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Guidelines of Polish National Societies Diagnostics and Treatment of Thyroid Carcinoma 2018 Update

Polish Endocrine Society, Polish Society of Oncology, Polish Thyroid Association, Polish Society of Pathologists, Society of Polish Surgeons, Polish Society of Surgical Oncology, Polish Society of Clinical Oncology, Polish Society of Radiation Oncology, Polish Society of Nuclear Medicine, Polish Society of Paediatric Endocrinology, Polish Society of Paediatric Surgeons, Polish Society of Ultrasonography

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Significant advances have been made in thyroid cancer research in recent years, therefore relevant clinical guidelines need to be updated. The current Polish guidelines "Diagnostics and Treatment of Thyroid Carcinoma" have been formulated at the "Thyroid Cancer and Other Malignancies of Endocrine Glands" conference held in Wisla in November 2015 [1].

The Chair of the Scientific Committee, Professor Barbara Jarzab, invited all scientific societies engaged in clinical management of thyroid carcinoma to delegate their official representatives to participate as authors in updating these guidelines. In response, the following scientific societies prepared and accepted the updated guidelines: the Polish Endocrine Society, Polish Society of Oncology, Polish Thyroid Association, Polish Society of Pathologists, Society of Polish Surgeons, Polish Society of Surgical Oncology, Polish Society of Clinical Oncology, Polish Society of Radiation Oncology, Polish Society of Nuclear Medicine, Polish Society of Paediatric Endocrinology, Polish Society of Paediatric Surgeons, and the Polish Society of Ultrasonography.

The Guidelines, prepared in a short time, were published in January 2016 by the Polish Journal of Endocrinology. However, in several instances, not only their style and clarity asked for improvement, but also new developments and new evidence-based medical data required reflection and modification of some of the recommended procedures. Thus the need arose to update the entire content of these guidelines [1].

At the initiative of Professor Andrzej Lewinski, National Consultant in Endocrinology and President of the Polish Thyroid Association, the Thyroid Cancer Guidelines Group was formed in January 2017. This group, which included Professor Marek Ruchała, President of the Polish Endocrine Society, and Professor Barbara Jarzab, President of the Polish Group for Endocrine Tumours (PGNE), authorised Professor Marek Dedecjus, President of the Polish Society of Organ Biopsy, to invite as co-authors recognised authorities in their relevant disciplines, to collaborate in updating these guidelines. The list of these experts as co-authors was approved by the whole collaborating group.

The Authors Group met in Warsaw on April 26, 2017. At this meeting recommendations were selected which urgently required correction and updating and recom-

mendations that would be updated in the future (the next updating round being foreseen in 2018). Professor Dedecjus led this discussion and later continued it on-line, recording all changes proposed. At the same meeting it was decided to supply the Polish recommendations with medical justification, in line with the Evidence-Based Medicine (EBM) approach [2]. This task was assigned to Professor Barbara Jarzab, who within her team of collaborators found a group of co-authors for this work. This group of co-authors consisted of the following experts: Daria Handkiewicz-Junak, Agnieszka Czarniecka, Agata Bałdys-Waligórska, Ewa Chmielik, Jolanta Krajewska, Dagmara Rusinek, Małgorzata Oczko-Wojciechowska, Beata Jurecka-Lubieniecka, Tomasz Gawlik, Kornelia Hasse-Lazar, Michał Kalemba, Agnieszka Kotecka-Blicharz, Aleksandra Kropińska, Aleksandra Kukulka, Aleksandra Ledwon, Barbara Michalik, Tomasz Olczyk, Ewa Paliczka-Cieślik, Zbigniew Puch, Józef Roskosz, Aleksandra Syguła, Sylwia Szpak-Ulczo, Zbigniew Wygoda, Emilia Kulik, Elżbieta Lewandowska-Jabłońska, and Ewa Zembala-Nożyńska. It was decided to base the Polish recommendations on the ADAPTE system [3] used by the European Thyroid Association (ETA) in their documents published over the years 2013–2017 [2, 3]. Within this system, each recommendation is evaluated according to its strength (Strength of Recommendation; SoR) — within grades G1; or G2; (Table I), and an additional grade to evaluate the quality of its supporting medical evidence. Thus, the ETA applies two evaluation criteria, with additional subdivisions (cf. Table I). Within the Quality of Evidence (QoE) criterion, we have added a third, lowest, grade if our recommendation is based on the Polish consensus — it is then labelled QoE: PolCon.

We have also strived to supply each recommendation with a reference to relevant literature, if available. References were taken from a set of publications gathered by ATA experts [4] who applied EBM rules in their selection. If the recommendation relevant to the Polish conditions is covered by the recommendations published by ATA, we quote the number of the relevant ATA recommendation. For example, ATA GL R5 indicates that the subject is dealt with in ATA recommendation number five (R5). Those interested should refer to the ATA recommendations [4] and ATA

Table 1. Evidence-Based Medicine (EBM) system evaluating the strength of a recommendation [2, 3] (modified)

	Strength of Recommendation (SoR)	Clinical Interpretation
G1	Strong recommendation (for or against) concerns all patients in most clinical conditions. Abiding by this recommendation is evidently advantageous to the patient	This recommendation may be applied without any doubt. It will benefit most patients in practically all cases
G2	Weak recommendation (for or against); an optimal management may differ depending on the epidemiology or on the patient's clinical workout. Application of this recommendation is to be decided by the acting clinician	This grade of a recommendation requires that analysis be performed by the acting clinician whether the patient is likely to benefit from its application. In this analysis the quality of supporting medical data needs to be considered as well as the patient's condition. The acting clinician should also correctly appraise his or her competence to apply this recommendation
Quality of evidences (QoE)		
+++	High quality data obtained from randomized clinical trials (RCT) or from unequivocal results of retrospective analyses directly concerning the subject of recommendation	
++	Moderate quality data obtained from studies judged by the EBM approach to be methodologically deficient or the conclusions of which are equivocal or indirect	
+	Low quality data based on case studies or on clinical observations only	
PolCon	Lack of direct data with regard to the conditions in Poland. The statement is based on a consensus reached via discussion among Polish experts (the number of Polish experts in support of this statement is given in parentheses)	

recommendations referring to medullary thyroid cancer (ATA GL MTC) [6].

We also wish to remind the reader that the Polish recommendations established in November 2015 were developed as a consensus based on the earlier-published Recommendations of the American Thyroid Association (ATA). These meticulously prepared recommendations (ATA GL) contained full references to published medical evidence. At the time, the Polish experts believed that reliance on ATA recommendations would be sufficient, but a consensus should be reached as to which of these recommendations would apply in the Polish conditions. In our current update of the Polish recommendations we were, however, aware that any oncological recommendations must be based on medical evidence. In the currently published Update of these Recommendations we were able to extend our 2016 Recommendations by adding the relevant medical evidence. We are also aware that future work on the Polish Recommendations will enable further, more accurate medical evidence relevant to the Polish conditions, to be included.

I. Diagnostics of thyroid cancer

1. Indications for thyroid ultrasound [5]:

- 1.1. Nodular goitre or palpable thyroid nodule
SoR: G1; QoE: +++; ATA GL R6
- 1.2. Neck lymph node enlargement not related to infection. SoR: G1; QoE: PolCon 62/62
- 1.3. Thyroid enlargement without any palpable tumour.
SoR: G1; QoE: PolCon 62/62
- 1.4. Thyroid lesion detected by ultrasonography performed due to other reasons or by other imaging tools.
SoR: G1; QoE: +++; ATA GL R6

1.5. RET germline mutation carriage and/or high serum calcitonin (Ct) concentration [6].

SoR: G1; QoE: +++; ATA GL MTC

1.6. History of exposure to previous neck radiation [7].
SoR: G1; QoE: +++

1.7. Other suspicion of thyroid disease.
SoR: G1; QoE: PolCon 62/62

1.8. Neck ultrasound is not a screening tool [8].
SoR: G2; QoE: PolCon 62/62

1.9. There is no sufficient evidence to recommend or not to recommend screening neck ultrasound in persons with a risk of familiar differentiated thyroid cancer (DTC) arising from the follicular cell.
SoR: G2; QoE: PolCon 62/62

1.10. Neck ultrasound together with physical examination is sufficient to exclude nodular goitre.
SoR: G1; QoE: PolCon 62/62

2. Other useful diagnostic examinations in nodular goitre include:

2.1. In every case of nodular goitre: TSH. If TSH is abnormal, assessment of serum fT4 or fT4/fT3 is recommended [4].

SoR: G1; QoE: ++; ATA GL R2

2.2. Anti-thyroid peroxidase antibodies (TPOAb) and other anti-thyroid antibodies, depending on experience of the particular centre.
SoR: G2; QoE: PolCon 61/62

2.3. Assessment of serum calcitonin (Ct) concentration is useful in diagnostics of nodular goitre, but it is not recommended in every case, due to low risk of medullary thyroid cancer (MTC). However, Ct assessment is useful [6].
SoR: G2; QoE: ++; PolCon 62/62; ATA GL 4

2.3.1. If there is clinical suspicion of MTC, and in RET mutation carriers [6].
SoR: G1; QoE: +++

- 2.3.2. To exclude MTC prior to planned thyroid surgery (see par. 3.3.1).
SoR: G2; QoE: PolCon 62/62
- 2.4. Assessment of serum thyroglobulin (Tg) is not recommended, as it provides no essential information on suspected malignancy in a thyroid lesion.
SoR: G1; QoE: ++; ATA GL R3 and R34
- 2.5. ^{99m}Tc thyroid scan is recommended only if TSH is close to, or below the lower limit of normal range, in a patient with nodular goitre [9].
SoR: G2; QoE: ++
- 2.6. Elastography is not routinely required in the assessment of thyroid lesions; however, it may be helpful in the selection of a thyroid lesion amendable to fine-needle aspiration biopsy (FNAB) [10–12].
SoR: G2; QoE: PolCon 62/62
- 2.7. MRI and CT are not routinely used in the evaluation of thyroid nodules [9].
SoR: G1; QoE: PolCon 62/62
- 2.8. FDG-PET-CT is not recommended in differential diagnostics of thyroid nodules [9].
SoR: G1; QoE: +; ATA GL R5 and R18
3. Features of increased malignancy risk in a thyroid lesion, evaluated prior to FNAB:
- 3.1. Clinical
- 3.1.1. Lymph node and/or distant metastases (see par. 11.2) [8].
SoR: G1; QoE: ++; ATA GL R9-R8
- 3.1.2. History of previous neck exposure to radiation [7].
SoR: G1; QoE: +++; ATA GL R2 and R20
- 3.1.3. History of familial thyroid cancer (it concerns MTC) [8].
SoR: G2; QoE: +; ATA GL R1
- 3.1.4. Clear tumour growth. Note that benign lesions may grow at the same rate [5–8].
SoR: G1; QoE: PolCon 62/62
IMPORTANT NOTICE: Rapid lesion enlargement (within a few weeks) may strongly suggest anaplastic thyroid cancer, requiring urgent consultation by an oncologist and/or oncological endocrinologist.
SoR: G1; QoE: PolCon 62/62
- 3.1.5. Hard nodule attached to neighbouring tissues.
SoR: G1; QoE: +
- 3.1.6. Tumour over 4 cm in diameter.
SoR: G1; QoE: +/PolCon 62/62; ATA GL R20
- 3.1.7. Nodule occurrence before 20 years of age.
SoR: G1; QoE: +/PolCon 62/62
- 3.1.8. Nodule occurrence after 60 years of age.
SoR: G1; QoE: +/PolCon 62/62
- 3.1.9. Paresis of recurrent laryngeal nerves, particularly unilateral.
SoR: G1; QoE: +/PolCon 62/62
- 3.2. Sonographic [5]:
- 3.2.1. Sonographic features suggesting probability of thyroid cancer metastases to cervical lymph nodes (see also par. 11.2.2) [1, 9].
SoR: G1; QoE: +++
- 3.2.2. Thyroid capsule infiltration with or without infiltration of adjacent neck structures.
SoR: G1; QoE: ++
- 3.2.3. Microcalcifications inside the thyroid lesion.
SoR: G1; QoE: +++/PolCon 62/62
- 3.2.4. Solid, hypoechoic tumour pattern.
SoR: G1; QoE: +++
- 3.2.5. Tumour shape (taller than wider).
SoR: G1; QoE: +/PolCon 62/62
- 3.2.6. Irregular tumour margins.
SoR: G1; QoE: +/PolCon 62/62
- 3.2.7. Increased tumour vascularisation.
SoR: G1; QoE: +
IMPORTANT NOTICE! Sonographic appearance of follicular neoplasms, including thyroid carcinoma, often does not present the above-mentioned sonographic risk features — lesions have regular margins, they could be isoechoic without microcalcifications.
SoR: G1; QoE: +
4. Indications for FNAB of a thyroid lesion:
- 4.1. Thyroid lesion ≥ 1 cm in at least one dimension and ≥ 5 mm in other dimensions, if there are no other lesions showing a higher risk of malignancy (evaluated according to rules given in par. 3), which require FNAB first — see par. 5 concerning multiple thyroid lesions.
SoR: G1; QoE: PolCon 62/62; ATA GL R7 and R8
- 4.2. A thyroid lesion below 1 cm in the greatest dimension if clinical or sonography risk features of malignancy are present and reliable FNAB is possible.
SoR: G1; QoE: PolCon 62/62; ATA GL R8
- 4.2.1. Sonography follow-up of a thyroid lesion below 1 cm in the greatest dimension every 3–6 months, depending on clinical risk, and postponement of FNAB until tumour diameter reaches 1 cm, is acceptable.
SoR: G1; QoE: PolCon 62/62; ATA GL R8

- 4.3. Thyroid lesions, regardless of their diameter, if lymph node or distant metastases from thyroid cancer, high calcitonin concentration or RET mutation carriage are present if reliable FNAB is possible.
SoR: G1; QoE: PolCon 62/62
5. Indications for FNAB in multifocal thyroid lesions [9]:
- 5.1. The risk of thyroid cancer in a patient with multifocal thyroid lesions and a single thyroid lesion are comparable [8].
SoR: G1; QoE: +++; ATA GL R21
- 5.2. The optimal strategy assumes selection of thyroid lesions for FNAB depending on their malignancy risk (lesions presenting the highest risk features should undergo biopsy first) and carrying out biopsy in all lesions in which it is indicated, or in at least four lesions with the highest clinical and sonography risk features.
SoR: G1; QoE: ++/PolCon 62/62
- 5.3. If a negative FNAB result is obtained in all lesions, selected as above, exclusion of malignancy risk may be considered with reasonable probability. In cases of sequential biopsy procedures all above-determined biopsy sites should be investigated within the following 3–6-month period, depending on risk assessment.
SoR: G1; QoE: + / PolCon 62/62
- 5.4. If thyroid lesions are multiple, they have a similar sonographic pattern and do not present significant features of malignancy, FNAB of the biggest lesion only is acceptable [5].
SoR: G1; QoE: + / PolCon 62/62
- 5.5. If diffuse changes in thyroid echostructure are present, indications for FNAB are relative and FNAB may be taken only from a single localisation. In such cases the National Cancer Institute (NCI) accepts biopsy without sonography guidance, particularly if thyroid is clearly enlarged [9].
SoR: G1; QoE: + / PolCon 62/62
- 5.6. Elastography may be helpful in the selection of a lesion for FNAB; however, it is not obligatory [10–14]
SoR: G1; QoE: PolCon 62/62
6. Indications for FNAB after diagnosis of thyroid lesion by other imaging modalities.
- 6.1. Thyroid lesions, incidentally detected in ultrasound performed for other reasons (such as Doppler ultrasound of carotid arteries), are subject to rules given in par. 3, 4, and 5.
SoR: G1; QoE: ++ / PolCon 62/62
- 6.2. Thyroid lesions, detected by CT or MRI, should be initially evaluated by ultrasound. Further management depends on the result of this ultrasound examination, subject to rules given in par. 3, 4, and 5.
SoR: G1; QoE: ++
- 6.3. Hot lesions, detected by FDG-PET, should be initially evaluated by ultrasound. Further management depends on the result of this ultrasound examination, subject to rules given in par. 3, 4, and 5. However, FNAB of a hot thyroid lesion on FDG-PET is obligatory [15, 16].
SoR: G1; QoE: + / PolCon 62/62 ATA GL R5
- 6.4. Hot lesions, detected incidentally by ^{99m}TcMIBI (a heart scan), should be initially evaluated by ultrasound. Further management depends on the result of this ultrasound examination, subject to rules given in par. 3, 4, and 5.
SoR: G1; QoE: ++ / PolCon 62/62
7. FNAB of a thyroid lesion is not advised:
- 7.1. In lesions less than 5 mm in all diameters FNAB is not routinely recommended due to low clinical risk with exceptions given in par. 4.3.
SoR: G1; QoE: PolCon 62/62
- 7.2. In pure cystic lesions, according to sonography criteria.
SoR: G1; QoE: ++; ATA GL R8
- 7.3. In lesions showing spongiform appearance on ultrasound in at least 50% of the lesion volume.
SoR: G2; QoE: + / PolCon 62/62; ATA GL R8
- 7.4. In lesions that appear as autonomous on the thyroid scan (so-called “hot nodule”) [9].
SoR: G2; QoE: ++; ATA GL 22
8. Cytological classification of lesions subjected to FNAB should be based on NCI guidelines, referred to the Bethesda System for Reporting Thyroid Cytopathology called “Bethesda Classification” in these “Recommendations” (Table II) [17, 18].
SoR: G1; QoE: ++ / PolCon 62/62; ATA GL R9
9. FNAB — execution and technique.
- 9.1. Requirements for ultrasound-guided FNAB [5, 9].
SoR: G1; QoE: PolCon 62/62; ATA GL R8 and R10
- 9.1.1. Concerning all FNAB procedures [5].
SoR: G1; QoE: PolCon 62/62; ATA GL R6
- 9.1.2. Ultrasound-guidance is recommended during biopsy of any thyroid lesion. It is not required in general thyroid enlargement with diffuse echostructure alterations with no clear lesions.
SoR: G1; QoE: PolCon 62/62
- 9.1.3. Ultrasound-guided FNAB is always required if FNAB is repeated due previous non-diagnostic result [4, 5].
SoR: G1; QoE: PolCon 62/62; ATA GL R10
- 9.2. Written, informed consent is always required.
SoR: G1; QoE: PolCon 62/62

Table II. The 2017 Bethesda System for Reporting Thyroid Cytopathology [17, 18]

Category	Recommended terminology	Risk of malignancy	Risk of malignancy considering NIFTP as postoperative outcome	The risk of malignancy in Polish patients	Cytological diagnoses included in a particular category and other comments
I	Nondiagnostic or unsatisfactory	5–10	5–10	5–10%*	Clinical context should be considered
II	Benign	0–3	0–3	< 1%*	Nodular goitre Thyroiditis, including chronic inflammations Hyperplastic nodule Colloid nodule (lots of colloid, sufficient cellularity) Cytological findings suggest colloid nodule (lots of colloid, insufficient cellularity) Thyroid cyst
III	Atypia of undetermined significance (AUS) or Follicular lesion of undetermined significance	~10–30	6–18	2.4–5.2%	This category should be used in rare cases when it is not possible to state a precise cytological diagnosis
IV	Follicular neoplasm or Suspicious for a follicular neoplasm	25–40	10–40	8.2–19%	At least 25% of lesions belonging to this category are not neoplastic tumors (hyperplastic nodules, inflammation). This category should not be diagnosed when nuclear features of papillary thyroid cancer are present
V	Suspicious for malignancy	50–75	45–60	75%	This category involves: — papillary thyroid cancer — medullary thyroid cancer — lymphoma — metastatic carcinoma — anaplastic thyroid cancer/vascular sarcoma due to the presence of necrotic tissues
VI	Malignant	97–99	94–96	95–100%*	This category involves: — papillary thyroid cancer — medullary thyroid cancer — lymphoma — metastatic carcinoma — anaplastic thyroid cancer/vascular sarcoma

*lack of Polish data — data given in the table are NCI data

10. Information, which should be provided in the referral form.

- 10.1. First name, last name, and address of the referring physician.
- 10.2. First name, last name of the patient or patient's identification number.
- 10.3. Patient's sex and age.
- 10.4. Initial clinical diagnosis.
- 10.5. Lesion location and diameter.

10.6. Data related to patient history (any primary cancer, exposure to neck irradiation, concomitant thyroid disorders).

10.7. Information related to administered treatment, if relevant to interpretation of cytological results.

10.8. Data about any previous FNAB (date, lesion location, diagnosis).

SoR: G1; QoE: PolCon 62/62

11. Selection of lesion for FNAB:

11.1. The selection of the lesion for FNAB is based on ultrasound according to the following rules [8, 9].

11.1.1. The main criterion is not lesion diameter but the presence of clinical and sonographic features of malignancy risk [9].

SoR: G1; QoE: +++; ATA GL R8

11.1.2. A large nodule requires several biopsies taken from different locations within the nodule [19].

SoR: G1; QoE: + / PolCon 62/62; ATA GL R

11.1.3. A cyst should be drained. If any of its solid part is present, FNAB is required. The liquid obtained by FNAB may undergo centrifuging and precipitation to prepare a smear [5].

SoR: G1; QoE: PolCon 62/62

11.2. In the case of neck lymph node enlargement [5].

11.2.1. If a thyroid nodule is accompanied by the presence of a suspicious lymph node, the lymph node should also undergo FNAB.

SoR: G1; QoE: ++

11.2.2. Sonography features of suspected metastatic lymph node are: transversal diameter greater than 5 mm, loss of hilar architecture, heterogenic echotexture with cystic areas, round shape, peripheral or mixed vascularity, microcalcifications [9].

SoR: G1; QoE: +++

12. Representativeness of FNAB.

12.1. Qualitative and quantitative assessment of the representativeness of a cytological aspirate is obligatory [17].

SoR: G1; QoE: PolCon 62/62

12.2. Qualitative evaluation is expressed dichotomously as satisfactory or unsatisfactory and should consider the differences related to lesion type (see par. 13.1) [17].

SoR: G1; QoE: PolCon 62/62

12.3. The following grading of quantitative assessment is recommended:

12.3.1. Diagnostic material: at least five groups of cells containing at least 10 well-preserved follicular cells. It is necessary to consider the clinical context when preparing this assessment.

SoR: G1; QoE: PolCon 62/62

12.3.2. Diagnostic material, in spite of its poor cellularity (see par. 14.1).

SoR: G1; QoE: PolCon 62/62

12.3.3. Non-diagnostic material, due to lack of, or small number of follicular cells.

SoR: G1; QoE: PolCon 62/62

12.3.4. Cyst liquid only.

SoR: G1; QoE: ++

13. Qualitative assessment of FNAB — clinical and radiological aspects [20].

13.1. Solid thyroid nodules.

13.1.1. With cytological cellular features indicating suspicion of malignancy (cellular atypia), a variant of Bethesda, class III category. Diagnosis of cells suspected of malignancy in a cytological smear must be given in the final FNAB report, even if the number of cells is small (see point 12.3.2, 14.3.4.2.) [20].

SoR: G1; QoE: + / PolCon 62/62

13.1.2. With inflammation [17, 19].

In this case the aspirate may contain fewer follicular cells; therefore, fulfilling the criterion of par. 12.3.1 is not absolutely crucial. The criterion given in point 12.3.2 should then be considered.

SoR: G2; QoE: +

13.1.3. With large colloid amount.

The presence of a large colloid amount is a reliable proof of a tumour being benign, so FNAB may be diagnostic despite its poor cellularity [17].

SoR: G2; QoE: + / PolCon 62/62

13.1.4. With follicular hypertrophy and small colloid amount.

Criterion 12.3.1 is optimal, particularly if fulfilled in one smear. However, excessively restrictive requirements regarding sample cellularity and quality may increase the percentage of non-diagnostic FNABs to 20% or higher [17].

SoR: G1; QoE: PolCon 62/62

13.2. Cysts.

13.2.1. Pure cyst (sonography criterion): the risk of cancer 1–4% [5, 9].

Aspiration of a pure cyst very rarely involves cancer diagnosis. The use of criterion 12.3.4 makes a clinically useful report possible. Adding the description “non-diagnostic material to fully exclude appearance of cystic cancer” may be considered.

SoR: G1; QoE: +

13.2.2. According to this consensus, in such cases FNAB of the solid part of the nodule should be performed.

SoR: G1; QoE: PolCon 62/62

14. Recommended diagnostic terminology.

It is recommended that six classes of cytological diagnosis be used, according to the Bethesda Classification [18, 20].

14.1. Non-diagnostic FNAB (Bethesda class I).

14.1.1. The FNAB result is defined as non-diagnostic if it does not fulfil representativeness criteria (see par. 12), considering the clinical-radiological context (see par. 13).
SoR: G1; QoE: PolCon 62/62; ATA GL R9

14.1.2. Non-diagnostic FNAB may be related to three causes [5]:

14.1.2.1. Inadequate cellularity.

14.1.2.2. Lack of follicular cells.

14.1.2.3. Incorrect sample fixation and storage.

SoR: G1; QoE: ++

14.2. Benign nodule (Bethesda class II).

This term represents final diagnosis of nodular goitre, thyroiditis (acute, subacute, and autoimmune), a single hyperplastic, or a colloid nodule. The risk of malignancy is minimal [18, 21]. See also par. 24.2.2.

SoR: G1; QoE: +++

14.2.1. The diagnosis of a "benign nodule" formally involves also the diagnosis of follicular adenoma; therefore, some centres apply the statement "FNAB negative with reference to malignancy" or "non-malignant lesion". The guidelines recommend the statement "benign lesion" in such a case.

SoR: G1; QoE: PolCon 62/62

14.2.2. FNAB smear should contain an adequate number of cells. If the number of cells is too small and a repeated FNAB shows mainly colloid and also few cells, the appearance of which does not suggest malignancy, the diagnosis "cytological picture suggests a colloid lesion/nodule" is recommended.

SoR: G1; QoE: PolCon 62/62

14.3. Follicular lesion of undetermined significance (Bethesda class III) [22, 23].

14.3.1. This diagnosis should be stated as rarely as possible [17].

SoR: G1; QoE: PolCon 62/62

14.3.2. This diagnostic category may be stated after exclusion of the five remaining Bethesda classes, to represent cytological findings that fulfil neither qualitatively nor quantitatively the "suspicious for a follicular neoplasm" or "suspicious for malignancy" criteria.

SoR: G2; QoE: + / PolCon 62/62

14.3.3. Qualification of Bethesda class III may be related to sample limitations (low cellularity, blood admixture, incorrect fixation), if cellular features do not un-

equivocally indicate their benign character or even if malignancy is suspected. Pathologist's comment is necessary.

SoR: G1; QoE: PolCon 62/62

14.3.4. In many centres this category is divided to two subcategories [4, 17]:

14.3.4.1 The first one is a "follicular lesion of undetermined significance — FLUS" — these lesions are characterised by a highly cellular smear, the presence of rosette architecture, variability of eosinophilic cytoplasm, and paucity of colloid.

SoR: G2; QoE: + / PolCon 62/62; ATA GL R15

14.3.4.2 The second subcategory is "Atypia of undetermined significance — AUS" — strong nuclear polymorphism, nuclear heterochromia, single grooves and nuclear clearances, macronucleosis in lesions, which have been not subjected to any previous therapy. The AUS subcategory indicates risk of malignancy at least two-times higher than that of the FLUS subcategory and mainly concerns thyroid cells with features suggesting papillary thyroid cancer (PTC).

SoR: G2; QoE: + / PolCon 62/62; ATA GL R15

14.3.5. The criteria that differentiate between categories "follicular lesion of undetermined significance" and "suspicious for a follicular neoplasm" are given in Table III.

According to Polish data, the risk of malignancy in follicular lesions of undetermined significance ranges between 2.4% and 5.2% [22–24]. So far, the vast majority of such lesions in Poland were benign nodules or follicular neoplasms demonstrating low risk of malignancy. Thereby, according to the authors of these guidelines the diagnosis of a follicular lesion of undetermined significance should not constitute in itself an indication for surgery. It has not yet been proven in Poland that this diagnosis significantly increases the risk of malignancy compared with benign nodules [21, 23, 25].

SoR: G2; QoE: + / PolCon 62/62

Table III. Cytologic criteria for diagnosis of „follicular lesion of undetermined significance” „suspicion for a follicular neoplasm”

Feature	Follicular lesion of undetermined significance	Suspicious for a follicular neoplasm
Hypercellular aspirate (subjective)	Rather yes	Yes
Prominent population of small arrangement (groups, nests, rosets)	Yes	Yes
Sheets of follicular cells	Might be seen	No or single
Colloid in background	Might be seen	No or trace
Foamy macrophages	Might be present	No or single
Anisocytosis/anisokaryosis	No or a little	No
Lymphocytes/plasmatic cells	No or single	No
Oncocytes	Non significant	If > 75% of cells — there is a suspicion for an Hurthle neoplasm Oncocytes have prominent nucleoli Anisocytosis of oncocytes Oncocytes in spatial arrangements
Indication for surgery	No	Yes, after confirmation of the second pathologist
Indication for a repeated FNAB	Yes	Rather no

14.3.6. If Bethesda III category is stated on the basis of abnormalities in a cell structure, a higher risk of malignancy has to be considered.

SoR: G2; QoE: PolCon 62/62

14.3.7. Particular caution in interpretation is required in diagnosis of a follicular lesion of undetermined significance in small lesions not exceeding 1 cm in any dimension.

SoR: G2; QoE: PolCon 62/62

14.3.8. Follicular lesion of undetermined significance constitutes a substitute diagnosis that requires further correction, in correlation with clinical and sonographic features of the lesion during the next FNAB (see par. 25).

SoR: G2; QoE: PolCon 62/62

14.4. Suspicious for follicular neoplasm (Bethesda class IV) [25, 26].

14.4.1. NCI recommends the statement “Suspicious for follicular neoplasm” because 25% of these nodules are not in fact neoplasms [17]. Diagnostic criteria are given in Table III.

SoR: G1; QoE: ++

14.4.2. This class involves lesions previously known as either “follicular/oncocytic neoplasm” or “follicular/oncocytic tumour”. It should not involve lesions that show nuclear features of papillary thyroid cancer (see par. 14.4.8).

SoR: G2; QoE: PolCon 62/62

14.4.3. “Suspicious for a Hurthle-cell neoplasm” (previously “suspicious for an oncocytic/oxyphilic neoplasm”; see also par. 14.4.8).
SoR: G2; QoE: PolCon 62/62

14.4.4. The risk of malignancy of a lesion “suspicious for a follicular neoplasm” in Poland is 8.2–19% [21, 25, 26] and depends on the centre. Therefore, the decision concerning surgery may be made with reference to the centre’s experience.

SoR: G2; QoE: PolCon 62/62

14.4.5. The diagnosis of “suspicious for a follicular neoplasm” should be stated in cases when the pathologist anticipates the necessity of surgery and final histopathological diagnosis [17, 25].

SoR: G1; QoE: +++

14.4.6. Considering this diagnosis, the risk of cancer should be evaluated individually together with clinical-epidemiological factors [20, 26].

SoR: G2; QoE: PolCon 62/62

14.4.7. If the diagnosis “suspicious for a follicular neoplasm” is an indication for surgery it should be confirmed by another pathologist.

SoR: G2; QoE: PolCon 62/62

14.4.8. This statement may reflect a final histopathological diagnosis of a follicular adenoma, follicular carcinoma, and follicular variant of papillary thyroid carcinoma, and their oxyphilic variants. However, it may also indicate a non-

neoplastic lesion such as a hyperplastic tumour showing a high cellularity or lymphocytic thyroiditis (in which disturbances of cell structure are often present, see par. 13.1.1). Therefore, the statement “suspicious for a follicular neoplasm”, recommended by NCI [18] is more adequate than “follicular tumour” or “follicular neoplasm” (these statements may be used as clinical terms only, not as a cytological diagnosis) [20, 26].

— We recommend using the term “Bethesda category IV” due to the difficulty in appropriate Polish translation.

— The diagnosis “suspicious for a follicular neoplasm” also involves a subclass “suspicious for Hurthle-cell neoplasm”.

— Because the authors of a new WHO classification accepted the evidence that oxyphilic adenomas and carcinomas are separate neoplasms and should not be treated any more as a variant of follicular neoplasms, the authors of current guidelines recommend the use of a “Hurthle neoplasm” category. To maintain consistency with Bethesda IV category the diagnosis “suspicious for Hurthle-cell neoplasm” should be used. If a pathologist diagnoses follicular cells with oxyphilic metaplasia (oncocyctic) one should not use the term “Hurthle cells” to facilitate an interpretation of cytological diagnosis and differentiation between lesions suspicious for a neoplasm and non-neoplastic lesions: (ex. inflammatory lesions, showing oxyphilic metaplasia).

SoR: G2; QoE: PolCon 62/62

14.5. Suspicious for malignancy (Bethesda class V).

14.5.1. Such a statement means that some features of malignant tumours are present but not all that would allow a diagnosis of malignancy. According to the Polish data, the risk of cancer ranges between 50 and 75% [21, 27].

SoR: G1; QoE: + / PolCon 62/62

14.5.2. Suspicion for papillary thyroid carcinoma most often concerns its follicular variant [17].

SoR: G1; QoE: ++ / PolCon 62/62

14.5.3. Suspicion for MTC should be accompanied by serum calcitonin assessment (basal Ct > 100 pg/mL allows MTC to be diagnosed with high probability) [6].
SoR: G1; QoE: +++ / PolCon 62/62; ATA GL MTC

14.5.4. Suspicion for lymphoma requires a second FNAB and flow cytometry [17].
SoR: G1; QoE: ++ / PolCon 62/62

14.6. Malignant tumours (Bethesda class VI) [17].

14.6.1. This category involves the diagnosis of papillary thyroid cancer, anaplastic thyroid cancer, or metastatic carcinoma.
SoR: G1; QoE: +++; ATA GL R12

14.6.2. MTC diagnosis and localisation of primary focus of a metastasis from other cancer and lymphoma require immunocytochemistry [17].
SoR: G1; QoE: PolCon 62/62

14.6.3. In the diagnosis of Bethesda class VI, the decision about surgery is obvious.

SoR: G1; QoE: PolCon 61/62 ATA GL R12

15. FNAB report.

FNAB report should contain:

15.1. Information related to the nodule location and its features enabling its identification [9].

SoR: G1; QoE: PolCon 62/62

15.2. Information concerning FNAB representativeness, both qualitative and quantitative [20].

SoR: G1; QoE: PolCon 62/62

15.3. Description of cytological examination of each nodule assessed.

SoR: G1; QoE: PolCon 62/62

15.4. Diagnostic conclusion that classifies FNAB findings to one of six Bethesda classes (Table II). See par. 16) [20].

SoR: G1; QoE: +++ / PolCon 62/62; ATA GL R9

15.5. IMPORTANT NOTICE: It is recommended that a comment be attached to the FNAB report [17].

SoR: G1; QoE: PolCon 62/62

16. Unacceptable diagnostic terminology.

16.1. The following statement should be avoided:

16.1.1. “Atypical cells have not been found”, “bloody smear”, “malignancy features have not been found”.

SoR: G1; QoE: PolCon 62/62

16.1.2. All examples given in par. 16.1.1 should unequivocally evaluate whether the FNAB result is benign (Bethesda II) or non-diagnostic (Bethesda I) [20].

SoR: G1; QoE: PolCon 62/62

16.1.3. One must not use the statement “FNAB result may arouse suspicion for a follicular tumour”.

SoR: G1; QoE: PolCon 62/62

16.1.4. The statement given in par. 16.1.3 does not provide the clinician with sufficient information about whether a pathologist formally diagnoses “suspicious for a follicular neoplasm” or whether there are some data suggesting this diagnosis but not sufficient to support it. In such cases the pathologist should consider whether or not to state a diagnosis of “follicular lesion of undetermined significance”, which is clear for a clinician because it gives information that the nodule requires further diagnostics. Additional information “suspicion for a follicular neoplasm is not excluded” or “suspicion for a follicular neoplasm was considered but not all criteria are fulfilled” is also acceptable.

SoR: G1; QoE: PolCon 62/62

17. FNAB reliability and limitations.

17.1. Differentiation between follicular carcinoma and adenoma on the basis of cytological examination is not possible [20].

SoR: G1; QoE: PolCon 62/62

17.2. Because there is always a risk of a false negative result of FNAB clinicians should evaluate the presence of clinical features of malignancy indicating surgical treatment [21].

SoR: G2; QoE: PolCon 62/62; ATA GL R23 and R24

17.3. This risk is usually related to insufficient sample cellularity, incorrect aspiration, wrong interpretation, or the occurrence of cystic form of thyroid carcinoma [18, 20].

SoR: G2; QoE: PolCon 62/62

17.4. The risk of false positive result is 1%.

SoR: G2; QoE: + / PolCon 62/62

18. Contraindications to FNAB [28].

18.1. Absolute.

18.1.1. Serious haemorrhagic diathesis.

18.1.2. Purulent skin lesions.

18.1.3. Lack of patient’s cooperation.

SoR: G1; QoE: PolCon 62/62

18.2. The use of anticoagulant drugs.

18.2.1. Acenocoumarol and Warfarin.

The authors of these recommendations believe, after consultation with specialists, that the use of acenocoumarol and warfarin does not constitute an absolute contraindication to FNAB, especially when a 0.4-mm diameter needle is used and INR ranges between 2.5–3. Replacement by a low molecular weight heparin may be considered.

SoR: G2; QoE: +++ / PolCon 62/62

18.2.2. Low molecular weight heparin.

An eight-hour interval between the last dose of the drug and FNAB is necessary.

SoR: G2; QoE: + / PolCon 62/62

18.2.3. Dabigatran (Pradaxa).

A 12-hour interval between the last dose of the drug and FNAB is necessary.

SoR: G2; QoE: + / PolCon 62/62

18.2.4. Rivaroxaban (Xarelto).

A 24-hour interval between the last dose of the drug and FNAB is necessary.

SoR: G2; QoE: + / PolCon 62/62

18.2.5. Clopidogrel.

If, for cardiological reasons, drug withdrawal is contraindicated, FNAB is acceptable in a patient using clopidogrel only if there is an absolute indication for FNAB. Replacement with a low molecular weight heparin is not justified due to the differences in the mechanisms of action of both drugs.

SoR: G2; QoE: + / PolCon 62/62

18.2.6. Acceptable drugs:

— Aspirin with doses < 0.3 g.

— Non-steroidal anti-inflammatory drugs.

SoR: G2; QoE: ++ / PolCon 62/62

19. FNAB complications [28].

19.1. Transient.

19.1.1. Haematoma (prevention — compression of FNAB site following biopsy. If deeply located lesions are aspirated, 30-minute observation is recommended).

SoR: G2; QoE: PolCon 62/62

19.1.2. Pain and oedema (prevention — ice compress, paracetamol).

SoR: G2; QoE: PolCon 62/62

19.1.3. Syncope.

SoR: G2; QoE: PolCon 62/62

19.1.4. Infection (rare even in patients with immune deficiency), increased risk in patients infected with HIV or with diagnosis of diabetes mellitus, tuberculosis, atopic dermatitis.

19.1.4.1. Staphylococcal infection. If skin hygiene is poor, skin should be thoroughly disinfected.

SoR: G2; QoE: PolCon 62/62

19.2. Serious — extremely rare.

19.2.1. Needle tract implantation from thyroid carcinoma has never been reported with reference to 23-gauge or smaller needle. These complications concerned mostly core biopsy.

SoR: G2; QoE: PolCon 62/62

19.2.2. Recurrent laryngeal nerve palsy (the total risk is 0.036%) — dysphonia and dysphasia typically develop on the second day after FNAB, and recovery takes up to four months.

SoR: G2; QoE: PolCon 62/62

19.2.3. Haemorrhage or haematoma requiring surgery.

SoR: G2; QoE: PolCon 62/62

20. Immunocytochemistry.

Immunocytochemistry in FNAB aspirate may provide some information, crucial for the diagnosis. "Cell block" technique is a preferable method mainly due to the possibility to perform a few reactions at the same time and simultaneously to evaluate some features of cell architecture like papillary or tubular structures. The Tg and Ct expression should be evaluated to confirm thyroid origin of the neoplasm. It is characterised by a high specificity. However, it is difficult for interpretation, particularly in smears (membrane and cytoplasmic reaction) and due to diffusion-related artefacts. The evaluation of TTF-1 and PAX 8 is characterised by a high sensitivity but low specificity. Therefore, if their expression has been demonstrated, it requires an additional evaluation of Tg expression. To establish the origin of metastatic thyroid tumour, considering the frequency of occurrence and similarity in cytological pictures, one should exclude:

- renal cancer (RCC+, PAX2+, CD10+) [29];
- lung adenocarcinoma (napsin A+, PAX8+, TTF-1+, Tg-), squamous cell carcinoma (p63+) [30];
- head and neck squamous cell carcinoma (p63, CK 5,6) [31];
- breast cancer (GATTA3+) [32];
- malignant melanoma (SOX10+, HMB45) [33];
- colon adenocarcinoma (CDX2+);
- if there is a suspicion of parathyroid tumour, the assessment of PTH concentration in FNAB wash-out is helpful;
- diagnosis of anaplastic thyroid carcinoma (ATC) may be confirmed by PAX8 expression (TTF-1 and Tg may be negative), p54 and a high mitotic activity of cancer cells in smear (Ki-67 > 30%).

SoR: G1; QoE: PolCon 62/62

21. Further follow-up after non-diagnostic FNAB [5].

21.1. Cyst.

In the case of a pure sonographic cyst without any solid part and failure of the first FNAB in obtaining diagnostic material, a repeated FNAB may be considered within 6–18 months. The risk of cancer is low, but not excluded [34]

SoR: G2; QoE: PolCon 61/62

21.2. Solid nodule.

A solid nodule, clinically benign with a non-diagnostic FNAB result requires a clinical and/or sonography follow-up and repeated FNAB, usually within 3–12 months, depending on clinical and sonography risk (see par. 3).

SoR: G2; QoE: PolCon 61/62

21.3. Solid nodule with cystic degeneration.

In the case of the first FNAB being non-diagnostic, repeated FNAB is indicated within 3–12 months. The solid part should be biopsied [5, 9] ATA consider surgical treatment in the case of non-diagnostic FNAB. The authors of these recommendations propose that in such a case the clinical and sonography risk factors of malignancy (see par. 3) should be relied upon.

SoR: G1; QoE: PolCon 61/62; ATA GL R10

22. Interval between non-diagnostic and second FNAB.

22.1. This interval should not be shorter than three months, unless clinical features strongly suggest a very high risk of malignancy (suspicion of poorly differentiated or anaplastic thyroid carcinoma or lymphoma), or an incorrect FNAB procedure is highly probable.

SoR: G2; QoE: PolCon 62/62

22.2. In the vast majority of cases, where the clinical risk is not high, repeated FNAB may be performed 6–12 months later [19].

SoR: G2; QoE: PolCon 62/62

23. Two non-diagnostic FNABs:

23.1. Two non-diagnostic FNABs in a cyst. If two FNABs in a pure cyst are non-diagnostic, it should be taken into consideration that cancer risk is very small (1%); however, it cannot be definitely excluded [5, 8, 9].

SoR: G2; QoE: PolCon 62/62

23.2. Two non-diagnostic FNABs in a solid lesion [5]

23.2.1. Due to the lack of cancer exclusion and possible higher probability of its detection, surgery should be considered depending on clinical and sonography risk factors [8, 9].

SoR: G2; QoE: PolCon 62/62

23.2.2. In the case of two non-diagnostic FNABs in a nodule subjected for further follow-up, subsequent FNAB performed in another centre, should be considered.

SoR: G2; QoE: PolCon 62/62

23.2.3. In the case of a significant lesion growth, surgery should be considered unless the clinical context explains the lack of adequate FNAB material [5], see also par. 13.

SoR: G2; QoE: PolCon 62/62

23.2.4. If neither nodule growth nor sonography risk factors are present, surgical treatment may be considered with reference to the clinical context and a decision is made together with the patient.
SoR: G2; QoE: PolCon

23.2.4.1. In a lesion < 1 cm in any diameter, which does not show significant growth and clinical risk factors and sonography features of invasiveness, surgery is not indicated.
SoR: G2; QoE: PolCon 62/62

24. Further follow-up after the diagnosis of a benign nodule on FNAB.

24.1. Benign FNAB result does not unequivocally negate surgery.
SoR: G1; QoE: + / PolCon 62/62

24.2. Follow-up of a solid nodule, with a benign FNAB result.

If clinical indications and the results of other examinations together with patient's preference do not indicate surgery, further follow-up should consider that the risk of malignancy in a nodule which has undergone FNAB is significantly lower than that in a nodule that had not been biopsied [35].

SoR: G1; QoE: ++ / PolCon 62/62

24.2.1. A solid nodule, benign on FNAB, requires clinical follow-up (physical examination or ultrasound) every 6–18 months.

SoR: G1; QoE: +++ / PolCon 62/62

24.2.2. Repeated FNAB is not required if no clinical doubt exists and the quality of the first FNAB is good. The frequency of the detection of thyroid cancer in histopathology examination in patients with a benign FNAB result, subjected to surgery without a repeated FNAB in Poland, is 3.6% [19].

SoR: G1; QoE: ++ / PolCon 62/62

24.2.3. Repeated FNAB in a lesion demonstrating sonography risk features of malignancy with a benign FNAB result, makes the diagnosis more reliable and diminishes the risk of cancer omission.

SoR: G1; QoE: PolCon 62/62

24.2.3.1. If no clinical risk factors exist, no tumour growth is observed, and no new sonography risk features have occurred, a repeated FNAB is usually indicated no earlier than after 6–12 months.

SoR: G1; QoE: PolCon 62/62

24.2.3.2. If the aggravation of sonography risk features is significant, particularly if signs of nodule invasiveness are present (par. 3.2), FNAB may be repeated earlier — no later than 3–6 months after [9].

SoR: G1; QoE: ++ / PolCon 62/62

24.2.3.3. In other lesions with risk features of malignancy, the time of repeated FNAB depends on the magnitude of clinical risk [9].

SoR: G2; QoE: PolCon 62/62

24.2.4. Indications for a repeated FNAB within 6–12 months may be related to nodule growth, the presence of clinical risk factors, or the lower reliability of the first FNAB — due to the very small lesion diameter or nodule location in the dorsal part of the thyroid lobe, leading to an increased risk of missing the lesion during FNAB.

SoR: G2; QoE: PolCon 62/62

24.2.4.1. An increase of the nodule size is not a sufficient criterion of its malignancy [34], but it constitutes an indication for a repeated FNAB (if its enlargement by 20% in every diameter within one year is observed).

SoR: G2; QoE: PolCon 62/62

24.2.4.2. The occurrence of new sonography high-risk features of malignancy in a benign nodule on the previous FNAB indicates the need for a repeated FNAB.

SoR: G1; QoE: +++ / PolCon 62/62

24.3. The recommendations given in par. 24.1–2 also concern solid-cystic nodules. Repeated FNAB is indicated if the solid part of the nodule grows significantly.

SoR: G2; QoE: PolCon 62/62

24.4. Further follow-up is acceptable, even if significant nodule growth is observed, if the repeated FNAB gives a benign result [34].

SoR: G2; QoE: PolCon 62/62

25. Further follow-up after diagnosis of a follicular lesion of undetermined significance.

25.1. The risk of cancer in such lesions is probably no higher than 5%. According to the Polish data, it ranges between 2.4% and 5.2%.

SoR: G2; QoE: ++ / PolCon 62/62

25.2. Follow-up (repeated sonography every six months), and repeated FNAB in 6–12 months

- (no sooner than after three months, due to the risk of the presence of repair changes), are recommended.
SoR: G2; QoE: PolCon 62/62
- 25.3. If sonographic risk factors of malignancy are present (see par. 3.2) or the FNAB reports disturbances in cell architecture suggesting malignancy, a repeated FNAB is recommended after a 3–6-month interval, depending on the clinical risk. If a similar result is obtained, surgery has to be considered, particularly if strong sonography risk factors or features of lesion invasiveness (see par. 3.2) are present or the FNAB report suggests malignancy.
SoR: G2; QoE: PolCon 62/62
- 25.4. Surgery is recommended in nodules > 4 cm, in smaller lesions if a significant nodule growth is present or if the second FNAB indicates a higher cancer risk.
SoR: G2; QoE: ++ / PolCon 62/62
- 25.5. If a nodule with this diagnosis has an autonomous appearance in scintigraphy, further follow-up may be recommended, together with ¹³¹I treatment, because the risk of cancer does not exceed ≤ 2% [9].
SoR: G2; QoE: ++ / PolCon 62/62
26. Further follow-up after the diagnosis of a lesion “suspicious for a follicular neoplasm”.
- 26.1. It has to be re-emphasised that this diagnosis should be stated only in cases where the necessity of surgical treatment is anticipated — to obtain material and to perform the final histopathological examination [20].
SoR: G1; QoE: +++
- 26.1.1. The diagnosis has to be confirmed by another pathologist prior to surgery.
SoR: G2; QoE: PolCon 62/62
- 26.1.2. If such confirmation has been achieved, repeated FNAB provides no further essential information, especially if performed soon after the first biopsy.
SoR: G1; QoE: PolCon 62/62
- 26.1.3. If there is no possibility to consult the FNAB result, surgery is acceptable in the case of urgent clinical indications.
SoR: G2; QoE: PolCon 62/62
- 26.2. Indications for surgery if a lesion suspicious for a follicular neoplasm is diagnosed.
- 26.2.1. If the FNAB result is Bethesda IV, surgery should be considered in order to resolve diagnostic doubts, particularly if clinical or sonography risk features are present. The risk of malignancy related to this Bethesda category, observed in a particular centre has also to be considered.
SoR: G2; QoE: PolCon 62/62
- 26.2.2. Surgery constitutes the optimal way to establish the final diagnosis in the nodule classified as Bethesda class IV.
SoR: G1; QoE: +++
- 26.2.3. In small lesions (up to 1 cm), if clinical and sonography risk features are absent, resignation from surgery and follow-up are acceptable only under strict sonography and clinical monitoring.
SoR: G2; QoE: PolCon 62/62
- 26.2.4. If the FNAB result is suspicious for Hurthle-cell neoplasm, surgery is recommended due to the risk of cancer of at least 15%.
SoR: G2; QoE: PolCon 62/62
- 26.2.5. Intraoperative nodule examination does not usually contribute any important information.
SoR: G1; QoE: PolCon 62/62
- 26.3. If the decision is to resign from surgery and the nodule is to be further followed, a repeated FNAB may be performed no earlier than after three months, usually after six months.
SoR: G2; QoE: PolCon 62/62
27. Further management after the diagnosis of a suspicion for a malignant neoplasm on FNAB.
- 27.1. Suspicion for malignancy (category V according to the Bethesda classification) [35].
- 27.1.1. Surgery is recommended regardless of the presence of sonographic risk factors.
SoR: G1; QoE: PolCon 62/62
- 27.1.2. Confirmation of FNAB diagnosis by a second pathologist is necessary.
SoR: G2; QoE: PolCon 62/62
- 27.1.3. In the case of suspicion for malignancy, intraoperative histopathological examination may be considered.
SoR: G2; QoE: ++
28. Malignant neoplasm (category VI according to the Bethesda classification) [27].
- 28.1.1. Surgery is necessary.
SoR: G1; QoE: +++; ATA GL R12
- 28.1.2. Confirmation of FNAB diagnosis by a second pathologist is necessary.
SoR: G2; QoE: PolCon 62/62
- 28.1.3. In the case of preoperative diagnosis of anaplastic thyroid cancer, thyroid lymphoma, or metastases from other cancer, it is necessary to evaluate whether the tumour is amendable to surgery, and to establish further management. In the

case of anaplastic thyroid carcinoma, diagnostics should be performed without delay.

SoR: G2; QoE: PolCon 62/62

29. Indications for FNAB and its interpretation in children.

29.1. Childhood thyroid diseases have been covered in separate guidelines prepared by a group of designated specialists [36, 79].

29.2. In children surgery is undertaken more often because the risk of tumour malignancy is higher and it also concerns autonomous thyroid nodules [36, 37].

SoR: G1; QoE: ++

30. Indications for FNAB and its interpretation during pregnancy.

30.1. Indications for FNAB in pregnant women and other patients are the same.

30.2. The cytological diagnosis "suspicious for a follicular neoplasm" does not constitute an absolute indication for surgery during pregnancy. Surgery, if considered, may be performed after delivery if sonographic appearance is stable.

SoR: G2; QoE: + / PolCon 62/62 ATA GL R31

30.3. If low advanced papillary thyroid carcinoma is diagnosed during pregnancy, sonographic tumour monitoring should be undertaken. If the tumour diameter increases, surgery should be performed in the second trimester, before the 24th week of gestation. If the sonographic appearance is stable or cancer is diagnosed in the second half of pregnancy, surgery may be delayed until after delivery.

SoR: G2; QoE: ++ / PolCon 62/62; ATA GL R31

31. Intraoperative histopathological examination.

31.1. Imprint cytology and frozen section (using cryostat only) are included in the intraoperative histopathological examination. If the centre is equipped with instrumentation of newest generation, able to perform histopathological examination within 48 hours of surgery, no intraoperative examination is required.

SoR: G2; QoE: PolCon 62/62

31.2. If follicular lesion of undetermined significance or lesion suspicious for a follicular neoplasm is diagnosed, intraoperative histopathological examination is not recommended.

SoR: G2; QoE: PolCon 62/62

32. The role of core biopsy.

32.1. Core biopsy does not significantly improve the differentiation between cancer and follicular adenoma.

SoR: G2; QoE: +

32.2. Some insufficiency in the accuracy of the FNAB result, as compared to core biopsy, is compen-

sated by its simplicity, lower cost, and lower patient discomfort related to FNAB.

SoR: G2; QoE: +

32.3. If no other possibility to state diagnosis exists, core biopsy may replace FNAB.

SoR: G2; QoE: +

33. The role of FDG-PET in the evaluation of tumour malignancy.

33.3.1. FDG-PET is not recommended in differential diagnostics of thyroid nodules.

SoR: G2; QoE: + / PolCon 62/62 ATA GL R18

33.3.2. However, if FDG-PET is performed for other reasons, increased focal tracer uptake in the thyroid indicates a significant risk of malignancy. In such a case, one should follow par. 6.3 [15, 16].

34. Molecular diagnostics of thyroid nodules (gene expression profile and sequencing) extends initial diagnostics of thyroid cancer. Molecular tests help to distinguish between benign and malignant nodules, particularly in indeterminate FNAB results (Bethesda III-V). Such an examination is particularly recommended in centres experienced in molecular investigations. One should adhere to the rule that the patient has to be fully informed about the significance of the obtained results. Cost-effective molecular testing, available in Polish conditions, should be worked out.

SoR: G2; QoE: + / PolCon 62/62; ATA GL R13 and R14

II. Histopathological examination of postoperative thyroid material

SoR: G1; QoE: PolCon 62/62; ATA GL R46

1. Recommendation related to the preparation of the histopathological specimen after thyroid surgery.

1.1. The management.

1.1.1. Measure and weigh the specimen.

1.1.2. Mark with ink the surface and the cut line before tissue fixation, if possible.

1.1.3. Orient the specimen and cut parallel slices 5 mm each.

1.1.4. Check whether parathyroid glands are present in the tissue surrounding thyroid gland.

1.2. General principles of grossing.

1.2.1. Type of surgery (lobectomy, isthmectomy, subtotal thyroid resection, total thyroidectomy, etc.).

1.2.2. Weight, shape, colour, and consistency of the specimen.

1.2.3. Cut surface: smooth or nodular, number, size, colour, and appearance of nodules and their characteristics: cystic, solid, calcified, haemorrhagic, necrotic, en-

- capsulated or invasive, distance to line of resection.
- 1.2.4. Photographic documentation may be considered.
- 1.3. Sections for histology.
 - 1.3.1. For diffuse lesions: three sections from each lobe and one from isthmus.
 - 1.3.2. For a solitary encapsulated lesions up to 5 cm in diameter: entire circumference; most of these sections should include tumour capsule and adjacent thyroid tissue, one additional section for each additional centimetre in diameter.
 - 1.3.3. For multinodular thyroid glands: one section of each nodule (up to five nodules) including rim and adjacent normal gland.
 - 1.3.4. For papillary thyroid cancer: the whole thyroid gland with the assessment of resection lines.
 - 1.3.5. For thyroid carcinoma other than papillary: three sections of tumour, three of non-neoplastic gland, one from line of resection closest to the neoplastic lesion.
 - 1.3.6. Take a parathyroid sample if parathyroid glands are present in the specimen.
 - 1.3.7. Collect each lymph node and report their number.
 - 1.3.8. Identify other anatomical structures present (ex. thymus) and take them whole for histopathological evaluation.
 2. Histopathological intraoperative assessment.
 - 2.1. The decision whether intraoperative histopathological examination is necessary or not should be made individually in each case suspected for malignancy.
 - 2.2. If there is a possibility to evaluate fresh specimen, the pathologist should carry out grossing of the specimen. In a case of the presence of a suspected lesion, microscopic frozen sections (using cryostat) should be performed.
 - 2.3. Intraoperative histopathological examination allows for distinction between non-neoplastic goitre and papillary, medullary, and undifferentiated thyroid carcinoma.
 - 2.4. Intraoperative histopathological examination of lymph nodes allows for diagnosis of lymph node metastases and for qualification for lymphadenectomy.
 - 2.5. If there is a suspicion for follicular thyroid carcinoma the decision referred to the extent of surgery should consider that final differentiation between follicular thyroid adenoma and follicular thyroid carcinoma is possible only on the basis of postoperative microscopic study. In the case of follicular tumours, tumour capsule infiltration and angioinvasion have to be demonstrated. It is possible only in paraffin-embedded specimens.
 - 2.6. In the case of follicular variant of papillary thyroid carcinoma, imprint cytology of tumour cut surface is necessary because it enables the identification of very characteristic nuclear features of cancer cells (grooves and intranuclear inclusions).
 - 2.7. Although most diagnoses may be unequivocally stated one should remember that the differentiation between lymphoma and poorly differentiated or medullary thyroid cancer as well as metastatic tumours from other cancers (such as clear cell renal carcinoma) require immunohistochemistry.
 3. Histopathological examination.
 - 3.1. Histopathological diagnosis must involve a precise assessment of thyroid cancer type and subtype, tumour diameter, and TNM staging (Table IV).
 - 3.2. In the case of lymph node metastases, their number and diameter should be given. The information whether neoplastic infiltration exceeds the nodule capsule and the assessment of the diameter of lesions in extrathyroidal and extranodal tissue should also be provided.
 - 3.3. The diagnosis should fulfil WHO histopathological criteria of thyroid tumours (Table V) including newly recognised cancer types with a significant clinical impact, such as hobnail variant of papillary thyroid cancer (PTC).
 - 3.4. The conclusion of the histopathological report should include TNM classification according to the Eighth Edition of AJCC/UICC criteria (Table IV and IVa).
 - 3.5. The following issues should be involved in the histopathological report.
 - 3.5.1. Type of specimen (whether it reflects the extent of surgery) with the information referred to its fixation, condition (any damage, intended or not), and topography.
 - 3.5.2. Histopathological diagnosis with a subtype and the following data:
 - tumour localisation;
 - tumour size (three dimensions are necessary) and grossing;
 - tissue located outside the tumour;
 - tumour capsule and its condition;
 - vascular invasion (number of invaded vessels: up to four or more than four);
 - infiltration of adjacent tissues with a differentiation between minimal

Table IV. 8th Edition of TNM AJCC/UICC of TNM classification of thyroid carcinoma

Primary tumor (T)	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour ≤ 2 cm in greatest dimension, limited to the thyroid
T1a	Tumour ≤ 1 cm in greatest dimension, limited to the thyroid
T1b	Tumour > 1 cm but ≤ 2 cm in greatest dimension, limited to the thyroid
T2	Tumour > 2 cm but ≤ 4 cm in greatest dimension, limited to the thyroid
T3	Tumour > 4 cm in greatest dimension, limited to the thyroid or tumour of any size with gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles)
T3a	Tumour > 4 cm in greatest dimension, limited to the thyroid
T3b	Tumour of any size with gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles)
T4	Gross extrathyroidal extension beyond the strap muscles
T4a	Tumour of any size with gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus or recurrent laryngeal nerve
T4b	Tumour of any size with gross extrathyroidal extension invading prevertebral fascia or carotid artery or mediastinal vessels
T feature is for all primary thyroid carcinoma, including anaplastic thyroid cancer	
Regional lymph nodes (N)	
Nx	Regional nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastases to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)
N1b	Metastases to unilateral, bilateral, or contralateral cervical (levels I, II, III, IV, or V) or retropharyngeal
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis is present

- extrathyroidal extension of soft tissues and sternocleidomastoid muscle (T₃) and gross extrathyroidal extension when cancer infiltrates subcutaneous fat tissue, larynx, trachea, oesophagus, or recurrent laryngeal nerve (T_{4a});
- radicalness of surgery including surgical margins marked with ink with unequivocal information on whether they are infiltrated or not;
 - multifocality;
 - pathological lesions in thyroid, outside the tumour.

- 3.5.3. The presence and number of parathyroid glands and information about any abnormalities, if present.
- 3.5.4. Total number of all lymph nodes, the number of involved lymph nodes, and the diameter of a metastatic lymph node. Lesions < 2 mm in diameter should be defined as micrometastases. The information on whether cancer cells exceed the nodal capsule should be provided.

- 3.5.5. Description of extrathyroidal tissues.
- 3.6. In addition, a histopathological report may involve the following data.
- 3.6.1. Grading (not widely accepted in thyroid carcinoma).
- 3.6.2. Mitotic activity.
- 3.6.3. Presence and extent of tumour necrosis.
- 3.6.4. Presence of squamous metaplasia and clear cell changes.
- 3.6.5. Presence and type of tumour calcification, stromal changes (such as diffuse fibrosis).
- 3.6.6. Results of immunohistochemistry.
- 3.7. Immunohistochemistry plays an important role in diagnostics of thyroid neoplasms. One should accept that in some tumour types they are essential.
- 3.7.1. In MTC immunostaining for calcitonin is obligatory.
- 3.7.2. In the case of suspicion for some PTC variants (such as follicular variant) it is worth evaluating cytokeratin 19, CD56, galectin 3, CITED 1, and HBME-1; however, it is not obligatory.

Table IVa. TNM AJCC/UICC 2017 classification — staging of thyroid cancer

Stage	T	N	M
Papillary or Follicular Carcinoma, < 55 years of age			
I	Any T	Any N	M0
II	Any T	Any N	M1
Papillary or Follicular Carcinoma, > 55 years of age			
I	T1a, T1b, T2	N0	M0
II	T3	N0	M0
	T1, T2, T3	N1	M0
III	T4a	Any N	M0
IVA	T4b	Any N	M0
IVB	Any T	Any N	M1
Medullary thyroid cancer			
I	T1a, T1b	N0	M0
II	T2, T3	N0	M0
III	T1, T2, T3	N1a	M0
IVA	T1, T2, T3	N1b	M0
	T4a	N1a	M0
	T4a	Any N	M0
IVB	T4b	Any N	M0
IVC	Any T	Any N	M1
Anaplastic thyroid cancer			
IVA	T1, T2, T3a	N0	M0
IVB	T1, T2, T3a	N1	M0
	T3b, T4a, T4b	Any N	M0
IVC	Any T	Any N	M1

- 3.7.3. In the case of suspicion for poorly differentiated thyroid carcinoma, immunostaining for thyroglobulin and Ki67 should be performed.
- 3.7.4. Vascular invasion in doubtful cases should be verified by the immunoreactivity for markers of endothelial cells (such as CD34 or CD 31).
- 3.8. In the case of suspicion for poorly differentiated or undifferentiated thyroid carcinoma (anaplastic) the histopathological report should provide information about whether residual DTC is present in the tumour.
- 3.9. Due to difficulties noticed in histopathological diagnosis of thyroid cancer it should be confirmed by the second pathologist from a centre that will carry out further treatment.
- 3.10. Regarding the new WHO Classification of Thyroid Tumours, Fourth Edition, 2017 (Table V), which recognises Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP) as a neoplasm that

metastasises in extremely rare cases (practically benign), we recommend use of this postoperative diagnosis following the criteria proposed by WHO.

- 3.10.1. Postoperative, histopathological diagnosis of NIFTP may be stated in patients with preoperative diagnosis of Bethesda III, IV, V, and VI categories.
- 3.10.2. NIFTP diagnosis is not possible on the basis of preoperative FNAB.
- 3.10.3. Diagnostic criteria for NIFTP, mentioned before, are currently widely investigated. Thereby their update in the nearest future is expected. One should accept that NIFTP diagnosis has to be confirmed by another pathologist.
- 3.11. Doubtful cases with divergent opinions referred to cancer diagnosis or histological variant are routinely examined by pathologists working under Polish Group for Endocrine Tumours.
SoR: G1; QoE: PolCon 62/62

Table V. 2017 WHO classification of thyroid tumours

Follicular adenoma	8330/0
Hyalinizing trabecular tumour	8336/1
Other encapsulated follicular-patterned thyroid tumours	
Follicular tumour of uncertain malignant potential	8335/1
Well-differentiated tumour of uncertain malignant potential	8348/1
Non-invasive follicular thyroid neoplasm with papillary-like nucleus features	8349/1
Papillary thyroid carcinoma (PTC)	
Papillary carcinoma	8260/3
Follicular variant of PTC	8340/3
Encapsulated variant of PTC	8343/3
Papillary microcarcinoma	8341/3
Columnar-cell variant of PTC	8344/3
Oncocytic variant of PTC	8342/3
Follicular thyroid carcinoma (FTC), NOS	
FTC, minimally invasive	8335/3
FTC, encapsulated angioinvasive	8339/3
FTC, widely invasive	8330/3
Hurthle (oncocytic) cell tumours	
Hurthle cell adenoma	8290/0
Hurthle cell carcinoma	8290/3
Poorly differentiated thyroid carcinoma	
Anaplastic thyroid carcinoma	
Squamous cell carcinoma	
Medullary thyroid carcinoma	
Mixed medullary and follicular thyroid carcinoma	
Mucoepidermoid carcinoma	
Sclerosing mucoepidermoid carcinoma with eosinophilia	
Mucinous carcinoma	
Ectopic thymoma	
Spindle epithelial tumour with thymus-like differentiation	
Intrathyroid thymic carcinoma	
Paraganglioma and mesenchymal / stromal tumours	
Paraganglioma	8693/3
Peripheral nerve sheath tumours	
— schwannoma	9560/0
— malignant PNST	9540/3
Benign vascular tumours	
— haemangioma	9120/0
— cavernous haemangioma	9121/0
— lymphangioma	9170/0
Angiosarcoma	9120/3
Smooth muscle tumours	
— leiomyoma	8890/0
— leiomyosarcoma	8890/3
Solitary fibrous tumour	8815/1

→

Table V. 2017 WHO classification of thyroid tumours. cont.

Hematolymphoid tumours	
Langerhans cell histiocytosis	9751/3
Rosai-Dorfman disease	
Follicular dendritic cell sarcoma	9758/3
Primary thyroid lymphoma	
Germ cell tumours	
Benign teratoma (grade 0 or 1)	9080/0
Immature teratoma (grade 2)	9080/1
Malignant teratoma (grade 3)	9080/3
Secondary tumours	

Commentary

The authors of the current classification of thyroid tumours (WHO 2017) introduced a category of encapsulated follicular-patterned thyroid tumours, which include three diagnoses: two of uncertain malignant potential and one benign neoplasm, which may develop distant metastases in extremely rare cases. The first one "well-differentiated tumour of uncertain malignant potential" is defined as a encapsulated or well demarcated tumour consisted of thyrocytes, which nuclei demonstrate complete or only partial features characteristic for papillary thyroid cancer and which are suspicious for tumour capsule infiltration or/and vascular invasion. Similar definition is related to "Follicular tumour of uncertain malignant potential". The difference between both above-mentioned tumours is related to the lack of nuclear features of papillary thyroid carcinoma or their suspicion in tumour cells. Thus, this is an intermediate category placed between follicular adenoma and follicular carcinoma.

The introduction of above mentioned group of tumours of uncertain malignant potential is a step back in the diagnostics of thyroid neoplasms. It allows, without any additional examinations (immunohistochemistry) or consultations, for the diagnosis fulfilling WHO criteria, which is useless from the clinical point of view.

As authors of these recommendations we may only appeal to pathologists to state these diagnoses as rarely as it possible if all accessible methods fail to establish unequivocal diagnosis regarding tumour malignancy.

Similarly, we also should be cautious about „non-invasive follicular thyroid neoplasm with papillary-like nucleus features" (NIFTP). This entity is characterized by extensive inclusion and exclusion criteria. Both good clinical experience and adequate sample quality involving the whole tumour capsule is required to diagnose NIFTP.

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III. Treatment and follow-up of thyroid cancer

1. The authors accept ATA classification of differentiated thyroid cancer (DTC; papillary or follicular) based on the risk of cancer relapse as a part of these recommendations [4] (Table VI).
SoR: G1; QoE: +++ / PolCon 62/62 ATA GL R 48
2. Response to treatment should be classified following ATA 2015 recommendations (Table VII).
SoR: G1; QoE: +++ / PolCon 62/62
3. Extent of diagnostics before surgery.
 - 3.1. Tests, recommended before surgery, necessary in a case of diagnosis or suspicion of thyroid malignant neoplasm.
 - 3.1.1. Medical history and clinical examination.
SoR: G1; QoE: +++ / PolCon 61/62
 - 3.1.2. Neck ultrasound:
 - thyroid;
 - lymph nodes.
 SoR: G1; QoE: ++ ATA GL R32

- 3.1.3. Ultrasound-guided FNAB — see part I of the Recommendations:
 - thyroid lesions;
 - suspicious lymph nodes.
 SoR: G1; QoE: +++
- 3.1.4. TSH evaluation to exclude thyroid functional disorders.
SoR: G1; QoE: ++
Note! In patients, in whom suppressive L-thyroxin doses are administered, low serum TSH level is a result of such treatment, and only L-thyroxine dose reduction before surgery is required. In contrast to patients with overt hyperthyroidism, any delay or additional therapy is not necessary.
SoR: G1; QoE: +++
- 3.1.5. Analysis of serum total calcium concentration.
SoR: G1; QoE: PolCon 61/62
- 3.1.6. Analysis of serum calcitonin concentration (see I, par. 2.3).
SoR: G2; QoE: +++

Table VI. Classification of the risk of papillary and follicular thyroid cancer recurrence according to ATA 2015 [4]

Low risk cancer	<p>Papillary thyroid cancer with all of the following:</p> <ul style="list-style-type: none"> — No local or distant metastases — All macroscopic tumour resected — No extrathyroidal extension — Tumour does not have aggressive histology (e.g. tall cell, hobnail variant, columnar cell carcinoma) — No RAI uptake outside thyroid bed in the first posttreatment whole body scan, if RAI given — No vascular invasion — Clinical N0 or ≤ 5 lymph node micrometastases (< 0.2 cm in the longest dimension) <p>Intrathyroidal well differentiated follicular thyroid cancer with capsular invasion, and no or minimal (< 4 foci) vascular invasion</p> <p>Intrathyroidal papillary microcarcinoma uni or multifocal, including BRAF^{V600E} mutated</p>
Intermediate risk cancer	<p>Microscopic extrathyroidal extension (ETE)</p> <p>RAI uptake outside thyroid bed in the first posttreatment whole body scan</p> <p>Aggressive histology</p> <p>Papillary thyroid cancer with vascular invasion</p> <p>Clinical N1 or > 5 involved lymph nodes (0.2–3 cm)</p> <p>Papillary thyroid cancer with ETE and BRAF mutated</p>
High risk cancer	<p>Gross extrathyroidal extension</p> <p>Incomplete tumor resection</p> <p>Distant metastases</p> <p>High postoperative serum Tg suggestive of distant metastases</p> <p>Metastatic lymph nodes > 3 cm in the greatest dimension</p> <p>Widely invasive follicular thyroid cancer with vascular invasion (> 4 foci)</p>

3.1.7. Chest X-ray (two views).

SoR: G1; QoE: PolCon 61/62

3.1.8. Laryngeal examination to evaluate function of vocal cords.

SoR: G1; QoE: PolCon 61/62

3.2. Examinations useful in differentiating diagnostics and staging of cancers:

3.2.1. Neck and upper mediastinum CT scan if there is a suspicion of inoperable tumour (ex. cT4 stage).

Note: In DTC CT without contrast administration is recommended if scintigraphy or ¹³¹I treatment is planned to be carried out within six weeks.

SoR: G1; QoE: +++ ATA GL R33

3.2.2. CT is not a routine pre-surgery imaging examination indicated in all cases of thyroid cancer.

SoR: G2; QoE: PolCon 62/62

3.2.3. Evaluation of the presence of distant metastases by other imaging examinations only if indicated.

SoR: G2; QoE: PolCon 62/62

3.2.4. In a case of MTC pre-surgical exclusion of the co-existence of adrenal pheochromocytoma.

SoR: G1; QoE: +++

3.3. Role of the evaluation of serum Ct concentration (see part I of the Recommendations) [6, 38].

3.3.1. Analysis of serum calcitonin concentration is recommended in a case of suspicion of MTC, particularly if the following conditions occur:

- a positive familial history;
- nodular goitre in patients with pheochromocytoma;
- exhaustive diarrhoea of unknown origin;
- suspicion of MTC in cytology;
- suspicious for a follicular neoplasm in cytology (Bethesda IV), particularly Hurthle cell neoplasm.

SoR: G2; QoE: ++

3.3.2. Serum calcitonin level evaluation in a patient qualified for surgery significantly reduces the risk of unrecognised MTC [38].

SoR: G1; QoE: +++

3.3.3. The authors of these recommendations propose it as a compromise solution in view of conflicting ETA and ATA statements: ETA recommendation to assess serum calcitonin in each case of nodular goitre and ATA position of no proof

Table VII. Classification of treatment response of papillary and follicular thyroid cancer according to ATA 2015 [4]

Excellent response	No clinical, biochemical and structural evidence of disease: — Negative imaging — Tg (suppression) < 0.2 ng/mL — Tg (stimulation) < 1 ng/mL
Incomplete biochemical response	Persistent abnormal Tg level in the absence of localizable disease: — Negative imaging — Tg (suppression) > 1.0 ng/mL — Tg (stimulation) > 10 ng/mL — Rising antiTg Ab
Incomplete structural response	Persistent or newly identified locoregional disease or distant metastases: — Structural evidence of disease regardless to Tg and antiTg levels
Indeterminate response	Non-specific biochemical or structural findings that can not be unequivocally classified as benign or malignant: — Nonspecific findings on imaging studies — Faint RAI uptake in thyroid bed — Non-stimulated Tg detectable but Tg < 1.0 ng/mL — Stimulated Tg detectable but < 10 ng/mL — Tg Ab stable or declining in the absence of structural and functional disease

of the usefulness of serum calcitonin evaluation in a case of nodular goitre [4].

SoR: G1; QoE: PolCon 62/62

- 3.3.4. Calcitonin level exceeding 100 pg/mL nearly unequivocally indicates MTC. However, it is necessary to differentiate from rare neuroendocrine tumours secreting calcitonin, especially lung cancer.

SoR: G1; QoE: ++

- 3.3.5. If calcitonin level ranges between 10–100 pg/mL, the risk of a false positive result indicating MTC should be considered.

SoR: G2; QoE: PolCon 62/62

4. Surgery in patients with diagnosed or suspected thyroid cancer.

4.1. General rules.

- 4.1.1. The most important part of surgical strategy is careful and full-profile pre-surgical diagnostics towards cancer in all cases of thyroid surgery (see Part I of the Recommendations).

SoR: G1; QoE: +++ ATA GL R33

- 4.1.2. Surgical treatment without an earlier FNAB may be acceptable only in exceptional cases.

SoR: G1; QoE: +++ / PolCon 62/62

- 4.1.3. If FNAB preceding surgery was negative or did not give an unequivocal cancer diagnosis but the suspicion of cancer is still strong, intraoperative histopathological examination of sus-

pected tumours may be useful, but is not mandatory.

SoR: G2; QoE: PolCon 62/62

- 4.1.4. The extent of surgery should be in line with the perceived cancer risk and clinical staging.

SoR: G2; QoE: PolCon 62/62; ATA GL R35

- 4.1.4.1 Thyroid surgery where risk of malignant goitre cannot be excluded, should avoid complications, especially postoperative hypoparathyroidism.

SoR: G1; QoE: ++ / PolCon 62/62

- 4.1.4.2 Thyroid surgery due to malignant goitre should be carried out by an experienced surgeon in a fully equipped, specialised centre.

SoR: G2; QoE: +++ / PolCon 62/62

- 4.1.5. Intraoperative visualisation of the recurrent laryngeal nerve is recommended. One should also aim to protect the superior laryngeal nerve during intraoperative tissue preparation next to the upper part of thyroid gland.

SoR: G1; QoE: +++

- 4.1.6. The use of intraoperative electrostimulation of the nerve (with or without neuromonitoring) to facilitate its identification and to evaluate its function is acceptable.

SoR: G1; QoE: PolCon 62/62

4.1.7. One should aim to protect normal, intraoperative vascularisation of parathyroid glands.

SoR: G1; QoE: +++

4.2. Surgical management if there is a suspicion for a follicular neoplasm on cytology (Bethesda class IV) [22, 24].

4.2.1. In a case of suspicion of a follicular neoplasm (including oxyphilic follicular neoplasm) there is no possibility of pre-surgical cytological differentiation between a benign and malignant nodule.

SoR: G1; QoE: +++

4.2.2. The principle to operate all nodules that are diagnosed as “suspicious for a follicular neoplasm”, proposed by ATA, cannot be literally applied in Poland due to its epidemiological conditioning: iodine deficiency in the 1980s and 1990s caused increased incidence of non-malignant thyroid nodules, which used to be diagnosed as follicular nodules on FNAB, which, according to recently proposed nomenclature, refers to “suspicion for a follicular neoplasm”. Polish published data estimate the risk of cancer in follicular neoplasm at 8.2–19% [25, 26].

SoR: G2; QoE: PolCon 62/62

4.2.3. In nodules cytologically diagnosed as “follicular lesion of undetermined significance” or “suspicious for a follicular neoplasm”, which show autonomous appearance in thyroid scan, the risk of malignancy is small, so there is no firm indication for surgery.

SoR: G2; QoE: PolCon 62/62

4.2.4. In small nodules (< 2 cm in diameter) with cytological diagnosis “suspicious for a follicular neoplasm”, well controlled during continuous follow-up, and if indicated by a repeated biopsy, it is accepted to resign from surgery due to low clinical risk.

SoR: G2; QoE: PolCon 62/62

4.2.5. Surgery is indicated in oxyphilic nodules (currently recommended diagnosis is: “suspicious for a Hurthle-cell neoplasm”), particularly if they are > 1 cm in diameter, because they show a higher risk of malignancy.

SoR: G2; QoE: PolCon 62/62

4.2.6. At the diagnosis “suspicious for a follicular neoplasm” in a single nodule the minimal extent of surgery involves hemithyroidectomy with isthmus and

its extension to the second lobe (near total or total resection of the second thyroid lobe) depending on the individual risk of malignancy and presence of focal lesions in the second lobe.

SoR: G2; QoE: PolCon 62/62

4.2.6.1 If the diagnosis “suspicion for a follicular neoplasm” concerns a single nodule and it is stated in multinodular goitre located only in one lobe, total or nearly total resection of this lobe and isthmus may be considered. Alternatively, total resection of that lobe, where a lesion “suspicious for a follicular neoplasm” is located, isthmus and subtotal resection of contralateral lobe are acceptable.

SoR: G2; QoE: PolCon 62/62

4.2.6.2 If there is a suspicion for a follicular or oxyphilic neoplasm in one of the nodules in multinodular goitre, bilateral subtotal thyroidectomy is inappropriate. One should follow par. 4.2.6.

SoR: G1; QoE: PolCon 62/62

4.3. In a case of diagnosis of follicular lesion of undetermined significance (see part I) surgery is not obligatory; however, it may follow from clinical indications.

SoR: G2; QoE: PolCon 62/62

4.3.1. As already stated above, calcitonin serum assessment is necessary in follicular lesions (both in a “follicular lesion of undetermined significance” and “suspicious for a follicular neoplasm”, particularly in a diagnosis of “suspicious of Hurthle-cell neoplasm”), especially if the surgery is not performed (because some of them may be MTC).

SoR: G2; QoE: PolCon 62/62

4.4. Surgical management if there is a suspicion or diagnosis of thyroid cancer.

4.4.1. Total/near total thyroidectomy is a basic surgical management.

SoR: G2; QoE: PolCon 62/62

4.4.2. Lobectomy with isthmus is acceptable in patients in whom papillary thyroid cancer was diagnosed in a single lesion ≤ 1 cm, cN0, if there are no indications for bilateral surgery and there is patient’s consent for such management.

SoR: G2; QoE: PolCon 62/62

- 4.5. Secondary thyroid surgery.
- 4.5.1. Secondary total thyroidectomy should be considered by a multidisciplinary therapeutic team in the case of thyroid cancer recognised after surgery of extent less than total or subtotal thyroidectomy (with the following exceptions given below).
SoR: G1; QoE: PolCon 62/62; ATA GL R38 and R39
- 4.5.2. The principle of secondary total thyroidectomy may be omitted if low-risk cancer was stated in a patient in whom total unilateral lobectomy with isthmus or total unilateral lobectomy with isthmus and subtotal resection of contralateral lobe or subtotal bilateral lobectomy were performed in the following situations.
SoR: G2; QoE: PolCon 62/62
- 4.5.2.1. Unifocal papillary thyroid cancer not exceeding 1 cm in diameter (pT_{1a}) if there are no lymph node and distant metastases and careful histopathological analysis of postoperative tissue was carried out to exclude multifocal tumour growth.
SoR: G2; QoE: + + / PolCon 62/62
- 4.5.2.2. Well-differentiated cancer with higher stage with reference to T feature (pT_{1b} , pT_2) if remnants of both lobes in ultrasound do not exceed 1 mL on each side and available data indicate complete surgical resection and low-risk cancer.
SoR: G2; QoE: PolCon 62/62
- 4.5.2.3. More advanced cancer if available clinical data indicate that total surgery is impossible or does not bring any benefits for patients (especially in poorly and undifferentiated cancers).
SoR: G2; QoE: PolCon 62/62
- 4.5.3. Exception from total thyroidectomy may refer to minimally invasive follicular cancer < 1 cm in diameter (pT_{1a}), diagnosed after total lobectomy or subtotal thyroidectomy, if distant or lymph node metastases were not found. So far, the improvement of long-term outcomes after secondary thyroidectomy has not been unequivocally confirmed. The extent of necessary surgery should be defined individually by a tumour board.
SoR: G2; QoE: PolCon 62/62
- 4.6. The assessment of the completeness of surgery.
- 4.6.1. If the extent of surgery is not unequivocal, the assessment of its completeness is based on joint interpretation of post-surgical histopathology, ultrasound, postsurgical neck radioiodine (RAI) scan, and thyroglobulin level. All examinations should be performed no earlier than 1–2 months after surgery. TSH stimulation is necessary for neck scan and Tg level assessment [39].
SoR: G2; QoE: PolCon 62/62
- 4.6.2. Surgery may be considered as near total thyroidectomy if the volume of remnant tissue in neck sonography does not exceed 1 mL at each side. The evaluation of the completeness of surgery by the use on ultrasound should include neck lymph nodes (see below, par. 5).
SoR: G2; QoE: + + + / PolCon 62/62
- 4.6.3. The assessment of RAI uptake and post-surgical thyroid scan, performed under TSH stimulation are useful in defining the extent of performed surgery; however, it is not an absolute criterion of its completeness. In a patient in whom total thyroidectomy was performed, RAI uptake after rhTSH stimulation is usually less than 1%. After L-thyroxin withdrawal (3–4-week break in L-thyroxine treatment) the expected RAI uptake is < 5%, whereas RAI uptake < 2% is reliable proof of total thyroid resection. Nevertheless, a higher RAI uptake with small volume of thyroid remnants on ultrasound is not an indication for reoperation. Secondary total thyroidectomy may be considered when ultrasound shows thyroid remnants significantly larger than 1 mL on each side (the examination should be performed after the recovery of a postsurgical swelling), if the tumour > T_1 was diagnosed and if in intermediate and high-risk thyroid cancer is diagnosed. Such a decision should be made by a tumour board.
SoR: G1; QoE: PolCon 62/62; ATA GL R38
5. Surgery of the lymphatic neck system in primary thyroid cancer.
- 5.1. Central neck dissection.
- 5.1.1. Dissection of central neck lymph nodes due to thyroid cancer should involve the group VI of neck lymph nodes — prelaryngeal, pretracheal, paratracheal, and parathyroidal lymph nodes. Such

- dissection diminishes risk of cancer relapse and significantly reduces the post-operative Tg level. However, according to ATA guidelines, this dissection is not necessary in low-risk cancer:
- Whenever involvement of this compartment or lateral neck lymph nodes occurs, surgery is a therapeutic procedure and is definitely indicated at each stage of primary tumour;
 - If there are no features of nodal involvement in the central neck compartment, surgery is prophylactic [40, 41].
SoR: G1; QoE: +++ ATA GL R36
- 5.1.2. ATA guidelines accept resignation from a routine prophylactic (elective) central neck dissection [40–42].
- 5.1.2.1. In low-risk papillary thyroid cancer, up to cT2 (particularly if tumour diameter is ≤ 1 cm) if there are no features of nodal involvement on preoperative neck ultrasound and during intraoperative evaluation.
SoR: G1; QoE: ++
- 5.1.2.2. In well-differentiated follicular thyroid cancer if a diagnosis is known preoperatively (presence of distant metastases) and intraoperative assessment of central lymph node gives no suspicion of metastases.
SoR: G2; QoE: PolCon 62/62
- 5.1.2.3. The relationship between prophylactic central neck dissection and the frequency of permanent postsurgical side-effects suggests limitation of number of indications.
SoR: G1; QoE: +++/PolCon 62/62
- 5.2. Lateral lymphadenectomy in differentiated thyroid cancers.
- 5.2.1. Uni- or bilateral lateral neck lymphadenectomy as a modified procedure (without dissection of jugular vein, sternocleidomastoid muscle, and XI nerve) is indicated if lymph node metastases are confirmed (by a positive FNAB or intraoperative biopsy) [4, 43].
SoR: G1; QoE: ++ ATA GL R37
- 5.2.2. Selective resection of metastatic lymph nodes ("berry picking") instead of modified lateral lymphadenectomy in differentiated thyroid cancer is not an optimal management and should not be performed.
SoR: G1; QoE: +++
- 5.2.3. Intraoperative bilateral biopsy of lateral lymph nodes is indicated for exclusion of lymph node metastases. If negative, stage N₀ can be defined. If the result is positive, modified lateral lymphadenectomy is indicated. Such lymphadenectomy is a curative procedure (selective — this name does not refer to selective dissection of metastatic lymph nodes, which is not recommended in this situation) [43–48].
SoR: G1; QoE: +++
- 5.2.3.1. Postoperative histopathological diagnosing of metastases in < 5 small neck lymph nodes (< 2 mm in the longest dimension) is not an indication for secondary lymphadenectomy, if there are no other clinically apparent metastases and there is an option of adjuvant RAI therapy.
SoR: G1; QoE: ++/PolCon 62/62
- 5.2.3.2. The presence of central lymph node involvement does not require a lateral neck lymphadenectomy if there are no lateral lymph node metastases.
SoR: G1; QoE: ++/PolCon 62/62
- 5.3. The extent of lymphadenectomy in MTC.
- 5.3.1. The extent of lymphadenectomy in hereditary MTC depends on the primary tumour diameter, serum calcitonin concentration, and the type of RET mutation — its detailed description is given elsewhere in these recommendations [49].
SoR: G1; QoE: +++
- 5.3.2. Central neck lymphadenectomy as a general rule is routine treatment in MTC except for patients in whom surgery is carried out at a very early stage of the disease. Unilateral lymphadenectomy on the tumour side is always recommended if there is enlargement of lymph nodes suggesting metastases or if they are found on FNAB. Elective surgery is also considered if the primary focus exceeds 1 cm in diameter and calcitonin level is high. In advanced MTC with a high calcitonin level bilateral neck lymphadenectomy should be considered.
SoR: G1; QoE: +++

- 5.3.3. In the case of prophylactic thyroidectomy, performed in proto-oncogene RET mutation carriers, indications for elective lymphadenectomy depend on type of germinal RET mutation (i.e. type of hereditary cancer) and age when the surgery is performed as well as on the current calcitonin level [49].
SoR: G1; QoE: ++
- 5.4. Extent of lymphadenectomy in poorly and undifferentiated (anaplastic) thyroid cancer.
- 5.4.1. In poorly and undifferentiated (anaplastic) thyroid cancers elective (routine) lymphadenectomy is recommended. However, usually the advancement of disease unequivocally suggests lymph node involvement, and the extent of surgery depends on whether these tumours are resectable or not. In undifferentiated (anaplastic) thyroid cancer a lateral neck dissection Jawdyski-Crile may be necessary.
SoR: G1; QoE: +++
- 5.5. Surgery of mediastinal lymph nodes.
- 5.5.1. Mediastinal lymph nodes are operated in the case of confirmed metastases or if suspected lymph nodes are present. There is no indication for elective mediastinal lymph node dissection as well as for a preoperative CT scan.
SoR: G1; QoE: ++
6. Multiple organ surgery.
- 6.1. In differentiated thyroid cancers multiple organ surgery may be carried out if there is infiltration of adjacent structures (larynx, oesophagus, blood vessels) and if complete resection (so called R0 resection) is possible. In undifferentiated cancer confirmed in histopathology the infiltration of adjacent organs requires a combined therapy.
SoR: G1; QoE: ++
7. Complications after surgery of thyroid carcinoma.
- 7.1. The most common complications after surgery are recurrent laryngeal nerve palsy and hypoparathyroidism.
SoR: G1; QoE: +++
- 7.1.1. Both complications may be transient or permanent. The frequency of permanent side effects is an important measure of a particular centre's experience; however, it is also related to the stage of the disease.
SoR: G1; QoE: ++
- 7.1.2. Centre experience in central and lateral lymphadenectomy is much more important than experience in total thyroidectomy to decrease the general frequency of complications.
SoR: G1; QoE: ++
- 7.2. Laryngeal recurrent nerve palsy.
- 7.2.1. Laryngological examination to evaluate vocal cords and indications for the treatment of this complication should be performed before and after each surgery.
SoR: G1; QoE: PolCon 62/62
- 7.2.2. In the case of vocal cord paresis, phoniatric voice rehabilitation is necessary, whereas if this complication is permanent, remedial surgery may be considered.
SoR: G1; QoE: ++
- 7.2.3. Bilateral vocal cord paresis in general requires tracheostomy immediately after surgery.
SoR: G1; QoE: +
- 7.3. Hypoparathyroidism.
- 7.3.1. The rules referring to the treatment of hypoparathyroidism follow the recommendations of the European Society of Endocrinology (ESE) [50].
- 7.3.2. Strict monitoring of serum-ionised (or corrected) calcium level is necessary immediately after surgery for the evaluation of parathyroid function.
SoR: G1; QoE: +++
- 7.3.3. PTH assessment immediately after surgery may support the evaluation of the risk of hypoparathyroidism.
SoR: G1; QoE: ++
- 7.3.4. If hypoparathyroidism lasts longer than a few days after the operation, it should be evaluated by more detailed tests — it is advisable to assess not only calcium but also serum PTH and phosphate levels.
SoR: G1; QoE: +++
- 7.3.5. Transient hypoparathyroidism recovers usually in 1–6 months; however, it may disappear even later, after 1–2 years. Therefore, assessment of indications for treatment continuation should be repeated six months, a year, and two years after operation [51].
SoR: G1; QoE: ++
- 7.3.6. To avoid clinical symptoms of hypocalcaemia, serum-ionised calcium (or corrected) should be maintained at lower range of the normal result or slightly below it. Calciuria should be maintained within the normal range, respectively to sex. Serum phosphate and magnesium concentration should be maintained

- within normal range, whereas calcium-phosphate index should remain below $4.4 \text{ mmol}^2/\text{L}^2$ ($55 \text{ mg}^2/\text{dL}^2$).
SoR: G1; QoE: ++
- 7.3.7. The treatment of hypoparathyroidism involves calcium supplementation and active vitamin D analogues.
SoR: G1; QoE: +++
- 7.3.8. Biochemical monitoring of hypoparathyroidism should involve analysis of serum-ionised (or corrected) calcium, phosphate, magnesium, creatinine every 3–6 months. In the case of treatment modification biochemical analyses should be carried out up to two weeks. Calciuria may be evaluated less frequently (every year or two).
SoR: G1; QoE: PolCon 62/62
- 7.3.9. In the case of hyperphosphatemia and/or elevated calcium-phosphate index, a low phosphate diet and/or correction of calcium and vitamin D substitution may be considered. Hypercalciuria may require a low-sodium diet, decrease of calcium substitution, and/or administration of thiazide diuretics.
SoR: G1; QoE: PolCon 62/62
- 7.3.10. Because active analogues of vitamin D do not provide adequate 25-OH-D₃ concentration at tissue level serum 25-OH-D₃ concentration above 30 ng/mL should be obtained using vitamin D supplementation.
SoR: G1; QoE: ++
- 7.3.11. PTH evaluation allows distinguishing between hypoparathyroidism and other reasons of hypocalcaemia. Normal PTH level is an indication to gradually decrease substitution doses.
SoR: G1; QoE: +++
8. Evaluation of cancer staging should be updated at subsequent diagnostics and therapy follow-ups [52].
- 8.1. According to TNM classification (the year of the last update should be provided). Currently the Eighth Edition of AJCC/UICC classification from 2017 is obligatory (Table IV).
SoR: G1; QoE: PolCon 62/62
- 8.2. According to ATA 2015 classification (Table VI) [52].
SoR: G1; QoE: +++ ATA GL R49
9. RAI treatment.
- 9.1. General rules obligatory in RAI treatment: the patient should be fully informed about the treatment goal, its course, including radiation safety procedures, possible consequences, and contraindications. Written, informed consent is required [53].
SoR: G1; QoE: PolCon 62/62
- 9.1.1. The aim of RAI treatment:
- To destroy thyroid remnants after surgery (ablation of thyroid remnants);
 - Sterilisation of the remaining cancer microfoci localised in the thyroid bed and lymph nodes (adjuvant therapy);
 - Sterilisation of distant micrometastases.
- SoR: G1; QoE: +++; ATA GL R51
- 9.2. Indications for RAI treatment.
- 9.2.1. Indications for RAI treatment may be considered only in DTC patients.
SoR: G1; QoE: +++
- 9.2.2. There is no indication for RAI treatment in patients with ATC and MTC.
SoR: G1; QoE: +++
- 9.3. Adjuvant RAI therapy [54].
- 9.3.1. Adjuvant RAI therapy concerns the patients showing no signs of persistent disease after radical surgery; however, possible cancer microdissemination is assumed. As a principle, patients with apparent distant metastases are not subjected to RAI adjuvant therapy.
SoR: G1; QoE: +++ / PolCon 62/62
- 9.3.2. Both oncological treatment and ablation of thyroid remnants are considered as adjuvant therapy. These managements have different aims.
- 9.3.2.1. Ablation of thyroid remnants after surgery may be considered in low-risk patients. This treatment is to facilitate further disease monitoring using thyroglobulin measurements [55].
SoR: G1; QoE: PolCon 62/62; ATA GL R51
- 9.3.2.2. The goal of adjuvant therapy is to sterilise possible cancer microfoci that are not detected by other examinations [39].
SoR: G1; QoE: +++
- 9.3.3. Postoperative RAI treatment should be considered in all patients with papillary and follicular thyroid cancer staged pT₃-T₄N₀ and in all patients staged N₁, regardless of tumour diameter after previous total thyroidectomy.
SoR: G1; QoE: +++

- 9.3.4. Benefits of RAI administration in patients staged $T_{1b}-T_2N_0M_0$, have not been unequivocally proven.
SoR: G2; QoE: ++ ATA GL R51
- 9.3.4.1. However, RAI treatment is recommended in this subgroup of patients if postoperative diagnostics shows serum thyroglobulin level > 10 ng/mL or RAI uptake outside thyroid bed [39].
SoR: G2; QoE: +++
- 9.3.4.2. Good previous experience of Polish centres speaks in favour of routine indications for this treatment also in patients staged $T_{1b}-T_2N_0M_0$ without increased risk of cancer recurrence. The decision regarding RAI treatment should be individualised and discussed with a patient, considering its potential benefits and risk.
SoR: G1; QoE: PolCon 62/62
- 9.3.5. In low-risk patients, staged $pT_{1a}N_0M_0$, who demonstrate a very low risk of cancer relapse, RAI treatment is not necessary [54, 56].
SoR: G1; QoE: +++; ATA GL R51
- 9.3.6. RAI treatment may complement the operation of incomplete thyroidectomy if there are contraindications for secondary total thyroidectomy or if a patient refuses surgery.
SoR: G1; QoE: PolCon 62/62
- 9.4. Indications for thyroid ablation in a patient with distant metastases.
If distant metastases showing no RAI uptake in diagnostic whole-body scan are present and simultaneously significant RAI uptake in thyroid bed is noticed, it is necessary to destroy thyroid remnants by ablative RAI dose administration before the final evaluation of metastases RAI avidity.
SoR: G2; QoE: ++ / PolCon 62/62
- 9.5. RAI activity used for adjuvant treatment.
- 9.5.1. RAI activities applied for ablation range between 1.1 and 3.7 GBq (30–100 mCi). So far, there are no convincing data speaking in favour of one, defined dose. The most positive Polish experiences refer to RAI activities of 2.2–3.7 GBq (60–100 mCi) [57].
— Lower RAI activities may be used in low-risk patients complying with the rule that a single administered activity should be no less than 1.1 GBq (30 mCi);
— The preparation for RAI ablation with the use of thyrotropin alpha is optimal with regard to the quality of life;
— If the risk of cancer microdissemination is high, administration of higher RAI activities of 3.7–5.5 GBq (100–150 mCi) may be justified, especially in high-risk cancer patients.
SoR: G1; QoE: +++
- 9.6. Indication for RAI treatment in disseminated thyroid cancers [58].
- 9.6.1. Treatment of disseminated DTC may be carried out with radical or palliative intent.
SoR: G1; QoE: +++
- 9.6.2. Radical treatment is possible in these DTC patients with RAI-avid metastases showing RAI uptake strong enough to respond to sterilising effect of ionising radiation — microdissemination or dissemination in which none of the metastases exceed 1 cm in diameter and all of them show iodine uptake.
SoR: G1; QoE: +++
- 9.6.3. Palliative treatment may be considered in DTC patients with inoperable primary tumour, inoperable local recurrence, or presence of distant metastases with iodine uptake insufficient to allow a sterilising effect of ionising energy. Radioiodine may then reduce the tumour size and slow cancer progression as well as alleviate disease symptoms (ex. pain).
SoR: G1; QoE: +++
- 9.7. Qualification for RAI therapy.
The patient should be informed about the aim of treatment, its course, including the principles of radiological protection, possible consequences, and contraindications.
SoR: G1; QoE: PolCon 62/62
- 9.7.1. Before RAI treatment of thyroid cancer, the following qualifying examinations should be performed and its goal should be defined.
In each case the following procedures are necessary:
— patient's history and clinical examination;
— neck ultrasonography;
— assessment of Tg and anti-Tg autoantibodies;

- haematology and serum calcium (ionised or total) concentration.
SoR: G1; QoE: +++ / PolCon 62/62
- 9.7.2. Imaging necessary if distant metastases are suspected [59]:
 - CT or MRI of selected areas. One should remember that the interval between iodide contrast administration and RAI treatment should not be shorter than one month;
 - whole-body scan to localise bone metastases (usually ^{99m}Tc MDP or Na^{18}F PET);
 - FDG PET-CT scan in selected cases [60].
SoR: G1; QoE: +++
- 9.7.3. Analysis of iodine urinary excretion allows exclusion of stable iodine contamination [61]:
 - There are no data demonstrating whether, considering the present iodine supply in Poland, any low-iodine diet is necessary before RAI treatment [61]. However, it should be emphasised that the efficacy of RAI treatment in Poland is comparable with European results, despite no recommendation for such a diet. As the supply of iodine in food increases, such an indication may arise;
 - Low-iodine diet may be ordered 1–2 weeks before radioiodine treatment (see www.thyca.org).
SoR: G2; QoE: PolCon 62/62
- 9.8. Contraindications to RAI treatment.
 - 9.8.1. Absolute contraindications involve pregnancy (in fertile female patients, pregnancy should be excluded by a pregnancy test) and breastfeeding (time interval between completed breastfeeding and RAI treatment should be at least six weeks). Patients should not continue nursing after RAI treatment [62].
SoR: G1; QoE: +++
- 9.9. Course of RAI treatment.
 - 9.9.1. RAI treatment is conducted in licenced centres.
SoR: G1; QoE: PolCon 62/62
 - 9.9.2. RAI treatment of thyroid cancer is possible only if sufficient stimulation of cancer cells with endogenous or exogenous thyrotropin (rhTSH) can be achieved:
 - Recombinant TSH — thyrotropin alpha allows adjuvant therapy to be carried out without L-thyroxine withdrawal, which prevents side-effects related to hypothyroidism and decreases exposure of healthy tissues to ionising radiation;
 - RAI treatment with thyrotropin alpha;
L-thyroxine is not withdrawn. One package of rhTSH includes two ampules of thyrotropin alpha, 0.9 mg each. On the first day of treatment, after routine tests, the patient receives an intramuscular injection of 0.9 mg of thyrotropin alpha dissolved in 1 mL of attached solvent; the dose is repeated after 24 h. RAI treatment is applied after the next 24 hours. Whole-body scan is performed no sooner than three days after RAI administration. Tg concentration test is performed 2–6 days after the onset of thyrotropin alpha administration. Some centres take blood sample on the second day, the others prefer day 6; however, they are aware of a possible false increased result after RAI treatment. This decision should be made according to the particular centre's experience;
 - Treatment after interval in thyroxine treatment;
RAI ablation after an interval in L-thyroxine administration is a second option in adults if stimulation with thyrotropin alpha is impossible. RAI treatment is introduced after 4–6 weeks of thyroxine withdrawal (during the first 2–4 weeks triiodothyronine is administered in the doses to maintain euthyroidism, and during last two weeks no thyroid hormone is administered). Serum TSH level 20–30 IU/L is the necessary condition for RAI treatment.
SoR: G1; QoE: ++ ATA GL R54
- 9.10. When RAI treatment should be administered.
 - 9.10.1. The optimum time is four weeks after completed surgery, when the wound is healed and swelling reduced, Tg level is lowered, and there are no immediate or transient postsurgical complications.
SoR: G1; QoE: PolCon 62/62
 - 9.10.2. RAI therapy up to three months after surgery is recommended; however, if this time is longer than 9–12 months the treatment is delayed [55].
SoR: G1; QoE: PolCon 62/62

- 9.10.3. If the patient still shows cancer remission one year after surgery, despite no RAI administration after surgery, indications for adjuvant therapy become doubtful.
SoR: G1; QoE: PolCon 62/62
- 9.11. Post-therapeutic whole-body scan.
The treatment should be finalised with a whole-body scan (a post-therapeutic scan) to assess RAI uptake in the patient's body.
SoR: G1; QoE: +++
- 9.12. Information which should be provided after completed RAI treatment.
- 9.12.1. After RAI treatment, the patient should be informed of the results of performed tests (neck ultrasonography, TSH level, stimulated serum Tg level, post-therapeutic scan, and others) with respect to the following issues:
— whether the results suggest persistent disease;
— how to interpret neck uptake, if present;
— the patient's risk category if there is no evidence of persistent disease;
— where and when follow-up examinations are to be performed.
SoR: G1; QoE: PolCon 62/62
- 9.12.2. After RAI therapy the patient should receive full information regarding whether and for how long to avoid contact with other people, especially with children and pregnant women. On average, 1–2 weeks after adjuvant RAI treatment following radical surgery is enough.
SoR: G1; QoE: PolCon 62/62
- 9.13. RAI treatment of DTC dissemination or local recurrence.
- 9.13.1. RAI therapy in disseminated cancer is usually carried out after L-thyroxine withdrawal.
SoR: G1; QoE: +++; ATA GL R53
- 9.13.2. Therapy of metastases with thyrotropin alpha may be conducted under clinical trials held in centres where full monitoring and treatment of possible side-effects as well as the assessment of its outcomes are available.
SoR: G1; QoE: ++ / PolCon 62/62
- 9.14. Dosimetry of RAI treatment.
- 9.14.1. Currently, there are no defined principles of dosimetry planning referred to RAI treatment. There are no widely accepted methods of therapeutic dose individualisation, that would safely sterilise cancer lesions without excessive side effects to healthy organs. Therefore, pre-therapeutic dosimetry is not obligatory.
SoR: G2; QoE: +
- 9.15. Complications after RAI treatment and how to avoid them.
- 9.15.1. After exceeding a cumulative dose of 18.5 GBq (500 mCi) a cost-benefit analysis should be performed, concerning the enhanced radiogenic risk of occurrence of secondary cancer.
SoR: G1; QoE: PolCon 62/62
- 9.15.2. Contraception is recommended for 6–12 months in women and 4–6 months in men after RAI therapy.
SoR: G1; QoE: PolCon; 62/62
10. Teleradiotherapy.
Teleradiotherapy of neck and mediastinum is recommended [63]:
— in undifferentiated/ anaplastic thyroid cancer;
— after non-radical surgery of DTC, if secondary surgery or radioiodine treatment is not possible;
— may be considered after non-radical surgery in MTC.
SoR: G2; QoE: PolCon; 62/62
- 10.1. Adjuvant teleradiotherapy.
- 10.1.1. In radically operated DTC usually there are no indications to adjuvant teleradiotherapy. It may be considered in advanced locoregional cases after R1/R2 surgery [63, 64].
SoR: G1; QoE: +++
- 10.1.2. There is no evidence of effectiveness of adjuvant teleradiotherapy in MTC after radical surgery.
SoR: G1; QoE: PolCon 62/62
- 10.1.3. It may be considered in patients with MTC lymph node metastases, in whom calcitonin level does not normalise after surgery and there are no data suggesting distant metastases.
SoR: G2; QoE: + / PolCon 62/62
- 10.2. Teleradiotherapy procedures.
- 10.2.1. Radical teleradiotherapy involves the administration of 50–60 Gy on the region neck lymphatic system and 60–66 Gy on thyroid bed/tumour [63, 65, 66].
SoR: G1; QoE: +++
- 10.2.2. Conformal radiotherapy with modulated dose intensity is recommended if it is possible in a particular centre [67–71].
SoR: G1; QoE: +++

- 10.2.3. Palliative teloradiotherapy is used in inoperable thyroid cancer [72–74].
SoR: G1; QoE: +++
- 10.2.4. Palliative teloradiotherapy of metastases, including radiotherapy to control pain, is used in thyroid cancer according to the principles applied in other types of cancer [72, 74, 75].
SoR: G1; QoE: +++
11. Assessment of the efficacy of combined treatment.
- 11.1. In patients who do not demonstrate an increase of Tg serum concentration during L-thyroxine treatment the assessment should be carried out 12 months after adjuvant RAI treatment.
SoR: G1; QoE: +++
- 11.2. DTC remission may be diagnosed if patients after total thyroidectomy and adjuvant RAI therapy do not demonstrate any symptoms of persistent disease in imaging examinations or an increase in serum Tg level after TSH stimulation. Such tests are particularly reliable in the absence of anti-Tg autoantibodies.
SoR: G1; QoE: +++
- 11.3. Minimal RAI uptake in thyroid bed is not unequivocal with ineffective ablation, and it does not constitute an indication for another RAI treatment itself, if: a) other tests do not show recurrent disease, b) stimulated Tg does not exceed 1–2 ng/mL, and c) thyroid remnants are absent in ultrasound.
SoR: G2; QoE: ++
12. Follow-up of the patients in whom excellent treatment response is diagnosed.
The criterion of persistent remission, stated after primary treatment, is a combination of negative neck ultrasound and TSH-stimulated serum Tg level \leq 1 ng/mL and simultaneously the lack of other features of persistent or recurrent disease [52].
SoR: G1; QoE: +++
- 12.1. The frequency of the above-mentioned examinations is given below. However, it seems that at least one examination confirming this condition should be performed 3–5 years after the first diagnosis of DTC remission.
SoR: G1; QoE: +++ / PolCon 62/62
- 12.2. Whole-body scan is currently not routinely performed in the follow-up of further course of the disease in patients showing excellent treatment response.
SoR: G1; QoE: +++
- 12.2.1. However, the authors of these recommendations believe that there is no reason to resign from whole-body scan together with an examination evaluating treatment efficacy with Tg stimulation test, because in the case of serum Tg increase simultaneously the information about the presence of any RAI-avid cancer foci is provided.
SoR: G1; QoE: PolCon 62/62
- 12.2.2. In a patient in whom the first evaluation after treatment revealed excellent response and a further course of disease is asymptomatic, control Tg tests do not require TSH stimulation.
SoR: G1; QoE: +++
13. Interpretation of serum Tg results in DTC patients.
- 13.1. Because increasing serum Tg constitutes the defined criterion for the detection of DTC recurrence, it is important to evaluate this marker in the same centre by the same method.
SoR: G1; QoE: +++
- 13.1.1. Optimally, for Tg estimation methods standardised to Certified Reference Material 457 (CRM-4570) should be used. Each laboratory should characterise the functional sensitivity of its own Tg analysis method [76].
- 13.2. Tg assessment should be accompanied by the evaluation of Tg antibodies, which should be performed at least once a year.
SoR: G1; QoE: +++
- 13.2.1. If anti-Tg antibodies are present, low serum Tg level cannot be a fully reliable criterion of treatment response.
SoR: G1; QoE: +++
- 13.3. Interpretation of serum Tg level should refer to earlier Tg results, level of Tg antibodies, present and previous TSH level, as well as extent of previous surgery and RAI treatment.
SoR: G1; QoE: +++
- 13.4. Ultrasensitive methods of serum Tg evaluation (functional sensitivity of 0.1 ng/mL) are recommended.
SoR: G1; QoE: +++
- 13.5. During the first five years after primary treatment in patients with excellent treatment response, if there are no other risk factors, it is recommended that Tg evaluation is maintained every 6–12 months, and later these intervals may be longer.
SoR: G1; QoE: PolCon 62/62
- 13.6. If the patient did not undergo total thyroidectomy and/or RAI therapy, the serum Tg level may be higher than 1 ng/mL, and only increasing Tg levels may speak for suspicion of cancer progression. Time intervals between subsequent Tg evaluations should at least fol-

- low the rules given in par. 13.5. If it is indicated, time intervals should be shorter.
SoR: G1; QoE: ++
- 13.7. Tg level should not constitute the only factor monitoring cancer remission in DTC patients. As well as the patient's history and physical examination, at least neck ultrasound should be performed in a similar time period [77].
SoR: G1; QoE: ++
14. Principles of the follow-up of DTC patients whom anti-Tg antibodies are present.
- 14.1. Neck ultrasound is the main follow-up examination in patients after radical surgery, in whom the presence of anti-Tg antibodies make reliable Tg level measurements and interpretation impossible. One should remember that medical history and physical examinations are necessary to determine the indications for other imaging studies.
SoR: G1; QoE: +++
15. Neck ultrasound in the evaluation of treatment efficacy and follow-up in DTC.
Neck ultrasound should be carried out every 6–12 months during first five years and then less frequently. In a case of suspicion of recurrence, the time intervals should be shorter. The diagnosis of cancer lesions in thyroid bed or enlarged lymph nodes are indications for FNAB, especially if the appearance of neck lymph nodes suggests their metastatic character (transversal diameter > 5 mm, loss of hilar architecture, heterogenic echotexture with cystic areas, round shape, peripheral or mixed vascularity, calcifications). See part I, par. 11.2.
SoR: G1; QoE: +++
- 15.1. If a suspected lymph node is < 1 cm in diameter, its follow-up may be accepted and FNAB may be performed in the case of its further growth.
SoR: G2; QoE: PolCon 62/62
- 15.2. Tg assessment in the aspirate taken on FNAB may be helpful in a diagnosis of lymph node metastasis.
SoR: G2; QoE: +++
- 15.3. Normal serum Tg level does not exclude lymph node metastases.
SoR: G1; QoE: +++
16. Whole-body scan after RAI administration.
- 16.1. Isotope examinations (particularly neck and whole-body scans) are usually useful for the first evaluation of RAI treatment efficacy; however, they are not obligatory.
SoR: G1; QoE: PolCon 62/62
- 16.1.1. However, if such examinations performed after RAI treatment indicate a very low risk of cancer relapse in a low-risk patient after radical surgical approach, it is acceptable to resign from diagnostic RAI scans.
SoR: G1; QoE: +++
- 16.1.2. In the case of an increase in serum Tg level (evaluated on L-thyroxine therapy or after TSH stimulation) neck and whole-body scans are obligatory to localise RAI-avid cancer foci and to assess indications for RAI treatment.
SoR: G1; QoE: +++
- 16.1.3. Routine, periodic whole-body scan in the further follow-up of patients, in whom cancer remission is stated, is not necessary because the chance of diagnosing RAI-avid recurrence without earlier increase in serum Tg level is low.
SoR: G1; QoE: +++
17. CT and MRI.
- 17.1. CT and/or MRI are performed if there is a suspicion of cancer recurrence resulting from an increasing serum Tg level or other symptoms. However, one should remember that CT with contrast administration attenuates RAI avidness for at least two months or longer.
SoR: G1; QoE: ++
- 17.2. Chest CT scan is performed as the first imaging in the case of serum Tg increase.
SoR: G1; QoE: +++
- 17.3. Suspicion of bone metastases, stated on the basis of patient's history, physical examination, or other examination, is an indication for bone scan.
SoR: G1; QoE: +++
- 17.4. FDG-PET/CT is useful to localise cancer relapse or distant metastases, especially in patients in whom serum Tg increase is not accompanied by the detection of cancer foci by other classical imaging examination and RAI whole body scan. It should be added that the intensity of glucose metabolism in cancer foci demonstrates a prognostic significance and that in some patients an increased glucose metabolism is revealed only after TSH stimulation [78].
SoR: G1; QoE: +++
- 17.5. A negative FDG PET/CT does not exclude DTC dissemination [60].
SoR: G1; QoE: +++
18. Treatment with L-thyroxine in DTC patients.
- 18.1. Hormonal therapy with L-thyroxine is an essential part of a combined DTC treatment.
SoR: G1; QoE: +++

18.2. The goal of L-thyroxine therapy in DTC patients is:

- supplementation of hormonal deficiency (substitutive treatment);
- reduction of the risk of cancer relapse because TSH is a growth factor for cancer cells (suppressive treatment is currently considered only in high-risk patients or in patients who do not demonstrate excellent treatment response).

SoR: G1; QoE: +++

19. Indications for TSH suppression.

19.1. Full TSH suppression (TSH < 0.1 mU/L) is necessary for the following reasons:

- in patients with persistent, clinically apparent DTC symptoms;
- in patients with incomplete biochemical response according to ATA guidelines, in whom clinically apparent disease is not present, but stimulated serum Tg level (> 10 ng/mL) and/or serum Tg level on thyroxine suppressive doses (> 1 ng/mL) are elevated or anti-Tg level increases.

SoR: G1; QoE: ++

19.2. Full TSH suppression may be considered in patients demonstrating a high risk of relapse if there are no contraindications for suppressive treatment or treatment benefits compensate the risk related to suppressive treatment.

SoR: G1; QoE: +++

19.3. Proof confirming safety of the resignation from L-thyroxine suppressive therapy has been published with reference to the lowest-risk group:

- patients staged pT_{1a}-N₀M₀;
- patients staged pT_{1b}-T₂N₀, radically treated, in whom excellent treatment response has been achieved.

In these patients, substitutive L-thyroxine doses should be administered. Incomplete TSH suppression (TSH 0.1–0.4 mU/L) is also acceptable, but the decision should be personalised.

SoR: G1; QoE: +++

19.4. In these patients, in whom an excellent treatment response has been confirmed by all possible methods, among them by a low serum Tg level with the absence of anti-Tg antibodies, and the remission lasts at least five years, substitutive L-thyroxine treatment is acceptable.

SoR: G1; QoE: +++

19.5. In all patients who undergo DTC treatment an increase of serum TSH level > 2 mU/L should be avoided except for short periods of TSH stimulation due to follow-up examinations.

SoR: G1; QoE: +++

19.6. In patients on full TSH suppression the addition of a beta-blocker or ACE inhibitor to prevent cardiac hypertrophy may be considered.

SoR: G1; QoE: ++

20. Dosage of L-thyroxine.

20.1. L-thyroxine dose is established individually, and is administered once a day, fasting, 20–30 minutes before food intake. Regardless of the fact that all L-thyroxine forms registered in Poland are considered equal, there are some differences in their bioavailability, and therefore one drug should not be replaced by another without justification and the decision of an aware physician because it may influence the precise serum TSH control.

SoR: G1; QoE: +++

20.2. If L-thyroxine dose requires modification, small dose changes are acceptable (in general, not higher than by 25 µg daily) and subsequent assessment of TSH level should be done in 6–8 weeks.

SoR: G1; QoE: +++

20.3. Serum TSH level should be measured every 3–6 months, using a third-generation assay, in the morning before L-thyroxine dose intake.

SoR: G1; QoE: +++

20.4. Treatment-related side effects of cardiovascular system, bones, and others should be monitored and, if indicated, concomitant medications should be administered.

SoR: G1; QoE: +++

21. L-thyroxine treatment in other types of thyroid cancer.

Patients diagnosed with MTC, poorly differentiated, and ATC require substitutive L-thyroxin doses only.

SoR: G1; QoE: +++

22. Thyroid cancer in children.

Thyroid cancer (papillary) in children and adolescents commonly shows more advanced stages than in adults and simultaneously is characterised by a good prognosis, mostly if the treatment radicalness is sufficient. Thus, the authors of these recommendations selected a Paediatric Working Group and prepared separate guidelines [79].

SoR: G1; QoE: +++

23. Cancer recurrence and persistent/progressive disease.

23.1. The risk of cancer relapse in DTC is the highest during the first five years; however, it should be considered life-long, and therefore continuous follow-up in a treating centre is required. Such follow-up should be carried out every 5–10 years.

SoR: G1; QoE: +++

- 23.2. The optimal solution assumes the follow-up in the same centre where the primary treatment was performed.
SoR: G1; QoE: PolCon 62/62
24. Treatment of locoregional DTC relapse.
- 24.1. Surgery is the main treatment option. RAI treatment may be administered if indicated.
SoR: G1; QoE: +++
- 24.2. In the case of non-resectable tumour showing no RAI avidness, which demonstrates progression despite previous treatment, radiotherapy is recommended [63].
SoR: G1; QoE: ++
25. Treatment of distant metastases.
- 25.1. RAI treatment is indicated if all metastatic lesions demonstrate RAI avidness.
SoR: G1; QoE: +++
- 25.2. In the case of a single metastasis, surgery should be considered if its resection is possible and other metastases are excluded with a high probability [80].
SoR: G1; QoE: ++
- 25.2.1. In a single brain metastasis the decision regarding the operation should be personalised, because in the case of difficult surgical approach, RAI treatment (if a lesion shows RAI uptake) may be more beneficial. Considering this issue, the authors' opinion is in contrast to the European consensus that recommends neurosurgery first.
SoR: G2; QoE: +
- 25.3. Induction of RAI avidness with the use of cis-retinoid acid is not an approved treatment method and should not be used outside clinical trials [81].
SoR: G1; QoE: +
26. Radiotherapy is used in the palliative treatment of metastases [63].
SoR: G1; QoE: +++
27. Pharmacological treatment of DTC.
- 27.1. L-thyroxine administration is a hormonal therapy of DTC (see par. 18–20).
SoR: G1; QoE: +++
- 27.2. There is no proof supporting the use of chemotherapy in DTC.
SoR: G1; QoE: +
- 27.3. Targeted therapy with the use of tyrosine kinase inhibitors is recommended in DTC patients with locally advanced or disseminated cancer, RAI resistant, demonstrating progression fulfilling Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1. This therapy is approved in the EU but not reimbursed in Poland [82].
SoR: G1; QoE: +++
- 27.3.1. If there is no possibility to use sorafenib or lenvatinib, it is recommended that the patients are treated under randomised clinical trials.
SoR: G1; QoE: +++
- 27.3.2. Sorafenib 400 mg BID [83].
SoR: G1; QoE: +++
- 27.3.3. Lenvatinib 24 mg QID [84].
SoR: G1; QoE: +++
- 27.3.4. This treatment should be carried out in centres experienced in targeted therapy and follow-up of treatment-related side-effects.
SoR: G1; PolCon: 62/62
28. Medullary thyroid carcinoma.
- 28.1. Management in medullary thyroid cancer is substantially different from that of DTC, for the following reasons.
- 28.1.1. In a high percentage of cases, it is a hereditary disease. Using DNA analysis a genetic predisposition in family members may be stated, in which case prophylactic surgery is necessary [85].
SoR: G1; QoE: +++
- 28.1.2. The high specificity and sensitivity of serum calcitonin (Ct) evaluation justifies application of this marker in MTC diagnosis, determination of the extent of surgery, early detection of MTC relapse/progression, and its prognosis [6].
SoR: G1; QoE: +++
- 28.1.3. Compared to DTC, more extensive elective lymphadenectomy is recommended, depending on serum Ct concentration [86].
SoR: G1; QoE: +++
- 28.1.4. High risk of pheochromocytoma in patients with hereditary MTC.
SoR: G1; QoE: +++
- 28.1.5. Different indications and other types of radioisotope treatment.
SoR: G1; QoE: +++
29. Diagnosis of MTC.
- 29.1. Diagnosis of MTC by FNAB is often difficult because it requires immunocytochemistry with the use of anti-Ct antibodies or confirmation of serum calcitonin increase.
SoR: G1; QoE: +++
- 29.2. Diagnosis of MTC may be based on serum Ct evaluation, and if serum Ct level exceeds > 100 pg/mL, it is highly probable [87].
SoR: G1; QoE: +++

- 29.3. The Ct stimulation test helps in resolving doubtful cases and improves the effectiveness of preoperative diagnostics and follow-up of MTC [88].
SoR: G1; QoE: +++
- 29.4. Measurement of Ct concentration in the needle washout improves FNAB accuracy in MTC diagnosis.
SoR: G1; QoE: +++
30. DNA tests in MTC.
- 30.1. A DNA test should be performed in every patient diagnosed with MTC, even if family history and physical examination do not indicate hereditary MTC [89].
SoR: G1; QoE: +++
- 30.2. Interpretation of DNA test with respect to probability of mutation carriage.
- 30.2.1. The DNA test is based on analysis of known RET proto-oncogene mutations in a sample of the patient's peripheral blood. It should be performed in accredited centres only [85].
SoR: G1; QoE: +++
- 30.2.2. A negative result of full DNA analysis excludes hereditary MTC with a probability of 95%.
SoR: G1; QoE: +++
- 30.2.3. A positive result of DNA analysis is an indication for testing family members of the patient [85].
SoR: G1; QoE: +++
- 30.2.4. Detection of asymptomatic gene mutation carrier and a negative DNA test in a family member have to be confirmed by a DNA test of another blood sample of this family member.
SoR: G1; QoE: ++ / PolCon 62/62
- 30.2.5. The probability of a positive DNA result in a patient with a negative family history is about 10% [89].
SoR: G1; QoE: +++
31. Management of families of RET gene mutation carriers.
- 31.1. Hereditary MTC occurs as a symptom of multiple endocrine neoplasia syndromes (MEN 2). In typical MEN2A and MEN2B syndromes, MTC coexists with pheochromocytoma, its risk of occurrence being up to 50%. Familial MTC (FMTC) without other endocrinopathies is a variant of the MEN2A syndrome [6].
SoR: G1; QoE: +++
- 31.2. In a family with hereditary MTC the risk of MTC in a first-degree relative is 50% [85].
SoR: G1; QoE: ++
- 31.3. DNA testing to detect RET mutation carriage in MEN2a/FMTC families should begin at age of 2–3 years, and must be performed before five years of age [6].
SoR: G2; QoE: ++
- 31.4. DNA tests in MEN2B families should be performed as soon as possible, optimally within the first year of life [6].
SoR: G1; QoE: +++
- 31.5. According to ATA MTC guidelines the following terminology concerning RET mutations carriers: ATA-MOD, ATA-H, and ATA-HST is recommended (Table VIII).
SoR: G2; QoE: +
32. Diagnostic management in RET mutation carriers [6]. Complete diagnostics to evaluate current stage of disease, performed in RET mutation carriers, should involve:
- Basal and stimulated serum Ct measurement;
 - Neck ultrasound;
 - FNAB if thyroid lesions are present;
 - Abdominal ultrasound;
 - Biochemical diagnostics, to exclude pheochromocytoma;
 - Serum calcium measurement.
- SoR: G1; QoE: +++
33. Total prophylactic thyroidectomy in RET mutation carriers.
- 33.1. In asymptomatic RET mutation carriers total prophylactic thyroidectomy should be considered [90].
It is accepted that prophylactic surgery offers better protection against MTC development than long-term follow-up of serum Ct level.
SoR: G1; QoE: +++
34. Total prophylactic thyroidectomy is indicated in the following cases [6]:
- Right after detection of RET mutation in MEN2B syndrome (in this syndrome, the DNA test is obligatory within the first year of life — ATA HST category — Table VIII);
 - After the age of five years in MEN2A syndrome and FMTC (DNA test is performed between two and three years of age — ATA H and MOD categories).
- SoR: G2; QoE: ++
35. In carriers with RET mutations with later MTC onset (ATA MOD category) it is acceptable to postpone prophylactic surgery to above five years of age if the patient or parents are fully informed of risk related to treatment delay and fully accept this option, if basal serum Ct concentration is normal, if there are no thyroid lesions in neck ultrasound,

Table VIII. Risk classification and proposed management in RET mutations carriers regarding the type of RET mutation [6]

ATA risk category	Type of RET mutation	Management
ATA-HST	MEN 2B / RET codon 918	Total thyroidectomy in the first year of life Level VI lymph node dissection dependent on the ability to identify or preserve or transplant the parathyroid glands
ATA-H	MEN 2A / RET codon 634	Total thyroidectomy at or before 5 years based on serum Ct levels
ATA-MOD	MEN 2A / other types — RET — mutation	Total thyroidectomy to be performed when the serum Ct level becomes elevated or in childhood if parents do not wish to embark on lengthy period of evaluation

and if family history confirms a relatively mild course of disease.

SoR: G2; QoE: ++ / PolCon 62/62

36. In RET mutation carriers, in whom prophylactic surgery has not yet been performed, stimulated serum Ct concentration evaluated every year may lead to MTC diagnosis earlier than evaluation of basal Ct concentration (pentagastrin is not available in Poland. Therefore calcium, administered intravenously, is used for stimulation test).

36.1. Normal increase in serum Ct concentration after intravenous calcium administration does not exceed 30 pg/mL.

SoR: G2; QoE: + / PolCon 62/62

36.2. An increase in serum Ct concentration above 100 pg/mL after calcium stimulation is interpreted as a positive result. However, this result does not uniquely confirm MTC diagnosis (because it may result from C-cell hyperplasia). Nevertheless, it is an absolute indication for surgery in RET mutation carriers.

SoR: G2; QoE: + / PolCon 62/62

36.3. Intravenous calcium infusion may be an alternative to pentagastrin test.

— Pentagastrin is not available in Poland.

SoR: G1; QoE: ++ / PolCon 62/62

37. Diagnosis and treatment of pheochromocytoma in MEN2 syndrome.

37.1. Recommended diagnostic tests for pheochromocytoma depend on the type of RET mutation [6, 91, 92].

SoR: G1; QoE: +++

37.2. Diagnosis of pheochromocytoma is based on yearly biochemical tests. In MEN2B and in RET codon 634 and 630 mutation carriers in MEN2A syndrome, these should begin at the age of eight years. In carriers of other types of RET mutation, they should begin at the age of 20 years [6, 91].

SoR: G1; QoE: ++

37.3. Screening abdominal CT is not necessary in MTC patients if there are no clinical symptoms

of pheochromocytoma and biochemical tests are negative.

SoR: G1; QoE: PolCon 62/62

37.4. Treatment of pheochromocytoma is based on surgery. Optimally, tumourectomy is recommended [93].

SoR: G1; QoE: ++

37.5. If pheochromocytoma and MTC coexist, adrenal surgery should be carried out as the first procedure, to avoid symptoms of excessive hormone secretion from this adrenal tumour.

SoR: G1; QoE: +++

38. Surgery for pheochromocytoma.

The operation should be preceded by at least two weeks of pharmacological pretreatment [93]

SoR: G1; QoE: +++

38.1. Tumourectomy should be performed instead of adrenalectomy, especially if surgery concerns the other adrenal gland, following previous unilateral adrenalectomy [93].

SoR: G1; QoE: ++

38.2. If bilateral adrenalectomy is necessary, the patient should be fully informed about the principles of substitution therapy. IMPORTANT NOTICE: in hereditary MTC in the course of MEN2 syndrome, a significant percentage of deaths are related to adrenal complications — adrenal crisis or adrenal insufficiency.

SoR: G1; QoE: ++

39. Diagnosis and treatment of primary hyperparathyroidism in the course of MEN2 syndrome.

39.1. Indications for diagnostics of primary hyperparathyroidism depend on the type of RET mutation [94].

SoR: G1; QoE: ++

39.1.1. Serum calcium evaluation once a year is recommended in RET codon 634 and RET codon 630 mutation carriers, while in FMTC it may be evaluated less frequently.

SoR: G1; QoE: +++

39.1.2. The treatment of hyperparathyroidism in the course of MEN2A syndrome

should follow generally accepted rules.
IMPORTANT NOTICE: Hyperparathyroidism is often caused by parathyroid hyperplasia; therefore, the risk of unsuccessful surgery is higher than in the case of single adenoma [95].

SoR: G2; QoE: +

40. Surgery in clinically apparent MTC.

40.1. If MTC is clinically apparent (the presence of a thyroid nodule and a positive result of FNAB) thyroid surgery should always involve total thyroidectomy accompanied by central neck dissection, both in hereditary and sporadic MTC.
 SoR: G1; QoE: +++

40.2. The extent of lateral neck lymphadenectomy depends on the presence of lymph node metastases in neck ultrasound and on serum Ct concentration [49].
 SoR: G1; QoE: +++

40.3. There are no unequivocal indications for lateral neck lymphadenectomy if no enlarged lymph nodes have been found and if preoperative serum Ct concentration is below 200 pg/mL [49].
 SoR: G1; QoE: ++

40.4. If serum Ct concentration is above 400 pg/mL, the result of abdominal CT scan should be known to the surgeon planning the extent of local surgery [86].
 SoR: G1; QoE: +++

40.5. ATA MTC guidelines specify serum calcitonin concentration of 150 pg/mL as the lower limit value for these indications.
 SoR: G1; QoE: ++

41. Surgery in early detected MTC.

41.1. If the reason for surgery is elevated serum Ct concentration in a patient with nodular goitre, total thyroidectomy is recommended.
 SoR: G1; QoE: +++

41.2. If a small MTC lesion below 10 mm has been incidentally diagnosed after less than total thyroidectomy, and postoperative both basal and stimulated serum Ct concentration is within the normal range, genetic testing for hereditary mutation in the RET gene is negative, and no other risk factors are apparent, resignation from secondary total thyroidectomy is acceptable.
 SoR: G2; QoE: +

42. Prophylactic surgery in RET mutation carriers.

42.1. Indications for prophylactic thyroidectomy given in par. 34 should include the result of DNA analysis (type of RET mutation), current Ct concentration, patient's age, and family history. In such a case thyroid cancer surgery, in general recommended in a specialist centre,

should only be performed in a highly experienced referral centre.

SoR: G2; QoE: +

42.2. Prophylactic total thyroidectomy performed in a timely manner (see par. 34 and 35) may not include central neck dissection if basal serum Ct concentration is normal and there are no symptoms of nodal involvement.

SoR: G2; QoE: ++

42.3. If at the age of five years a RET mutation MEN2A/FMTC predisposing a carrier shows no increase in basal serum Ct concentration, the calcium stimulation test may be useful in deciding whether surgery may be postponed. However, the type of RET mutation should also be considered.

SoR: G2; QoE: + / PolCon 62/62

42.4. If prophylactic operation has not been performed at the optimal age, as given in par. 36, and if basal serum Ct concentration is normal, a calcium stimulation test performed once a year may decrease the chance of missing the optimum time to perform surgery.

SoR: G2; QoE: + / PolCon 62/62

43. Postoperative evaluation and follow-up in MTC.

43.1. Postoperative assessment of serum Ct concentration.

43.1.1. Normalisation of postoperative Ct concentration is the best indicator of achieving radical surgery and is a positive prognostic factor.

SoR: G1; QoE: +++

43.1.2. While the authors of these recommendations are aware that some American specialists consider the calcium stimulation test to be unnecessary, the experience of many European centres supports calcitonin stimulation tests in patients with normal basal Ct concentration. The negative result of calcium stimulation test (some authors suggest no increase of Ct concentration as the optimum response to this test) is a reliable prognostic factor.

SoR: G2; QoE: + / PolCon 62/62

43.1.3. One should remember that if Ct concentrations above 300–500 pg/mL are stated, serum dilution is required in order to obtain a reliable result.

SoR: G2; QoE: + / PolCon 62/62

43.1.4. Estimation of serum Ct doubling time is recommended because it is of proven prognostic and predictive value.

SoR: G1; QoE: + / PolCon 62/62

- 43.2. Further MTC follow-up involves:
- serum Ct evaluation;
 - neck ultrasound;
 - serum CEA concentration;
 - imaging tests — only if serum Ct concentration exceeds 150 pg/mL or rather 400 pg/mL.
- SoR: G1; QoE: ++ / PolCon 62/62
- 43.3. Management in the case of asymptomatic increase in serum Ct concentration.
- Ct concentration is a very sensitive marker of tumour mass.
- SoR: G1; QoE: +++
- 43.3.1. At Ct concentration below 150 pg/mL, imaging tests such as CT, MRI, or PET/CT are not justified as they are not able to detect cancer foci.
- SoR: G1; QoE: ++
- 43.3.2. At Ct concentration range 150–1000 pg/mL, a possible false negative result in the localisation of cancer foci by imaging tests should be considered.
- SoR: G1; QoE: +++
- 43.3.3. If Ct concentration ranges between 400 and 1000 pg/mL the possibility of cancer foci localisation increases [96].
- SoR: G1; QoE: +++
- 43.3.4. At asymptomatic increase of Ct concentration, central neck dissection (if not previously performed) and/or elective lateral neck lymphadenectomy may be considered.
- SoR: G2; QoE: ++
- 43.3.5. IMPORTANT NOTICE: liver micrometastases may often be the reason for increased serum Ct concentration.
- SoR: G1; QoE: +++
44. Management in recurrent MTC.
- 44.1. Surgery is the basic treatment of local and locoregional recurrence.
- SoR: G1; QoE: +++
- 44.2. If local/locoregional recurrence is accompanied by distant metastases, the indications for neck/mediastinal surgery are equivocal.
- SoR: G2; QoE: +
- 44.3. Disseminated MTC very rarely involves a single metastatic lesion; therefore, surgical treatment of metastatic disease, particularly of liver metastases, is generally not justified.
- SoR: G2; QoE: + / PolCon 62/62
- 44.4. Adjuvant teloradiotherapy is indicated only in the case of non-radical surgery at the micro- or macroscopic level. Palliative teloradiotherapy is often used in bone and brain metastases, and rarely in other metastatic locations.
- SoR: G2; QoE: +
- 44.5. Classical chemotherapy it is not recommended.
- SoR: G1; QoE: +++
- 44.6. Isotope therapy with different radiopharmaceuticals selectively taken up by cancer cells is usually a palliative treatment.
- SoR: G1; QoE: +++
- 44.7. The effectiveness of somatostatin analogues in MTC stabilisation has not been demonstrated.
- SoR: G1; QoE: +++
- 44.8. Targeted therapy with the use of tyrosine kinase inhibitors is recommended in MTC patients with locally advanced or disseminated cancer, demonstrating progression fulfilling RECIST 1.1 criteria. This therapy is approved in the EU but not reimbursed in Poland (June 2017) [97].
- 44.8.1. If use of vandetanib or cabozantinib is not possible, treatment of the patients under randomised clinical trials is recommended.
- SoR: G1; QoE: +++ / PolCon 62/62
- 44.8.2. Vandetanib — 300 mg once a day [98]
- SoR: G1; QoE: +++
- 44.8.3. Cabozantinib — 140 mg once a day [99].
- SoR: G1; QoE: +++
45. Treatment of poorly differentiated and undifferentiated (anaplastic) thyroid cancer.
- 45.1. The prognosis in anaplastic thyroid carcinoma is poor. Radical surgery or radical radiotherapy are rarely possible and results of chemotherapy are disappointing [100, 101].
- SoR: G1; QoE: +++
- 45.2. Pharmacological treatment.
- 45.2.1. Chemotherapy is based on doxorubicin or on multidrug regimens. However, the superiority of the latter has not been proven. Concomitant radio- and chemotherapy is still at the stage of experimental therapy.
- SoR: G1; QoE: +++
- 45.2.2. New schemes of chemotherapy and targeted therapy should be applied within clinical trials.
- SoR: G1; QoE: PolCon 62/62
46. Diagnostics and treatment of primary thyroid lymphoma.
- 46.1. In the diagnostics of primary MALT thyroid lymphoma, imaging tests including ultrasound, CT, or MRI are necessary to exclude thyroid involvement in the course of disseminated lymphoma [102].
- SoR: G1; QoE: +++
- 46.2. Indications for surgery in primary thyroid lymphoma are not unequivocal, and surgery does not improve the long-term outcome.
- SoR: G1; QoE: ++

46.3. Radio- and chemotherapy are often the main treatment and their postoperative indication depends on tumour grade and advancement.

SoR: G1; QoE: +++

47. Rehabilitation, psychological care, and psychotherapy.

Adequate emotional and social support should be provided for patients with thyroid cancer, during and after completion of their oncological therapy, including full psychosocial recovery. Centres in which thyroid cancer is treated should offer specialised psycho-oncological and psychiatric care whenever necessary. Development of psychotherapy programmes aimed at rehabilitation and full return to the social roles held by patients prior to their treatment, is recommended.

SoR: G1; QoE: PolCon 62/62

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