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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 : Follow-up: How and how long?

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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 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, surgeons, and other specialists. Therefore, this consensus statement was established jointly by 3 societies: the French Society of Endocrinology (SFE), French Association of Endocrine Surgery (AFCE) and French Society of Nuclear Medicine (SFMN); the various working groups included experts from other specialties (pathologists, radiologists, pediatricians, biologists, etc.). This section deals with the follow-up of thyroid nodules, low-grade tumors and microcarcinomas.

1. Introduction

The aim of the following guidelines is to provide simple answers to common questions in medical practice regarding thyroid nodules. They were drawn up in the light of current scientific knowledge, and will evolve over time. In any case, they should be explained to patients, whose views should be taken into account in any decision, especially as alternatives are often available.

Topics covered in this section comprise the timing and duration of nodule surveillance, indications for repeat fine-needle aspiration biopsy (FNAB), iodine supplementation of unoperated nodules on levothyroxine, surveillance of cancers operated on by lobectomy, surveillance of NIFTP (Non-Invasive Follicular Thyroid neoplasm with Papillary-like nuclear features) and TUMPs (Tumors of Uncertain Malignancy Potential), surveillance of microcarcinomas and nodules with indeterminate FNAB findings. Throughout the text, "risk of malignancy" includes risk of cancer and risk of NIFTP, which is a tumor not classified as cancer but nevertheless requiring surgical management.

2. Ultrasound monitoring of nodules: how often and for how long?

Following the initial clinical, ultrasound and (if warranted) cytological work-up, if there are no significant functional or cosmetic complaints or arguments in favor of carcinoma, monitoring can be considered (Table 1).

The aim is to detect cancer that may have gone undiagnosed on initial assessment or that may appear during follow-up, and to monitor nodule growth [1]. These risks are low. The risk of malignancy in a nodule initially classified as benign on FNAB is between

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Table 1
Ultrasound monitoring schedule for nodules for which surgery is not indicated according to their ultrasound classification, size and Bethesda classification.

	EU-TIRADS 2–4	EU-TIRADS 5
Bethesda II or FNAB initially not indicated	1–2 years then 2–4 years and/or discontinuation of monitoring if no progression	Every 1–2 years for 5 years and then at longer interval if stable[a]
Bethesda III twice and Bethesda IV	Usual indication for surgery. However, for nodules ≤ 2 cm, active surveillance is a possible alternative to be discussed: at 6, 12 months then annually for 5 years, then spaced out according to progression	

FNAB: fine needle aspiration biopsy.
[a] For nodules highly suspicious on ultrasound, defined by presence of several features of high suspicion of malignancy, control FNAB is indicated.

1% and 3% [2,3]. A new nodule is detected during monitoring in 9% to 14% of patients, at 5–10 years [4,5]. Nodule growth is observed in 11% to 29% of nodules over a 5-year period. The mean increase in size is 5.9 mm over 5 years' follow-up of nodules with a mean size of 13.2 mm [5]. Spontaneous decrease in nodule size is observed in 13 to 18% of patients. Risk factors for nodule growth comprise number of nodules, volume > 0.2 cm^3 (size > 7.5 mm), male gender, and age < 45 years.

Overall, most nodules are stable, and diagnosis of an initially undetected or newly appearing cancer is rare. Ultrasound examination should therefore not be repeated too frequently.

When nodular involvement is insignificant (no EU-TIRADS 5 nodules, EU-TIRADS 4 nodules ≤ 5 mm or EU-TIRADS 3 nodules < 10 mm), ultrasound monitoring is not mandatory.

When the initial work-up is reassuring and concordant (EU-TIRADS 2, 3 or 4 nodules with benign cytology if FNAB has been performed), a follow-up ultrasound scan can be proposed for most patients 1 to 2 years later and then 2 to 4 years later. A recent retrospective study even advocated first check-up at 3 years [6], then 4 to 5 years later. Discontinuation of monitoring may also be considered in old non-suspicious nodular disease.

However, in some particular cases, it seems useful to maintain closer surveillance: firstly, in asymptomatic nodules >4 cm and of recent discovery, in order to determine their growth slope and be able to provide the most appropriate therapeutic response if necessary (surgery or thermal ablation); secondly, nodules with ultrasound-cytology discrepancy, with EU-TIRADS 5 score and benign cytology [1], for which the risk of malignancy is in the range of 3–8.6% [3,7]; and finally, in the same spirit, nodules classified as indeterminate on FNAB, but for which active surveillance is appropriate.

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.
Level of evidence: Expert opinion: Grade A

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.

Table 2
Risk of malignancy according to EU-TIRADS score and cytology.

		Risk of cancer/NIFTP[a]
EU-TIRADS ultrasound score	2	≈0%
	3	2–4%
	4	6–17%
	5	> 26–87%
Bethesda System	I	5–10%
	II	0–3%
	III	10–30%
	IV	25–40%
	V	50–75%
	VI	97–99%

NIFTP: non-invasive follicular thyroid neoplasm with papillary-like nuclear features.
[a] NIFTPs are included in this column as they are lesions requiring surgery.

Level of evidence: Expert opinion, Grade A

3. Repeat FNAB: is it necessary? (Table 2)

Some situations require repeat FNAB. Indications depend on the risk of cancer, which varies according to ultrasound score and Bethesda category [8,9] (Table 2). The growth profile and size of the nodule must also be taken into account. Furthermore, there is a general principle to bear in mind: series that assessed the risk of cancer in a given group of patients with surgery as gold standard overestimate the risk due to selection bias, compared with studies in which the gold standard was monitoring or FNAB.

3.1. In case of initial non-diagnostic FNAB (Bethesda I)

The risk of cancer in case of Bethesda I cytology (defined in the Cytology section) is 5% to 10% depending on the series, with either monitoring or repeat FNAB as gold standard [10]. The smaller the nodule, the higher the rate of failure of the first biopsy. Non-diagnostic results are not uncommon due to small nodule size [11,12].

Repeat FNAB is recommended when the specimen is Bethesda I, except for nodules that were not initially indicated for FNAB because of their size and for purely cystic nodules classified as EU-TIRADS 2. In the latter case, the pauci-cellular or acellular specimen is mainly or exclusively colloid. Although the sample may be considered non-contributory, it is a representative sample of the cystic nodule and allows diagnosis of a benign colloid nodule. Apart from these two situations, initial Bethesda I cytology in a EU-TIRADS 3 > 2 cm, EU-TIRADS 4 >15 mm or EU-TIRADS 5 > 10 mm nodule will require repeat FNAB.

In case of second Bethesda I FNAB, there is a theoretical indication for diagnostic surgery. The alternatives are core-needle biopsy or monitoring [13].

The minimum time to repeat FNAB is 1–3 months. [14,15]. The only emergency is clinical suspicion of aggressive cancer because of rapid increase in size, for which urgent repeat FNAB is indicated or even urgent biopsy if anaplastic thyroid cancer is suspected [16].

3.2. In case of benign initial cytology (Bethesda II)

Prevalence of cancer in large retrospective studies varies from 1% to 2.6% for series where the gold standard was monitoring or repeat FNAB [3,17–20], and 3.2% where the gold standard was histology [21].

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

3.2.1. Importance of EU-TIRADS ultrasound score

After benign FNAB, the risk of malignancy is 0.6% for nodules that are not sonographically suspicious (EU-TIRADS score 2, 3, 4) and up to 3% for suspicious nodules (EU-TIRADS score 5) [7]. The risk is all the greater the greater the number of criteria for classification as EU-TIRADS 5: higher than wide, hypoechogenicity, irregular margins, microcalcifications. It is therefore recommended that FNAB be repeated in case of benign FNAB in a highly suspicious nodule, which may be defined by the presence of several features of high suspicion of malignancy [22].

For EU-TIRADS 4 and 3 nodules, repeat FNAB is not recommended unless there is a change in the nodule on ultrasound or a significant increase in size.

3.2.2. Importance of nodule size

The risk of cancer has long been considered higher in large than in small benign nodules. Series with surgery as gold standard reported cancer rates greater than 10% [23]. Studies where the gold standard was cytology or monitoring reported low cancer rates of less than 1.5% [24,25]. In studies of large nodules with benign FNAB, the undiagnosed cancers actually had suspicious ultrasound criteria. It is therefore not possible to affirm that the risk of cancer in Bethesda II nodules is higher when the nodule is large.

3.2.3. Importance of nodule progression

It is usually thought that a nodule that increases in size should prompt repeat FNAB. An increase in size is considered significant when two of the three dimensions increase by at least 20%. However, account must be taken of initial size (a 20% increase in the size of an 8 mm nodule does not have the same importance as a 20% increase in the size of a 4 cm tissue nodule), the ultrasound characteristics (an increase in size of an essentially cystic nodule does not have the same importance as an increase in size of a solid nodule), and the way in which the ultrasound examination was carried out, which determines inter-operator reproducibility.

3.3. In case of atypia or follicular lesion of undetermined significance (Bethesda III)

The risk of malignancy in case of Bethesda III FNAB ranges between 10% and 30% (Table 2).

Repeat FNAB is indicated for ≥10 mm nodules within 1–12 months [13].

If the FNAB result is again Bethesda III, surgery is recommended, but may also be considered if the nodule is ≤20 mm: it is in this indication that molecular analysis is being developed and will eventually take on a decisive role. For nodules larger than 40 mm with atypia, surgical removal is an alternative to repeat FNAB, especially if the nodule is clinically and sonographically suspicious or compressive.

3.4. In case of follicular neoplasm (Bethesda IV)

The risk of malignancy in case of Bethesda IV FNAB is 25–40%. Repeat FNAB is usually unnecessary; surgery is generally recommended. As with Bethesda III nodules, surveillance is also a feasible alternative for ≤20 mm nodules, depending on patient age and comorbidities, and, as with Bethesda III nodules, it is in this indication that molecular analyses are being developed.

3.5. In case of cytology suspicious of malignancy or malignant in favor of papillary carcinoma (Bethesda V and VI)

The risk of malignancy with Bethesda V and VI FNAB is 50–75% and 97–99% respectively. It is not necessary to repeat FNAB. The recommended treatment is surgery.

In Bethesda categories III, IV, V and VI, preoperative plasma calcitonin assay is recommended to rule out medullary thyroid carcinoma.

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

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

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

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

Recommendation 6.7

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

Level of evidence + ++ Grade A

4. Should patients with unoperated nodules be supplemented with iodine?

Large iodine deficiencies are associated with goiter. However, a recent Chinese cross-sectional study found no association between ioduria and prevalence of benign nodules [26]. Analysis of the impact of iodine intake on nodule progression must take account of the natural history of nodules, which vary in size over time.

In a large prospective randomized study, moderate iodine supplementation (150ug) did not significantly reduce nodule volume compared to placebo (−9% with iodine vs. −5% for placebo, p= 0.328) [27].

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. Should unoperated nodules be treated with levothyroxine?

The natural history of nodules was discussed in the first part of this article.

Several prospective randomized studies investigated the contribution of levothyroxine versus placebo in reducing thyroid nodule size [27–33]. However, the number of patients included was small. The studies showed that treatment with levothyroxine to achieve subclinical hypothyroidism (< 0.3 mIU/l) for a period of 6–18 months could reduce the size of nodules and goiters.

However, the decrease in volume and size of nodules was small: volume decrease of 12.1% under treatment vs. 5.2% under placebo [27] and size decrease of −1.25 mm vs. +0.44 mm [32]. Furthermore, a significant decrease of more than 50% was seen in only a small number of patients: 7.6% on levothyroxine vs. 9.5% on placebo in one study, and 26.6% vs. 16.9% in another [27,32]. This was confirmed by meta-analyses which showed a length reduction of more than 50% in 22% of patients on levothyroxine versus 10% on placebo, a difference which may or may not be significant, depending on the study [34,35]. This effect may be greater in iodine-poor geographical areas. There is little evidence for the long-term efficacy of levothyroxine replacement, but two studies reported that nodular goiters returned to their initial size when levothyroxine was stopped [28,33]. The decrease in size is not an argument in favor of benignity. In addition, suppressed TSH may be associated with an increased risk of cardiac disease and osteoporosis. Levothyroxine treatment is therefore not recommended in this indication. There is also no evidence in favor of levothyroxine therapy if TSH is normal.

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

6. Should levothyroxine be used after lobectomy?

One of the advantages of lobectomy over thyroidectomy is that it can be expected to spare the patient long-term treatment.

After lobectomy for a benign nodule, long-term treatment is necessary when there is hypothyroidism [36]. Predictive factors for long-term levothyroxine therapy comprise age > 55 years, preoperative TSH greater than 2 or 2.5mIU/L, presence of anti-peroxidase antibodies, and small residual lobe volume [37–39]. The presence of nodules in the remaining lobe is not an indication for levothyroxine treatment.

After lobectomy for cancer, the TSH target is typically 0.5–2mIU/mL. This recommendation applies to cancers at low and intermediate risk of recurrence (Table 3) [13].

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 >10mIU/l, and discussed if >4mIU/l depending on symptoms and associated risk factors: age, presence of anti-peroxidase antibodies.

Expert opinion Grade A

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 >2mIU/L

Expert opinion Grade A

Table 3
Classification criteria for follicular thyroid cancers according to level of risk of recurrence/residual disease.

	ATA 2015, Haugen *et al.* [13]
Low	Papillary carcinoma of the thyroid with the following characteristics: M0 Intrathyroidal Complete surgery R0 No aggressive histology No vascular invasion Clinically N0 or if N1 < 5 and < 2 mm Without iodine fixation outside the thyroid bed if iodine has been administered
	Encapsulated follicular variant of papillary carcinoma
	Follicular carcinoma with capsular invasion without vascular invasion or with minimal vascular invasion (< 4 foci)
	Single or multifocal papillary microcarcinoma with BRAF mutation (if known)
Intermediate	Minimal extrathyroidal extension Aggressive histology Iodine fixation outside the thyroid bed if treatment has been given Papillary carcinoma with vascular invasion Clinical N1, or > 5 N1 all < 3 cm Multifocal papillary microcarcinoma with extrathyroidal extension and BRAF mutation if known
High	Macroscopic extrathyroidal extension Incomplete surgery R1, R2 Remote metastases N1 ≥ 3 cm Follicular carcinoma with vascular invasion (> 4 foci)

7. Monitoring after lobectomy for cancer

For cancer patients treated by lobectomy, the TSH target to be maintained is 0.5–2IU/L. Levothyroxine treatment is often necessary to reach this, but not needed in all patients.

In patients treated by lobectomy alone, thyroglobulin level is not easily interpreted, and recurrences have been reported with stable, increasing and decreasing thyroglobulin levels [40,41]. Monitoring of these patients is based on cervical ultrasound.

The frequency of ultrasound monitoring after lobectomy for cancer should be adapted to the risk of cancer recurrence (Table 3). After a normal postoperative ultrasound scan (6–12 months), carcinoma at very low risk of recurrence (size ≤10 mm, unifocal, without extra-thyroid extension or metastasis or aggressive histology) can be followed up every 5–10 years, due to a near-zero risk of recurrence [42,43]. For carcinoma at low risk of recurrence (i.e., minimally invasive follicular cancers without vascular invasion, single or multifocal papillary cancers without extra-thyroidal extension, metastases, aggressive histology or vascular invasion), recurrence is usually indolent and amenable to curative surgery [44]. Recurrence may be late, but the majority of lymph node recurrences occur during the first years of monitoring (contralateral recurrence: 2.6% at 10 years, 6% at 25 years; lymph node recurrence: 5% at 10 years and 6% at 25 years) [45]. Monitoring can therefore rapidly be spaced out (e.g., 1, 3, 5 years and then every 3 to 5 years). A monitoring protocol is proposed in Fig. 1. Carcinomas at intermediate risk of recurrence include papillary cancers with minimal extra-thyroid extension and/or lymph node metastases (excluding cases with < 5 lymph node micro-metastases of < 0.2 mm, which are considered low risk, and those with macro-metastases of ≥ 3 cm, which are considered high risk) and/or a histological type considered aggressive (e.g., tall cell papillary cancers). Lobectomy alone is not usually considered

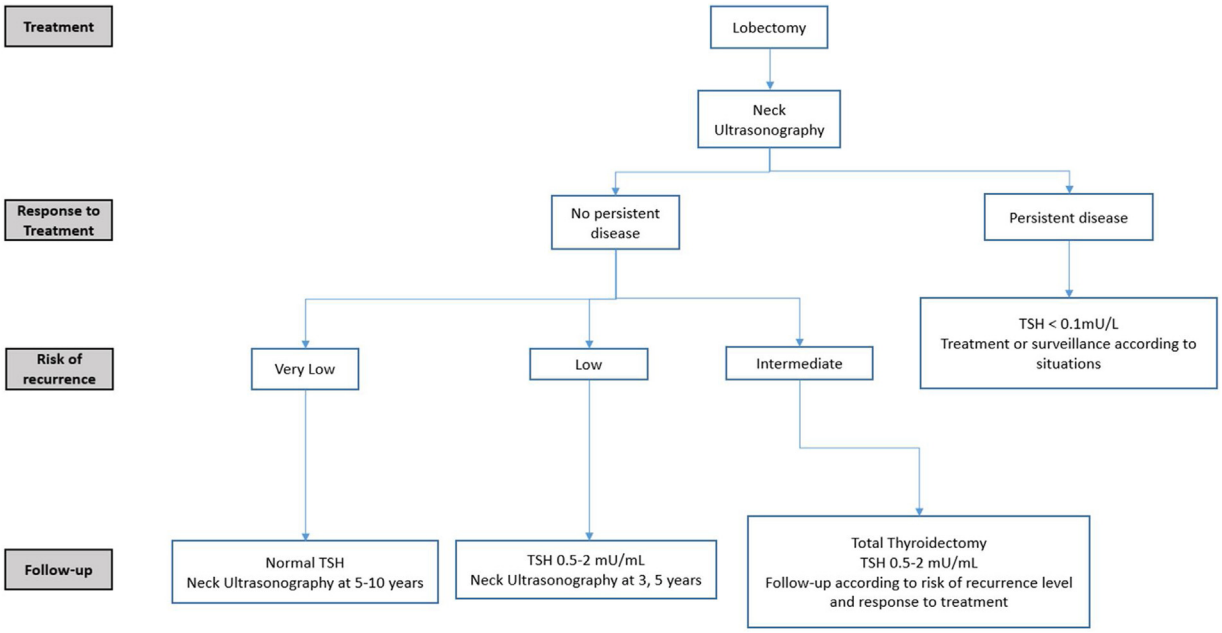

Fig. 1. Follow-up after lobectomy for follicular-cell-derived thyroid cancer.

sufficient for carcinomas at intermediate risk of recurrence. In cases where total thyroidectomy is not performed, the risk of recurrence can be as high as 25% [44,45]. Annual ultrasound monitoring is therefore recommended.

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.
Expert opinion, Grade A

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.
Expert opinion, grade A

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
Expert opinion, grade A

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.
Expert opinion, grade A

8. How should patients treated for NIFTP and TUMP be monitored?

The diagnostic entity of non-invasive follicular thyroid tumor with papillary like nuclear features (NIFTP) [46,47] was proposed in 2016 and introduced in the World Health Organization classification of thyroid tumors in 2017 (see Chapter 3).

The diagnosis is possible only postoperatively. These tumors are considered low-grade, and the risk of recurrence is almost negligible in properly diagnosed cases: 0% in published retrospective series (Table 4) [48,49]. Initial treatment by thyroid lobectomy is sufficient, regardless of size, and neither total thyroidectomy nor radioactive iodine (RAI) treatment is recommended for NIFTP [50,51]. Experience with long-term follow-up for these tumors is limited, and minimal surveillance may be discussed on a case-by-case basis [51].

Tumors of unknown malignancy potential (TUMP) are another category of thyroid tumors for which the risk of recurrence is very low (1%), although distant metastases have been reported [52].

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.
Expert opinion, grade B

9. Active surveillance of microcarcinomas (= Bethesda VI), of Bethesda III, IV, V nodules and of nodules at high risk of malignancy (EU-TIRADS 5 with several criteria for suspicion of malignancy), not biopsied

Microcarcinomas represent 30% to 50% of all thyroid carcinomas. Active surveillance has been used since 2003 in certain situations as an alternative to surgery or thermal ablation [53–65]. Specific mortality is nil and the risk of distant metastatic disease is very low.

The ultrasound criteria specifically assessed in proven or suspected microcarcinoma are as follows [66]: size of the nodule with three diameters and volume in mm^3; location within the gland;

Table 4
Risk of relapse in patients after surgery for NIFTP: retrospective studies with slide review for confirmation of diagnosis.

Article	Number of patients analyzed	Number of patients with recurrence	Duration of follow-up median (unless otherwise specified)
Zurikat et al., 2020 [82]	32	0	67.5 months
Chung et al., 2021 [83]	15	0	69 months (average)
Richard et al., 2020 [84]	65	0	14 years
Cubero Rego et al., 2020 [85]	25	0	70 months (average)
Borda et al., 2020 [86]	89	0	67.9 months
Seo et al., 2019 [87]	125	0	25 months
Xu et al., 2019 [88]	61 (NIFTP with oncocytic cells)	0	5 years
Cherau et al., 2019 [89]	363	0	5 years
Kim et al., 2018 [90]	43	0	41 months (average)
Xu et al., 2018 [91]	52 (size ≤ 1 cm)	0	6 years
Cho et al., 2017 [92]	105 (95 with strict criteria)	0 (3% with lymph node metastasis at diagnosis)	3 years
Xu et al., 2017 [93]	79 (size ≥4 cm)	0	5.8 years
Rosario et al., 2017 [94]	129	0	6 years
Thompson et al., 2016 [95]	77	0	12 years

distance from the thyroid capsule, trachea and inferior laryngeal nerve; features of extra-thyroidal extension; context of lymphocytic thyroiditis; multifocality or other significant nodules; cervical lymph node extension; and laryngeal mobility.

Patient eligibility is based on ultrasound criteria, but is also related to patient and medical team characteristics [66–68]. This strategy classifies patients in three categories of eligibility: ideal, possible, and contraindicated. The ideal situation is that of a patient over 60 years of age [69], with a solitary microcarcinoma located at a distance from the thyroid capsule, the inferior laryngeal nerve and the trachea, and without suspicious metastatic lymph node. The patient must be able to understand the proposed strategy and be compliant with regular monitoring [70], consenting in a dedicated, detailed and fair information consultation [71]. The medical team must be experienced in active surveillance. Patients for whom active surveillance is contraindicated are those who, in contrast, present a nodule close to the capsule, close to the inferior laryngeal nerve, with signs of extra-thyroidal macroscopic or lymph node extension, aggressive cytological type (tall cells, poorly differentiated. . .), age < 18 years, inability to adhere to or refusal of regular monitoring and, of course, absence of a medical facility adapted to this practice. There are intermediate situations where multifocality is suspected [72], there is proximity to the thyroid capsule, the patient is of intermediate age (40–60 years), there is desire for pregnancy [73] or multiple family history of thyroid carcinoma. In these situations, active surveillance should be proposed on a case-by-case basis, taking account of the patient's comorbidities and preference.

It is recommended that sub-centimetric nodules should not undergo FNAB, and therefore situations of < 10 mm Bethesda VI nodules should be rare. The management of EU-TIRADS 5 nodules without cytology can be considered under the same conditions as microcarcinoma [74,75]. However, the advantage of biopsying these nodules lies in the possibility of excluding malignancy, and thus limiting monitoring.

Active surveillance for Bethesda III, IV and V nodules is evolving [76–79]. For Bethesda V nodules, the conditions for active surveillance are the same as for microcarcinoma, thus reserved for ≤ 10 mm nodules. This threshold could be raised to 15 mm in the coming years if sufficient evidence is provided. For Bethesda III and IV nodules, the threshold might be raised to 20 mm.

The recommended monitoring schedule is: first ultrasound 6 months after initial diagnosis, then 6 months after that, followed by annual ultrasound until the end of the 5th year, then at 7 years, 10 years and then every 2–3 years. Monitoring will therefore be lifelong.

The application of this strategy in Bethesda VI nodules has been shown to include approximately 55% to 88% of patients to whom it is offered. It is likely that there is a medical influence bias, depending on how the strategy is presented and the degree of conviction of the practitioner. In the Japanese experience, after 10 years, the rate of volumetric increase and of occurrence of cervical lymph node metastasis were 15.9% and 3.4% respectively [54]. No potentially lethal distant metastases, local recurrences or deaths related to thyroid carcinoma in patients treated with conversion surgery were found. In the United States [80] and South Korea [60,61], progression rates of between 2% and 3.8% were reported, albeit over shorter periods of 30 months. The diversity of these findings is most likely related to the proportion of ideal situations included in the series, but also to inter- and intra-observer variability in measurement.

The indications for conversion surgery are above all the patient's wish, appearance of metastatic neck lymph nodes of thyroid origin or signs of extra-thyroidal extension, and proven volumetric increase in the nodule on 2 consecutive examinations. The criteria for growth vary greatly between authors:

- in diameter: increase of more than 3 mm, or more than 2 mm in 2 distinct diameters, or more than 20–24%;
- in volume: increase of more than 50% to 72%.

The rate of these conversion surgeries is between 1.6% and 7.1%, and appears to decrease with the experience gained by the teams over time [81].

Recommendation 6.17
Cytologically proven carcinomas and EU-TIRADS 5 nodules of ≤ 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 ≥ 45 years are better candidates for active surveillance than younger patients.
Level of evidence +++ Grade A

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

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

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

Disclosure of interest

The authors declare that they have no competing interest.

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