Modern Diagnostics and Treatment of Differentiated Thyroid Cancer

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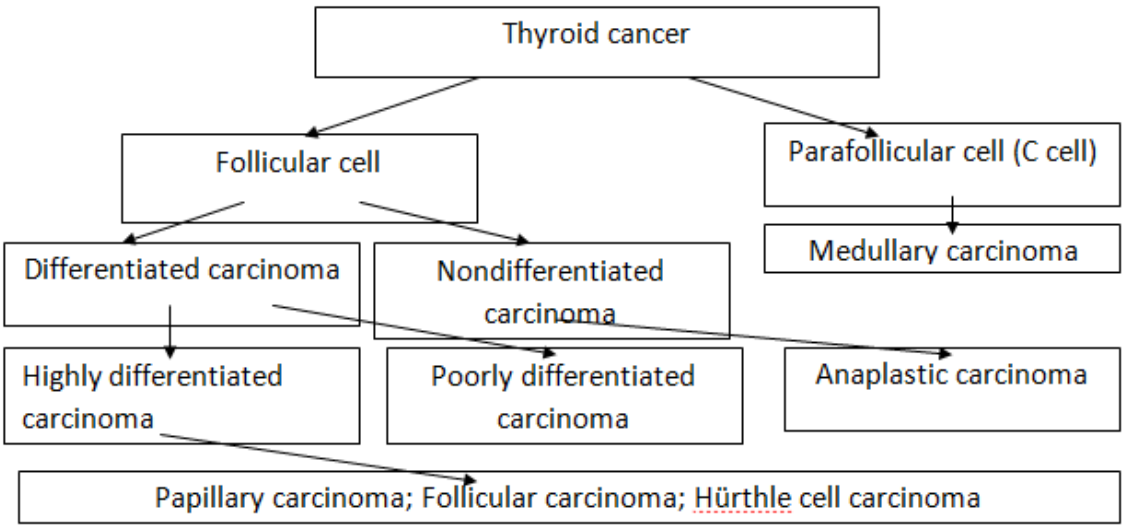
Summary.

Thyroid cancer is a relatively rare disease, accounting for about 1% of all new cancer cases each year. However, it is the most common neoplasm of the endocrine system, and its incidence has been increasing over the past few decades. The reasons for this are not entirely clear, but are partly due to improvements in diagnostic methods that allow for early diagnosis. Thyroid cancers usually have a very good long-term prognosis, but nevertheless, about 20% of patients fail due to local or distant tumor recurrence, inability to absorb radioactive iodine, or, in rare cases, progression of well-differentiated tumors to poorly differentiated or undifferentiated. carcinomas. In this article, we would like to highlight the main provisions of the modern approach to the introduction of patients with thyroid cancer.

Keywords: thyroid cancer, well-differentiated carcinoma, fine needle aspiration biopsy, dynamic recurrence risk assessment.

When we talk about thyroid cancer, we mean a tumor that grows from follicular and parafollicular (C - cells) cells of the thyroid tissue. From follicular cells, such types of thyroid cancer as papillary, follicular, Hürthle cell, poorly differentiated, anaplastic thyroid carcinomas can develop. And from parafollicular cells, medullary thyroid carcinoma can develop (Scheme 1) (1).



Scheme 1. Classification of thyroid cancer.

The incidence of thyroid cancer has increased in the last three decades. This is largely due to the active involvement in the diagnostic process of ultrasound, which can detect even very small nodules, the increased use of fine needle aspiration biopsy (FNA), as well as, in general, the increase in the availability of medical care. Incidence figures vary by country (2) (Table 1).

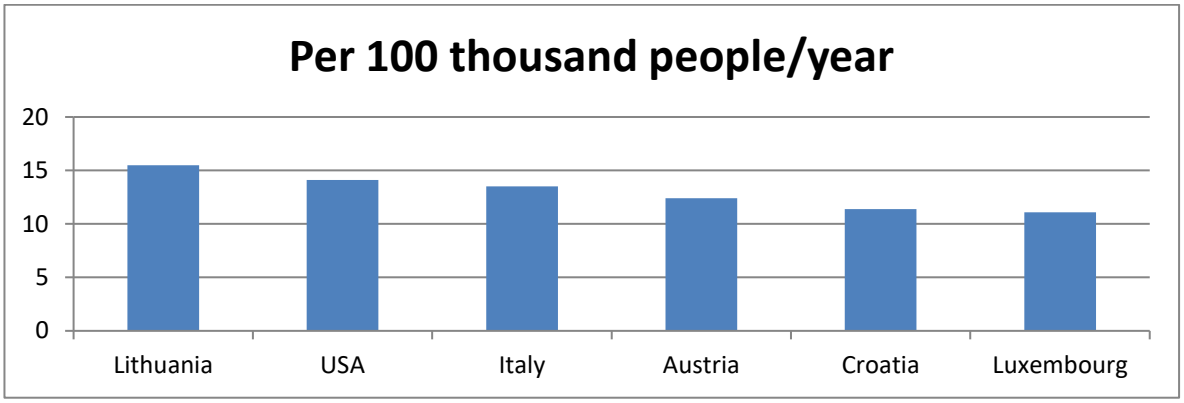


Table 1. Incidence of thyroid cancer in selected countries.

In women, thyroid cancer occurs three times more often than in men (9.1: 3.1, respectively) (2).

However, despite the frequent detection of thyroid cancer, mortality remains at the same level - 0.7 - 0.5 deaths per 100 thousand people per year (3,4,5,6). It is also necessary to say that over the past decade, the detection rate of the so-called "calm" papillary thyroid carcinomas has generally increased, while the incidence of anaplastic, undifferentiated, medullary and follicular carcinomas remains almost stable (7,8,9,10). Another work that is illustrative in this respect is by Olson E. et al. (11) (Table 2).

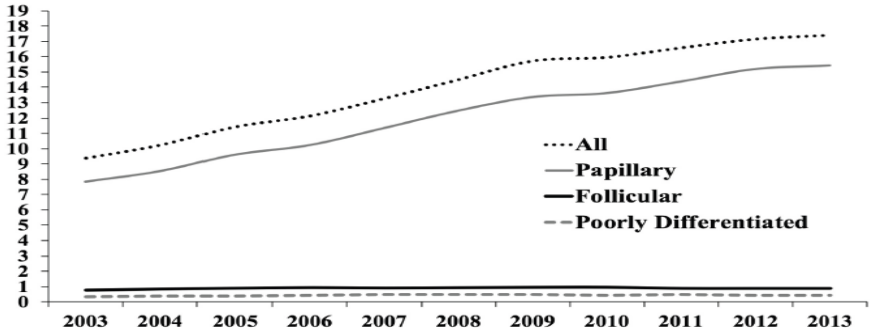
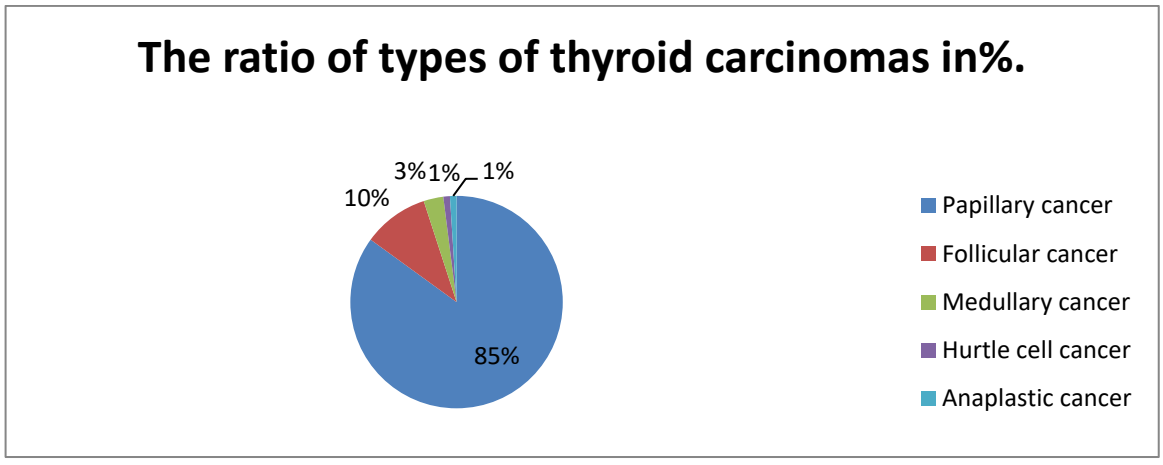


Table 2. Incidence of different types of thyroid cancer in the United States.

The ratio of thyroid cancers among themselves also explains the increase in the incidence of papillary thyroid cancer relative to other types of thyroid carcinomas (Graph 1) (12).



(Graph. 1). The ratio of types of thyroid carcinomas in%.

An increase in the incidence rate, mainly due to the papillary form, and unchanged mortality rates from thyroid carcinomas have influenced the modern strategy for the treatment of carcinomas. In international clinical guidelines for the diagnosis and treatment of thyroid carcinomas, in turn, there is a shift towards active observation, organ-preserving surgical interventions in cases where carcinomas do not appear to be aggressive in terms of histological type, by the presence of germination in neighboring tissues, damage to regional lymph nodes, aggressive mutations , aggressive histological picture, etc. (13,14,15,).

Detection of thyroid carcinomas is preceded by a survey of patient complaints, palpation of the thyroid gland and other laboratory and instrumental diagnostic methods. In practice, most patients do not make any complaints, but in cases where the thyroid gland is enlarged due to nodular formations or diffusely, then compression symptoms may appear. These may be a violation or difficulty in swallowing, breathing, a feeling of tightness in the throat, voice changes due to damage to the recurrent laryngeal nerves innervating the vocal cords.

Palpation also allows you to assess the volume and presence of thyroid nodes. As a rule, malignant nodes can be of stony density, inactive, soldered to surrounding tissues, and regional lymph nodes of the neck can also be enlarged if there are metastases in them. It should be noted that there are factors that can make it difficult to identify nodes using palpation of the thyroid gland. These are the small size of the node (less than 1 cm), the presence of thick subcutaneous fatty tissue, the retrosternal location of the node, as well as the abnormal location of the thyroid gland (goiter of the root of the tongue). Also, when interviewing a patient, it is necessary to take into account the presence of a possible family history of thyroid cancer, exposure to the head and neck area, work associated with a source of radiation or various carcinogenic chemicals.

If you suspect the presence of a thyroid nodule or the presence of a palpable node, a diffuse increase, it is necessary to conduct an ultrasound diagnosis of the thyroid gland. When a node is detected using this method, an assessment is made of the visualized node according to a number of echographic features (shape, echo structure, echogenicity, shape of the edges of the node, the presence of inclusions inside the node), after which, summing up all these data, a conclusion is made about the degree of possible malignancy (16). At the moment, there are various systems for assessing thyroid nodules and determining their possible malignancy (classification of malignant nodules according to ATA, K-TIRADS, EU-TIRADS, BritishU-grade) (17,18,19). One such classification system is the TI-RADS system proposed in 2017 by the American College of Radiology (ACRTI-RADS)(20). There are 5 categories in this system, such as TIRADS - 1 (benign), TIRADS -2 (not suspected to be malignant), TIRADS -3 (probably benign), TIRADS -4 (suspicious), TIRADS -5 (high risk of malignancy).) (twenty).

The use of this system provides clear indications for fine needle aspiration biopsy or monitoring of thyroid nodules depending on the TIRADS category and nodule size (Table 3).

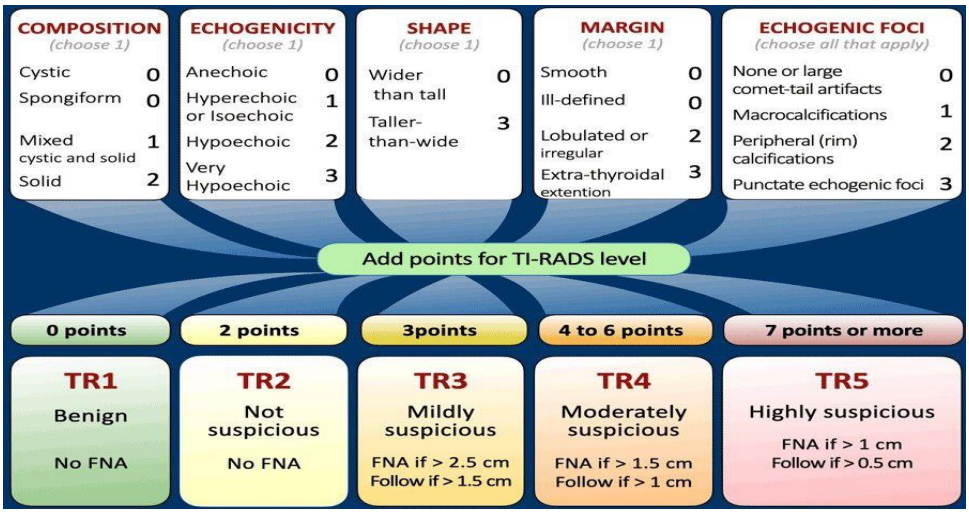


Table 3. Thyroid Nodule Ultrasound Assessment System (ACR-TIRADS).

According to this system, all nodes are classified as:

TI-RADS 3 - a node larger than 2.5 cm in diameter should be subjected to fine needle aspiration biopsy (FNA);

- a node from 1.5 cm to 2.4 cm should be under dynamic observation by ultrasound for 1.3 and 5 years, respectively.

TI-RADS 4 - a node larger than 1.5 cm should be subjected to FNA;

- a node from 1.0 cm to 1.4 cm should be under dynamic observation by ultrasound for 1,2,3 and 5 years, respectively.

TI-RADS 5 - a node larger than 1.0 cm should be subjected to FNA;

- a node less than 1 cm should be under dynamic observation by ultrasound for 1,2,3,4 and 5 years, respectively.

The growth of the node is considered significant if, during the course of observation, the size of the node increased by 20% or 2 mm in any two dimensions, or the volume of the node increased by 50%. In multinodular goiter, it is recommended to monitor not the two largest nodules, but the two nodules with the highest ACR TI-RADS scores (20,21).

In the presence of suspicious nodes, FNA of this node is performed under ultrasound control. The biopsy is taken with a 21G needle. The sample taken from the needle is applied in a thin layer on a glass slide and then sent for cytological examination. The results of the latter are assessed using a special reporting system for thyroid cytopathology, adopted for the first time in 2010. in the USA, Bethesda. At the moment there are revised versions, the latest of which was published in 2017 (22).

According to the Bethesda system for thyroid cytopathology, the following conclusions are possible:

Bethesda - 1 - Nondiagnostic or unsatisfactory

Bethesda - 2 - Benign

Bethesda - 3 - Atypia of undetermined significance or follicular lesion of undetermined significance

Bethesda - 4 - Follicular neoplasm or suspicious for a follicular neoplasm

Bethesda - 5 - Suspicious for malignancy

Bethesda - 6 - Malignant

If the result of the cytological examination: Bethesda - 1 - Non-diagnostic / Unsatisfactory

According to clinical guidelines, in the presence of Non-diagnostic / Unsatisfactory result of FNA, a second biopsy is required. If the result remains Non-diagnostic / Unsatisfactory even with repeated FNA, then 2 options are possible:

- Or observation of the node under the control of ultrasound according to the specified terms in the ACR TI-RADS system

- Either resection of the node in the presence of: ultrasound signs of the node suspicious for malignancy, suspicious clinical risk factors for malignancy, an increase in the size of the node (by 20% in two planes).

If the result of a cytological examination: Bethesda - 2 - Benign ;

No immediate diagnostic tests or treatment is required. Continued monitoring of the node(s) is required. In the presence of "strong suspicious" sonographic features, an ultrasound scan followed by FNA every 12 months is required. If there are no sonographic suspicious signs, or they are mildly or moderately suspicious, then an ultrasound of the node may be performed every 12-24 months. At the same time, if there are signs of strong suspicious sonographic signs or node growth is detected, then FNA is necessary. If repeated FNA gives the result - Bethesda 2, then further ultrasonic monitoring of the node in dynamics is not shown.

If the cytology result is: Bethesda – 3– Atypia of undetermined significance or follicular lesion of undetermined significance;

With such a biopsy result, it is possible to conduct repeated FNA or conduct genetic studies for the presence of certain mutations if the patient has clinical or sonographic risk factors for malignancy (BRAF, NRAS, HRAS, KRAS, RET/PTC1, RET/PTC3,PAX8/PPAR). The sensitivity of genetic studies ranges from 63-80%. If the latter have not been carried out or do not give results that determine

further tactics, then two options are further possible: 1 - active sonographic monitoring of the node; 2 - diagnostic surgical removal of the node with express diagnostics and subsequent final histological examination. The choice of one or another method depends on the presence of clinical and sonographic risk factors, as well as on the informed preference of the patient.

If cytology result: Bethesda - 4 - Follicular neoplasm or suspicious for a follicular neoplasm;

In the presence of this cytopathological diagnosis, diagnostic surgical removal of the node with express diagnostics and subsequent final histological examination is recommended. Conducting genetic studies for the presence of certain mutations (BRAF,NRAS,HRAS,KRAS,RET/PTC1,RET/PTC3, PAX8/PPAR) is also recommended to assess the risk of malignancy.

If the result of a cytological examination: Bethesda - 5 - Suspicion of malignancy (PM);

If papillary carcinoma is suspected, then surgical treatment should be the same as for diagnosed papillary carcinoma.

What volume of surgical intervention is preferable for such results of FNA as Bethesda -3, Bethesda -4, Bethesda -5?

Hemithyroidectomy is indicated for:

- as a result of FNA Bethesda -3, Bethesda -4, while there are no other factors that increase the risk of malignancy.

Total thyroidectomy indicated for:

- result of FNA - Bethesda - 5

- result of FNA are Bethesda -3 or Bethesda -4 with a positive result for RAS, BRAFV600E mutation (this category should be considered as Bethesda - 5).

- FNA results - Bethesda -3, Bethesda -4, Bethesda -5 with positive results for mutations in the BRAF, RET, PAX8/PPAR genes (this category should be considered as Bethesda - 6)

- family history of thyroid carcinoma

- a history of exposure to the head and neck area

- sonographic evidence of strong suspicious signs of malignancy

- a node with a size of more than 4 cm

- the presence of a node on the contralateral side with the results of FNA - Bethesda3,4,5.

- the presence of hyperthyroidism of non-autoimmune etiology

- if the patient wishes to avoid a possible final (repeated) operation.

If the result of a cytological examination: Bethesda - 6;

When this cytological result is obtained, surgical treatment is required.

However, active surveillance may be an alternative to surgery in the presence of papillary microcarcinoma (tumor size less than 1 cm) in the following cases:

- If there are no signs of active tumor growth or signs of metastasis to regional lymph nodes

- If life expectancy is short

- If there is a high surgical risk

- If there is a concomitant severe pathology.

Economical or extended resection of the thyroid lobe(s), subtotal thyroidectomy (when more than 1 g of thyroid tissue remains) are unacceptable in case of possible malignancy of the thyroid nodule(s) (23).

The main goals of initial therapy for patients with differentiated thyroid cancer should be:

1. Removal of the primary focus of the disease, taking into account the spread of the latter beyond the thyroid capsule and clinically significant changes in the regional lymph nodes of the neck. The usefulness of the resection of the primary focus is a key factor determining the prognosis, while incorrect (for certain reasons) left metastatic lymph nodes are the most common cause of persistence/relapse of the disease.

2. Minimize the risk of recurrence or metastasis. Adequate surgical treatment is the most important factor influencing the prognosis, while RAI, TSH suppression, etc. play only an additional role.

3. Acceleration of postoperative radioiodine therapy (RAI), where it is justified and necessary. For patients receiving RAI, or for suspected (adjuvant therapy) or confirmed residual or metastatic disease, removal of all thyroid tissue is a key element of initial surgical intervention.

4. Accurate staging and assessment of the risk of possible recurrence is necessary. This is necessary in order to evaluate the initial prognosis and treatment, as well as to evaluate the algorithm for p / o observation. To assess the risk of a possible recurrence, it is also necessary to take into account the results of postoperative final histology, the dynamics of the level of thyroglobulin TG and Antibodies to TG.

5. Minimize possible complications associated with treatment. The amount of intervention, the experience and competence of the surgeon are important factors in determining the risk of possible surgical complications.

For clinical classification of the extent and staging of thyroid cancer, the American Joint Committee on Cancer (AJCC) 7th revision TNM classification for thyroid cancer is used (Table 4).

TNM classification of differentiated thyroid cancer. (American Joint Committee on Cancer, 7th edition, Chicago, Illinois.)	
T0	No evidence for primary tumor
T1a	Tumor less than 1 cm, no extrathyroid extension
T1b	Tumor 1 to 2 cm in greatest dimension, without extrathyroidal extension
T2	Tumor 2 to 4 cm in greatest dimension, without extrathyroidal extension
T3	Tumor larger than 4 cm in greatest dimension, without extrathyroidal extension or Tumor of any size with minimal extrathyroidal extension (eg, extension to the sternothyroid muscle and/or soft tissues around the thyroid gland)
T4a	Tumor of any size extending beyond the thyroid capsule with invasion of subcutaneous fat, larynx, trachea, esophagus, or recurrent nerve
T4b	Tumor of any size with invasion of the prevertebral fascia or enveloping the carotid artery or mediastinal vessels
N0	No metastatic lymph nodes
N1a	Metastases at level VI (pretracheal, paratracheal and prelaryngeal / Delphian nodes)
N1b	Metastases are unilateral, bilateral or contralateral at the level of the cervical lymph nodes (I, II, III, IV or V zones), or metastases in the retropharyngeal lymph nodes, or in the upper mediastinal lymph nodes (zone VII).
M0	No distant metastases
M1	Have distant metastases

Table 4. TNM classification of differentiated thyroid cancer.

Before and after surgery, all patients with thyroid cancer are evaluated for risk of recurrence or persistence to determine further tactics of introduction. This assessment categorizes patients into three groups: low, moderate and high risk of recurrence (Table 5)(24).

ATA Risk groups	Description	Indication for RAI
low risk T1a, No/Nx, Mo/Mx	The size of the tumor is less than 1 cm.	No indication
low risk T1b/T2, No/Nx, Mo/Mx	The size of the tumor is 1-4 cm.	May be indicated for aggressive histology, vascular invasion.
low risk and intermediate risk	The size of the tumor is 4 cm.	It is possible to use in case of

T3, No/Nx, Mo/Mx		inadequate preoperative ultrasound assessment of the node, inexperience of the surgeon performing the operation, inaccessibility and / or poor quality of the determination of TG - thyroglobulin.
low risk and intermediate risk T1-3, N1a, Mo/Mx	The size of the tumor is up to 4 cm, with metastases in the central group of neck l / n (VI and VII zones)	Indicated
low risk and intermediate risk T1-3, N1b, Mo/Mx	The size of the tumor is up to 4 cm, with metastases in the lateral group of neck l / n (VI and I,II, III, IV, V zones)	Indicated
High risk T4, N - any, M – any	Any size	Indicated
High risk M – 1, T - any, N - any,	Any size	Indicated

Table 5. ATA risk groups in differentiated thyroid cancer.

Radioiodine therapy is aimed at destroying residual tissues that perceive iodine. In this case, the radioactive isotope of iodine 131 is used. There are necessary rules before prescribing this procedure (25,26,27,28):

1. After removal of the thyroid gland, TSH begins to rise within 2 weeks and reaches a maximum at 4-6 weeks. This ensures high radiopharmaceutical uptake and gives the best chance for successful ablation with radioactive 131I.

2.According to our analysis, residual tissue ablation was better when TSH was over 30 mIU/mL. The data suggest that adequate TSH stimulation is the most important condition for successful ablation.

3. After surgery, T4 drugs are not prescribed and diagnostic tests are performed at 4-6 weeks.

4. Avoid all iodine-containing substances 4-6 weeks before RAI or thyroid scintigraphy.

After surgery and/or RAI, the degree of response to the interventions is assessed by the levels of TG and antibodies to TG, as well as the presence or absence of residual tissue of the primary tumor or lymph node (Table 7) (24).

Category	**Definition**	**Clinical Consequences**	**Change in treatment**
Excellent response	Lack of evidence for residual tissue, metastases, and/or non-stim. TG less than 0.2 ng / ml or stim. TG less than 1 ng/ml.	Relapse in 1-4% Less than 1% mortality	Should reduce the intensity and frequency of observation and the level of suppression of TSH
Biochemical incomplete response	Lack of data for the presence of residual tissue, metastases and no stim. TG more than 1.0 ng / ml or stim. TG more than 10 ng / ml or an increasing level of antibodies to TG.	Recurrence in 20% of cases in the form of metastases or tumor growth from residual tissue Less than 1% mortality	Recurrence in 20% of cases in the form of metastases or tumor growth from residual tissue Less than 1% mortality
Structural incomplete response	Presence of evidence for residual tissue, metastases and/or any TG level with or without anti-TG antibodies	50-85% have persistent disease (structural) Mortality rate is 11% with	It is possible to involve additional treatment and long-term monitoring of various clinical and pathological

		locoregional metastases and more than 50% with distant metastases.	characteristics of the disease (tumor size, growth intensity, areas of radiopharmaceutical accumulation zones, etc.)
Indeterminate response	Non-specific data when scanning the bed of the thyroid gland and neck l / n Weak accumulation of radiopharmaceuticals in the thyroid bed during scintigraphy. Nonstim. TG less than 1.0 ng / ml or stim. TG less than 10 ng / ml or a decreasing level of antibodies to TG. without a structural basis of the disease	Recurrence in 15 - 20% of cases in the form of metastases or tumor growth from residual tissue. Less than 1% mortality	Follow-up with TSH suppression should be continued with TG measurements and scanning for suspicious lesions with possible follow-up biopsy.

Table 7. Response variants for the treatment of differentiated thyroid cancer according to ATA 2015.

Depending on the response to treatment, suppressive therapy with levothyroxine according to ATA 2015 is prescribed. The level of suppression is also determined by the presence of comorbidities (Table 8) (24).

Risks of TSH suppression	**Excellent response**	**Indeterminate response**	**Biochemical incomplete response**	**Structural incomplete response**
No known risk	**TSH 0.5 - 2.0 mIU / l**	**TSH 0.1 - 0.5 mIU / l**	**TSH less than 0.1 mIU/l**	**TSH less than 0.1 mIU/l**
Menopause	**TSH 0.5 - 2.0 mIU / l**	**TSH 0.1 - 0.5 mIU / l**	**TSH 0.1 - 0.5 mIU / l**	**TSH less than 0.1 mIU/l**
Tachycardia	**TSH 0.5 - 2.0 mIU / l**	**TSH 0.1 - 0.5 mIU / l**	**TSH 0.1 - 0.5 mIU / l**	**TSH less than 0.1 mIU/l**
Osteopenia	**TSH 0.5 - 2.0 mIU / l**	**TSH 0.1 - 0.5 mIU / l**	**TSH 0.1 - 0.5 mIU / l**	**TSH less than 0.1 mIU/l**
Age over 60	**TSH 0.5 - 2.0 mIU / l**	**TSH 0.5 - 2.0 mIU / l**	**TSH 0.1 - 0.5 mIU / l**	**TSH less than 0.1 mIU/l**
Osteoporosis	**TSH 0.5 - 2.0 mIU / l**	**TSH 0.5 - 2.0 mIU / l**	**TSH 0.1 - 0.5 mIU / l**	**TSH less than 0.1 mIU/l**
Atrial fibrillation	**TSH 0.5 - 2.0 mIU / l**	**TSH 0.5 - 2.0 mIU / l**	**TSH 0.5 - 2.0 mIU / l**	**TSH 0.1 - 0.5 mIU / l**

Table 8. Suppressive therapy according to ATA 2015.

There are three types of suppressive therapy:
TSH 0.5 - 2.0 mIU / l - no suppression of TSH 0.1 - 0.5 mIU / l - mild suppression of TSH less than 0.1 mIU / l - strong suppression.

Conclusion. Thus, in this review article, we have described the existing modern approaches to the diagnosis and treatment of patients with differentiated thyroid cancer. Thyroid cancer, as discussed, can have highly varied manifestations, from a clinically indolent low-risk disease that can be managed with only active surveillance to a highly aggressive metastatic disease that needs extensive surgical resection. A close collaboration between all interprofessional team members, including but not limited to the thyroid surgeon, the endocrinologist, the pathologist, the radiologist, and possibly the oncologist, plays a vital role in providing the most appropriate treatment for the patient while avoiding overtreatment at the same time.

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