	100.00%	
Accuracy	22.58%	15.56% - 30.96%

Indicator	**Echogenicity**	
	Value	**95% CI**
Sensibility	72.73%	49.78% - 89.27%
Specificity	45.10%	35.22% - 55.26%
FPR	1.32	0.97 - 1.81
TPR	0.60	0.30 - 1.24
PPV	22.22%	17.32% - 28.04%
NPV	88.46%	78.95% - 94.00%
Accuracy	50.00%	40.89% - 59.11%

Indicator	**Shape**	
	Value	**95% CI**
Sensibility	22.73%	7.82% - 45.37%
Specificity	94.12%	87.64% - 97.81%
FPR	3.86	1.29 - 11.53
TPR	0.82	0.65 - 1.04
PPV	45.45%	21.82% - 71.33%
NPV	84.96%	81.75% - 87.68%
Accuracy	81.45%	73.48% - 87.86%

Indicator	**Margin**	
	Value	**95% CI**
Sensibility	9.09%	1.12% - 29.16%
Specificity	84.31%	75.78% - 90.76%
FPR	0.58	0.14 - 2.34
TPR	1.08	0.92 - 1.26
PPV	11.11%	3.00% - 33.55%
NPV	81.13%	78.62% - 83.41%
Accuracy	70.97%	62.14% - 78.77%

Indicator	Echogenic foci	
	Value	**95% CI**
Sensibility	9.09%	1.12% - 29.16%
Specificity	83.33%	74.66% - 89.98%
FPR	0.55	0.14 - 2.19
TPR	1.09	0.93 - 1.28
PPV	10.53%	2.84% - 32.10%
NPV	80.95%	78.39% - 83.27%
Accuracy	70.16%	61.29% - 78.04%

Indicator	Cervical lymphadenopathy	
	Value	**95% CI**
Sensibility	18.18%	5.19% - 40.28%
Specificity	94.12%	87.64% - 97.81%
FPR	3.09	0.95 - 10.04
TPR	0.87	0.71 - 1.06
PPV	40.00%	17.03% - 68.41%
NPV	84.21%	81.32% - 86.72%
Accuracy	80.65%	72.58% - 87.19%

A high sensitivity of solid and hypoechogenic nodules is revealed, inversely proportional to accuracy. While nodules of "taller than wide" shape, with irregular margins, echogenic foci accompanied by neoplastic cervical lymphadenopathy are distinguished by high specificity and accuracy.

Malignant TNs, possessed mostly mixed and active vascularization, despite data reported by other authors by which the intranodular type means a TC. Intranodular vascularization was documented in two patients with PTC and one patient confirmed with FTC. Thus, the diagnostic value of dopplerography is indicated in table 9.

Table 9. **Statistical indicators of diagnostic accuracy of TNs dopplerography**

Indicator	Dopplerography	
	Value	**95% CI**
Sensibility	75.00%	47.62% - 92.73%
Specificity	38.81%	27.14% - 51.50%
FPR	1.23	0.87 - 1.72
TPR	0.64	0.26 - 1.59
PPV	22.64%	17.22% - 29.16%
NPV	86.67%	72.54% - 94.12%
Accuracy	45.78%	34.79% - 57.08%

Therefore, we noted a high sensitivity of dopplerography, which helps to establish the malignant features of nodules.

The statistical parameters of sonoelastography in relation to malignant TNs were also assessed (table 10).

Table 10. **Statistical indicators of diagnostic accuracy of TNs sonoelastography**

Indicator	**Sonoelastography**	
	Value	**95% CI**
Sensibility	53.00%	48.32% - 89.37%
Specificity	89.69 %	76.54% - 95.18%
FPR	0.1	0.08 - 0.6
TPR	0.53	0.11 - 0.6
PPV	47.36%	36.79% - 57.08%
NPV	91.57%	84.75% - 97.27%
Accuracy	84.21%	80.63% - 94.98%

Table 11. **Ultrasound manifestations of TNs with FTC**

Indicators	**Number of patients**
Composition	
Solid	n=1
Cystic	n=1
Combined	n=8
Echogenicity	
Isoechogenic	n=8
Hypoechogenic	-
Hyperechogenic	n=2
Shape	
Taller than wide	-
Wider than taller	n=10
Margins	
Regular	n=9
Irregular	n=1
Echogenic foci	
Present	-
Absent	n=10
Lymphadenopathy	
Present	n=1
Absent	n=9
Vascularization	
Perinodular	n=3
Intranodular	n=1
Mixed	n=6

Similar to other diagnostic methods, sonoelastography showed significant specificity, NPV and accuracy.

We want to specify that the ultrasound picture is not identical for all cancers. It is known that TI-RADS criteria have been accepted based on common ultrasound features of PTC, which are not found with the same probability in the FTC. We aimed to systematize the ultrasound characteristics of patients confirmed with FTC (table 11).

The divergences of TNs harboring FTC from those with PTC are notable and are characterized by solid composition with fluid inclusions, predominantly isoechogenic, ovoid shape with horizontal diameter larger than anteroposterior, with regular margins and mixed vascularization. The presence of calcinates and lymphadenopathy are not typical for FTC.

The definitive diagnosis of malignant TNs was also correlated with preoperative cytological specimens. The diagnostic value of FNA is given in table 12.

Table 12. **Statistical indicators of diagnostic accuracy of FNA in malignant TNs**

Indicator	**FNA**	
	Value	**95% CI**
Sensibility	69.20%	55.51% - 82.89%
Specificity	29.51%	17.17% - 41.85%
FPR	1.06	0.79 – 1.33
TPR	0.97	0.29 – 2.23
PPV	22.50%	13.45% - 31.55%
NPV	76.47%	71.24% - 81.70%
Accuracy	61.40%	50.17% - 72.63%

The low informativeness of the method in our research is possible determined by some technical factors and pathological anatomy. It is technically important to take suitable cellular material, even if most TNs is combined. It is also difficult to differentiate benign and malignant follicular structures without visualization of the tumor capsule.

Table 13. **Statistical indicators of diagnostic accuracy of IFS in malignant TNs**

Indicator	**IFS**	
	Value	**95% CI**
Sensibility	75.00%	47.62% - 92.73%
Specificity	96.97%	89.48% - 99.63%
FPR	24.75	6.14 - 99.74
TPR	0.26	0.11 - 0.60
PPV	85.71%	59.82% - 96.03%
NPV	94.12%	87.25% - 97.40%
Accuracy	92.68%	84.75% - 97.27%

The occurrence of tissue changes following repeated FNA, leading to fibrosis, necrosis, hemorrhage, vascular thrombosis, squamous metaplasia, cystic and adenomatous degeneration, pseudo capsular invasion, is also not excluded.

Intraoperative histological results were also correlated with histopathological outcome (table 13).

IFS in our study is the almost ideal diagnostic test due to sensitivity and specificity values. According to the ROC curve representation and estimate, AUC has moderate diagnostic accuracy (figure 9).

AUC: 0,701
Standard error: 0,078
P: < 0,003
95% CI: 0,548-0,854

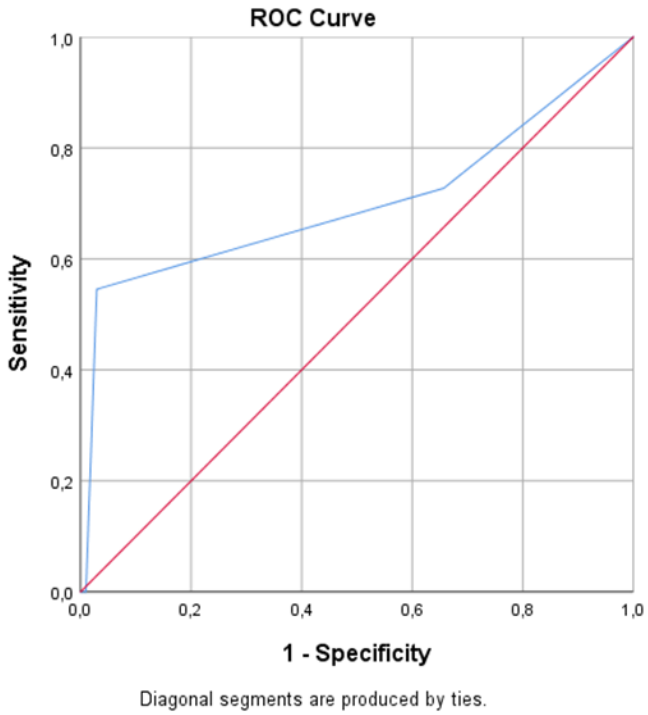

Figure 9. **ROC and AUC curve of IFS in malignant TNs assessment**

4. MEDICAL-SURGICAL MANAGEMENT OF PATIENTS WITH THYROID NODULES

4.1. Decision factors in gauging the extent of surgery for thyroid nodules

According to the opinions of international experts, the research results, and the gained experience, we established the following indications to surgical treatment for TNs:

- ✓ Nodule ≥ 1.0 cm with signs of malignancy (clinical and/or imaging and/or cytological);
- ✓ "Cold" nodule associated with mixed and active vascularity or stiffness;
- ✓ Constantly growing nodule despite thyrotropic suppression treatment and iodine preparations;
- ✓ Thyroid nodule or nodular goiter with hyperthyroidism refractory to antithyroid treatment;
- ✓ Nodular or multinodular goiter with compressive symptoms;
- ✓ Goiter with multiple nodules ≥ 0.8 cm.

Contraindications to surgical treatment have patients with concomitant diseases with high anesthetic or surgical risk. Other contraindications related to nodular pathology and surgical intervention we have not determined.

Due to the role and function of TG on the body, eminently in interference with TNs, determining the extent of thyroidectomy is a key task for surgeon. The selection of thyroid resection volume is decided in accordance with:

- uni- or bilateral lesions of the thyroid gland;
- presence of regional metastases;
- recommendations of International Guidelines;
- patient preference;
- patient age;
- result of intraoperative frozen section.

A particularly valuable role in intraoperatively determining the volume of necessary surgical intervention for the patient belongs to the IFS. The benefit of applying the method consists in performing organ-preserving surgeries, avoiding total thyroidectomy in inappropriate cases or in obtaining a malignant result, and extending thyroidectomy in the same surgical operation.

It is important to decide on the initial type of thyroidectomy, justified by the result of IFS, and to prevent "completion" thyroidectomy, which accompanies postoperative complications.

4.2. The algorithm of diagnosis and treatment of patients with thyroid nodules

Based on the results obtained, the individual particularities of each case, the personalized surgical approach and, on the other hand, the study of the recommendations of international guidelines, the newly published data and the controversial points among professionals concerned with TNs management, we have developed and propose an efficient algorithm for the conduct of patients with solitary and multiple TNs to avoid hyperdiagnosis with unjustified excessive testing and treatment and to satisfy expectations and needs of TNs patients (figure 10, 11).

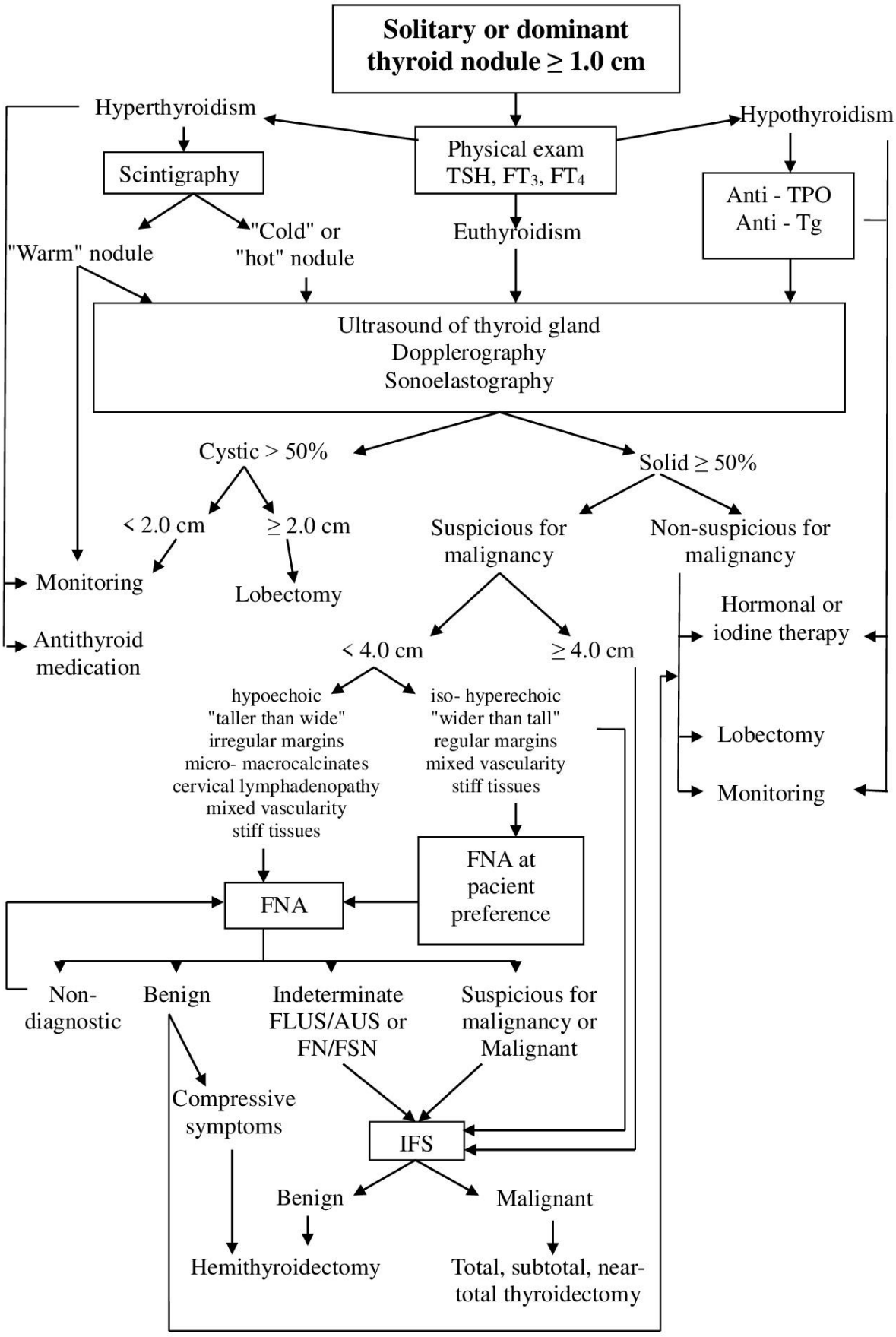

Figure 10. **Algorithm of diagnosis and treatment of patients with solitary or dominant TN**

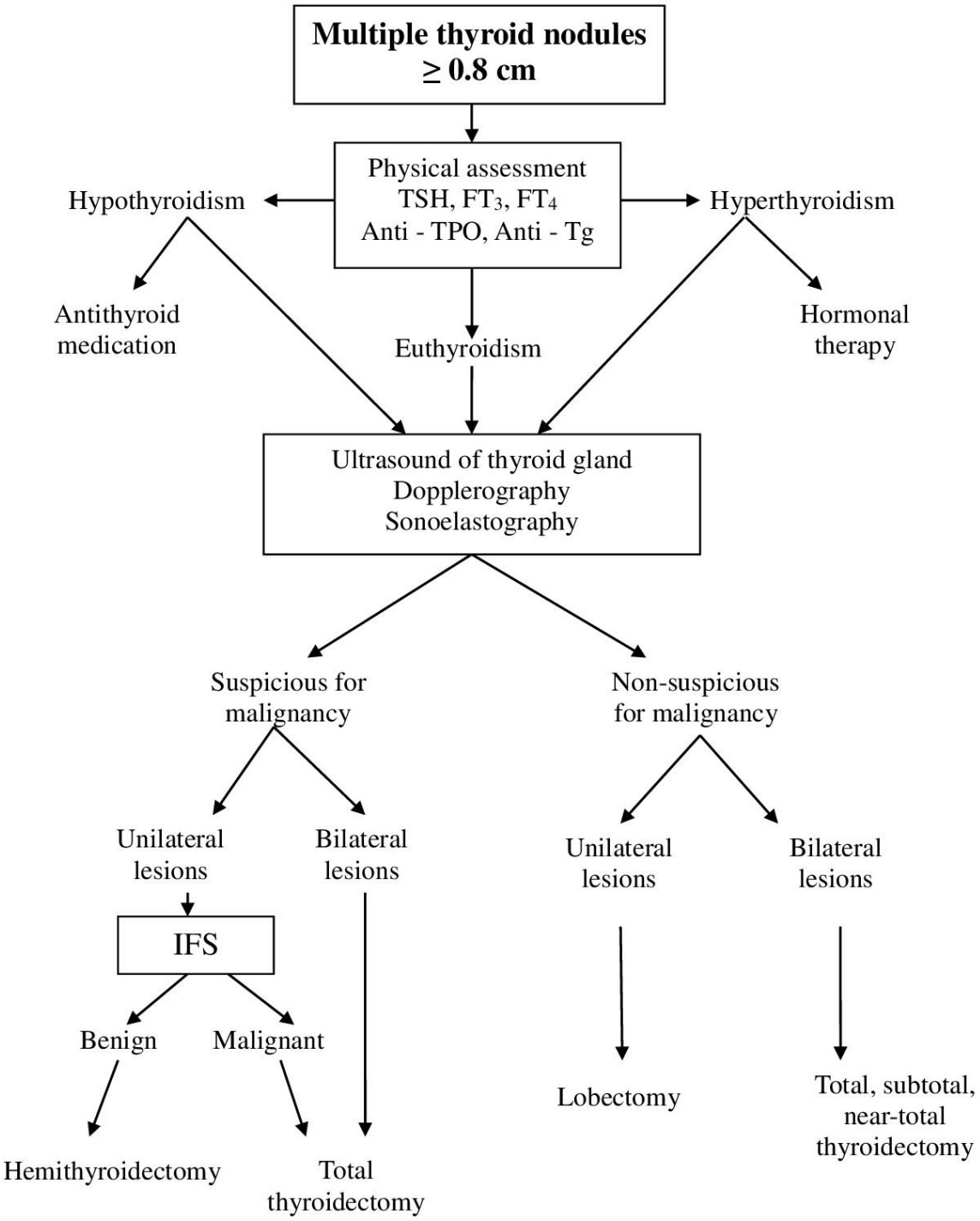

Figure 11. **Algorithm of diagnosis and treatment of patients with multiple TNs**

4.3. The results of surgical treatment in patients with thyroid nodules

Preoperative preparation of patients with TNs did not include special measures. Patients with thyrotoxicosis were prepared with antithyroid preparations (tab. Tyrosol 10 mg 1 tab. x 2-3 times a day), and patients with hypothyroidism prolonged Levothyroxine therapy in particular adjusted doses by the endocrinologist. Antibacterial prophylaxis was performed in all patients, and prevention of venous thromboembolic complications (VTE) with anticoagulant preparations was

performed only in high-risk cases. The preoperative period lasted from 0 to 7 days, with an average of 1.52 days.

The performed surgeries are relieved in the following structure: Hemithyroidectomies (lobectomy) - 72 (58.1%) (95% CI 49.2 - 66.9); Total thyroidectomies - 28 (22.6%) (95% CI 15.3 - 30.6); Combined operations (unilateral hemithyroidectomy and enucleation of the nodule in the contralateral lobe or unilateral hemithyroidectomy and partial resection of the contralateral lobe) - 11 (8.9%)(95% CI 4.0 - 13.7); Subtotal thyroidectomies - 5 (4.0%) (95% CI 0.8 - 8.0); Isthmectomies - 3 (2.4%) (95% CI 0.0 - 5.6); Nodulectomies (nodule enucleation) - 3 (2.4%) (95% CI 0.0 - 4.8); Repeated operation (ablation of ipsilateral nodules) - 1 (0.8%) (95% CI 0.0 – 2.4); Total thyroidectomy with lymphadenectomy - 1 (0.8%) (95% CI 0.0 - 2.4) case.

The average duration of thyroidectomies was 129.35 minutes. The time of surgery varied depending on their type. Total thyroidectomy was performed on average in 177.86 minutes (95% CI 157.86 - 197.86); Subtotal thyroidectomy - in 156.0 minutes (95% CI 121.05 - 190.95); Combined interventions - in 136.82 minutes (95% CI 108.66 - 164.97); Hemithyroidectomy - in 109.17 minutes (95% CI 100.20 - 118.13); Isthmectomies - in 86.67 minutes (95% CI 43.05 - 130.29); Nodulectomies - in 100.0 minutes (95% CI 79.13 - 279.13). The repeated intervention lasted 165.0 minutes, and the total thyroidectomy with lymphadenectomy – 190.0 minutes.

The duration of thyroidectomy was influenced by the duration of IFS. IFS result was obtained within 15 to 85 minutes, with a mean of 41.08 minutes and a median of 40.00 minutes (95% CI 38.08 - 44.09). In our study, we extent to total thyroidectomy, after initial hemithyroidectomy in 14 cases that TC was confirmed at IFS.

4.4. Evolution of postoperative period and long-term follow-up of patients with thyroid nodules

In the postoperative period, the active conduct of patients was monitored. Levothyroxine replacement therapy was instituted from the 1st postoperative day in doses of 50-75 mcg after hemithyroidectomies or combined interventions and 100 mcg after (sub)total thyroidectomies, individually corrected by outpatient endocrinologists according to serum thyroid hormone values. Prophylactically were administered intravenous calcium preparations 10% - 10 ml for 3-5 days.

In our early postoperative outcome, transient RNL paresis occurred in 1 (0.8%) (95% CI 0.0 - 2.4) patient and was probably caused by posttraumatic edema (post thyroidectomy).

The postoperative evolution was favorable for all patients, being discharged in satisfactory state. The hospital average length of stay was 6.95 days. The healing of the wound was "per primam intentionem" in all cases.

All patients were monitored clinically and hormonally 1st month postoperatively without further complications, except the reported case with transient RNL paresis, which had completely recovered. At 3, 6, 12, 24 months postoperatively, patients were monitored clinically, hormonally and imaging (table 14).

Relapse of pathology was not detected in any case, and other early and late postoperative complications were not recorded.

Table 14. **Postoperative monitoring of patients with thyroid nodules**

Period (months)	**Frequency** no. (%)	**95% CI**	**Clinical signs** (frequency no., %)	**Functional status** (frequency no., %)	**USG of TG** (frequency no., %)	**Post-operative compli-cations** (freq. no., %)
1	124 (100.0)	100.0 - 100.0	Asymptomatic 123 (99.0%)	Euthyroidism 124 (100.0%)	---	Transient dysphonia 1 (0.8%)
3	124 (100.0)	100.0 - 100.0	Asymptomatic 124 (100.0%)	Euthyroidism 124 (100.0%)	No changes 124 (100.0%)	0
6	124 (100.0)	100.0 - 100.0	Asymptomatic 124 (100.0%)	Euthyroidism 124 (100.0%)	No changes 124 (100.0%)	0
12	114 (91.9%)	87.1 - 96.8	Asymptomatic 114 (100.0%)	Euthyroidism 114 (100.0%)	No changes 114 (100.0%)	0
24	103 (83.1%)	76.6 - 89.5	Asymptomatic 103 (100.0%)	Euthyroidism 103 (100.0%)	No changes 103 (100.0%)	0

GENERAL CONCLUSIONS

1. The ultrasound aspect of thyroid nodules based on size, composition, echogenicity, shape, margins, presence or absence of calcinates and lymphadenopathy in common with the type of vascularization of the nodule and tissue elasticity, signifies triage benchmarks in the next stage of investigation, monitoring or treatment. The detection of nodules with high TI-RADS scores or solid, isoechogenic nodules, ovoid nodules with regular margins associated with mixed active vascularization and stiff tissues raises the suspicion of malignancy.
2. Sensitivity (Sn) and Specificity (Sp) of methods for evaluating thyroid nodules, recommended and used in research, were estimated in values of: hormonal serological tests - Sn 13.64%, Sp 94.12%; scintigraphy - Sn 10.53%, Sp 89.29%; ultrasound composition - Sn 100.0%, Sp 5.88%; echogenicity - Sn 72.73%, Sp 45.10%; ultrasound form - Sn 22.73%, Sp 94.12%; ultrasound margins - Sn 18.18%, Sp 94.12%; echogenic foci - Sn 9.09%, Sp 83.33%; ultrasound lymphadenopathy - SN 9.09%, Sp 84.31%; sonoelastography - Sn 53.0%, Sp 89.70%; dopplerography - Sn 75.0%, Sp 38.81%; FNA - Sn 69.20%, Sp 29.51%.
3. Extemporaneous histological investigation was found to be a diagnostic method, which meets a sensitivity of 75.0%, specificity of 96.97% and accuracy of 92.68% in the evaluation of thyroid nodules, being the most important instrument of diagnostic certainty and intraoperative guidance.
4. The indications for surgical treatment in thyroid nodules are nodules ≥ 1.0 cm with signs of malignancy (clinical and/or imaging and/or cytological); "cold" nodules associated with mixed and active vascularization or stiffness; nodules constantly growing despite thyrotropic suppression treatment and iodine preparations; thyroid nodules or nodular goiter with hyperthyroidism refractory to antithyroid treatment; nodular or multinodular goiter with compressive symptoms;

goiter with multiple nodules ≥ 0.8 cm. Contraindications to surgical treatment are concomitant diseases with high anesthetic or surgical risk .

5. The selection of the type of thyroidectomy is decided in consensus with uni- or bilateral lesions of the thyroid gland; presence of regional metastases; recommendations of International Guidelines; patient preference; age of patient and IFS result.

6. After surgical treatment, early postoperative complications were detected in 1 (0.8%) patient after total thyroidectomy, manifested by transient dysphonia that restored completely after one month. In the patient's follow-up after 1 month, 3 months, 6 months, 12 months and 24 months, signs of relapse of pathology or other complications were not detected.

7. The optimization of methods of diagnosis and surgical treatment of patients with thyroid nodules is achieved by implementing a rational management algorithm, based on principles of early detection of malignant nodules, complete and individualized evaluation of patients, exclusion of invasive and expensive diagnostic methods in unjustified cases, selection of optimal treatment methods and tendency to organ-preserving surgical treatment.

RECOMMENDATIONS

1. During the counseling of patients with thyroid nodules ≥ 1.0 cm, the opinion of the surgeon or oncologist should also be sought to determine the appropriate moment of surgery in order to avoid thyroid carcinoma, most common in nodules with dimensions 1.0 - 2.0 cm and to prevent compressive symptoms, especially in posterior hyperplasia.

2. The ultrasound examination in combination with color Doppler and sonoelastography must be performed routinely in the ultrasound assessment of nodules and mandatory by radiologist specialized in this field.

3. Fine needle aspiration should be reserved for ultrasonographically informative and suspicious cases with high TI-RADS scores and cold nodule at scintigraphy.

4. Intraoperative frozen section is indicated in all patients with unilateral nodular involvement, in indetermined cases (Bethesda III and IV), which allows optimizing the volume of surgery in one operation.

5. Conservative treatment intended to reduce the size of the thyroid nodules will be carried out with iodine preparations, taking into account the residence of the local population in an endemic iodine-deficient area, and the administration of Levothyroxine should be indicated in cases of hypothyroidism and the need for hormone replacement.

6. We recommend the implementation in the management of thyroid nodules the Algorithm of diagnosis and differentiated treatment for solitary and multiple nodules developed on the basis of the research, both for family doctors, endocrinologists, radiologists, together with surgeons and oncologists.

SELECTIVE BIBLIOGRAPHY:

1. Dubinin O. Metodele de diagnostic și tratament în gușa nodulară. *Anale stiintifice ale Universității de Stat de Medicină și Farmacie "Nicolae Testemitanu"*. 2005. Vol. 4, p. 117-120.
2. Sturza R., Ghendov-Moşanu A. Food, nutrition, and health in Moldova. In: *Nutritional and Health Aspects of Food in the Balkans. Amsterdam. Netherlands: Elsevier*, 2021; 249-262. ISBN 978-012820782-6.
3. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2016;26(1):1–133. http://dx.doi.org/10.1089/thy.2015.0020.
4. Mu C, Ming X, Tian Y, Liu Y, Yao M, Ni Y, et al. Mapping global epidemiology of thyroid nodules among general population: A systematic review and meta-analysis. *Front Oncol.* 2022;12:1029926. http://dx.doi.org/10.3389/fonc.2022.1029926
5. Clipca A. Aspecte clinico-morfologice ale cancerului tiroidian "ocult" și incipient. *Autoreferatul tezei de doctor în științe medicale*. Chișinau, 2008, 26 p.
6. Dean DS, Gharib H. Epidemiology of thyroid nodules. *Best Pract Res Clin Endocrinol Metab*. 2008 Dec;22(6):901-11. doi: 10.1016/j.beem.2008.09.019. PMID: 19041821.
7. Cojocaru C, Bour A. Relevanța clinică a nodulilor tiroidieni. În: *Arta Medica*. Chișinău, 2020, vol. 76 (3), pp. 44-47. ISSN 1810-1852.
8. Țîbîrnă A. Particularitățile epidemiologice, clinico - morfologice și chirurgicale ale adenomului și cancerului glandei tiroide. *Autoreferatul tezei de doctor în științe medicale.* Chișinau, 2010, 38 p.
9. Zamora EA, Khare S, Cassaro S. Thyroid Nodule. In: *StatPearls. Treasure Island (FL):* StatPearls Publishing, 2022. https://www.ncbi.nlm.nih.gov/books/NBK535422/
10. Floridi C, Cellina M, Buccimazza G, Arrichiello A, Sacrini A, Arrigoni F, et al. Ultrasound imaging classifications of thyroid nodules for malignancy risk stratification and clinical management: state of the art. *Gland Surg.* 2019;8(Suppl 3):S233–44. http://dx.doi.org/10.21037/gs.2019.07.01.
11. Mittal M, Ganakumar V, Shukla R, Kumar Garg M. Thyroid nodule: approach and management. In: Agrawal NK, editor. Goiter - Causes and Treatment. London, England: *IntechOpen*; 2020.
12. Wong R, Farrell SG, Grossmann M. Thyroid nodules: diagnosis and management. *Med J Aust.* 2018;209(2):92-98. doi: 10.5694/mja17.01204. PMID: 29996756.
13. Protocol clinic național „*Cancerul glandei tiroide*”, Chișinău, 2013.
14. Țîbîrnă A. *Cancerul glandei tiroide*. Chișinău: Universul; 2017: 24-30.
15. Zaid AM, Eid E, Gouda SI, Aboelnaga MM, Abdelsalam RA, Elbeltagy AMG, et al. Evaluation of risk factors for malignancy in patients with thyroid nodules. *J Endocrinol Metab.* 2022;12(2):66–72. http://dx.doi.org/10.14740/jem770.
16. Țîbîrnă Gh, Țîbîrnă A, Lisița N, Bejenaru L. Particularitățile evoluției clinice ale cancerului glandei tiroide în Republica Moldova. *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale* 2020;1(65): 312-326.
17. Валдина Е. А. *Заболевания щитовидной железы:* Руководство. СПб: Питер,2006, с. 142-159.
18. Рудницкий Л. В. *Заболевания щитовидной железы: лечение и профилактика.* Питер, 2009, с. 99-114.
19. Arora N, Scognamiglio T, Zhu B, Fahey TJ 3rd. Do benign thyroid nodules have malignant potential? An evidence-based review. *World J Surg.* 2008;32(7):1237–46. Available from: http://dx.doi.org/10.1007/s00268-008-9484-1.
20. Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedüs L, Paschke R, Valcavi R, Vitti P; AACE/ACE/AME Task force on thyroid nodules. American Association Of Clinical Endocrinologists, American College Of Endocrinology, and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules - 2016 update. *Endocr Pract.* 2016;22(5):622-39. doi: 10.4158/EP161208.GL. PMID: 27167915.
21. Tessler FN, Middleton WD, Grant EG, Hoang JK, Berland LL, Teefey SA, et al. ACR thyroid imaging, reporting and data system (TI-RADS): White paper of the ACR TI-RADS committee. *J Am Coll Radiol.* 2017;14(5):587–95. http://dx.doi.org/10.1016/j.jacr.2017.01.046
22. Russ G, Bonnema SJ, Erdogan MF, Durante C, Ngu R, Leenhardt L. European Thyroid Association Guidelines for Ultrasound Malignancy Risk Stratification of Thyroid Nodules in Adults: The EU-TIRADS. *Eur Thyroid J.* 2017;6(5):225-237. doi: 10.1159/000478927. PMID: 29167761; PMCID: PMC5652895.
23. Ullmann TM, Gray KD, Moore MD, Zarnegar R, Fahey TJ III. Current controversies and future directions in the diagnosis and management of differentiated thyroid cancers. *Gland Surg*. 2018;7(5):473–86. http://dx.doi.org/10.21037/gs.2017.09.08.
24. Patel KN, Yip L, Lubitz CC, Grubbs EG, Miller BS, Shen W, et al. The American association of endocrine surgeons guidelines for the definitive surgical management of thyroid disease in adults. *Ann Surg.* 2020;271(3): e21–93. http://dx.doi.org/10.1097/sla.0000000000003580.
25. Cojocaru C, Bour A. The time for surgery in thyroid nodules. Rev. Med. Chir. Soc. Med. Nat., Iaşi, 2022;126(4):520-527. http://dx.doi.org/10.22551/msj.2022.04.08.

LIST OF SCIENTIFIC PUBLICATIONS AND EVENTS

SCIENTIFIC PUBLICATIONS

- **Articles in ISI, SCOPUS journals and other international databases:**
  - ✓ **Articles in journals Web of Science**

1. Cojocaru C., Bour A. The time for surgery in thyroid nodules. *Rev. Med. Chir. Soc. Med. Nat.,* Iaşi, 2022; 126(4): 520-527. http://dx.doi.org/10.22551/msj.ISSN 2286-2560.

- **Articles in accredited national scientific journals:**
  - ✓ **Articles in B category journals**

2. **Cojocaru C.**, Bour A. Relevanța clinică a nodulilor tiroidieni. În: *Arta Medica.* Chișinău, 2020; 76(3), pp. 44-47. ISSN 1810-1852.
3. **Cojocaru C**., Bour A. Vigilența oncologică în nodulii tiroidieni. În: *Buletinul Academiei de Ştiinte a Moldovei. Ştiinţe Medicale.* Chișinău, 2020; 4(68), pp. 88-92. ISSN 1857-0011.
4. **Cojocaru C**., Bour A. The current assessment and management of thyroid nodules. În: *Revista de Ştiinţe ale Sănătăţii din Moldova*. 2023, vol. 10, nr. 1, pp. 73-81. ISSN 2345-1467. doi: 10.52645/MJHS.2023.1.11.

- **Articles in the proceedings of scientific conferences:**
  - ✓ **national with international participation**

5. Bour A., **Cojocaru C.** Aspecte clinico-practice în diagnosticul și tratamentul chirurgical al nodulilor tiroidieni. În: *Sănătate Publică, Economie şi Management în Medicină,* 2022*,* nr. 2(93-S), pp. 22-27. ISSN: 1729-9697.

- **Abstracts/theses submitted at national or international scientific conferences**

6. Bour A., **Cojocaru C.**, Bazeliuc Iu. Gușa nodulară: o indicație către tratament chirurgical. În: *Arta Medica*. Chișinău, 2016, nr. 3(60), p. 37. ISSN 1810-1852.
7. **Cojocaru C.** The surgical approach of thyroid nodule(s). In: *Abstract Book. The 7th International Medical Congress for Students and Young Doctors MedEspera.* Chisinau, 2018, pp. 136-137. ISBN 978-9975-47-174-9.
8. **Cojocaru C.**, Bour A. Rolul investigației histologice extemporanee în tratamentul chirurgical al nodulilor tiroidieni. În: *Revista medicală ştiinţifico-practică „Arta Medica". Ediţie specială.* Chișinău, 2019, nr. 3(72), pp. 118-119. ISSN 1810-1852.
9. Dolința V., **Cojocaru C.** Toxic goiter associated with carcinoma. In: *Abstract Book. The 8th International Medical Congress for Students and Young Doctors MedEspera.* Chisinau, 2020, pp. 25-26. ISBN 978-9975-151-11-5.
10. **Cojocaru C.** Preoperative evaluation of patients with thyroid nodules. In: *Abstract Book. The 8th International Medical Congress for Students and Young Doctors MedEspera.* Chisinau, 2020, pp. 70-71. ISBN 978-9975-151-11-5.
11. **Cojocaru C.**, Bour A. Relevanța clinică a nodulilor tiroidieni. În: *Abstract book. Congresul consacrat aniversării a 75-a de la fondarea USMF „Nicolae Testemițanu".* Chișinău, 2020, p. 401.

12. **Cojocaru C.**, Bour A. Diagnosticul histologic intraoperator - instrument de ghidaj în tratamentul chirurgical al nodulilor tiroidieni. În: *CONFER 2020. Volum de rezumate.* Iași, România, 2020; 9, pp. 180-181.
13. **Cojocaru C.**, Bour A. Abordarea chirurgicală actuală a nodulilor tiroidieni. Caz clinic. In: *Abstract book. Conferinţa ştiinţifică anuală „Cercetarea în biomedicină şi sănătate: calitate, excelenţă şi performanţă*". Chișinău, 2021, p. 249.
14. **Cojocaru C.**, Bour A. Paraclinical features of thyroid nodules harboring follicular carcinoma. In: *SECEBT 2022. Abstracts volume*. Iasi, Romania, 2022, p. 17.
15. **Cojocaru C.** Limitations of fine-needle aspiration biopsy (FNAB) in thyroid nodules diagnosis. In: *Abstract Book. The 9th International Medical Congress for Students and Young Doctors MedEspera.* Chisinau, 2022, p. 422. ISBN 978-9975-151-11-5.
16. **Cojocaru C.**, Bour A. Optimizarea tratamentului chirurgical al pacienților cu noduli tiroidieni. În: *Chirurgia, 117 (Supplement 1).* Sinaia, România, 2022, pp. 56-57. ISSN 1221-9118.
17. **Cojocaru C.**, Bour A. Selectarea volumului tiroidectomiei la pacienții cu noduli tiroidieni. In: *Moldovan Journal of Health Sciences. Culegere de Rezumate. Conferinţa ştiinţifică anuală „Cercetarea în biomedicină şi sănătate: calitate, excelenţă şi performanţă".* Chişinău, 2022, nr. 3(29), p. 309. ISSN 2345-1467.
18. Bour A., **Cojocaru C.** Acuratețea metodelor de diagnostic în depistarea nodulilor tiroidieni maligni. În: *CONFER 2022. Volum de rezumate.* Iași, România, 2022; 11, pp. 80-81.

- **Invention patents, patents, registration certificates, materials at invention salons**
  - ✓ **Innovation certificate**
    19. Bour A., **Cojocaru C.** *Algoritm de diagnostic și tratament al pacienților cu noduli tiroidieni.* Certificat de inovator Nr. 6028, 2023.04.25.
    20. Bour A., Parnov M., **Cojocaru C.** *Investigația histologică extemporanee în diagnosticul pacienților cu noduli tiroidieni.* Certificat de inovator Nr. 6029, 2023.04.25.
    21. Bour A., **Cojocaru C.,** Calistru N. *Sonoelastografia și Dopplerografia în diagnosticul pacienților cu noduli tiroidieni.* Certificat de inovator Nr. 6030, 2023.04.25.
  - ✓ **Implementation acts**
    22. Bour A., **Cojocaru C.** *Algoritm de diagnostic și tratament al pacienților cu noduli tiroidieni*. Act de implementare nr. 58, 2023.04.27.
    23. Bour A., Parnov M., **Cojocaru C.** *Investigația histologică extemporanee în diagnosticul pacienților cu noduli tiroidieni.* Act de implementare nr. 59, 2023.04.27.
    24. Bour A., **Cojocaru C.,** Calistru N. *Sonoelastografia și Dopplerografia în diagnosticul pacienților cu noduli tiroidieni.* Act de implementare nr. 60, 2023.04.27.

- **Participations with communications at scientific forums:**
  - ✓ **international**
    25. Dolința V., **Cojocaru C.**, Bour A. Toxic goiter associated with carcinoma. The 8th *International Medical Congress for Students and Young Doctors MedEspera*. Chisinau, 24-26 september 2020.
    26. **Cojocaru C.,** Bour A. Optimizarea tratamentului chirurgical al pacienților cu noduli tiroidieni. *Congresul Național de Chirurgie*. Sinaia, România, 8-11 iunie 2022.

27. Bour A., **Cojocaru C.** Acuratețea metodelor de diagnostic în depistarea nodulilor tiroidieni maligni. *Conferinţele Institutului Regional de Oncologie Iaşi (CONFER).* Iași, România, 23-26 noiembrie 2022.

✓ **national**

28. **Cojocaru C.** Experienţa clinicii în managementul chirurgical al nodulilor tiroidieni. *Ședința Asociației Chirurgilor „Nicolae Anestiadi" din Republica Moldova.* Chișinău, 24 septembrie 2021.
29. **Cojocaru C.**, Bour A. Abordarea chirurgicală actuală a nodulilor tiroidieni. Caz clinic. *Conferinţa ştiinţifică anuală consacrată aniversării a 76-a de la fondarea USMF „Nicolae Testemiţanu"*. Chişinău, 20-22 octombrie 2021.
30. **Cojocaru C.**, Bour A. Selectarea volumului tiroidectomiei la pacienții cu noduli tiroidieni. *Conferinţa ştiinţifică anuală „Cercetarea în biomedicină și sănătate: calitate, excelență și performanță".* Chişinău, 19-21 octombrie 2022.
31. Bour A., **Cojocaru C.** Aspecte clinico-practice în diagnosticul și tratamentul chirurgical al nodulilor tiroidieni. *Zilele Medicale ale Spitalului Clinic Municipal „Sfântul Arhanghel Mihail.* Chişinău, 21 noiembrie 2022.

- **Participations with posters at scientific forums:**

✓ **international**

32. **Cojocaru C.**, Bour A. Diagnosticul histologic intraoperator - instrument de ghidaj în tratamentul chirurgical al nodulilor tiroidieni. *CONFER 2020. Conferințele Institutului regional de oncologie Iași.* Iași, România. 19-22 noiembrie 2020, p. 49.
33. **Cojocaru C.**, Bour A. Paraclinical features of thyroid nodules harboring follicular carcinoma. *Southeastern European Club of Endocrine and Breast Tumors (SECEBT).* Iasi, Romania, 14-16 april 2022.

✓ **national**

34. **Cojocaru C.**, Bour A. Criterii de malignitate a nodulilor tiroidieni. *Conferinţa ştiinţifică anuală a colaboratorilor şi studenţilor USMF „Nicolae Testemiţanu"*. Chișinău, 17-19 octombrie 2018.
35. **Cojocaru C.**, Bour A. Rolul investigației histologice extemporanee în tratamentul chirurgical al nodulilor tiroidieni. *Al XIII-lea Congres al Asociației Chirurgilor „Nicolae Anestiadi" și al III-lea Congres al Societății de Endoscopie, Chirurgie miniminvazivă și Ultrasonografie „V. M. Guțu" din Republica Moldova (cu participare internaţională).* Chișinău, 18-20 septembrie 2019.
36. **Cojocaru C.**, Bour A. Relevanța clinică a nodulilor tiroidieni. *Congresul consacrat aniversării a 75-a de la fondarea USMF „Nicolae Testemiţanu".* Chişinău, 21-23 octombrie 2020, p. 39.

LIST OF ABBREVIATIONS

AACE - American Association of Clinical Endocrinologists
ACE - American College of Endocrinology
ACR - American College of Radiology
AHT - arterial hypertension
AME - Associazione Endocrinologists/ Association of Endocrinologists
ATA - American Thyroid Association
ATC - anaplastic thyroid carcinoma
TC - thyroid carcinoma
DM - diabetes mellitus
ECG - electrocardiogram
FNA - fine-needle aspiration
FTA - follicular thyroid adenoma
FTC - follicular thyroid carcinoma
TG - thyroid gland
HTC - Hürthle cell thyroid carcinoma/ oncocytic carcinoma
IFS - intraoperative frozen section
CI - confidence interval
MTC - medullary thyroid carcinoma
TN - thyroid node
TNs - thyroid nodules
RNL - recurrent nerve of the larynx
WHO - World Health Organization
PTC - papillary thyroid carcinoma
Sn - sensitivity
Sp - specificity
T3 - triiodthyronine
T4 - tetraiodthyronine/ thyroxine
TBSRTC - The Bethesda System for Reporting Thyroid Cytopathology
Tg - thyroglobulin
HT - Hashimoto's thyroiditis
TIRADS - Thyroid Imaging Reporting and Data System
TSH - thyrotropic hormone
USG - ultrasonography

COJOCARU Cristina

OPTIMIZATION OF DIAGNOSTIC METHODS AND SURGICAL TREATMENT OF PATIENTS WITH THYROID NODULES

321.13 SURGERY

Summary of doctoral thesis in medical sciences

Approved for printing: 31.10.2023 80gr/m^2 paper. Digital print. Pattern sheets: 1.92	Paper format: 60x84 1/16 Circulation: 5 ex. Order no.: 4

Typography: ÎI „Covalciuc Maria”
61/3 Vl. Korolenko st., Chisinau
Tel.: (+373 68) 04 45 10