Review Article

Stages of benign thyroid nodules: principles and ultrasound signs

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Abstract: Benign thyroid nodules are significantly common and occur in 50–60% of the population. Therefore, differentiation from malignant nodes and the choice of treatment tactics in some cases of benign pathology remain relevant. Despite advances in the clinical evaluation of thyroid nodules, methodological challenges exist due to empirically simplistic understandings of the nodular process. Different opinions on the pathogenesis of thyroid nodules and the history of the formation of the idea of the stages of nodules are considered. For the first time, based on natural principles and many years of ultrasound analysis of changes in benign thyroid nodules, three stages of the nodular process were identified: Development, Wasting and Scarring. The stage of exhaustion has three substages: Initial, Moderate and Significant Wasting. The principles of stage-by-stage changes in nodules are explained and their ultrasound signs are shown. The key principle of the stages of nodules is the ratio of the magnitudes of the processes of regeneration (proliferation) and destruction in the nodule. Separate stage changes may occur in node segments. In such cases, part of the segments may show signs of the Development stage, another part—Wasting, and the third part—Scarring. The different variants of thyroid nodules are explained in terms of stages. Practical recommendations for differentiating ultrasound signs of nodules associated with stages are proposed. Knowledge about the staged changes in thyroid nodules helps reduce the likelihood of diagnostic errors, better navigate the prognosis and choice of treatment tactics, and recommend preventive ultrasound examination of the thyroid.

Keywords: Thyroid nodules; thyroid ultrasound; nodules stage

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Introduction

Nodular pathology of the thyroid gland is widespread in society. According to various researchers, thyroid nodules are detected by ultrasound in 50–60% of people (1-3). This frequency, structural diversity of nodules, and the need for prognosis criteria for choosing rational tactics indicate the need to identify the natural principles of these pathological formations.

The thyroid nodule functions relatively independently (less interconnected with the state and activity of the extra-nodal gland tissue) (4,5). This is also why the nodule, as a separate section, develops and transforms in stages. These successive changes in the nodule occur in one direction and represent a natural principle that, unfortunately, remains unnoticed by sonologists. Stages of nodules were not reflected in ultrasound articles and guidelines (6,7).

This situation is likely due to the fact that radiologists usually observe nodes once in each patient and rarely monitor changes in nodules over many years. Over such a long period, complete information about previously identified nodules and the processes occurring in them is not always preserved. In addition, sometimes, the nodule is removed along with the gland or part of it, which also interrupts the observation. Additional reasons for inattention to the stages of benign nodules can be considered the increased interest in signs of malignancy,

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despite the prevalence of cancer in nodes only up to 5%, and the predominance of statistical criteria in ultrasound diagnostics.

The purpose of this article is to reveal the principles and clinical significance of the stages of thyroid nodules, with a description and demonstration of their sonographic features.

Research methodology

Analysis of clinical practice data and literature search were used to identify the stages of thyroid nodules. All cases of benign nodules over the past 16 years in a specialized thyroid clinic were included (1,988 patients). The study of the condition and changes in nodules was mainly carried out using ultrasound. Ultrasound examination (in gray scale and Doppler mode) was carried out by one specialist (the author) together with an assessment of the medical history, blood test data, and, when indicated, also cytological examination data, scintigraphy and computed tomography.

A literature search was conducted in PubMed. Modern manuals on thyroid ultrasound and books from library collections were used. The publications analyzed the pathogenesis and morphogenesis (cytologically and histologically) of thyroid nodules, ultrasound and radioisotope manifestations of structural and functional processes in the nodules.

Ideas about the essence and pathogenesis of thyroid nodules

Changes in thyroid nodules are associated with the characteristics of their pathogenesis. But despite the significant achievements of researchers, a unified harmonious knowledge of the mechanism of development of nodules, apparently, has not been achieved. What is known?

Thyroid nodules are common benign tumors with clonal or polyclonal development (8). At the same time, studies of the histostructure by Ramelli *et al.* showed that nodular tissue consists of follicles that are morphologically and functionally identical to extranodular parenchyma (9). According to their information, the majority of thyroid nodules are formed from actively replicating areas of ordinary follicular epithelium, which have both further development and subsequent destruction with the formation of hemorrhagic areas and their scarring. According to their hypothesis, this histological dynamic is associated with the inability of the capillary network to sprout along with the active growth of groups of follicles.

Despite the similarity of processes in nodal and extranodal tissue, nodular enlargement occurs independently of the rest of the thyroid tissue, indicating locally controlled nodular development (4,5). As follows from the observations of Brigante *et al.*, nodules form in healthy thyroid tissue, and the key conditions in this are female gender and the need to activate the production of thyroid hormones, especially free triiodothyronine (5). Complementing the understanding of the nodular process is the reappearance of nodules after lobectomy. It may be associated with the persistence of conditions predisposing to nodule formation in the body, increased thyroid proliferation after surgery (10,11), in patients relatively young age (in particular to 45 years) and with repeated pregnancies (12-14).

An increase in the size of nodules during pregnancy and the appearance of new thyroid nodules, regardless of iodine supply, is indicated by the results of a study by Kung *et al.* (15). As you know, pregnancy increases energy metabolism and, accordingly, the activity of the thyroid gland. Therefore, a more active process in the nodule compared to the rest of the tissue may be associated with an increase in the rate of formation of calorigenic hormones (16).

The appearance of new nodules during pregnancy can also be assessed as the activation of adaptive changes in order to create intrathyroidal sources of enhanced hormone production. A similar conclusion must be made in the case of a decrease in the total volume of thyroid tissue as a result of surgery. Increased compensatory tension of the remaining lobe after lobectomy creates the condition for more intense activity. Including locally, forming nodules in certain areas of the thyroid parenchyma.

Based on the main function of the thyroid gland, which is associated with ensuring energy metabolism, it can be assumed that there is more active nodulation in the thyroid gland in various diseases, due to increased energy consumption and consumption of calorigenic thyroid hormones. Therefore, more active formation of nodules or an increase in the total volume of the gland is determined not only during pregnancy (15), but also with diabetes mellitus (17,18), metabolic syndrome (19,20), inflammatory process (21), colon polyps (22) and other diseases, regardless of the sufficiency of iodine in the body (23).

The formation of nodules in the thyroid gland is associated with genetic influence and the action of metabolites (8,24-26). Stimulation of local proliferation of thyrocytes is associated with the influence of thyroid stimulating hormone (TSH), activation of the cyclic

adenosine monophosphate (cAMP) pathway, mutation in the TSH receptor and the Gs-alpha gene (27,28), insulin resistance (17,18,29), the effect of estrogen (26) and mutation of the sodium-iodine symporter (30). However, according to Derrien *et al.* mutation of the TSH receptor gene has not been confirmed (31), and, mutations of the TSH receptor and Gs-alpha gene are very rare in iodine-sufficient areas, suggesting other mechanisms of nodular tissue proliferation independent of the TSH receptor, Gs-alpha gene, and cAMP mechanisms (32). Moreover, the sources of tumor proliferation in the thyroid gland are associated with increased expression of various growth factors, their corresponding receptors and signaling proteins (32).

In addition to the genetic and metabolic hypotheses, there is an idea of nerve conduction involvement in the formation of thyroid nodules (33,34). It is based on: (I) direct nerve-conducting contact with each lobule and follicle of the thyroid gland (33,35,36); (II) research-confirmed almost separate neural supply to each lobule and groups of lobules (medium and large segments) (34-37); (III) Wahlerian degeneration of groups of neurons in the sympathetic ganglia due to the destruction of individual lobules or segments of the thyroid gland (37,38); (IV) structural changes in groups of sympathetic ganglion neurons in nodular goiter (34) and other evidence of the participation of the peripheral autonomic nervous system in the development and transformation of nodules.

For example, the approach of several main vessels to the nodule, often encountered during ultrasound, sprouting and forming a peripheral and internal network in it, as well as the spread along with the vessels of many nerve fibers ending on the follicles, shows the obligatory peripheral nervous participation in the activity of the nodular tissue, as well as the validity local neuro-metabolic control not only of the entire nodule, but also of each of its segments.

In particular, there is a simplified view about the nature of thyroid nodules. For example: a nodule is defined as "a discrete lesion" (39).

History of the development of knowledge about the stages of thyroid nodules

The existence of stages of thyroid nodules, occurring with destruction and fibrosis, was first reported in 2002 by the morphologist O.K. Khmelnitsky, who observed during histological studies typical signs of changes in the nodules, including those located in one lobe (40). In 2008, fundamental explanations and a diagram of ultrasound changes in nodules by stage were proposed, in 2013 these stages were given names with comments (41), and in 2018—a theoretical explanation, ultrasound description and illustrations (42). From 2008 to the present time, knowledge about the stages of nodules has been confirmed and tested practically.

Since some signs of stage changes in the nodules attracted the attention of specialists, the last stage of the nodules was presented in 2016 by Lacout *et al.* as a phenomenon of mummification (43). Despite the correct description of some signs of a staged process in the form of the possibility of mummification of nodules and cystic transformation, these authors pointed out the spontaneity of such changes. According to Lacout *et al.* scarring and mummification in the nodules are caused by thyrocyte hypoxia and bleeding (43). At the same time, as far as we know, these and other specialists have not identified or described changes in thyroid nodules from the standpoint of a common stage principle for them, with characteristic ultrasound manifestations for each stage.

Principal and structural features of the three stages of thyroid nodules

The condition of benign thyroid nodules changes in accordance with natural principles. One of them is stage-by-stage transformation of nodules. Ultrasound analysis allows us to distinguish three main stages of nodules based on the principles of their changes (*Table 1*, *Figure 1*).

The Development stage is the first stage of the nodular process. New tissue arises from stem cells inside the small (lobule) or middle segment of the gland due to regeneration (proliferation) and continues to form for a certain period. Simultaneously with the formation of follicles and their union into lobules, vessels and nerves penetrate into this new tissue, creating a segmental connective tissue system (44). All of these events correspond to the development of new tissue and enlargement of the nodule.

The Development stage usually lasts several years. During this stage, regenerative processes (proliferative) in the nodule significantly predominate over destructive ones (*Figure 1A*). Therefore, the volume of the node increases. But this increase depends on the intensity of metabolic and neural influences. One might think that the magnitude of such stimulation does not characterize the stages of the nodules but may influence their duration.

The Wasting stage is the second stage of the nodal process. It is based on an increase in destructive processes

Table 1 Principles of the staged process of thyroid nodules

No.	Principles of stages of thyroid nodules
1	Stage-by-stage changes in benign thyroid nodules are a natural and obligatory process
2	The key criterion for the stages of nodules is the ratio of the magnitudes of the processes of regeneration (proliferation) and destruction in the nodule
3	Stage transformations at nodules proceed only in one direction
4	Separate stage changes may occur in nodule segments. In such cases, part of the segments may show signs of the Development stage, another part—Wasting, and the third part—Scarring

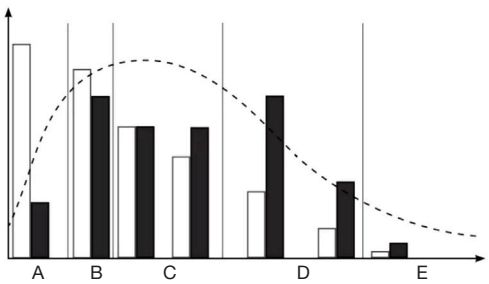

Figure 1 Schematic diagram of the relationship between the severity of regeneration (proliferation) and destruction during the stages of the thyroid nodular process. The abscissa axis corresponds to time (years). The ordinate axis corresponds to the volume of the nodule and the severity of the relationship between regenerative (proliferative) and destructive changes. White columns correspond to regeneration (proliferation) of the node tissue. Black columns show the amount of node tissue destruction. The dotted line demonstrates the principle of change in the volume of the nodule during stages and substages. (A) Development stage. (B) Initial Wasting substage. (C) Moderate Wasting substage. (D) Significant Wasting substage. (E) Scarring stage.

and a decrease in reparative processes (*Figure 1B-1D*). Depending on the ratio of destructive and reparative processes in the nodule, it is appropriate to distinguish three substages: Initial Wasting, Moderate Wasting and Significant Wasting. Each substage can last for years.

During the Initial Wasting substage, reparative processes in the nodule predominate over destructive ones (*Figure 1B*). Therefore, the volume of the nodule may increase slightly. In this substage, comparable to the Development stage, the growth of the nodule slows down. The tissue of the nodule usually contains a small number of lymphoid lobules and stromal swelling.

During the Moderate Wasting substage, the rates of regeneration and cell death in the nodule are equalized (*Figure 1C*). The volume of tissue in the nodule remains almost unchanged or decreases very little. Characterized by a small or moderate number of lymphoid lobules, stromal swelling, and a small number of cystic areas.

The Significant Wasting substage is characterized by a gradual increase in nodule destruction and a decrease in regeneration (*Figure 1D*). Accordingly, the volume of the nodule or the amount of tissue in it decreases. The following may be present to a moderate or significant extent: stromal swelling, cystic areas, stromal fibrosis (thickening of connective tissue septa, etc.), lymphoid lobules. Calcifications are rare.

The Moderate Wasting substage corresponds to the predominance of tissue in the node. However, it contains a small number of hypoechoic lobules (and/or groups of such lobules) and isolated anechoic areas. There may be very small amounts of hyperechoic arcuate elements. Moderate hypoechogenicity of the tissue is often determined in the entire node or its parts. Less commonly, such nodes are slightly or significantly hypoechoic. However, isoechoic tissue may be present, including in medium to small segments. A slight hyperechogenicity can be detected dorsally from such nodes.

The Scarring stage is the third and final stage of the nodular process (*Figure 1E*). During this period, residual tissue, accumulations of lymphocytes, many connective tissue elements, including compaction of fibrous tissue, and often calcification are determined in the nodule. Such nodules are usually small. This stage strives for fibrosis and its utilization.

Ultrasound signs of thyroid nodule stages

The Developmental stage is usually noticeable by the isoechoic and almost homogeneous tissue of the nodule with a lobular structure. The isoechogenicity usually predominates in the nodule (*Figure 2A*,*2B*). However,

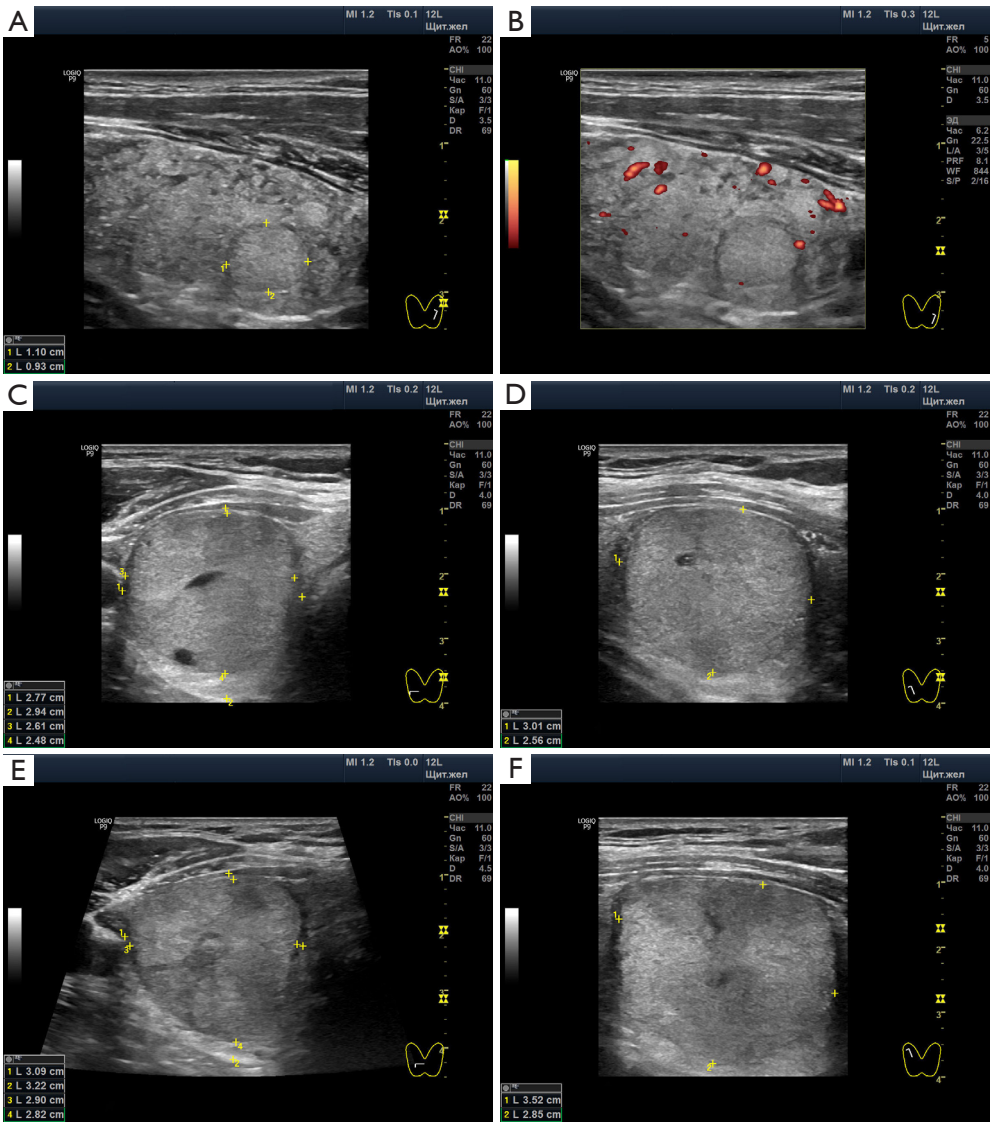

Figure 2 Thyroid nodules at the Development stage. (A,B) Predominantly isoechogenicity tissue in the nodule (indicated by measurement marks). Patient, 42 years old, hypothyroidism, autoimmune thyroiditis. (C-F) Transition from the Development stage to the Initial Wasting substage. The nodule is dominated by slightly hypoechoic tissue (a sign of stromal edema) with a small amount of isoechoicity. Patient, 46 years old, euthyroidism. (C,D) In February 2020, the dimensions of the nodule are 30.1×25.6×26.1 mm. (E,F) Almost 3 years later (December 2022) the size of the nodule is 35.2×28.5×29 mm.

some mild hypoechogenicity (a sign of stromal swelling) may occur (45). During this stage, follow-up ultrasound examinations after a sufficient period (usually after a year or more; less often after 3–6 months) show an increase in the volume of the nodule (*Figure 2C-2F*).

The Initial Wasting substage is determined by a small number of hypoechoic lobules. The nodule tissue is often slightly or moderately hypoechoic (*Figures 3*,*4*). There is usually little isoechoic tissue. Isolated small anechoic areas may be visible. The increase in nodule volume after one year is very small (*Figure 4*). For example, the largest size increases by 1–2 mm per year for nodules of medium or large size. There may be slight hyperechogenicity dorsal to the nodules.

The Moderate Wasting substage corresponds to the predominance of tissue in the nodule (*Figure 5*). However,

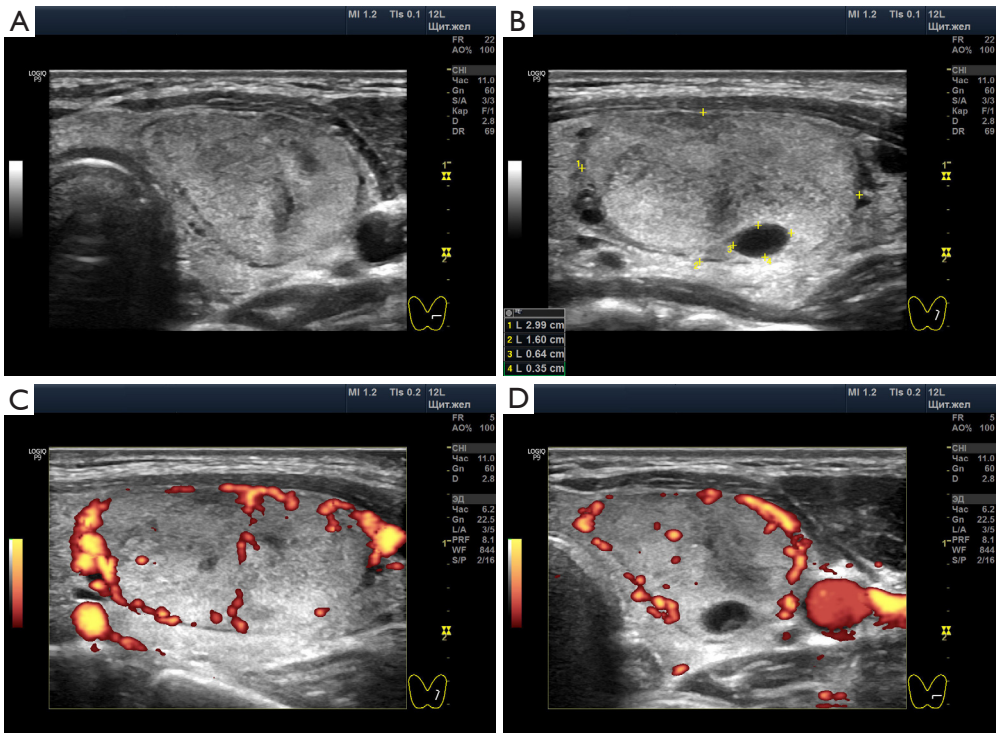

Figure 3 Thyroid nodule at the substage of Initial Wasting. The patient is 34 years old, euthyroidism. (A,B) The nodule contains isoechoic and slightly hypoechoic tissue, single hypoechoic lobules and an anechoic small area. Hyperechogenicity is determined dorsal to the nodule. (C,D) Moderate intensity of blood flow to the nodule (mainly along its perimeter).

it contains a small number of hypoechoic lobules (and/or groups of such lobules) and isolated anechoic areas (*Figure 6*). There may be very small amounts of hyperechoic arcuate elements. Moderate hypoechogenicity of the tissue is often determined in the entire nodule or its parts. Less commonly, such nodule are slightly or significantly hypoechoic. However, isoechoic tissue may be present, including in medium to small segments. A slight hyperechogenicity can be detected dorsally from such nodules.

The Significant Wasting substage is usually characterized by a predominance of hypoechoic lobules and anechoic areas (*Figure 7A-7D*), but not always. In total, anechogenicity can occupy more than 40%. The echogenicity of the residual tissue may vary. A combination of different echogenicity in the segments of the nodule is possible. Arc-shaped and/or pinpoint hyperechoic elements are present in small or moderate quantities (*Figure 7E,7F*). There may be relatively large hyperechoic elements (2–4 mm largest) extending hypoechogenicity dorsally. Hyperechogenicity of the tissue is often visible dorsal to the nodule.

The Scarring stage is often defined as an area of significant hypoechogenicity with many pinpoint hyperechoic elements (*Figure 8*). The latter can be of different sizes, located separately or in groups (*Figure 8A-8D*). Often a hypoechoic shadow extends dorsally from these hyperechoic elements. Occasionally, a hyperechoic nodule outline with a dorsally directed hypoechoic shadow may be visible (common in small nodules) (*Figure 8E,8F*).

Discussion

Stage changes are characteristic of living nature. Many events in the human body occur in stages or phases. The stages proceed in only one direction, and the phases are usually cyclical (46). Many organs have regular physiological regeneration, which, with reservations, can be classified as phase processes. For example, the thyroid in healthy people is gradually completely regeneratively renewed in almost 5.5–8 years (47,48).

Isolated structures within organs, like benign thyroid nodules, have a relatively independent life span. They are

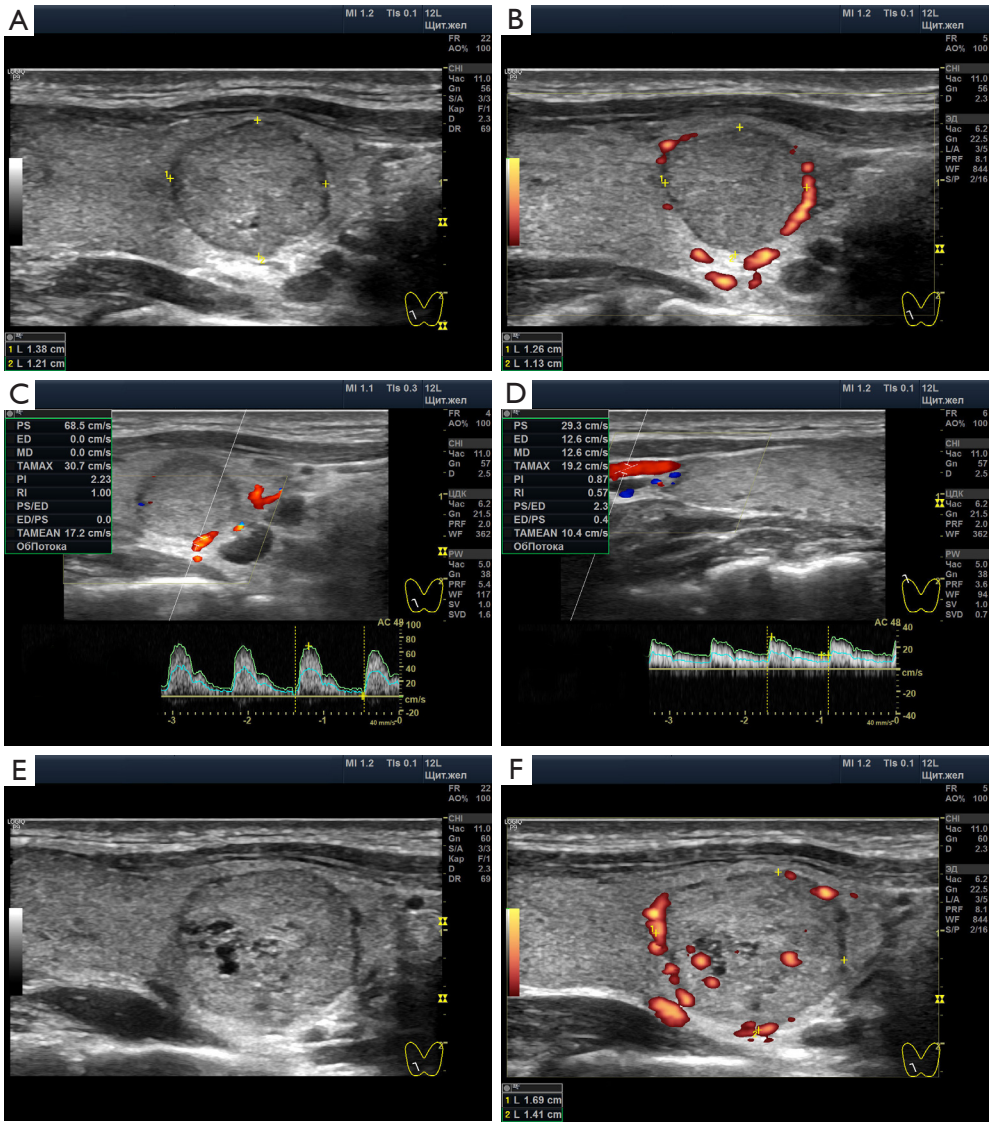

Figure 4 Thyroid nodule at the substage of Initial Wasting. The patient is 39 years old, euthyroidism. Little hypoechoic tissue is visible in the nodule. Single small anechoic areas are noticeable. Hyperechogenicity is determined dorsal to the nodule. (A,B) In January 2019, the size of the nodule in the longitudinal projection is 13.8×12.1 mm. In the power Doppler mode, low active blood flow of the nodule is determined. (C,D) In January 2019, the nodule artery had a peak systolic velocity of 68 cm/s, and the superior thyroid artery had a peak systolic velocity of 29.3 cm/s. (E,F) In October 2020, the size of the nodule in the longitudinal projection is 16.2×13.3 mm. The blood flow of the nodule is poorly expressed.

not an obligatory part of the organs. They arise during life under certain conditions and have a relatively autonomous regulatory system. In addition, benign thyroid nodules can be considered as a compensatory phenomenon in the form of areas with additional tissue for more active hormone production.

Of course, not all nodules are sufficiently hormone-forming. Some nodules produce little hormones, which can be seen with scintigraphy. However, this functional feature of the nodules does not allow one to deny the compensatory nature of the occurrence of nodules in the gland.

Consequently, the emergence of nodules, their relative autonomy and more active processes in the nodules represent the main conditions for changes that are unidirectional in

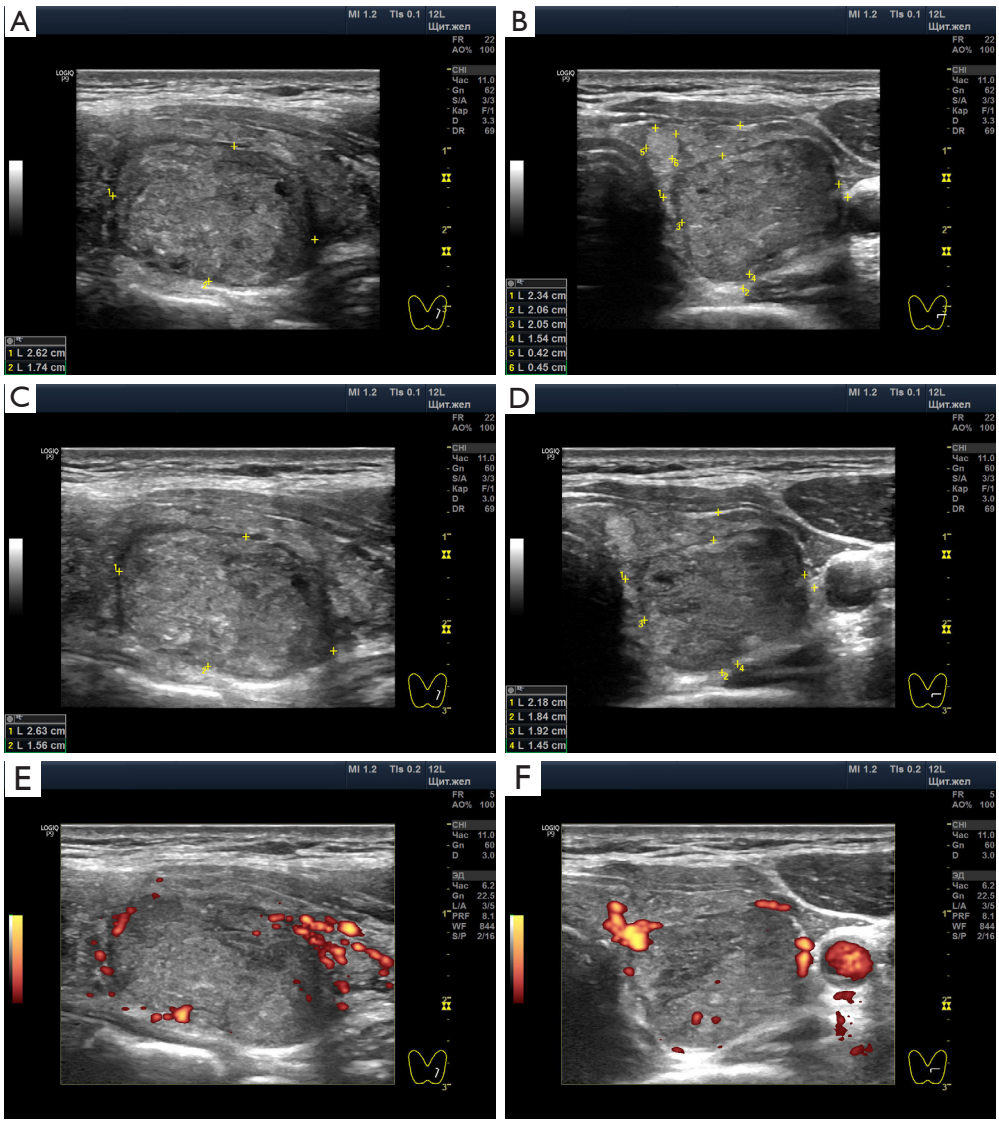

Figure 5 Thyroid nodule at the substage of Moderate Wasting. The patient is 51 years old, hypothyroidism, autoimmune thyroiditis. During control measurements after 3 years, the size and structure of the nodule changed very little. Fine needle biopsy was performed twice. In both cases, benign signs with phenomena of destruction and proliferation were identified; Bethesda 3. (A,B) December 2020. Longitudinal and transverse projections of the left lobe of the gland in gray scale. In a nodule 26.2×20.5×15.4 mm, moderately hypoechoic tissue is visible, among which there are isolated significantly hypoechoic and isoechoic lobules. (C,D) January 2024. Nodule 26.3×19.2×14.5 mm. Longitudinal and transverse projections of the left lobe of the gland in gray scale. Moderately hypoechoic tissue is visible, among which there are isolated significantly hypoechoic and isoechoic lobules. (E,F) January 2024. Power Doppler mode. The blood flow of the nodule is inactive, mainly along the perimeter.

time. That is, they are signs characteristic of a staged process. Fundamental stage changes in the nodules are visible during ultrasound examination. For example: (I) similarly changed nodules in different people, (II) certain changes in nodules over a sufficient period, (III) certain changes in nodules within one lobe.

The entire period of existence of a nodule in the thyroid is also rationally divided into three stages. The main criteria in this division are the predominance (including intensity) of regeneration or destruction. The first stage of nodule transformation corresponds to a significant dominance of regeneration. Usually with great intensity. Therefore, it

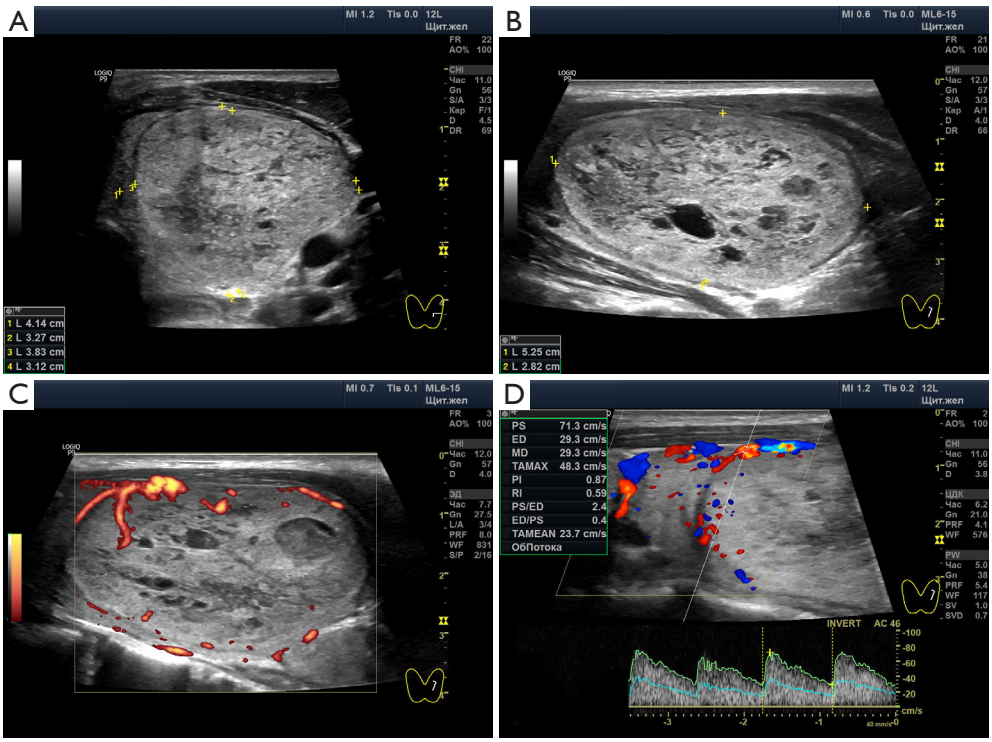

Figure 6 Thyroid nodule at the substage of Moderate Wasting. The patient is 47 years old, euthyroidism. (A,B) Isoechoic and slightly hypoechoic tissue of a large nodule is determined. It also contains a single small anechoic (fluid) area, an almost moderate number of small hypoechoic elements in the lobules, and single significantly hypoechoic medium-sized segments. (C) Power Doppler mode detects little active blood flow in the nodule. (D) The artery approaching the nodule has a peak systolic velocity of 71 cm/s.

was called the "Development stage". During this period, ultrasound shows almost perfect thyroid tissue in the nodule.

In the second stage of this process, there is a significant slowdown and a decrease in the superiority of regeneration over regressive events and the subsequent predominance of destruction, with its intensification. The term "Wasting stage" indicates the onset, intensification and progression of destructive processes. During ultrasound examination, signs of tissue destruction in the nodules become visible and increase. As can be seen, the duration of the stages and substages depends on the intensity of the processes in the nodule.

The third stage of thyroid nodules represents the maximum destruction of their tissue. At this stage, the proportion shifts significantly towards immune and fibrotic processes. Therefore, the ultrasound picture demonstrates hyperechoic elements against a background of significant hypoechogenicity.

The simplicity of ultrasound diagnosis of nodular stages is combined with the complexity of interpretation of some cases and other characteristics of the nodular process. If an isoechoic nodule can almost certainly be attributed to the Development stage, then the presence of 1–3 hypoechoic lobules in it or general hypoechogenicity may raise doubts: are these sufficient signs for the Initial Wasting substage. In other words, are there enough signs of destruction (hypoechoic lobules, anechoic areas and hyperechoic elements) to choose between the substages of Initial, Moderate and Significant Wasting? How to evaluate a cystic nodule in which only residual tissue is visible?

Such doubts may be associated with a transitional state from one stage (or substage) to another. In this case, it is appropriate to denote a nodule in a state of transition. For example: "a nodule is in a state of transition from the Development stage to the Wasting stage." Or more simply: "the transition from Primary to Moderate Wasting."

Another criterion for interpreting the stage (substage) of nodules is a control ultrasound assessment after 6 or 12 months (less often 3 months). If the nodule has signs of destruction, but its volume increases due to tissue, then

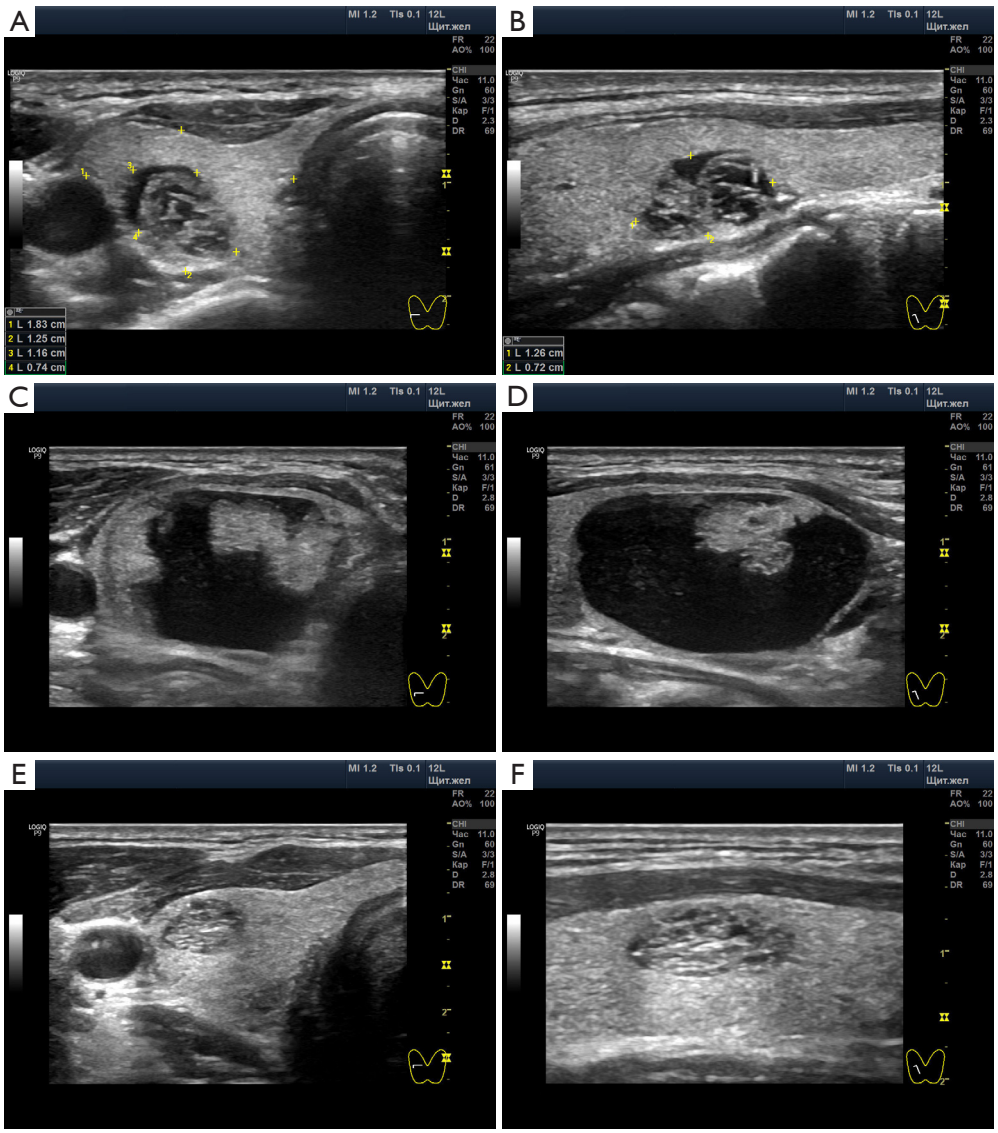

Figure 7 Thyroid nodules at the substage of Significant Wasting. (A,B) The patient is 48 years old, euthyroidism. Inside the nodule, residual slightly hypoechoic tissue, hyperechoic arcuate elements, anechoic and significantly hypoechoic lobules are visible. There is hyperechogenicity dorsal to the nodule. (C,D) Patient, 65 years old, euthyroidism. A small amount of isoechoic tissue is present among the anechoic nodule. (E,F) Patient, 43 years old, euthyroidism. Microcystic thyroid nodule at the substage of Significant Wasting.

the nodule is at the Initial Wasting substage. If, during annual monitoring, the size of the nodule remains the same, then this is the substage of Moderate Wasting. If the control ultrasound shows a decrease in the volume of tissue in the nodule, then this corresponds to the substage of Significant Wasting. Ultrasound signs of the Scarring stage usually do not require evaluation after a period of time for confirmation.

Additionally, the interpretation of the stages of thyroid nodules is influenced by the intensity of the processes in them (with the participation of physical and chemical factors) and the segmental organization of large nodules. On this side, it should be understood that the size of the nodule is not a sufficient criterion for assessing its stage. Large nodules (including nodules that fill almost the entire lobe) can be at any stage, including the Development stage. Signs of fibrosis and calcification of one medium-sized segment in a large nodule are not sufficient to classify the

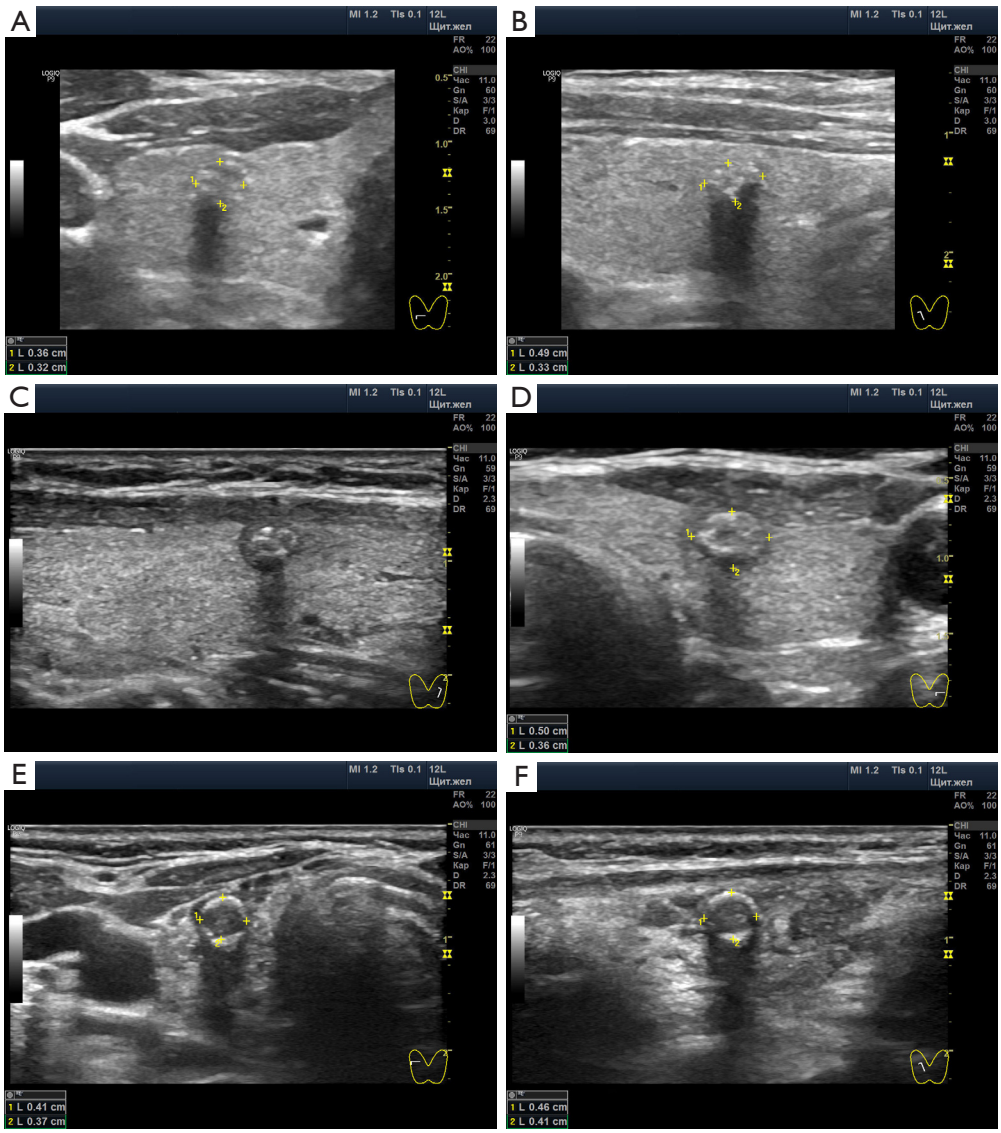

Figure 8 Thyroid nodules at the Scarring stage. (A,B) The patient is 70 years old, euthyroidism. In the right lobe there is a small nodule, in the tissue of which, mainly along the perimeter and partially inside, pinpoint moderately hyperechoic elements are identified. A significantly pronounced hypoechoic shadow extends dorsally from the nodule. (C,D) The patient is 55 years old, euthyroidism. There is a small nodule in the left lobe. Along the perimeter and inside the nodule, pinpoint significantly hyperechoic elements are visible, located together and separately. A slightly pronounced hypoechoic shadow extends dorsally from the nodule. (E,F) Patient, 52 years old, hypothyroidism. A small nodule with a significantly hyperechoic contour is identified in the right lobe. A significantly pronounced hypoechoic shadow extends dorsally from the nodule.

nodule as the Scarring stage.

At the substage of Significant Wasting, areas of new tissue may appear in the nodule. This phenomenon is especially noticeable in cystic nodules, when ultrasound shows a certain isoechoic polyp (new tissue) among the anechoic (fluid). Observations show that such an increase in regenerative (proliferative) processes does not reach significant values. These areas are relatively small and after a certain time period, sign of destruction, appear in them. Reports that processes in nodules can develop in reverse (in stages) usually contain inaccuracies and resemble the discoveries of *perpetuum mobile* (49).

Knowledge of the stages of thyroid nodules significantly improves diagnosis, prognosis and choice of tactics. For example, Lacout *et al.* quite rightly pointed out the importance of differential diagnosis of papillary cancer with the stage of Scarring of benign nodes, calling it mummification (43), or with the condition after alcohol sclerotization (43,50). This clinical problem can be successfully solved by focusing on previous full-fledged ultrasound data. Unfortunately, such information is not always available or it is insufficient (ultrasound images are missing, the nodule's location in a multinodular process in the gland is not indicated, etc.). Due to this feature, preventive ultrasound diagnostics of the thyroid can be recommended for middle-aged people (starting from 30 years old), as well as after suffering overloads of the body (long-term work, mental stress, diseases, etc.). Ultrasound monitoring of the thyroid is appropriate for adults every 10 years of life. This frequency is relevant to the entire spectrum of thyropathies, including nodules.

The lobular segmental organization of some nodules, together with knowledge of their stage changes, makes it possible to classify such processes as absolutely benign variants. For example, "microcystic" nodules, which are empirically referred to as "spongiform" (51). Ultrasound signs of destruction in the lobules of nodules and compaction of connective tissue septa around such anechoic segments can be expressed to varying degrees. Accordingly, one does not necessarily expect the Severe Wasting substage (i.e., the "spongiform" variant), which has been declared completely benign by many experts and included in Thyroid Imaging Reporting and Data System (TI-RADS) protocols (52). Careful ultrasound examination allows for earlier identification of the lobular structure and initial signs of destruction of individual lobules. That is, at the substages of Initial and Moderate Wasting. In them, small anechoic areas and signs of minor fibrosis occupy less than 50%. In particular, one should take into account the natural utilization of fluid from lobular cysts of the nodes during the substage of Significant Depletion (*Figure 7E*,*7F*). Such nodules can also be referred to as "microcystic" with a substage, and are characterized as benign by TI-RADS without an indication for needle biopsy (49).

Determining the stage of a nodule allows us to assume, to varying degrees, the nature of morphological events within it and the likely period of further changes. This opportunity is provided by a combination of assessments of the stage of the nodule, its size (including the dynamics of the volume of the nodule for 6–12 months) and signs of activity of the intranodular process. This intensity is usually indicated by the magnitude of nodule Doppler blood flow (53,54), depending on direct neural, metabolic and physical influences (*Figures 2B*,*3C*,*3D*,*4B*,*4C*,*4F*,*5E*,*5F*,*6D*). This assessment is complemented by determining the systolic peak velocity in the arteries of the nodule (*Figures 4D*,*6C*).

Therefore, it is possible to roughly predict the timing of subsequent changes, indications for a certain type of operation, or the choice of other tactics. In particular, we have to admit that the existence of nodules and the duration of their stages usually lasts for years. Ultrasound observations show that in most patients this period is approximately 10–30 years.

A relatively limited aspect of the analysis of the stages of thyroid nodules is the difficulty of annual monitoring of different variants of nodes throughout the entire period of their existence in the gland. It is not easy to detect a nodule at the very beginning of its formation, and then monitor its condition with ultrasound every year for 20–30 years. Especially if the patient lives far away or goes to another city/country. Even the offer of free regular diagnostics does not always discipline patients (There are also circumstances independent of the will of patients and doctors that interrupt the regularity of ultrasound monitoring). However, in our clinic, the same specialist was able to evaluate changes in nodules in several patients both annually and after periods of 3–5 or more years. The data from all these cases did not contradict the ideas about staged transformations of nodules, but confirmed and supplemented them. However, the bulk of ultrasound data for the analysis of nodule stages has been obtained in the form of single examinations. In almost every case, similar changes in nodules were determined, corresponding to the principles of the three stages.

The presented knowledge about the stages of thyroid nodules has significant advantages over the empirical characteristics of individual conditions of the nodules and attempts to give them a scientific form. However, it requires further research to clarify the features of this process, including for different variants of benign nodules.

Conclusions

Benign thyroid nodules are transformed according to stages. These stages are based on the relationship of severity between the regenerative (proliferative) and destructive processes of the nodule tissue. There are ultrasound signs of three stages of thyroid nodules: Development, Wasting and

Scarring. The Wasting stage has three substages: Initial, Moderate and Significant Wasting. Assessing the stage of the nodule improves the quality of diagnosis, prognosis and choice of tactics. Preventive thyroid ultrasound helps in assessing the stage of the nodule.

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Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-477/coif). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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