

# Knotted bull Diagnosis Treatment methods (Comment)

**Karimova M. M. Ibrokhimova N.R.**  
Fergana Public Health Medical Institute.  
Endocrinology dispensary of Faghana region

## Summary

In this article analyzed the scientific literature of the last years on the nodal formations of thyroid glands. It highlights the methods of diagnosis and treatment of nodular goiter.

**Keywords:** Thyroid Gland, Nodular goiter

Nodular goiter is one of the most common diseases of the thyroid gland, and despite the numerous studies conducted, it remains an unexplored issue of modern medicine. Nodular goitre is a generalized concept, which is used by clinicians until cytological verification of the diagnosis. Conducting differential diagnosis of nodular tumors of the thyroid gland in the process of clinical - instrumental examination - is an important stage that determines the future tactics of treatment and monitoring of the patient (1,2-7).

Thyroid nodules are a common clinical finding with an estimated prevalence of 3–7% (1.2) based on palpation of the thyroid gland.

According to UTT, the prevalence of clinically unrepresentative thyroid nodules is 20–76% in the general population, and this is consistent with pathologic–anatomical data (3–5). Additionally, 20-48% of patients with a single palpable thyroid nodule will have additional nodules on UTE examination (5,6). Thyroid nodules are more common in the elderly and in women, as well as in individuals with iodine deficiency and a history of radiation exposure.

Nodular forms of thyroid diseases

(WHO classification):

I. Nodular colloid growing at different levels;

II. Tumors:

1. Epithelial tumors:

A. Safe:

- follicular adenoma;
- others.

B. Dangerous:

- follicular cancer;
- papillary cancer;
- medullary cancer;
- undifferentiated (anaplastic) cancer;
- others.

2. non-epithelial tumors:

A. Safe;

B. Dangerous:

- mixed tumors;
- secondary tumors;
- unclassified tumors;
- neoplastic lesions.

Modern treatment of patients with nodular diseases of the thyroid gland is based on the use of high-resolution ultrasound examination, high-sensitivity method of quantitative determination of TTG and fine needle aspiration biopsy (IIAB). The use of a method such as thyroid scintigraphy for diagnosis is not necessary in most cases, but it is justified to use the same method to assess the condition of patients with low

levels of serum TTG or to determine the functional anatomy of the multinodular thyroid gland in patients with more iodine deficiency. Measurement of serum TTG levels is the best initial laboratory test of thyroid function. When conducting this test, it is necessary to determine the free thyroxine and triiodothyronine in the case of a decrease in TTG level, and in the case of an increase in the TTG level, the level of antibodies to thyroperoxidase should be determined.

Both benign and malignant tumors may present as thyroid nodules (Appendix 1) (9). In this regard, the primary task of diagnosing newly identified nodes is to exclude a poor-quality process. (6,10)

In the form of thyroid nodules, the following are manifested:

- Good quality knotted bull;
- Chronic lymphocytic thyroiditis;
- Simple or hemorrhagic cysts of the thyroid gland;
- Follicular adenoma;
- Acute subthyroiditis;
- Papillary carcinoma;
- Follicular carcinoma;
- Carcinoma derived from Grtle cells (oxyphilic carcinoma);
- Undifferentiated carcinoma;
- Medullary carcinoma;
- Anaplastic carcinoma;
- Primary thyroid lymphoma;
- Sarcoma, paratoma and other categories of tumors;
- Metastatic tumors.

During the examination, it is necessary to give detailed answers to the questions regarding whether the patient and his descendants had good or bad quality diseases of the thyroid gland. This is especially true for familial medullary thyroid cancer (QBOMS), multiple endocrine neoplasia type 2 (MEN-2), familial papillary thyroid cancer, familial pollinosis of the intestinal system, Cowden's disease, and Gardner's syndrome (12-14).

Record the following information:

- age of the patient;
- availability of information about thyroid diseases or cancer in the family anamnesis;
- previous irradiation in the head and neck area;
- severity of weight gain in the neck area;
- dysphonia, dysphagia or wheezing;
- symptoms of hyper or hypothyroidism;
- taking iodine-containing drugs or biosupplements.

When is a UTE thyroid examination performed?

Ultrasonography with high accuracy is the most sensitive method that allows to identify thyroid lesions, measure their size, compare their contents, and evaluate diffuse changes occurring in the thyroid gland (33, 34).

Patients with a palpable nodular or multinodular thyroid nodule (PTB) should undergo UTE for the following purposes, such as:

- to aid in diagnosis in complex cases (for example, chronic lymphocytic thyroiditis);
- for the search of incidental thyroid nodules or diffuse changes of the thyroid gland;
- For detection of poor quality growth using UTE and IIAB to select appropriate targets;
- to choose the size and length of the biopsy needle;
- to achieve an unbiased measurement of basal thyroid volume and lesions requiring appropriate observation or conservative management.

#### **Guidelines for IIAB.**

- size larger than 1 cm, solid and hypoechoic in UTE;

- signs of extracapsular growth or metastases in neck lymph nodes of any size during UTE;
- in patients irradiated in childhood and adolescence, of any size. 1 in cases of KBPK, QBMS or MEN-2 in relatives of the 1st degree of consanguinity.

Previous operations for thyroid cancer. When there are factors distorting the results of the analysis, an extremely high level of calcitonin;

- the size is less than 10 mm, when the signs of poor quality are detected during the UTE, the presence of 2 or more criteria accompanying the UTE, leading to the opinion of poor quality, significantly increases the risk of developing thyroid cancer.

- "hot" nodes on the scintigram should not be passed through IIAB.

IIAB of a multi-node bull.

- There is a rare need to biopsy more than 2 nodes, if their selection is based on the criteria described above;

- "hot" nodes should not be biopsied when radioisotope scanning is available;

- In the presence of suspected neck lymphadenopathy, both the lymph node and the suspected thyroid node should be subjected to IIAB.

### **Laboratory studies.**

For the majority of patients with thyroid nodules, in order to avoid unnecessary tests, it is recommended to follow the following path of laboratory analysis, namely:

- Normal level of TTG: additional analyzes are not recommended (except for the risk of central hypothyroidism);
- Very high level of TTG: detection of levels of free thyroxine antibodies to thyroperoxidase to assess the possibility of hypothyroidism;
- Decreased levels of TTG: determination of free thyroxine and free triiodothyronine levels to evaluate the possibility of hyperthyroidism.

Thyroperoxidase antibodies should be measured in patients with elevated serum TTG levels (79, 80). A coarse, diffusely enlarged, or small thyroid gland with high levels of serum antibodies to thyroperoxidase is more suggestive of Hashimoto's autoimmune thyroiditis (11, 80, 81).

Quantitative determination of thyroglobulin levels Determination of serum thyroglobulin levels is not recommended in the diagnosis of thyroid nodules (84).

### **Radioisotope scanning.**

Thyroid scintigraphy is the only method that allows the assessment of thyroid function and the identification of autonomously functioning thyroid nodular areas (100).

Nodes are divided into hyperfunctioning ("hot"), hypofunctioning ("cold") and indeterminate nodes according to radioisotope uptake (100). Boiled nodules are almost never clinically significant low-grade lesions, whereas cold or undetectable nodules have a 3% to 15% chance of poor quality (42, 101–103). Because the majority of thyroid lesions are cold or unresectable nodules, and only a small proportion are of poor quality (104, 105), the likelihood that a hypofunctioning or unresectable nodule is predictive of involvement in a poor-grade process is very low. Furthermore, as the size of nodules decreases, the diagnostic specificity of scintigraphy decreases in small nodules (<1 cm) because these nodules are present below the detection threshold (100, 106, 107).

### **Indications for thyroid scintigraphy.**

Thyroid scintigraphy is indicated for the following scores (108–111):

- except for a single thyroid nodule and a decreased level of TTG, it is not mandatory to carry out IIAB for hot nodules;
- Selection of cold and undefined areas in KTB, even without elimination of TTG, selection of suitable areas for IIAB, for hot nodules that cannot be subjected to cytological examination;

- in large KTB, especially in breast growth;
- for the diagnosis of ectonic thyroid tissue;
- in the case of subclinical hyperthyroidism, to identify the hidden parts of the tissue, except for the hyperfunctioning limit (excessive processing);
- in follicular lesions, to detect cellular adenoma, which may be of good quality, although most of these nodules appear cold on scintigram;
- to determine the acceptability of radioiodine therapy;
- to distinguish thyrotoxicosis with a low absorption rate from thyrotoxicosis with a high absorption rate.

There is no one-size-fits-all treatment for simple nodular goitre. There are different ways to treat non-toxic nodular goitre.

Non-toxic multinodular goiter treatments.

1. Surgical method.
2. Radioiodotherapy.
3. Treatment with thyroid hormones.
4. Treatment with iodine preparations.
5. Treatment original (observation).

Table 1. Advantages and disadvantages of nontoxic multinodular goiter treatment options.

	Advantages	Disadvantages
Operation	A significant reduction in the size of the pupil. Rapid decompression of the trachea. Rapid relief of symptoms. Accuracy of histological diagnosis	The need for hospitalization. Cost of treatment. High surgical risk. Vocal cord paralysis: ~1%. Hypoparathyroidism: ~1%. The risk of developing hypothyroidism depending on the type of resection. Risk of recurrence depending on the type of resection.
<sup>131</sup> I	In most cases, it is carried out on an outpatient basis. In hospitalization: the price is not high. Fewer side effects. Sometimes a 50% reduction in the size of the goiter within 1 year. Long-term increase in breathing capacity. Chances of a successful replay	Availability of restrictions on the introduction of radioactivity. Negative impact on others. The need to use contraceptives for women of childbearing age. A gradual decrease in the size of the pupil. Decreased effectiveness of the increase in the size of the pupil. The presence of a non-high risk of sudden enlargement of the goiter. The risk of developing thyroiditis; 3% Risk of progression to Graves' disease: 5%. Risk of developing hypothyroidism within 1 year: 15-20%. The level of risk of developing cancer much later is not known.
Levothyroxine	Possibility of outpatient treatment. The price is not high. Ability to eliminate the formation of a new node.	Lack of efficiency. Lifelong treatment. Additional effects (bones, heart). It is not advisable to transfer when the level of TTG is low.

### 1. Use of levothyroxine in the treatment of nodular goiter

The choice of a conservative method of treatment is justified only when the patient has a goitre, in which the nodular colloid is profiled (increased) to varying degrees, and the size is not large (the size of the nodule is < 2 cm (no more than 3 cm). The main goal of the treatment is to eliminate or slow down the further growth of the nodule. The patient's risk In the absence of factors and/or clinical and cytological signs of a QB tumor, as well as after the level of thyrotropin hormone has been checked, treatment with thyroid hormone drugs is started. Therapy with L-thyroxine or combined drugs is carried out. In the first stage of treatment, it is advisable to use motor therapy with L-thyroxine, which is provides an opportunity to evaluate the effectiveness of therapy more quickly. The duration of treatment with L-thyroxine should not be less than one year, and after its cancellation, the appointment of iodine preparations (iodomarin), combined drugs (thyrocomb, thyreotome) or iodine-rich products (iodized table salt, etc. .) should be recommended (2-6).

It is hypothesized that thyroid hormone therapy in non-autonomously degenerated thyroid tissue should slow down or even reverse thyroid growth when TTG levels decrease. Treatment of diffuse euthyroid endemic goiter with 200 mcg plus 100 mcg of levothyroxine for at least 6 months followed by iodine alone has been recommended. When the effect of levothyroxine is compared in nodular and diffuse goiters, its effectiveness in diffuse goiters is more convincing.

Indications for the appointment of levothyroxine in nodular colloid proliferative goiter.

Solitary node in QB.

Treatment with L-thyroxine is recommended for patients with a solitary, functionally inactive colloid goiter with a normal or slightly elevated basal TTG level. Treatment should be continued for 6-12 months, nodule sizes are evaluated using UTT.

#### **Instructions:**

- the size of the follicle is 10-33 mm (the volume of the follicle is not larger than 3 ml);
- weak proliferative activity or absence of proliferative activity of thyrocytes obtained from the node in IPB (rare);
- recurrence of nodular colloid goitre during the first three years from the time of operative treatment.

If further growth of the nodule is noted during treatment, treatment with L-thyroxine is stopped, re-puncture biopsy is performed, and the question of surgical treatment is decided. If under the conditions of treatment there is a decrease in the size of the goiter, or at least its growth is stabilized, the treatment with L-thyroxine is continued, with the level of TTG in the blood periodically monitored.

#### **Limitations in the use of L-thyroxine in patients with nodular goiter**

L-thyroxine should be administered with caution to elderly patients with nodular goitre, as well as to patients with cardiovascular disease. Treatment with L-thyroxine should be started with very low doses (12.5-25 µg per day), and the dose should be carried out under strict control of the ECG. In elderly patients, it is justified to add L-thyroxine together with calcium antagonists or selective beta-blockers, which have a negative chrono- and inotropic effect and reduce myocardial oxygen demand.

Patients with clearly visible severe pathology of the cardiovascular system and a nodular bull are only under dynamic observation with repeated QB UTT and, if necessary, a puncture biopsy.

Diseases in which it is absolutely inappropriate to prescribe L-thyroxine to patients with nodular goiter:

Cardiological:

- CHD (ischemic heart disease) with severe disturbances of heart rhythm, lipid arrhythmia, polytope or frequent extrasystole;
- tension angina or frequent extrasystole;
- unstable angina pectoris;
- obvious lack of blood circulation (starting from 2 b).

Endocrinological:

- TTG basal level <0.5 µM IU/ml;
- Signs of high activity of thyrocytes during punctate cytological examination;
- When scanning "hot! Nodes.



### **Treatment of QB nodes with initial size <1 cm (volume <1ml).**

These nodes in QB are often "discovered by chance" during ultrasound examination. Depending on their location in the QB tissue, they can be either palpable or non-palpable. In the future, a fine needle puncture biopsy with cytological examination of the punctate is the optimal method to determine the future tactics for this type of nodule.

If it is possible to puncture, it is necessary to conservatively treat the nodular colloid growing goiter. But often for objective reasons (primarily due to the small size of the nodules) either it is impossible to take the material from the nodule, or its quantity is clearly not enough for cytological verification of the diagnosis. In this case, it is necessary to prescribe the iodine preparation in a preventive dose to the patient and repeat the UTT after taking it for 12 months.

### **2. Iodine preparations in the treatment of nodular goitre rats**

In the treatment of nodular goitre, only preventive doses of iodine (100-200 µg per day) are used. The following are indications for the use of iodine preparations:

- small size of nodes (up to 2 cm in diameter);
- a nodular colloidal boil successfully treated with L-thyroxine for a year.

Both positive and negative effects are observed when using iodine preparations.

Positive effect:

• iodine affects all factors responsible for the activation of the growth of cells in the thyroid gland in conditions of iodine deficiency;

• iodine eliminates the "withdrawal syndrome" associated with L-thyroxine.

Clinical, instrumental and laboratory signs that allow predicting a positive result from conservative treatment with L-thyroxine are summarized below.

Clinical factors:

- small initial size of the nodule (diameter up to 3 cm or volume up to 3 ml);
- the drug is well tolerated by the patient when using its appropriate doses.

Cytological factors:

- abundance of colloid;
- the presence of a group of thyrocytes with signs of dystrophy;
- a large number of phagocytes;
- weak or moderate proliferative activity of thyrocytes.

Treatment with L-thyroxine is not expected to be effective in the presence of the following factors.

Clinical factors:

- large initial size of the nodule (more than 3 cm in diameter or more than 3 ml in volume);
- patient's intolerance to the drug.

Cytological factors:

- fibrosis;
- degenerative changes;
- clear cellular hyperplasia;
- lymphoid infiltration;
- active proliferation of thyrocytes;
- cases of adenomatosis and/or dysplasia in the nodule.

When starting treatment with thyroid hormone preparations, in addition to the factors mentioned above, it is necessary to take into account the patient's age, susceptibility to diseases of the cardiovascular system or their presence, functional activity of the QB nodes. Good tolerance of the drug and absence of its side effects should be the main criterion of safety of treatment with thyroid hormone drugs.

When prescribing a specific therapy to a patient, it is always necessary to take into account the main pharmacokinetic properties of the substance contained in the drug. We remind you that the half-life of thyroxine from the body is 6-7 days. Alternative therapy with L-thyroxine usually stabilizes TTG levels within 3-4 weeks.

The risk of developing iodine-induced thyrotoxicosis increases during the use of iodine in the treatment of nodular goitre after the age of 50. In this way, it is necessary to prescribe preparations with iodine together with caution and only in the case of nodular goitre with iodine deficiency. It is better to start

the treatment of euthyroid nodular goiter with L-thyroxine, because other goiter gene factors may be involved in the pathogenesis of goiter, besides iodine deficiency, as well as congenital defect of thyroid hormone synthesis. When choosing the dose of the drug, first of all, it is necessary to approach each patient individually.

### 3. Surgical intervention.

Although L-thyroxine therapy is the mainstay of treatment for small to moderately toxic nodules, certain complicating factors such as a large nodule and suspected thyroid malignancy mean that surgery is not recommended for most clinicians (8, 9). The advantage of surgery is the rapid resolution of symptoms and the possibility of a clear histological diagnosis and a significant reduction in the size of the goiter, but there are several problems that should be kept in mind (Table 6). Numerous reports of studies have described the immediate and prospective results of surgical intervention in thyroid disease. Specific complications associated with this type of surgery include damage to the recurrent laryngeal nerve and parathyroid glands. During operations in specialized clinics, damage to these structures occurs in less than 1% of patients. The rate of complications depends on the size of the goiter and the size of the resection.

Removal of large tonsils can cause postoperative respiratory complications in 30% of cases. Large goiters often grow intrathoracic, for example, among patients scheduled for thyroidectomy, such goiters are detected in 5-17% of patients. When the removal of a breast cyst is mainly performed through an incision in the neck area, there are many complications in the resection of breast cysts.

The high prevalence of QB cancer in Kokrakorti cattle is causing concern. But this high rate may be the result of systematic errors of assessment related to the subjective factor. It remains to be proven that the location of the mole behind the breast itself is associated with a more malignant tumor.

The risk of developing hypothyroidism in the future after subtotal resection of non-toxic multinodular goiters is not well defined, but its rate does not differ from 10-20% typical for toxic multinodular goiters.

### 4. Radioiodotherapy

During the second half of the 20th century, <sup>131</sup>I-therapy was used to treat hyperthyroid disorders, primarily Graves' disease. It is hyper <sup>131</sup>I-therapy showed a reduction in QB sizes even in the case of unchanged eos. Because of this effect, <sup>131</sup>I-therapy has been used for the past 20 years to treat non-toxic compressive nodular goiter, but in individuals with hyperthyroidism in most countries (8, 9). With the exception of one case, none of the studies showed an effect of <sup>131</sup>I-therapy on pupil size reduction in the control group. In general, patients are satisfied with the results of <sup>131</sup>I-therapy, but there are few qualitative analyzes of symptom changes. Data on recurrence rates after <sup>131</sup>I-therapy are scarce.

### Used literature

1. Aloumanis K, Daramaras A, Ioannidou M. Hashimoto thyroiditis: A "true" adenoma visualized as a hot nodule in the presence of overt hypothyroidism. *Hell J Nucl Med*. 2011 Sep;14(3).
2. Akgul O, Ocak S, Keskek M, Koc M, Tez M. Risk of malignancy in non-diagnostic thyroid fine-needle aspiration biopsy in multinodular goitre patients. *Endocr Regul*. 2011 Jan;45(1):9-12.
3. Valdina E.K. Uzlovoy zob i rak shchitovidnoy zhelezly // *Vestn. snort*. 2015. N26.S. 23-26.
4. Bonnema SJ, Fast S, Hegedüs L. Non-surgical approach to the benign nodular goiter: new opportunities by recombinant human TSH-stimulated <sup>131</sup>I-therapy. *Endocrine*. 2019 Dec;40(3):344-53. Epub 2011 Oct 5.
5. Buzduga C, Mogoş V, Găleşanu C, Vulpoi C, Ungureanu M, Cristea C, Preda C, Ciobanu D, Ferariu D, Florea N, Zbranca E. Epidemiology and histology of malignant thyroid nodules in North East Region of Romania (Moldavia ) before and after alimentary salt universal iodination. *Rev Med Chir Soc Med Nat Iasi*. 2015 Jan-Mar;115(1):45-8.
6. Bahn RS, Castro MR. Approach to the patient with nontoxic multinodular goiter. *J Clin Endocrinol Metab*. 2019 May;96(5).
7. Bakhshae M, Davoudi Y, Mehrabi M, Layegh P, Mirsadaee S, Rad MP, Layegh P. Vascular pattern and spectral parameters of power Doppler ultrasound as predictors of malignancy risk in thyroid nodules. *Laryngoscope*. 2018Dec;118(12):2182-6.

8. Wilhelm SM. Utility of I-123 thyroid uptake scan in incidental thyroid nodules: an old test with a new role. *Surgery*. 2008 Oct;144(4):511-5; discussion 515-7. Epub 2015 Aug 29.
9. Gaitan E 2000 Environmental natural goitrogens. In: Peter F, Wiersinga WM, Hostalek U, eds. *The thyroid and environment*. New York: Schattauer; 69–78
10. Giuffrida D, Gharib H 1995 Controversies in the management of cold, hot, and occult thyroid nodules. *Am J Med* 99:642–650
11. Gutekunst R, Smolarek H, Hasenpusch U, Stubbe P, Friedrich HJ, Wood WG, Scriba PC 1986 Goitre epidemiology: thyroid volume, iodine excretion, thyroglobulin and thyrotropin in Germany and Sweden. *Acta Endocrinol (Copenhagen)* 112:494–501
12. Grineva E.N. Differential diagnosis of the cervical spine Department of faculty therapy, Center of Endocrinology, Saint Petersburg. *Journal Tironet #5-6/2002*.
13. Gozü HI, Yavuzer D, Kaya H, Vural S, Sargin H, Gezen C, Sargin M, Akalın S. Alterations of NIS expression in functioning thyroid nodules. *Ear Nose Throat J*. 2010 Nov-Dec;20(6):285-92.
14. Gul K, Dirikoc A, Kiyak G, Ersoy PE, Ugras NS, Ersoy R, Cakir B. The association between thyroid carcinoma and Hashimoto's thyroiditis: the ultrasonographic and histopathologic characteristics of malignant nodules. *Thyroid*. 2010 Aug;20(8):873-8.
15. Dedov I.I. i dr. Diagnostics and treatment of the cervical spine. Methodological recommendations. 2003. Orenstein H, Peskind A, Raskind MA 1988 Thyroid disorders in female psychiatric patients with panic disorder or agoraphobia. *Am J Psychiatry* 145:1428–1430
16. Daniels G.H. Physical examination of the thyroid gland. In: Braverman L.E., Utiger R.D., eds. *Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text*. 6th ed. Philadelphia: JB Lippincott; 2017.
17. Dedov I.I., Melnichenko G.A., Fadeev V.V. *Endocrinology*. Moscow 2002: 222-227
18. E.A. Trash. Konservativnoe lechenie uzlovogo zoba. Endocrinological scientific center RAMN. *Journal Tironet #5-6*. 2016.
19. Zayratyants O.V. Epidemiology and etiological structure of the nodular bone po dannym autopsy Moskovskoy gorodskoy Tsentr patologoanatomicheskikh issledovaniy. *Journal Tironet #5-6/2002*.
20. Zhuraev ShSh, Baïmakhanov BB, Fedotovskikh GV, Kyzhyrov ZhN, Enin EA. [Fine-needle aspiration biopsy in the diagnosis of nodular thyroid lesions]. *Khirurgiia (Moscow)*. 2009;(6):40-3. Russian.
21. Isik S, Gokay F, Ozuguz U, Topaloglu O, Tutuncu Y, Berker D, Guler S. Comparison of the prevalence and sonographic features of thyroid nodules accompanying autoimmune thyroid diseases. *Endocrinol Pol*. 2010 Nov-Dec;61(6):658-64.
22. Iodine supplementation in Sweden and regional trends in thyroid cancer incidence by histopathologic type. Pettersson B, Coleman MP, Ron E, Adami HO. *Int J Cancer*. 1996 Jan 3;65(1):13-9.
23. Iodine intake and incidence of thyroid cancer in Denmark. Sehestedt T, Knudsen N, Perrild H, Johansen C. *Clin Endocrinol (Oxf)*. 2006 Aug;65(2):229-33.
24. Qiu L, Crapanzano JP, Saqi A, Vidhun R, Vazquez MF. Cell block alone as an ideal preparatory method for hemorrhagic thyroid nodule aspirates procured without onsite cytologists. *Acta Cytol*. 2008 Mar-Apr;52(2):139-44