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**PARTICULARS OF DIAGNOSIS AND TREATMENT OF  
THYROID CARCINOMA ASSOCIATED WITH AUTOIMMUNE THYROIDITIS**

**Specialty: 321.20. ONCOLOGY AND RADIOTHERAPY**

**Self-report of the doctoral thesis in medical sciences**

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The thesis was conducted in the Department of Oncology, PI and State University of Medicine and Pharmacy "Nicolae Testemitanu", and MSPI Oncological Institute, tumor section head and neck region, The founding consortium of the Doctoral School in the field of Medical Sciences.

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## TABLE OF CONTENTS

List of abbreviations .....	3
Conceptual guidelines of the research, the topicality of the topic and the importance of the problem addressed.....	4
The content of the thesis .....	8
1. Contemporary conceptions of the etiopathogenesis, diagnosis and treatment of thyroid cancer associated with autoimmune thyroiditis .....	8
2. Characteristics of research material and methods .....	9
3. Results of the diagnosis of thyroid cancer associated with autoimmune thyroiditis.....	11
4. Surgical treatment of patients with thyroid cancer associated with autoimmune thyroiditis ....	20
General conclusions .....	23
Practical recommendations .....	23
List of papers published on the topic of the thesis .....	25
Annotation in (Romanian, Russian, English) .....	27
Selective bibliography.....	30

## LIST OF ABBREVIATIONS

AUS	atypical of undetermined significance
FMTC	familial medullary thyroid cancer
CS	Cowden Syndrome
TC	thyroid cancer
FTC	follicular thyroid carcinoma
MTC	medullary thyroid carcinoma
PTC	papillary thyroid carcinoma
FAP	familial adenomatous polyposis
FLUS	follicular lesion of undetermined significance
HB	healthy background
RM	Republic of Moldova
SCN	solid cell nest
AT	autoimmune thyroiditis
ATM	associated tumor-macrophages
TG	thyroglobulin
TI-RADS	Thyroid Reporting and Data System
NHS	thyroid malignancy
TSH	thyrotropin

## CONCEPTUAL GUIDELINES OF THE RESEARCH

**The topicality and importance of the problem addressed:** In the structure of endocrine cancers, the thyroid gland is the most common and also accounts for about 5% of the number of human malignancies diagnosed annually worldwide. Incidence of thyroid cancer varies in developed countries from 1.2% 000 to 5.0% 000 for women and from 0.6% 000 to 1.6% 000 in men. High thyroid cancer morbidity was recorded in Iceland at 18.2% 000 in women and 6.3% 000 in men [1]. In the Republic of Moldova, the incidence of CT is 8.3% 000 and ranks 9th in the oncology structure [2,3].

In medical practice, early diagnosis of CT is difficult because the neoplasm coexists or develops against the background of thyroid nodule-inflammatory pathologies, which have a slow evolution, CT is frequently associated with multi-nodular goiter. The association of thyroid carcinoma with autoimmune thyroiditis remains debatable. In the literature, this combination is noted in 1% to 75% of cases[5-9]. In recent years, there has been a steady increase in the number of thyroid cancers developed against the background of autoimmune thyroiditis, this being explained by improved methods diagnosis, living environment and increasing the number of elderly people. The relationship between inflammation and cancer is known in patients with autoimmune thyroiditis who are at increased risk of developing thyroid cancer. In the literature they are not fully elucidated features of the diagnosis and treatment of thyroid cancer associated with lymphocytic thyroiditis (autoimmune).

In conclusion, the main problem related to clinically suspected autoimmune thyroiditis in malignancy is to confirm the preoperative oncological element to appreciate the volume subsequent surgical treatment. Dimensions, ultrasound appearance and clinical evolution a thyroid nodules on the background of autoimmune thyroiditis are not enough to establish a definite diagnosis of thyroid cancer. Only the aspiration puncture performed under ultrasound guidance will perfectly direct this process of collecting cytological material, and the results obtained will approve optimizing the treatment method for this category of patients by customizing interventions surgical. The use of this method will allow early detection of thyroid carcinoma associated with autoimmune thyroiditis in the case of small formations, dynamic monitoring of patients with benign formations, confirmation or preoperative refutation of the oncological element what leads to the appreciation of the correct treatment tactics, thus improving the survival rate and quality patients' lives.

The exposed data motivate the need to implement the preoperative ultrasound puncture in the detection thyroid cancer associated with autoimmune thyroiditis that will determine the volume subsequent treatment.

**The aim of the research:** Analysis of hormonal, imaging, cytological features, morphological and surgical treatment results to optimize management diagnostic treatment of patients with thyroid cancer associated with autoimmune thyroiditis.

**The research objectives:**

1. Study of the frequency of thyroid carcinoma associated with autoimmune thyroiditis in the Republic Moldova (2017-2019);
2. Implementation of the eco-guided aspiration method of thyroid gland formations in MSPI OIM and its role in the diagnosis of thyroid carcinoma associated with autoimmune thyroiditis;
3. Analysis of the results of surgical treatment applied to patients with associated thyroid carcinoma with autoimmune thyroiditis;
4. Development of practical recommendations as an algorithm in the diagnosis and treatment of patients with CT associated with TA.

**The scientific problem solved:** The study demonstrates the priority of performing the puncture ultrasound guide of thyroid formations in patients with suspected thyroid cancer associated with thyroiditis autoimmune at the diagnostic stage. This allowed the implementation and development of new ones Diagnostic and surgical approaches in patients with thyroid carcinoma associated with autoimmune thyroiditis.

**The novelty and originality of the scientific results obtained:**

1. The epidemiological peculiarities were studied for the first time on the territory of the Republic of Moldova of thyroid carcinoma associated with autoimmune thyroiditis, by sex, age, living, territorial-administrative region, blood type. The frequency of this has been determined diseases during the years (2017-2019); studied the clinical, cytological, histopathological features in this category of patients.
2. The method of ultrasound-guided aspiration puncture of thyroid gland formations has been implemented in IMSP IOM and the role of ultrasound-guided puncture of thyroid gland formations was appreciated in the diagnosis of thyroid carcinoma associated with autoimmune thyroiditis.
3. The results of the surgical treatment applied to the patients with thyroid carcinoma were analyzed associated with autoimmune thyroiditis.
4. Practical recommendations have been developed as an algorithm in the diagnosis and treatment of patients with CT associated with TA.

**The theoretical importance of the paper:** The results of the paper aim to assess the role of puncture ultrasound of the thyroid gland as a component of diagnosis and treatment thyroid carcinoma associated with autoimmune thyroiditis. This will allow us to conduct ourselves

personalized assessment of patient groups at the stage of assessing the diagnosis of this disease, a surgical treatment as well as postoperative supervision of these patients through elaboration of the conduct algorithm.

**Applicative value of the study:** Practical guidelines for conduct were developed oncologists and endocrinologists to optimize diagnosis and treatment patients with CT associated with BP, with the development of the algorithm for diagnosis and treatment possible customization of treatment tactics.

The method of ultrasound-guided puncture of thyroid formations has been implemented within the CCD Oncological Institute of the Republic of Moldova

**The implementation of scientific results:**

The results of the study were implemented in the daily practice of the tumor section of the head and neck region as well as in the offices of the Diagnostic Consultative Center (CCD) of IMSP OI.

**Approval of the thesis results:**

Conferences of the Regional Institute of Oncology Iași, November 21-23, 2013; Conferences of the Iași Regional Institute of Oncology, November 27-30, 2014; Symposium dedicated to the 40th anniversary of the Department of Oncology, Hematology and Radiotherapy with international participation: Oncological surveillance in medical activity, early detection and treatment of tumors, 2016; IX СЪЕЗД ОНКОЛОГОВ И РАДИОЛОГОВ СТРАН СНГ И ЕВРАЗИИ, June 15-17 2016, Minsk; Conferences of the Iași Regional Institute of Oncology, November 23-26, 2017; Conferences of the Iași Regional Institute of Oncology, November 21-24, 2019; Congress of Oncologists of the Republic of Moldova with international participation, 5th edition Cancer prevention and control - a continuous challenge, Chișinău, October 8-9, 2020; VII Международной научно-практической конференции NOWADAYS CHALLENGES IN SCIENCE (November 26-28, 2020 Washington D.C., USA) online; VIII Международной научно-практической конференции NOWADAYS CHALLENGES IN SCIENCE (April 4-5, 2021 Washington D.C., USA), online; Внеочередной XII Съезд онкологов и радиологов стран СНГ и Евразии им. Трапезникова Н.Н., посвященный 25-летию АДИОР, (April 7-9, 2021), online; IV Международной научно-практической конференции SCIENTIFIC COMMUNITY: INTERDISCIPLINARY RESEARCH (May 18-19, 2021, Hamburg, Germany), online; III Международной научно-практической конференции EXPERIMENTAL AND THEORETICAL RESEARCH IN MODERN SCIENCE (June 26-28, 2021 Chișinău, Moldova).

**Publications on the topic of the thesis:** On the topic of the study, 16 papers were published, of which 5 articles in international journals, 4 in reviewed national journals (category B), 6

abstracts of presentations at international congresses and conferences, a summary of the presentation was published at national scientific congresses, conferences and symposia, 12 publications without co-authors and two innovator certificates.

**Thesis summary:** The thesis includes annotations in Romanian, Russian and English, list of abbreviations, introduction, 4 chapters, summary of results obtained, general conclusions, practical recommendations. The bibliographic index, annexes, the statement on the undertaking are attached responsibility, the author's CV.

**Synthesis of the obtained results.** The main results of the scientific study are reported carried out in comparison with the results of identical scientific research.

**Keywords:** Thyroid cancer, autoimmune thyroiditis (Hashimoto), ultrasound-guided aspiration puncture, cytological examination.

In order to elaborate the doctoral thesis, the Positive Opinion of the Research Ethics Committee of the IP "Nicolae Testemițanu" State University of Medicine and Pharmacy was obtained. (Report no. 76 of 14 November 2016).

## **THESIS CONTENT**

### **1. CONTEMPORARY CONCEPTS OF ETIOPATHOGENY, DIAGNOSIS AND TREATMENT OF THYROID CANCER ASSOCIATED WITH SELF-IMMUNE THYROIDITIS**

This chapter presents data from the literature on the subject thesis that relates the etiopathogenesis, diagnosis and treatment of CT associated with BP. Performed the analysis detailed studies on the informativeness of the methods applied in the diagnosis thyroid gland formations associated with autoimmune thyroiditis. The role was studied in more detail ultrasound-guided puncture of the thyroid gland.

Thyroid cancer is the most common endocrine neoplasm, with an upward trend in in terms of global impact. According to the latest report of the World Organization a In 2018, 567,233 new cases of thyroid cancer were diagnosed in the world of health, of which 78,418 in Europe and with a global mortality rate of 41,071 cases[1]. In the The Republic of Moldova had an annual thyroid cancer morbidity index in 1985 1.35 new cases per 100,000 population, in 2000 - 2.5 new cases, and in 2011 - 6.8 new cases of disease per 100,000 population. In 2016, 12.8 were registered in the Republic of Moldova new cases of thyroid cancer per 100,000 population[2,3].

The precise reasons for the increase in incidence are not clearly elucidated, but can be linked, at least partly due to the introduction of an improved diagnostic methodology (ultrasonography, thyroid scan and fine suction biopsy) and improved cancer [4]. Several factors are also considered

to be risk factors for thyroid cancer etiological: iodine deficiency in food and the environment[10], ionizing radiation[11,12], heredity (genetic factor), diet, different pathologies, obesity, peculiarities of the female reproductive system[13], sex[14,15], race, age, endemic conditions and autoimmune thyroiditis. Lymphocytic thyroiditis is the most common autoimmune thyroid disease and the most common cause of hypothyroidism. Epidemiological and histological data indicate that thyroid cancer (CT) occurs frequently in the context of one of the most common autoimmune thyroid diseases. Coexistence Autoimmune thyroiditis and thyroid carcinoma have a frequency of <1% -23% ( Cheng, 2009). A link between thyroid cancer and autoimmune thyroid disease has long been recognized, although the exact relationship between the two diseases remains unclear. In recent years, there has been a steady increase in the number of thyroid cancers developed against the background of autoimmune thyroiditis. In the specialized literature the peculiarities of cancer diagnosis and treatment of thyroid associated with lymphocytic thyroiditis (autoimmune) are not fully elucidated.

In connection with the development of thyroid carcinoma against the background of autoimmune thyroiditis occurs the problem of preoperative diagnosis of the oncological element. Dimensions, and ultrasound appearance Clinical evolution of thyroid nodules against the background of autoimmune thyroiditis are not enough to establish a definite diagnosis of thyroid cancer. Only the ultrasound-guided aspiration puncture gave us allowed the collection of material for cytological analysis and the results of cytological investigation obtained by ultrasound-guided puncture of nodules located in the thyroid gland allowed us to optimize diagnosis and treatment of this category of patients by personalizing interventions surgical. Using this method allowed us to detect thyroid carcinoma early associated with autoimmune thyroiditis in the case of small formations, dynamic monitoring of patients with benign formations, confirmation or preoperative refutation of the oncological element what led to the appreciation of the correct treatment tactics, thus improving the survival rate and quality patients' lives.

## **2. CHARACTERISTICS OF THE RESEARCH MATERIAL AND METHODS**

In order to achieve the purpose and objectives proposed in the research, a study was conducted based on the diagnosis and treatment of patients with thyroid cancer associated with autoimmune thyroiditis treated in the tumor laboratory head and neck region IMSP Oncological Institute during the years 2016-2021. The study is descriptive, integral and analytical observational of the cohort. Research unit - simple, morphologically confirmed patient with malignant thyroid tumor.

The research began with the accumulation of clinical data for the representative volume of the analyzed sample. A comprehensive analysis of groups of patients with gland carcinoma was performed thyroid associated with autoimmune thyroiditis. The differences that appear in the



distribution were highlighted pathology according to sex, age, diagnostic methods, morpho-pathological result of the tumor, the volume of surgery performed and was developed for the algorithm of diagnostic conduct and for treatment.

The L<sub>1</sub> research group consisted of patients with thyroid cancer associated with thyroiditis being in turn divided into two groups, respectively group 1 which included respondents, who underwent preoperative investigation adapted to the requirements of the proposed puncture research ultrasound of the thyroid gland with the collection of material for cytological examination and group 2 included patients with usual preoperative investigations (USG thyroid gland and hormone tests thyroid) without preoperative ultrasound-guided puncture.

The L<sub>0</sub> control group consisted of patients with thyroid cancer developed on a healthy background.

The basic criteria according to which patients were included in the study research group were:

1. Acceptance of the patient by signature; 2. Age  $\geq$  18 years; 3. Patients with thyroid cancer associated with autoimmune thyroiditis.

The research group consisted of 112 patients, who in turn were divided into two groups, group 1 of 55 patients with preoperative thyroid puncture and group 2 of 57 patients without preoperative ultrasound-guided puncture.

Criteria for exclusion from the research group:

1. Patients with thyroid nodules without associated autoimmune thyroiditis; 2. Patients who refused participation in a clinical trial; 3. Persons up to 18 years of age; 4. Patients with severe concomitant diseases; 5. Pregnancy and lactation.

The control group consisted of 122 patients with background thyroid cancer healthy.

Criteria for inclusion in the control group: 1. Acceptance of the patient by signature; 2. Age  $\geq$  18 years; 3. Patients with thyroid cancer developed on a healthy background.

Criteria for exclusion from the control group: 1. Persons who refused to participate in the clinical trial; 2. Patients up to 18 years; 3. Patients with thyroid cancer developed against the background of other pathologies.

### **3. RESULTS OF DIAGNOSIS OF ASSOCIATED THYROID CANCER WITH AUTOIMMUNE THYROIDITIS**

The research was carried out within the Institute of Public Medical Sanitary Institution Oncology from Moldova IMSP IO, tumor section head and neck region, during the years 2016-2021. The study is descriptive, comprehensive, and observational of the cohort. Research unit - simple, patient with morphologically confirmed thyroid malignancy. The work is complex, which is based on prospective data from 234 thyroid cancer patients investigated and treated in the profile

offices, head and neck region tumors department, cytology departments and morphopathology within the CCD and the Oncological Institute. Prior to enrollment in the study all patients signed the agreement by signing the informed consent. Research participants have been selected based on inclusion and exclusion criteria. The study was approved positively by the Research Ethics Committee of IP USMF "Nicolae Testemițanu" no. 76 of 14.11.2016. In total, during these years, 754 primary patients with a confirmed histopathological diagnosis of thyroid carcinoma were registered in the National Cancer Registry, of which 163 patients had thyroid cancer associated with autoimmune thyroiditis, 215 were cancer patients Thyroid developed on a healthy background and 376 patients had developed thyroid carcinoma of other pathologies.

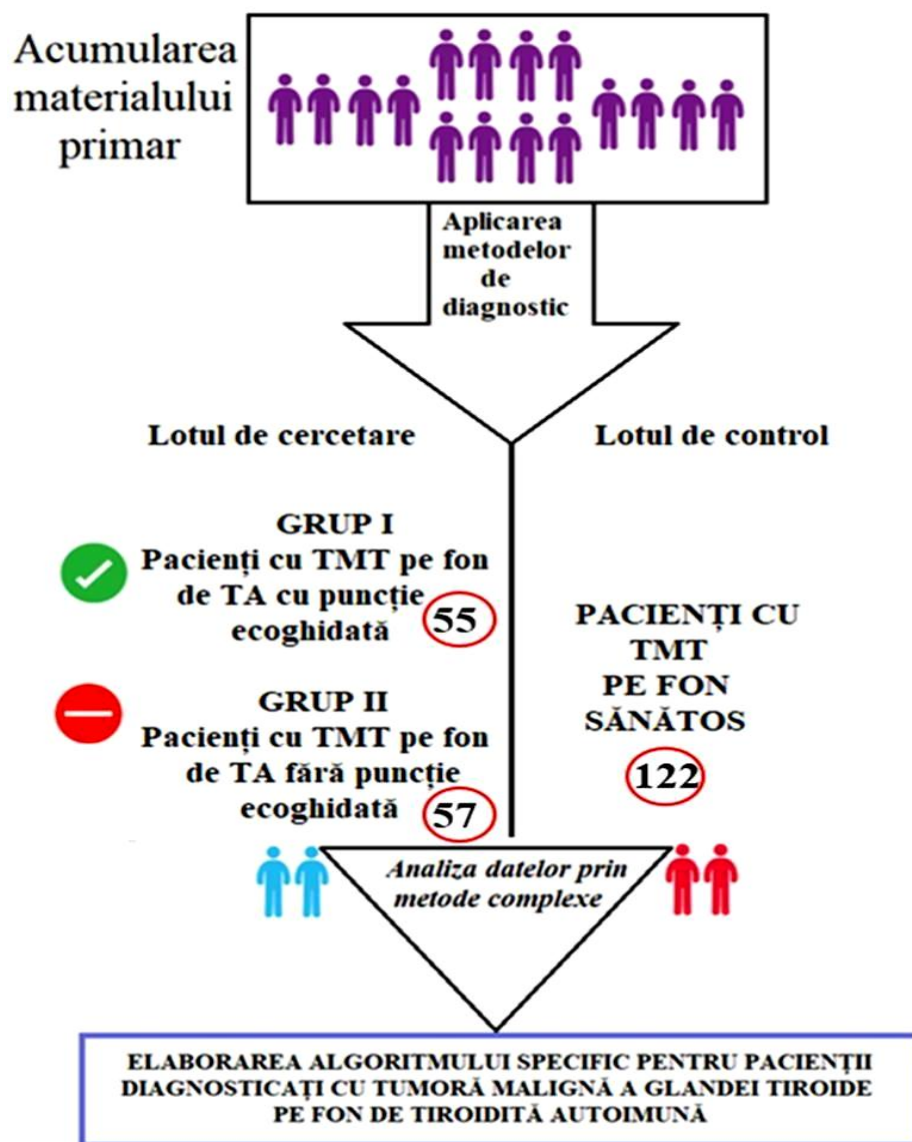
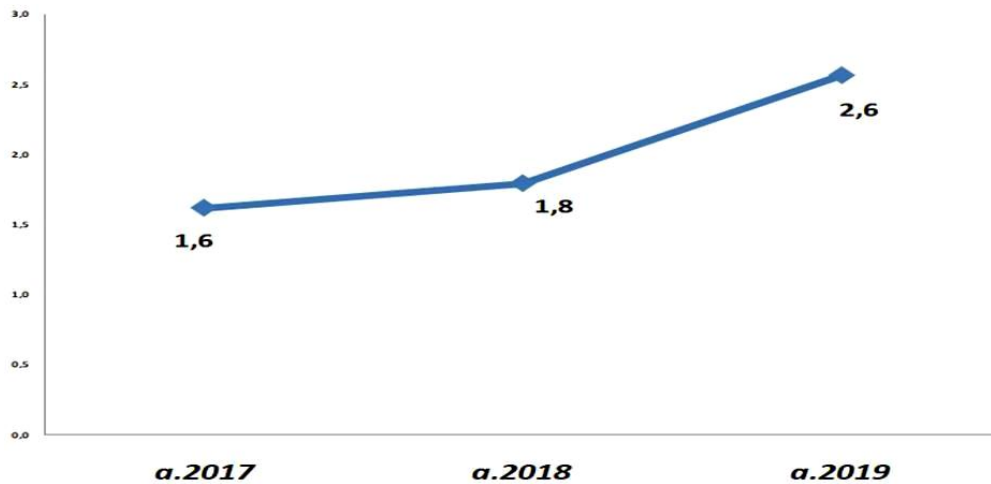


FIG. 2.1 Study design

Share of patients with thyroid carcinoma associated with autoimmune thyroiditis included in the study of the total number of primary thyroid cancer patients registered in the year correspondingly varied from 1.6 (per 100,000 population) 2017, to 2.6 (per 100,000 population) 2019. Analyzing these data we observe a continuous increase in the number of carcinoma cases thyroid associated with autoimmune thyroiditis.



**Figure 3.1 Dynamics of the incidence of thyroid carcinoma associated with autoimmune thyroiditis period 2017-2019**

The distribution of patients according to age showed that both in both groups of research and in the control group, patients up to 55 years of age predominated.

**Table 3.1 Distribution of patients included in the study by age**

	Research group (Lot I) n=112		Control batch (Lot II) n=122		Chi-scor gl p
	Abs.	%	Abs.	%	
< 55 years	58	51,8	84	68,9	6,878 1
> 55 years	54	48,2	38	31,1	
Total	112	100,0	122	100,0	0,009

*Chi- score a statistically significant difference*

The distribution of patients by sex reveals a higher incidence of the disease in women, compared to men, especially in the association of thyroid carcinoma with autoimmune thyroiditis.

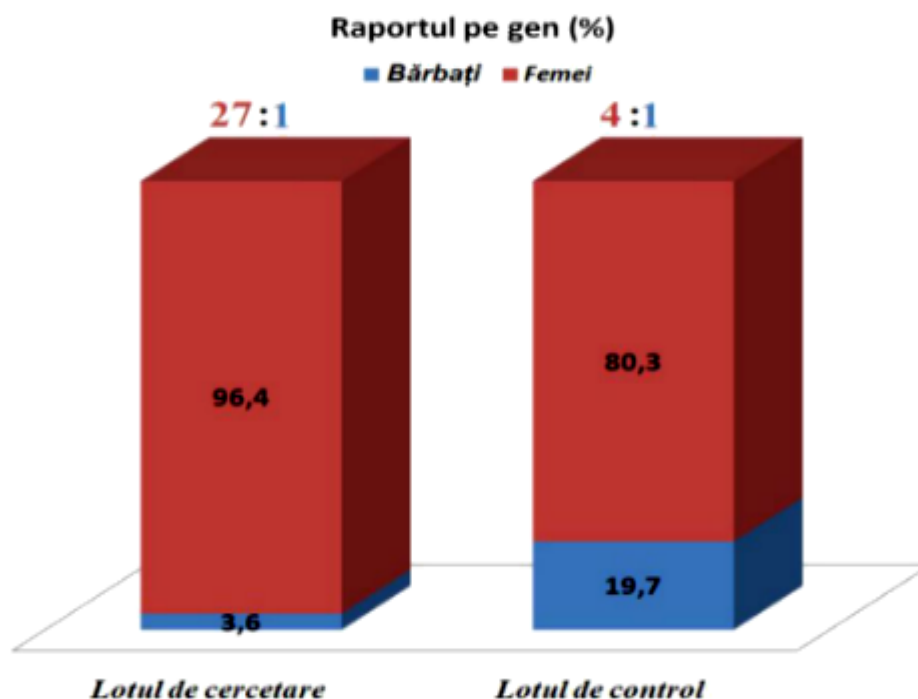
**Table 3.2 Distribution of patients included in the study by gender**

	Research group (Lot I) n=112		Control batch (Lot II) n=122		Chi-scor gl p
	Abs.	%	Abs.	%	
Ladies	108	96,4	98	80,3	14,370 1 0,000
Barbie	4	3,6	24	19,7	
Total	112	100,0	122	100,0	

*Chi- score a statistically significant difference*

The absolute risk for women to be in the research group is 52.4% (II: 45.4% -59.6%), for men 14.3% (II: 3.4% -28.6%). Relative risk (RR) for women to be in the group research is 3,670 (II: 1,468-9,177) times higher than for men.

Respectively in the research group predominate the female patients who constitute 96.4%, and in the control group they constitute 80.3%. The ratio of women / men in the research group constituting 27/1 and in the control group 4/1.



**Figure 3.2 Gender ratio of research patients**

The study on the living environment showed that patients from urban areas prevailed with 55.3% (n = 62) in the research group and 54.9% (n = 67) in the control group.

The absolute risk for the inhabitants of the urban area to be in the research group is 48.1% (II: 39.8% -56.8%), for the inhabitants of the rural area of 47.6% (II: 37.9% -57.3%). Relative risk (RR) is not statistically significant.

Assessing the territorial-administrative region of origin of the patients, it was found a predominance of the inhabitants of the central and southern region of the Republic of Moldova among patients included in the study.

**Table 3.3 Distribution of patients according to the territorial administrative unit (incidence per 100 thousand population with habitual residence)**

	Lot CT+TA (Lot I) n=112	Lot CT+FS (Lot II) n=122
NORTH	4,2	3,8
CENTER	4,6	4,7
SOUTH	4,4	6,8

During the formation of patient groups, they were evaluated with the classification in force. At the end of the study, all patients were analyzed for the latest TNM classification 8th edition adopted by AJCC 2016.

**Table 3.4 Structure of patients depending on the clinical stage of the disease**

	Reserch group (Lot I) n=112				The lot of control (Lot II) n=122		Chi-scor gl p
	Grupul 1		Grupul 2		Abs.	%	
	Abs.	%	Abs.	%			
St.I	10	18,2*	54	94,7*	50	41,0*	78,801 6 0,000
St.II	17	30,9#	2	3,5*#	22	18,0*	
St.III	28	50,9#	1	1,8*#	46	37,7*	
St.IV	0	0,0	0	0,0	4	3,3	
Total	55	100	57	100	122	100	

*Chi- score a statistically significant difference, \* difference compared to the control group, # difference between subgroups of the research group*

Respectively, we observe a predominance in the group 1 research group of stage patients III (50.9%), and in group 2 of the research group predominate the patients with stage I (94.7%).

In the control group, stage I patients predominate (41.0%). Thus, we observe a distribution in patients included in the study with a focus on stage I and stage III.

The absolute risk for patients with stage I of being in the research group is 56.1% (II: 47.3% -65.1%), RR 1.40 (II: 1.069-1.843); for patients with stage III of 39.2% (II: 27.9% - 50.0%), RR is not statistically significant.

An important role in assessing the diagnosis in thyroid cancer associated with thyroiditis autoimmune has the hormonal status and autoimmune markers.

The absolute risk for patients with normal TSH in the research group is 39.6% (II: 32.8% -46.4%), RR 0.431 (II: 0.354-0.525), ie 0.431 of the risk presented by patients with high or low TSH value. The TSH value is within the norm in most patients included in both the study the research group as well as in the control group, and the increased value of the TSH index was observed more much in patients with thyroid carcinoma associated with autoimmune thyroiditis.

**Table 3.5 Distribution of patients included in the study depending on the outcome of TSH**

	Research group (Lot I) n=112				The lot of control (Lot II) n=122		Chi-scor gl p
	Group 1		Group 2		Abs.	%	
	Abs.	%	Abs.	%			
Under the norm	-	-	1	1,8	2	1,6	43,784 4
Norm	41	74,5*	37	64,9*	120	98,4*	0,000
Increased	14	25,5	19	33,3	-	-	
Total	55	100	57	100	122	100	

*Chi- score a statistically significant difference,, confirmed bz the Fisher Exact test, \* difference compared to the control group*

The distribution of patients depending on the antiTPO test showed a prevalence of this index increased in most patients in the research group, both groups, while he was in the norm in patients in the control group. (Table 3.6)

**Table 3.6 Distribution of patients depending on the anti-TPO result**

	Research group (Lot I) n=112				The lot of control (Lot II) n=122		Chi-score gl p
	Grupul 1		Grupul 2		Abs.	%	
	Abs.	%	Abs.	%			
<b>Norm</b>	<b>11</b>	<b>20,0*</b>	<b>9</b>	<b>15,8*</b>	<b>122</b>	<b>100*</b>	<b>165,350</b> <b>2</b>
<b>Increased</b>	<b>44</b>	<b>80,0*</b>	<b>48</b>	<b>84,2*</b>	<b>0</b>	<b>0,0*</b>	
<b>Total</b>	<b>55</b>	<b>100</b>	<b>57</b>	<b>100</b>	<b>122</b>	<b>100</b>	

*Chi- score shows a statistically significant difference confirmed by the Fisher Exact test,\* difference compared to the control group*

The antiTG index shows an increased value in both groups in the research group patients, compared to the control group where this value is normal in all patients, situation similar to the value of antiTPO data.

**Table 3.7 Distribution of patients depending on the antiTG result**

	Research group (Lot I) n=112				The lot of control (Lot II) n=122		Chi-score gl p
	Group 1		Group 2		Abs.	%	
	Abs.	%	Abs.	%			
<b>Norm</b>	<b>34</b>	<b>61,8*</b>	<b>34</b>	<b>59,6*</b>	<b>122</b>	<b>100*</b>	<b>59,114</b> <b>2</b>
<b>Increased</b>	<b>21</b>	<b>38,2*</b>	<b>23</b>	<b>40,4*</b>	<b>0</b>	<b>0,0*</b>	
<b>Total</b>	<b>55</b>	<b>100</b>	<b>57</b>	<b>100</b>	<b>122</b>	<b>100</b>	

*Chi- score shows a statistically significant difference confirmed by the Fisher Exact test,\* difference compared to the control group*

Analyzing the calcitonin values, we deduced that they are within the norm of both patients with CT developed on a healthy background as well as those with CT associated with BP.

**Table 3.8 Distribution of patients according to calcitonin outcome**

	Research group (Lot I) n=112				The lot of control (Lot II) n=122		Chi-scor gl p
	Group 1		Group 2		Abs.	%	
	Abs.	%	Abs.	%			
Norm	51	92,7	51	89,5	118	96,7	3,841 2
Bigger	4	7,3	6	10,5	4	3,3	
Total	55	100	57	100	122	100	

*Chi- score does not indicate a statistically significant difference*

According to the data presented in the table below regarding the value of Thyroglobulin we notice that in both groups in the research group and in the patient control group records the normal TG value in most patients.

**Table 3.9 Distribution of patients depending on the outcome of TG**

	Research group (Lot I) n=112				The lot of control (Lot II) n=122		Chi- scorgl p
	Group 1		Group 2		Abs.	%	
	Abs.	%	Abs.	%			
Norm	51	92,7	50	87,7	106	86,9	1,342 2
Bigger	4	7,3	7	12,3	16	13,1	
Total	55	100	57	100	122	100	

*Chi- score does not indicate a statistically significant difference*

Thus, we certainly notice that in thyroid cancer associated with autoimmune thyroiditis or on a healthy background, patients with calcitonin and TG predominate within the norm.



Ultrasonography of the thyroid gland was performed in the preoperative period in all patients included in the study, being the method by which the presence of thyroid nodules, the number, their size and location. The appreciation of the size of the thyroid gland formations at usg, showed a predominance in the group 1 research group of patients in whom the thyroid malignancy extracapsular extension in 23 patients (41.8%). Different diametrically with group II of the research group where the absolute majority of 93% - 53 patients had a tumor of the thyroid gland less than 2 cm.

In the control group, patients with extracapsular thyroid damage representing 63 patients (51.6%).

Absolute risk for patients with the size of the formation up to 2 cm to be in the group of research is 62.1% (II: 53.0% -70.8%), RR 1,831 (II: 1,371-2,445); the absolute risk for patients with extracapsular formation to be in the study group is 29.2% (II: 20.0% -38.7%), RR 0.493 (II: 0.347-0.699).(table 3.10)

**Table 3.10 Distribution of patients in the study according to the size of the formations thyroid usg**

	Reaserch group (Lot I) n=112						The lot of control (Lot II) n=122		Chi- scor gl p
	Group 1		Group 2		Total		Abs.	%	
	Abs.	%	Abs.	%	Abs.	%			
Up to 2 cm	19	34,5	53	93,0	72	64,3*	44	36,1*	62,970 6 0,000
Between 2-4 cm	12	21,8#	1	1,8#	13	11,6	12	9,8*	
Greaten than 4 cm	1	1,8	0	0,0	1	0,9	3	2,5	
Extracapsular	23	41,8#	3	6,5#	26	23,2*	63	51,6*	
Total	55	100	57	100	112	100	122	100	

*Chi- score shows a statistically significant difference confirmed bz the Fisher Exact test,\* difference compared to control batch # difference between batches of batch of research*

After analyzing the data regarding the location of the process depending on the lobe damage thyroid gland we notice a predominance in the group 1 research group of patients in whom the formation was located in both lobes with 41.8%, and in group 2 of the research group predominates the involvement of the left lobe of the thyroid gland with 47.4%. In the control group, patients with 41% damage to the right lobe. Thus, we observe a diverse distribution among the included patients in the study.

The absolute risk for patients with left lobe involvement to be in the research group is of 62.3% (II: 50.7% -73.6%), RR 1,490 (II: 1,152-1,927).

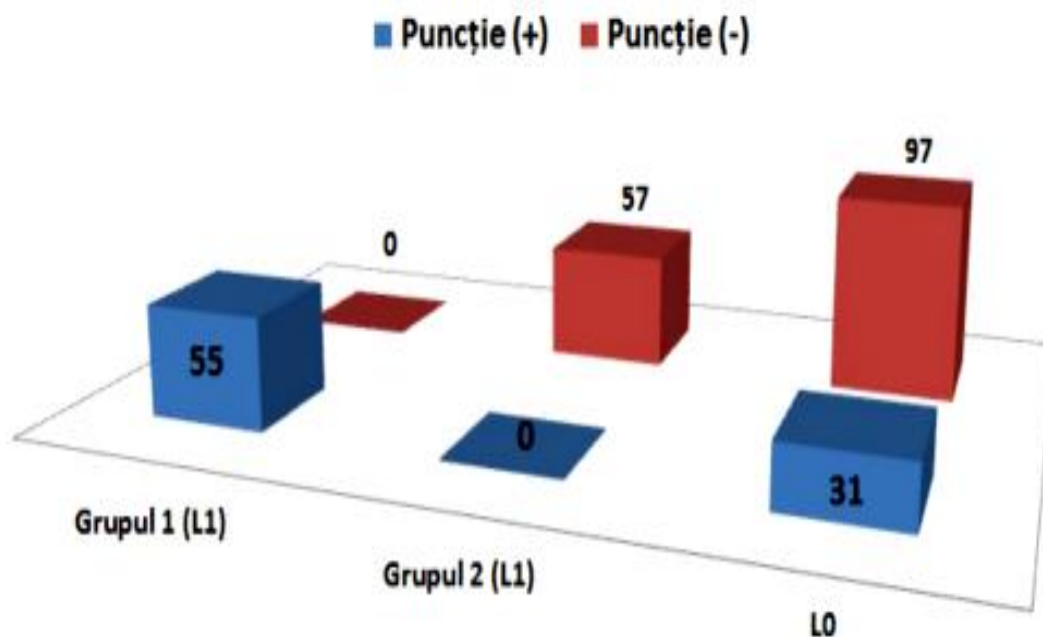
The role of ultrasound-guided puncture of the thyroid gland with cytological examination Eco-guided puncture performed preoperatively on suspicious thyroid gland formations at Malignancy associated with autoimmune thyroiditis, in our study, was performed in 55 patients from research group.

**Table 3.11 Distribution of study patients according to thyroid lobe involvement at USG**

	Research group (Lot I) n=112						The lot of control(Lot II) n=122		Chi-scor gl p
	Group 1		Group 2		Total				
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	
Right lobe	15	27,3	21	26,8	36	32,1	49	40,5	21,105 8 0,007
Left lobe	16	29,1 <sup>#</sup>	27	47,4 <sup>#</sup>	43	38,4 <sup>*</sup>	26	21,5 <sup>*</sup>	
Isthmus	1	1,8	0	0,0	1	0,9	1	0,8	
Bilateral	23	41,8 <sup>#</sup>	9	15,8 <sup>#</sup>	32	28,6	42	34,7	
Lob+isthmus	0	0,0	0	0,0	0	0,0	3	2,5	
Total	55	100	57	100	112	100	122	100	

*Chi- score shows a statistically significant difference confirmed bz the Fisher Exact test,*

*\*difference compared to control batch, # difference between batches of batch of research*



**Figure 3.3 Structure of patients depending on preoperative ultrasound-guided puncture**

The results of the cytological examination obtained after the ultrasound-guided puncture of the thyroid formations were performed according to the 2017 Bethesda classification.

**Tabel 3.12 Distribution of patients depending on the cytological result**

	Research group (Lot I), grupul 1			
	n=55			
	Abs.	%	ÎI-	ÎI+
Lack of data	0	0,0	-	-
Benign	2	3,6	0,0	9,3
Atypia	1	1,8	0,0	6,1
Suspect of neoplasm	6	10,9	3,6	20,3
Suspect of malignancy	10	18,2	8,2	29,0
Malignant	36	65,5	50,0	77,8
Total	55	100		

From the data illustrated above, we observe a maximum dominance registered for the processes of the thyroid gland against the background of autoimmune thyroiditis, which is represented by Bethesda VI, in 36 cases (approx. 65% patients). At the opposite pole we have registered 3 false negative cases (summary approx. 5% patients) which indicates a rate that

certainly influences the sensitivity and specificity of the method described. For Bethesda V, respectively Bethesda IV, we recorded approx. 18% and 11%, respectively.

In summary, we can say that the method applied allows the processes to be established with maximum accuracy malignant thyroid gland, in approx. 94% of cases. Involving modern methods, with minimal costs and without exaggerated risks (complications, side effects, etc.) we can apply the optimal method of treatment agreed to the complete and correct diagnosis.

#### **4.TREATMENT OF THYROID CANCER PATIENTS ASSOCIATED WITH SELF-IMMUNE THYROIDITIS**

In the present study, all patients in both the research group underwent surgical treatment. as well as from the control group.

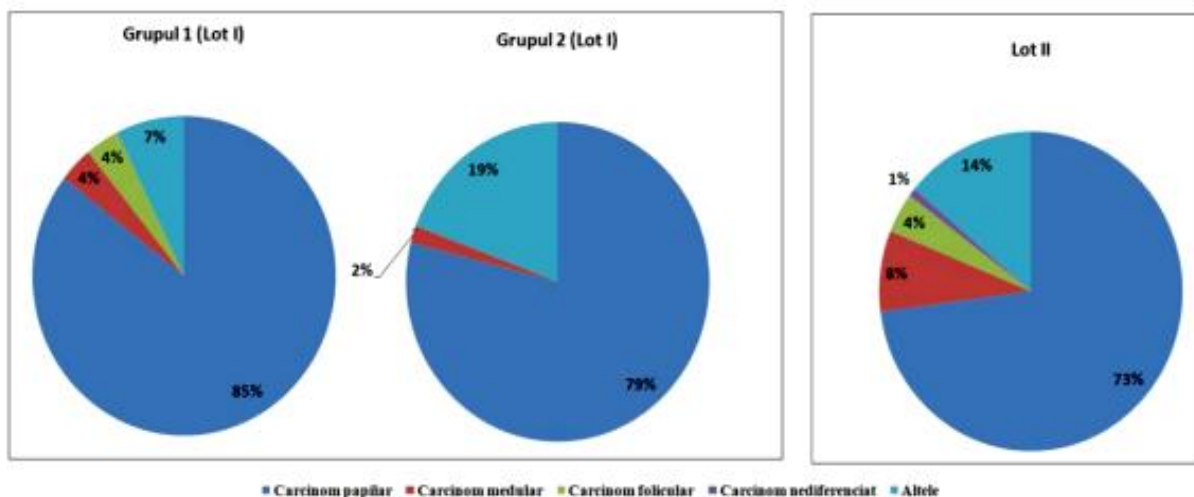
Out of a total of 234 primary surgeries, 195 were performed thyroidectomy (83.33%), 29 thyroid resections (12.39%), 10 cervical lymph node excisions(4.27%). Analyzing the above data, we deduced a predominance in our study of thyroidectomies both in the research group and in the control group, followed by resections of the thyroid gland.

**Table 4.1 Types of surgery applied to patients**

	Research group(Lot I) n=112				Control batch (Lot II) n=122		Chi-scor gl p
	Group 1		Group 2		Abs.	%	
	Abs.	%	Abs.	%			
Gland ezection (lob+istmus)	3	5,5	7	12,3	19	15,6	7,121 4 0,118
Thyiroidectomy	48	87,3	50	87,7	97	79,5	
Thyroidectomi +Excision reg. gangl. limph	4	7,3	0	0,0	6	4,9	
Total	55	100	57	100	122	100	

*Chi-score does not indicate a statistically significant difference*

Histopathological examination was performed in all patients included in the study -112 patients from the research group and 122 patients in the control group.



**Figure 4.1 Distribution of patients according to histological form**

Analyzing the data on the histological type of tumors, we determined a predominance of papillary carcinomas in the study research group 85% in group 1 and 79% in group 2, the form that was also highlighted in the control group with a frequency of 73%. Follicular carcinomas were found in the study in 4% of cases both in the control group and in the research group. carcinomas 4% were found in group 1 in the research group and 2% in group 2 of the same group, representing 8% in the control group. Undifferentiated carcinomas were found only in the batch of control, representing 1% of the total.

Examining the lymph nodes excised as a result of regional lymph node excision, metastases were found in the lymph nodes. Thus, in patients who are part of the group of research group 1 metastases were present in 8 patients (14.5%). In patients in group 2 aIn the research group, metastases were present in only 3 patients (5.3%). The trend is preserved with on the metastasis of thyroid cancer (identical to patients in group I group 1) for patients in the control group, where metastases were present in 23 patients (18.9%).

Following the histopathological examination, we determined cases of thyroid carcinoma with different number of foci, they being unifocal, bifocal and multifocal.

**Table 4.2 Distribution of patients depending on the number of outbreaks in the gland thyroid according to the histological result**

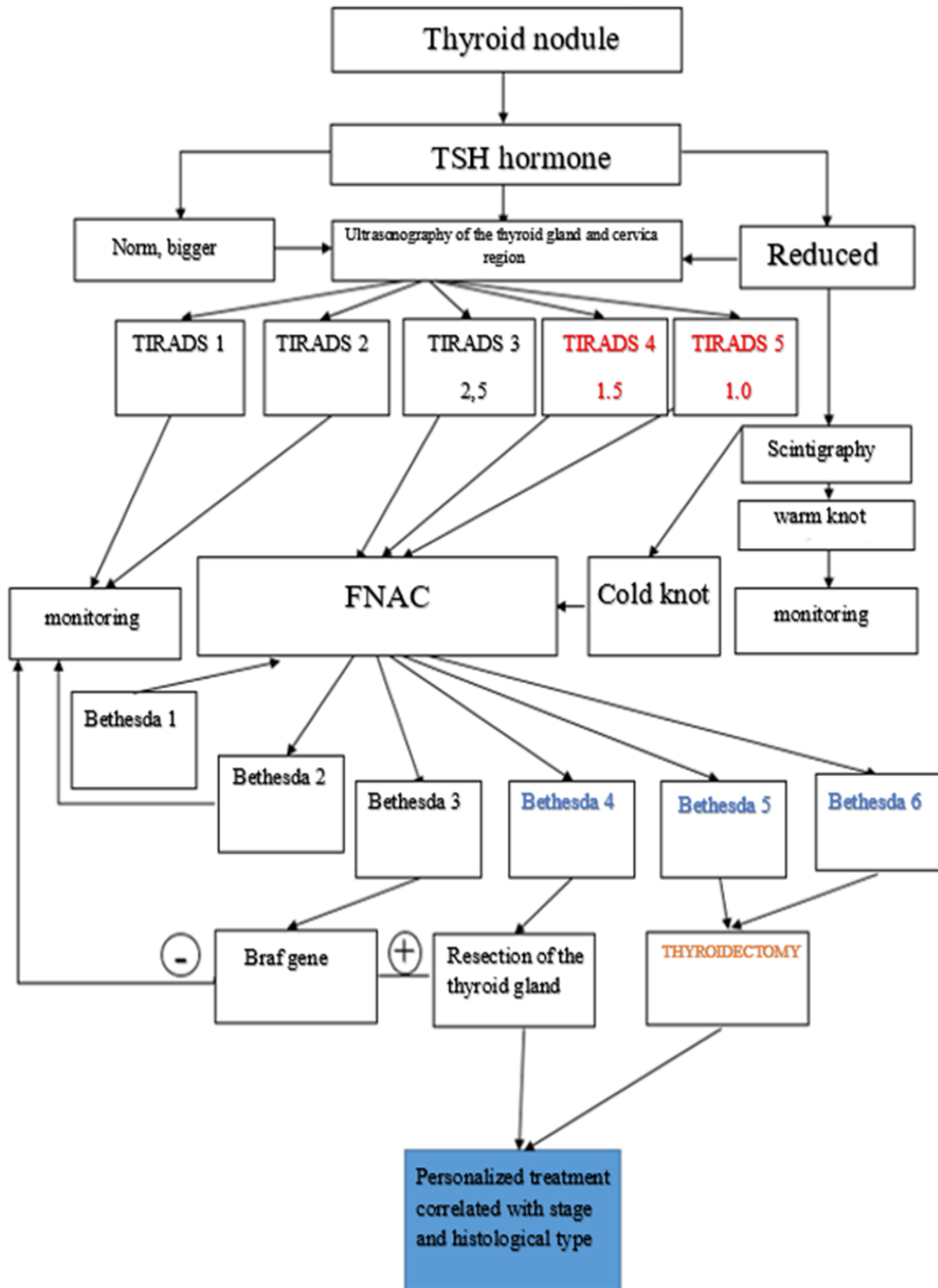
	Research group (Lot I) n=112				Control batch (Lot II) n=122		Chi-score p
	Group 1		Group 2		Abs.	%	
	Abs.	%	Abs.	%			
unifocal	26	47,3	44	77,2*	70	57,4*	11,582 4 0,020
2 outbreak	15	27,3#	6	10,5#	23	18,9	
multifocal	14	25,5	7	12,3	29	23,8	
Total	55	100	57	100	122	100	

*Chi- score shows a statistically significant difference, \*difference compared to control batch, # difference between batches of batch of research*

By dividing the patients according to the number of outbreaks in the thyroid gland, we determined a uniform distribution in terms of unifocal pathology of the thyroid in both groups included in the study.

Algorithm for diagnosis and treatment of thyroid nodules associated with autoimmune thyroiditis developed from research, is based on clinical examination, sonography, ultrasound and ultrasound-guided puncture. Ultrasound and cytological examination were found to be more informative of the point collected by guided aspiration, which will allow the detection of early cancer on background of autoimmune thyroiditis in 94% of cases. Recommended surgical treatment for cancer thyroiditis associated with autoimmune thyroiditis is thyroidectomy.

# Clinical examination



## GENERAL CONCLUSIONS AND PRACTICAL RECOMMENDATIONS

### CONCLUSIONS

1. Thyroid carcinoma associated with autoimmune thyroiditis has a continuous increase in R. Moldova, so in 2017 it was 1.6 (per 100,000 population), in 2018-1.8 (per 100,000) population), and in 2019 it reached 2.6 (per 100,000 population), mainly affecting young people up to the age of 55 (Chi-score denotes a statistically significant difference (Chi score / gl / p-6,878 / 1 / 0.009), predominating Chi-score women denotes a statistical difference significant (Chi-score / gl / p-14,370 / 1 / 0.000).

2. Implementation of the eco-guided puncture method of suspicious thyroid formations substantially improves the results of the diagnosis as well as the surgical treatment of thyroid cancer associated with autoimmune thyroiditis. Summary, according to the results of the study we can say that the sensitivity of the applied method is 94%.

3. Analysis of surgeries performed on patients with thyroid cancer associated with autoimmune thyroiditis showed that total thyroidectomy predominated with (87.3%) in the group 1 of the research group and 87.7% in group 2 of the research group, followed by resections unilateral thyroid disorders by 5.5% in group 1 of the research group and 12.3% in group 2 of the the same batch Chi-score does not denote statistically significant difference -Chi scor / gl / p / 7,121 / 4 / 0,118. These operations ensure ablation, radicalization and risk reduction recurrent laryngeal nerve damage in relapses.

4. Algorithm for diagnosis and treatment of thyroid nodular formations associated with autoimmune thyroiditis developed from research, is based on clinical examination, hormonal, sonographic and ultrasound-guided puncture. Ultrasound was found to be more informative and cytological examination of the point collected by guided aspiration, which allowed detection thyroid cancer on the background of autoimmune thyroiditis in 94% of cases.

### RECOMMENDATION

For oncologists tumors head and neck region and endocrinologists

1. In order to optimize diagnostic-curative management and increase efficiency surgical treatment in patients with autoimmune thyroid nodular form with suspicion of malignancy is recommended for use „The algorithm for diagnosing and treating carcinoma thyroid associated with autoimmune thyroiditis”, proposed and developed in accordance with local conditions.

#### **For the IMSP OMI administration**

2. The eco-guided puncture method is a new method for IMSP IOM, that is why it is need specializations in the field of CCD physicians to perform that method.



3. In order to provide the service to all patients who need it, it is necessary to increase the number these investigations performed according to the insurance policy, which will ensure an established diagnosis faster and treatment in earlier stages, respectively.

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###### ✓ **articles in category B magazines:**

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✓ **international:**

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## ADNOTARE

Sclifos Ina

### „Particularități ale diagnosticului și tratamentului carcinomului tiroidian asociat cu tiroidita autoimună,,

Teză de doctor în științe medicale

Chișinău, 2022

**Structura tezei:** introducere, 4 capitole, sinteza rezultatelor obținute, concluzii generale, recomandări practice, bibliografie, 4 anexe, 113 pagini de text imprimat, 40 figuri, 25 tabele. Rezultatele obținute au fost publicate în 16 lucrări științifice.

**Cuvinte cheie:** carcinom tiroidian, tiroidită autoimună, puncție aspirațională ecoghidată, examen citologic, tratament chirurgical.

**Domeniu de studiu:** Oncologie și radioterapie

**Scopul studiului:** Analiza particularităților clinice, imagistice, citologice, morfologice și a rezultatelor tratamentului chirurgical pentru optimizarea managementului diagnostic-curativ al pacienților cu cancer tiroidian asociat cu tiroidita autoimună.

**Obiectivele studiului:**

1. Studiarea frecvenței carcinomului tiroidian asociat cu tiroidita autoimună în Republica Moldova (2017-2019);
2. Implementarea metodei de puncție aspirativă ecoghidată a formațiunilor glandei tiroide în cadrul IMSP IOM și aprecierea rolului ei în diagnosticul carcinomului tiroidian asociat cu tiroidita autoimună;
3. Analiza tratamentului chirurgical aplicat pacienților cu carcinom tiroidian asociat cu tiroidita autoimună .
4. Elaborarea algoritmului de diagnostic și tratament al pacienților cu CT asociat cu TA.

**Noutatea și originalitatea științifică:** Pe materialul clinic autohton în Republica Moldova au fost studiate particularitățile epidemiologice, evoluția clinică, rolul puncției ecoghidate a glandei tiroide precum și examenul histopatologic postoperator ale carcinomului tiroidian asociat cu tiroidita autoimună. Au fost analizate rezultatele intervențiilor chirurgicale efectuate în funcție de fundalul de bază asociat cancerului tiroidian( tiroidită autoimună sau fundal sănătos). A fost elaborat un algoritm de diagnostic și tratament pentru pacienții cu carcinom tiroidian asociat cu tiroidita autoimună.

**Problema științifică soluționată:** Rezultatele cercetării vor permite implementarea și dezvoltarea noilor abordări diagnostice și de tratament chirurgical la pacienții cu carcinom tiroidian asociat cu tiroidită autoimună.

**Semnificația teoretică a lucrării:** Rezultatele lucrării vizează aprecierea rolului puncției ecoghidate a glandei tiroide drept parte componentă a diagnosticului și tratamentului carcinomului tiroidian asociat cu tiroidita autoimună.

**Valoarea aplicativă a lucrării:** Au fost elaborate recomandări practice în conduita specialiștilor oncologi pentru optimizarea diagnosticului și tratamentului pacienților cu CT asociat cu TA, cu elaborarea algoritmului de diagnostic și tratament ce va face posibilă personalizarea tacticii de tratament.

**Implementarea rezultatelor științifice:** Rezultatele studiului au fost implementate în practica cotidiană a secției tumori regiunea cap și gât precum și în cabinetele din Centrul Consultativ Diagnostic(CCD) al IMSP IO.

## АННОТАЦИЯ

Склифос Инна

### «Особенности диагностики и лечения рака щитовидной железы, ассоциированного с аутоиммунным тиреоидитом»

Докторская диссертация по медицинским наукам.

Кишинев, 2022 г.

**Структура диссертации:** введение, 4 главы, обобщение полученных результатов, общие выводы, практические рекомендации, библиография, 4 приложений, 113 страниц печатного текста, 40 рисунки, 25 таблицы. Результаты опубликованы в 16 научных статьях.

**Ключевые слова:** рак щитовидной железы, аутоиммунный тиреоидит, пункция под контролем УЗИ, цитологическое исследование, хирургическое лечение.

**Специализация:** онкология и лучевая терапия.

**Цель исследования:** Анализ клинических, визуализирующих, морфологических особенностей и результатов хирургического лечения для оптимизации лечебно-диагностического ведения пациентов с раком щитовидной железы, ассоциированным с аутоиммунным тиреоидитом.

**Задачи исследования:**

1. Изучение частоты рака щитовидной железы, ассоциированного с аутоиммунным тиреоидитом, в Республике Молдова (2017-2019);

2. Внедрение метода экзогенной аспирационной пункции образований щитовидной железы в рамках IMSP IOM и оценка его роли в диагностике карциномы щитовидной железы, ассоциированной с аутоиммунным тиреоидитом;

3. Анализ лечения пациентов с карциномой щитовидной железы, ассоциированной с аутоиммунным тиреоидитом.

4. Разработка алгоритма диагностики и лечения пациентов с РЩ, ассоциированным с АТ

**Научная новизна и оригинальность:** На местном клиническом материале в Республике Молдова были изучены эпидемиологические особенности, клиническое развитие, роль пункции щитовидной железы под ультразвуковым контролем, а также послеоперационное гистопатологическое исследование карциномы щитовидной железы, ассоциированной с аутоиммунным тиреоидитом. Были проанализированы результаты операций, выполненных в зависимости от исходного уровня, связанного с раком щитовидной железы (аутоиммунный тиреоидит или здоровый фон). Разработан алгоритм диагностики и лечения пациентов с карциномой щитовидной железы, ассоциированной с аутоиммунным тиреоидитом.

**Решенная научная проблема:** результаты исследования позволят внедрить и разработать новые диагностические и хирургические подходы к лечению пациентов с карциномой щитовидной железы, ассоциированной с аутоиммунным тиреоидитом. Теоретическая значимость статьи: результаты работы направлены на оценивание роли пункции щитовидной железы под УЗИ как составная часть диагностики и лечения карциномы щитовидной железы, ассоциированной с аутоиммунным тиреоидитом.

**Практическое значение статьи:** разработаны практические рекомендации в ведении онкологов по оптимизации диагностики и лечения пациентов с РЩ, ассоциированным с АТ, с разработкой диагностического и лечебного алгоритма, которые позволят настроить тактику лечения.

**Внедрение научных результатов:** Результаты исследования были внедрены в повседневную практику отделения опухоли области головы и шеи, а также в кабинетах Диагностического консультативного центра (ГКЦ) IMSP IO.

## ANNOTATION

Sclifos Ina

### "Particularities of the diagnosis and treatment of thyroid carcinoma associated with autoimmune thyroiditis"

Doctoral thesis in medical sciences Chisinau, 2022

**Thesis structure:** introduction, 4 chapters, synthesis of the obtained results, general conclusions, practical recommendations, bibliography, 4 annexes, 113 pages of printed text, 40 figures, 25 tables. The results were published in 16 scientific papers.

**Key words:** thyroid carcinoma, autoimmune thyroiditis, ultrasound-guided puncture, cytological examination, surgical treatment

**Study domain:** Oncology and radiotherapy

**Study purpose:** Analysis of clinical, imaging, cytological, morphological features and results of surgical treatment to optimize the diagnostic-curative management of patients with thyroid cancer associated with autoimmune thyroiditis.

**The objectives of the study:**

1. Study of the frequency of thyroid carcinoma associated with autoimmune thyroiditis in the Republic of Moldova (2017-2019);

2. Implementation of the method of echo-guided aspiration puncture of thyroid gland formations within IMSP IOM and assessment of its role in the diagnosis of thyroid carcinoma associated with autoimmune thyroiditis;

3. Analysis of treatment applied to patients with thyroid carcinoma associated with autoimmune thyroiditis;

4. Development of the algorithm for the diagnosis and treatment of patients with CT associated with BP.

**Scientific novelty and originality:** On the autochthonous clinical material in the Republic of Moldova were studied the epidemiological peculiarities, the clinical evolution, the role of the ultrasound guided puncture of the thyroid gland as well as the postoperative histopathological examination of the thyroid carcinoma associated with the autoimmune thyroiditis. The results of the surgeries performed depending on the basic background associated with thyroid cancer (autoimmune thyroiditis or healthy background) were analyzed. A diagnostic and treatment algorithm has been developed for patients with thyroid carcinoma associated with autoimmune thyroiditis.

**The scientific problem solved:** The research results will allow the implementation and development of new diagnostic and surgical treatment approaches in patients with thyroid carcinoma associated with autoimmune thyroiditis.

**Theoretical importance:** The results of the paper aim to assess the role of echo-guided puncture of the thyroid gland as a component part of the diagnosis and treatment of thyroid carcinoma associated with autoimmune thyroiditis.

**The applicative value of the paper:** Practical recommendations were developed in the conduct of oncologists to optimize the diagnosis and treatment of patients with CT associated with BP, with the development of the diagnosis and treatment algorithm that will make it possible to customize treatment tactics.

**Implementation of scientific results:** The results of the study were implemented in the daily practice of the tumor section of the head and neck region as well as in the offices of the Diagnostic Consultative Center (CCD) of IMSP OI

**Annex 1** Algorithm for diagnosis and treatment of thyroid cancer associated with autoimmune thyroiditis

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