ORIGINAL ARTICLE

CONTENTS

Diagnostic measures in patients with thyroid diseases complicated by tracheal compression syndrome

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ABSTRACT

Aim: Aim of the study is analysis of results of diagnostic studies in patients with diseases of thyroid complicated by tracheal compression syndrome which were operated on urgent and immediate indications.

Materials and Methods: The study comprised 167 patients, who were admitted to the clinic of State University «Institute of General and Emergency Surgery named after V. T. Zaitsev National Academy of Sciences of Ukraine» with thyroid diseases complicated by tracheal compression syndrome. All the patients were operated on by urgent and immediate indications. Condition of thyroid and residual tissue were assessed with the help of ultrasound examination, elastography, gland function according to the level of hormones, the results of histological examination and immunohistochemical studies were also taken into account.

Results: The conducted immunohistochemical studies proved presence of three stages of proliferative activity of the thyroid gland; correlation was established between the characteristics of elastography and markers of proliferative activity. Further tactics of patient's management depends on determination of type of elastogram and degree of proliferative activity of thyroid tissue: referral for dynamic observation or surgical treatment with the selection of the scope of surgical intervention including minimally invasive one.

Conclusions: Diagnostic measures in patients with thyroid diseases complicated by tracheal compression syndrome are aimed first of all at receiving comprehensive data on patient's actual condition and disease to determine optimal treatment tactics and decrease the level of postoperative complications and lethality in surgical interventions performed by urgent and immediate indications.

KEY WORDS: diagnostics, cytological examination, elastography, thyroid disease, immunohistochemical study, compression syndrome of trachea

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INTRODUCTION

For our country thyroid diseases including so-called iodine deficiency state, are of particular importance, as far as for weakened attention to iodine prevention some territories turned out to be endemic for goiter. Results of ecological catastrophe in Chornobyl emphasize again the relevance of program research related to pathology of thyroid gland [1-3].

Frequency of nodular forms of goiter among thyroid diseases according to different authors varies from 42 to 98.9%, among which the multiple defeat makes about 25-62% [3, 4].

Clinical concept of "thyroid disease" combines focal and diffuse lesions of thyroid gland with different pathomorphological changes: thyroiditis, cysts, and true nodes, benign and malignant tumors of the thyroid gland. Their nature is completely different: benign proliferation, primary and secondary dysplasia, autoimmune lymphoid infiltration. Great number of existing thyroid disease classifications is represented with isolated from one another histological, cytological, clinical and prognostic schemes [5, 6]. Most of them are devoted to classification of thyroid cancer; this actually determines the necessity of preliminary diagnostics [7].

Thus, the problem of adequate diagnostics of thyroid diseases complicated by tracheal compression syndrome in patients operated by urgent and immediate indications has not been solved and highlighted enough.

AIM

The aim of the study is analysis of results of diagnostic studies in patients with thyroid diseases complicated with tracheal compression syndrome, which were operated by urgent and immediate indications.

MATERIALS AND METHODS

The research comprises 167 patients with tracheal compression syndrome induced by thyroid diseases who were admitted to the clinic of State University «Institute of General and Emergency Surgery named after V. T. Zaitsev National Academy of Sciences of Ukraine» urgently. 88 of them were patients with polynodous euthyroid cervicosternal goiter and 79 patients with differentiated forms of thyroid cancer.

The research met international requirements CONSORT and had corresponding design – retrospective and prospective randomized clinical trial in which the results of diagnostics of polynodous euthyroid cervicosternal goiter complicated with tracheal compression syndrome and thyroid cancer were studied.

Ethical principles of the research were observed. The ethical commission of Educational granted permission for the research and Scientific Medical Institute of National Technical University «Kharkiv Polytechnic Institute» (Protocol of the meeting №3 from 22.01.2024). Written informed consents for the use of the results of treatment for the research were gained from all the patients.

All the patients were operated on and classified into two groups depending on the terms of performing emergency surgical interventions: 1st group of patients comprises those who underwent urgent surgery intrusion during the first day. There were 52 (31.1%) of them; second group of patients were 115 (68.9%) patients who underwent emergency surgery intrusion during the second and third day since the moment of admission.

In the vast majority of observations, (132/79.0%) operations were performed by urgent and immediate indications in patients aged over 60 years. The age of operated patients by urgent indications varied from 54 to 86 years (on average 72.0 ± 1.28 years). In 35 (67.3% of the number of urgently operated) patients the age was more than 70 years. Women prevailed among the patients. The ratio of men and women was 1:9.4.

The age of those operated by urgent indications varied between 54 and 85 years. Average age of such patients (on average 62.6±1.49 years) was considerably lower than in the group of urgently operated ($p < 0.05$). Age of majority (66/57.4%) of patients of this group turned out to be lower than 70 years. There were 108 (93.9%) women operated on urgently, and 7 (6.1%) men. The ratio of men and women was 1:15.4.

When assessing comorbidity of these patients it has been found: 52 (31.1%) of patients have 3 and more concomitant pathologies, all of them had pathology of the cardiovascular system – coronary heart disease, tension angina, arterial hypertension, part of patients had arrhythmic variant of coronary heart disease, including atrial fibrillation. Comorbidity index of these patients made 6.2±0.61, which is characterized as high.

All the patients with tracheal compression syndrome underwent laboratory and instrumental studies on admission to the hospital, with estimation of objective and local status before the operation, condition of thyroid gland and residual tissue during ultrasound examination, as well as function of the gland according to the level of hormones, we took into account the results of histological examination and immunohistochemical examination.

Against the background of the underlying disease, many patients with tracheal compression syndrome had concomitant pathology: ischemic heart disease, hypertension, diabetes, chronic heart failure, chronic obstructive bronchitis and others. Moreover, most patients had more than one concomitant disease.

STATISTICAL PROCESSING OF THE OBTAINED DATA

To compare average absolute values the Student's criteria (t) was used. Because of the comparative analysis of relative indicators, the ratio criterion was used χ^2. Confidence intervals were calculated with the help of Fisher's method. The criterion of statistical reliability of the obtained results was considered to be the value $p<0.05$. Statistical processing of digital data was conducted on a personal computer IBMPC with the help of program system Statistica V 10.0. Patient survival was calculated using Kaplan-Meier survival tables.

RESULTS

ELECTROGRAPHY IN COMPLEX ULTRASOUND EXAMINATION OF THE THYROID GLAND

All the patients in the preoperative period underwent ultrasound examination of the thyroid gland. Following changes in thyroid gland tissue were observed: single nodules of thyroid tissue, diffuse-nodular formations, cystic-nodular formations, adenomas of the thyroid gland. The highest percentage made patients with multiple thyroid nodules - 68 (62%).

For patients of the main group standard ultrasound examination was supplemented with electrography

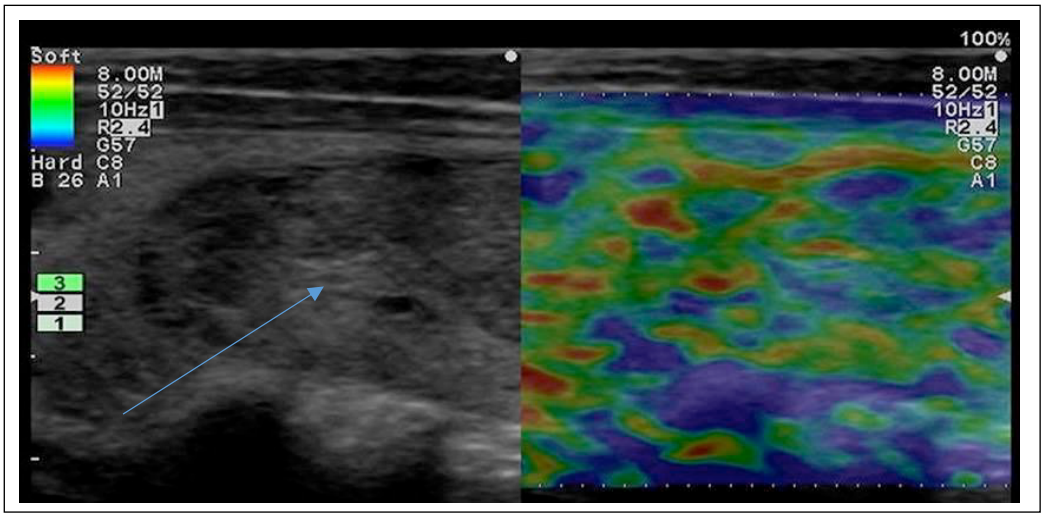

Fig. 1. Nodular goiter. Ultrasound of the neck, gray scale mode: longitudinal scanning and sonoelastography. On the sonoelastography there is intensive yellow staining, stiffness coefficient 1.0 kPa (blue arrow)
Picture taken by the authors

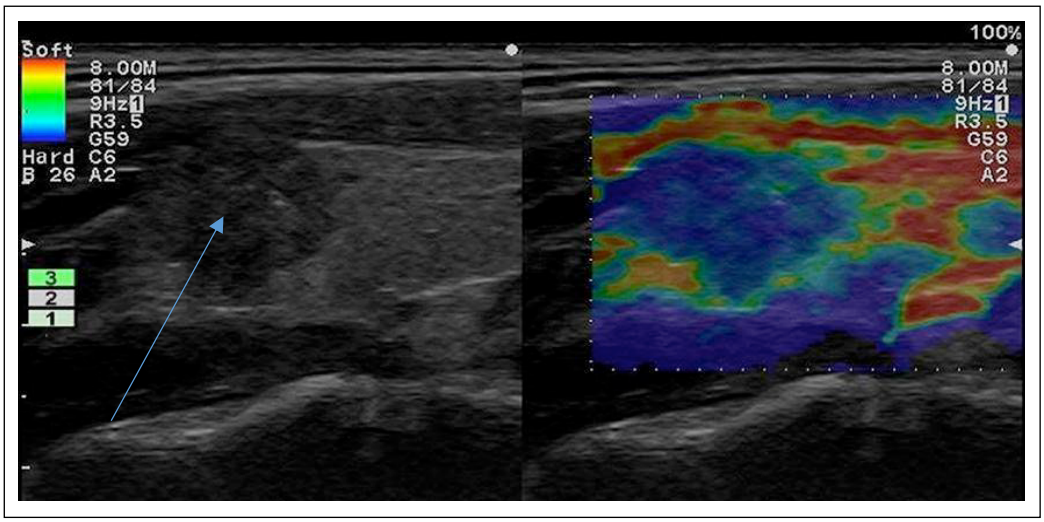

Fig. 2. Nodular goiter. Ultrasound of the neck, gray scale mode: longitudinal scanning and sonoelastography. Hypoechoic nodule with indistinct edges and microcalcifications. On the sonoelastography there is intensive blue staining, stiffness coefficient 5 kPa (blue arrow)
Picture taken by the authors

performance with determination of stiffness coefficient and shear wave speed. Determination of benignity of thyroid gland changes was established based on staining of nodules in relation to the surrounding gland tissue, by measuring stiffness coefficient and speed of shear wave.

The identified changes allowed classifying 3 types of elastograms. Under first type of elastogram the formation is colored red and yellow, as well as the parenchyma of the thyroid gland. When measured, the density of the studied formation did not exceed 1.0 kPa, speed of shear wave did not exceed 2.0±0.4 m/s. This data proves benign changes in thyroid gland. Under second type of elastogram the formation had a mosaic structure with a predominance of green or blue areas with stiffness coefficient 1-4 kPa, speed of shear wave made from 2.5 to 4.5 m/s. This indicates dubious result and requires further examination. Under third type of elastogram the formation has mosaic structure with intense blue areas, with stiffness coefficient over 4 kPa, speed of shear wave exceeded 4.5 m/s. It indicates high probability of malignant changes in thyroid gland tissue.

Types of elastogram are shown on fig. 1, fig. 2, fig. 3, fig. 4.

During the study, it has been established: in 26 patients (43.3%) – 1 type of elastograms, in 28 patients (46.7%) – 2 type of elastograms; in 6 patients – 3 type of elastograms (10%). Among patients with 1 type of elastograms, characteristic of benign changes in the tissue of the thyroid gland, 10 – were patients of old and senile age (over 65 years).

When assessing thyroid gland condition it has been found: 2 degree of increase, absence of compression syndrome, multiple nodes up to 2.0 cm, during elastography red and yellow staining of nodes, stiffness coefficient 0.5 – 1.2 kPa, speed of shear wave 1 5 -2.1 m/s, corresponds to benign nodes. These patients were refused operative treatment, were directed to dynamic supervision under the conditions of the polyclinic. At the follow-up examination after 6 and 12 months growth of nodes according to ultrasound data was not observed, characteristics of elastograms did not change.

16 patients with 1 type of elastograms, all the patients with 2 and 3 types of elastograms were directed to

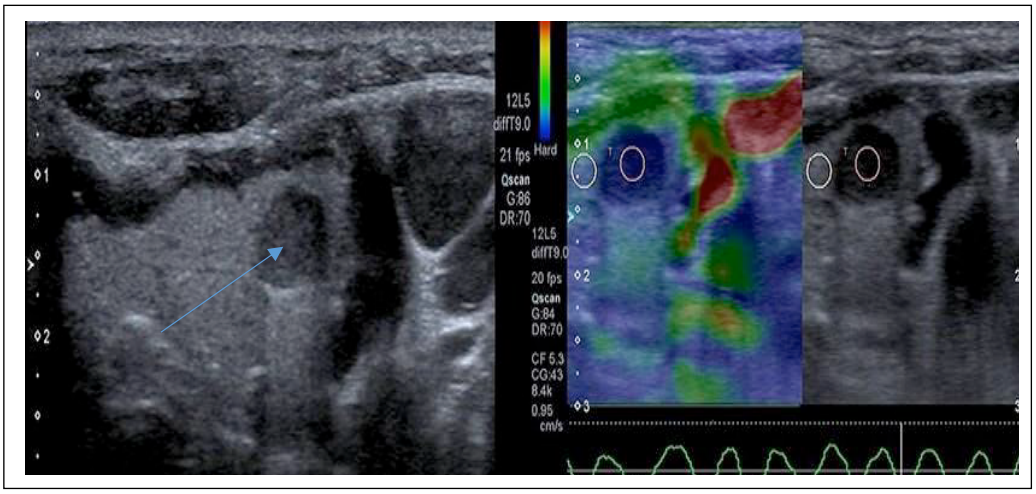

Fig. 3. Ultrasound of the neck, gray scale mode: transverse scanning and sonoelastography. Isoechogenic node (blue arrow). On the sonoelastography speed of shear wave is 1.9 m/s
Picture taken by the authors

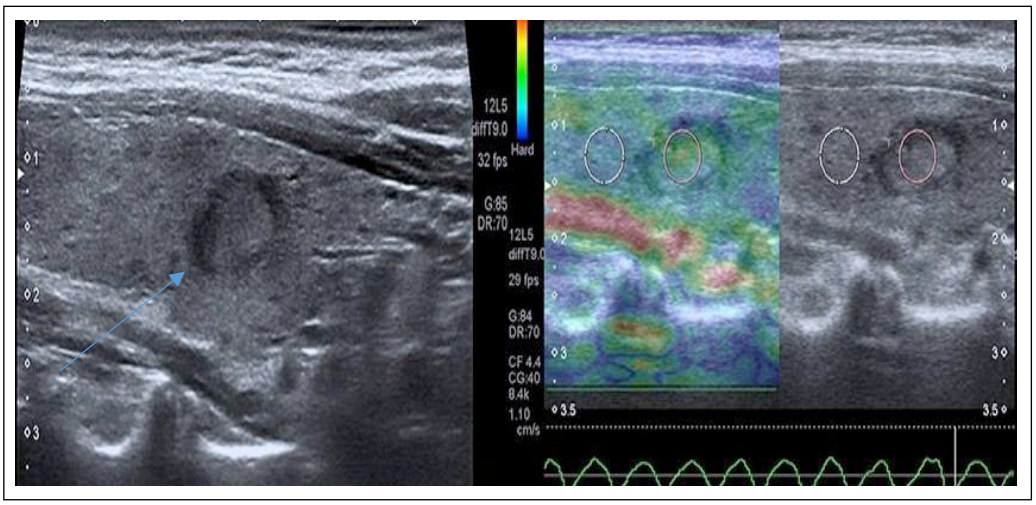

Fig. 4. Ultrasound of the neck, gray scale mode: transverse scanning and sonoelastography. Hypoechoic node (blue arrow). On the sonoelastography there is intensive blue staining, speed of shear wave is 4.8 m/s
Picture taken by the authors

surgical treatment. The indications for surgery in these patients were increased thyroid gland of more than 50 cm^3, presence of nodes of more than 5 cm in diameter, presence of compression syndrome (squeezing of neck vessels, hoarseness of voice).

CYTOLOGICAL CHARACTERISTICS OF THYROID GLAND DISEASES AND EVALUATION OF ELASTOGRAPHY RESULTS COMPARED TO FNA OF THYROID NODULES

Cytological study was conducted taking into account material received with fine needle aspiration biopsy (FNA). Changes in the form of a colloid-proliferating goiter were detected in 45 patients (41%), colloid-cystic – in 32 (29%), colloidal goiter without signs of proliferation – in 21 (19%), B-cell transformation was less common – in 12 (11%). The result is represented in table 1.

We have conducted a comparative analysis of results of elastography and FNA of thyroid nodules. The result is represented in table 2.

The obtained results testify the predominance of benign changes in the tissue of the thyroid gland in patients with 1 type of elastograms, they comprise colloidal goiter without signs of proliferation (11 patients) and colloid-cystic goiter (11 patients). Proliferating forms of goiter predominate in patients with type II of elastograms (19 patients), under III type of elastograms the majority are patients with B-cell adenoma of the thyroid gland.

Thus conducting elastography in complex ultrasound examination of thyroid gland allows not only identifying nodules but also to evaluate their qualitative characteristics based on the color of staining nodular formations, calculating stiffness coefficient and speed of shear wave. Establishing of the I type of elastogram allows predicting benign changes in the thyroid gland tissue, in the absence of reliable indicators for surgical treatment conducting dynamic monitoring of the patient. Establishing of the II type of elastograms provides additional methods of examinations in the form of repeated FNA. Establishing of the III type of elastograms involves risk of malignancy of nodular formations of the thyroid gland and is subject to surgical treatment.

Moreover identification of such characteristics of nodular formations of thyroid gland detected during

Table 1. FNA results in the studied groups

	Main group (60)		Comparison group (50)	
	abs	%	abs	%
Colloid-proliferating goiter	24	40	21	42
Colloid-cystic goiter	18	30	14	28
Colloidal goiter without signs of proliferation	13	22	8	16
B – cellular adenoma	5	8	7	14

Source: compiled by the authors of this study

Table 2. Elastography and FNA results

FNA	Type of elastogram		
	1	2	3
Colloid-proliferating goiter	4	19	1
Colloid-cystic goiter	11	6	1
Colloidal goiter without signs of proliferation	11	2	-
B – cellular adenoma	-	1	4

Source: compiled by the authors of this study

Table 3. Nature of morphological changes

Morphological changes	Main group		Comparison group		Total	
	abs	%	abs	%	abs	%
Nodular colloidal goiter without signs of proliferation	15	30	24	48	39	39
Nodular colloidal goiter with proliferation	12	24	6	12	18	18
Cystic nodular goiter	11	22	11	22	22	22
Follicular adenoma	3	6	5	10	8	8
B – cellular adenoma	4	8	3	6	7	7
Embryonic - fetal adenoma	1	2	1	2	2	2

Source: compiled by the authors of this study

Table 4. Distribution by markers of proliferation activity

N - 30	Ki 67			p 53			Thyroglobulin		
	Up to 49%	50-70%	More than 71%	Up to 49%	50-70%	More than 71%	Up to 49%	50 – 70%	More than 70%
abs.	18	8	4	17	11	2	20	7	3
%	60	27	13	57	37	6	67	23	10

Source: compiled by the authors of this study

Table 5. Correlation of elastography indicators depending on proliferation markers

Indicator	stiffness coefficient		speed of shear wave	
	Correlation	Value	Correlation	Value
Ki 67	0.456**	0.03	0.399*	0.11
P 53	0.547**	0.00	0.553**	0.00
thyroglobulin	0.641**	0.00	0.620**	0.00

** correlation is significant only at 0.01.

* correlation is significant only at 0.05

Source: compiled by the authors of this study

elastography as intense blue staining, stiffness coefficient more than 4.0 kPa, speed of shear wave more than 4.5 m/s, allows identifying the most dubious nodes for FNA conducting, provides high accuracy when conducting cytological examination, decrease number of unfounded puncture biopsies.

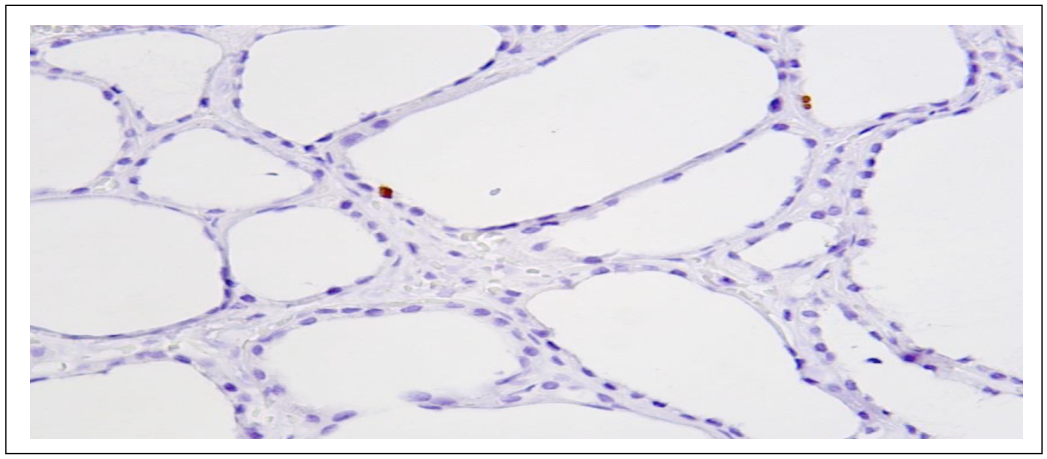

Fig. 5. Expression of Ki67 in macrofollicular goiter. Low proliferation index of follicular epithelium – up to 1% positive cells, Hematoxylin staining, magnification 50
Picture taken by the authors

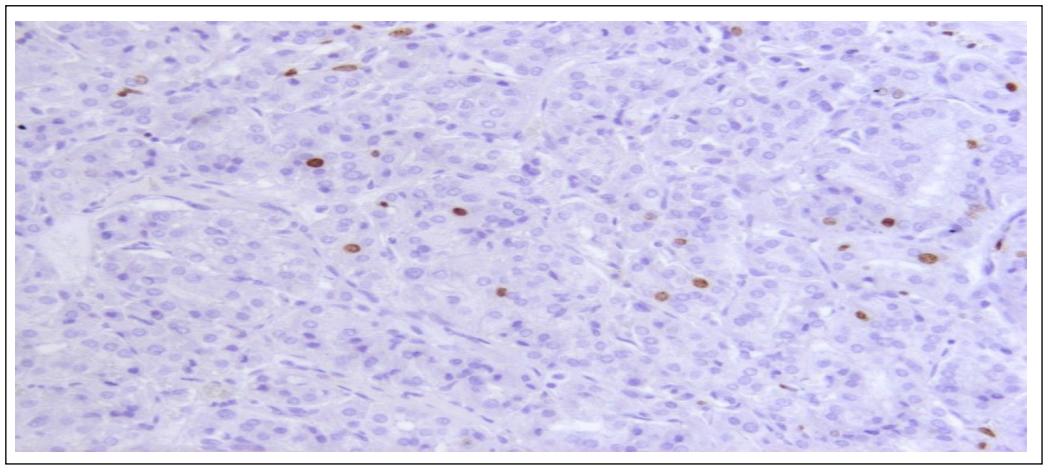

Fig. 6. Expression of Ki67 in microfollicular nodular goiter. Highest proliferation index of follicular epithelium – up to 5% positive cells, Hematoxylin staining, magnification 50
Picture taken by the authors

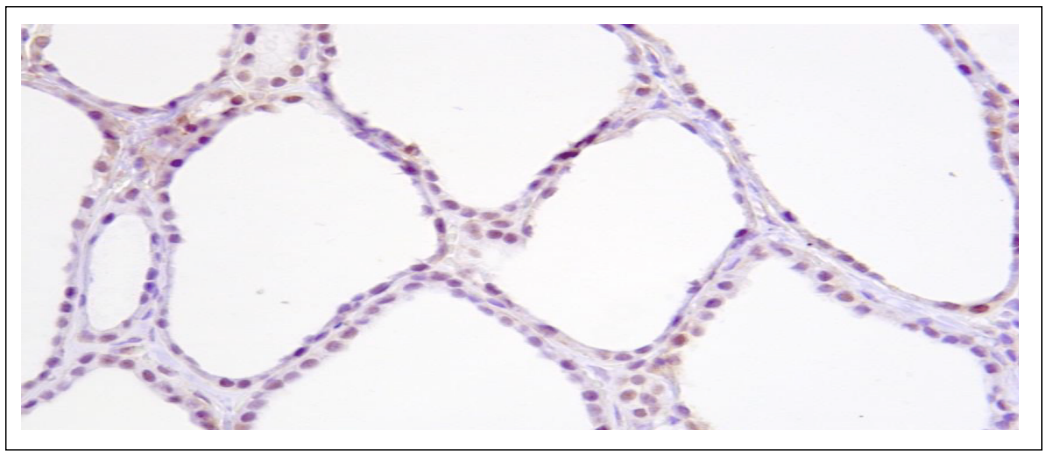

Fig. 7. Expression of p53 protein in normal thyroid gland tissue. Weak yellow-brown staining of nuclei on blue-violet background, p53 gene expression, Hematoxylin staining, magnification 100
Picture taken by the authors

IMMUNOHISTOCHEMICAL ANALYSIS IN NODULAR DISEASES OF THE THYROID GLAND

Histological studies were carried out taking into account the operating material of thyroid gland tissue. The most common is nodular colloidal goiter without signs of proliferation – in 39 patients; colloid-proliferating goiter - in 18; cystic nodular goiter - in 22; follicular adenoma – in 8; B – cellular adenoma – in 7; embryonic - fetal adenoma - in 2; follicular carcinoma – in 1; papillary carcinoma - in 3.

Distribution of histological changes in groups is represented in table 3.

In the main group nodular colloidal goiter without signs of proliferation was identified in 30%, in the comparison group in 48% of cases; colloidal proliferative goiter in the main group was identified in 24%, and in the comparison group in 12% of cases, cystic nodular goiter occurs in the main group - in 22% of cases, in the comparison group - in 22%. The most frequent is nodular colloidal goiter without signs of proliferation in 39% of cases, in equal quantities cystic nodular goiter can be seen – in 22 cases.

We have conducted research on the basis of immunohistochemical analysis of removed thyroid gland

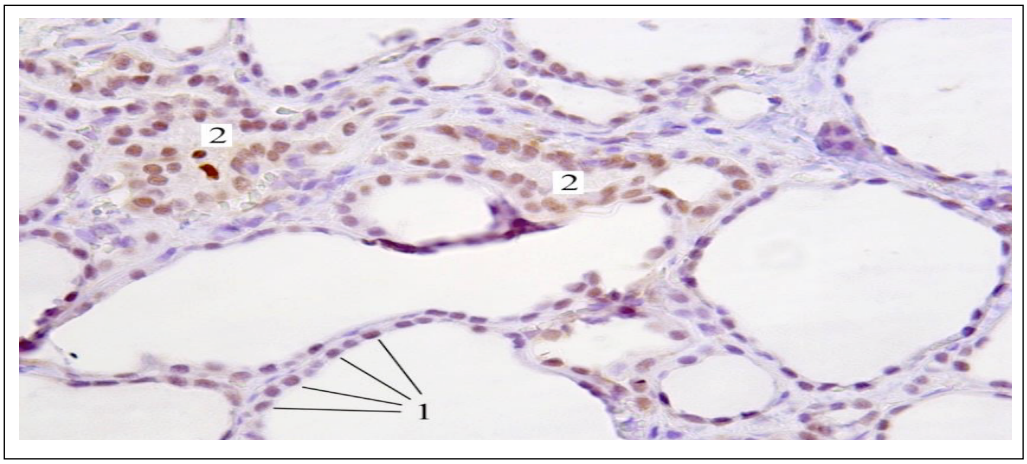

Fig. 8. p53 protein expression in micro-macrofollicular goiter. Weak yellow-brown staining of nuclei. 1, 2 arrows - p53 gene expression in large follicles. Magnification 100
Picture taken by the authors

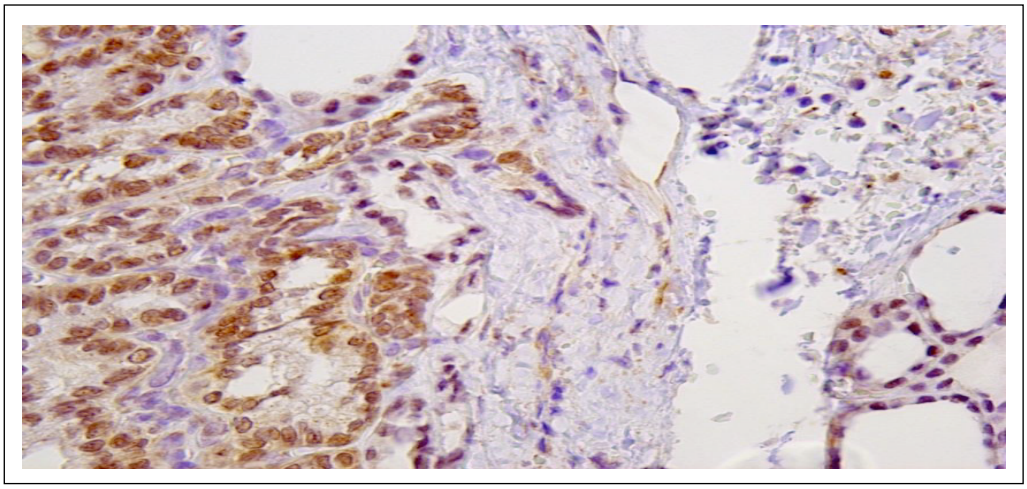

Fig. 9. Hyperexpression of the p53 mutant gene in the area of microfollicular epithelial proliferation with signs of severe dysplasia. Hematoxylin staining, magnification 100
Picture taken by the authors

tissue. We have studied proliferative activity of thyroid gland tissue based on determination of expression of Ki67 proteins (clone MIB-1), p53 (clone DO-7), thyroid transcription factor TTF-1 (clone 8G7G3/1), thyroglobulin (clone DAK-Tg6).

The analysis comprised 30 immunohistochemical studies of removed thyroid gland tissue preparations of patients. Marker of proliferative activity Ki67 is determined by brown staining of nuclei, and then the percentage of positive cells in the population was calculated. The results of immunohistochemical studies are presented in Fig. 5, Fig. 6, Fig. 7, Fig. 8, Fig. 9, Fig. 10, Fig. 11.

Thyroid transcription factor TTF-1 is determined by brown staining of cell nuclei. In all cases of goiter intensive expression of TTF-1 in follicular epithelium is observed.

On the basis of the obtained results 3 degrees of proliferation of nodular formations were revealed: I degree of thyroid gland tissue proliferation: Ki-67 proliferation index makes up to 49%; P53 protein expression made up to 49%; proliferation of follicular and parafollicular epithelium takes up to 49% of follicles.

II degree of proliferation is characterized by: Ki-67 proliferation index makes 50-70%; P53 protein expression makes 50-70%; proliferation of follicular and parafollicular epithelium takes 50 % of follicles;

III degree of thyroid gland tissue proliferation is characterized by: proliferation of follicular and parafollicular epithelium takes more than 70 % of follicles; Ki-67 proliferation index makes more than 70%; P53 protein expression – more than 705-80 %;

The obtained results are represented in table 4.

After conducted immunohistochemical analysis 3 groups of patients were identified according to the degree of proliferative activity of thyroid tissue. Presence of the 1 degree of proliferation was detected in 18 patients (60% cases), this degree is not a risk of disease recurrence and possible malignancy, accordingly, the performance of organ-preserving operations is justified. Second degree of proliferative activity was detected in 9 patients (30% cases), this state is border one, in this case there is high risk of disease recurrence. Under such proliferation it is advisable to perform radical operations. Presence of 3 degree of proliferation was detected in 3 patients (10% cases). Patients with third degree of proliferation have the highest risk of malignancy, therefore, it is more appropriate to perform surgical interventions according to oncological principles.

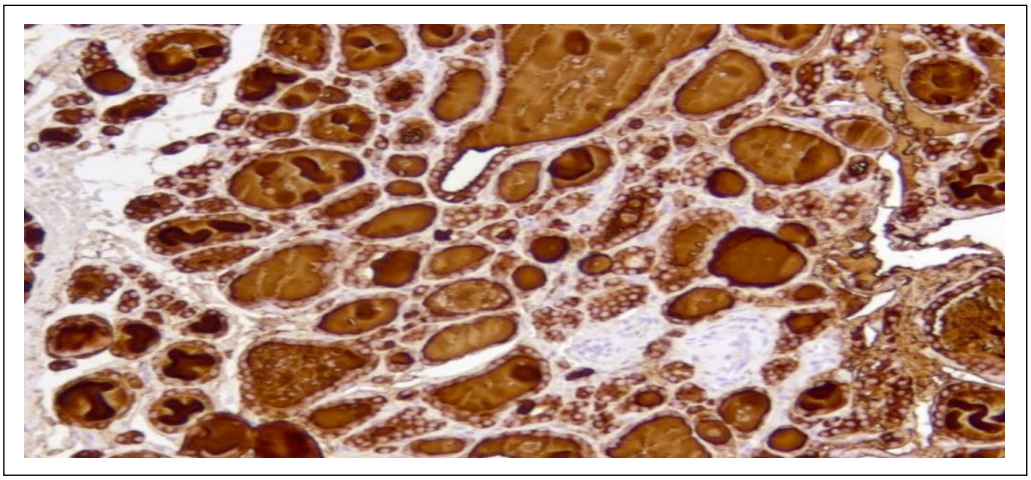

Fig. 10. Thyroglobulin in micromacrofollicular goiter. Intense reaction in the colloid of the follicles and in the cytoplasm of the follicular epithelium. Hematoxylin staining, magnification 100
Picture taken by the authors

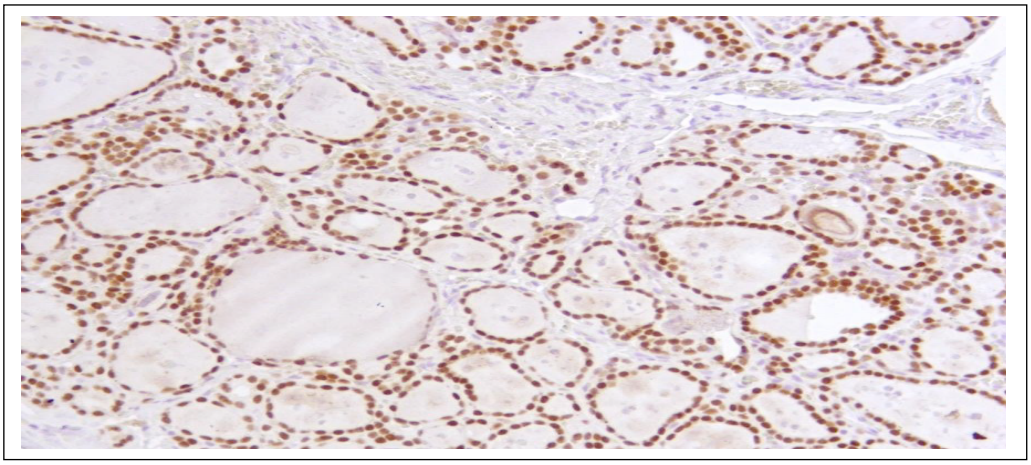

Fig. 11. Micromacrofollicular goiter. Intensive expression of thyroid transcription factor in in the nuclei of all cells of the follicular epithelium. Hematoxylin staining, magnification 100
Picture taken by the authors

We have calculated correlation coefficient of such characteristics of elastography indicators depending on proliferation markers as tissue stiffness coefficient and speed of shear wave depending on the degree of proliferation markers Ki 67, P 53, thyroglobulin. The obtained data is represented in table 5.

According to correlation coefficient relationship between stiffness coefficient, speed of shear wave and proliferation markers in all the cases is moderate and significant, apart from dependence of Ki 67 marker and speed of shear wave.

DISCUSSION

The vast majority of works in emergency thyroid surgery are devoted to the description of compression syndrome in patients with malignant tumors. Undifferentiated (anaplastic) thyroid cancer is the most aggressive human carcinoma, doubling in size 2 times in 117 hours. In the structure of malignant tumors of thyroid origin, it is on average 7-12% [8-10].

In a short period of time (1-3 months), the thyroid capsule sprouts and infiltrates the surrounding tissues and organs, causing compression and deviation of the larynx, trachea, esophagus, vascular-nerve bundle of the neck, and recurrent laryngeal nerves [11].

In most cases, the clinical picture and complaints of patients with undifferentiated thyroid cancer are caused by manifestations of the local spread of carcinoma, its invasion into surrounding structures and mechanical pressure on organs and tissues, which leads to the occurrence of a compression syndrome, the severity of which depends on the size of the tumor and the degree of cervicothoracic spread. The authors emphasize that 45% of their patients with undifferentiated thyroid cancer came to the clinic as an emergency due to deterioration of the condition caused by obstruction by carcinoma of the upper respiratory tract (trachea). Moreover, 5 out of 27 patients needed emergency tracheal intubation to facilitate breathing [12, 13].

According to the data of a number of authors, the progression of compression of the neck and mediastinum in the case of undifferentiated thyroid cancer led to the fact that 36 (36.4%) of 99 patients were operated on urgent indications in conditions of severe respiratory failure. In 21 (21.2%) patients, it was possible to carry out conservative measures, which included the correction of disturbed functions of breathing, blood circulation, digestion, nor-

malization of the acid-base state, and the operation was performed urgently 2-3 days after admission after relative stabilization of vital important functions [14, 15].

Locally spread differentiated carcinomas of the thyroid gland, sprouting into surrounding tissues and organs, such as the trachea, esophagus, recurrent laryngeal nerve, can lead to emergency conditions [16].

The reasons for the appearance of thyroid tumors at the border of the organ can be different. It is possible to formulate the following reasons for the local prevalence of thyroid tumors: late referral of patients; observation, diagnosis and treatment errors; peculiarities of the "biological behavior" of the tumor [16].

In some cases, the course of the tumor becomes aggressive after inadequate primary surgical interventions, which may be related to the phenomenon of non-differentiation of tumors [17].

Respiratory failure caused by compression of the trachea by benign thyroid diseases is usually caused by a giant goiter of the cervical or cervicosternal localization. Compression of the trachea caused by a giant benign goiter is rare. Nevertheless, the cervical-thoracic location of the thyroid gland can lead to progressive respiratory failure up to respiratory arrest [18].

Benign thyroid diseases of cervicosternal localization, chronic obstructive diseases of the respiratory tract, and a long history of thyroid disease are considered risk factors for acute respiratory failure, and therefore, life-threatening conditions [18].

The proliferative activity of a neoplasm is one of the most important characteristics of its phenotype, which determines the growth rate of the neoplasm, its ability to metastasize, and the effectiveness of therapeutic measures. The proliferative activity index as a quantitative criterion is quite actively used in assessing the aggression of the malignant process. Many studies demonstrate a high level of expression in malignant pathology of the thyroid gland, in particular in papillary thyroid cancer, as well as as a prognostically unfavorable factor in the differential diagnosis of follicular adenomas and follicular thyroid cancer [19].

The pronounced expression of Ki-67 in follicular thyroid cancer, according to the results of our studies, is consistent with the generally accepted hypothesis. The closeness of the proliferation marker Ki-67, follicular adenomas and follicular thyroid cancer of fetal-embryonic structure in terms of indicators is noteworthy, which probably indicates the highest potential of the latter for malignancy and subsequent metastasis. The low level of Ki-67 expression indicates the relative efficiency of cell cycle regulation, which is characteristic of unchanged thyroid tissue, which, according to our data, normofolliary adenomas demonstrate. According to numerous studies, increased expression of p53 has been found in many cancer cell lines. In normal tissues, the level of p53 remains low, but in response to DNA damage, p53 is activated with a large accumulation of its level. However, there is evidence that does not support differences in p53 expression in patients with follicular adenoma and follicular carcinoma, or conversely, shows a decrease in expression in differentiated forms of thyroid cancer [19, 20]. Mutations of this gene in patients with benign and autoimmune thyroid diseases are also poorly studied [20].

CONCLUSIONS

The conducted immunohistochemical studies have proved presence of three degrees of proliferative activity of thyroid gland; correlation dependence has been identified between characteristics of elastography and proliferative activity markers. Upon determination of elastogram type and degree of proliferative activity of thyroid gland depends further tactics of patient's management: referral for dynamic observation or surgical treatment with the selection of the scope of surgical intervention, including minimally invasive one.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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