

ORIGINAL PAPER

THE EXTENT OF SURGERY FOR UNILATERAL NODULAR GOITER WITH COMPRESSION SYNDROME AGAINST THE BACKGROUND OF AUTOIMMUNE THYROIDITIS

Oleksandr V. SHIDLOVSKYI¹, Michael I. SHEREMET^{2✉}, Viktor O. SHIDLOVSKYI¹, Dragos CRETOIU³, Yan V. GYRLA², Oleksandr V. BILOOKYI², Oleksandr V. LAZARUK⁴, Vitaliy V. MAKSYMUK², Volodymyr V. TARABANCHUK², Andriy I. POPOVYCH⁴, Oksana Y. OLINIK⁵, Tetyana Y. LAZARUK⁵, Galyna Y. STELMAKH⁶

¹ Surgery Department, I. Horbachevsky State Medical University, Chernivtsi, Ukraine

² Surgery Department N°1, Bukovinian State Medical University, Chernivtsi, Ukraine

³ Carol Davila“ University of Medicine and Pharmacy, Bucharest, Romania

⁴ Department of Pathology, Bukovinian State Medical University, Chernivtsi, Ukraine

⁵ Department of Internal Medicine and Infectious Diseases, Bukovinian State Medical University, Chernivtsi, Ukraine

⁶ Department of Human Anatomy named M.G. Turkevich, Bukovinian State Medical University, Chernivtsi, Ukraine

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ABSTRACT

Introduction. Nodular goiters are clinically recognizable enlargements of the thyroid gland characterized by structural and/or functional transformation of one or several areas within the normal thyroid tissue. In the absence of thyroid dysfunction, autoimmune thyroid disease, thyroiditis, and thyroid malignancy, they constitute an entity described as simple nodular goiter. **The objective of the study** was to determine the scope of surgery in patients with unilateral nodular goiter with autoimmune thyroiditis (NGAIT) with compression syndrome and predict the long-term results of surgical treatment, based on the study of proliferation of apoptosis and autoimmune disorders.

RÉSUMÉ

Choix de l'étendue de la chirurgie pour le goitre nodulaire unilatéral avec syndrome de compression dans le cadre de la thyroïdite auto-immune

Introduction. Les goitres nodulaires sont des hypertrophies cliniquement reconnaissables de la glande thyroïde caractérisées par une croissance excessive et une transformation structurelle et/ou fonctionnelle d'une ou plusieurs zones du tissu thyroïdien normal. En l'absence de dysfonctionnement thyroïdien, de maladie thyroïdienne auto-immune, de thyroïdite et de malignité thyroïdienne, ils constituent une entité qualifiée de simple goitre nodulaire.

✉ Address for correspondence:

Michael I. SHEREMET
Surgery Department N°1, Bukovinian State Medical University, Chernivtsi, Ukraine
Address: Holovna st, 191, 58018 Chernovtsy, Ukraine
E-mail: mihayl71@gmail.com

Materials and methods. Long-term results of hemithyroidectomy were analysed in 101 women aged between 23-72 years, with unilateral NGAIT. We analysed the volume of the gland lobe and the echo structure variant before surgery, blood levels of thyroid-stimulating hormone (TSH), free thyroxine and triiodothyronine, thyroid peroxidase antibodies (TPOab), apoptosis and proliferation indicators showing satisfactory or unsatisfactory treatment results.

Results. In 75 patients, three years after hemithyroidectomy, no thyroid dysfunction was detected. At ultrasound, in the remaining thyroid the signs of autoimmune thyroiditis (AIT) did not progress. Twenty-six patients showed an increase in the remaining thyroid gland and progression of the autoimmune disease, with hypothyroidism.

Conclusions. Hemithyroidectomy can be performed in patients with NGAIT and compression syndrome in conditions of preserved gland function, activation of proliferation and apoptosis, and pseudo micronodular parenchymal echo structure.

Keywords: nodular goiter, autoimmune thyroiditis, apoptosis, proliferation, surgical treatment.

List of abbreviations:

TG – thyroid gland
NGAIT – nodular goiter with autoimmune thyroiditis
FNAPB – fine-needle aspiration puncture biopsy
TPOab – thyroid peroxidase antibodies
TSH – thyroid-stimulating hormone
IIRC – index of immunoreactive cells
IPA – index of immunoproliferative activity

INTRODUCTION

The choice of the extent of thyroid surgery for unilateral nodular goiter with compression syndrome is important for surgeons. In such cases, surgical treatment is absolutely indicated. In this case, possible options are thyroidectomy and hemithyroidectomy¹⁻⁷. Thyroidectomy will eliminate the autoimmune aggression in the body, but in such cases the patient is doomed to use thyroxine preparations for life⁸⁻¹¹. Hemithyroidectomy, provided that the hormone-producing function in one of the lobes of the thyroid gland (TG) is preserved, will protect the patient from unjustified thyroidectomy and lifelong thyroid hormone replacement therapy¹²⁻¹⁹.

The simplified approach to choose the extent of surgery, based mainly on ultrasound data, is almost

Objectif. Déterminer les indications pour le choix de l'étendue de la chirurgie chez les patients atteints de goitre nodulaire unilatéral avec thyroïdite auto-immune (NGAIT) et prédire les résultats à long terme du traitement chirurgical en se basant sur l'étude de la prolifération et de l'apoptose et des maladies auto-immunes.

Matériels et méthodes. Les résultats à long terme de l'hémithyroïdectomie ont été analysés chez 101 femmes âgées de 23 à 72 ans atteintes d'une NGAIT unilatérale. Nous avons analysé les paramètres du volume du lobe de la glande et de la variante d'échostructure avant la chirurgie, les taux sanguins d'hormone stimulant la thyroïde (TSH), de thyroxine et de triiodothyronine libres, d'anticorps de la peroxydase thyroïdienne (TPOab), les indicateurs d'apoptose et de prolifération montrant des résultats satisfaisants ou insatisfaisants du traitement.

Résultats. Chez 75 patients, trois ans après l'hémithyroïdectomie, aucun dysfonctionnement thyroïdien n'a été détecté. A l'échographie dans la partie restante des signes d'AIT n'ont pas progressé, et 26 patients ont montré une augmentation de la glande thyroïde restante et une progression du processus auto-immun avec hypothyroïdie.

Conclusions. L'une des options possibles pour le traitement chirurgical des patients en association avec le syndrome de compression, l'hémithyroïdectomie peut être réalisée dans des conditions de fonction hormonale préservée de la glande avec des processus modérés de prolifération et d'apoptose et des modifications structurales du parenchyme au niveau hypoéchogène et hétérogène, variantes échostructurales pseudomicro-nodulaires.

Mots-clés: goitre nodulaire, thyroïdite auto-immune, apoptose, prolifération, traitement chirurgical.

the major reason for performing unjustified surgical interventions. The diagnosis of nodular goiter against the background of autoimmune thyroiditis (NGAIT) presents certain difficulties due to specific morphological and structural changes in the TG tissue²⁻⁷.

The morphological assessment of the node before surgery can only be obtained by fine-needle aspiration puncture biopsy (FNAPB). The accuracy of cytological diagnosis using FNAPB is about 96.0-98.0%⁸⁻¹⁰. However, against the background of AIT, the accuracy of the morphological diagnosis of nodules decreases by about 25.0% and, accordingly, the number of questionable results increases¹⁴⁻¹⁸. In such cases, sequential cytomorphological and immunocytochemical studies on the same smear of puncture material increase the accuracy of cytological diagnosis²⁰⁻²³.

An important step in the diagnosis is the identification of cell cycle regulation disorders, in particular proliferation and apoptosis. Their markers include membrane Fas and Fas-L receptors, Bcl-2 proteins, the nuclear gene suppressor phosphoprotein p53, and the Ki-67 antigen^{24,32}. According to literature data, the inclusion of these markers in the diagnosis algorithm allows an accurate assessment and interpretation of the intensity and severity of autoimmune processes in the TG. In our opinion, these can be used to assess the extent of surgical treatment for unilateral NGAIT with compression syndrome – hemithyroidectomy or thyroidectomy.

THE OBJECTIVE OF THE STUDY was to assess the indicators of the extent of surgery in patients with NGAIT with compression syndrome, and long-term results of surgical treatment.

MATERIALS AND METHODS

The criteria for inclusion in the study were: age between 18-45 years; verified diagnosis of thyroid adenoma, NGAIT with compression syndrome in the stage of euthyroidism or subclinical hypothyroidism; thyroid-stimulating hormone (TSH) level 0.4-4.0 mIU/mL, taking into account the dose of replacement therapy; thyroid peroxidase antibodies (TPOab) level 60-225.15 mIU/L; the volume of the node or nodes, according to thyroid ultrasound, from 2.25 to 7.55 cm³; birth and residence in a iodine-deficient region; the patients' signed informed consent to be included in the study.

The exclusion criteria for all groups were: age less than 18 and more than 45 years; fibrous morphological variant of AIT; insufficient data for diagnosis; anamnestic data on acute bacterial or viral infections and vaccinations during the last six months; severe somatic pathology (diabetes, infection with human immunodeficiency virus, systemic autoimmune diseases, oncological diseases), use of immunosuppressive or immunostimulant drugs during the last year; pregnancy, lactation; refusal of the patient.

The patients were examined in Chernivtsi Regional Endocrine Specialized Clinic (Ukraine) from May 5, 2016 to April 27, 2019.

The long-term results (from 3 to 5 years) of hemithyroidectomy were analysed in 101 women aged between 23-72 years with unilateral NGAIT with compression syndrome. The duration of AIT ranged from 7 to 22 years. The diagnosis was established based on clinical symptoms, ultrasound, laboratory, morphological and immunohistochemical studies. At the clinical examination, attention was paid to local and general manifestations of AIT.

According to ultrasonography data, the TG structure and blood supply, the presence, structure, volume and localization of pseudo and true nodular masses and displacement of the neck organs were studied. According to the Beskin et al ultrasonographic classification (2018), the study included patients with only the first three variants of the echographic data: hypoechoic and heterogeneous, pseudo micronodular and pseudo macronodular⁹⁻¹³. There were 51 patients with hypoechoic and heterogeneous variants, 27 with pseudo micronodular variants, and 23 with pseudo macronodular variants.

The levels of TSH, free thyroxine (T4), triiodothyronine (T3) and TPOab were determined. Punctates from the nodal masses and parenchyma of the opposite lobe were studied. The morphological characteristics of nodes' punctates were determined according to the Bethesda system classification for reporting thyroid cytopathology, and in the puncture tissue from the parenchyma of the opposite lobe the activity of the autoimmune process was studied using proliferation and apoptosis indicators. In the preparation of smears, FNAPB was used, developed and patented at the V.P. Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Medical Sciences of Ukraine method of restoring the activity of antigenic determinants, which allows combining cytomorphological and immunocytochemical studies on one cytological preparation and makes it possible to objectively characterize individual cellular elements³³. The results of immunohistochemical reactions were evaluated by semi-quantitative analysis, developed by Khmelnytskyi³⁴. Immunoreactive cells were calculated by the formula index of immunoreactive cells (IIRC) (Fas, FasL, Bcl-2, P53) = $N1 / N2 \times 100\%$, where N1 is the number of cells immunopositively to Fas, FasL, Bcl-2, P53 receptors, N2 is the total number of cell nuclei per square millimeter. The index of immunoproliferative activity (IPA) was evaluated using the formula $NKi-67 / N \text{ total} \times 100\%$, where NKi-67 is the total number of nuclei immunopositively to the Ki-67 protein, N total the total number of cell nuclei per square millimeter. The Bresser Bio Science Bino microscope (Germany) with a Nikon DS-Fil digital camera and a personal computer with NIS-Elements F 3.2 software were used for morphometric studies.

The results of ultrasonography (echo structure, volume of the gland and lobes without a node), indicators of TPOab, hormonal function, markers of apoptosis and proliferation, and data from cytological studies were considered when planning the possibility of performing hemithyroidectomy in patients with NGAIT with compression syndrome.

Table 1. Long-term treatment results depending on the variant of echo structure in one of the two TG lobes before surgery.

| Echographic data before surgical treatment | Treatment results | |
|--|---------------------|-----------------------|
| | Satisfactory result | Unsatisfactory result |
| Hypoechoic and heterogeneous (n = 51) | 51 | 0 |
| Pseudo micronodular (n = 27) | 21 | 6 |
| Pseudo macronodular (n = 23) | 3 | 17 |
| Definitely hypoechoic | 0 | 3 |
| Total n = 101 | 75 | 26 |

All patients underwent hemithyroidectomy according to the generally accepted method. During surgery, the express histological examination of nodular masses was performed. There were virtually no matches between the results of rapid histological examination and the examination of puncture material.

The long-term results of hemithyroidectomy (from 3 to 5 years) were evaluated three years after surgery based on clinical data, ultrasound results (size, echo structure and volume of the remaining gland lobe), hormone levels (TSH, T4, T3, TPOab, proliferation and apoptosis activity). We studied the indicators of the studied tests after surgical treatment, the progression of AIT in one part of the gland with the development of hypothyroidism, which caused an unsatisfactory treatment result.

The statistical processing of the research results was made using Microsoft® Office Excel spreadsheets and the BioStat statistical calculation program. The critical significance level (p) when testing statistical hypotheses in this study was assumed to be 0.05.

All patients were informed about the scope of the examinations and informed consents were signed.

The approval for this study was obtained from the Ethics Committee of the “Bukovinian State Medical University” and Chernivtsi Regional Endocrine Specialized Clinic, Ukraine (approval number 11-07.04.2016).

RESULTS AND DISCUSSION

The patients were divided in two groups:

Group I (satisfactory result) consisted of 75 patients who had euthyroidism three years after hemithyroidectomy, with ultrasound signs of AIT in one of the lobes of the TG, without the development of hypothyroidism.

Group II (unsatisfactory result) consisted of 26 patients who had hypothyroidism three years after hemithyroidectomy, and in whom ultrasound revealed minor irregularities and scalloped contours of TG, with pseudo-nodes and nodules in the remaining

TG. At colour Doppler, mapping deterioration of a blood-groove on entire TG was noted.

In three cases, the progression of the autoimmune process was accompanied by a change in the echo structure variant from pseudo macronodular to clearly hypoechoic (Table 1). To compensate for hypothyroidism, the patients received replacement therapy with thyroxine preparations in doses from 50 to 150 mcg per day.

The data presented in Table 1 indicate that there were no unsatisfactory treatment results in the hypoechoic and heterogeneous variants of the echo structure pattern in the TG. In the case of the pseudo micronodular variant, in 6 (22.2 %) out of 27 patients an unsatisfactory treatment result was found, manifested by the progression of AIT and the development of hypothyroidism. A similar clinical situation occurred in 17 (73.9%) out of 23 patients with pseudo macronodular variant of ultrasound changes in the TG.

We have found that in the group of patients with satisfactory results, the volume of the lobe of the gland did not significantly differ from the initial indicators, and its function was determined as euthyroidism. In cases with an unsatisfactory result in 18 out of 26 patients, the volume of the lobe increased by 15-47% compared to initial data. The hormone levels at the required dose of replacement therapy were within the reference values. The TPOab level in both groups of patients was increased. Only in the group with unsatisfactory results, it was significantly higher than in the group of patients with a satisfactory treatment result (Table 2).

The comparative evaluation of proliferation and apoptosis markers before surgery, between the groups with satisfactory and unsatisfactory treatment results, showed the inhibition of apoptotic activity and a pronounced activation of proliferation processes. In patients with unsatisfactory results, it manifested by significantly higher values of IIPA Ki-67, IIRC FasL, IIRC Bcl-2 and lower IIRC Fas and IIRC p53. These data suggest that the proliferative processes in the thyroid parenchyma progressed in patients of this group

Table 2. Comparative assessment of the share and functional state of the TG and TPOab levels depending on treatment results.

| Indicators | The value of studied indicators depending on the results of treatment | | | |
|---|---|-----------------------------------|----------------------------------|-----------------------------------|
| | Satisfactory (n=75) | | Unsatisfactory (n=26) | |
| | before surgery | after surgery | before surgery | after surgery |
| Volume of the TG unaffected by nodes (cm ³) | 9.77 ± 0.27 | 1028 ± 0.13 <0.5 ² | 10.82±0.21 <0.01 ¹ | 20.86±1.17 <0.01 ² |
| TSH (mIU/L) | 2.35 ± 0.19 | 2.63 ± 0.17 <0.5 ² | 3.27±0.33 <0.01 ¹ | 3.92±0.25 <0.5 ² |
| T4 (pmol/L) | 19.38 ± 0.37 | 18.02 ± 0.18 <0.5 ² | 15.24±0.31 <0.01 ¹ | 16.52±0.25 <0.01 ² |
| T3 (pmol/L) | 5,91 ± 0,31 | 6.12 ± 0.18 <0.5 ² | 4.51±0.29 <0.5 ¹ | 4.46 ± 0.34 <0.5 ² |
| TPOab (mIU/L) | 73.21 ± 0.19 | 74.45±0.56 <0.5 ² | 14.44±1.15 <0.01 ¹ | 215.68±1.88 <0.01 ² |

Note. ¹ - comparison between groups before treatment; ² - in groups of patients after surgical treatment, comparison with data before treatment.

Table 3. Comparative evaluation of indicators of proliferation and apoptosis markers in one of the TG lobes in patients with satisfactory and unsatisfactory treatment results.

| Indicator | Satisfactory result (n=75) | | Unsatisfactory result (n=26) | |
|---------------|----------------------------|---------------|------------------------------|-------------------------|
| | before surgery | after surgery | before surgery | after surgery |
| IPA Ki-67, % | 8.45±0.22 | 8.85±0.23 | 10.91±0.24 ² | 11.82±0.19 ¹ |
| IIRC FasL, % | 41.71±0.19 | 42.63±0.19 | 56.17±0.76 ² | 64.26±0.98 ¹ |
| IIRC Bcl-2, % | 86.71±0.38 | 88.12±0.27 | 93.33±0.85 ² | 97.41±0.86 ¹ |
| IIRC p53, % | 66.63±0.25 | 65.19±0.29 | 54.72±0.61 ² | 48.14±1.19 ¹ |
| IIRC Fas, % | 53.11±0.57 | 51.83±0.47 | 41.16±0.54 ² | 38.13±0.63 ¹ |

Note. ¹ - reliability of the indicators differences before and after surgery (<0.01); ² - reliability of the indicators differences before surgery, between groups with satisfactory and unsatisfactory treatment results (p<0.01).

during the follow-up period after surgical treatment, which led to deterioration of the TG echo structure and development of hypothyroidism (Table 3).

The next step in the study was to establish the relationship between long-term treatment outcomes, variants of the echo structure of TG parenchyma, indicators of hormonal function, TPOab, proliferation and apoptosis (Tables 4, 5).

The comparative analysis of the indicators of satisfactory and unsatisfactory treatment results indicates that with the alteration of the TG echo structure its hormone-producing function decreases, the level of TPOab increases, the activity of proliferative processes increases, and apoptosis is suppressed.

These results offer approximate indicators of TG volume, its function, TPOab, activity of proliferation and apoptosis processes, types of TG echo structure, for choosing hemithyroidectomy surgery and predicting treatment outcomes (Table 6).

Regarding the pseudo micronodular echo structure, there were 6 (22.2%) patients with an unsatisfactory treatment result, in whom the volume of the lobe

without a node was > 13.5 cm³, TPOab >150 mIU/L, TSH was > 3 mIU/L, the activity of IIPA Ki-67 and IIRC Bcl-2 was higher, 10.5 and 89.1%, respectively, and IIRC p53 was < 60.2%. Therefore, when choosing hemithyroidectomy with this variant of echo structural changes in the TG lobe, special attention should be paid to the indicators of the lobe volume, TSH and TPOab levels, and the activity of proliferation and apoptosis processes. If there is a discrepancy between the values of the recommended indicators, thyroidectomy should be performed.

The study indicates that the tests used by us to select the extent of surgery allow to distinguish between indications for thyroidectomy or hemithyroidectomy in patients with NGAIT with compression syndrome.

At the same time, we emphasize that the conclusions of this study are based on the results of long-term observations and can be recommended for widespread implementation in clinical practice.

Autoimmune processes can cause structural changes in TG tissue, which in some cases serves as

Table 4. Indicators of gland function and TPOAB before surgical treatment in patients with different echo structure types.

| Echo structure type | Indicators of TG function | | | TPOab (mIU/L) |
|-----------------------------------|---------------------------|---------------------------|--------------------------|----------------------------|
| | TSH (mIU/L) | Free T4 (pmol/L) | Free T3 (pmol/L) | |
| Hypoechoic and heterogeneous (51) | 2.42 ± 0.12 | 19.07 ± 0.11 | 6.32 ± 0.13 | 108.9 ± 5.38 |
| Pseudo micronodular (27) | 2.97 ± 0.39 | 17.04 ± 0.17 ¹ | 5.93 ± 0.12 ¹ | 123.9 ± 8.38 ¹ |
| Pseudo macronodular (23) | 3.62 ± 0.43 ¹ | 16.14 ± 0.16 ¹ | 5.27 ± 0.17 ¹ | 149.9 ± 12.54 ¹ |

Note. ¹ – changes are significant compared to those in patients with hypoechoic and heterogeneous variants of the TG echo structure (p<0.01).

Table 5. Indicators of proliferation and apoptosis before surgical treatment in patients with different types of TG echo structural changes.

| Types of TG echo structure | Indicators of proliferation and apoptosis | | | | |
|-----------------------------------|---|--------------------------|-------------------------|-------------------------|-------------------------|
| | IIPA Ki-67 | IIRC FasL | IIRC Bcl-2 | IIRC p53 | IIRC Fas |
| Hypoechoic and heterogeneous (51) | 7.91±0.22 | 40.18±0.16 | 85.32±0.14 | 68.71±0.12 | 53.98±0.14 |
| Pseudo micronodular (27) | 8.42±0.34 | 42.93±0.43 ¹ | 86.32±0.37 ¹ | 65.93±0.48 ¹ | 48.73±0.63 ¹ |
| Pseudo macronodular (23) | 9.27±0.41 ¹ | 43.27 ±0.48 ¹ | 89.72±0.51 ¹ | 63,61±0,55 ¹ | 45.31±0.52 ¹ |

Note. ¹ – changes are significant in comparison with the indicators in patients with hypoechoic and heterogeneous variants of the echo graphic structure (p<0.01).

Table 6. Indicators of the studied tests for selecting hemithyroidectomy and predicting a satisfactory outcome of NGAIT surgical treatment.

| Indicators | Limit values of indicators for satisfactory results |
|--|---|
| Volume of the unaffected TG (cm ³) | <12.7 |
| TSH (mIU/L) | <2.85 |
| fT4 (pmol/L) | >16.7 |
| fT3 (pmol/L) | >5.3 |
| TPOab (mIU/L) | <137 |
| IIPA Ki-67 (%) | <8.6 |
| IIRC FasL (%) | <43.1 |
| IIRC Bcl-2 (%) | <87.2 |
| IIRC p53 (%) | >64.6 |
| IIRC Fas (%) | >47.3 |
| Variant of TG echo structure | Hypoechoic and heterogeneous, pseudo micronodular |

a trigger for the initial nodal transformation. In addition, nodes with severe cystic degeneration are also often accompanied by more pronounced thyroid dysfunction on the background of sclerotic changes in thyroid tissue and a general decrease in blood supply to the gland in NGAIT¹⁻³.

The morphological characteristics of the node before its surgical removal can be clarified only by FNAPB⁵. Even though in most types of nodal transformation of thyroid tissue, the accuracy of the method, according to some authors, reaches 96-98%, in

some types of thyroid pathology, such as NGAIT, in 25% of cases it provides limited information due to insufficient cellular elements in a biopsy or questionable diagnosis⁶⁻⁹.

Treatment of NGAIT in most cases is conservative, as it is traditionally considered a medical disease. Treatment consists of long-term follow-up with periodic examination of the small euthyroid goiter before thyroid insufficiency and replacement with a full dose of thyroxine in thyroid insufficiency or suppressive TSH therapy for regression of large symptomatic

goiter⁴⁷. NGAIT is rarely an indication for surgery, but surgery is indicated in many clinical and pathological conditions associated with AIT, such as large nodules, malignancies, symptoms of compression, etc. There are only a few articles that comprehensively consider the indications for surgery in NGAIT¹¹⁻¹⁹.

The overdiagnosis of nodules on the background of AIT's simplified approach, based only on ultrasound data, inevitably leads to unreasonable operations, with a frequency of up to 21%²⁰⁻²². At the same time, the diagnosis of true nodules on the background of AIT presents certain difficulties, associated with specific changes in the TG²³. Despite the use of modern diagnostic methods, it is not always possible to correctly establish the morphological nature of thyroid nodules on the background of AIT²⁴⁻²⁵.

Thus, the analysis of literature data shows that the lack of standardized approaches to early diagnosis of NGAIT and insufficient efficiency of its comprehensive treatment are the main causes of unsatisfactory treatment outcomes. To date, there are no clear indications for the surgical treatment of this pathology, timing of surgical interventions, optimal volume.

We consider that, for a correct evaluation of indications and contraindications to surgery, it is necessary to perform FNAPB of nodes, in addition to ultrasound and clinical evaluation.

Research limitations

This study has some limitations. There are differences in age, sex, degree of thyroid enlargement, cytological type of thyroid tissue, underlying disease, etc., which somewhat limits the direct comparison of apoptosis and proliferation processes in the puncture material of thyroid tissue with autoimmune changes.

CONCLUSIONS

In patients with NGAIT and compression syndrome, hemithyroidectomy can be performed in conditions of preserved hormonal function of the TG, with moderate processes of proliferation and apoptosis and structural changes in the parenchyma (hypoechoic and heterogeneous and pseudo micronodular echo structure types).

We are against the use of hemithyroidectomy in cases of pseudo-large-nodes and macronodular echo structure of the thyroid parenchyma, regardless of the indicators of hormone-producing function, TPOab, proliferation and apoptosis.

Author Contributions:

Conceptualization, V.O.S, M.I.S and O.V.S; methodology, D.C.; software, Y.V.G.; validation, O.V.B. and M.I.S.; formal analysis, O.V.L.; investigation, O.V.B.;

resources, O.V.B.; data curation, J.J. and K.K.; writing—original draft preparation, A.I.P; writing—review and editing, V.O.S, M.I.S; visualization, T.Y.L and O.Y.O; supervision, A.I.P; project administration, O.Y.O. All the authors have read and agreed with the final version of the article.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study"

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