Consensus

Guidelines of the French society of endocrinology for the management of thyroid nodules[☆]

Recommandations de la Société française d'endocrinologie pour la prise en charge des nodules thyroïdiens

J.-L. Wémeau [a,*], J.-L. Sadoul [b], M. d'Herbomez [c], H. Monpeyssen [d], J. Tramalloni [d], E. Leteurtre [e], F. Borson-Chazot [f], P. Caron [g], B. Carnaille [a], J. Léger [h], C. Do [a], M. Klein [i], I. Raingeard [j], R. Desailloud [k], L. Leenhardt [l]

[a] Hôpital Claude-Huriez, clinique endocrinologique, CHRU, 59037 Lille cedex, France
[b] Endocrinologie, hôpital de l'Archet, CHU 06202 Nice cedex, France
[c] Département de médecine nucléaire, centre de biologie pathologie, centre hospitalier régional, 59037 Lille cedex, France
[d] Centre de radiologie, imagerie médicale et échographie thyroïdienne, hôpital Necker, 141, rue de Sèvres, 75015 Paris, France
[e] Inserm U560, service d'anatomie pathologique, CHRU de Lille, Lille, France
[f] Hôpital Louis-Pradel, CHU des hospices civils de Lyon, 28, avenue Doyen-Lépine, 69500 Bron, France
[g] CHU Larrey, avenue du Jean-Poulhès, 31400 Toulouse, France
[h] Service d'endocrinologie et diabétologie pédiatriques, hôpital Robert-Debré, 48, boulevard Sérurier, 75935 Paris cedex 19, France
[i] Service d'endocrinologie, CHU de Nancy, rue du Morvan, 54500 Vandœuvre-lès-Nancy, France
[j] Service des maladies métaboliques et endocriennes, hôpital Lapeyronie, 34295 Montpellier cedex 5, France
[k] Service d'endocrinologie, diabétologie et nutrition, hôpital Sud, CHU d'Amiens, avenue René-Laënnec, 80054 Amiens, France
[l] Service de médecine nucléaire, hôpital Pitié-Salpêtrière, université Paris VI, 47-83, boulevard de l'Hôpital, 75651 Paris cedex 13, France

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Résumé

Le document ici proposé s'inscrit dans la lignée des recommandations pour la pratique que la Société française d'endocrinologie a constituées à l'usage de ses membres et mises à la disposition des communautés scientifiques et des médecins qui le souhaitent. Se fondant sur une analyse critique des données de la littérature, des consensus et recommandations déjà parues au plan international, il constitue une actualisation du rapport sur la prise en charge diagnostique du nodule thyroïdien, proposé en France, en 1995, sous l'égide de l'Agence nationale d'évaluation médicale. Les actuelles recommandations ont été préalablement réfléchies par un certain nombre de médecins reconnus pour leur expertise de la thématique, émanant de l'endocrinologie (groupe de recherche sur la thyroïde), de la chirurgie (Association française de chirurgie endocrinienne), de représentants de la biologie, de l'échographie, de la cytologie, de la médecine nucléaire. Elles ont été présentées et soumises à l'avis des membres de la société, présents au congrès annuel qui s'est tenu à Nice en octobre 2009. Le document amendé a été placé sur le site Internet de la société et a bénéficié de remarques complémentaires de membres de la société. La version finale ici proposée n'a pas fait l'objet d'une validation méthodologique. Elle n'a pas prétention à l'universalité et nécessitera d'évoluer parallèlement aux progrès des techniques et des conceptions. Elle constitue un document que la société juge utile de diffuser, pour une gestion actuelle, efficace et rentable de l'approche diagnostique et thérapeutique des nodules thyroïdiens.
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* Corresponding author.
  E-mail address: jl-wemeau@chru-lille.fr (J.-L. Wémeau).

Abstract

The present document is a follow-up of the clinical practice guidelines of the French Society of Endocrinology, which were established for the use of its members and made available to scientific communities and physicians. Based on a critical analysis of data from the literature, consensuses and guidelines that have already been published internationally, it constitutes an update of the report on the diagnostic management of thyroid nodules that was proposed in France, in 1995, under the auspices of the French National Agency for Medical Evaluation (l'Agence nationale d'évaluation médicale). The current guidelines were deliberated beforehand by a number of physicians that are recognised for their expertise on the subject, coming from the specialities of endocrinology (the French Thyroid Research Group) and surgery (the French Association for Endocrine Surgery), as well as representatives from the fields of biology, ultrasonography, cytology and nuclear medicine. The guidelines were presented and submitted for the opinion of the members of the Society at its annual conference, which was held in Nice from 7–10 October 2009. The amended document was posted on the website of the Society and benefited from additional remarks of its members. The final version that is presented here was not subjected to methodological validation. It does not claim to be universal in its scope and will need to be revised in concert with progress made in technical and developmental concepts. It constitutes a document that the Society deems useful for distribution concerning the management of thyroid nodules, which is current, efficient and cost effective.

1. Introduction

The standard practice for a very long time in the treatment of thyroid nodules was their resection in all cases, due to the inability of clinicians to recognise the nature of the nodules and the fear of missing a cancer diagnosis. Lobectomy-isthmectomy and intraoperative histopathological study were the rule, especially in cases of nodules with decreased uptake on scintigraphy, since around 10% of these formations prove to be cancerous. Such an approach had the advantage of early affirmation with regard to the diagnosis of a nodule, thus freeing patients and doctors from the constraints of monitoring. Over time however, many interventions proved to be useless, and recurrence on the contralateral side was common, leading to complete surgical ablation in one-third of cases.

There is currently better understanding and consideration of the usual benign status of nodules, which is supported by cytologic assessment. There is recognition of their frequent integration with multinodular dystrophy of the thyroid parenchyma, which is detectable by ultrasound, and which becomes apparent over the years and decades.

In 1995, the report from the French National Agency for the Development of Medical Evaluation (ANDEM) ensuing from preparatory meetings of the French Society of Endocrinology (SFE), the Thyroid Research Group (GRT), the Francophone Association of Endocrine Surgery (AFCE) and the French National Pedagogical Association for Therapeutics Education (APNET), proposed a diagnostic management plan for thyroid nodules [1]. This was not intended to define the optimal strategy of evaluation, but to propose consistent approaches in conducting exploratory investigations. Since then, other guidelines have been issued, notably from the American Thyroid Association [2], the American Association of Clinical Endocrinologists and Associazione Medici Endocrinology [3] from the Thyroid Section of the Germanic Society of Endocrinology [4]. Finally, in July 2009, international guidelines were proposed on the website of the European Thyroid Association (http://www.eurothyroid.com/), submitted to the consensus of the international community of thyroidologists.

Thus came about, in France, a need to update evaluation of strategies and therapeutic management of thyroid nodules. This concern led the Scientific Committee of the XXVlth Conference of the French Society of Endocrinology of Nice to dedicate its meeting to the guidelines. A large sampling of endocrinologists, biologists, ultrasonographers, cytologists and surgeons devoted themselves to this subject for 1 year and compared their views and opinions. The results from these reflections are the subject of this report. It is expressed in the form of responses to the most common questions of clinicians.

1.1. Definition

The word "nodule" refers to any localised hypertrophy of the thyroid gland (nodulus = small knot *Latin*).

Surprisingly, there is not a precise scientific definition of nodule. For clinicians, nodosity that distinguishes itself from the rest of the thyroid parenchyma can be recognised when it is superficial, of sufficient volume (4 to 10 mm in diameter) and observed in slim subjects with long necks. Ultrasonographers have highly efficient probes available (up to 13 and 18 MHz) that can detect formations from 1 to 3 mm. For the pathologist, nodular formations are identified as focal spots of hyperplasia that can be distinguished from the relative homogeneity of the rest of the parenchyma. Even molecular biology is unable of providing definitive recognition, since contrary to expectations, the proliferation related to thyroid nodules is not necessarily monoclonal.

The nature of the main nodules is presented in Table 1.

Table 1
Nature of the main thyroid nodules.

Benign nodules
Follicular adenomas (colloids, macrofollicular, microfollicular and foetal)
Simple and haemorrhagic cysts (haematoceles)
Acute, subacute or chronic thyroiditis
Malignant nodules
Papillary, follicular, medullary, anaplastic cancers
Lymphomas
Metastases

1.2. The issues

They are diagnostic, therapeutic, economic and medicolegal.

It is well known that nodulation constitutes physiological modifications of the thyroid parenchyma, and that the large majority of nodules that form in the thyroid are, and will remain, benign. However, it is at the nodular stage that thyroid cancers, when treated, have the best prognosis.

The arguments used to claim that nodules are or are very likely to be benign or malignant are particularly lacking in consistency. Ordinarily, it is rather the comparison of clinical, biological, sonographic, and cytologic information that provides a likely diagnosis. The only certainty comes from the histological study of surgical specimens, albeit surgery is not devoid of difficulties or consequences.

The cost of explorations and monitoring in highly prevalent conditions needs to be taken into account. The psychological impact related to the uncertainty of the patients' present situation and their future and to the diversity of opinions, must be taken into account. The medicolegal impact also weighs heavy in cases of therapeutic abstention and delay in the diagnosis for a malignant nodule, or conversely of consequences of interventions recommended for nodules that have been definitively determined to be benign.

This all contributes to the great deal of confusion on the part of clinicians and patients confronted with management of thyroid nodules.

2. Epidemiology and clinical aspects

2.1. What is the prevalence of nodules?

In countries with sufficient iodine intake (e.g., USA, UK), the clinical prevalence is 5.3 and 6.4% for women and 0.8 and 1.6% for men, respectively. The prevalence is about three times higher in women and increases with age [5].

The prevalence according to ultrasound is about 10 times higher, roughly equal to that of the age decade of the examined subjects [5]. In France, it was estimated to be between 11% (men 45–60 years, SU.VI.MAX study, 7.5 MHz transducer [6]) and 55% (men and women age 40 years and over, 13 MHz transducer [7]). In the USA, the observed prevalence also ranged from 10 to 50% on average, while in Germany, it was from 20 to 29% [4].

The prevalence on autopsy was 8.2 to 65% [8], also according to age, sex and the size threshold.

The prevalence of thyroid incidentalomas was estimated to be 9.4% in vascular examinations of the neck, and 16% on CT scan or MRI.

2.2. What are the predisposing factors for the occurrence of nodules?

Inherent factors [9–11]: the effects of age, female sex, parity (three times lower prevalence in nulliparas) are well established. Overweight is also a promoting factor.

Certain factors stimulate the multiplication or growth of thyroid cells: iodine deficiency, even if relative, promotes the genesis of nodules (normal functioning nodules and autonomous nodules) [9]. The incidence of thyroid cancers is not linked to iodine intake; however, an abundance of iodine or correction of an iodine deficiency reduces the proportion of follicular cancers in favour of papillary cancers [9], possibly by promoting the growth of *BRAF* mutations, the main oncogene specific to papillary cancers [10]. TSH promotes the emergence of such clones. This mechanism would explain the correlation between the TSH level and the prevalence of cancers among the nodules [11–13], as well as the higher prevalence of nodules in smokers [9,11]. Increased TSH is also involved in the prevalence of cancers in goitres related to congenital hypothyroidism and to states of inappropriate TSH secretion.

Certain rare monogenic diseases predispose to thyroid cancers and thyroid nodules. The history-taking portion of the physical examination can detect this, except in cases of *de novo* mutation [14,15]:

- familial multiple endocrine neoplasia type 2 (MEN 2) or medullary thyroid cancer (MTC): autosomal dominant disease from mutation of the RET gene (20–25% of MTC);
- Cowden's disease: autosomal disease linked in 80% of cases to an inactivating mutation of the PTEN gene. It causes benign or malignant thyroid tumours and breast tumours;
- familial polyposis coli (with or without Gardner syndrome): autosomal dominant disease linked to an APC gene mutation. Papillary thyroid cancer is rare in this instance (1–2%) but occurs early, with a female sex ratio of 10:1, and an unusual and rather specific histological expression (cribriform, the observation of which in itself justifies an investigative work-up for polyposis);
- Carney complex: autosomal dominant multiple endocrine diseases linked in 60% of cases to a germinal, inactivating mutation of the PRKAR1A gene. Thyroid tumours, both benign and malignant, have been observed in 16 to 28% of patients. Somatic anomalies of this gene have been found in sporadic cancers;
- McCune-Albright syndrome: disease resulting from a postzygotic, activating mutation of the GNAS gene. Thyroidal involvement is incidental, with cystic and solid nodules, some of which are autonomous.

Other factors:

- familial forms of papillary cancer represent less than 5% of thyroid cancers. The study of pairs of twins suggests that thyroid nodules are due to genetic factors in two cases out of three, and environmental factors in one third [16];
- susceptibility genes are under investigation [17]. The most recent studies implicate close polymorphisms of genes coding for transcription factors (TTF1 and TTF2) [18];
- acromegaly, promotes the occurrence of nodules and cancers, undoubtedly by means of prolonged overexposure to GH or IGF-1. The role of IGF-1 has also been suggested in populations without acromegaly [19];
- therapeutic or accidental irradiation: external radiation therapy at low or moderate doses increases the risk of nodules

(by 2- or 3-fold) and cancer (even though the large majority of nodules are benign) [20–22]. This risk is proportional to the dose (from 10 cGy), is increased in males and is especially relevant in cases of irradiation at a young age. The maximum incidence occurs 15–20 years after the irradiation. Radiation-induced cancers are mainly the papillary type, characterised by RET/PTC rearrangements, and do not exhibit more aggressiveness [23].

Accidental irradiation (the Chernobyl accident) resulted in early development of radiation-induced cancers with similar characteristics in children and adolescents from Belarus and Ukraine [24]. It also promoted the occurrence of benign nodules [25]. There is no scientific support for the notion that the chernobyl accident had an influence on thyroid diseases in France [26–28].

2.3. What proportions of nodules are malignant?

This proportion is only an estimate, since not all nodules are assessed. The percentage of malignant nodules was estimated to be between 3 and 20% in surgical series. A large single-centre series ($n = 21,748$) reported 3.9% of cancers [29]. Five percent is the figure that is usually selected by all experts.

The risk of cancer is similar, whether for a solitary nodule or a multinodular goitre. In multinodular thyroids, the dominant nodules are only responsible for cancer in 50 to 70% of cases [5,8,9,30]. Males and subjects aged less than 20 years or more than 60 years have a two-fold increased risk of cancer [5,30,31]. The size of the nodule does not influence the cancer risk [1,26,29]. If the nodule proves to be cancerous, however, the size does influence its prognosis. This is why convention calls for exercising caution with nodules whose volume is close to or exceeds 3–4 cm. In cases with a history of external radiation therapy, the risk of cancer reaches 14 to 39% [20,22].

These data can be compared to the epidemiology of thyroid cancers and the very high frequency of occult cancers. Diagnosed thyroid cancers make up only 1.3% of all cancers in France, and their incidence is 7.5/100,000 per year for women and 2.2/100,000 per year for men [32]. These cancers have an excellent prognosis overall (representing only 0.3% of cancer deaths in France). On the other hand, the prevalence of incidentally discovered cancers on thyroidectomy is 5–10%, while autopsy studies identify between 2.5 and 37% of thyroid microcarcinomas. Thus, it is estimated that only one out of 15 occult cancers will ultimately progress to a symptomatic stage [33].

2.4. What becomes of thyroid nodules?

With regard to apparently benign nodules, several studies, which were rarely prospective [34–38], suggested that:

- spontaneous regression of at least 50% of the volume was observed in 30% of cases on average (8–52%);
- stabilisation was attained in 30% of nodules;
- an increase in volume of at least 15% was identified in 20–56% after a follow-up of at least 3 years.

The secondary assessment of apparently benign nodules for cancer, particularly in cytology studies, is poor, and the slow increase in size on its own must not be considered a suspicious element of malignancy [36,38,39]. The weak progression of thyroid microcarcinomas [33] was corroborated through the observation of 162 microcarcinomas left in place after a diagnosis of malignancy on cytology [40].

Appearance of new nodules during monitoring: after lobectomy for solitary or unilateral lesions, nodular recurrence is rare before 4 years and affects from 3 to 28% of subjects [41]. The prevention of recurrence through the use of levothyroxine provided contradictory results. In the cohort of subjects followed for nodular disease, this treatment seemed to reduce the incidence of occurrence of new nodules [35,37].

Can a benign nodule become malignant? The malignant transformation of a benign nodule is a fear expressed by patients. Focal cancerous lesions among otherwise benign lesions must be taken into account: 2.3% in a series of 826 thyroidectomies, 346 of which were cancerous [42]. In addition, some lesions have a very difficult histological classification and are grouped together under the diagnosis of tumours of uncertain malignant potential [43]. These encapsulated follicular lesions with moderate nuclear atypia have an intermediate immunohistochemical profile between those lesions that are decidedly benign or malignant. The presence in some of these lesions of gene mutations (*Ras, Ret, Met, p53*) that are involved in thyroid tumorigenesis (with the notable exception of *B-RAF*) also provokes the thought that benign clonal lesions have a potential for malignant transformation [42]. This malignant transformation of a benign tumour is, therefore, uncertain and rare, as demonstrated by the high predominance of papillary carcinomas, whereas the degeneration of follicular adenomas should result rather in follicular carcinomas. On the other hand, the transformation of papillary carcinoma to anaplastic carcinoma is well documented.

Change to frank hyperthyroidism of a nodule that is pretoxic: this possibility is estimated to be 4% per year in warm nodules [9,44]. The risk increases for nodules greater than 3 cm, in elderly subjects and in cases of iodine overload.

2.5. Can the nature of nodules be clinically predicted?

In some circumstances, the clinical data can immediately orient the clinician towards a specific diagnosis, thus limiting the assessments [1,45,46] (Fig. 1).

Therefore, a painful nodule of sudden appearance is suggestive of a haematocele. This may be a true haematocele or related to haemorrhage within a pre-existing lesion. In the latter case, 90% of haemorrhagic nodules are benign, with the remaining 10% malignant, particularly when the bleeding recurs after aspiration [1,45].

Thyroiditis nodule:

- acute thyroiditis: an inflammatory swelling accompanied by fever suggests a thyroid abscess. In this rare situation (immunodeficient, child, piriform sinus fistula), the high quantity of

Nodules with accompanying clinical signs

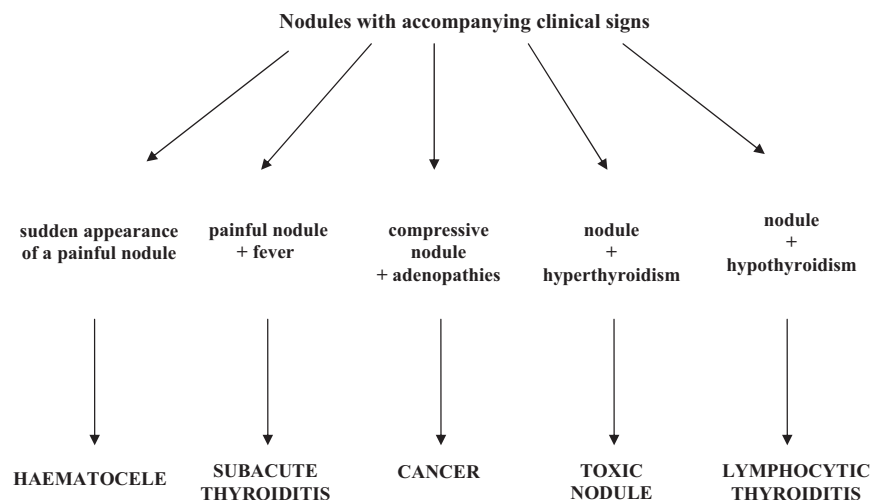| sudden appearance of a painful nodule	painful nodule + fever	compressive nodule + adenopathies	nodule + hyperthyroidism	nodule + hypothyroidism
HAEMATOCELE	**SUBACUTE THYROIDITIS**	**CANCER**	**TOXIC NODULE**	**LYMPHOCYTIC THYROIDITIS**

Fig. 1. Baseline physical examination of thyroid nodules according to French National Agency for the Development of Medical Evaluation.

granulocytes and identification of the bacteria in the aspirate fluid will lead to the diagnosis;

- subacute thyroiditis: the clinical (fever, pain) and biological (very high CRP, suppressed TSH) picture distinguishes the rare focal forms of this thyroiditis. Needle aspiration, if performed, will be very painful and will show inflammatory infiltrate with multinucleated giant cells [47];
- chronic lymphocytic thyroiditis: increased thyroid lobulation, heterogeneous involvement of the parenchyma, firmness of the nodule, and a rise in the TSH level can suggest this diagnosis to the clinician. The measurement of antithyroperoxidase antibodies and hypoechoic patterns on ultrasound assist in the diagnosis. Fine-needle aspiration showing abundant cellularity, which is poor in colloid and high in polymorphous lymphocytes, sometimes closely linked to epithelial cells (often oncocytic), suggests the nodule diagnosis of lymphocytic thyroiditis;
- Riedel's thyroiditis: this very rare, rapid spreading and infiltrating thyroiditis can suggest an anaplastic cancer, differing by the absence of lymph node invasion. Fine-needle aspiration cannot always distinguish these two diseases [48], thus justifying histological verification;
- toxic nodule: 5 to 10% of thyroid nodules (solitary or originating from a multinodular thyroid) are associated with lowered TSH levels [1,9,44,45], which rarely coincides with immediate thyrotoxic symptomatology suggestive of toxic nodule. However, the question of malignancy is not settled definitively due to the possible presence of other cancerous nodules and the low risk of cancer among hyperfunctional nodules [1,9,38,49].

2.6. Can the benignity or malignancy of a nodule be suspected based on clinical evidence?

Although some clinical criteria may help to orient the clinician towards a malignant diagnosis (Table 2), none of them is totally specific [44,46,47,49]. Their sensitivity is poor, since only a minority of patients with cancer present with one or several

Table 2
Clinical markers of cancer risk in the presence of a thyroid nodule.

Age < 16 years or > 65 years
Male sex
Familial background of papillary carcinoma (more than 2 subjects in the family), medullary carcinoma or multiple endocrine neoplasia type 2
Concurrent Cowden's disease; familial polyposis coli, either isolated or with Gardner syndrome; Carney complex; von Recklinghausen's disease
History of neck irradiation
Recent or rapidly progressing nodule
Hard, irregular or fixed nodule
Recurrent laryngeal nerve palsy
Proximal adenopathy

of these criteria. They should be investigated, however, if they have a high positive predictive value; therefore, when at least two highly suspicious criteria are present, the risk of malignancy is close to 100% [45].

The size of the nodule does not play a role in the cancer diagnosis [1,45]. It is, however, a factor relative to the prognosis of the cancer. Therefore, caution is usually exercised when nodules exceed 3 or 4 cm.

There are some rare instances when immediate histological confirmation is indicated. Nevertheless, ultrasonography, laboratory exams and even fine-needle aspiration will also be carried out in order to optimise the care [50,51]. No clinical diagnostic indicator can justify holding to a purely clinical approach and putting aside any other form of investigation.

3. Biological measurements

3.1. Is the baseline TSH measurement sufficient?

All consensus reports, recommendations and guidelines are unanimous in that TSH is the only measurement needed for first-line investigation. In the presence of a nodule, its sensitivity

and specificity enable it to detect all known thyroid dysfunctions, as well as those that are subclinical [1–4,50–54].

Subsequent determinations serve to quantify and specify the origin of the dysfunction when it exists. Free T3 and T4 assays will be carried out if the TSH is low; if it is high, free T4 and anti-TPO antibodies will be measured.

In populations of subjects seen for thyroid nodules, it has been shown that the risk of cancer is increased if TSH is in the high-normal values, and is decreased with low-normal values. This cannot be used, however, for individual prognostic evaluations.

There is no reason to measure the circulating thyroglobulin level, which does not constitute a marker of malignancy. It will subsequently be used to monitor operated cancer nodules. However, its diagnostic value only should be assessed when there are diffuse metastasis: its level is usually very high (> 1500 ng/ml) in largely metastatic differentiated carcinomas of follicular origin. In the absence of specific antibodies, a normal value reasonably rules out the thyroidal origin, even in the presence of an incidentally discovered occult thyroid nodule.

3.2. Should calcitonin be systematically measured?

Screening for medullary thyroid cancer (MTC) through the systematic measurement of calcitonin (CT) in nodular thyroid disease remains a controversial subject.

The serum calcitonin level is a sensitive diagnostic marker of MTC and thus MEN 2. It is proportional to the size of the primary MTC and the TNM stage [55–57]. CT doubling time is correlated to RECIST progression and survival [58,59]. CT is, therefore, a sensitive diagnostic and prognostic marker [55].

Criteria required by WHO for considering screening useful:

- the disease should be an important public health problem: in France, the incidence of thyroid cancer is 4–8 per 100,000 inhabitants/year. The number of new cases of MTC is 150–250 per year, representing 0.18% of thyroid nodules. These data are in accordance with the recently published data of Rink et al. (21,928 subjects included) [55,60]. MTC is not a public health problem;
- the disease must have a recognisable latent stage: in the familial forms of MTC, the continuum of C-cell hyperplasia (CHC), microcarcinoma and then, macrocarcinoma was perfectly demonstrated in both humans and animal models [55,61,62]. MTC fully meets this condition;
- the natural history of the disease must be fully understood: there is no specific data concerning the natural history of sporadic forms of MTC (target of screening). Mortality from MTC is 10% of thyroid cancers, while it only has a 5% incidence, suggesting that MTC has greater aggressiveness versus the differentiated thyroid cancers. The genetic or sporadic nature of MTC does not constitute a formally established major prognostic factor. Some MTC may progress over many years [55]. The natural history of sporadic MTC is not completely known;
- there must be effective screening tests available: the screening test is the assessment of the circulating monomeric CT level. This measurement is more sensitive than palpation, as well as

fine-needle aspiration [55]. However, the percentage of MTC screened only through the measurement of baseline CT is very low, around 0.06% of clinical thyroid nodules [63,64]. Of MTC screened by CT measurement, 20–60% were suspected on fine-needle aspiration. Calcitonin levels can also be increased in circumstances other than MTC, particularly in instances of C-cell hyperplasia, so-called physiological or reactive. In autopsy series by Guyetant et al., the prevalence was 33%, with a clearly male predominance [54,62,64]. The prevalence of these serum calcitonin elevations not due to MTC varies according to the decisional threshold used. It has been assessed between 0.9 and 4.9% for a decisional threshold of 10 pg/mL but decreases between 0.43 and 1.15% for a 20 pg/mL threshold [16]. Therefore, the majority of cases of hypercalcitoninaemia currently found that are not due to MTC are between 10 and 20 pg/mL (76% in the Italian study by Costante et al.) [64]. The major functional causes of increased CT are renal failure and hypergastrinaemia (which may be iatrogenic) and the presence of another endocrine tumour. CT stimulation tests increase the diagnostic sensitivity but not the specificity. There is a significant overlap of CT values observed for patients with microscopic MTC and those presenting with C-cell hyperplasia (moderately increased baseline CT values). The CT measurement has good sensitivity but limited specificity [65–67];

- there must be effective treatment available for patients with the disease: MTC is cured by total thyroidectomy with lymph node dissection for the types found before the stage of significant lymph node invasion. The current cure rate for sporadic MTC is about 30%. The impact on survival of earlier surgery based on screening has not been demonstrated in a randomised or case-control study [55]. Surgery is an effective treatment for MTC if it is performed sufficiently early and in a specialised milieu for limiting morbidity;
- the test must be acceptable for the population: there are no available acceptability studies on CT measurement in the general population, but the test is based on a simple blood sample;
- the advantages must be analysed by integrating the economic factors: the two medical-economic models [68,69] (one conducted in the American context, the other in the French context) conclude that the systematic measurement of calcitonin in patients with thyroid nodules has a favourable cost-effectiveness ratio. Both studies emphasise, however, that these results are very sensitive to the variations in specificity of the test (therefore, to the proportion of false-positives) and to the prevalence of the disease, and should, therefore, be confirmed on prospectively collected data;
- the screening must lead to a drop in mortality: two studies showed that the systematic measurement of CT was able to diagnose MTC at an earlier stage, including the discovery of microscopic MTC. It could only be demonstrated that this early diagnosis resulted in an improvement in mortality (absence of randomised or case-control study) [63,65]. The tumoural aggressiveness is widely variable. It was not quantified by either anatomopathological or molecular data, but rather by the kinetics in the CT and CEA levels. There

is a risk of overdiagnosis for slowly progressing MTC. The decline in mortality remains to be demonstrated, even though it has been suggested.

In conclusion, the screening of sporadic MTC through systematic CT measurement in thyroid disease only meets one part of the criteria required by WHO. The limited specificity of the measurement (medullary cancer marker, but also of C-cell hyperplasia and other tumours) and the absence of knowledge with regard to the natural evolution of sporadic microscopic MTC are the main limitations. It is essential that progress be made in the specificity of the measurement and that there is certitude concerning a drop in mortality before claiming that the measurement of calcitonin must be carried out for all nodules.

The recommendation for the time being, therefore, in order to avoid any loss of opportunity and inappropriate care, is to measure the CT at a minimum:

- when there is a known genetic background of MTC, flushing, motility-related diarrhoea;
- in case of suspicion of malignancy (suspicious nodule based on clinical, ultrasound and cytology evidence);
- as a rule before any intervention for goitre or nodule.

The measurement of calcitonin can also be considered more generally during the initial assessment of a nodule, being careful not to repeat its measurement if the value is normal.

The diagnostic value of an increased baseline level of calcitonin is to be assessed in comparison to the volume of the nodule, and in relation with the data from the cytological examination, or even that of immunocytochemistry, or measurement of calcitonin in the rinse fluid from the aspiration needle. The comparison with age, sex, weight status, renal function, and current or former tobacco usage is essential: calcitonin levels are frequently increased in middle-aged men that are overweight and have a history of heavy smoking.

For intermediate profiles, there is no need to consider immediate surgical intervention given only a moderate increase in the calcitonin level. The pentagastrin-stimulated calcitonin test (or calcium-stimulated, when it is available) provides non-specific evidence of primary thyroid origin, but does not make a distinction between cancer and hyperplasia. It is only recommended when an extrathyroid tumour is suspected.

If there is a moderate increase in calcitonin however, the performance of a second measurement is recommended after 3-12 months (contingent on the clinical context); then, in the event of permanent CT elevation (> 15 pg/ml in women, > 30 pg/ml in men):

- consider surgery if (in the absence of other individual causes) the baseline CT level exceeds 50 pg/ml or if a greater than 20% progression is observed;
- repeat the measurements by doubling the monitoring interval if the CT is stable;
- stop the monitoring if the CT decreases.

4. Ultrasound evaluations

Ultrasonography has become the reference imaging for thyroid nodules [53].

This distinction applies to the detection, diagnosis, investigation for signs of malignancy and monitoring of nodules (or multinodular thyroid nodules).

4.1. What is necessary for the ultrasound examination?

The operator must be well experienced in performing thyroid ultrasonography and aware that the decision tree will depend on his or her conclusions.

The equipment must be suited to the exam and include in particular:

- a very high frequency (≥ 12 MHz) linear transducer. As the thyroid gland is very superficial, the use of high frequencies offers a resolution potential that is essential to the assessment of the nodule;
- a low beam, high frequency (8 MHz) sequential transducer for the study of nodules involving the area behind the manubrium;
- colour and flow Doppler modules;
- an elastography module is ideal.

The patient must not present with contraindications to neck ultrasound examination.

The study of the nodule must of course be integrated in a complete thyroid ultrasound examination, with characterisation of the non-nodular parenchyma and lymph nodes present in the drainage areas.

4.2. What does ultrasound add to the diagnostic and prognostic evaluation of nodules?

4.2.1. Ultrasound characterisation of nodule(s)
4.2.1.1. B-mode ultrasound [34,52,70–74].
 4.2.1.1.1. Localisation–relation to other structures. It is important to specify whether the nodule is located:

- within a normal volume thyroid or a goitre;
- in normo- or hypoechoic tissue;
- in a uni- or multinodular thyroid.

The ultrasound locates the position of the nodule in the lobe or isthmus with precision.

Furthermore, certain locations have their own significance:

- external part of the middle third or the upper third-middle third junction (medullary tumour site);
- in the pyramidal lobe or the thyroglossal duct;
- below the lobes (plunging character);
- on the ectopic thyroid parenchyma.

The location relative to the neighbouring structures is specified through investigation of:

- compression (tracheal, in particular);
- posterior dysfunction when swallowing.

4.2.1.2. Volume. It is imperative to measure the volume of each nodule using the three orthogonal measurements in the ellipsoid of revolution formula (depth × length × width × 0.52). It is the only technique that enables objective monitoring of the nodules.

4.2.1.3. Echographic structure. A nodule can be solid, cystic (fluid-filled) or mixed. In the latter case, it is advisable to indicate what the predominant component is and in what proportion.

The characterisation of mixed nodules is done based on the echogenicity of the solid portion.

Thick fluid-filled nodules (colloid, blood, etc.) may falsely take on a solid hypoechoic appearance. Doppler and elastography are then very useful, as a cystic nodule has no vascularity. Its elastographic appearance is characteristic (very contrasted bizone image).

The cystic nodule is defined by four characteristics in B-mode ultrasound:

- anechoic at the normal gain setting;
- filling up with fine echos in gain saturation;
- without its own wall or with a fine and regular wall;
- with posterior reinforcement.

The cancer risk for this type of nodule was reported to be less than 2%.

In some cases, it may contain solid formations in suspension (presenting with Brownian movements) or in deposits (distinct level of mobile sedimentation when changing to seated position). It is, then, no longer a true cystic nodule.

4.2.1.4. Echogenicity. This applies to solid and mixed nodules. It is assessed in comparison with the neighbouring parenchyma (which can pose a problem when the latter is hypoechoic, as in the case of thyroiditis).

A nodule can be hypo-, iso- or hyperechoic. Some solid nodules have complex echogenicity, which is important to report.

4.2.1.5. Edges and shapes. The following should be described:

- the contours of the nodule, which can be smooth, ill-defined or lobulated (smooth but irregular). The possible presence of a hypoechoic halo must be reported;
- possible contact with the anterior capsule (deformity or invasion);
- the shape of the nodule;
- usually round or oval;
- it should be reported if the thickness of the nodule is greater than its width (anteroposterior diameter greater than transversal diameter).

4.2.1.6. Calcifications. They are very hyperechoic, and when they are sufficiently voluminous, they produce a posterior

acoustic shadow cone, which can prevent the anteroposterior measurement of the nodule. The following can be identified:

- peripheral eggshell macrocalcifications;
- intranodular macrocalcifications;
- microcalcifications, which are more or less diffuse throughout the nodule, and which do not produce shadow cones. In the event of accumulation however, reduction of the acoustic beam can be noted. They correspond to psammomas or calcospherites, described in the histology of papillary cancers [75].

A clear distinction must be made between these microcalcifications and the artefacts relative to the presence of colloid. The presence of a posterior comet-tail (repetition artefact) is one such valuable indicator [76].

4.2.1.7. Doppler mode [77,78]. Colour or power Doppler ultrasound assessment classifies the nodules into four groups:

- I: no vascularity (increasingly rare event with the increased sensitivity of Doppler modules);
- II: almost exclusive perinodular vascularity;
- III: high peri- and intranodular vascularity;
- IV: exclusive or predominant intranodular vascularity.

Pulsed Doppler ultrasound can highlight two characteristics:

- the resistance index, which in the case of follicular nodules would have a pejorative value above 0.78 [79,80];
- the intranodular blood flow velocity, which in the case of high values directs the diagnosis towards an autonomous formation (on the condition that it is measured at a distance from the periphery of the nodule and compared with that recorded on the corresponding afferent artery) [78,81,82].

4.2.1.8. Elastography [83–85]. This technique is used to assess the stiffness of a nodule. Clinically, a stiff nodule is known to be suspicious, and histological observations confirm this.

Studies conducted on thyroid nodules used the strain elastography technique with colour or grey-scale coding. It assesses the stiffness of a nodule compared to the healthy neighbouring tissue.

All of the publications observed that the stiffness of the nodule is predictive of tumour malignancy. Direct quantification techniques confirm these results.

The transient (*shear wave*) elastography technique enables a calculable quantification to be made by not requiring comparison with healthy tissue.

4.2.2. Differential diagnoses

The differential diagnoses are the following:

- pseudonodule behind a septum (posterior area);
- pseudonodule of thyroiditis. It is a major obstacle since the improper description of a nodule risks the performance of
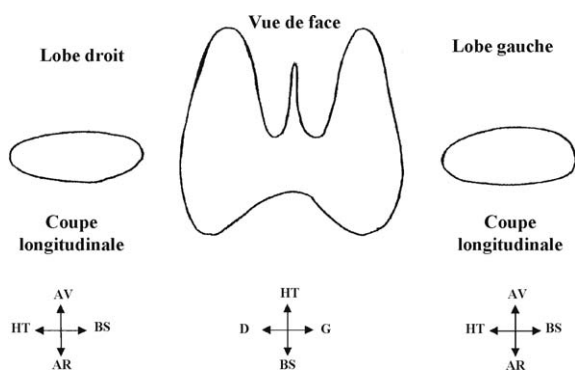
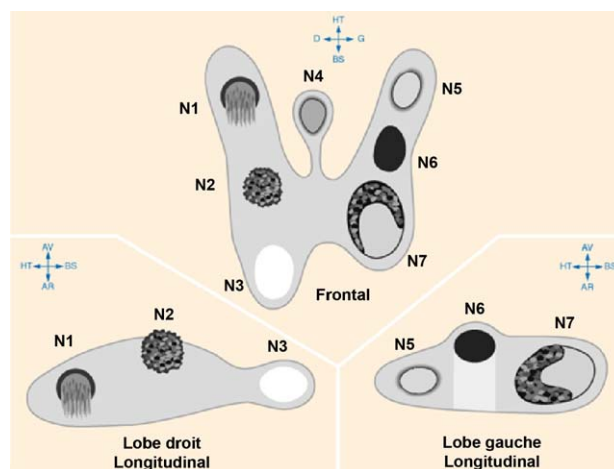Fig. 2. Anatomical frontal and profile view of each lobe.

Fig. 3. Nodule presenting with easily recognisable unique features. N1: right apex. Egg shell calcification. Posterior shadow cone; N2: right mediolobular. Hypoechoic, spiculated. Capsular break. Microcalcifications; N3: on inferior extension. Hyperechoic; N4: on the pyramidal lobe. Moderately hypoechoic; N5: left apex. Isoechoic. Complete peripheral halo; N6: left mediolobular. Cyst with posterior reinforcement. Capsular deformity without breakage; N7: left base. Mixed, balanced, with solid isoechoic zone and non-true fluid zone.

a non-justified needle aspiration procedure. In the case of pseudonodules, there is no mass syndrome, peripheral vascularity effect or rigidity gradient in elastography;

- lymph node (recurrent taken nerve mistaken for a posterior nodule, or if upper zone 6, mistaken for an isthmus nodule);
- non-thyroid nodule, particularly parathyroid;
- unusual oesophageal image (right oesophageal bulge, Zenker's diverticulum, tumours);
- neighbouring tumours adhering to the capsule.

4.2.3. Limitations of ultrasonography

Certain factors may hinder the procedure of the ultrasound examination and limit the validity of the nodular assessment (and in doing so, of the ultrasound-guided needle aspiration): very large number of multiple nodules, convergence of total lobe nodules, substernal nodules, certain locoregional conditions (macrocalcifications, sequelae of surgery or radiation therapy, obesity, amyloidosis).

4.2.4. Location schema [86]

The location scheme is obligatory. It is an essential item for monitoring multinodular thyroids.

The scheme that includes an anatomical frontal and profile view of each lobe (Fig. 2):

- completes the sonographic description and simplifies the report (which it cannot replace);
- is easily used during the monitoring;
- can be modified according to;
  - changes in the nodule,
  - the appearance of new nodules;
- enables, compared to scintigraphy, autonomous formations to be located.

Each nodule:

- is drawn from a frontal view and one of the profiles. It is, thus, fully localisable in the three dimensions of space;
- is numbered. In consideration of standardisation of ultrasound practices, it seems logical that the numbering begins at the right apex, go through the isthmus and finish at the left base. The same numbering must be followed at each examination.

When a nodule resolves, its number is not reattributed to a newly appearing formation;

- is represented as closely as possible, both with regard to volume and B-mode appearance (echographic structure, echogenicity, calcifications, etc.) [87]. This helps to provide orientation of a nodule presenting with easily recognisable unique features, in the event of multinodular thyroid monitoring (Fig. 3).

4.2.5. Lymph node characterisation

In spite of not being integrated in the study of the nodule, the group agrees that certain ultrasound characteristics of lymph nodes can be noted here to reinforce the pejorative character of a nodule; (cf. guidelines for the management of follicular carcinoma of the thyroid [88]).

Three fundamental criteria of malignancy enable the comparison of normal lymph nodes and adenopathy:

- shape: Steinkamp index less than 2 with adenopathy (ratio of the largest to the smallest of the three diameters);
- structure: systematic disappearance of the hilum in adenopathies;
- vascularity: adenopathy loses the central character of its vascularity, which can become diffuse, anarchic, mixed or peripheral.

   Certain signs are very suggestive of thyroid cancer metastases:

- microcalcifications;
- cystic zone;
- echogenic lymph node resembling the thyroid parenchyma;
- a small diameter greater than 7 mm.

The normal lymph node is spindle-shaped, structured (with a visible central hilum) and with central vascularity.

Table 3
Positive predictive value (PPV) and odds ratio (OR) in favour of malignancy according to the ultrasound criteria in the series of Nam-Goong et al. [91].

	PPV	OR
Solid nodule	25.6	6.5
Hypoechoic nodule	27	3.6
Microcalcification	39	4.1
Solid and hypoechoic nodule	34.6	6.3
Solid nodule with microcalcifications	53.3	8.8
Hypoechoic nodule with microcalcifications	60	6.6
Solid and hypoechoic nodule with microcalcifications	75	13.1

In some cases, it is the discovery of adenopathy that results in an exhaustive assessment of the nodule. It is important to specify the lymph node zone that the adenopathy is located in.

4.2.6. Results

Ultrasound criteria that modify the assessment of cancer risk: many articles report that the presence of microcalcifications, irregular contours, the hypoechogenic nature of the nodule, its mixed (peripheral and central) or radial penetrating vascularisation is associated with an increased risk of malignancy [89]. Each of these variables on its own confers to the nodule an increased risk of malignancy by a factor of 1.5 to 3. However, when these variables are combined, risk of malignancy significantly increases [27,90]. In the series of Nam Goong [91], the solid hypoechoic nature, the presence of microcalcifications, and to a lesser degree, the not very distinct contours and intranodular vascularity were variables significantly associated with a risk of malignancy. The Table 3 below shows the positive predictive value (PPV) and odds ratio (OR) of malignancy, which increases according to the combination of variables.

Table 5
Sonographic signs suggestive of malignancy.

Solid and hypoechoic nodule [247]

Unclear, lobulated or spiculated margins

Quadrangular shape

Capsular break

Invasion of adjacent structures

Extinction of mobility during swallowing

Anteroposterior (AP) diameter > transverse (T) diameter [248]

Microcalcifications [249]

Peripheral, discontinuous macrocalcifications [249]

Type IV vascularization (exclusive or predominant intranodular hypervascularization)

Vascular resistance index (RI) > 0.8

High stiffness index on elastography [84]

Adenopathy(ies) in the drainage regions

On the other hand, nodules that are predominantly cystic (> 50%) have a low risk of malignancy. True cysts (> 99%) appear to have a very low risk of malignancy (< 1%) [88].

The 2009 series of Horvath proposes the use of ultrasonography risk scores (thyroid imaging reporting and data system [TIRADS]) in order to avoid aspiration biopsy of all thyroid nodules [92] (Table 4).

In terms of this analysis, there is agreement that malignity and benignity can be suggested based on the conjunction of the following signs (Tables 5 and 6): certain sonographic characteristics (very high peri- and intranodular vascularity, increased intranodular circulatory velocity) are suggestive of functional nodules, thus leading to careful assessment of the TSH level and the possibility of including scintigraphic evaluation [93].

Table 4
Ultrasonography risk scores (Tirads).

Ultrasound characterisation	US pattern	Malignancy (%)	Tirads
Anechoic with hyperechoic spots. Lack of vascularity	Colloid type 1	0	Tirads 2: benign
Non-encapsulated, mixed, non-expansile with hypoechoic spots. Spongiform appearance; vascularized	Colloid type 2		
Non-encapsulated, mixed, with solid portion; with hyperechoic spots; vascularized	Colloid type 3		
Hyper-, iso- or hypoechoic; partially encapsulated, peripheral vascularization, in Hashimoto's thyroiditis	Pseudonodule	< 5	Tirads 3: probably benign
Solid or mixed; hyper-, hypo- or isoechoic, with a thin capsule	Benign	5–10	Tirads 4A: undetermined
Hypoechoic with ill-defined borders, or without calcifications	De Quervain		
Hyper-, hypo- or isoechoic; hypervascularized with a large halo; micro or macrocalcifications	Suspicious		Tirads 4B: suspicious
Hypoechoic; without halo, with irregular margins; penetrating vascularity, with or without calcifications	Malignant pattern 1	10–80	
Iso- or hypoechoic, without halo, with multiple microcalcifications and hypervascularization	Malignant pattern 2	> 80	Tirads 5: consistent with malignancy
Without halo; iso- or hypo-, mixed vascularity with or without calcifications; without colloid artefact	Malignant pattern 3 cytology +	> 100	Tirads 6: malignant

Table 6
Sonographic signs in favour of benignity.

Cystic nodules
Solid or hyperechoic or microcystic
Thin and complete peripheral halo
Complete peripheral calcification
Peripheral vascularization
Absence of adenopathy
Absence of personal or familial history that could raise fears of cancer
Absence of stiffness gradient with surrounding tissue

5. Which nodules should be biopsied?

Fine-needle aspiration biopsy (FNAB) for detailed study is contraindicated when there are major alterations in haemostatic function, and in patients undergoing anticoagulant treatment. Interruption of treatment with platelet suppressive agents is recommended 1 week before the procedure.

According to the guidelines of the National Cancer Institute (NCI), published in 2008, on the cytologic indications for incidentalomas, fine-needle aspiration should be performed if the nodule has a diameter greater than at least 10–15 mm, with the exception of true cysts or septated cysts without a detectable solid component [88]. FNAB is recommended, regardless of the size of the nodule, if it presents sonographic signs suggestive of malignancy (Table 5).

The American Thyroid Association (ATA), Academy of Clinical Thyroidologists (ACT), American Association of Clinical Endocrinologists (AACE) and the Society of Radiologists in Ultrasound (SRU) issued more detailed recommendations concerning the indications for FNAB, which take into consideration the different sonographic aspects. In addition, two recent series from McCartney (2008) and Horvath (2009) make an attempt to prioritise these FNAB indications by assessing the diagnostic cost-effectiveness of different diagnostic approaches [90] or by establishing ultrasonography risk scores (TIRADS) [92] in order to avoid aspiration of all thyroid nodules. The approach of systematically aspirating any nodule greater than one centimetre in diameter was not found to be very cost-effective [90].

After analysis of this literature, agreement was made to recommend FNAB in the following situations:

- a high-risk context:
  - history of external radiation therapy in childhood,
  - family history of MTC or MEN2,
  - personal or family history of Cowden's disease, familial polyposis coli, Carney complex, McCune-Albright syndrome,
  - elevated baseline calcitonin level on two occasions,
  - nodule accompanying suspicious adenopathy,
  - nodule discovered as part of the work-up for frequent metastasis;
- an at-risk nodule:

  - nodule with suspicious clinical characteristics: hardness, compression signs, increased volume over several weeks or months,
  - nodule with a 20% increase in volume (or that had a minimum increase in two or more dimensions of at least 2 mm) since the last size measurement,
  - nodule with at least two of the following suspicious sonographic criteria: solid and hypoechogenic, microcalcifications, indefinite margins/borders, a taller (anteroposterior) than wide (transverse) shape, type IV vascularization (Table 6),
  - nodule found during 18F-FDG PET imaging with a zone of focal hypermetabolism,
  - nodule in which the initial cytologic smears were found to be non-contributory, or included a follicular lesion of undetermined significance;
- in cases of multiple nodules without high risk profile or at-risk nodule (as defined above): dominant nodule superior to 2 cm (not true cyst) within a multinodular thyroid: FNAB is justified in order to avoid misinterpreting a large-sized follicular tumour (corresponding to a pT2 tumour) that may appear unremarkable on ultrasound.

6. Cytological evaluations

The composition of this work is based to a very large extent on the results of the Bethesda Conference of October 2007 [94].

6.1. What are the requisite conditions for an effective cytologic examination?

An effective thyroid cytologic examination is founded on an optimal fine needle aspiration technique and a high-quality cytologic interpretation. These two prerequisites are based on a series of essential steps [95].

6.1.1. Fine needle aspiration technique
The fine needle aspiration technique is as follows:

- fine needle aspiration of the nodule must be carried out by an experienced operator, whose skilled proficiency in nodule selection for biopsy and in the procurement of aspirate material has been confirmed, regardless of the biopsy technique used (palpation or ultrasound-guided). Teams with a single or a few operators and that carry out many aspirations are the most effective;
- needles are 25 to 27 gauge. Aspiration is not necessary (Zajdela technique) except if the sampling is fluid, as the cellular material enters the needle through capillary action. A dwell time of 2 to 5 seconds is used with forward and back oscillations of the needle (3/sec). Each pass should produce one to two slides;
- for cysts, it is preferable to empty them very slowly; otherwise, there is the risk that they will refill immediately with blood;
- the number of passes depends on whether or not intraoperative reading is available. The benefit of this type of reading is debatable. If it is not available, two to five passes are recom-

mended; if it is available, two passes are recommended and considered sufficient if:

○ there is a diagnosis of malignancy,
○ if the cellular material is sufficient for an interpretation,
○ with cysts, if there is no fluid or residual solid lesion. Whether a nodule is cystic or not does not have bearing on the number of passes made; the passes must be carried out in different zones with large-sized, heterogeneous nodules. Slides from different passes must be identified as such;

• whether or not a local anaesthetic is used is left to the discretion of the operator with the agreement of the patient. If local anaesthesia is chosen, use 0.5 to 1.5 ml of 1–2% lidocaine with slow subcutaneous injection or prescribe an anaesthetising ointment (such as EMLA), which takes effect in 1 hour;

• an ultrasound-guided fine needle aspiration is indicated when the thyroid nodule is not palpable, when the nodule contains a cystic component greater than 25% or when a fine-needle aspiration was previously performed but appeared to be unsatisfactory for the diagnosis;

• when ultrasound-guided fine needle aspiration is carried out, the needle must not pass through the gel lying between the ultrasound probe and the skin. Indeed, if this gel collects on the specimen slide, it can cover the cells and hinder cytological interpretation.

6.1.2. Cytologic technique

It is currently accepted that the optimal method is direct smear done by an experienced operator. Techniques using liquid based cytology (LBC) and the inclusion of the cellular pellet in paraffin (cell block) take longer, are more costly and have not proven their superiority. These techniques are acceptable, however, in particular situations:

• with solid nodules and if intraoperative reading is available, then direct smear is mandatory; otherwise, direct smear and/or LBC cytology and/or cell block preparation. If smears are done, an optimum technique must be used;

• with cysts, cytocentrifugation (cytospins), or LBC and cell block preparation if microscopic fragments in suspension;

• staining: air-dried slides for staining with May-Grünwald-Giemsa or equivalent (Diff-Quik, Giemsa, etc.) and fixed for the Papanicolaou staining technique or equivalent (Harris-Schorr);

• the interpretation is dependent on the specific proficiency of the cytopathologist who must be trained and regularly evaluated. Teams with a single or a few readers and who examine many thyroid fine needle aspirations are the most effective;

• as a general rule, fine needle aspiration is considered sufficient when it includes five to six smears, each including more than 10 thyroid epithelial cells. Certain diagnostic situations are exceptions to this rule, as a diagnosis can be proposed while the studied cells are less numerous: the presence of rare suspicious or malignant cells justifies a diagnosis of suspicious or malignant lesion; the presence of a few epithelial

cells observed in conditions of cytological inflammation leads to a diagnosis of thyroiditis.

6.2. How are the results presented?

Formulation of the results of a fine-needle aspiration requires that information be delivered concerning the patient, the physician operator, the cytopathologist, clinical data, nodule characteristics, the type of material presented, the techniques used and the result. The conclusion of the report follows the recommendations defined in the Bethesda guidelines (2008 NCI conference) [94]. These factors can be compiled as a standard text or integrated in a form (see below). The diagnosis of a follicular lesion of undetermined significance is optional, and its use must remain exceptional (Appendix A).

6.3. When is the cytology examination repeated?

Once the baseline work-up of the nodule is done, and after analysis of the clinical and paraclinical characteristics of the nodule, the question of repeating the cytology examination is raised in two different situations:

• when the sample is not satisfactory for the diagnosis or includes a follicular lesion of undetermined significance. In accordance with the recommendations of the majority of authors and the Bethesda guidelines, this new fine needle aspiration is to be carried out under ultrasound guidance within 3 to 6 months for solid nodules, or 6 to 18 months for nodules with mixed echographic structure [38,53,96–101];

• during monitoring of cytologically benign nodules. This new fine needle aspiration is to be carried out;

• in principle after 6 months or 1 year, at the time of the first reassessment;

• or only secondarily, and thereafter imperatively when clinical or suspicious sonographic modifications justify it (especially a greater than 20% increase in volume of the nodule in 1 year) [38,39,53,96,100,102,103].

6.4. What is the role of immunocytochemistry?

The following report is a summary of articles published over the last 3 years and selected among the list of references obtained by the PubMed research engine using the keywords "thyroid and fine needle aspiration". The selection includes three reviews and/or expert analyses [104–106], one meta-analysis of studies on GAL-3 (galectin-3) [48], one review of the recommendations from three American and European scientific societies [3], the conclusions of the Bethesda conference in October 2007 on "the state of the science in thyroid cytology/use of complementary techniques" [107] and a limited number of studies on GAL-3 [19,108], TPO (thyroid peroxidase), DPP4 (dipeptidyl-aminopeptidase-4) and HBME 1 (Hector Battifora mesothelial cell-1) [109,110], the protocols of which are mostly in accordance with the international standards with regard to diagnostic test studies [111]. A more detailed analysis of previous data in the literature on immunocytochemistry markers in thyroid cytol-

ogy can be found in these articles and the review by Vielh et al. (2006) [106].

Immunocytochemistry techniques can be carried out on paraffin-embedded cell pellets using technical methods that are identical to those developed for tissues. These techniques can also be done on cell smears that are cryopreserved at −20 °C or on monolayer smears after specific validation. The performance of these techniques depends on consideration of the cost of reagents and the availability of antibodies.

The indications for immunocytochemistry in thyroid cytology are the following:

- suspicion of medullary carcinoma: if the morphology is not clear, the fine needle aspiration product can be investigated for expression of calcitonin, and/or chromogranin, carcinoembryonic antigen, and possibly thyroglobulin. A serum measurement of calcitonin is indicated;
- suspicion of anaplastic carcinoma: pan-cytokeratin staining can be performed;
- suspicion of secondary tumour: perform immunocytochemistry of TTF1. If negative, diversify the range of antibodies according to the standard morphology and the clinical context;
- suspicion of lymphoma: the expression of T and B lymphocytic markers can be investigated with immunocytochemistry. Some teams perform this phenotypic characterisation using the flow cytometry technique;
- suspicion of parathyroid lesion: perform immunocytochemistry of the parathyroid hormone, TTF1 and chromogranin. A parathyroid hormone measurement on the fine needle aspiration product complements the immunocytochemistry study;
- suspicion of lymph node metastasis of thyroid carcinoma: if the morphology is not clear, the lymph node fine needle aspiration product can be investigated for the expression of TTF1, thyroglobulin and calcitonin according to the context. A thyroglobulin measurement on the biopsy product complements the immunocytochemistry study;
- undetermined or suspicious fine needle aspiration: there is not adequate proof for establishing a recommendation on the use of markers of malignancy or benignity.

6.4.1. What is the role of the study of molecular markers?
Application of molecular techniques for the management of thyroid nodules is still an area of clinical research [107].

7. Role of scintigraphy, CT scan, PRI, PET imaging?

7.1. Does scintigraphy still play a role?

The role of thyroid scintigraphy has decreased in recent years since its efficacy is lower than that of ultrasound and cytologic assessments for the diagnosis of malignancy. Scintigraphy is, however, the only technique to provide a functional image of the thyroid and to detect autonomous focal spots. It, therefore,

retains its indications, particularly in the investigation of toxic and pre-toxic nodular involvement.

7.1.1. Background [31,38,53,112–116]
Scintigraphy differentiates nodules that are hyperfunctional (hot), hypofunctional (cold) or indeterminate (homogenous uptake). Hot nodules practically never correspond to massively malignant lesions, while 3 to 15% of cold or indeterminate nodules are malignant.

The predictive value of scintigraphy for the diagnosis of malignancy is poor and quite inferior to that of cytology since only 6–11% of solitary nodules have high uptake, and the malignant nodules only make up a small proportion of cold or indeterminate thyroid nodules. The specificity is likewise reduced for small nodules under 1 cm, whose size is less than the resolution threshold of scintigraphy.

Finally, ultrasound has a much greater resolution than that of scintigraphy, which cannot measure the size of the nodules and only has a small role in the topographic assessment of nodular goitres.

Thyroid scintigraphy, however, retains a place in the evaluation of thyroid nodules since it provides useful information on their functional characteristics. It can diagnose an autonomous nodule, which is generally accompanied by confirmed or subclinical hyperthyroidism, and can prioritise nodules for biopsy in the case of multinodular goitres. In regions of iodine deficiency, the TSH level may remain normal in the presence of autonomous focal spots due to the low rate of thyroid cell proliferation and synthesis of thyroid hormones in a gland depleted of iodine. Microscopic, autonomous focal spots of euthyroid goitres, deficient in iodine, which have acquired activator mutations of the TSH receptor, are at risk of progressing to hyperthyroidism, particularly in cases of inadequate iodine intake. Their identification can modify therapeutic decision-making and monitoring by instituting yearly monitoring of TSH, a contraindication for thyroxine treatment and the possibility of using isotope therapy.

7.1.2. Indications
The exploration of a nodular goitre begins by a measurement of TSH concentration and an ultrasound.

Thyroid scintigraphy is recommended as a first-line investigation for biologically confirmed hyperthyroidism. It is the only examination capable of declaring the functional nature of the nodule, of specifying whether the hyperfunctional nodule is partially or completely extinctive with regard to the rest of the parenchyma. It rules out hyperthyroidism of other origins, particularly autoimmune related to Grave's disease, and associates with a nodule in which the degree of uptake and the nature will then be specified. It is used to identify the possible need for radioactive isotope treatment, either in the present or the future.

Thyroid scintigraphy may be useful as a second-line investigation in multinodular goitres (nodules > 10 mm), regardless of the TSH level, when the anatomical conditions (predominant substernal development) do not enable a precise analysis of the entire gland with ultrasound, or the nodules identified on ultrasound are not accessible to biopsy. It can be used to:

- qualify possible mediastinal spread;
- assist in the selection of hypocontrasting nodules that require cytologic assessment, as an accompaniment to ultrasonography;
- plan for radioactive isotope treatment.

It can be discussed on a case-by-case basis in the following situations where the identification of high uptake in a nodule will have an impact on the care:

- when there is a contraindication to biopsy (alteration in haemostasis);
- when a surgical procedure is planned due to cytology results that were unable to be interpreted on several successive samples, or that had intermediate classification (follicular lesion of undetermined significance), or in case of regular volume increase of a nodule that was cytologically negative;
- when the vascularity on Doppler ultrasound is suggestive of a functional nodule;
- when the TSH is regularly close to the lower limit of normal, in order to rule out an adenoma or pretoxic multinodular thyroid.

The demonstration of one or several hyperfunctional nodules suggests a risk of progression towards hyperthyroidism, especially with iodine intake; it contraindicates treatment with levothyroxine, does not justify biopsy (except in case of other strong criteria of suspicion), and enables radioactive isotope treatment to be planned.

Scintigraphy is not a monitoring examination. It does not have to be repeated when the first examination shows a nodule with low or normal uptake.

The tracer used is preferably I-123 since it quantifies the image (uptake) useful for the diagnosis and treatment of hyperthyroidism [116]. Otherwise, Tc-99 m can be used, which is widely available and less costly; the image it produces can diagnose typical forms [117–119]. Tc-99 m MIBI or TI-201 can be used with a hypocontrasting nodule (I-123/Tc-99 m), which is suspicious on ultrasound, and when the cytology examination is contraindicated or non-contributory. The suspicious nodules have higher uptake and have greater retention than that of healthy parenchyma. They are however expensive exams, which have a good negative predictive value but low specificity [120].

Thyroid scintigraphy is prescribed in the first phase of the menstrual cycle, except when the quality of the contraception used is certain. In the event of accidental injection during pregnancy, foetal irradiation is very low (around 0.008 mSv/MBq). Irradiation of the foetal thyroid is negligible before the 3rd month.

The indication of scintigraphy during breastfeeding must be weighed, since the examination may often be deferred. If not, Tc-99 m is used with temporary interruption of breastfeeding for 24 hours. The milk is pumped and thrown out during this period of time. I-123 may not be used during breastfeeding due to the radioactive contaminants, which would require suppression of 10 periods, i.e., around 100 hours [117–119].

7.2. What are the benefits of conventional CT scan, MRI and 18F-FDG PET imaging?

The indications of conventional imagery are limited to retrosternal nodules and multinodular goitres [38,112]. CT scan is useful for detailing the mediastinal extension, the existence of tracheal or oesophageal compression and preoperatively for vascular locations. Caution is warranted with the use of iodine radiocontrast agents, which are likely to trigger the hyperactivity of functional nodules. CT scan can be coupled with scintigraphic functional imagery using a hybrid SPECT/CT camera. MRI offers the advantage of being less irradiating and can visualise the vascular locations better, but it is expensive.

18F-FDG PET imaging has no indication in the assessment of nodules and thyroid dysfunction [121–127]. For cytologically suspicious thyroid nodules, the benefits of 18F-FDG PET for helping to differentiate between benign and malignant lesions have not been demonstrated. Studies are conflicting and have found an overall good sensitivity on examination, but poor specificity between 30 and 60%. There is no correlation between the intensity of uptake as judged with standardised uptake values (SUV) and the risk of malignancy. Focal areas of high intensity uptake are notably observed in cases of thyroiditis. The absence of uptake cannot formally rule out malignancy either.

8. Therapeutic decision-making and monitoring

8.1. Who should be operated on?

The evaluation of any thyroid nodule can recognise nodules that are suspicious for malignancy and even provide details on their nature (medullary, papillary). This, then, affects the relative urgency of thyroid surgery, preoperative assessments (ultrasound investigation of adenopathies, CT scan to investigate visceral metastases with medullary carcinomas), and the importance of the surgical and lymph node procedure. Only surgical ablation of a thyroid nodule can enable anatomopathologic examination and provide diagnostic confirmation of thyroid cancer. Surgical excision is also used to treat hyperfunctional nodules and those resulting in compression signs.

Thus, surgical intervention must be proposed to patients with:

- a nodule that is malignant or suspicious for malignancy on clinical, ultrasound or cytological data;
- a frank increase in serum calcitonin;
- a voluminous nodule genuinely responsible for local compression symptoms (swallowing disorders, dysphonia);
- a secondary appearance of suspicious signs clinically, sonographically or cytologically.

It will be also considered with:

- a nodule resulting in aesthetic problems, anxiety or cancer phobia of the patient;
- a solid or mixed nodule after two cytological examinations that are non-contributory or that indicate the presence of a follicular lesion of undetermined significance;

- a hyperfunctional or toxic nodule, even though radioisotope treatment is an alternative to surgery in these circumstances;
- retrosternal or endothoracic nodules, if their characteristics justify it;
- inadequate compliance with the proposed follow-up.

This will be done by informing the patient of the operative risks (compressive haematoma, recurrence, hypoparathyroidism after a thyroidectomy) and drawbacks (scar, postoperative hormone therapy).

Simple enucleation and subtotal thyroidectomy are not recommended. Lobectomy is inadequate for the treatment of cancers and the prevention of recurrence with benign nodules. Patients usually benefit from total thyroidectomy (which imposes substitutive treatment with levothyroxine) due to the frequency of thyroid dystrophies demonstrated in the opposite lobe on preoperative ultrasound examination.

8.2. Who should be monitored and how?

Monitoring is an alternative to surgery for patients with non-suspicious or benign nodules, notably on cytological examination. The evolution of a thyroid nodule can be marked by the appearance of an anomaly of thyroid function or a neck disturbance related to the volume of the nodule.

Monitoring of patients with a thyroid nodule must include:

- screening for previously undetected or undiagnosed cancers (false-negative of fine-needle aspiration biopsy < 5%);
- screening for the appearance of thyroid dysfunction;
- assessment of the appearance of a functional disturbance.

Monitoring is based on:

- a physical examination with investigation of functional or physical signs of thyroid dysfunction (hypothyroidism, thyrotoxicosis), an increased volume of the nodule or the appearance of compression signs (dysphonia, swallowing disturbance, dyspnea, collateral circulation), or the presence of anterior neck adenopathies;
- TSH monitoring, possibly with measurement of T3 or free T4 if there are signs of thyrotoxicosis and if the TSH is low;
- a thyroid ultrasound, with data compared to the baseline or previous examination;
- a new biopsy for cytologic study in the presence of suspicious clinical signs (hard nodule, adherent, presence of homolateral adenopathy, etc.), of rapid and significant increase in size (increase of diameter greater than 20% or of 2 mm in two dimensions) of a non-cystic nodule or when there is modification of ultrasound data.

The first monitoring examination (clinical, TSH, ultrasound) can be carried out 6, 12 or 18 months after the baseline work-up, according to the initial characteristics, then according to a progressive schedule of intervals after 2, 5 and 10 years, subject to progressive clinical, biological or sonographic signs by involvement of the patient and attending physician in the monitoring. If there is a significant increase in the volume of a nodule on physical or ultrasound examination, a new cytologic investigation must be considered.

8.3. What is the role of TSH suppressive therapy?

TSH plays a role in the appearance and development of dystrophies and thyroid nodules. The objective of suppressive treatment with levothyroxine is to reduce the concentration of TSH in order to stop the growth of existing benign thyroid nodules and to prevent the occurrence of new ones in multinodular dystrophies; their disappearance is anecdotal however. Increase in the size of nodules is not mandatory and consistent; the potential beneficial effect observed during the suppressive treatment is likely to disappear after the levothyroxine treatment is stopped.

Randomised clinical studies (compared to placebo) and meta-analyses have provided disparate results [37,128–134]. They suggest that particularly in regions of relative iodine deficiency suppressive treatment with levothyroxine may lead to a decrease in the volume of thyroid nodules, especially when the nodules are small, recent and colloid. The treatment also confers a protective effect on the progression of perinodular dystrophy [37].

Long-term suppressive treatments, which lower TSH below the usual values, results in subclinical thyrotoxicosis with a risk of cardiac (atrial fibrillation, increased cardiovascular morbidity and mortality) and bone (demineralisation, osteoporosis) complications, particularly in post-menopausal women. Moderate suppressive treatments, which lower TSH to values close to the lower limit of normal, have also demonstrated efficacy on thyroid morphology.

Therefore, moderate TSH suppression therapy with levothyroxine (TSH concentration = 0.2–0.6 mIU/L):

- may also be indicated in:
  - patients presenting with a recent colloid thyroid nodule that is stable or progressive, without evidence of autonomy and who live in an area of iodine deficiency,
  - young patients with nodular thyroid dystrophy, particularly in women before pregnancy and from families with a history of multinodular goitres that underwent surgical intervention;
- is not justified in the majority of patients, and in post-menopausal women in particular;
- is contraindicated in patients with a TSH less than 0.5 mIU/L, an established multinodular goitre, presenting with osteoporosis, cardiac disease or a concurrent chronic disorder.

In all cases, the prescription of suppressive treatment with levothyroxine must be preceded by an assessment of the risk-benefit balance on an individual level. The treatment tolerance, its efficacy on the nodule and perinodular dystrophy will be reconsidered during the monitoring in order to decide whether to prolong or discontinue its use.

9. Special situations

9.1. Thyroid nodules in children

9.1.1. What is the epidemiology?

The prevalence of thyroid nodules is less common in children than in adults, ranging from 1–1.5% from detection by palpation and 3% with ultrasound. This prevalence increases with age and after puberty [5]. The increased risk of developing nodules has been shown during puberty, but also when there is a family history of congenital (hypothyroidism with goitre and hormonal synthesis disorder) or autoimmune (Hashimoto's thyroiditis, Graves' disease) thyroid disease; iodine deficiency; genetic disease, such as familial adenomatous polyposis; Cowden's disease, Carney complex; and especially external irradiation (irradiation as part of cancer treatment in children, Hodgkin's disease, prophylactic radiation before bone marrow transplantation in leukaemia) [135].

9.1.2. What are the risks?

Thyroid nodules in children are usually benign. Nevertheless, the risk of malignancy is higher in children than in adults: an estimated 10 to 25% are malignant in children versus only 5% in adults [135]. The prevalence in females is less than that found in adults and is estimated to be 1.5:1. The incidence is around one child per one million children in the prepubertal period and from 5–20 children per one million in children during or after puberty. Boys, children under 10 years and those with a history of external radiation exposure have a higher risk. In the latter group, the risk of thyroid cancer is higher if irradiation was done at a younger age. Before 5 years, the risk of developing cancer is two times higher than when the irradiation took place between 5 and 10 years, and five times higher than when the irradiation took place between the age of 10 and 14 years. The risk appears after a latency period of 5 to 10 years, is maximum between 15 and 20 years and then decreases but continues to persist for more than 40 years [135].

The cancers are predominantly (over 95% of cases) differentiated epithelial strain cancers (papillary 85%, follicular 15%), and more rarely (less than 5% of cases) medullary cancers or lymphomas.

As in adults, exploration of a thyroid nodule in children is based on fine-needle aspiration biopsy, which must be done by experienced teams using ultrasound guidance and possibly with an intraoperative examination for improving the performance. The sensitivity and specificity of the needle biopsy in children is low and similar to that of adults [136,137]. Children with differentiated thyroid cancers have a higher risk than adults of presenting lymph node (70%) and lung (20%) involvement. The risk of recurrence is also higher [138,139].

9.1.3. What is the prognosis?

The prognosis mainly depends on whether the nature of the lesion is malignant or benign. Age and the extent of the disease at the time of diagnosis are the most important prognostic factors of differentiated thyroid cancers. In the pTNM classification, thyroid cancers in children without metastasis are Stage I, and those with metastasis are Stage II. This classification indicates that young patients have a low risk of death from thyroid cancer despite an often widespread involvement at the time of diagnosis; however, the classification underestimates the risk of relapse, which is clearly more common than in adults. Some series report the absence of death, but those with the longest follow-up (27 years) report up to 15% [140]. These deaths occur mainly in children that were initially treated before the age of 10 years. Survival at 10, 15 and 20 years evaluated by Durante et al. was 100, 90 and 87%, respectively [141]. Papillary cancers occurring before the age of 10 years are in fact more aggressive than in older children. In these young children, the tumour is often a large size, multifocal, with extracapsular extension and associated with multiple cervical adenopathies and lung metastases [142]. The risk of relapse is greater than in older children and mortality from thyroid cancer is higher [139]. On the other hand, the initial spread of the disease in older children and the progress of patients are similar to those observed in young adults [140].

9.1.4. Are there specific management measures?

The general risks of any thyroid gland intervention (haemorrhage, infection) are rare. The particular risks of thyroidectomy (recurrence, parathyroid) have a higher probability of occurrence than in adults, especially before 10 years of age: 3 to 5% recurrent laryngeal nerve palsy and 16% hypocalcaemia [138]. This increase in risk is partially related to the anatomy: voluminous head; thin and short neck, which makes exposure of the thyroid region more difficult and requires a suitably long incision. The small size of the elements requires the use of telescopic magnifying glasses for the dissection. The recurrent nerve must be located and followed up to its entry beneath the inferior pharyngeal constrictor muscle. The location of the parathyroids is more difficult due to their small size, the volume of the thymus, and sometimes the existence of adenopathies that mask them. They can be confused with a fatty lobule, be masked or included in the thymus, sometimes in an ectopic thymus residual (the upper parathyroids); they may also be nodular and confused with lymph nodes.

If a tumour proves to be benign following surgery due to uncertainty in the assessments, total thyroidectomy will be performed as a priority as soon as diffuse homo- or bilateral dystrophy occurs in order to prevent the risk of relapse. If it is malignant, as in adults, the surgical objectives are to perform the excision as completely as possible at the cervical-mediastinal area, with minimal morbidity; to carry out complete staging for documenting the prognosis and follow-up; to facilitate postoperative treatment with radioactive iodine; and to facilitate long-term monitoring by minimising the risk of recurrence [138,143]. The surgery must be adapted to the characteristics of the tumour relative to the histology, which is usually papillary, with variants occurring more frequently than in adults: tumours are commonly multifocal and bilateral with lymph node invasion. However, age is also an important surgical factor, with the disease being more aggressive before the age of 10 years, showing more significant locoregional extracapsular spread and more

frequent lymph node metastases [138,142]. Surgery includes a total thyroidectomy and selective dissection (uni- or bilateral, jugular-carotid preservation, central dissection); the parathyroids will be transplanted upon request. This must be done by a surgeon trained in thyroid surgery in children [138,144]. Lateral cervical dissection causes lateral cutaneous hypoaesthesia, which regresses slowly; sometimes spinal paresis occurs (which is much less common in children than in adults); rarely persistent lymphorrhea; and Horner's syndrome, which generally regresses. The postoperative course is often less complicated than in adults; very moderate postoperative pain, very unremarkable functional disturbance, even in cases of complete cervical dissection, sometimes bilaterally.

9.2. Thyroid nodule and pregnancy

9.2.1. What is the epidemiology?

Nearly 10% of pregnant women present with a palpable thyroid nodule, which is usually benign. In a cohort of 221 pregnant women followed in Hong Kong, the prevalence on ultrasound was, respectively, 15.3, 22.6 and 24.4% in the first trimester, third trimester and 3-month post-partum. The study conducted by Struve in Northern Germany in 212 women, aged 36 to 50 years, indicates that in areas with iodine deficiency the prevalence of thyroid nodules on ultrasound increases with age and parity: 9% (in nullipara), 20.7% (after one or two pregnancies), and 33.9% (after three or more pregnancies) [145,146].

Among the factors that promote nodular dystrophy during pregnancy, iodine deficiency plays a critical role [147]. Thyroid hypertrophy is correlated with iodine deficiency and can be prevented if the diet is sufficiently enriched in iodine during pregnancy. The synthesis of growth factors during pregnancy, as well as the production of hCG stimulating the TSH receptor favour the development of thyroid follicular hyperplasia. Moreover, oestrogen effect on thyroid follicular cells – known to express oestrogen receptors on their surface – may contribute to the growth of the epithelium and reduce the activity of the sodium/iodide symporter.

9.2.2. What are the risks?

Thyroid stimulation during gestation promotes not only the growth of existing nodules (increase of 40–50% of their volume), but also contributes to the development of new nodules (11–20% observed *de novo*), predisposing the patient to the subsequent progression to multinodular goitre. The thyroid volume increases by about 30%, sometimes leading to neck discomfort, and in rare cases, to complications like dyspnea or intranodular bleeding. Variations in the structure or volume of the thyroid gland are partially reversible in the post-partum period.

In epidemiological studies, the influence of female hormone factors (including pregnancies) on the occurrence of thyroid cancer was diversely estimated. In a cohort of 221 pregnant women followed-up prospectively, of whom 24.4% had thyroid nodules at the end of pregnancy, no occurrence of cancer was detected. In contrast, previous historical publications have reported a 39–43% risk of malignancy for thyroid nodules discovered during pregnancy. These institutional series were

nonetheless jeopardized by selection bias. The risk of clinical cancer is currently stressed to be around 10% in thyroid nodules investigated during pregnancy, quite similar or slightly higher than the risk assessed in general population. Thus, thyroid cancer would affect about one per 1000 pregnant women. Thyroid cancers observed in pregnant women are generally well differentiated, primarily of papillary type, and exhibit an indolent course, despite sporadic observations of rapid neoplastic evolution during pregnancy. The overall prognosis of these cancers is similar to that occurring in non-pregnant women of the same group of age. Therapeutic abortion is, therefore, not justified at all [147–151].

9.2.3. What are the specific management measures?

The evaluation of thyroid nodules recommended in pregnancy does not differ from general cases, except for the use of scintigraphy, obviously contraindicated. Regardless the advancement of pregnancy, it is recommended to carry out a TSH measurement, neck ultrasound and if necessary, a fine-needle aspiration of the dominant nodule and/or of preselected nodules with suspect clinical or sonographic features. With the patient's agreement, the needle cytology can be optionally deferred in the post-partum period whenever a cytological diagnosis of malignancy does not modify the timing of surgical management. A calcitonin measurement may be proposed, even without a family history of medullary thyroid cancer. The interpretation of the calcitonin level must accordingly take into account a physiologic gestational peak in the second trimester, which can exceed the baseline value by two-fold. The fine-needle aspiration biopsy is a procedure devoid of risk for the pregnancy and should preferably be undertaken with ultrasound guidance. There are few data available to evaluate the diagnostic accuracy of cytology in pregnancy. Enhanced follicular hyperplasia does not cause major difficulties for the cytology reading, but such cytological studies in pregnant condition are scarce. The risk of follicular carcinoma in the case of aspirates demonstrating follicular cytology appears grossly identical to that of the general population [152–154].

9.2.4. Management of a presumed benign nodule

Nodules screened during pregnancy mostly show cytological benign patterns. Even though, they should be surveyed and checked with ultrasound at 3–6 months intervals and be biopsied again if there is significant enlargement. Given the key role of iodine metabolism in thyroid regulation, it is of great importance to support the 2007 international guidelines for implementing iodine supply during pregnancy. Iodine intake should be close to 250 µg/day and should not exceed 500 µg/day. It is not recommended to use TSH suppressive therapy in pregnant women for supposed benign, asymptomatic thyroid dystrophy, since there is no proof of benefits and no assessment of the risks and consequences on pregnancy of such treatment [155–157].

9.2.5. Management of a suspicious or malignant nodule

An intervention performed during pregnancy holds the usual risks of thyroid surgery, in addition to teratogen and miscarriage risks if anaesthesia is used in the first trimester. Surgery

also exposes the patient to the risks of premature birth if the pregnancy is near term. It is, therefore, recommended to operate during the second trimester of pregnancy if truly necessary. Most publications, all dealings with a small number of patients, did not report any complications of thyroidectomies in the second trimester of pregnancy. In the study of Nam et al., the length of hospitalisation was approximately the same, whether the women were operated on during or shortly after their pregnancy term [158]. A more recent study on 201 women operated on during their pregnancy for thyroid or parathyroid disease conversely demonstrated more extended hospital stays, with more surgical complications compared with interventions conducted on 31,155 non-pregnant women.

Can thyroid surgery be deferred until after the birth? The studies by Moosa, and by Herzon et al. showed that the overall survival of women with thyroid cancer that was diagnosed during pregnancy and operated post-partum was identical to that of non-pregnant women of the same age receiving standard care for thyroid cancer [150,151]. No difference was either stated regarding free-recurrence survival. In addition, retrospective data indicate that postponing surgical treatment for differentiated thyroid cancer 1 to 2 years after diagnosis does not lower patient survival.

The management of differentiated thyroid cancers diagnosed during pregnancy finally depends on the gestational age, the presumed histotype, the tumour progression, the concern of the patient and the surgeon experience. Planning surgical treatment in the second trimester of pregnancy would be more suitable in case of early diagnosis, demonstration of tumour growth or overt anxiety. However, as there is no proven negative impact of pregnancy on cancer outcome and considering the controversy regarding the increased risk of obstetrical complications, thyroid surgery can also be deferred until after the birth if tumour size remains stable or whenever the suspicious lesion is diagnosed lately in the third trimester. For those patients with suspicious or malignant nodule awaiting surgery, moderate TSH suppressive therapy may be individually discussed despite the actual lack of data on such approach, adapting the level of TSH suppression to the prognostic factors: TSH between 0.1 and 0.5 mIU/L, and FT4 below the upper limit of normal (one must keep in mind the difficulties in interpreting measurements of free T4 during pregnancy) [157–161].

9.3. Nodules occurring with Graves' disease

In Graves' disease (GD), characterised by the production of autoantibodies that attach to TSH receptors (TSH-R), the TSH receptors might be considered as proto-oncogene, and the TSH-R antibodies as promoting factors of malignant proliferation.

9.3.1. What is the epidemiology?
9.3.1.1. Prevalence of nodules in Graves' disease. The clinical prevalence of nodules in GD varies from 10 to 35% [162]. It was 15.8% in a study of over 36,000 patients [163], and around 13% in two more recent studies [164,165]. Using the main data in the literature, a nodule prevalence of around 10% in Graves' disease can be calculated before 1998 and 15% after 1998. The

data, however, are not comparable from one study to another due to the very different analytical criteria. The ultrasound prevalence is close to 34% [166,167] and can exceed 50% [164]. Marine-Lenhart syndrome, which combines a hyperfunctional nodule and GD, has a prevalence of less than 3%. This syndrome, which is considered relatively resistant to radiation, requires a greater dose of iodine-131 for therapeutic purposes or surgical management.

9.3.1.2. Prevalence of thyroid cancers in Graves' disease. The prevalence of thyroid cancer in GD varies between 0.3 and 16.6% according to the iodine status, the type of surgery proposed, to the thoroughness of the histopathological slide reading and the clinical or occult nature of the cancer [162]. It is between 2.3 and 45.8% in the presence of palpable nodules [165]. The palpation of a macroscopic nodule makes the nodule more suspicious [166]. A history of radiation therapy was reported in 1/3 of the oldest studies [166–168]. Recent studies demonstrate a majority of cancers that are less than 1 cm in size or those discovered incidentally [162,164,169–175]. The estimated prevalence of thyroid cancers was around 0.6% of Graves' disease cases before 1998 and from 3.2 to 4.5% after 1998, with the majority of them being microcarcinomas [176]. The "hot" character in scintigraphy does not eliminate the risk of cancer for a given nodule [177,178]. In children, 5% of cancers have been described as mainly occult [176], which is close to that seen in adults.

9.3.2. What are the risks?
For some patients, multifocality, lymph node invasion, recurrence and metastases are more common in GD [179–183], undoubtedly due to thyrostimulating antibodies encouraging the process of carcinogenicity [184].

Some recent studies invalidate this idea and conclude that the prognosis is the same in thyroid cancers associated with GD [185–189], undoubtedly due to the fact that microcarcinomas are very common, which is an obvious bias [190].

Some studies have observed a negative correlation between the status of thyrostimulating antibodies and the size of the tumour, which seems paradoxical. Autoimmune thyroiditis might protect against the development of cancer.

GD that is treated with iodine-131 is associated either with reduced incidence of thyroid cancer or microcarcinomas, suggesting a less aggressive phenotype [191], or in some occasional reports with anaplastic cancers, which suggests a role in the dedifferentiation [192].

9.3.3. Is there a specific protocol for assessment and management?
9.3.3.1. Is the reading of needle biopsy slides different in Graves' disease [192,193]? The cytologic analysis of GD poses a diagnostic problem: certain Graves cytomorphologic modifications may resemble those seen in papillary cancer. The treatments used, notably iodine-131, may also induce alterations in cytology. Cytological difficulty is also imposed due to the fact that the epithelial cells that are attacked by the lymphocytes present suspicious nuclear dystrophies, with grooves, increased nuclear diameter and chromatin clearing. These lesions may

easily be mistaken for papillary carcinomas. Some cytomorphologic characteristics are particular to cancerous nodules occurring in GD. These aspects are based on nuclear features: elongated nuclei, nuclear grooves, chromatin clearing and eccentric prominent nucleoli. Oncocytic features are common. The diagnosis may be difficult with a hyperplastic nodule, which is common in thyroiditis.

9.3.3.2. How is it treated? It has been concluded that nodules from a Graves' patient undoubtedly have as much risk of being cancerous as ungraded thyroid nodules.

The cancer can have two facets [183]:

- microcarcinoma, by far the most common. It has an excellent prognosis and needs no special type of management and follow-up;
- cancerous macronodules, particularly when the size exceeds 2 cm. Its potential for progression seems greater and its prognosis is less promising. The pejorative factors in this case are: age greater than 45 years, tumour greater than 10 mm, multifocal nature, extracapsular invasion and clinical detection of the cancer.

A study on cancer mortality in 30,000 cases of Graves' disease [194] found no significant difference compared to the general population, nor did there seem to be a more marked increased risk of cancer or progression on the readings from recent studies. Therefore, the most reasonable attitude is to propose the same approach as for all nodules, especially with consideration of needle biopsy for any nodule greater than 1 cm in size. The measurement of TSH-R antibodies could be useful for monitoring cancers associated with Graves' disease, and the clinician must be alerted to their continued presence [31].

9.4. Nodules that occur with chronic lymphocytic thyroiditis (besides Graves' disease)

The forms of lymphocytic thyroiditis that are hypertrophic (adolescent lymphocytic thyroiditis, Hashimoto's thyroiditis) and atrophic (formed in the absence of pregnancy and after menopause) are characterised by chronicity and a tendency to lobulation, colloid impoverishment and fibrosis [195]. The presence of nodules may be related to two entities:

- nodular (or focal) thyroiditis within a diffuse thyroiditis or normal parenchyma;
- the combination of a diffuse thyroiditis and nodules of another nature: focal spot of hyperplasia, adenoma, cyst, carcinoma or lymphoma.

9.4.1. What is the epidemiology?

Lymphocytic thyroiditis is a common disease: 45% of women and 20% of men have thyroiditis according to an autopsy study in the United Kingdom [196].

9.4.2. Benign nodules and chronic lymphocytic thyroiditis (CLT)

All types of nodules can coexist with thyroiditis; no study has shown the predominance of a particular type. In children with lymphocytic thyroiditis, the prevalence of nodules is 31.5% [197].

The prevalence of the nodular form of lymphocytic thyroiditis is rare. A retrospective Italian study identified 15 cases of nodular thyroiditis in 1243 postoperative patients, i.e., 1.2% [198].

9.4.3. Thyroid cancers and CLT

The association with carcinoma is the main concern, even though predisposition due to the thyroiditis process has never been established [199].

An observational study did not show more frequent occurrence of cancers in patients with thyroiditis that were followed-up for over 10 years [199]. Surgical studies and those of cytology monitoring per needle biopsy of patients with thyroiditis report a carcinoma prevalence of 0 to 53% [200–208]. The bias of surgical studies is linked to the selection of the operated patients. The most significant study is a prospective survey of cytologic monitoring conducted in Sweden from 1959 to 1981 in 829 patients with lymphocytic thyroiditis compared to 829 patients with goitres, matched for age and sex. There was no increase in the risk of thyroid cancer observed in the patients with thyroiditis. The prevalence of lymphomas however increased, even though the nodular forms of lymphoma are rare. Lymphomas predominate in females, notably around 65–75 years, and lymphocytic thyroiditis is the only known predisposing factor [209].

Conversely, the prevalence of thyroiditis is greater in patients with cancer [210–215]. The presence of circulating antibodies is not always known however, and it is difficult to differentiate real autoimmune thyroiditis from a reactional infiltrate; indeed, a peritumoural infiltrate is present in 20% of cancers [195,216]. The most frequent histological type described in adults with thyroiditis is papillary carcinoma [197].

The prevalence of cancers in children with nodules is estimated at 26.4% [135]. In children with thyroiditis, the prevalence of cancer is similar, from 1 to 30% [200,204]. The criteria of suspicion are male sex and adenopathies. The only histotype observed is papillary carcinoma [197].

9.4.4. What are the risks?

9.4.4.1. Role of TSH, paracrine or autocrine factors, and apoptosis. Lymphocytic thyroiditis causes a rise in TSH, which then stimulates mitogenesis. Stimulation of the TSH receptor activates adenyl cyclase (AC) and protein kinase (PKA), which promotes cellular growth, or even malignant transformation. In order to reach the thyroid hyperplasia stage, stimulation of the receptor must be continuous [217]. These mechanisms have been observed in rats but have not been proven in humans [218]. Some clinical studies have, however, found TSH to be a risk factor of cancer, independent of age [8,219].

Autocrine or paracrine mechanisms could be involved in the initiation or perpetuation of cellular growth, and the development of hyperplastic nodules or adenomas. Hormones or

cytokines that are possibly involved are cytokines of lymphocytic origin, including IL1 and IFNγ; and cytokines and hormones from endothelial and fibroblastic tissue, including IGF-I and II, FGF, endothelin I, TGF-α and EGF [220].

Increased apoptosis contributes to the formation of cysts. These cells in apoptosis are observed in the periphery of the nodules and cysts. Subsequent to the thyroiditis, the IL-1 produced by the lymphocytes induces the expression of Fas-ligand in the thyrocytes [221–223]. The Fas ligand-induced apoptosis could be a mechanism for the occurrence of frequently observed microcysts.

It has been suggested that some immunoglobulins could have a stimulating effect on the growth of pre-existing microcarcinomas [224]. It is important, however, to differentiate the association of CLT with a cancer of the reactive lymphocytic infiltrate from cancer possibly due to the production of thyroglobulin isoforms [225].

9.4.4.2. Tumour prognosis. The prognosis of carcinomas described in association with thyroiditis is in principle favourable due to their good differentiation, mainly the papillary type. Furthermore, the inhibitor role of apoptosis on the growth of normal and tumour tissue must be taken into account. In fact, survival without recurrence as well as overall survival is better in the group of patients with infiltrate for the advanced stages (tumoural adenopathies and extrathyroidal extension) [215,216,226,227].

A particular factor that contributes to diagnostic difficulty and uncertain prognosis is nevertheless comprised of diffuse sclerosing carcinoma, which is frequently multifocal, invasive and recurrent. It is frequently associated with the phenomena of thyroiditis with increased titres of anti-TPO antibodies, which sometimes explains its misinterpretation and the delay in diagnosis.

At the nodular stage, lymphomas, especially the well-differentiated lymphocytic and MALT types, are accessible to medical treatment and have a good prognosis.

9.4.4.3. Specific risks related to treatment management. Some authors have considered that peroperative complications are not more frequent in the group with thyroiditis [206,215,228]. However, in the specialised surgical milieu, infiltration of the capsule and perithyroidal inflammation are ordinarily considered to be the main risk factors of thyroidectomy. The risk of injuring the recurrent nerve and the parathyroids was assessed at up to 12% of interventions practiced for thyroiditis.

9.4.4.4. Is there a specific assessment and management? The physical examination of the nodules in patients with chronic thyroiditis is difficult. They are usually firm, regardless of whether they are a focal area of thyroiditis or carcinoma. The presence of adenopathies is possible with thyroiditis but must prompt the performance of fine-needle aspiration for cytologic study. Signs of compression are rather suggestive of carcinoma. The increase in calcitonin related to autoimmune infiltration has been described [226] but this concept is controversial.

On ultrasound, hyperplastic foci of thyroiditis or carcinomas are usually hypoechoic but with some specificities. In particular, the presence of calcifications is more frequent, there are fewer psammomas, the hypoechogenicity is less marked and the margins of the carcinomatous nodules are more irregular in patients with thyroiditis [229,230]. The very hypoechoic character of lymphomas has been highlighted [230].

Scintigraphy (iodine-123 or technetium) is likely to recognise foci of uptake, corresponding to hyperplasia of normal parenchyma, spared by the process of thyroiditis, the development of which is promoted by the increase of TSH.

With regard to the cytologic aspect, it is accepted that the nodules in patients with thyroiditis must be addressed in the same manner. Fine-needle aspiration biopsy may, however, result in false-positives, and it is particularly important that the cytologist is informed of the thyroiditis as suggested by clinical, biological and ultrasound evidence. Malignant cytology results and those found to be indeterminate are actually more frequent in patients with anti-TPO antibodies. Malignant cytology results, however, seem to display a good predictive value (around 90%), contrary to indeterminate cytology results [197,214,215,230,231]. False-positives may be due to modifications from thyroiditis, to the increased presence of oxyphilic cells (Hurthle cells or Askanazy cells) that are falsely interpreted to be cells with nuclear atypia or as thyroid carcinoma with oxyphilic cells. A histological exam is then necessary to distinguish it from simple adenoma [135,232–234]. Conversely, if the lymphocyte population is too great, fine-needle aspiration can then result in false-negatives [200]. The diagnostic distinction is difficult in cases of lymphoma and is assisted by the recognition of monoclonality in flow cytometry and the immunoenzymatic labelling of lymphocytic sub-populations.

The LT4 suppression test was used previously for deciding the operative indication: the diminishing nodules were considered to be benign and the non-diminishing nodules as potentially malignant [214,235], especially in children [197]. A greater than 50% reduction was considered reassuring for some authors [223]. However, only 20 to 30% of the benign nodules diminish with treatment and 13% of carcinomas diminish with treatment [236], which does not enable this treatment to be recommended as a diagnostic test.

9.5. Thyroid occult nodules or incidentalomas

A "thyroid incidentaloma" is defined as any nodule discovered inadvertently during morphological examinations: ultrasound, CT scan, MRI, and FDG-PET imaging. The morphological examination should not have been justified in any case by the suspicion or assessment of thyroid disease. The very large majority of these formations are clinically unapparent and not felt on neck palpation (occult nodules). This is explained by the usually small size of these incidentalomas. Some incidentalomas, however, are more voluminous, with a size exceeding 2 or 3 cm in diameter. The negative results on physical examination can also be explained by their posterior development and the morphological type of the subject (elderly, stooping posture, degree of adiposity or neck thickening). This

definition also excludes the nodules, benign or malignant, discovered through anatomopathological analysis of surgical specimens.

The progress made in imaging techniques, particularly high-resolution ultrasound, has consequently increased the discovery of these asymptomatic thyroid nodules. The management of thyroid incidentalomas is a common clinical problem, a source of interrogations, psychological incidences and high economic cost.

There are no clear guidelines for the management of these thyroid incidentalomas for the time being [2]. There is currently no Grade I or II level of proof in this domain.

9.5.1. What is the epidemiology?

Several older autopsy series [237] showed the high frequency of non-palpable nodular formations, without a relation with death, present in 50% of the population.

The sonographic prevalence depends on age, sex, technical conditions (operator, probe) and the minimal size considered. The very high resolution of ultrasound presently enables the detection of millimetre size lesions. The selected values in France (see Chapter 1) fluctuate between 11 and 55%. One prospective study comparing the results of the physical examination to those of ultrasound showed that 46% of the nodules over 1 cm that were discovered on ultrasound were not palpable [47]. One study done on the general population in Germany reported the discovery of incidentalomas on ultrasound in 20% of the patients between 20 and 79 years [238]. The prevalence increased with age, affecting 52 and 29% of women and men aged from 70 to 74 years, respectively. In other series, 45% of the women and 32% of the men presented with one or more thyroid nodules [239].

Using CT scan or MRI, thyroid incidentalomas were found in 16% of neck examinations [240].

The unexpected discovery of an incidentaloma in the thyroid during an FDG-PET exam while performing a work-up for another cancer is not rare (1.2–2.3%), and the risk of malignancy then usually seems to be high (25 to 50%) [241].

9.5.2. What are the risks?

There are hardly any prospective surveys available that specify the spontaneous evolution of these formations; therefore, it is unknown whether they have the ability to progress to palpable and symptomatic nodular formations or on the contrary, to diminish. Likewise, there is no information with regard to the risk of hyperthyroidism occurring related to the development of functional nodules, which are hormone producers.

9.5.2.1. Risk of cancer. History-taking from the patient has been based above all on the risk of thyroid cancer. The general risk factors for developing thyroid cancer can be used for thyroid incidentalomas. These include age, sex (with a carcinoma rate that is two times higher in men than in women) and the exposure to ionising radiation in the neck region during childhood and especially before the age of 2 years.

Nevertheless, incidentaloma frequency contrasts with the low prevalence of diagnosed thyroid cancers (see Chapter 1),

suggesting that the very large majority of incidentalomas are benign. There are rare cases of incidentalomas, however, that can correspond to (or evolve into?) papillary microcarcinomas. The question of the potential malignancy of thyroid incidentalomas ties up with that of nodules in general. The risk of cancer in the presence of an incidentaloma seems to be at least equivalent to that of symptomatic nodules [5,30,45]. This cancer risk has been assessed in different series of incidentalomas to be between 10 and 15% [2,70,71,91,100,242]. Immunohistological and molecular studies suggest that several types of benign nodules (encapsulated follicular adenomas with cytologic atypia, some hyperplastic lesions found in multinodular goitres and Hurthle cell tumours) have malignancy potential [38,42,46].

Although uncertain since they went undetected with palpation, the natural history of incidentally discovered thyroid carcinomas does not seem to differ from that of the general population. Around 15% of them can evolve in an aggressive manner. They have an invasive initial presentation in 15 to 50% of cases: Yokozawa et al. (1996) reported that 16% of carcinomas less than 1 cm present extrathyroidal extension; the same occurred in 33% in the series by Papini et al. (2002) and 50% in the series by Nam-Goong et al. (2004) [91,100,243]. These data confirm that a small size nodule does not guarantee a low risk of evolution and that some small cancers can have an initially invasive presentation. Nevertheless, the high frequency of incidentalomas, the low incidence of clinical thyroid cancers, and their very low mortality should temper these data. Several series, including that of Pellegriti, recall the good prognosis of microcarcinomas, regardless of whether they are less than a centimetre in size or between 11 and 15 mm [244].

Therefore, although the risk of cancer for incidentalomas appears to be equivalent to that of thyroid nodules in general, the "size" criteria of this incidentaloma temper its severity. In fact, tumour size is an essential factor of prognosis. In differentiated thyroid cancers, the prognosis worsens only for tumours greater than 1 or even 1.5 cm, and survival only seems distinctly altered beyond 3 cm.

9.5.2.2. Risk of excessive medicalisation. Excessive medicalisation is anxiety producing and can be weighed against the relative risk of late diagnosis.

No studies have assessed the improvement in life expectancy as a result of the recognition of microcarcinomas. Does the supposed benefit of their excision exceed the inherent risks related to their treatment? Health campaigns for early-stage detection of cancers (lung, breast, prostate and neuroblastoma) have not demonstrated differences in mortality between the screened and the unscreened populations, despite the detection of a greater proportion of cancer at an early stage.

If the guidelines lead to an increase in the number of patients undergoing fine-needle aspiration biopsy and subsequently thyroidectomies, what are the consequences in terms of cost/benefit ratio? Conversely, the consequences of late management of cancerous incidentalomas of 10–14 mm without metastases is poorly known [90]. Despite the absence of scientific response

to these questions, the guidelines take the uncertainties into account.

9.5.3. Is there a specific management?

The inadvertent discovery of thyroid incidentalomas must lead to the performance of a specific ultrasound examination for detailing the characteristics of the nodule, the rest of the thyroid gland and the lymph node areas. If the formation was discovered as a result of thyroid uptake in FDG-PET imaging, a thyroid ultrasound and ultrasound-guided fine-needle biopsy should be conducted immediately due to the high prevalence of thyroid carcinomas with this method of detection.

9.5.4. Which nodules should be biopsied?

The decision to explore a thyroid incidentaloma is based on a group of risk factors with variable levels of proof:

- age, sex, pathological context;
- existence of thyroid cancer risk factors: familial, history of neck irradiation in childhood;
- TSH level;
- size of the nodule;
- sonographic characteristics of the nodule (see tables on the sonographic criteria of the benignity and malignancy of nodules);
- isolated character or integrating a more diffuse dystrophy of the gland.

The guidelines of the National Cancer Institute (NCI), published in 2008, concerning the indications for cytology studies of incidentalomas proposed that a fine-needle aspiration biopsy be performed if the nodule had a diameter of at least 10–15 mm, with the exception of true cysts or septated cysts without notable solid component [89]. Biopsy was also advised, regardless of the size, if the nodule presented with signs suggestive of malignancy on ultrasound. This approach is controversial since there are no demonstrated benefits of the cytological diagnosis of microcarcinomas.

The American Thyroid Association (ATA), the Academy of Clinical Thyroidologists (ACT), the American Association of Clinical Endocrinologists (AACE) and the Society of Radiologists in Ultrasound (SRU) issued more detailed guidelines [70,89], which take into consideration the sonographic aspects. Two recent series from McCartney and Stukenborg (2008) and Horvath et al. (2009) attempted to create a hierarchical division of biopsy indications, which considered the diagnostic cost benefit of different diagnostic approaches [90] or sonographic risk scores (TIRADS) [92]. The systematic biopsy of all incidentalomas over 1 cm has been found to be of little benefit [90,134].

In the final analysis, taking into account this bibliographic data and on the basis of a professional consensus, the recommendations for fine needle aspiration indications are formulated in Table 7.

Table 7
Indications for fine needle aspiration during the ultrasound assessment of incidentalomas.

Nodular incidentalomas ≥ 1 cm
Restrict the performance of biopsies to the following cases
High-risk profile
History of external radiation therapy in childhood
Family history of MTC or MEN-2
Personal or family history of Cowden's disease, familial polyposis coli, Carney complex, McCune-Albright syndrome
High baseline calcitonin on two occasions
Nodule accompanied by adenopathy
Nodule discovered during an assessment for metastases

At-risk nodule
Nodule that increased by 20% in volume (or in which at least two dimensions increased a minimum of 2 mm) since the last size measurement
Nodule with at least two suspicious sonographic criteria: solid and hypoechoic, microcalcifications, indefinite margins/borders, taller than wide shape, type IV vascularization
Nodule located during an F-18 FDG-PET scan with a zone of focal hypermetabolism
Nodule that had a previous non-significant FNA

Size > 2 cm
Even in the absence of a high-risk profile or risk relative to ultrasound characteristics of the nodule, FNA is justified to avoid misreading a large size (T2) follicular tumour with uncertain evolution potential

Nodular incidentaloma < 1 cm
The large proportion of sampling failure in nodules < 7 mm in diameter, the low risk of a potential microcarcinoma in these circumstances, without disregard for the stress related to the FNA procedure incites careful consideration of the FNA indications for incidentalomas with smaller dimensions. Only incidentalomas between 7 and 10 mm presenting with risk factors (high-risk profile, at-risk nodule) can benefit from ultrasound-guided biopsy

9.5.5. Which nodules should not be biopsied?

FNA is not recommended in the following situations:

- incidentaloma < 1 cm AND absence of risk factors;
- true cyst, regardless of size.

9.5.6. If biopsy is decided upon, what level of efficacy can be expected in small-sized incidentalomas?

The efficacy of the examination is related to the skill of the physician performing the FNA but also to the size of the biopsied formation [245]. The smaller the volume of the nodule, the greater the proportion of specimen samples that are non-contributory or insufficient. Therefore, for a nodule with a diameter of 7 mm, the proportion of FNA failure was 35.6%. In the series by Nam-Goong (2004) however, the mean size of biopsied incidentalomas was 0.9 ± 0.3 cm (range 0.2–1.5 cm) and the proportion of sampling failure varied from 30 to 36%, with no significant difference according to the size classification of the nodules (< 5 mm, 0.5–1 cm and 1–1.5 cm), although the size criteria was studied in classes and not as continuous variables [245]. In the recent series by Kim, biopsies were less contributory and the diagnostic sensitivity was less favourable
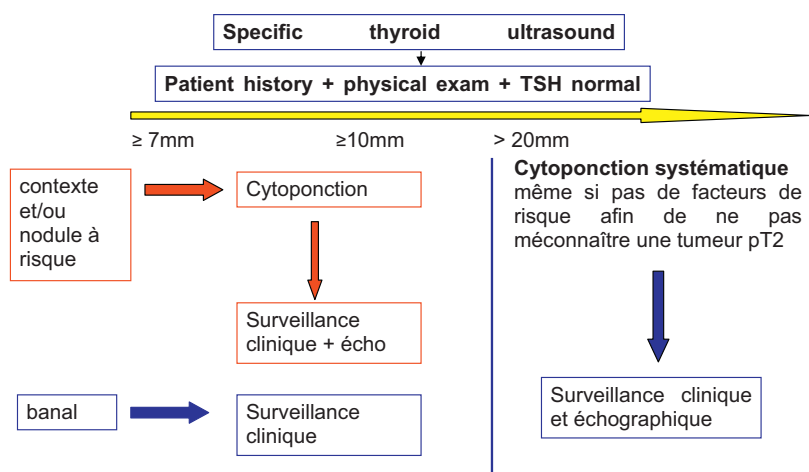
Fig. 4. Management of occult thyroid nodules. * High-risk profile: history of external radiation therapy in childhood; familial history of MCT or MEN-2; personal or familial history of Cowden's disease, familial polyposis coli, Carney complex, McCune-Albright syndrome; high baseline calcitonin level on two occasions; nodule accompanied by suspicious adenopathy; nodule discovered as part of a work-up for frequent metastasis; ** at-risk nodule: nodule with 20% increase in volume (or in which at least two dimensions increased by a minimum of 2 mm) since the last measurement of size; nodule with at least two of the following suspicious criteria on ultrasound: solid and hypoechoic, microcalcifications, indefinite margins/borders, shape that is taller than wide, type IV vascularisation; nodule located during an F-18 FDG-PET scan with a zone of focal hypermetabolism; nodule that had a non-significant previous FNA; *** presence of at least 2 suspicious signs on ultrasound: nodule with at least two of the following suspicious criteria on ultrasound: solid and hypoechoic, microcalcifications, indefinite margins/borders, shape that is taller (anteroposterior diameter) than wide (transverse diameter), type IV vascularization.

for nodules less than 5 mm than for those 5–10 and greater than 10 mm [246].

9.5.7. Who operates? Who monitors? How is monitoring carried out?

1. With thyroid incidentalomas, operative indications are rare and are restricted to:

- nodules in which the cancerous nature has been genuinely authenticated;
- nodules posing problems due to the significance of their volume or of their plunging nature.

The intervention is preceded by measurement of the calcitonin level. Total thyroidectomy is preferred if the nodular dystrophy appears to be diffuse.

2. The majority of incidentalomas require only monitoring:

- to avoid excessive medicalisation, the recommendation is clinical monitoring through occasional palpation of the thyroid region when the clinical context and sonographic aspects are reassuring and the size of the incidentaloma is less than

2 cm. This incidentally discovered formation was not found on screening and does not justify monitoring that is different from that of the general population. Ultrasound re-evaluation should be done if a palpable neck anomaly unexpectedly appears;
- if conversely there are risk factors of cancer, if the nodule is greater than 2 cm or if the ultrasound results are rather ambiguous, even if the nodule appeared cytologically benign (Fig. 4), monitoring will be clinical, sonographic and cytological.

The initiation of TSH suppression therapy is not recommended, the validity, efficacy and safety of which have not been evaluated in these circumstances.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgments

Appendix A.

Patient[a,b]

Surname: . . . . First name: . . . .

Maiden name[d]: . . . . Date of birth and/or age: . . . .

Home address postal code: |__|__|__|__|__| Birth town postal code: |__|__|__|__|__|

Physician operator[a]

Surname: . . . . Institution where the sampling was done: . . . .

Date of sampling[d]: |__|__|/|__|__|/|__|__|__|__|

Physician cytopathologist

Report no.: . . . .

Name of the pathological anatomy and cytology facility: . . . .

Signer of the report: . . . .

Date of report signature: |__|__|/|__|__|/|__|__|__|__|

Clinical information*(To be filled in by the operator and sent completed with the specimen)*

☐ Multinodular goitre
☐ Hypothyroidism
☐ Autoimmune thyroiditis
☐ Presence of anti-thyroid antibodies
☐ Graves' disease
☐ History of radiation therapy (date: . . . .)
☐ Personal history of cancer: . . . .
☐ Familial history of thyroid cancer: . . . .
☐ History of neck radiation (date: . . . .)
☐ History of fine-needle aspiration
☐ Levothyroxine
☐ Inhibitors of thyroxine synthesis
☐ TSH: . . . .
☐ Scintigraphy, result: . . . .

Nodule characteristics   *(Fill in one form per nodule)*

Topography of the nodule[d]

☐ Right lobe   ☐ Left lobe   ☐ Isthmus   ☐ Other: . . . .

Localisation in the organ[d]: . . . .

Size: |__|__| mm

☐ Scintigraphy[d]   ☐ Low uptake   ☐ Homogenous uptake   ☐ High uptake

Ultrasound examination[d]

Nodule characteristics

☐ Single   ☐ In a goitre

☐ Solid   ☐ Mixed   ☐ Cystic

☐ Anechogenicity ☐ Hypoechogenicity ☐ Heteroechogenicity ☐ Isoechogenicity ☐ Hyperechogenicity

☐ Microcalcifications

☐ Margins regular   ☐ Irregular   ☐ Extrathyroidal extension

☐ Type of vascularization: . . . .

☐ Lymph nodes   ☐ Suspicious   ☐ Non-suspicious

Comments: . . . .

Material presented

☐ Conventional smears, number of slides: . . . .   ☐ Cellular suspension

Techniques

☐ Stains   ☐ Immunocytochemistry   ☐ Other: . . . .

Result

☐ Diagnostic   ☐ Non-diagnostic   ☐ Poor fixation or preservation

Appendix A (Continued)

Result

☐ Limited cellularity
☐ Absence of follicular cells
☐ Other: . . . .

Cytopathologic description
_____

Optional (full text)

Diagnostic conclusion (6 categories)[c]

☐ Non-diagnostic (undetermined cancer risk)
☐ Benign

      ☐ Thyroiditis
      ☐ Hyperplastic nodule

☐ Atypia of undetermined significance
☐ Follicular neoplasm / Oncocytic neoplasm (Hurthle cells)

      ☐ Follicular neoplasm
      ☐ Oncocytic neoplasm

☐ Suspicious for malignancy

      ☐ Papillary carcinoma
      ☐ Medullary carcinoma
      ☐ Undifferentiated carcinoma
      ☐ Lymphoma
      ☐ Metastasis
      ☐ Other: . . . .

☐ Malignant

      ☐ Papillary carcinoma
      ☐ Medullary carcinoma
      ☐ Undifferentiated carcinoma
      ☐ Lymphoma
      ☐ Metastasis
      ☐ Other: . . . .

Comments: . . . .

ADICAP code: |__|__|__|__|__|__|__|__|__| Other: |__|__|__|__|__|__|__|__|__|

Pathologist signature: _____

NB: the essential items for interpretation or decision-making are yellow highlighted in the text.

Some data may be unable to be determined; this should be explained in the report.
  [a] Names provided by the operator.
  [b] Identification no. (PIN or social security no.) and address of the patient are currently optional.
  [c] According to recommendations defined by the Bethesda guidelines (2008 NCI conference).
  [d] The operator cannot collect the data; the item will then be filled in as: non-communicated (NC).

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