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SFE-AFCE-SFMN 2022 consensus on the management of thyroid nodules

SFE-AFCE-SFMN 2022 consensus on the management of thyroid nodules: Synthesis and algorithms

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ABSTRACT

The SFE-AFCE-SFMN 2022 consensus deals with the management of thyroid nodules, a condition that is a frequent reason for consultation in endocrinology. In more than 90% of cases, patients are euthyroid with benign and non-progressive nodules that do not warrant specific treatment. The clinician's objective is to detect malignant thyroid nodules at risk of recurrence and death, toxic nodules responsible for hyperthyroidism or compressive nodules warranting treatment. The diagnosis and treatment of thyroid nodules requires close collaboration between endocrinologists, nuclear medicine physicians and surgeons but also involves other specialists. Therefore, this consensus statement was established jointly by 3 societies, the French Society of Endocrinology (SFE), the French Association of Endocrine Surgery (AFCE) and the French Society of Nuclear Medicine (SFMN); the various working groups included experts from other specialties (pathologists, radiologists, pediatricians, biologists, etc.). This specific text is a summary chapter taking up the recommendations from specific sections and presenting algorithms for the exploration and management of thyroid nodules.

An overview of the consensus is shown in Fig. 1.
The recommendations are given below for each section.

1. Section 2: initial assessment

1.1. Recommendation 2.1 (Fig. 2)

Medical history-taking should include diagnostic circumstances and the time course of thyroid nodule development, age, gender, comorbidities, history of neck radiation therapy, family history of thyroid nodules or thyroid cancer, and genetic disorders that can increase the risk of thyroid cancer.

Level of evidence +++ Grade A

1.2. Recommendation 2.2

Clinical examination should assess thyroid volume, signs of hyper- or hypothyroidism, consistency of the nodule or nodules, their size, topography and mobility with respect to surrounding tissue, thyroid pain, compressive signs and their progression, and screen for cervical lymph nodes.

Level of evidence +++ Grade A

Recommendation 2.3:

- recommendation 2.3a: TSH should be measured as part of the initial work-up of thyroid nodules, to screen for thyroid dysfunction. Level of evidence +++ Grade A;

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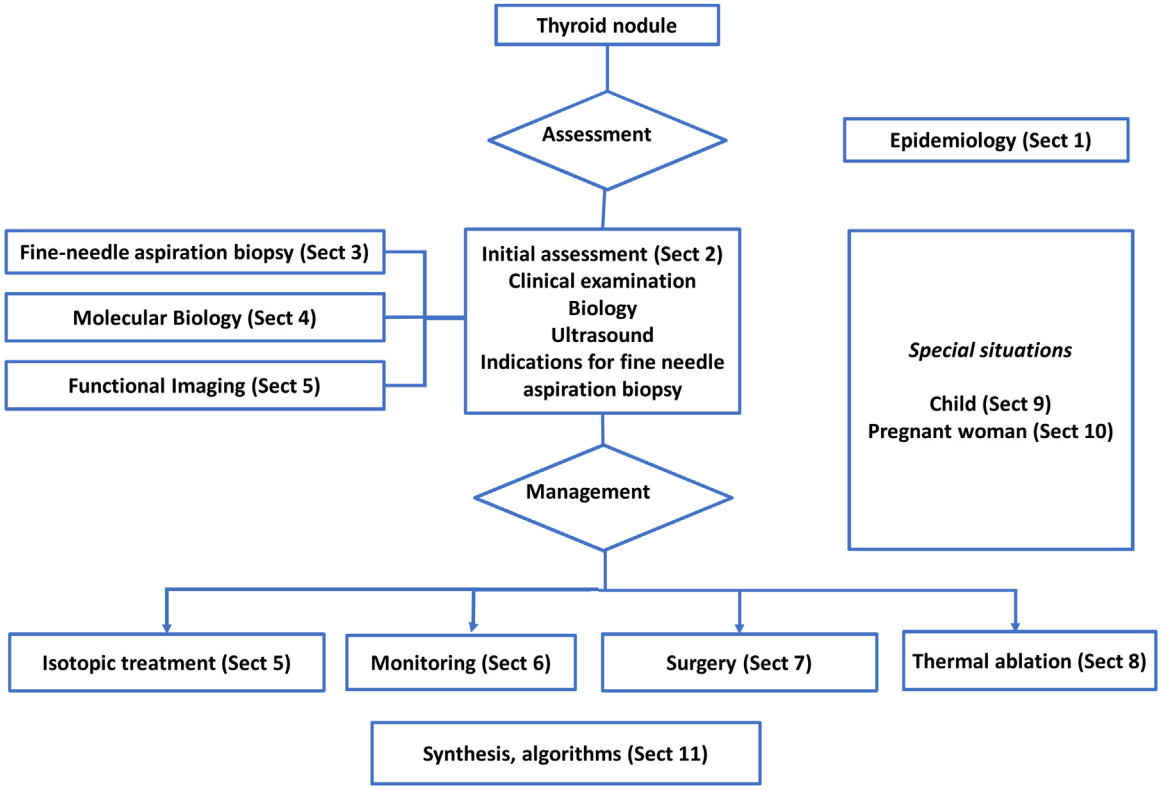

Fig. 1. General presentation of the consensus.

- recommendation 2.3b: a low TSH level between 0.1 mIU/L and 0.4 mIU/L should be checked after a few weeks. If the TSH is below 0.1 mIU/L, or if low TSH is confirmed, FT4 and possibly FT3 should be measured to assess the severity of hyperthyroidism or to distinguish between overt and subclinical hyperthyroidism. Level of evidence +++ Grade A;
- recommendation 2.3c: a moderately elevated TSH level (< 10 mIU/L) should be checked after a few weeks, as it may normalize during follow-up. If TSH is > 10 mIU/L, or if moderately elevated TSH is confirmed, a FT4 assay should be performed to assess the severity of hypothyroidism or to distinguish between overt and subclinical hypothyroidism. Level of evidence +++ Grade A.

1.3. Recommendation 2.4

Routine calcitonin testing is not recommended for all thyroid nodules.

Level of evidence ++ Grade A

- recommendation 2.4a: calcitonin testing should be performed in the following situations: personal or family history of MTC or MEN2; thyroid nodule associated with diarrhea, flushing or lymph node metastasis; suspect thyroid nodule. Level of evidence +++ Grade A
- recommendation 2.4b: calcitonin should be measured before any thyroid surgery or thyroid thermal ablation. Level of evidence +++ Grade A
- recommendation 2.4c: a normal calcitonin test should not be repeated in the absence of a genetic predisposition to MTC. Level of evidence +++ Grade A

1.4. Recommendation 2.5

- recommendation 2.5a: routine measurement of serum calcium, corrected serum calcium and/or PTH in the presence of a thyroid nodule is not recommended. Level of evidence ++ Grade B
- recommendation 2.5b: prior to thyroid surgery, measurement of serum calcium is recommended. Level of evidence +++ Grade B

1.5. Recommendation 2.6

Routine measurement of serum thyroglobulin for the initial assessment of thyroid nodules is not recommended.

Level of evidence +++ Grade A

1.6. Recommendation 2.7

Thyroid ultrasound is recommended for the investigation of palpable nodules and incidentalomas. It is not recommended for routine screening.

Level of evidence +++ Grade A

1.7. Recommendation 2.8

The ultrasound report should describe the nodules and display them on a diagram. Risk stratification according to the EU-TIRADS score is advised, as well as including cervical lymph nodes and areas of the thyroglossal tract and upper mediastinum in the description.

Level of evidence +++ Grade A

1.8. Recommendation 2.9

Thyroid fine-needle aspiration biopsy (FNAB) is recommended for the following nodules, based on EU-TIRADS score and size:

- EU-TIRADS 3 nodules > 20 mm where the risk of malignancy is between 2% and 4% (very low risk);
- EU-TIRADS 4 nodules > 15 mm where the risk of malignancy is between 6% and 17% (low to intermediate risk);
- EU-TIRADS 5 nodules > 10 mm where the risk of malignancy is between 26% and 87% (intermediate to high risk);
- most suspicious nodules, when there is a lymph node suspected of metastasis of thyroid origin. FNAB should also be performed on the suspicious lymph node with in situ thyroglobulin/calcitonin measurement.

Level of evidence +++ Grade A

1.9. Recommendation 2.10

EU-TIRADS 5 nodule of size ≤ 10 mm should not undergo routine FNAB.
Level of evidence ++ Grade B

1.10. Recommendation 2.11

In the case of multiple nodules, indications for FNAB are case-by-case according to the size and EU-TIRADS score of each nodule. Priority should be given to nodules most likely to be cancerous (2 to 3 nodules maximum).
Level of evidence ++ Grade A

1.11. Recommendation 2.12

In mixed nodules, the solid tissue portion of each nodule should be accurately described, with size (or volume) and EU-TIRADS score, separately from the fluid portion. The indication for fine-needle aspiration biopsy depends on the EU-TIRADS score, ensuring that the tissue portion of the mixed nodule is accessible for FNAB and > 10 mm in size.
Level of evidence +++ Grade B

1.12. Recommendation 2.13

Lymph-node fine-needle aspiration biopsy should be performed for ultrasound-diagnosed lymph-node disease. Depending on the case, thyroglobulin or calcitonin measurement in the washout fluid of the suspicious lymph-node FNAB is indicated.
Level of evidence +++ Grade A

1.13. Recommendation 2.14

In the case of a symptomatic thyroid tumoral mass and/or rapid clinical progression suggesting anaplastic cancer or lymphoma, the patient should be referred urgently to an expert center for surgical biopsy or thyroid microbiopsy (possibly combined with FNAB) under ultrasound guidance, for diagnostic purposes and molecular genotyping.
Level of evidence ++ Grade A

1.14. Recommendation 2.15

Thyroid ultrasound is routinely recommended for incidental findings of focal thyroid uptake on 18F-FDG PET.
Level of evidence +++ Grade A

- recommendation 2.15a: in the case of a thyroid incidentaloma on 18F-FDG PET/CT, ultrasound criteria remain relevant for discrimination of benign versus malignant nodules. However, as the risk of malignancy is higher in thyroid nodules with focal 18F-FDG uptake, FNAB is recommended for all supracentimetric hypermetabolic nodules classified as EU-TIRADS 4 and 5 and hypermetabolic EU-TIRADS 3 nodules measuring 2 cm or more. Level of evidence ++ Grade A
- recommendation 2.15b: 18F-FDG PET/CT incidentalomas corresponding to subcentimetric or <2 cm EU-TIRADS 2 and 3 thyroid nodules can be monitored by ultrasound at 6-12 months and then managed according to progression, like thyroid nodules with unknown metabolic status. Level of evidence ++ Grade B

1.15. Recommendation 2.16

CT and MRI are usually not required in the assessment of thyroid nodules at initial work-up or during follow-up.
Level of evidence +++ Grade A

1.16. Recommendation 2.17

CT or MRI may be useful to investigate the substernal extension of a nodule or retrosternal goiter, to assess tracheal or esophageal compression or invasion, to study vascular anatomy preoperatively, and to map lymph nodes, in addition to ultrasound imaging.
Level of evidence ++ Grade A

2. Section 3: thyroid cytology recommendations: from technique to interpretation

2.1. Recommendation 3.1

Effective thyroid fine-needle aspiration biopsy relies on optimal technique and the quality cytological interpretation (Fig. 2).
Level of evidence +++ Grade A

2.2. Recommendation 3.2

It is recommended that thyroid fine-needle aspiration biopsy be performed by an experienced operator whenever possible, and guided by ultrasound.
Level of evidence +++ Grade A

2.3. Recommendation 3.3

It is recommended to use a fine 23–27 gauge needle, with or without aspiration, depending on the characteristics of the nodule.
Level of evidence +++ Grade A

2.4. Recommendation 3.4

It is recommended that the risk/benefit ratio of discontinuing coagulation-modifying therapy be assessed on an individual basis.
Level of evidence ++ Grade A

2.5. Recommendation 3.5

Direct smear thyroid FNAB: learning and experience are required for smear quality.
Level of evidence ++ Grade B

2.6. Recommendation 3.6

Liquid-based thyroid FNAB: liquid-based cytology eliminates the need to master the direct smear technique. The slide is easily analyzed; the cells are well conserved: complementary techniques are applicable.
Level of evidence +++ Grade A

2.7. Recommendation 3.7

Cell blocks allow complementary techniques (immunocytochemistry and molecular cytopathology) to be performed more easily.

Level of evidence +++ Grade A

2.8. Recommendation 3.8

Microbiopsy of a thyroid nodule is useful for solid nodules after at least 2 non-diagnostic FNABs.

Level of evidence +++ Grade A

2.9. Recommendation 3.9

Cytology results should be presented using the Bethesda system, specifying the year of the version.

Level of evidence ++ Grade A

2.10. Recommendation 3.10

It is recommended to send the FNAB to the cytologist with a form containing information detailing the ultrasound characteristics of the thyroid nodule and the clinical context.

Level of evidence ++ Grade A

2.11. Recommendation 3.11

The thyroid cytology report should include: 1) the Bethesda diagnostic category in full, possibly followed by its number (from I to VI) as often used in common practice; and 2) the cytological diagnosis.

Level of evidence +++ Grade A

Recommendation 3.11a – additional comments or explanatory notes may be added to the report by the cytopathologist.

Level of evidence +++ Grade B

Recommendation 3.11b – management recommendations or risk of malignancy may also be indicated in the report.

Level of evidence +++ Grade B

Recommendation 3.11c – the report may be written as free text or as a standardized form.

Level of evidence + Grade C

2.12. Recommendation 3.12

Immunocytochemistry techniques are recommended for:

- lesions suspected of being non-follicular in nature (parathyroid, medullary carcinoma, lymphoma, metastases). Level of evidence +++ Grade A;
- indeterminate categories III and IV of the Bethesda terminology.

Level of evidence ++ Grade B

3. Section 4: molecular biology

3.1. Recommendation 4.1

Given the cost of commercial tests, we advocate developing less expensive academic tests in France, in particular by high-throughput NGS, screening for mutations and gene fusions reportedly involved in thyroid tumorigenesis (Fig. 2).

Level of evidence: expert opinion, Grade B

3.2. Recommendation 4.2

We suggest that, considering the very good sensitivity and NPV, molecular testing should have a place in the management of cytologically indeterminate Bethesda III or IV nodules, with the aim of avoiding diagnostic surgery.

Level of evidence: expert opinion, Grade B

4. Section 5: the place of functional imaging and isotope therapy

4.1. Recommendation 5.1

In case of thyroid nodule, we recommend thyroid scintigraphy if the serum TSH is below the lower limit of normal (< 0.4 mIU/L) (Figs. 2 and 5). If serum TSH is between 0.4 and 1 mIU/L, we recommend thyroid scintigraphy only if fine-needle aspiration cytology is indicated.

Level of evidence ++ Grade A

4.2. Recommendation 5.2

Recommendation 5.2a: if TSH is $\geq$ 1 mU/L, thyroid scintigraphy is not recommended as a first-line procedure to characterize a solitary or prevalent nodule.

Level of evidence ++ Grade A

Recommendation 5.2b: the presence of a hot nodule on thyroid scintigraphy performed despite serum TSH being $\geq$ 1 mU/L does not contraindicate thyroid ultrasound and FNAB.

Level of evidence: expert opinion, Grade B.

4.3. Recommendation 5.3

For purely diagnostic purposes, thyroid scintigraphy can use either ^{99m}Tc or ^{123}I.

Level of evidence ++ Grade A

4.4. Recommendation 5.4

FNAB is not recommended for autonomous nodules with serum TSH in the low range of normal (< 1 mU/L).

Level of evidence ++ Grade A

4.5. Recommendation 5.5

In Bethesda III nodules, when TSH is < 1 mIU/L, thyroid scintigraphy, ideally with iodine 123, may be used to screen for an autonomous nodule. However, the added value of combined ultrasound/cytological classification has not been assessed.

Level of evidence ++ Grade C

4.6. Recommendation 5.6

99mTc-MIBI scintigraphy can be performed for thyroid nodules > 15 mm, not hot on thyroid scintigraphy (99mTc or 123I) and indeterminate on FNAB (Bethesda III–IV), due to its high NPV.

Level of evidence ++ Grade C

4.7. Recommendation 5.7

18F-FDG-PET/CT is not recommended for FNAC-indeterminate thyroid nodules (Bethesda III–IV), due to suboptimal NPV in recent studies and the lack of added value over and above combined ultrasound/cytology.

Level of evidence ++ Grade A

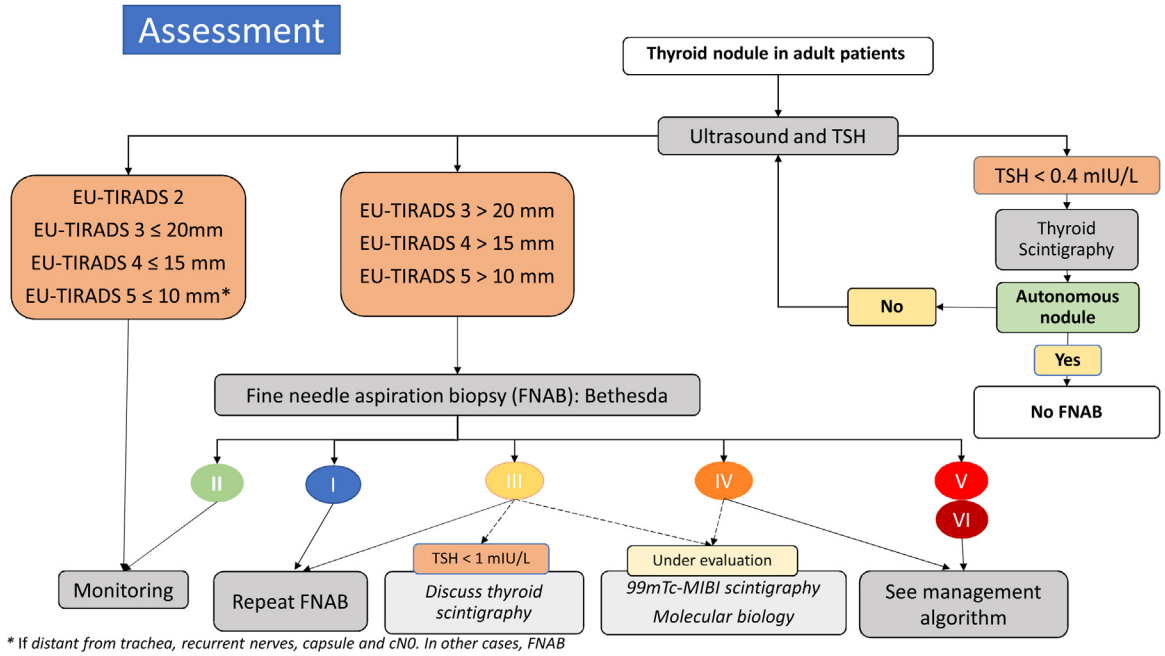

Fig. 2. Assessment algorithm.

4.8. Recommendation 5.8

RAI therapy should be performed in first line patients with overt hyperthyroidism (or subclinical hyperthyroidism requiring radical treatment) related to an autonomous nodule. Surgical treatment should be preferred in case of compressive nodules suspected on ultrasound, if pregnancy is planned within 6 months, or according to patient preference.

Level of evidence ++ Grade A

4.9. Recommendation 5.9

Preparation with beta-blockers (propranolol) and synthetic anti-thyroid drugs is not systematic before RAI therapy, but may be considered in cases of cardiovascular risk and high FT3, preferably using imidazoles, with two precautions:

- maintaining TSH suppression to limit the risk of permanent hypothyroidism secondary to RAI therapy;
- interrupting treatment 5 to 7 days beforehand to preserve the effectiveness of the RAI therapy.

Resumption of TSAs should be discussed with the endocrinologist.

Level of evidence ++ Grade B

4.10. Recommendation 5.10

The radioiodine activity delivered should be as low as possible, according to the ALARA principle, possibly based on dosimetric methods.

Level of evidence +++ Grade B

4.11. Recommendations 5.11

After treatment with iodine-131, biological monitoring of TSH is necessary at 1, 3, 6 and 12 months in order to assess therapeutic efficacy. After the first year, annual TSH measurements are justified in the long term to detect late hypothyroidism.

Level of evidence ++ Grade A

Fig. 2 summarizes the recommendations for diagnostic assessment (sections 2, 3, 4, 5)

5. Section 6: how to monitor and until when

5.1. Recommendation 6-1

Thyroid nodules without sonographic features of high suspicion of malignancy, (EU-TIRADS 2-3-4) with a benign cytology result (Bethesda II) or no indication for FNAB (due to their size) should be monitored 1–2 years after discovery and then 2-4 years later (Figs. 3 and 5).

Level of evidence: expert opinion: grade A

5.2. Recommendation 6-2

Ultrasound-suspicious thyroid nodules (EU-TIRADS 5) with a benign FNAB result (Bethesda II) should be monitored every 1–2 years for 5 years after discovery, and thereafter monitoring should be spaced out if stable.

Level of evidence: expert opinion, Grade A

5.3. Recommendation 6.3

For nodules with initial Bethesda I cytology, FNAB should be repeated under ultrasound guidance for supra-centimetric nodules with EU-TIRADS score of 3, 4 or 5. If the second FNAB is still non-diagnostic, core-needle biopsy may be considered. If diagnosis is still not possible, depending on the size of the nodule and the clinical situation, surgery is to be discussed.

Level of evidence +++: Grade A

5.4. Recommendation 6.4

In case of a purely cystic EU-TIRADS 2 Bethesda I nodule, repeat FNA aims at treatment (drainage, ethanol), but not diagnostic purposes.

Level of evidence ++ Grade B

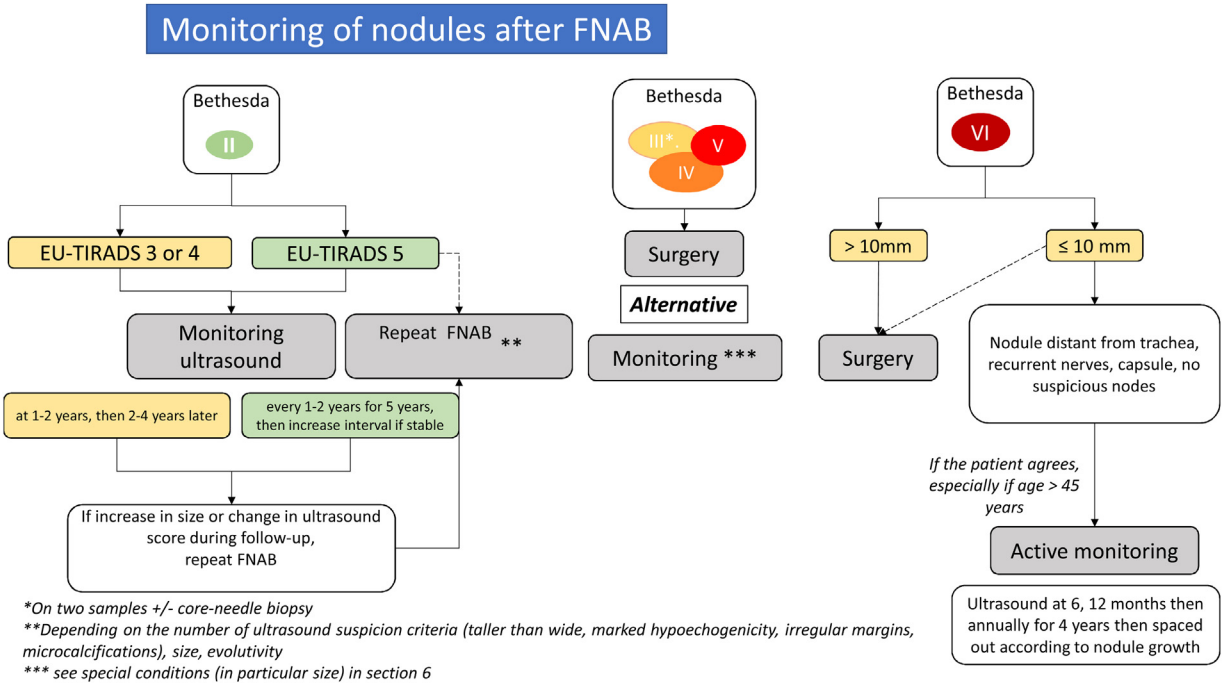

Fig. 3. Follow-up algorithm for nodules with FNAB.

5.5. Recommendation 6-5

In Bethesda II nodules, there is no need to systematically repeat FNAB except if characteristics of the nodule, including ultrasound score, size and/or progression justifies it.

The indication to repeat depends on the risk of malignancy, which is greater if the nodule is EU-TIRADS 5 with several features of high suspicion of malignancy (marked hypoechogenicity, higher than wide, microcalcifications and irregular margins), or in the event of an increase in size or ultrasound changes.

Level of evidence ++ Grade A

5.6. Recommendation 6-6

In case of Bethesda III cytology, repeat FNAB is advised. For large nodules, immediate surgery is an alternative. If FNAB is again Bethesda III, surgery is usually recommended. Active surveillance is an alternative for nodules ≤ 2 cm.

Level of evidence ++ Grade B

5.7. Recommendation 6-7

If cytology is Bethesda IV, V and VI, repeat FNAB is not recommended.

Level of evidence +++ Grade A

5.8. Recommendation 6-8

Iodine supplementation is not indicated to reduce nodule size. Normal dietary iodine intake is sufficient, outside of pregnancy.

Level of evidence +++ Grade A

5.9. Recommendation 6–9

It is not recommended that euthyroid patients with thyroid nodules be offered levothyroxine therapy. The indications for levothyroxine treatment in these patients are those for treatment of hypothyroidism.

Level of evidence +++ Grade A

5.10. Recommendation 6.10

After lobectomy for a benign nodule, levothyroxine therapy is not routinely initiated. TSH measurement 6–8 weeks after lobectomy is recommended. Levothyroxine treatment is indicated if postoperative TSH is > 10 mIU/l, and discussed if > 4 mIU/l depending on symptoms and associated risk factors: age, presence of anti-peroxidase antibodies.

Level of evidence: expert opinion Grade A

5.11. Recommendation 6.11

After lobectomy for cancer, levothyroxine therapy is not routinely initiated. TSH testing is recommended 6–8 weeks after lobectomy. In the absence of residual disease, for low- and intermediate-risk cancer, levothyroxine therapy is indicated if postoperative TSH is > 2 mIU/L

Level of evidence: expert opinion Grade A

5.12. Recommendation 6.12

After lobectomy for thyroid cancer, it is not recommended that monitoring be based on thyroglobulin or thyroglobulin antibody levels, but rather on cervical ultrasound.

Level of evidence: expert opinion, Grade A

5.13. Recommendation 6–13

Monitoring after lobectomy for cancer at very low risk of recurrence (≤ 1 cm) is based on cervical ultrasound. Monitoring should rapidly be spaced out: at 6–12 months postoperatively and then at 5–10 years.

Level of evidence: expert opinion, grade A

5.14. Recommendation 6.14

Monitoring after lobectomy for low-risk cancer is based on cervical ultrasound. Monitoring should be progressively spaced out: 6–12 months, 3 and 5 years, then every 5 years

Level of evidence: expert opinion, grade A

5.15. Recommendation 6.15

Lobectomy alone is not usually considered sufficient for carcinoma at intermediate risk of recurrence. Ultrasound monitoring once a year is recommended if surgical completion is not performed.

Level of evidence: expert opinion, grade A

5.16. Recommendation 6–16

NIFTP and TUMP show very low risk of recurrence, regardless of size (< 1%). The need for routine monitoring is as yet unclear, as these diagnostic categories are recent, introduced in 2017. Ultrasound at 6–12 months after surgery can be proposed regardless of tumor size, without further morphological examination if normal.

For large NIFTP or TUMP (> 4 cm), minimal monitoring may be proposed on a case-by-case basis: postoperative ultrasound, repeated at 5–10 years. The contribution of thyroglobulin assay has not been demonstrated but, if thyroidectomy has been performed, this marker can be used, as it can be interpreted for follow-up.

Level of evidence: expert opinion, grade B

5.17. Recommendation 6–17

Cytologically proven carcinomas and EU-TIRADS 5 nodules of $\leq$ 10 mm, without ultrasound evidence of lymph node metastasis or gross extra-thyroidal extension, distant from the recurrent nerve and trachea can be actively monitored in consultation. Patients aged $\geq$ 45 years are better candidates for active surveillance than younger patients.

Level of evidence +++ Grade A

5.18. Recommendation 6–18

Active surveillance includes ultrasound at 6, 12 months and then annually until the end of the 5th year, then at 7 years, then every 2–3 years.

Level of evidence ++ Grade B

5.19. Recommendation 6–19

Nodules with indeterminate cytology (Bethesda III to V), without sonographic evidence of lymph node metastasis or extra-thyroid extension may be actively monitored in consultation, using the same modalities. The size threshold has not been determined. It does not seem reasonable to apply active surveillance for Bethesda III or IV nodules larger than 20 mm or for Bethesda V nodules larger than 15 mm.

Level of evidence ++ Grade B

5.20. Recommendation 6-20

Indications for conversion surgery are: patient's wish, appearance of metastatic neck lymph node of thyroid origin or signs of extra-thyroid extension, or proven volumetric enlargement of the nodule on 2 consecutive examinations.

Level of evidence ++ Grade B

6. Section 7: surgical management

6.1. Recommendation 7.1

The interview screens for signs of compression or invasion: dyspnea, dysphagia, dysphonia (Figs. 4 and 5). It specifies the circumstances of discovery of the thyroid pathology.

Level of evidence ++ Grade A.

6.2. Recommendation 7.2

The surgeon should be familiar with the EU-TIRADS and Bethesda classifications to assess the risk of malignancy and explain this to the patient. The surgeon should know how to interpret a cervical ultrasound scan to propose the appropriate procedure for the pathology.

Level of evidence +++ Grade A.

6.3. Recommendation 7.3

A cervicothoracic CT (or MRI) scan should be ordered if there is suspicion of mediastinal extension of a substernal goiter, either clinically (lower pole of the lobe not palpable behind the clavicle, dyspnea, dysphagia, collateral circulation), or sonographically. It specifies relationships with adjacent organs, assesses extension to the aortic arch and the position of the goiter (anterior, posterior or mixed), in order to plan the appropriate approach (classic cervicotomy, manubriotomy, or sternotomy) (Grade A, ++). Injected cervical CT may also be used in cases of macroscopic lateral lymph-node involvement, for the diagnosis of lymph node metastasis at both ends of the neck.

Level of evidence ++ Grade A

6.4. Recommendation 7.4

FDG-PET is not a routine imaging test, even in case of suspicious nodules. Thyroid scintigraphy should only be used in case of TSH < 0.4 μIU/mL

Level of evidence ++ Grade A

6.5. Recommendation 7.5

Serum TSH, serum calcitonin and serum calcium should be measured prior to thyroid surgery Level of evidence ++ Grade A

6.6. Recommendation 7.6

Frozen section biopsy of the nodule is not recommended in Bethesda II, III and IV because it is not very discriminating between benign and malignant status. It is unnecessary in Bethesda V of $\leq$ 2 cm and Bethesda VI because the extent of thyroidectomy would not depend on the result. Frozen section biopsy of cervical lymph nodes is possible but not routinely recommended, as it is not very informative on macroscopically normal lymph nodes.

Level of evidence +++ Grade A.

6.7. Recommendation 7.7

Lobo-isthmectomy is recommended in the case of a single Bethesda II nodule or Bethesda II nodule limited in a single lobe (compressive, esthetic blemish, patient's wish. . .), Bethesda III (on 2 FNABs) or IV, and $\leq$ 2 cm Bethesda V or VI without aggressive criteria, without suspicious lymphadenopathy and without large contralateral nodule.

Level of evidence +++ Grade A

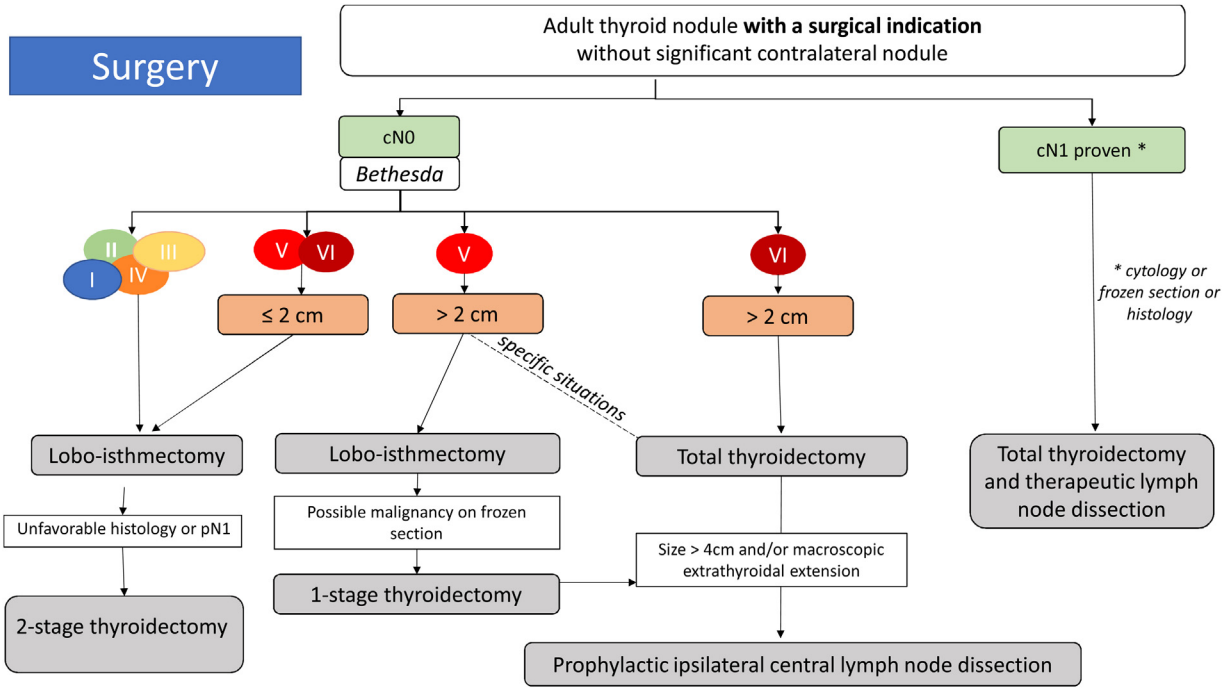

Fig. 4. Surgical management algorithm.

6.8. Recommendation 7.8

Frozen section biopsy of the nodule may be performed in case of Bethesda V > 2 cm. Total thyroidectomy during the same anesthesia may be proposed if the result is positive. However, this depends on preoperative discussion with the patient, the reliability of the FNAB, the frozen section biopsy and the quality of follow-up in the local health facilities.

Level of evidence + Grade B

6.9. Recommendation 7.9

Total thyroidectomy is indicated for nodular lesions in the following situations: bilateral Bethesda II compressive nodules, taking account of surgical risk; Bethesda III or IV with bilateral nodules with at least one > 4 cm suspicious nodule (sonographically, or because of a predisposition to thyroid cancer); > 2 cm Bethesda V or VI, in classically shaped papillary cancer, in men and women ≥ 55 years of age, or regardless of size in aggressive variants on FNAB, macroscopic lymph node involvement, or predisposition to thyroid cancer.

Level of evidence ++ Grade A

6.10. Recommendation 7.10

Patients should always be informed, in the initial surgery consultation, that, in case of lobo-isthmectomy, a second procedure may be indicated to complete the thyroidectomy if pathological examination shows thyroid cancer needing RAI treatment.

Level of evidence ++ Grade A

6.11. Recommendation 7.11

When ipsilateral central metastatic lymphadenopathy is demonstrated pre- or intra-operatively (cN1a), ipsilateral central neck dissection should be performed at the same time as thyroidectomy. In case of proven N1a on one side, prophylactic contralateral central neck dissection may be discussed. If there are no suspicious lymphadenopathies on ultrasound in the lateral sector, prophylactic dissection of sectors III and IV is not recommended.

Level of evidence + Grade A

6.12. Recommendation 7.12

It is recommended that neck dissection of the affected compartment be performed in the treatment of thyroid cancers with lymph-node involvement in the ipsilateral lateral compartment (cN1b). This may be limited to sectors III and IV when one or both of these sectors are involved and ultrasound does not show suspicious nodes in the other lateral sectors (Level of evidence + Grade B). Associated prophylactic dissection of sectors IIA and IIB is not recommended due to the risk of accessory spinal nerve palsy. Similarly, dissection of sectors V and, exceptionally, sector I is indicated only when there is proven metastatic lymphadenopathy in these sectors.

Level of evidence ++ Grade B

6.13. Recommendation 7.13

Prophylactic neck dissection of sector VB may be discussed in the presence of proven lymphadenopathy in sectors II, III and IV.

Level of evidence ++ Grade B

6.14. Recommendation 7.14

When there is evidence of isolated lateral metastatic lymphadenopathy (cN1b), it is recommended that, in addition to ipsilateral lateral neck dissection, prophylactic dissection of the central compartment (sector VI) should be performed, at least ipsilaterally to the lateral compartment lymph-node metastasis.

Level of evidence + Grade B

6.15. Recommendation 7.15

There is insufficient evidence to recommend contralateral prophylactic neck dissection for unilateral cN1b tumor. It may be

discussed for tumors at high risk of recurrence, bilateral tumors, in case of > 3 cm ipsilateral lateral lymphadenopathy or in the presence of > 4 metastatic lymph-node metastasis in the central compartment.

Level of evidence ++ Grade B

6.16. Recommendation 7.16

Prophylactic neck dissection is only discussed for papillary cancer. It is not indicated for vesicular or oncocytic cancer. Nor should it lead to secondary surgery in the event of incidental discovery of papillary cancer in a thyroidectomy specimen.

Level of evidence +++ Grade B

6.17. Recommendation 7.17

Prophylactic ipsilateral central dissection is warranted for papillary cancer with ≥ 4 cm diameter on ultrasound and/or intraoperative evidence of macroscopic perithyroid tissue invasion. The benefits and risks of this procedure should be assessed and discussed on a case-by-case basis Level of evidence ++ Grade B

6.18. Recommendation 7.18

In physiologically healthy elderly patients at low operative risk, prophylactic ipsilateral central neck dissection may be discussed for aggressive types of cancer at high risk of recurrence.

Level of evidence ++ Grade B

6.19. Recommendation 7.19

Only central neck dissection ipsilateral to the tumor is recommended, except for bilateral or isthmic cancers, for which a prophylactic bilateral central dissection may be proposed. This bilateral neck dissection is associated with an increased risk of complications (hypoparathyroidism, RLN injury).

Level of evidence +++ Grade B

6.20. Recommendation 7.20

Prophylactic lateral neck dissection is not recommended.

Level of evidence ++ Grade B

6.21. Recommendation 7.21

Preoperative laryngoscopy is mandatory for patients with history of cervical or thoracic surgery, dysphonia, thyroid carcinoma with posterior extension, or significant nodal involvement in the central compartment.

Level of evidence ++ Grade B

6.22. Recommendation 7.22

Postoperative laryngoscopy should be performed for any postoperative dysphonia, swallowing disorder, respiratory symptoms or loss of signal on neuromonitoring of the recurrent and/or pneumogastric nerve.

Level of evidence ++ Grade B

6.23. Recommendation 7.23

Neuromonitoring is useful in thyroid surgery as it reduces the rate of transient RLN palsy, but impact on definitive RLN injury has not been demonstrated. It facilitates identification of the recurrent nerve.

Level of evidence ++ Grade B

6.24. Recommendation 7.24

Prior to total thyroidectomy, routine vitamin D replacement has been suggested, but there is no clear evidence of its effectiveness.

Level of evidence: expert opinion, Grade B

6.25. Recommendation 7.25

Ligation of the terminal branches rather than the trunks of the inferior and superior thyroid arteries is recommended, as it reduces the risk of postoperative hypocalcemia and permanent hypoparathyroidism.

Level of evidence +++ Grade A

6.26. Recommendation 7.26

Identification of the upper parathyroid glands and conservation of their vascularity is recommended (level of evidence: expert opinion, Grade A). Auto-transplantation of devascularized glands, particularly when identified in the thyroidectomy specimen, is recommended (level of evidence: expert opinion, Grade A). In contrast, resection and auto-transplantation of parathyroid glands due to an ischemic aspect is not recommended.

Level of evidence +++ Grade A

6.27. Recommendation 7.27

The combination of PTH and blood calcium assay within 24 hours of total thyroidectomy can detect hypoparathyroidism. The combination of PTH > 15 ng/L and serum calcium > 2.00 mmol/L has a negative predictive value of close to 100%.

Level of evidence +++ Grade A

6.28. Recommendation 7.28

Early serum PTH measurement (≤ 6 hours after surgery) accelerates diagnosis of hypoparathyroidism and optimizes management by guiding vitamin and calcium replacement therapy. The optimal time between thyroid resection and serum PTH assay, assay method and diagnostic thresholds are still under discussion.

Level of evidence +++ Grade C

6.29. Recommendation 7.29

Thyroid surgery involves intermediate risk of bleeding according to the French Society of Anesthesia and Intensive Care Medicine (*Société française d'anesthésie-réanimation*: SFAR); it is therefore feasible without interruption of acetylsalicylic acid. Perioperative management of other antiplatelet and anticoagulant drugs should follow the recommendations for surgery at intermediate risk of bleeding.

Level of evidence +++ Grade A

6.30. Recommendation 7.30

New mechanical coagulation devices have not been shown to be effective in preventing hematoma, nor have inactive (cellulose) or active (fibrin) hemostatic agents.

Level of evidence + Grade C

6.31. Recommendation 7.31

Routine drainage of the surgical site is not recommended. It does not reduce the risk of hematoma, and increases hospital stay, pain and risk of local infection.

Level of evidence +++ Grade A

6.32. Recommendation 7.32

Prevention of compressive cervical hematoma requires protocols for intraoperative and immediate postoperative blood pressure monitoring, as well as effective control of pain, nausea and vomiting

Level of evidence ++ Grade A

The recognition and emergency management of compressive cervical hematoma should be the subject of written protocols and specific training of medical and paramedical teams.

Level of evidence +++ Grade B

Recommendation 7.33: the surgeon should inform the patient and their family of the normal postoperative course after thyroidectomy, the potential complications (compressive hematoma requiring urgent revision surgery, recurrent nerve damage and hypocalcemia due to hypoparathyroidism), and the specificities of outpatient management. The information collected from the patient on the conditions of discharge home (family environment, organization of the journeys) and that given to them during the preoperative consultation (postoperative consequences, specificities of outpatient management) must be recorded in the file.

Level of evidence +++ Grade A

6.33. Recommendation 7.34

Ambulatory thyroidectomy should only be performed by an experienced surgeon within a trained medical and paramedical team. The healthcare facility should be fully resourced for outpatient management, with 24-hour, 7-days-a-week care for emergency readmission. In all cases, contact between the facility and the patient the day after surgery is crucial.

Level of evidence ++ Grade A

6.34. Recommendation 7.35

Ambulatory management can be proposed for loboisthmectomy or isthmectomy (unless contraindicated: anticoagulants at effective dose, absence of escort on discharge and at home the night following surgery, poor comprehension), even with associated neck dissection. It is also feasible for secondary totalization of thyroidectomy (after lobectomy). On the other hand, the indications for one-stage total thyroidectomy should be limited, giving priority to the proximity of the place of residence to a care facility with an appropriate technical platform, and to the pathology operated on (euthyroid goiter without substernal extension).

Level of evidence ++ Grade B

6.35. Recommendation 7.36

A precise clinical pathway must be established with formalized pre-, intra- and postoperative protocols for both surgery (hemostasis procedures) and anesthesia (prevention of pain, vomiting and hypertensive episodes). We recommend a minimum 6 hours' postoperative monitoring in the ambulatory facility.

Level of evidence +++ Grade B

6.36. Recommendation 7.37

Where outpatient management is not possible or not recommended, hospital stay after thyroidectomy may be limited to 24 hours, with some exceptions (effective-dose anticoagulant therapy, postoperative complication).

Level of evidence ++ Grade B

6.37. Recommendation 7.38

Transaxillary robotic thyroidectomy is not the gold-standard approach. It is sometimes proposed for highly selected patients with a small (2 cm) unilateral nodule, exclusively cervical and without lymph-node involvement, within a thyroid lobe not exceeding 6 cm, in a slim subject wishing to avoid a cervical scar. Patients should be informed of the specific risks of the technique and the lack of evidence that it is equivalent to cervicotomy in terms of quality of life and satisfaction.

Level of evidence ++ Grade B

6.38. Recommendation 7.39

Patients with malignant nodules or suspected malignancies > 2 cm, cancers with gross lymph-node metastasis, plunging goiters, history of cervical surgery or active thyroid disease should be excluded from robotic surgery.

Level of evidence ++ Grade B

6.39. Recommendation 7.40

Robotic thyroidectomy should be performed in centers with expertise in both thyroid surgery and robotic surgery.

Level of evidence: expert opinion, Grade B

6.40. Recommendation 7.41

Transoral thyroidectomy can be proposed in selected patients with a thyroid < 45 mL and/or a nodule < 4 cm in case of Bethesda II, III or IV lesion, or < 2 cm in case of Bethesda V or VI lesion, without suspicion of lateral lymph-node involvement or mediastinal extension, wishing to avoid a cervical scar, with satisfactory dental status, and who have been informed of the specific risks of the transoral route and the need for perioperative oral care, as well as the lack of evidence of its effectiveness in terms of quality of life and patient satisfaction.

Level of evidence ++ Grade B

6.41. Recommendation 7.42

Patients should be informed of the possibility of postoperative neck and chin pain that may persist for days to weeks after surgery.

Level of evidence + Grade A

Recommendation 7.43: transoral thyroidectomy should be performed in centers with expertise in thyroid surgery.

Level of evidence +++ Grade A

7. Section 8: thermal ablation

7.1. Recommendation 8.1

Prior to any non-surgical treatment of a thyroid nodule, a dedicated consultation assessing the indication and feasibility of treatment and informing the patient of the benefits, harms and risks compared to surgery should be carried out (Fig. 5).

Level of evidence: expert opinion, Grade A

7.2. Recommendation 8.2

Two ultrasound-guided fine-needle aspiration biopsies or core-needle biopsies should be performed for EU-TIRADS 3 and 4 nodules, and a single FNAB or core-needle biopsy for EU-TIRADS 2 nodules. The result should be in favor of benignity.

Level of evidence +++ Grade A

7.3. Recommendation 8.3

In autonomous nodules, FNAB is not systematic but at the discretion of the medical team. If it is performed, the functional status of the nodule should be reported to the cytopathologist.

Level of evidence: expert opinion, Grade B

7.4. Recommendation 8.4

The operator must have experience in thyroid ultrasound and interventional procedures for diagnostic (FNAB, core-needle biopsy) and therapeutic purposes (aspiration and removal, percutaneous ethanol injection). The operator must have received specific training and have assisted a trained operator in several procedures. He or she must be supervised for the first procedures.

Level of evidence: expert opinion, Grade A

7.5. Recommendation 8.5

Percutaneous ethanol injection is the first-line treatment for symptomatic cystic and predominantly cystic nodules that recur after aspiration, whether fluid or thick.

Level of evidence +++ Grade A

7.6. Recommendation 8.6

The effectiveness of ethanol injection should be assessed clinically and by cervical ultrasound 3-6 months after the procedure, and then as appropriate according to progression.

Level of evidence +++ Grade A

7.7. Recommendation 8.7

Thyroid thermal ablation is indicated for the treatment of certain symptomatic benign thyroid nodules and/or those with documented ultrasound volumetric progression.

Level of evidence +++ Grade A

7.8. Recommendation 8.8

Thermal ablation is a treatment option for selected cases of autonomous nodules.

Level of evidence ++ Grade B

7.9. Recommendation 8.9

Thyroid nodule thermal ablation, regardless of the technique used (radiofrequency, microwaves or laser), should be performed by a trained operator within a dedicated care pathway.

Level of evidence ++ Grade A

7.10. Recommendation 8.10

Clinical, ultrasound and biological monitoring after thermal ablation is recommended at 3–6 months and then at 12 months and annually for the first 5 years.

Level of evidence ++ Grade A

7.11. Recommendation 8.11

Nodule reduction < 20% and/or rapid significant regrowth should prompt discussion of repeat FNAB to ensure that a carcinomatous lesion is not overlooked.

Level of evidence: expert opinion, Grade A

7.12. Recommendation 8.12

Mixed nodules with a solid component > 10–20% of total volume may be treated sequentially by ethanol injection and thermal ablation.

Level of evidence + Grade B

7.13. Recommendation 8.13

Thermal ablation (radiofrequency, microwave or laser) of papillary microcarcinoma (WHO definition $\leq$ 1 cm) may be considered in selected cases as an alternative to surgery or active surveillance. The case should be discussed in a multidisciplinary consultation meeting.

Level of evidence +++ Grade B

7.14. Recommendation 8.14

After thermal ablation (radiofrequency, microwave or laser) of papillary thyroid microcarcinoma, regular ultrasound monitoring should be performed.

Level of evidence ++ Grade A

Fig. 5 summarizes the recommendations for therapeutic management (sections 5, 6, 7, 8).

8. Section 9: thyroid nodules in children

8.1. Recommendation 9.1

Given the rarity of this clinical situation, we recommend that children with one or more thyroid nodules be referred to a physician experienced in childhood thyroid pathology (Fig. 6).

Level of evidence ++ Grade A

8.2. Recommendation 9.2

The discovery of a thyroid nodule in a child should lead to screening for personal and familial clinical history, which may point to a tumor predisposition syndrome, particularly in case of multinodular thyroid (DICER1 and PTEN).

Level of evidence: ++ Grade A.

8.3. Recommendation 9.3

We recommend fine-needle biopsy of any nodule > 1 cm because of the greater risk of malignancy than in adults for TI-RADS scores 3, 4 and 5.

Level of evidence: ++ Grade A.

8.4. Recommendation 9.4

Regular prolonged clinical and/or ultrasound monitoring of the thyroid every 3 to 5 years should be conducted in case of history of irradiation, especially if early, given the increased risk of thyroid cancer.

Level of evidence: +++ Grade A.

8.5. Recommendation 9.5

Fine-needle biopsy should always be ultrasound-guided, and if possible performed by a practitioner with expertise in thyroid fine-needle biopsy.

Level of evidence, ++ Grade A

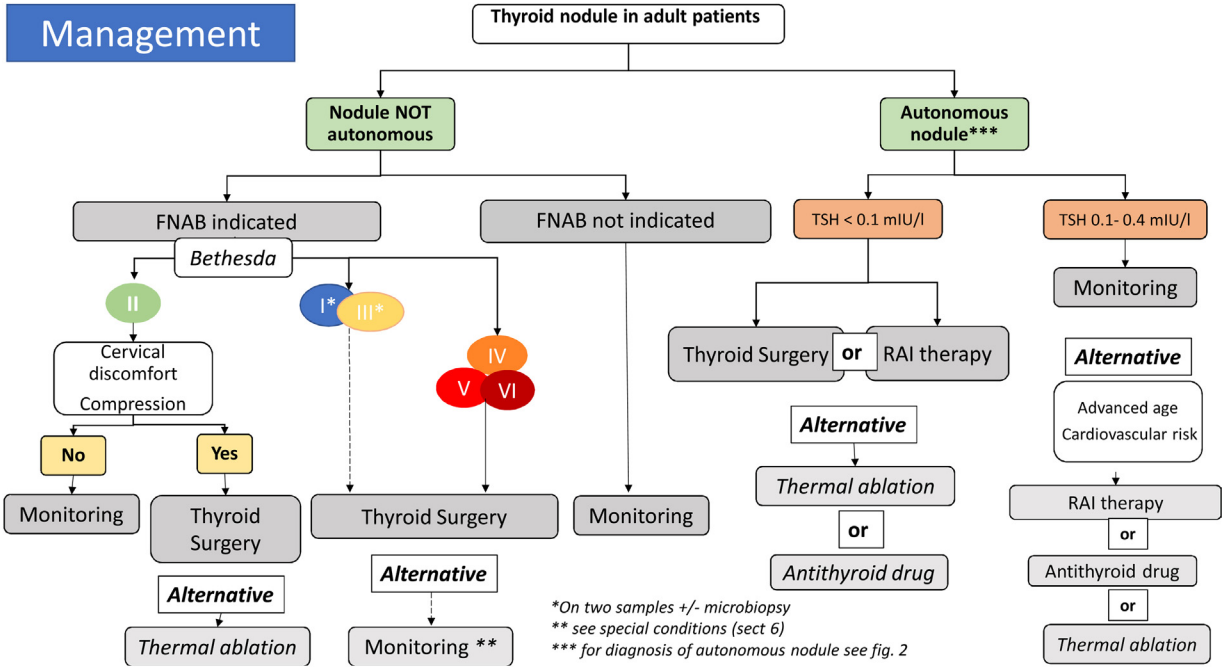

Fig. 5. Therapeutic management algorithm.

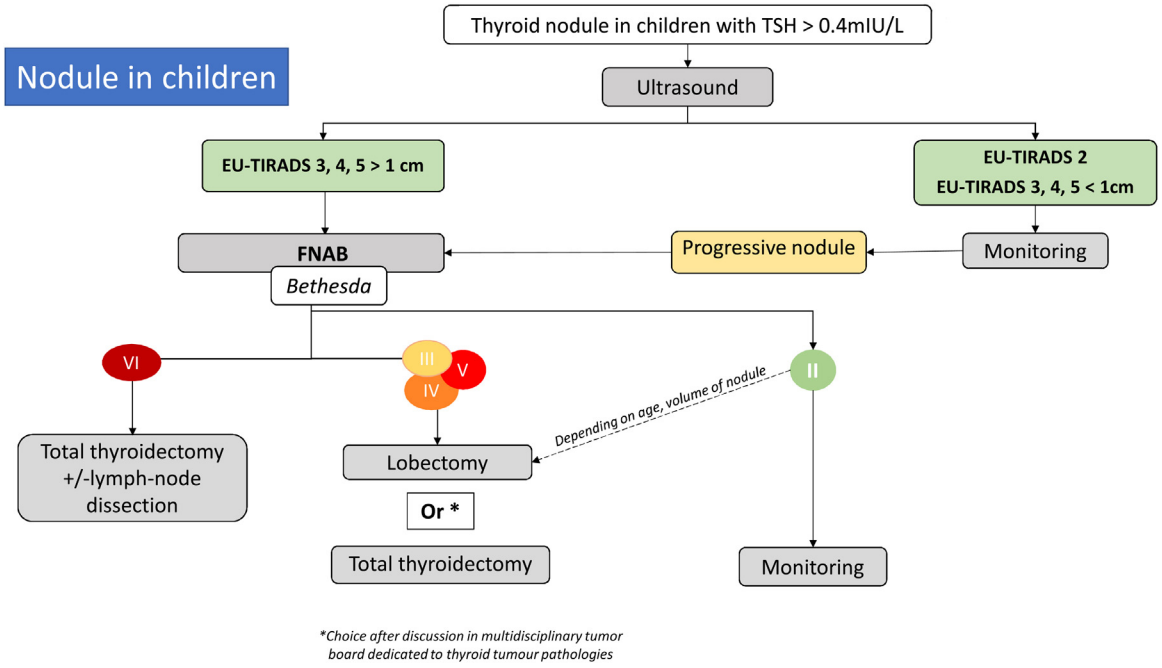

Fig. 6. Management algorithm for nodules in children.

8.6. Recommendation 9.6

We recommend that the surgical management of thyroid nodules in children be validated and carried out by a medical-surgical team trained in thyroid surgery and, as far as possible, that children be operated on in a pediatric setting. Level of evidence: ++ Grade A.

8.7. Recommendation 9.7

Recommendation 9.7a: given the significantly increased risk of cancer in Bethesda III, IV, V and VI cytology in children compared with adults, we recommend thyroid surgery, the modalities of which (lobectomy or total thyroidectomy) should be discussed in a specialized thyroid tumor board.

Level of evidence: ++ Grade A.

Recommendation 9.7b: if lobectomy is proposed, we recommend basing the discussion of the potential need for surgical totalization on the final histology findings.

Level of evidence: ++ Grade B.

8.8. Recommendation 9.8

We do not recommend radiofrequency treatment of thyroid nodules in children.

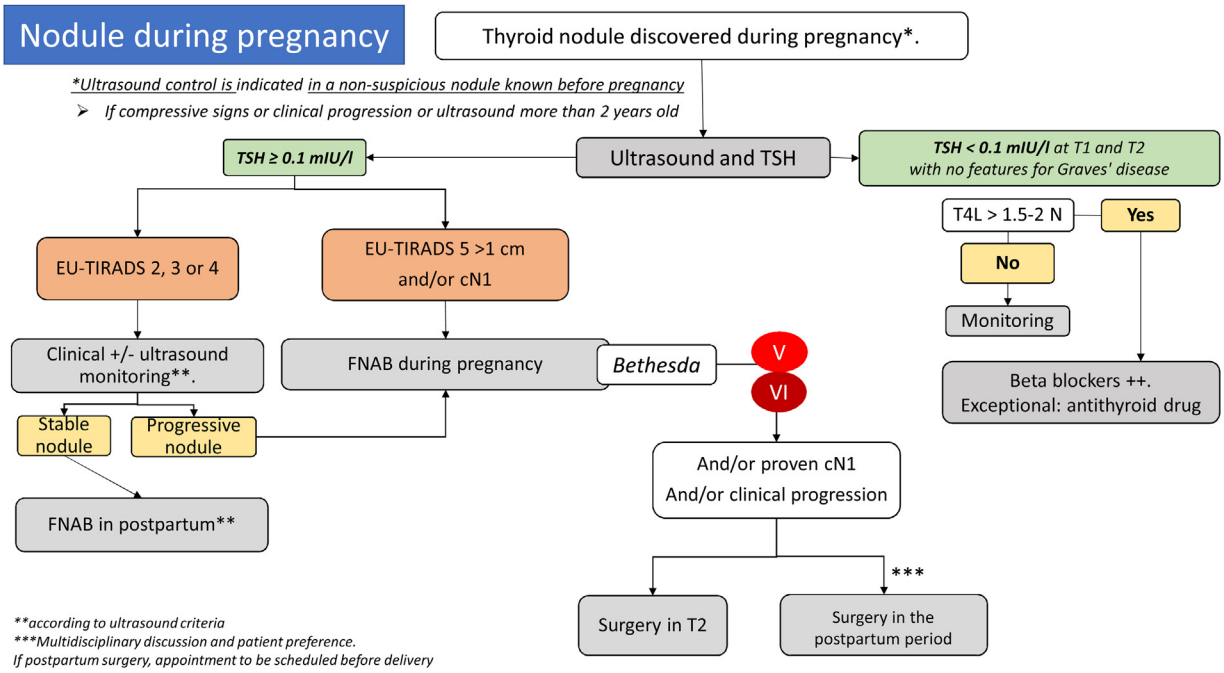

Fig. 7. Management algorithm for nodules in pregnancy.

Level of evidence: + Grade B.

9. Section 10: thyroid nodule and pregnancy

9.1. Recommendation 10.1

Recommendation 10.1a – TSH testing is recommended for thyroid nodules found in pregnancy (Fig. 7).

Level of evidence, ++ Grade A

Recommendation 10.1b – A functional nodule should be considered during pregnancy if TSH is < 0.1 mIU/l, and remains so in the second trimester.

Level of evidence ++ Grade A

9.2. Recommendation 10.2

Calcitonin testing in pregnancy is not recommended unless there is personal or familial history suggestive of MEN2 or surgery is intended.

Level of evidence: expert opinion, Grade A

9.3. Recommendation 10.3

Thyroid scintigraphy is contraindicated in pregnancy.

Level of evidence +++, Grade A

9.4. Recommendation 10.4

Recommendation 10.4a: thyroid ultrasound should be performed as soon as a nodule is diagnosed during pregnancy.

Level of evidence: expert opinion, Grade A

Recommendation 10.4b: the EU-TIRADS classification should be used in pregnancy.

Level of evidence: expert opinion, Grade A

9.5. Recommendation 10.5

Recommendation 10.5a: if the thyroid nodule is known prior to pregnancy with EUTIRADS classification 2–3 or 4 without fine-needle biopsy criteria in the 2 years prior to pregnancy, we do not recommend ultrasound monitoring during pregnancy, subject to reassuring cervical palpation at the end of the 1st trimester.

Level of evidence: expert opinion, Grade B

Recommendation 10.5b – If the thyroid nodule is known prior to pregnancy with an old ultrasound scan (> 2 years), we recommend ultrasound monitoring during the 1st trimester of pregnancy.

Level of evidence: expert opinion, Grade A

9.6. Recommendation 10.6

Recommendation 10.6a – fine-needle biopsy is recommended for EU-TIRADS 5 nodules > 1 cm or suspicious lymphadenopathy in the first half of pregnancy.

Level of evidence: expert opinion, Grade B

Recommendation 10.6b – in other cases, fine-needle biopsy, if indicated, should be delayed until after delivery.

Level of evidence: expert opinion, Grade A

9.7. Recommendation 10.7

Ultrasound should be checked at the beginning of the second trimester if there is clinical suspicion of progression or an EU-TIRADS 4 or 5 nodule.

Level of evidence: expert opinion, Grade A

9.8. Recommendation 10.8

In all cases, organization of post-pregnancy surveillance is necessary. The timing of the consultation should be decided jointly with the patient according to ultrasound and/or cytological criteria, ideally within 6 months of delivery if malignancy is suspected.

Level of evidence: expert opinion, Grade A

9.9. Recommendation 10.9

Recommendation 10.9a – in the case of symptomatic hyperthyroidism, symptomatic treatment (beta blockers) should be prescribed in first line. Treatment with antithyroid drugs (ATD) at

the minimum effective dose (target T4l at the upper limit of normal) is necessary in rare cases.

Level of evidence: expert opinion, Grade B

Recommendation 10.9b – RAI treatment of a toxic nodule is contraindicated during pregnancy and should be deferred until after delivery.

Level of evidence +++ Grade A

9.10. Recommendation 10.10

In pregnancy, L-thyroxine treatment for thyroid nodule is contraindicated.

Level of evidence: expert opinion, Grade A

9.11. Recommendation 10.11

We do not presently recommend thermal ablation in pregnancy.

Level of evidence: expert opinion, Grade A

9.12. Recommendation 10.12

Recommendation 10.12a – in case of known non-progressive papillary microcarcinoma, we recommend that surgery should not be performed during pregnancy and that reassessment should be scheduled within 6 months of delivery.

Level of evidence: ++ Grade A

Recommendation 10.12b – in case of known progressive papillary microcarcinoma in pregnancy, we recommend that the indication for surgery or continued surveillance should be discussed in a multidisciplinary team meeting.

Level of evidence: ++ Grade A

9.13. Recommendation 10.13

Recommendation 10.13a – we do not recommend routine surgery for thyroid cancer diagnosed in pregnancy in the absence of aggressive criteria.

Level of evidence: +++ Grade A

Recommendation 10.13b – thyroid cancer surgery in the second trimester of pregnancy may nevertheless be considered if the patient prefers and gives informed consent.

Level of evidence: expert opinion, Grade B

Recommendation 10.13c – we recommend thyroid cancer surgery in the second trimester of pregnancy in case of tumor progression or aggressive criteria.

Level of evidence: +++ Grade A

9.14. Recommendation 10.14

If thyroid surgery is considered in pregnancy, we recommend that it be performed in the second trimester by a trained team in a suitable obstetric and neonatal environment.

Level of evidence: +++ Grade A

9.15. Recommendation 10.15

We recommend that the postpartum appointment be brought forward in case of any cancer with surgical indication but not operated on during pregnancy.

Level of evidence: expert opinion, Grade A

9.16. Recommendation 10.16

Breastfeeding is not contraindicated; duration is conditional on histology and indications for radiation therapy.

Level of evidence: expert opinion, Grade A.

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Disclosure of interest

The authors declare that they have no competing interest.

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