Good practice guide for cervical ultrasound scan and echo-guided techniques in treating differentiated thyroid cancer of vesicular origin

Guide de bonnes pratiques pour l’usage de l’échographie cervicale et des techniques écho-guidées dans la prise en charge des cancers thyroïdiens différenciés de souche vésiculaire

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Résumé

Des recommandations américaines, européennes et françaises pour la prise en charge des cancers thyroïdiens différenciés de souche vésiculaire ont été récemment publiées. L’échographie cervicale apparaît désormais comme un examen clé du suivi de ces cancers. Non invasif, facile à réaliser et à obtenir, peu coûteux, cet examen reste, cependant, opérateur dépendant. Il n’existe pas, à ce jour, de recommandations publiées rassemblant les aspects techniques, les résultats, les indications et les limites de cet examen dans le bilan initial et le suivi de ces cancers. Un groupe de travail fait d’un panel d’experts sensibilisé à la pratique de l’échographie s’est réuni en vue d’établir un guide de bonnes pratiques sur l’usage de l’échographie cervicale et des techniques écho-guidées dans la prise en charge des cancers thyroïdiens différenciés de souche vésiculaire. Les objectifs sont de : (a) standardiser la procédure et les comptes rendus, (b) définir les critères de malignité et de bénignité d’une lésion identifiée par une échographie cervicale, (c) standardiser les indications de la cytologie et du dosage des marqueurs in situ, (d) aider le médecin à sélectionner les patients qui doivent bénéficier d’une échographie cervicale et ou d’une cytologie, (e) discuter du rythme des examens en fonction du risque de récidive.

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Abstract

Good practice guide for cervical ultrasound scan and echo-guided techniques in treating differentiated thyroid cancer of vesicular origin. American, European and French Recommendations for the treatment of differentiated vesicular thyroid cancer were recently published.

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Cervical ultrasound scanning is now considered a key examination in the follow-up of these cancers. This examination is noninvasive, easy to perform and to obtain, is not costly, but remains operator-dependent. To date, there are no recommendations published that assemble all the technical aspects, results, indications and the limits of this examination in the initial medical report and the follow-up of these cancers. In order to standardise the procedure and validate the quality of the examination, a workgroup made up of a panel of experts particularly involved in carrying out ultrasound scans was set up. The aim was to draw up a good practice guide for performing cervical ultrasound scans and echo-guided techniques in treating patients with differentiated thyroid cancer of vesicular origin. The main objectives are to: (a) standardise the procedure and reports, (b) define the criteria for establishing whether lesions identified during a cervical ultrasound scan are malignant or benign, (c) standardise the indications for carrying out cytological tests and an in situ assay of markers, (d) help doctors to select the patients who ought to receive a cervical ultrasound scan and or cytological tests, (e) discuss how frequently the examinations should be carried out depending on the risk of recurrence.

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1. Statement of the problem

1.1. Why is an ultrasound scan good practice guide necessary?

Recommendations for the treatment of differentiated vesicular thyroid cancer were published recently following a French consensus conference on the initiative of the French Endocrinology Society (SFE) and Thyroid Research Group (GRT), and were supported by various learned societies.

These recommendations made it possible to:

- propose a rational strategy based on the level of risk for the patient, taking into account the recent scientific progress made and the required multidisciplinarity strategy of the treatment;
- adapt the European and American recommendations to the specificities of France thereby giving French doctors access to reference material for multidisciplinary due diligence oncology meetings (RCPO).

Within the technological, exploratory and monitoring progress made for these cancers, ultrasound scanning is now considered a key examination, as attested to by recent European and American recommendations [1–3]. This examination is noninvasive, easy to perform and to obtain, is not costly, but remains operator-dependent. To date, there are no recommendations published that encompass all the technical aspects, results, indications as well as the limitations of this examination in the initial medical report and the follow-up of patients with these cancers.

In order to standardise the procedure and validate the quality of the examination, a workgroup made up of a panel of experts was set up. This group, particularly aware of the issues involved in carrying out ultrasound scans, took part in establishing a general consensus. The aim was to draw up recommendations based on a good practice guide for performing cervical ultrasound scans and echo-guided techniques in treating differentiated vesicular thyroid cancers.

1.2. Objective of this project

The main objective is to draw up a good practice guide for performing cervical ultrasound scans and echo-guided techniques in treating patients with a differentiated thyroid cancer of vesicular origin.

To be more precise, this consensus aims to:

- standardise the procedure and reports;
- define the criteria for establishing whether lesions identified during a cervical ultrasound scan are malignant or benign;
- standardise the indications for carrying out cytological tests and an in situ assay of markers;
- help doctors to select the patients who ought to receive an ultrasound scan or cytological tests;
- discuss how frequently the examinations should be carried out depending on the risk of recurrence.

These objectives are part of a broader reflective approach that aims to:

- present current perspectives of ultrasound scanning and echo-guided techniques and encourage the development of innovative projects on diagnostic and interventional cervical ultrasound scans;
- identify the issues that are of concern to the doctor and which might justify prospective or observational multicentre studies (France, Europe, USA).

1.3. General context

The WHO classification identifies the following differentiated cancers of the thyroid derived from vesicular cells: well-differentiated, papillary and vesicular cancers. This represents the vast majority. Less well-differentiated forms are also identified and for which the prognosis is worse.

Recent epidemiological studies have reported a strong predominance of papillary carcinomas which account for 85–90% of cases, while vesicular cancers account for a mere 5–8% of cases. The forms which are less or poorly differentiated (oncocytic and insular cancers) account for 3–5%.

It is estimated, at the moment, that there are 4000 to 5000 new cases of thyroid cancer discovered every year in France. On the whole, the prognosis is good. Only 5% of patients die from their cancer and 10 to 20% of them suffer a recurrence, in most cases locoregional. However, relapse may occur at a much later stage, therefore warranting a very long monitoring period.
The incidence of small papillary tumours has increased in recent years as the result of more active testing and changes in practice. Of the thyroid cancers operated on, 40–45% of them measure less than 1 cm. In almost 25% of cases, they are discovered fortuitously. Since 2002, these microcarcinomas have been defined as pT1 of the new pTNM classification which now includes tumours of 2 cm or less along the major axis. The predominantly lymphatic spread of these papillary cancers with lymph node metastasis is further evidence of the benefits of performing cervical ultrasound scans as the preferred method of diagnosis, especially since these small pT1 tumours, when discovered histologically, had not been subject to a lymph node procedure in conjunction with a thyroidectomy.

In recent years, new diagnostic tools have been developed which have radically changed the treatment and the therapeutic methods for monitoring patients. Ultrasound scans take up a central position in association with recombinant TSH and new and effective imaging techniques such as PET-CT with FDG.

These methods make it easier to detect recurrences early on. Recurrences most often occur within the first 5 years, although much later recurrences are possible. The treatment of thyroid cancers must be adapted to the patient’s risk level. Serious forms must be detected through monitoring, so that recurrences can be detected early on and treated accordingly. At the same time, unnecessary checkups, which can be a source of anxiety and additional cost, should be avoided if the risk of a recurrence is very low, which is the case for most patients.

The need for long-term monitoring due to the possibility of a recurrence, even in the long term, has led, over the years, to nonspecialists being involved in the monitoring. From the range of available imaging examinations, these doctors prefer to opt for cervical ultrasound scans on account of the simplicity of use. It is important to be able to refer to recommendations on the practical methods, indications and limits of this examination.

This ties in perfectly with the French national cancer plan that recommends that a treatment and follow-up protocol be proposed to each patient in line with local reference documents after a recurrence, even in the long term, has led, over the years, to nonspecialists being involved in the monitoring. From the range of available imaging examinations, these doctors prefer to opt for cervical ultrasound scans on account of the simplicity of use. It is important to be able to refer to recommendations on the practical methods, indications and limits of this examination.

1.4. Working method

The basis for reflection was the European, American and French consensus published in 2006 and 2008 [1,2,4]. The workgroup was set up to be representative of the different learned societies involved in treating cancer (the SFE, the GRT, the Ultrasound Imaging Society (SIU), the French Nuclear Medicine Society (SFNM), the French-speaking Association of Endocrine Surgery (AFCE), the French Ear Nose and Throat Society (SFORL), the French Clinical Cytology Society (SFCC), the French Oncology Society (SFORL).

The present work involved six multidisciplinary groups comprising endocrinologists, radiologists, nuclear medicine specialists, endocrine and ENT surgeons, cytopathologists, biologists, oncologists, whether members of hospital staffs or in private practice, with expertise in the treatment of thyroid cancer or in cervical ultrasound scans. The groups worked under the aegis of reporters who were in charge of writing up a text that responded to the questions asked.

The objectives were presented and the texts discussed at three meetings of the workgroup in March, June and September 2008 in Paris at the Hôpital de la Pitié. Thanks to these meetings, the final document was written up comprising a summary and recommendations with annexes. This final document was proofed and validated by a group of three experts from outside the workgroup. The report will be transmitted, via the website of the SFE and the SIU, to all members of these societies and possibly to others.

These recommendations on the practice of ultrasound scans are in line with the recommendations of the European and American consensus. These recommendations were presented in September 2008 at the ETA conference at the behest of this committee. The aim is to work on putting these international, European and American recommendations into practice.

1.4.1. Composition of the workgroups and the questions asked

**Coordination:** L. Leenhardt

**Group 1:** Objectives, Position of the problem
Reporter: L. Leenhardt, S. Leboulleux
Participants: A. Rouxel, JL. Sadoul
Questions: objectives of the project, methodology. What are the issues? Review of the literature on recurrences, types, method of detection, localisation, and survival rate depending on the type of recurrence (lymph node/space).

**Group 2:** Ultrasound scan technique
Reporter: J. Tramalloni.
Participants: A. Rouxel, G. Le Clech, F. Tranquart
Questions: anatomical reminder, compartments, equipment, carrying out the examinations, standard report, diagram, qualify criteria for a cervical ultrasound scan, reproducibility of the ultrasound scan, training of the operator.

**Group 3:** Results
Reporter: A. Rouxel
Participants: H. Monpeyssen, J. Tramalloni, J.L. Sadoul, S. Leboulleux
Questions: normal results after total thyroidectomy, assessment of residue in the thyroid bed
Criterion for determining whether a lymph node is benign
Criterion for determining whether a mass in the space is malignant
Criterion for determining whether an adenopathy is malignant
Criterion for determining whether a disease is persistent after surgery
Effectiveness criterion for radiiodine ablation

**Group 4:** Indications for an ultrasound scan and the frequency of checkup visits
Reporter Group 4a: G. Le Clech.
Participants: H. Monpeyssen, F. Menegaux, B. Carnaille
Questions:

- Thyroid in place and diagnosis of thyroid cancer highly suspected: indications for a preoperative ultrasound scan,
information provided by this examination, are there any suspicious lymph nodes?

- Remaining lobe in place: indications of ultrasound scan of the remaining lobe and study of lymph node areas.
- Repeat surgery: indications of the ultrasound scan

Reporter Group 4b: L. Leenhardt, S. Leboulleux.
Participants: C. Do Cao, M. Calzada

Questions:
- Total thyroidectomy: indications according to risk, decision tree from the results of the ultrasound scan. Frequency of ultrasound scans.

**Group 5: echo-guided fine-needle aspiration biopsy and assay of the tumoral markers in situ**

Reporters: B. Cochand-Priollet, G. Mansour. Participants: A. Charrié, J.L. Sadoul

Questions:
- Performing the echo-guided fine-needle aspiration biopsy, standard report, diagram, quality criteria of the echo-guided fine-needle aspiration biopsy. Results of the echo-guided fine-needle aspiration biopsy. Limits, traps. Indications for an echo-guided fine-needle aspiration biopsy of the lymph nodes and the spaces.
- Criteria for assessing the quality of the methods used to assay the markers (Tg), detection of interference.
- Thresholds of response. Indications for an in situ Tg assay.

**Group 6: other applications and development of the ultrasound scan**

Reporters: F. Tranquart.

Questions:
- Diagnosis of recurrences: lymph node marking, elastography, contrast agents.
- Treatment of recurrences: ethanol, radiofrequency, laser, HIFU.

**Summary of the entire document**

Reporters: L. Leenhardt
Proofed by the entire group

1.5. Data in the literature

1.5.1. Affected lymph nodes at the outset

Lymph nodes are frequently affected in cases of differentiated thyroid cancer. This invasion affects 30 to 50% of patients. It is more frequent in papillary cancers than follicular cancers and is more marked in children. It can be detected clinically; in this case, adenomegaly can reveal a cancer, either at preoperative ultrasound scan, or more commonly through a histological examination of the removed lymph nodes if lymph node dissection is carried out. Lymph node metastases are mainly located in the central (Group VI) and lateral (Groups III, IV) compartments, but the spinal areas may also be affected (Group V) (Fig. 1) [5,6].

The influence of lymph node metastasis on the patient survival rate remains controversial [7–10]. However, if lymph nodes are affected at the outset, the rate of recurrence is higher [6,11]. A preoperative cervical ultrasound scan is recommended to obtain a full assessment of any affected lymph nodes [1]. The sensitivity of this examination, however, is said to be limited to 37%, in particular for the detection of lymph nodes which are often set deep in the central compartment [12]. A recent study by Roh et al., points out clearly how a cervical ultrasound scan can identify lymph node metastases prior to surgery in the central compartment in 57.9% of cases, and in the lateral compartment in 25.6% of cases. The sensitivity of the ultrasound scan for detecting metastases of the central compartment is 61.0% and the specificity is 92.8% [13]. A recent study emphasizes the benefits of complete staging gained by carrying out a lymph node dissection of the central compartment, thus restricting the indications for radioiodine ablation to patients with invasion of the central compartment undetected by an ultrasound scan [14].

1.5.2. Cervical recurrences

Around 5 to 27% of patients suffering from a differentiated thyroid cancer will suffer a recurrence [15–18], 8.9% in a recent series by Peltarri, and 10.3% in the Frasoldati series [6,19]. These recurrences are generally located in the cervical lymph nodes (60 to 75%), more rarely in the thyroid space (20%) and
series [6], recurrences appear on average 3.5 years, and 71% in the first 5 years [19]. In the Frasoldati et al.’s Ninety-three percent of recurrences occur within the first 10 after 6–12 months [11].

significantly associated with a risk of persistent disease. An additional three lymph nodes with capsular invasion are factors that are nodes in the central compartment and the presence of more than nodes at initial lymph node dissection, location of these lymph tumour of over 4 cm, the presence of over 10 affected lymph

1.5.4. Prognostic factors of local recurrence and survival after recurrence

The prognostic factors of local recurrence are age > 45 years, male gender, the size of the tumour, extrathyroidal invasion, the extent of lymph node extension, follicular histology, partial rather than total thyroidectomy and the lack of radioiodine ablation. The rate of recurrence is higher in patients with initial lymph node metastases (18.7%) than in those without (N0) (6.5%, P < 0.001) [6]. In the Leboulleux et al.’s series, an initial tumour of over 4 cm, the presence of over 10 affected lymph nodes at initial lymph node dissection, location of these lymph nodes in the central compartment and the presence of more than three lymph nodes with capsular invasion are factors that are significantly associated with a risk of persistent disease. An additional, significant recurrence factor, is the Tg level on stimulation after 6–12 months [11].

Once recurrence (all locations combined) has been diagnosed, the estimated survival rate 10 years after the recurrence is 49.1% [16], 62% [33] or 68% [23] depending on the series. This estimate varies according to the age of the patient at the time of recurrence diagnosis: 89.3% for patients aged under 45 versus 32.1% for those over 45 years [16].

In patients with a recurrence, the factors significantly associated with an increased mortality rate are, in a multivariable analysis (except for age ≥ 45 years), the vesicular type, capsular invasion, the absence of initial radioiodine ablation, the initial presence of distant metastases, and two characteristics of the recurrence, namely, the absence of radioiodine uptake and the location in the thyroid bed as compared to lymph nod metastases. The relative risk of death is five times higher if a recurrence occurs the thyroid bed as compared to lymph node recurrence: RR 5.05 (CI 95% 2.62–9.74; P < 10–5) [16]. Mazzaferri’s group has reported that the specific 30-year mortality rate of cancer in patients with cervical recurrence in the thyroid bed is 30%, i.e. twice the one observed in patients with lymph node recurrence [21].

1.5.5. Method of detection

Cervical ultrasound scan has proved to be a reliable method for early testing of recurrences [32,34]. A recurrence is detected using an ultrasound scan in 94.1 to 96% of patients [6,16]. The average diameter of recurrences is 16.2 ± 9.1 mm [6]. These recurrences are rarely palpable (17.6% of cases) and infracentimetric in 29.2% of cases [6]. Clinically detectable lymph node involvement at initial diagnosis of cancer only account for 39% of cases in the Leboulleux series [11]. Ultrasound scan sensitivity is better than that of clinical examination. Frasoldati et al. report that for 51 recurrences, nine were palpable and 48 were detected at ultrasound scan [6]. The low effectiveness of clinical examination is accounted for by the small size or the central location of the lymph node lesions. Törlofano et al. report that 50% of lymph node lesions were < 1 cm [34].

Ultrasound scan shows a marked heterogeneity in the presentation of recurrences in terms of size, location and histological type (lymph node versus thyroid tumoral tissue). Consequently, ultrasound scan also contributes to the prognostic evaluation of the recurrence, better in the case of small lateral lymph node metastases than, of course, if tumoral tissue extends to subcutaneous tissue or the aerodigestive axis in the thyroid bed.

A high level of serum Tg demonstrates the persistence or the recurrence of tumoral tissue, but does not indicate where it is located. Moreover, serum Tg assayed on 1-Thyroxin treatment is undetectable in 20% of patients with isolated cervical lymph node metastases, and in 5% of those with a distant metastasis [24]. Upcoming ultrasensitive assays of Tg could improve the detection sensitivity.

The combination of a positive ultrasound scan and an increased serum thyroglobulin on stimulation is the best criterion for determining recurrence [6,32,35]. In the Pacini et al.’s study, the diagnostic sensitivity of the rate of stimulated Tg was 85% and its negative predictive value 98.2%. The combination of this Tg level with the result of the ultrasound scan, increased the

sensitivity to 96.3% and the negative predictive value to 99.5% [32].

The follow-up diagnostic ¹³¹I scintigraphy with activity of 74–185 MBq (2–5 mCi) has a low level of diagnostic sensitivity [18,32,36]. It is indicated for the follow-up of cases where there are anti-Tg antibodies, for cases of doubtful post-therapeutic scintigraphy or with intense cervical hyperfixation creating artefacts on the thorax or in cases where there is a high risk of a tumour.

Cervical CT scan appears to provide a real added value to that of the cervical ultrasound scan in the study of the lateral compartment. In the Kim et al.’s series, the sensitivity, specificity, positive predictive value of the association of an ultrasound scan and cervical scan are respectively 66%, 88%, 77% for all compartments [37].

The PET-CT with FDG is complementary to the ultrasound scan [6]. This examination is indicated in particular in isolated cases of raised Tg levels with negative ultrasound scan as well as total body scan after a therapeutic dose of radioactive iodine.

2. Cervical ultrasound scan technique and echo-guided methods

2.1. Cervical ultrasound scan technique

Cervical ultrasound scan has become a key examination, in patients with thyroid cancer, both initially and in the follow-up after surgery. The procedure and as well as the report of the examination must be standardised in order to narrow interoperator variability.

In order to insure an effective examination, four quality control levels are mandatory.

2.1.1. Equipment

The type of device and its commissioning date must be stated. A quality check of the devices must be carried out regularly. Two types of probe are recommended to study the cervical region correctly after total thyroidectomy:

- a high frequency linear probe (10 to 14 MHz). This is an indispensable tool which offers the advantage of high resolution but the disadvantages of a small field and limited depth. Today, there are probes on the market with a field of over 40 mm in width offering very good quality. It should be noted that small field probes are easy to use on short necks;

- a convex small radius probe (6–8 MHz). This type of probe is useful for carrying out ultrasound-guided fine-needle aspiration biopsy and to study submaxillary and subclavicular regions.

The device must be equipped with a sensitive Doppler module capable of recording flows in small vessels for pulsed and colour Doppler energy imaging (signals picked up regardless of the direction of the circulation) to enable vascularisation of the lymph nodes and any remnants to be studied.

Electronic trapezoid formats, nonlinear imaging (harmonic) and the composite mode are new methods that help to delimit and characterise cervical anomalies more effectively.

2.1.2. Operator

Specific training in the follow-up of thyroid cancer is required. The experience of the operator is a guarantee of quality. The reproducibility is better if the same operator also carries out the follow-up. In each team, the aim must be to narrow the variability within and between observers as far as possible through discussion of the cases and feedback.

2.1.3. Performing the examination

The patient is in the supine position with the neck stretched out. The operator must methodically explore the central and lateral compartments by passing the probe over the area. Examination of the V and II B sector is made easier by rotating the head. The analysis in B mode is systematically followed by a colour Doppler.

2.1.4. Limitations of the ultrasound scan examination

The cervical ultrasound scan does not reveal retroesophageal, retrotracheal or upper mediastinal lesions.

It is not usually possible to distinguish between tumoral recurrences within the thyroid bed and recurring adenopathies of the VI sector (same ultrasound appearance, same topography).

It is difficult to carry out an ultrasound scan of the thyroid bed soon after thyroidectomy because of the edematous changes. Surgical clips can also make the examination difficult. It is advisable to wait for 3 months after surgery to be able to analyse the central thyroid bed.

After a total thyroidectomy, additional difficulties may arise:

- the omo-hyoid muscle is often sectioned during the initial total thyroidectomy with lateral lymph node dissection. In this case, it may be difficult to distinguish compartment III from IV;

- the vascular jugulocarotid axis is close to the lateral side of the trachea and can make the adenopathies of the lateral VI sector retract. It may be difficult to distinguish between sector IV and VI lymph nodes.

Adiposity of the neck, neck shortness as well as hypertrophic scars interfere with the technical quality of the examination and decrease the accuracy.

2.2. Technique of ultrasound-guided methods

2.2.1. Ultrasound-guided fine-needle aspiration biopsy

2.2.1.1. Equipment. Two types of probe can be used for fine-needle aspiration biopsy (FNAB), a high frequency linear probe (7.5 to 14 MHz) or a small radius convex probe (6–8 MHz) depending on the operator’s routine. Twenty-two to 27 gauge needles are used. The Group recommends the use of 25 to 27 gauge needles.
2.2.1.2. Operator. The examination must be carried out by an operator used to performing cervical ultrasound scans for diagnostic purposes and fine-needle biopsies assisted by an ultrasound scan.

2.2.1.3. Performing the examination. The patient is in the same position as for a classic cervical ultrasound scan: lying flat with the cervical area stretched out. An examination of the thyroid bed and the lymph node areas is carried out in order to methodically explore all the compartments before carrying out the needle aspiration (refer to the ultrasound examination diagram).

Once the suspect lymph node has been spotted, an FNAB is carried out. The needle aspiration product can either be blown away onto slides using an empty syringe, spread and smeared, and stained with May Grünwald and Giemsa (MGG) or placed suspended in a specific liquid medium. The needle is then rinsed for further Tg assay (see paragraph 2.2.2).

If several lymph nodes appear suspect in the same area, aspiration of a single lymph node is sufficient. It is preferable to choose the one that has the greatest number of suspicious characteristics. However, if the level of suspicion is similar for several lymph nodes in the same area, then the most accessible lesion should be selected for fine needle aspiration.

It is advisable to mark out the lymph node which has been biopsied. Methylene blue can be used although with the disadvantage of fast spreading; colloidal carbon can also be used. Studies are underway. Identification of suspicious lymph node(s) is likely to help efficient subsequent surgical dissection and removal.

2.2.1.4. Limitations, precautions and contraindications of ultrasound-guided FNAB. Ultrasound-guided FNAB is a benign but nonetheless invasive procedure. The usual rules for all invasive procedures with regard to asepsis, anticoagulant and platelet aggregation inhibitor drugs must be applied:

2.2.1.4.1. Precautions. All precautions must be taken to ensure asepsis:

- clean hands;
- clean skin;
- protection of the probes: the probes may come into contact with the patient’s blood during the needle aspiration: it is therefore essential to have a system for protecting and cleaning the probes. The probes must be physically protected during the needle aspiration with appropriate sterile equipment. If several probes are available, a sterile bath system that complies with hygiene standards may be used. The probes must be cleaned with a steriliser between each examination.

2.2.1.4.2. Contraindications. Anticoagulant and platelet aggregation inhibitor drugs: there are no studies available on the frequency of serious haemorrhagic complications during lymph node biopsies. In everyday practice, this type of complication rarely occurs. According to the GHET-SFAR recommendations published in April 2008, invasive procedures that lead to less frequent, low-intensity or easily-controlled bleeding can be carried out on patients treated with anti-vitamin K in the usual therapeutic zone (INR between 2 and 3), after checking to ensure that there is no overdose. If the intended procedure is considered to have a high haemorrhagic risk (i.e. a haemorrhagic risk of above 1%), good practice dictates replacing anti-vitamin K with heparin. It is advisable to stop aggregation inhibiting drugs 7 days before the needle aspiration in primary prevention patients. On the other hand, in secondary prevention patients (cerebrovascular or coronary pathology), long-term treatment with aggregation inhibiting drugs can only be stopped if the specific haemorrhagic risk from the procedure appears to be clearly above that of the cardiovascular risk taken by stopping the medication (GHET-SFAR 2001 expert conference, updated in 2006). The risk is at its highest after stent insertion (especially of the pharmacoactive type) and requires a double aggregation inhibition treatment for several months (aspirin-clopidogrel). In this situation, before a planned procedure that entails a low haemorrhagic risk, it is recommended to maintain the aggregation inhibition treatment. Stopping clopidogrel for 5 days can be considered in patients at risk of moderate stent thrombosis if the haemorrhagic risk from the procedure is considered to be intermediate. In short, stopping aggregation inhibition treatment by way of secondary prevention can only be justified if the haemorrhagic risk is high (>1%). All these elements must be risk-benefit analysed when considering needle aspiration. Needle aspiration biopsy in patients on antivitamin K or aggregation inhibition drugs must be ultrasound-guided and use fine needles (25 or 27 gauge); the number of biopsies (1 or 2) must be limited, and the point of entry of the needle must be compressed firmly after the procedure.

Clotting abnormalities are a relative contraindication. Biopsies must be avoided as far as possible and the risk must be carefully weighed up against the benefits. If it is finally decided to proceed with the aspiration, the procedure must be carried out with all the precautions deemed necessary by the haematologist.

2.2.1.4.3. Limitations of the examination. The main point concerns the contributory value of the sample. The smaller the lymph node, the greater the risk of failure. Retro-oesophageal lymph nodes or those behind large vessels in the neck are inaccessible to needle aspiration.

2.2.2. Assay of Tg in situ

Ultrasound-guided aspiration is carried out with a fine needle, preferably 25 to 27 gauges. After aspiration, the needle is then rinsed using either of the following medium:

- physiological saline solution (0.9% NaCl) [6,38–41]. With saline, Baskin et al. obtained “blank” values (“assay background noise”) which were significant but remained below 5 ng/mL [42]. A study carried out by Snozek et al. showed that in a recovery test with exogenous Tg, the values of Tg are 25% higher with the saline solution than with a serum matrix [43];
- an assay buffer or a “Tg-free” serum pool supplied by the laboratory [6,38,42,44,45].

The volume of saline or buffer used to rinse the needle may vary from 0.5 to 1 mL. Snozek et al. pool several rinsings 0.1 to
Table 1
Classification of neck dissection.

Compartiments cervicaux.

The topographic lymph node classification proposed by Robbins to the American Head and Neck Society [46] divides the neck into 6 levels or sectors designated by a roman numeral. These levels form 3 main groups, one central group and two lateral groups.

Central group located between the 2 carotids
Level I: between the mandible and the upper border of the hyoid bone
Level VI: between the lower border of the hyoid bone and the brachiocephalic vein. It includes 4 sub levels:
  VI superior, above the isthmus, with the Delphian node
  VI right and VI left, along the recurrent nerve
  VI inferior, above the brachiocephalic vein or the cervical transverse

Lateral groups: on each side
Level II: subdivided into IIa (above the ostium of the upper thyroid artery) and more posteriorly and superiorly, level IIb
Level III: above the intersection between the omohyoid muscle and the internal jugular vein
Level IV: above this intersection
Level V: more laterally, behind the posterior border of the sternocleidomastoidian muscle, divided into:
  Va facing II and III
  Vb facing IV


0.5 mL each to obtain a final volume of 0.5 to 1 mL [43]. The French consensus recommends using a volume of 1 ml [4].

Needles are often rinsed with a physiological saline solution for practical reasons. Before using the physiological saline solution, it is recommended to check for the absence of matrix effect in the usual assay method. However, it is always preferable to use the assay buffer of the kit to be used. The volume used for rinsing is generally 1 ml. If the needle has to be inserted several times into the same lymph node, the needle rinse solution can be poured into the same tube.

3. Results

3.1. Results of the cervical ultrasound scan

3.1.1. Anatomical reminder

Robbins et al. suggested to the American Head and Neck Society that a lymph node topographical classification based on surgical anatomical markers be used as these markers can be easily identified using imaging and in particular when using an ultrasound scan [46] (Table 1).

All surgeons specialising in thyroid surgery know this classification and it must be used systematically for ultrasound scanning when monitoring thyroid cancers [47].

3.1.2. Ultrasonographic markers

The surgical markers in the Robbins classification have a practical echographic correspondence.

The ostium of the upper thyroid artery is difficult to identify with the ultrasound scan. It can easily be replaced by the carotid bifurcation (the upper thyroid artery is the first collateral branch of the outer carotid artery) which is at the same level.

3.1.3. Report and iconography

3.1.3.1. Report. The date and the type of initial treatment, the position of the lesion, the pTNM classification and additional treatment and the date(s) (radioiodine, secondary surgery... ) should be recorded. It is the responsibility of the physician who has ordered the examination to fill up the patient’s chart to be transferred to the sonographer.

The report must include a minimum list of items (Table 2):

- condition of the spaces;
- lymph node images with the sector location and the level of suspicion. The term “adenopathy” must only refer to lymph nodes deemed to be pathological according to ultrasonographic criteria. The lymph nodes that appear normal on the ultrasound scan do not have to be mentioned;
- muscle and subcutaneous plane;
- presence and permeability of both internal jugular veins.

3.1.3.2. Iconography. This is compulsory for all ultrasound scan procedures. It must include at least two correctly oriented, annotated perpendicular sections for each pathological or significant structure. The callipers must be visible to help to maintain the reproducibility of the measures for monitoring purposes.
3.1.3.3. Marker diagram. A diagram of the lesions based on the surgical classification by Robbins is indispensable in order to avoid any inaccuracies regarding the location of a lesion. The diagram below proposed by Tramalloni and Monnyssen is inspired by this classification and gives details of each of the compartments [48] (Fig. 1). Remnants, adenopathies and lymph nodes are indicated in the corresponding sector. This diagram is important for echographic monitoring and especially when surgery is considered because it will help guide the surgeon when carrying out the dissection procedure.

3.1.4. Results

The ultrasound scan is particularly effective in screening for lymph node metastases with a sensitivity of 90 to 95% [6,16], and 96% for Pacini et al. when combined with an assay of stimulated serum Tg [32]. An ultrasonographic study of the cervical region after thyroidectomy makes it possible:

- to search for and assess the size of any remnants in the thyroid bed;
- to search for any tumoral masses in the spaces after a thyroidectomy;
- to search for and characterise any suspect adenopathies in the cervical lymph node chains.

The characteristics of normal cervical lymph nodes have been widely studied and are now well established. However, studying the space is difficult and can be misleading. Many publications do not include information regarding the criteria for ascertaining whether a mass in the space following a thyroidectomy is malignant or not; and distinguishing between an ordinary remnant and a tumoral mass is not always easy. Other imaging examinations may be necessary (diagnostic scintigraphy, PET-CT with FDG).

3.1.4.1. Assessment of the thyroidectomy spaces.

3.1.4.1.1. Normal appearance of the thyroid bed after a thyroidectomy. A more or less homogenous hyperechoic zone can normally be seen between the trachea and the carotid, and an internalisation of the jugulocarotid bundle is usually more obvious on the side of the oesophageal overhang, which is most often observed on the left side. The appearance may vary from one patient to another. Thyroid tissue remnants are often observed, but this is not pathological in nature. The description must include the size, echogenicity, form and vascularisation.

3.1.4.1.2. Criteria for determining the malignancy of a mass in the thyroid bed. There are very few publications that describe the echographic characteristics of cervical recurrences in the thyroid bed [49]. Any hyperechoic, highly vascularised mass must be considered suspect.

It is difficult to distinguish between a true recurrence in the space and a non-tumoral lesion [49]. The ultrasound scan cannot always differentiate sufficiently between the two: it is not easy to distinguish between a recurrence in the space and an adenopathy of the VI sector. The causes of a non-tumoral mass in the thyroid bed may include:

- glandular remnants: these are ovoid tissue masses with an echogenicity similar to that of thyroid tissue; they may be hypoechoic or hypervascularised in the case of a remnant of autoimmune thyroiditis (Hashimoto’s or Graves’ disease);
- fibrosis: this looks like a nonovoid zone, that is hyperechoic, and nonvascularised;
- muscular structures;
- reactional lymph nodes;
- a parathyroid, difficult to distinguish from a sector VI lymph node;
- lymphocele, difficult to distinguish from a cystic adenopathy of sector VI;
- more rarely, tracheal cartilage or fatty necrosis.

3.1.4.2. Assessment of the cervical lymph node chains. Studying the cervical lymph nodes is an essential step in echographic assessment and monitoring of patients treated for a thyroid carcinoma. It is vital to distinguish between physiological and benign reactional lymph nodes and adenopathies so as to ensure the detection of a cervical lymph node recurrence in the first instance, but also to avoid subjecting the patient to unnecessary monitoring of lymph nodes that are not pathological in nature. The echographic and topographical characterisation of various visible lymph node chains make it possible to select lymph nodes that require monitoring or an FNAB.

3.1.4.2.1. Topography. The neck is physiologically the seat of around 300 lymph nodes varying in average size between 3 and 30 mm. Around 10 lymph nodes on average (5 or 6 at least) are generally visible using an ultrasound scan in an individual [50–56]. The number of visible lymph nodes depends on the type of probe used. Using current high frequency probes (10–14 MHz), a larger number of physiological lymph nodes can be seen. The number of visible lymph nodes tends to decrease with age [55]. There appears to be no significant difference in number, size, appearance or topography of lymph nodes according to the ethnic origin of the patients [55].

Benign reactional lymph nodes may be visible in all cervical lymph node compartments. Their appearance may differ from one compartment to another. Hypertrophic lymph nodes which can measure 2 or 3 cm along the major axis are frequently observed and are often found in the submandibular region (sector II).

Physiological or reactional lymph nodes are distributed in order of frequency into:

- the spinal region (posterior triangle, sector V) for 32 to 37.5%;
- submandibular and upper cervical (sectors IIA and IIB) for 30 to 50% (same frequency in both locations);
- parotid for 15 to 16%;
- less frequently submental (sector I) for 3 to 4%;
- medio- or basicervical (sectors III and IV) for 4 to 9%;
- supraclavicular for less than 1% [50,54–56].

Only one is generally observed in each location, except in sectors IIA and IIB where they may come in pairs, and in sector V where they come in groups [54]. The presence of multiple lymph node formations in sectors III and/or IV, where generally
speaking few physiological lymph nodes are seen (see above), should arouse suspicion [50]. This data should probably be qualified, because they come from studies that are a little outdated and which were mainly carried out with 7.5 MHz probes. Current practice with high frequency probes of 10 to 14 MHz usually reveals multiple physiological lymph nodes in sectors III and IV in particular.

Lymph node metastases of differentiated thyroid carcinomas may be located in the central and/or lateral compartments. They are most often homolateral to the initial tumour (3 to 16% occur bilaterally) [55,56]. They tend to be located, in order of frequency in sector VI and in particular in a paratracheal location, in the lateral compartments (Groups IIa, III and IV), and more rarely in the lower part of sector V (posterior triangle), in sector IIb, or in sector I [57,59–62]. The presence of lymph nodes in several compartments is frequent. If the lateral sectors are affected, they tend to be associated with sector VI [57,58,60,61], but skip metastases appear to occur in 10 to 15% of patients [11,63].

3.1.4.2.2. Echographic characterisation and Doppler of cervical lymph nodes. An echographic assessment of cervical lymph nodes must include a study in mode B and a colour or energy Doppler study. The cervical ultrasound scan is highly effective for diagnostic purposes in detecting lymph node metastasis [5,64,65]. Most publications do not deal specifically with adenopathies of thyroid origin, which accounts for some of the disparities between studies. Some criteria for determining malignancy are common to metastatic adenopathies of varying kinds of neoplasia like ENT cancers, lymphomas, whilst others are more specific to metastases of thyroid origin. None of the criteria are pathognomonic of malignancy alone, but taken together they may constitute a strong argument for presuming malignancy [53]. The most specific criteria for determining whether an adenopathy is thyroid in origin are the presence of microcalcifications or cystic zones [5]. The following seven criteria must be systematically studied in order to characterise the lymph node formation: size, form, echogenicity, hilus, microcalcifications, cyst formation, and distribution of vascularisation.

3.1.4.2.3. Size. There is no significant difference in the size of the lymph nodes according to age or gender [55]. Lymph nodes in sector II are often more voluminous than those seen in other regions of the neck [50]. Normal lymph nodes tend to be smaller in young subjects (20–39 years) [55]. The size is not a formal criterion for determining whether the lymph node is malignant or not [66]. The small diameter is an interesting criterion which appears to be more discriminating than a large diameter [67]. Different threshold values have been proposed: above 8 mm [52,54,55,65], above 7 mm (for lymph nodes in sector II) or 6 mm (for lymph nodes in other sectors) in the study by Van den Brekel et al. [68]. Ninety five to 100% of benign lymph nodes have a small diameter of under 0.8 cm [52,54,55]. Three studies deal specifically with adenopathies of thyroid origin. In the Kuna et al. study, the size was significantly associated with malignancy, and a small diameter appeared as the weakest criterion: 97% of benign lymph nodes had a small diameter of under 1 cm, as opposed to 52% of metastatic adenopathies, and small average diameters were 0.5 ± 0.26 cm and 1.2 ± 1.2 cm, respectively (P < 0.01) [69]. The sensitivity of the small diameter (> 5 mm) was set at 61%, and its specificity at 96%, in the study by Leboulleux et al. [5]. In the study by Frasoldati et al., the threshold value used is 8 mm with a sensitivity of 42% and a specificity of 87% for the detection of lymph node metastases [6].

3.1.4.2.4. Shape of the lymph node. The shape of the lymph node is defined by the L/S ratio (diameter of the largest axis/diameter of the smallest axis). Sixty-eight to 88% of benign lymph nodes have a L/S ratio of above or equal to 2 [52,55,66,69]. In other words, they are oval or spindle-shaped. The L/S ratio is lower in the submandibular and parotid regions, where normal lymph nodes are generally more rounded [50,70]. Metastatic adenopathies are frequently rounded with an L/S ratio of below 2; 65.6 to 85% of malignant adenopathies conform to this criterion [66,69]. The sensitivity of this criterion is evaluated at 46 to 95%, while its specificity is 64 to 95% [5,65,70]. The excellent specificity identified in the Steinkamp et al.’s study is explained by the population studied, as only large lymph nodes were included. So the greater the size of the lymph node, the more specific is the L/S < 2 criterion [70].

3.1.4.2.5. Hypoechogenicity. Over 90% of benign lymph nodes are hypoechoic. Metastatic adenopathies are generally hyperechoic. However, papillary adenopathies of thyroid origin can be hyperechoic [71]. The echogenicity of the lymph node resembles that of normal thyroid tissue. The hypoechoic nature of a lymph node appears not to be very discriminating for the identification of adenopathies of thyroid origin, with a sensitivity of 39% and a specificity of 18% [5].

3.1.4.2.6. Hilus. A centrally located hyperechoic hilus that is visible would appear to suggest that it is benign. The thickness of the hilus can vary from very fine and linear to thick, and can take up almost the entire volume of the lymph node, which can make it difficult to distinguish between a well-structured lymph node and an echogenic adenopathy. The frequency with which a hilus is seen tends to increase with age [55]. A hilus is visible in 68 to 100% of benign lymph nodes [54–56], and is easier to see, the greater the volume of the lymph node. The loss of hilus is a sign that might suggest malignancy. However, 9 to 73% of normal lymph nodes may not have a visible hilus [66,67,69]. In the Leboulleux et al.’s study, none of the lymph nodes that had a visible hilus turned out to be malignant in histology [5]. The presence of a hilus therefore appears to be a major criterion in favour of its being benign in this study (sensitivity 100%), whilst the absence of hilus was not particularly specific (29%) to malignancy. In the Frasoldati et al.’s study, the absence of hilus also appeared as a sensitive sign that suggested malignancy (88%) and that was not specific (35%) [65].

The hilus must also be sought in the colour or energy Doppler mode. It may not be visible in mode 2B, but should show up in the colour or energy Doppler mode thanks to its vascularisation [72]. In the study by Ahuja, 91.5% of metastatic adenopathies (thyroid and other malignant tumours) had no visible hilus in mode 2B. If the hilus was revealed in the energy Doppler mode, in 58.3% of cases it was associated with peripheral vascularisation [73].
3.1.4.2.7. Microcalcifications or hyperechoic punctuate foci. The presence of microcalcifications is very specific to adenopathies of thyroid origin [5,65,67,71]. They can be seen in 5.4 to 52% of cases [5,69,72]. They must not be confused with postoperative scar tissue. Hyperechoic punctuate foci are evocative of colloid granulations.

3.1.4.2.8. Cystic zones. The presence of cystic zones is highly evocative of malignancy [53,67]. Cystic thyroid adenopathies present with a wall, vegetation or internal septa, and rarely occur in a purely cystic form [74]. The frequency with which cystic formation occurs in adenopathies of thyroid origin varies from one series to another, 5 to 70% of cases [5,69,72,75,76]. The sensitivity of this sign of cystic formation varies from 11 to 70% and its specificity reaches 100% in the detection of adenopathies in patients monitored for thyroid carcinomas [5,65,75]. Cystic formation can nonetheless be seen in other aetiologies, in particular lymph nodes of tuberculous origin and metastases of malpighian cell carcinomas. It can also be linked to a lymphocele.

3.1.4.2.9. Vascularisation. The vascularisation of benign physiological or reactional lymph nodes is purely hilar (60 to 98% of lymph nodes), while in others no vascularisation is present (32–35%), but it is never anarchic [53,55]. In several studies, vascularisation varies significantly, depending on the type and the age of the equipment used, which makes the interpretation and comparison of the results of the studies difficult. Submental or submandibular lymph nodes tend to appear more vascularised than other topographies [77].

The vascularisation of adenopathies is disorganised. It can be anarchic or peripheral as a result of vessels being repressed by the tumoral mass [53,67]. The study by Ahuja et al. that deals with adenopathies of varying aetiologies describes the different types of vascularisation according to whether hilus is visible or not in mode 2B: 80% of adenopathies with visible hilus and 58.3% of cells without visible hilus have mixed vascularisation, while 36.1% of adenopathies without visible hilus have exclusively peripheral vascularisation [72]. Metastatic adenopathies with exclusively hilar vascularisation are rare (2.5%), but this observation is perhaps less true for adenopathies of thyroid carcinoma as reported is one single study: Ahuja et al. report that 24% of adenopathies of papillary origin have exclusively hilar vascularisation, 29% have capsular vascularisation and 47% have mixed vascularisation; none was avascular [72]. In the study by Leboulleux et al. [4], the presence of peripheral vascularisation is an excellent sign for suggesting malignancy, with a sensitivity of 86% and a specificity of 82%. In the study by Frasoldati et al., the presence of mixed vascularisation is associated with a sensitivity of 65% and a specificity of 95% [65].

The pulsed Doppler study within a lymph node formation is difficult, and is even harder to reproduce than with the colour or energy Doppler. The results of studies are sometimes contradictory. Malignant adenopathies have a rather high resistance index, above 0.7 or 0.8 [53,67,73]. This criterion is not found in the study by Ahuja et al., which specifically studied metastases of papillary cancer: in this study, 80% of 21 adenopathies studied had a resistance index of less than 0.7 [72]. The use of this criterion is not recommended routinely.

3.1.4.2.10. Summary of the analysis of the seven echographic criteria. The occurrence of the following four echo-Doppler criteria raise suspicion, and the presence of at least one of them is enough to recommend an FNAB with an in situ assay of Tg:

- microcalcification;
- the presence of cystic zone(s);
- peripheral and/or mixed peripheral and anarchic internal vascularisation (except in an infectious obvious context);
- hyperechogenic lymph node that looks like thyroid tissue.

The following three echo-Doppler criteria are not highly discriminating when taken individually but when combined an FNAB with an in situ assay of Tg should be considered depending on the context (level of risk, Tg rate):

- small axis ≥ 8 mm;
- AND L/S ratio < 2;
- AND absence of hilus.

The following criteria are highly suggestive of benignity and do not require an FNAB:

- absence of the four major criteria of suspicion;
- and hyperechogenic hilus and/or central hilar vascularisation without peripheral vascularisation.

3.1.4.2.11. The significance of small lymph nodes. Normal lymph nodes of less than 8 mm are often round and without hyperechoic hilums (or hilus) The group recommends:

- Not to systematically carry out a fine needle aspiration for lymph nodes with a diameter of less than 5–7 mm;
- To carry out a fine needle aspiration if the serum Tg level is elevated and if the lymph nodes present at least two ultrasound criteria for malignancy,

If no fine needle aspiration is carried out, an ultrasound scan is recommended to ensure they do not increase in size and that no suspicious ultrasound criteria appear. The ultrasound scan must be done within 6 to 12 months. This time limit should be adapted according to the pTNM stage, the number of metastatic lymph nodes, capsular invasion and the Tg level.

3.1.4.3. Diagnosis of subcutaneous and or muscular recurrences. There are no echographic series in the literature that describe the characteristics of subcutaneous and/or muscular recurrences of thyroid cancer. Embedded in the superficial musculocutaneous tissue, the group has agreed to describe them as solid tissue zones that are highly hypoechonic, presenting varying levels of vascularisation. Their anterior topography and their hypoechonic nature should rule out a postoperative granuloma.
3.2. Results of the ultrasound-guided fNAB

3.2.1. Report

An FNAB plays an important role in treating patients with differentiated vesicular thyroid cancer. It can confirm an echographic suspicion of a local tumoral recurrence on thyroid residue or of lymph node metastasis. It is therefore important to correlate the cytological and echographic data correctly.

Initially, it is essential to obtain a quality cytological sample, i.e. in the case of a smear, regular, well-standardised fine spreading with a May-Grünwald-Giemsa coloration. The cells may also be recuperated in a liquid medium.

The cytology report may form the ideal document to gather, compare and store the clinical, echographic and cytological information. It must include a section that has been fully completed by the physician stating the clinical context, the echographic appearance of the lesions, a description of the cytological data gathered by the cytopathologist, and a conclusion.

3.2.2. The section of the cytology report to be filled in by the physician

The echographic report is sent by the radiologist or the doctor who performs the biopsy to the cytologist. It enables the cytopathologist to interpret the cytological data (Table 3).

3.2.3. Descriptive part of the cytology report

A distinction must be made between the cytology of the thyroid residue and that of the lymph node lesions. When monitoring thyroid remnants, an FNAB may be considered a diagnostic test for papillary carcinoma benign vesicular nodules and well differentiated vesicular carcinomas are essentially characterised by a microvesicular architecture. Consequently, all microvesicular cytoarchitecture will be suspected as being malignant, although the malignancy cannot be confirmed [78].

The cytology report must include a description for each needle aspiration site indicating the number of slides or tubes sent for analysis. The main items (analysed according to the thyroid or lymph node focus for the needle aspiration) and which must be recorded in the report are given in Table 3 (Table 3).

3.2.4. Conclusion of the cytology report

The conclusion of the cytopathologist must state whether the equipment is satisfactory for assessment. An unsatisfactory sample comprises erythrocytes without lymphoid material, plasmocytes and epithelial cells.

If insufficient material is available, a benign lesion may correspond to a reactionary adenopathy or a normal thyroid remnant. A reactionary adenopathy is characterised by the presence of lymphocytes, tangible body macrophages and plasmocytes without epithelial cells. A normal thyroid remnant shows up in cytology as vesicular epithelial cells without any malignancy criteria.

A malignant adenopathy is most often the metastasis of a thyroid carcinoma of vesicular origin; but other conclusions may be drawn, in particular in the case of a lymph node metastasis of another type of cancer. It is defined by the presence of atypical epithelial cells.

Tumoral tissue in the space is defined by the presence of atypical cytonuclear cell, a papillary architecture with pseudo-inclusions (perforated nuclei) [79]. In the absence of nuclear criteria suggesting a papillary carcinoma, the diagnosis is based on the presence of ring-formation epithelial cells, the absence of colloid, and the oncocyte appearance of the cytoplasm.

3.2.5. Results, limitations and pitfalls of lymph node cytology

The results of the lymph node FNAB when monitoring thyroid cancer are only rarely reported as such and are rarely sufficiently distinct to be assessed. In most of the articles on this subject, the results are combined with those of the ultrasound scan or an assay of Tg. Two recent sufficiently documented studies to assess the sensitivity, specificity, positive and negative predictive values of the cytology came respectively to 94 and 77.3%; 100 and 98%; 100 and 98.9%; 87 and 64% [80,81]. In other studies of the literature, overall results on the ultrasound scan combined with the cytology results can be found. The sensitivity then varies between 65 and 98% with, in the Torlontano et al.‘s study, sensitivity and specificity of 100% even though the analysis included small lymph nodes of under 8 mm (size between 4 × 4 mm and 14 × 15 mm) [34].

Lymph node cytology therefore offers encouraging results but has its limits, with, in particular, a higher risk of false negatives than false positives, while the specificity and PPV were always excellent. In the literature, the following points are stressed:

- the quality of the results of an FNAB is very operator-dependent, requiring both the radiologist and the cytopathologist to be motivated. One of the main causes of “non diagnostic cytology” is the absence of lymph node material or weak cellularity;
- the quality of the results also depends on the size of the metastatic foci. Another major cause of “nondiagnostic cytology” is the presence of a metastatic microfocus not touched by the needle aspiration;
- however, the size of the lymph node does not appear to have an influence on the quality of the needle aspiration, as the effective results have been obtained from biopsies of small lymph nodes [34,80].

One particular point remains open to debate: how to insure that a lymph node FNAB is representative? There is no consensus or any definition in the literature. Lymph node FNAB is commonly considered as representative when it includes lymph node material. However, it is not defined what amount of lymph node material should be obtained. But it should be noted that if a lymph node is almost entirely metastatic only few lymphoid elements would be observed so that a low quantity of lymph node material is not a sign of nonrepresentativeness.

Are there other means to improve the diagnostic reliability of lymph node FNAB for monitoring thyroid cancer?

- Immunocytochemistry, using antibodies against cytokeratin 19, calcitonin, TTF1, thyroperoxydase or HBME1, or lectins such as galectin 3, is not necessary if the initial cancer is
Table 3
Cytology sheet report.

Information concerning the lesion
Identification of the structure:
- suspected lymph node
- mass in the space
- subcutaneous mass
- nodule in the remaining lobe

Localisation:

Size:

Number of slides for analysis

Descriptive report

Nodal lesion

| Cellularity: | 0 | + | ++ | +++ |
| Lymphocyte background: | 0 | + | ++ | +++ |
| Tingible body macrophages: | yes | no |
| Epithelial cellules: | yes | no |
| Cytonuclear atypia: | yes | no |

Arguments in favour of papillary carcinoma on thyroid residue

- Large angular oval nuclei: yes | no |
- Pale chromatin (fine granulations): yes | no |
- Ground glass chromatin (in liquid medium): yes | no |
- Small eccentric nucleolus: yes | no |
- Longitudinal nuclear grooves: yes | no |
- Intracellular pseudoinclusions: yes | no |
- Nuclear overlapping: yes | no |
- Papillae: yes | no |
- Large sheets (in liquid medium): yes | no |
- Psammoma bodies: yes | no |
- Multinucleate giant cells: yes | no |
- Thick hypereosinophil colloid: yes | no |

If nuclear criteria in favour of papillary carcinoma are lacking

- Macrovesicular cyto-architecture (in favour of a benign lesion): yes | no |
- Monolayer syncytial sheets: yes | no |
- Abundant colloid: yes | no |
- Small round nuclei with dense chromatin: yes | no |
- Orderly arranged nuclei: yes | no |
- Oncocyte aspect of cytoplasm: yes | no |

Microvesicular cyto-architecture (suspected malignancy):

- Rings of epithelia cells (6–12): yes | no |
- Less abundant colloid: yes | no |
- Rows of epithelial cells: yes | no |
- Oncocyte aspect of cytoplasm: yes | no |
- Cytonuclear anomalies: yes | no |

known and the tumoral cells are numerous enough to be identified. However, immunocytochemistry is highly recommended when lymph node FNAB shows epithelial cells of undetermined origin. The combination of anti-TTF1, calcitonin and Tg antibodies appears to be the more effective in favour of the thyroidal origin [82].

- It does not appear necessary, at the moment, to use biological markers such as BRAF, RET oncogene, etc. However, a study combining the detection by PCR of the TSH receptor and Tg transcripts showed a diagnostic sensitivity and specificity of 100% for lymph nodes measuring less than 15 mm if lymph node material was present [83].

3.3. Results of the assay of Tg

3.3.1. Method of expressing the results – decision threshold

3.3.1.1. In a lymph node. Studies on the assay of Tg on the lymph node needle aspiration liquid were carried out over the period 1992–2008. The assay kits used are very different in terms of analytical and functional sensitivities. The initial studies mentioned sensitivities in the order of 3 μg/L [42].

The assay kit used for the assay on aspiration material and serum Tg were the same. Current assays use immunometric methods calibrated according to the international standard CRM 457. Functional sensitivity is in general less than 1.0 μg/L.
Two methods for expressing the results of Tg are used in the literature:

- ng/ml is used by many groups. Some, however, mention that they do not take into account dilution due to rinsing [38,39,41,43–45,81,84–86]. However, this approach does give the actual concentration of Tg in the lymph node.
- ng/fine-needle aspiration: a more suitable result which reflects the quantity of Tg in the needle after rinsing and not the concentration in the lymph node [32,40,83,87].

The decision threshold applied varies from one study to another and concerns the functional sensitivity of the assay: 0.9 to 1.0 ng/FNAB [41,43] or the average plus two standard deviations of the values of Tg in situ obtained in a negative control group [32,44,45,84,87]. In several studies, the Tg in situ is compared with serum Tg [38,39], but it has been shown that there was no correlation between serum Tg and Tg in the lymph node [86]. Kim et al. rely on the aspiration/serum Tg ratio [79]. Finally, some use “arbitrary” thresholds: 10 or 100 µg/L [81,85].

The decision threshold must be linked to the functional sensitivity of the assay. The medium used for the collection of the sample must be checked to ensure there is no matrix effect which could be the cause of “false positives” if the decision threshold were too low.

A Tg value above the functional sensitivity of the assay may signify the presence of Tg [4]. The recommendations of the group have been listed in a box in paragraph 5.3.

3.3.2. Interference with the assay of Tg in situ

3.3.2.1. Contamination with serum Tg. Significant contamination with serum Tg does not exist [38,40]. An assessment of this contamination was carried out by Borel et al.: it is in the order of 0.003–0.012%, and is therefore negligible [40].

3.3.2.2. Interference with anti-Tg antibodies. Several studies have shown that there was no interference due to anti-Tg antibodies in the assay on the rinsing liquid [38,40,41,45,84]. For Baskinet al., Tg in the fine-needle aspiration liquid could even constitute a safe method of monitoring patients with anti-Tg antibodies [84]. Boi et al. carried out a retrospective study showing a sensitivity and specificity rate of 100%, regardless of whether there were any anti-Tg antibodies or not [45]. An explanation for this could be that the excessively high concentration of Tg in the rinsing liquid of the fine-needle aspiration may be able to saturate the binding sites of the anti-Tg antibodies.

4. Indications for a cervical ultrasound scan and echo-guided techniques

4.1. Indications for a cervical ultrasound scan

4.1.1. Before thyroidecotomy if cancer is suspected

A cervical ultrasound scan is recommended to obtain an accurate assessment of the lymph node chains. Accurate analysis of all the cervical lymph node groups on both sides should enable an accurate assessment of the lymph node extension [1]. This cartography, which is easy to carry out and interpret, should be shown on a diagram, since the result of the ultrasound scan may change the extent of the lymph node dissection. The lateral compartments are frequently affected (78% of 50% of patients who have lymph node metastases in the Leboulleux et al.’s series) [11]. It is therefore essential to define, before surgery, the extent of the supposed metastases. Furthermore, an echographic study of the central compartment is difficult, or even impossible if the thyroid is in place. This limitation is a good argument in favour of immediate central lymph node dissection as the morbidity for further surgery in this zone is high [14,88].

4.1.2. After a total thyroidecotomy and before radioiodine 131 ablation

It is advisable to perform an ultrasound scan to check the lateral compartments (especially if the cancer is fortuitously discovered at histology). It is meant to detect the persistence of any lymph node metastasis (absence of lymph node dissection or incomplete lymph node dissection) and enables the size of any possible remnants to be assessed which is also helpful to assess the risk of an inflammatory reaction induced by radioiodine ablation.

4.1.3. Six to 12 months after a total thyroidecotomy

A cervical ultrasound scan must be carried out to examine the thyroid space, the central and lateral lymph node compartments, whether radioiodine ablation has been carried out or not.

A Tg measurement done under rTSH stimulation ensures that ablation is complete and that there is no residual disease. The future development of super sensitive Tg measurements will most likely reduce the need to repeat the rTSH stimulation tests, when the first check up shows no abnormalities.

4.1.4. During the follow-up

4.1.4.1. Cervical ultrasound scan. A cervical ultrasound scan is recommended if the serum Tg level rises [4] and/or in case of clinical cervical abnormalities. The frequency of the scans depends on the predictive factors for recurrence which depend on the patient and on the characteristics of his/her cancer. If the Tg is high 6 months later, whatever the level of risk, the Tg level must be taken into account. If it worsens, an ultrasound scan must be carried out in conjunction with
other forms of imaging (cervicothoracic scanner, PET-CT with FDG).

4.1.4.2. Patients at low risk. In patients at low risk (80% of patients), it is not advisable to carry out an ultrasound scan every year if Tg has been undetectable under stimulation and the ultrasound scan satisfactory at the first 6–12 month check-up. In this case, the frequency of monitoring can be reduced (risk of recurrence under 1% over 10 years) [32,89–92]. The group proposes a last ultrasound scan 5–7 years after initial treatment, i.e. at the end of this period during which the risk of recurrence has been reported to be the highest. This proposal has been put forward by experts. However, it is not supported by firm data. Afterwards, monitoring is then continued on l-Thyroxin.

4.1.4.3. Patients at high risk. In patients at high risk (20%), the group suggests echographic monitoring combined with an assay of serum Tg under stimulation after 1, 3, 5 and 7 years in accordance with the HAS and the National Institute of Cancer, published in May 2010 (www.has-sante.fr and www.e-cancer.fr), the frequency being adapted to the initial status concerning the invasion of the lymph node capsule or not (more than 3) since this is a risk factor for recurrence [11].

In contrast, in patients at high risk, when the check up after 6 months is normal, the risk of recurrence should be reassessed and can lead to a less frequent ultrasound follow-up as mentioned above [93].

4.1.4.4. pT4 tumours. For pT4 tumours extending to the oesophagus and/or the trachea, and the R1 stage, it is worthwhile to reassess after 3 months the cervical ultrasound scan as well as other imaging methods (cervicothoracic scanner with an injection of contrast fluid, PET-CT with FDG, MRI).

4.1.5. After a lobectomy

After a lobectomy (which usually means the discovery of small secondary cancer), scintigraphy with iodine is ineffective so that ultrasound scan is the main monitoring tool [1]. The ultrasound scan can be used to analyse both sides of the area around the lymph nodes, test for the recurrence or persistence of a tumour in the thyroidectomy bed and to give details of the appearance of the controlateral lobe while searching for nodules which might justify an FNAB, or even a total thyroidectomy. This ultrasound scan is advisable 1 year after surgery. There are no guidelines regarding the frequency of ultrasound follow-up after a year. The group suggests doing an ultrasound examination at 3 and 5 years if there is no abnormality. The Tg level is of limited signification. On L-T4 treatment, low serum concentrations of Tg are usually detected but no reference values have been defined. Serum Tg should remain stable.

4.2. Indications for an echo-guided fine-needle aspiration biopsy

4.2.1. A mass detected in the thyroid bed

Echo-Doppler criteria indicating an echo-guided FNAB of the thyroidectomy space are: hypoechogenic mass with mixed or internal vascularisation and/or cyst formation and/or microcalcifications.

4.2.2. Lymph nodes

The four echo-Doppler criteria are highly suspect and the presence of at least one of them leads to the recommendation of an FNAB with in situ assay of Tg:

- microcalcifications;
- and/or cyst formation;
- and/or peripheral vascularisation and/or mixed peripheral and internal anarchic vascularisation (except in a clearly infectious context);
- and/or echostructure resembling thyroid tissue (hyperechogenic lymph node).

Each of the three following echo-Doppler criteria alone (small axis ≥ 8 mm AND L/S < 2 ration AND absence of hilus) is not specific enough. However, if the three criteria are present altogether, an FNAB with in situ assay of Tg should be considered depending on the circumstances (risk level, Tg level).

The following echo-Doppler criteria are strong indicators of benignancy and thus do not require fine needle aspiration:

- Absence of all the highly suspicious criteria AND presence of hyperechogenic hilus and/or central vascularisation AND/OR surgery not recommended.

4.2.3. Indications and benefits of in situ Tg assay

The value of this assay has been established for the first time in 1992 by Pacini et al., subsequently confirmed by many other groups.

It is recommended to combine any fine-needle aspiration biopsies of a lymph node suspected of being a metastasis of a cancer of the thyroid with an assay of Tg on the needle rinsing liquid [4].

The major benefit in the case of cystic lymph nodes, if the FNAB is paucicellular, is that the assay of Tg in situ provides a great deal of information [87].

For poor differentiated cancers, the in situ Tg values will be, in general, low or nil, depending on the groups, and can produce “false negatives” [45,87].

For Lee et al., adding the assay of Tg in situ to the cytology tests improves the sensitivity by 91 to 100% [44]. The sensitivity of the in situ assay is 100% for Pacini and Cignarelli, Snozek, Sigstad and for Cunha and Frasoldati, who also mentioned a specificity of 100%. For Snozek et al., the specificity is 96.2% and the predictive value is positive at 97.2% at the threshold of 1 μg/L [43].
5. Good practice guide

5.1. Recommendations of the SFE

The recommendations published are as follows [4]:

“The cervical ultrasound scan has become a key examination for the initial evaluation and monitoring of operated thyroid cancer. The procedure and the results of this examination must be standardised to limit subjectivity.

The cervical ultrasound scan is an examination that is operator-dependent, and a training period can improve individual performance. It is more sensitive than palpation and is routinely used to check the lymph node chain and the thyroid bed. It can detect lymph nodes as small as 2–3 mm in diameter. Benign lymph node hyperplasia is frequent. For chronic lymph nodes, the specificity of the cervical ultrasound scan is improved by studying the echographic characteristics (form, structure, vascularisation, size). Lymph nodes that do not have worrying suspicious characteristics only require a detailed description and regular checkups using an ultrasound scan, and the patient should be reassured. If a lymph node is deemed to be echographically suspect, the echographic characteristics are not sufficiently discriminating criteria and an echo-guided FNAB must be carried out. If several lymph nodes are found to be echographically suspect in the same area, FNAB need only be carried out on one of these lymph nodes. It is recommended to also carry out a Tg assay on the rinsing liquid at the same time as a fine-needle aspiration of a lymph node suspected of thyroid cancer metastasis”.

“Six to 12 months after surgery, a cervical ultrasound scan must be performed to examine the thyroid space and the central and lateral lymph node compartments, whether a radioiodine ablation has been performed or not and depending on the risk of a relapse and the Tg level.

In patients at low risk, there is no justification for carrying out an ultrasound scan every year after the first 6–12 month checkup. If the ultrasound scan results are normal, and the Tg level is undetectable after TSH stimulation, the risk of relapse is under 1% over 10 years. The cervical ultrasound scan is recommended if the Tg level rises during monitoring. If the ultrasound scan reveals clearly pathological lymph nodes, an FNAB and an assay of the Tg level on the rinsing liquid are indicated.

In high risk patients, echographic monitoring is advisable but there is no consensus as to the frequency of checkups (1, 3 and 7 years?).

5.2. Standardisation of technical procedures

**Ultrasound scan**

- The type of device and the date it was commissioned must be stated.
- Two types of probe are recommended:
  - high frequency linear probe (10 to 14 MHz);
  - small radius convex probe (6–8 MHz).

- Powerful colour Doppler module necessary
- Experienced operator
- Patient in the dorsal decubitus position with the neck stretched out. Rotating the head can make examination easier.
- It is advisable to wait 3 months after a total thyroidectomy to be able to effectively analyse the spaces.
- Identification of the omohyoid muscle to distinguish between compartment III and IV.

**Echo-guided fine-needle aspiration biopsy and assay of thyroglobulin in situ**

- Fine needles (25 to 27 gauge)
- Trained operator
- To be avoided in the cases of blood crasis problems. If unavoidable, preventative treatment and precautions to be taken in consultation with the haematologist
- Precautions in the case of antivitamin K treatment or aggregation inhibiting drugs with an assessment of the risks/benefits.
- Precautions for asepsis
- Echographic diagram to identify the structure into which the fine-needle is to be inserted
- Smearing, drying in air, coloration with MGG or liquid media
Total thyroidectomy

131 I ablation and post-therapy WBS

3 months: Check for appropriate LT4 therapy
TSH, FT4, FT3, on LT4

6-12 months: rhTSH-Tg* and neck US on LT4

Undetectable Tg
No other abnormalities
Decrease LT4 dose
Yearly evaluation LT4 with
TSH, FT3, FT4, Tg, neck US

Detectable Tg < institutional cut-off: no
other abnormalities
Repeat rhTSH with Tg at >
yearly interval

Detectable Tg > institutional cut-off and/or no other
abnormalities
Withdraw LT4 Treatment with
large activity of 131 I and post-
therapy WBS (and/or surgery)

Undetectable
Decreased but still
detectable: continue TSH
suppression, re-test in 1
year
Increased

Rinsing of each aspiration needle in a volume
of 1 mL (if several aspirations are carried out on
the same lymph node, the rinsing liquid from each
needle can be collected in the same tube):

• either with a physiological saline solution (0.9%
NaCl);
• or with a buffer of the assay or a pool of
“Tg-free” serum provided by the laboratory per-
forming the assay.

Assay of Tg using the current technique. No cor-
relation between the serous Tg and the Tg in the
lymph node.

No significant contamination by the serous Tg.
No interference dye to the anti-Tg auto-antibodies
in the assay on the rinsing liquid. It is therefore
not necessary to assay the anti-Tg antibodies in
the rinsing liquid. If there are several suspect
adenopathies in the same area, a fine-needle aspi-
ration of one only is sufficient.

5.3. Standardisation of the results

Recommendations for standardising the
results of cervical ultrasound scan

Learn the echographic markers and segmen-
tation of the neck compartments (Table 1).

Standardised report of the key words that must
be included in the report (Table 2).

Obligatory iconography for all procedures
listed. Measurements of structures with views of the
callipers.

Marking diagram (Fig. 1)

Definitions

Normal space after a thyroidectomy: hypere-
chogenic zone, that is more or less homogenous,
between the trachea and the carotid, and inter-
nalisation of the jugulocarotid bundle, possible
remnant in the form of a zone of tissue that is
more or less echogenic.

Suspect space: hypoechogetic mass and mixed
or internal vascularisation and/or cyst formation
and/or microcalcification.
Metastatic adenopathies, most often homolateral to the tumour, mainly in sector VI, and in IIA, III, and IV, and more rarely in sector V.

The most specific criteria of thyroid origin are the presence of microcalcifications (or punctuate hyperechogenic foci) and/or cystic zones and/or an echostructure similar to thyroid tissue (hyperechogenic lymph node).

The study of the following 7 criteria must be systematic for the characterisation of lymph node formations: size, form, echogenicity, hilus, microcalcifications, cyst formation, distribution of the vascularisation.

Highly suspect adenopathy: microcalcifications and/or cyst formation and/or peripheral vascularisation and/or peripheral mixed and internal anarchic vascularisation (except if there is an obvious infectious context) and/or and echostructure similar to thyroid tissue (hyperechogenic lymph node).

Benign lymph node: absence of all the highly suspicious criteria AND presence of hyperechogenic hilus and/or central vascularisation.

**Definitions:**
- biopsy not satisfactory: comprising erythrocytes without lymph material or epithelial cells;
- reactional adenopathy: presence of lymphocytes, tangible body macrophages and plasmocytes without epithelial cells;
- normal thyroid remnant: presence of vesicular epithelial cells without criteria for malignancy;
- malignant adenopathy: most often metastasis of a thyroid carcinoma of vesicular origin, but a lymph node metastasis of another type of cancer is possible although rare. It is defined by the presence of atypical epithelial cells;
- tumoral tissue in the space is defined by the presence of cytonuclear anomalies, of a papillary architecture with pseudo inclusions (perforated nuclei). In the absence of nuclear criteria suggesting a papillary carcinoma, the diagnosis is based on the presence of epithelial cells in a ring-like formation, the absence of colloid, the oncocyte appearance of the cytoplasm.

**Recommendations for standardising the results of an echo-guided fine-needle aspiration biopsy**

Date and name of the doctor(s) carrying out the biopsy and of those who will read the report.

Identification of the structure (Table 3).

Attached echographic diagram (Fig. 1):
- suspect lymph node;
- mass in the space;
- subcutaneous mass;
- nodule on the remaining lobe.

Location:
Size:
Number of slides sent for analysis:

Descriptive report of cytology results proposed in Table 3

Conclusion: must state whether the equipment is satisfactory or not for assessment purposes.

**Recommendations for standardising the results of the assay of thyroglobulin on the lymph node needle-aspiration biopsy liquid**

Assay of Tg in situ carried out using the immunometric assay method calibrated in line with the CRM 457 standard (functional sensitivity between 0.1 and 1.0 μg/L) [4]. The results of an ng/FNAB express the quantity of Tg in the rinsing liquid of the needle used for the biopsy (1 ml per rinsed needle).

**Definition**

The decision threshold applied varies from one study to another. It must be viewed in conjunction with the functional sensitivity of the assay. The group recommends:

- Tg < 1 ng/FNAB: normal;
- Tg between 1 and 10 ng/FNAB: to be compared with the results from cytology (little data available in the literature);
- Tg > 10 ng/FNAB: suggest the presence of tumoral tissue.
5.4. Indications for a cervical ultrasound scan and echo-guided techniques

5.4.1. Indications for a cervical ultrasound scan

**Indications for a cervical ultrasound scan**

Before a thyroidectomy for suspected cancer, an ultrasound scan must be performed to obtain an accurate description of the lymph node chains.

After a total thyroidectomy and before ablative treatment with iodine 131, an ultrasound scan is advisable to check the lateral compartments (especially if the cancer is fortuitously discovered at histology). This scan also provides information regarding the size of the remnant tissue.

Six to 12 months after a total thyroidectomy, a cervical ultrasound scan must be carried out to examine the thyroid space, the central and lateral lymph node compartments, whether radioiodine ablation has been carried out or not.

During the monitoring period, a cervical ultrasound scan is recommended if the serous Tg rises.

In patients at low risk, it is not advisable to carry out an ultrasound scan every year if the Tg is undetectable under stimulation and the ultrasound scan is satisfactory during the first 6–12 month checkup. The group recommends a final checkup after 5 or 7 years under stimulation combined with an ultrasound scan and a dosage of Tg under stimulation.

In patients at high risk, the group suggests echographic monitoring combined with an assay of Tg under stimulation after 1, 3, 5 and 7 years in accordance with the HAS recommendations and the Inca regarding the ALD 30 guide on the management of thyroid cancer. This frequency can be adjusted depending on whether there is an initial invasion of the lymph node capsule or not (more than 3) since this is a risk factor for recurrence.

For pT4 tumours that have invaded the oesophagus and/or trachea and the R1, it is worthwhile doing an assessment after 3 months including a cervical ultrasound scan and another imaging method (cervicothoracic scanner with an injection of contrast fluid, PET-CT with FDG, MRI) (mediastinal analysis).

After a lobectomy and the accidental discovery of a microcarcinoma, echographic monitoring of the remaining lobe and the areas around the lymph nodes is recommended at 1 year. A check up can be suggested at 3 and 5 years if no change occurs.

Generally speaking, screening tests and their frequency should be adapted to the patient’s level of risk. Since recurrences are relatively rare, these screening tests must have a high negative predictive value to avoid unnecessary treatment for cured patients. The result of the check up at 6 months after initial treatment must be taken into account and it should be used to review the evaluation of the risk of recurrence indicated by the initial pTNM status.

5.4.2. Indications for an echo-guided fine-needle aspiration biopsy

**Thyroid bed**

Echo-Doppler criteria indicating an echo-guided FNAB of the thyroidectomy space are:

- Hypoechogenic mass and mixed or internal vascularisation and/or cyst formation and/or microcalcifications.

**Lymph nodes**

Indications for fine needle aspiration with in situ Tg measurement depend on the results of the Doppler-scan:

- **Echo-Doppler criteria highly suspect:**
  - Microcalcifications
  - and/or cyst formation
  - and/or peripheral vascularisation and/or mixed peripheral and internal anarchic vascularisation (except in a clearly infectious context)
  - and/or echostructure resembling thyroid tissue (hyperechogenic lymph node)

Intermediate echo-Doppler criteria make it necessary to consider an FNAB with in situ assay of Tg depending on the circumstances (risk level, Tg level)

- Small axis $\geq 8\text{ mm}$ AND L/S $< 2$ ration AND absence of hilus

Criteria for not carrying out a fine needle aspiration

- Absence of all the highly suspicious criteria
- AND presence of hyperechogenic hilus and/or central vascularisation AND/OR surgery not recommended.

5.4.3. Indications and benefits of an in situ Tg assay

It is recommended to combine any fine-needle aspiration biopsies of a lymph node suspected of...
being a metastasis of a cancer of the thyroid with an assay of Tg on the needle rinsing liquid.

5.4.4. Decision tree

Fig. 3 suggests creating a decision tree from the results of the ultrasound scan combined with the assay of Tg under stimulation carried out 6 to 12 months after the initial treatment (Fig. 3). If there are any anti-Tg anti-bodies, suspicious post-treatment scintigraphy or intense cervical hyperfixation or if the patient has a high risk tumour, scintigraphy at a diagnostic dosage may be kept up in conjunction with an ultrasound scan and an assay of Tg.

This diagram offers an approach for cases where the echo-graphic result is suspect or malignant. The case of patients with a normal cervical ultrasound scan is described briefly.

Two groups of patient can be identified after 6 months:

- Patients at a low risk of recurrence:
  - normal ultrasound scan and undetectable Tg level under stimulation: in the article by Kloos, an undetectable Tg level after 1 year with a normal ultrasound scan result predicts the absence of a relapse within 3 to 5 years [94]. A final ultrasound scan may be carried out with an assay of Tg under stimulation after 5 or 7 years;
  - an abnormal ultrasound scan result and undetectable Tg under stimulation: false positive from the ultrasound scan?; ultrasound scan checkup for anomalies and/or an FNAB. Some lymph node metastases of more aggressive tumours do not secrete Tg. It is therefore more prudent to perform an FNAB if there is the slightest doubt;

- Patients with a high risk of recurrence:
  - normal ultrasound scan and undetectable Tg under stimulation: checked after 1, 3, 5 or 7 years (scan + Tg under stimulation);
  - abnormal ultrasound scan and undetectable Tg under stimulation (here again, prudence should be exercised for histologically aggressive forms or forms that are highly differentiated): FNAB;
  - abnormal ultrasound scan and detectable Tg (analyse the gradient compared with the value before radioiodine ablation): FNAB and assay of Tg in situ.

6. Prospects for the development of ultrasound scans

In recent years, a certain number of developments have come to light improving the quality of images and as a result, the quality of the information obtained. Some of these advances are now available on all machines, but others are only obtainable on some US machines. Among those that can be cited are elastography, contrast imaging and high intensity focussed ultrasound (FUS).

6.1. Contrast imaging

The principle of the contrast ultrasound scan is based on following highlighted tissue after strictly intravascular administration of ultrasound contrast agents (PCUS), which are microbubbles measuring just a few micrometers in diameter; after being injected via a peripheral venous line, they constitute powerful markers of the vascular compartment so that microvessels can be identified within a given organ. For the thyroid in particular, the SonoVue™ has been less widely used due to the limitations observed which are principally connected with the size of these microbubbles. Indeed, it is mainly suited to low frequencies below 5–6 MHz, but not high frequencies equal to or above 10 MHz. For high frequencies, more agent must be injected to compensate for the lower level of sensitivity while maintaining the mechanical index sufficiently low (<0.3) [95].

It appears, however, that after injection of contrast agents, a benign nodule does not empty quickly over time whilst a malignant node empties quickly and thus shows up as an empty space 60 s after injection. It can also be used for cervical lymph nodes in order to differentiate between inflammatory lymph nodes that become strongly highlighted over a long period of time and metastatic lymph nodes that are not highlighted or only weakly so (in connection with the invasion by neoplastic cells). However, it would appear that micrometastases cannot be detected satisfactorily using this method [96,97].

6.2. Ultrasound elastography

The theoretical principle of elastography imaging techniques [98–103] is based on the analysis of differentiated characteristics of tissue using a tissue rigidity/elasticity modulus (Young’s modulus) [99,100]. Young’s modulus expresses the relationship between the deformation of a solid and the stress applied. In order to detect differences in tissue behaviour, it is necessary to disturb the medium being explored and at the same time detect the influence of this disruption on the medium. Various methods can be proposed: external or internal palpation or the propagation of a shear wave into the medium.

The first method involves external compression and is based on the fact that a soft region will move and become deformed, while a rigid region will only move. These tissue deformation imaging methods are referred to as static elastography. The deformations caused are recorded in real time in the medium studied so that areas with differing relative behaviour can be distinguished thus revealing any suspected differences in rigidity. These methods cannot be used to quantify the Young modulus because in fact they create an image of the compressibility module and not the shear module. They are limited by a certain number of artefacts in the liquid zones or are dependent on the application of external, nonuniform compression, on disregarding lateral deformation and finally on the relative differences in behaviour between hard and soft tissue.
To determine the Young modulus using ultrasound, the shear modulus of the tissue must be measured. This entails propagating a shear wave through the tissue (being studied) and creating an image of the deformation caused by this wave. If the propagation of an external mechanical wave is not available for the thyroid, it is now, however, possible to study the propagation of an ultrasound wave or its effect on the tissue. This technology is currently being developed and evaluated by Supersonic Imagine (Aix-en-Provence). A specific module (Acoustic Radiation Force Impulse [ARFI]) is adaptable to a Siemens machine. These methods that are currently available in 2D can determine shear modulus and consequently accurately measure the Young modulus. The reported absence of artefacts with these techniques will undoubtedly improve the quality of the diagnosis.

Elastography can be used to supplement a classic ultrasound scan and thereby improve the accuracy of the diagnosis of thyroid tumours which appear to be harder than the surrounding tissue. In a recent study, tissue found to be hard during a static ultrasound scan is closely correlated with a diagnosis of cancer, while soft nodules are systematically considered benign [100]. These results are similar to those reported by the Rago and Lyshchik teams who found a high prevalence of malignant nodules in those considered to be hard (with respective sensitivity of 97% and 82% and specificity of 100% and 97%) [101,102].

If no surgery is carried out, the hardness of the tissue will probably lead to an FNAB being carried out without delay, whilst if the tissue is soft FNAB does not necessarily have to be proposed, even if no response is obtained from cytological tests [100].

6.3. Ultrasound therapy

The aim of high intensity FUS is to maximise the energy deposit caused by the interaction between high intensity ultrasound and the tissue which raises the temperature locally in the target area. Two parameters must be adapted: the acoustic intensity and the focus of the ultrasound beam. The acoustic intensity should be set at around 100 W/cm². This is obtained by using specific transducers together with powerful electronics. Multiple, convergent transducers are used to actively focus the ultrasound beam, creating a concentration of energy at a focal point and producing the ablative effect, in much the same way as the sun’s rays can be concentrated by using a magnifying glass. An effective treatment area of around 5 to 8 mm and around 1 mm in diameter is obtained for each sequence of ultrasound impulses which generally lasts about 5 s seconds, and is called sonication. For each treatment cycle, around 100 J of energy are delivered, heating up the focal point, the objective being to exceed 70 to 75 °C locally in order to destroy the target cells. This method is extremely accurate: tissue 0.3 mm away from the point focal remains intact.

The cervical zone is positioned in front of the FUS transducer built into the treatment head which also contains an ultrasound
probe that can locate the zone to be treated during the session. The trachea, the oesophagus and other parts potentially at risk such as the carotid must be carefully avoided.

The first papers reported satisfactory destruction of the nodule without any noteworthy complications: there was no local damage due to burns, nor any general damage done through modification of the thyroid count [104–107].

This approach might make it possible to treat a certain number of benign or malignant lesions of the thyroid without having to resort to surgery and without disrupting any subsequent treatment. It would appear more difficult to implement on the lymph nodes and on recurrences.

In conclusion, recent advances in ultrasound technology have significantly improved diagnoses through improved image quality, especially in terms of providing essential, additional information to characterise lesions. Its therapeutic applications are still in their infancy, but it should considerably change the way in which nodules are treated in years to come.

6.4. Other alternative therapies

Other therapies, alternative to surgery are developing such as treatment of metastatic lymph nodes with ethanol injections in years to come.

Laser, radiofrequency and focalized ultrasound are being developed to treat thyroid nodules and could be used in the future in the therapeutic management of thyroid cancers [109].

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