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DIAGNOSIS AND TREATMENT GUIDELINES IN THYROID CARCINOMA AMERICAN AND EUROPEAN CONSENSUS, ADAPTED TO ROMANIA

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Abstract

The optimization of the diagnosis and therapy strategies, and also their standardization represent a continuous activity of the professional societies. The aim of the study is to review the data from the literature, regarding the thyroid cancer guidelines and to propose a national consensus, especially for differentiated thyroid cancers. There were analyzed the guidelines of diagnosis and treatment for thyroid nodules and thyroid cancer published by the European and American Thyroid Associations (ETA, ATA), by British Thyroid Association, American Association of Clinical Endocrinologist (AACE) and endocrine surgeons (AAES), by European Association of Nuclear Medicine (EANM) and American and European Societies of Clinical Oncology (ASCO and ESMO). We studied the national cancer registry, the institutional cancer registry and the database of nuclear medicine departments from Romania, regarding the limits and instruments as are registered at the National Nuclear Committee.

The significant increase of the incidence of thyroid cancer and of the epidemiological data concerning the high percentage of clinically and ultrasoundly detected thyroid nodules, requires a debate around a consensus for the diagnosis and treatment of the differentiated thyroid carcinoma.

Key words: differentiated thyroid carcinoma, guidelines, Romania.

INTRODUCTION

Considered a rare malignant disease, thyroid carcinoma has presented in the past several years an increasing incidence and a modified evolution, fact that requires a new approach regarding the diagnosis ant the therapeutical strategies.

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Thyroid carcinoma is rare among human malignancies (<1%), but is the most frequent endocrine cancer, accounting for about 5% of thyroid nodules (1) and is responsible for the mortality by cancer for ~ 1 % (2). The incidence, even if there are a lot of varieties, according to age, sex, environment, diet, is still low between 1 and 4.9 at 100.000 inhabitants (3,4,5).

The differentiated thyroid cancers forms represent about 80% of all thyroid cancers (6,7), with a good prognosis, while medullary, respectively anaplastic forms, with considerable lower incidences, have an aggressive evolution, frequently very severe and fast (8,9,10).

Medullary thyroid cancer for the initial diagnosis and for the follow-up is a challenge for the physician because of the possible association with other endocrine tumors and because of the genetic determination (11-17). This thyroid carcinoma has very limited diagnosis tools in Romania: lack of radiopharmaceuticals with neurosensitivity, total absence of imaging instruments able to detect the molecular metabolic disturbances such as PET (positron emission tomography) and PET/CT (positron emission tomography fusion with computer tomography); even the serum level of calcitonin in many centres is impossible to be done by routine; calcitonin serum gradient is not used anywhere in Romania. It is important to be mentioned the fact that the genetic tests for the familial screening of this malignancy are not available in Romania, at this moment. Only few cases are in the evidences, with the genetic tests performed in other European medical centres (18-22) or in some research trials. According to this situation, in Romania, it is impossible to speak about a gold standard in the diagnosis, treatment and follow-up of the medullary thyroid carcinoma.

Anaplastic thyroid cancer with a considerable lower incidence, unfortunately is not a problem of positive diagnosis, but is problem of delay of the diagnosis and of the adequate treatment. More than 55% (2,23,24) are referred to the physician in the moment of palliative treatment, with distance metastases and severe locoregional invasion of the tumor. Most oncological chemotherapy trials are not able to rise the 5 years survival rates more than 10% (25,26). Recent studies focus also on better management of the poorly differentiated thyroid carcinoma, with severe prognosis (27). Actually there is no treatment guideline available, in case of an impossible surgical sequence.

European Thyroid Association (ETA) — European Thyroid Association-Cancer Research Network (ETA-CRN) Guidelines and American Thyroid Association (ATA) Guidelines

The majority of studies are targeted to elaborate guidelines for differentiated thyroid carcinoma (DTC). ETA and ETA-CRN published in 2006 the protocols (1) based on several specific arguments: clinical presentation is changing; diagnosis and treatment tools have been improved in recent years; the existence of the guidelines in the Netherlands from1988- updated 2006, in United Kingdom from 2002- updated 2006, in Italy from 2004, in Portugal from 2005, (28-31).

The guidelines dictate the need of applying more effective, less invasive and less expensive procedures able to guarantee the best management and the best quality of life for these patients.

In the USA approximately 23,500 cases of differentiated thyroid carcinoma (DTC) are diagnosed each year and the incidence may be increasing. ATA (32) developed a strategy similar to that used by the National Institutes of Health, with strength of panelists recommendations based on available evidence. Existing guidelines, published by the American Association of Clinical Endocrinology (AACE) and the American Association of Endocrine Surgeons (AAES) in 2001 and those published by the National Comprehensive Cancer Network (NCCN) in 2005 (33,34), were reviewed and updated by this new ATA report for thyroid nodule and thyroid cancer diagnosis and treatment.

Following the spirit of concrete cultural and scientific integration among the countries participating in the new reality of the European Unoin, the European Thyroid Association has endorsed the implementation of this consensus for the management of thyroid nodules and differentiated thyroid carcinoma (1).

In 2005, in Romania were reported 783 new cases of thyroid carcinoma, which represented the 9th position in the National Cancer Registry. In the "Prof. Dr. I.Chiricuță" Institute of Oncology from Cluj-Napoca, in the same year there were treated 284 new cases of thyroid carcinoma, which represent the 4th position (after breast carcinoma, lung carcinoma and cervix cancer) in the institutional cancer registry. According to these figures, it would be very useful to have a common database for reporting this pathology.

The increasing incidence of thyroid cancers is related with the progressive number of nodular goitres (35, 36). In Fig. 1 are represented the cases from the latest 35 years, 1970-2005, regarding the total number of thyroid cancers and nodular goitres treated in the "Prof.I.Chiricuță" Institute of Oncology Cluj-Napoca.

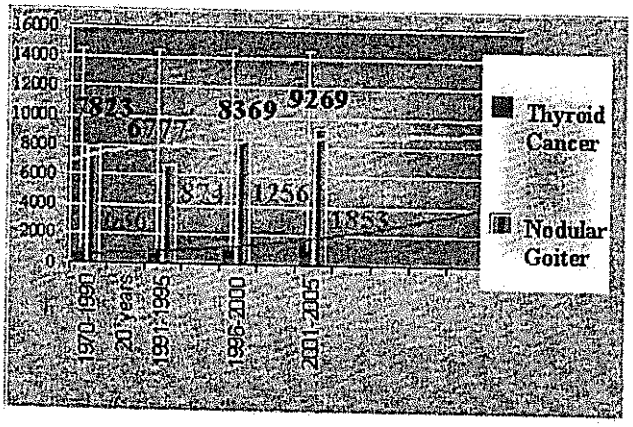

Figure 1. Thyroid Cancers and Nodular Goiters treated in the "Prof.I.Chiricuță" Institute of Oncology Cluj-Napoca

ETA-CRN 2006 pre-surgical evaluation of thyroid nodules (1):

- Clinical evaluation of thyroid nodules: complete history, including family and physical examination

- Neck ultrasonography - the most accurate imaging technique, with some suggestive malignant features.

- Thyroid scan - limited to patients with thyroid nodules and low or undetectable TSH (thyroid stimulating hormone) or in multinodular goitre.

- Fine needle aspiration cytology (FNAC) — at any solitary nodule > 1cm, if TSH is proven not to be low. If thyroid nodule is < 1cm — FNAC only if there are strong ultrasound criteria of malignancy. Limit of the method is follicular carcinoma.

- Laboratory evaluation: TSH, FT4 (free thyroxine), FT3 (free triiodothyronine) routinely, but Anti-TPO (antibody thyroid peroxidase) and Tg (thyroglobulin) have no importance in differential diagnosis. Calcitonin measurement is recommended in the initial evaluation of thyroid nodules.

Recommendations ATA 2006, pre-surgical evaluation of thyroid nodules (32): **A**- strongly recommended (+++) — consistent clinical trials; **B** — Recommended (++) - fair evidence; **C** — Recommended (+) - experts opinion; **D**- Recommended against (-) — experts opinion; **E** — Recommended against (- -) - fair evidence; **F** — Strongly recommended against (- - -) — good evidence; **I** — recommended neither for nor against (-/+).

- Measure TSH level at initial evaluation of thyroid nodules — recommendation C

- Sonography must be done at every patient with one or more suspected thyroid nodules — recommendation B

- Tg is not recommended for initial evaluation — recommendation F

- Calcitonin in initial evaluation — recommendation I

- FNAC is the procedure of choice in the evaluation of thyroid nodule - recommendation A

ETA-ATA differences in thyroid nodule evaluation

- FNAC is the first procedure of choice in evaluation thyroid nodules in ATA guidelines

- Serum Calcitonin measurement in ETA is recommended at initial evaluation, but has a recommendation I in ATA guidelines.

- Routine suppression therapy of benign thyroid nodules is not recommended, by ATA — recommendation F

ROMANIA

- Less than 30% of patients with thyroid cancer referred at the Institute of Oncology had FNAC prior the surgery, so the number of second surgery for the completion of thyroidectomy is high, especially in case of follicular carcinoma (37), Fig 2.

According to the published guidelines, the thyroid nodules in Romania are evaluated correctly, but there is a strong need for improving methods:

1. better cytology diagnosis, with professional strictly dedicated to thyroid pathology

2. Introduction of nuclear parameters in the morphological description of cytology, special operating soft for the processing of multiple data.

3. Introduction of thyroglobulin determination from the tissue obtained by FNAC

4. Regularly quality control of immunological serum determination, with a proper standardization of methods at national level and international control.

5. It is mandatory to have at least 2 genetic centres in Romania, for the family screening of medullary thyroid carcinoma and for the detection of RET proto-oncogene mutation.

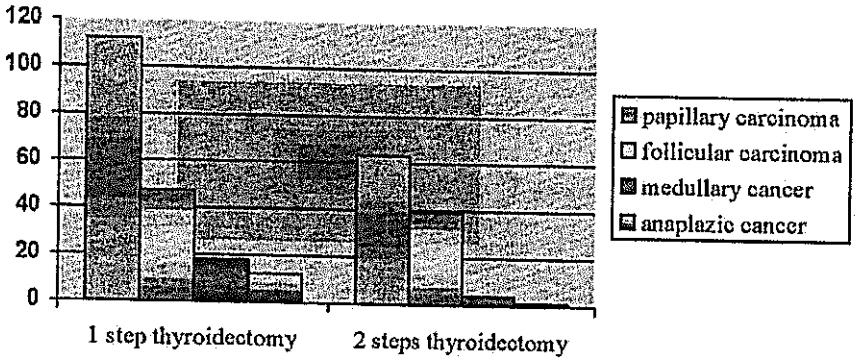

Figure 2. Number of patients submitted to thyroidectomy for thyroid carcinoma in the Institute of Oncology "Prof. Dr. I. Chiricuta" Cluj-Napoca, in the year 2006.

ETA 2006- Surgical treatment

- Standard — total or near total thyroidectomy; exception - solitary cancer = 1 cm, no nodal invasion or metastases or radiation exposure.

- Prophylactic central node dissection — controversial; act in case of clinical evidence

ATA 2006 - Surgical treatment

- Total or near total thyroidectomy is a standard procedure - recommendation A

- Lobectomy only in small, low risk, isolated, intrathyroidal papillary thyroid cancer, in the absence of cervical nodes metastases - recommendation A

- Dissection of central lymph node level (VI) is considered for papillary and Hurthle carcinomas, not for follicular cancers followed by radioiodine.— recommendation B

ETA-ATA DTC surgical treatment differences

- Dissection of level VI, central, of lymph nodes: ATA recommends as routine in the mentioned situations, ETA only in case of clinical involvement.

ROMANIA

- The Institute of Oncology Cluj-Napoca strongly recommend respecting the indication of surgery and of the extension of surgery, according to the risk classification and the tumor dimensions. A better pre surgical diagnosis will lead to a limited number of second surgeries for completion of thyroidectomy;it will also limit the unnecessary total thyroidectomy.

- Lymphadenectomy will be targeted to all the patients with clinical involvement of the lymph nodes and the central lymph node dissection will be recommended as a routine.

- The retrospective analysis of the total thyroidectomies performed in 2006, at the Institute of Oncology performed by three of the most experimented surgeons reveals that the neoplasm was present in 3 of 56 cases (5.35%), in 7 of 36 cases (19.4%), respectively 4 of 16 cases (25%). This data shows the necessity to respect the indication of total thyroidectomy according to the guideline for thyroid nodule.

ETA 2006- indication for post surgical radioiodine thyroid ablation (Table 1)

Table 1. Risk groups for radioiodine ablation

Very low-risk group	Low-risk group	High-risk group
Unifocal microcarcinoma (≤ 1 cm)	Less than total thyroidectomy, no lymph node dissection	T3, T4, N1, M1
No extension beyond the thyroid capsule	Age < 18 years,	Incomplete surgery
No lymph node metastases Complete surgery	Unfavourable histology, T1>1 cm, T2, N0, M0	High risk of recurrence
No indication for postoperative ^{131}I	**Probable indication - No consensus**	**Definitive indication**

Radioiodine procedure: high- risk group — 100 mCi I^{131} after withdrawal; low-risk group - 30-100 mCi I^{131} after withdrawal or 100 mCi I^{131} on 3rd day after rhTSH 0.9 mg day 1 and 2. Scan before ablation may be avoided. TSH must be over 30 mUI/l, Tg before ablation. WBS post therapy at 2-5 days.

ATA 2006 — radioiodine thyroid remnant ablation

Radioiodine ablation is recommended for:

- Patients with stage III and IV (AJCC sixth edition, TNM classification) (38).
- All patients with stage II younger than 45 years
- Most patients with stage II, 45 years or older
- Selected patients with stage I, with multifocal (> 2 foci) disease, nodal metastases, extrathyroidal and vascular invasion and/or aggressive histology - recommendation B.

Radioiodine thyroid remnant ablation procedure: pretherapeutic evaluation can be performed only with small activities 1-3 mCi I^{131} or I^{123}, when the uptake is necessary to dictate the ablation and the level of activity — recommendation C. The increase of TSH may be obtained by withdrawal or rhTSH — recommendation B.

ROMANIA

- Limited number of therapy centers
- Delay of treatment, after surgery. According to the National Committee of Nuclear Activities, in Romania, is actually impossible to do WBS 131- I, in all therapy centers. The majority of nuclear medicine departments still work with planar scanners, or have no authorization to use 131- I in high doses.

A comparative study led by IAEA in 2005 (39), published information about facilities of nuclear medicine in each country for thyroid cancer therapy and about the waiting time for treatment. In Table 2 are presented these data, also same information from the U.K. published in 2002 (40), from USA published in 2005 (41) and from Japan (42).

Table 2. Nuclear Medicine Facilities in different countries

Country	Inhabitants millions	Therapy centres	No. beds	In-pts/out-patients	Waiting time (weeks)
Austria	8.1	10	58	647/0	0-3
Belgium	10.4	154	38	329/0	0-4
Finland	5.2	16	14	148/13	0-4
Greece	11	16	11	279	12-19
Hungary	10.3	4	16	No data	0-3
Italy	57.3	75	120	1197/0	0-16
Netherlands	16.2	30	66	466/1	2-4
Spain	40.7	60	30	226	2-12
Japan	126.1	1167	No data	3347/0	No data
U.S.A.	282	7000	No data	23500 new cases	0
U.K.	60.1	102	84	911	1-5
Romania	**21.3**	**3**	**18**	**No data**	**0-24**

In Romania the situation is still critical, not only because of the delay of treatment, but also because of the absence in 2 of the departments of the gamma cameras able to do whole body scans (WBS) with I-131.

Even if radioiodine procedure is conducted in Romania following the recommendations of EANM guidelines (43) without WBS I-131, the follow-up is based on Tg evaluation and ultrasound.

Our experience recommends:

1. Optimizing the appointments of patients for treatments at 4-6 weeks post surgery.

2. Avoid hormonal substitution after surgery and before radioiodine

3. Do not use CT with contrast media for staging, the cervical ultrasound is the best non-invasive method for correct establishment of the local extension, before treatment.

4. Avoid WBS I-131 before radioiodine treatment

5. Increase TSH more than 40 mUI/ml

6 Quantitative determination of ablative doses (24h uptake of radioiodine, estimated by using less than 100 mCi I-131 and serum Tg and anti-Tg levels).

7. Do not use any medication that may influence the uptake of radioiodine

8. Do not use an aggressive wash out of radioiodine

9. Use WBS after therapy at 2-5 days, for a correct staging of the disease extension.

10. Sialadenitis can be limited by liberal hydratation and by lemon juice given 24 h after radioiodine (1). Our personal experience recommends 500-1000 mg of vitamin C during the first 5 days of treatment.

11. The mean single administered activity was 2,59 GBq of I^{131}, range from 1.11 - 3.7 GBq, more than 75% of the patients during the last 5 years were treated with activities less than 1.85 GBq, with a total response in 89% of cases.

ETA — staging after thyroidectomy and radioiodine therapy (Table 3).

Table 3. European Thyroid Association: risk group staging after thyroidectomy and radioiodine therapy

Very low-risk group	Low-risk group	High-risk group
Unifocal T1a (≤ 1 cm) N0M0 and no extension beyond thyroid capsule	T1b (> 1cm, but less than 2cm) N0M0 T2N0M0 or multifocal T1aN0M0	Any T3 and T4 or Any T, N1 or M1
LT4 replacement: TSH - 0.5-1 µUI/ml	LT4 replacement: TSH -0,5-1 µUI/ml, if cured LT4 suppressive dose TSH < 0.1 µUI/ml for 6- 12 months	LT_4 suppressive dose TSH < 0.1 UI/ml for 3-5 years

ATA- staging after thyroidectomy and radioiodine therapy- see Table 4.

ETA — diagnosis tools for follow-up (1)

- Neck US and FNAC in suspected nodes > 5 mm (Tg measurement in specimens)

- Serum Tg, rule out the anti-Tg: must be undetectable after radical treatment; no measurements for 3 months after treatment

- WBS I^{131} — 2-3 days after 2-5 mCi I^{131} and T_4 withdrawal or rhTSH

- Other: neck CT, MRI, FDG F18 etc, if negative WBS I^{131}.

Table 4. American Thyroid Association: risk groups staging after thyroidectomy and radioiodine therapy

Low-risk group	Intermediate risk group	High-risk group
No local or distant metastases. All macroscopic tumor removed No tumor invasion of locoregional tissues No aggressive histology TSH - between 0.3-2 µUI/ml	Microscopic invasion in perithyroidal soft tissues Aggressive histology or vascular invasion	Macroscopic tumor invasion Incomplete tumor resection Distant metastases I^{131} uptake outside the thyroid bed after the post-treatment WBS scan. TSH must be between 0.1-0.5 µUI/ml for 5-10 years

ATA — diagnosis tools for follow-up (32)

- Tg must be measured every 6-12 months by immunometric assay in the same laboratory, for all the patients with DTC and radical treatment. Anti-Tg every time in the same sample determined. Recommendation A

- Low risk patients with radical treatment (surgery and radioiodine), with negative neck ultrasound and TSH suppression 6 months after treatment, Tg stimulated after T4 withdrawal or rhTSH at 12 months with undetectable values, is uncertain for subsequent stimulated determinations. Recommendation A

- Low risk patients with radical treatment (surgery and radioiodine), with negative Tg stimulated after T4 withdrawal or rhTSH, after the first WBS negative, do not need further WBS.

ROMANIA

- Tg, anti-Tg must be measured every 6-12 months in the same laboratory, at all the patients with DTC and radical treatment, after TSH rising by withdrawal of thyroid hormone for at least 2 weeks and confirming the TSH elevation. In our department we reviewed the serological data from 12 patients on the same day (October 2005), same laboratory and we observed that after radical treatment 8 patients (66.6%) had TSH 10.000 times higher in 15 days of withdrawal of hormone, from undetectable levels (TSH < 0.005 mUI/l) to values between 4.12-96.7 mUI/l. Three of patients were at the beginning with TSH levels detectable and they raised it in the same interval between 17 mUI/l and >100 mUI/l. One patient had TSH rising in 15 days from undetectable to 0.13 mUI/l and he presented a persistent disease.

- The use of human recombinant TSH in the Institute was not performed and in our opinion it is recommended to the patients with no optimum rising of TSH: rare circumstances in which the patient cannot elicit a sustained release of endogenous TSH include hypothalamic or pituitary dysfunction, long term corticosteroid administration and an unusually slow response, particularly in the elderly (1).

- We recommend performing functional studies with other radiotracers, in case of I-131 WBS negative.Technetium 99m methoxyisobutylisonitril (MIBI) is available in Romania (Fig. 3).

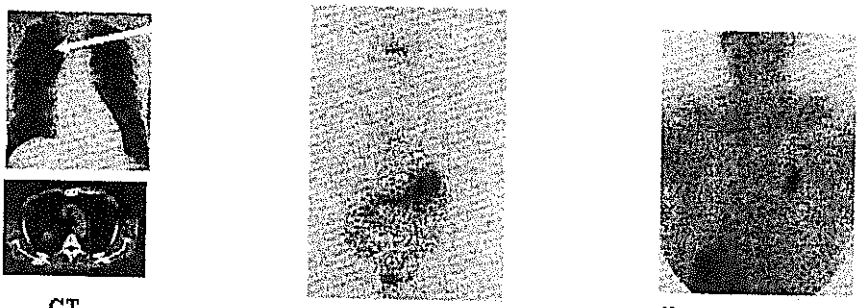

Figure 3. Lung metastases, with WBS ^{131}I negative, but positive Tc-99m MIBI. Image IOCN.

Management of metastatic and recurrent disease

Local and regional recurrence

- Surgery and I-131
- External beam therapy in 40-60 Gy in 25-30 sessions only if surgery is not possible and there is no I-131 uptake

Distant metastases

- Lung:100-200 mCi every 4-8 months during first 2 years
- Bones : surgery and I-131, external beam therapy
- Brain: surgery and external beam therapy, with short course of high dose corticosteroids, I-131 only after external beam therapy (1)

In Romania it is very important to have a strict follow-up and early detection of the recurrency of the disease and it is mandatory to do our best to have an accurate staging and precision of the extension. The optimal treatment for this pathology remains surgery, all other adjuvant therapies being restrictive, not easily available: radionuclide therapy centres very limited, external beam therapy with long waiting time lists, only 2 linear accelerators in Romania.

Second malignancies

- ETA — doses over 600 mCi I-131, the risk is significantly higher for second malignancy (44).
- ATA — the risk of second malignancy is dose related, long term follow-up studies demonstrate a very low risk. There appears to be an increased risk of breast cancer, unclear whether this is a result of screening basis, radioiodine therapy or other factors — recommendation C.
- ROMANIA — we strongly suggest having a cancer screening programme to all the patients with thyroid malignancy, most of them women, who have the opportunity of regular breast examination and genital control.

CONCLUSION

At this moment there are no significant differences between the American and European task forces that may influence the standard decision in diagnosis and treatment of thyroid nodule and differentiated thyroid carcinoma.

It is very important to have a national registry and uniform medical decision regarding the thyroid cancers; it is necessary to have an urgent upgrade of the equipments in the nuclear medicine departments and therapy units, also to introduce these units in international quality control management. To do our best for this disease means to have a real relation between all the specialists involved in the diagnosis and treatment of this pathology.

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