Management of thyroid nodules

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Abstract. *Management of thyroid nodules.* These Belgian guidelines for ENT surgeons about thyroid nodules were elaborated in the light of personal practical experience and the recent advances in diagnosis and management described in the literature. Thyroid nodules are a common finding, particularly in women and in areas of iodine depletion. The prevalence in the general population averages 3 to 7% on palpation and almost 50% on ultrasound. The major difficulty facing the clinician is how best to assess and manage these thyroid nodules. The authors have attempted to simplify the assessment of thyroid nodules, to classify them, and to present the most common current therapeutic management options.

1. Introduction

The following guidelines are based on recent peer-reviewed articles evaluated by the authors to rate between Ia and III according to Belgian evidence levels (BEL).[1-9]

1.1. *Definition*

A thyroid nodule is a tumefaction of a part of the thyroid gland.

Its prevalence and incidence can vary greatly according to the investigations carried out, the population studied, gender, age as well as the patients' past medical history.

1.2. *Epidemiological overview*

The finding of thyroid nodules by simple palpation increases by 0.1% every year of life of the patient with a prevalence averaging 3 to 7% in the general population. Thyroid nodules are four times more common in women than in men and the prevalence increases in areas with iodine deficiency and ionizing radiation exposure.[10]

On ultrasonography the prevalence ranges from 19% to 46% in the general population, may be even higher at autopsy, and may reach 49.5% in clinically healthy people.[11]

1.3. *Classification of thyroid nodules*

Thyroid nodules are either benign or malignant and are further subdivided following on histopathology. Benign nodules are classified into adenomas, cysts and other benign lesions.[12] Malignant tumours are predominantly epithelial in nature, and are either classified into differentiated types which can be papillary, follicular or medullary carcinomas or into undifferentiated tumours such as insular and anaplastic carcinomas.

2. Benign nodules

2.1. *Adenomas*

2.1.1. Follicular adenoma is a common thyroid tumour, with a greater incidence in women than in men.

Around 90% of solitary thyroid nodules are adenomas, which may undergo haemorrhagic transformation, cystic or necrotic degeneration. Malignant transformation is rare. Most patients are euthyroid and consult for a painless tumefaction but rapid growth due to haemorrhage may cause neck pain.

At histopathology, a follicular adenoma is an encapsulated tumour that consists of cells reproducing the thyroid architecture. It is either round or oval and surrounded by a fibrous capsule. It is 4-5 times more frequent than cancer. Several types exist, namely: macrofollicular (colloid), microfollicular (fetal), trabecular (embryonic) and normofollicular.

2.1.2. Variants:

– A toxic adenoma is a benign thyroid tumour that has escaped pituitary control. It corresponds to a solitary nodule with autonomous function.
– Hürthle cell adenoma is a totally encapsulated tumour composed mainly of oncocytic cells (75%), and is synonymous with oxyphilic or Askenazy's adenoma.

2.2. *Cysts*

Cystic nodules account for 15 to 25% of thyroid nodules, are benign and are the result of degenerative changes either within the normal thyroid parenchyma or a nodular goitre. Malignant change can occur in 20% of nodules larger than 4 cm. Cystic nodules can appear rapidly as a mass that is often very sensitive.

2.3. *Other benign nodules*

Other benign nodules can be seen in Hashimoto's thyroiditis, de Quervain's thyroiditis and rarely in cases of infection.

3. Malignant nodules

3.1. *Well differentiated carcinomas*

Well differentiated carcinomas of the thyroid represent 80-85% of thyroid cancers. They are divided according to their histopathology into papillary, follicular and less commonly, medullary carcinomas.

3.1.1. Papillary carcinoma

Papillary carcinoma is the commonest thyroid cancer with 12,000 new cases per year in the United States. It is often multifocal, has a peak incidence between 30 and 40 years of age, is two to three times more frequent in women, and has a good prognosis. It presents as a firm, mostly non-encapsulated mass.

At histopathology, there are some purely papillary carcinomas, some with a follicular predominance, a diffuse sclerosing variant, tall and columnar cell variants, and they may also present as microcarcinomas. The histological criteria of a papillary carcinoma are the presence of papillae formed by cells bordering a fibrovascular axis, the presence of laminated calcified nodules (psammoma bodies, found in 50% of the cases), and voluminous pale nuclei with early lymphatic invasion.

Papillary carcinoma has the best prognosis among the various types of thyroid cancers with the risk of recurrence increasing after the age of 40. Microcarcinomas (smaller than 1 cm) have an excellent prognosis. Patients with extension outside the thyroid and distant and lymphatic metastases at diagnosis have a less favourable prognosis.[13]

3.1.2. Follicular carcinoma

Follicular carcinoma constitutes 10-20% of thyroid cancers. It is typically a solitary, encapsulated nodule with a greyish-white macroscopic appearance, and metastasizes by vascular invasion to the lung and bone. Follicular carcinoma with minimal invasion has an excellent prognosis, while the invasive form less so. It occurs at a later age than papillary carcinoma (50-60 years of age) and its prevalence increases by a factor of 2 in areas that are iodine deficient.

At histopathology, this malignant epithelial tumour of the thyroid has a follicular differentiation, which makes it difficult to distinguish from a follicular adenoma: differential diagnosis is based on signs of capsular and vascular invasion, a high mitotic index and the presence of metastases.

There are particular types of follicular carcinomas, such as *Hürthle cell carcinomas*, or follicular carcinomas with oxyphilic cells. They are in fact uncommon aggressive variants of follicular carcinomas and account for 3-6% of thyroid tumours.[14,15] They generally present as a hot solitary nodule at scintigraphy and are more frequent in women in their fifties. Malignancy indicators are clear vascular and capsular invasion.

3.1.3. Medullary carcinoma

Medullary carcinomas originate from the C cells of the thyroid gland and represent 5-10% of thyroid carcinomas. Parafollicular C cells do not capture iodine and are not regulated by TSH. A genetic enquiry has to be pursued in every case as there is a familial form transmitted in an autosomal dominant mode and in which both thyroid lobes can be affected from the start. The existence of specific tumour markers facilitates diagnosis.

Medullary carcinomas have a firm consistency at histopathology, their colour varies from brown-yellow to pale pink and they have regular nuclei and abundant granular cytoplasm. The diagnosis is confirmed by immunohistochemistry with anti-calcitonin antibodies and carcino-embryonic antigen.

Medullary carcinoma tends to metastasize to the cervical and mediastinal lymph nodes and less frequently to the lung, liver and

bone. In suspected familial cases of medullary carcinoma, the close relatives should have calcitonin levels measured as well as a pentagastrin test from the age of 5. The prognosis varies according to the age at first treatment and the 10-year survival rate is around 85% in patients under the age of 30 who have no metastases or lymphadenopathy and a tumour diameter less than 4 cm. For the other patients, the 10-year survival rate drops to 10%. The sporadic forms have a worse prognosis than the familial forms.

3.2. *Poorly differentiated carcinomas*

3.2.1. Insular carcinoma

The insular thyroid carcinoma usually presents as a nodule with or without an associated goitre.

At histopathological examination, insular carcinomas have a leveled architecture filled with cavities. The association of carcinoma cells of both follicular and papillary types is frequent, suggesting this type of carcinoma may well represent an intermediate stage in the differentiation process. This tumour also displays collagen-rich dense areas, which is the reason for which some have been wrongly diagnosed as medullary carcinomas. Thyroglobulin but not calcitonin is positive.

The prognosis is intermediate between those of well differentiated and anaplastic tumours. Local recurrence is frequent and metastases to the lung occur in 40% and to bone in 20% of the cases. Metastasis is often early and early aggressive treatment is warranted.

3.2.2. Anaplastic carcinoma

Anaplastic carcinoma of the thyroid is one of the most aggressive types and accounts for less than 5% of thyroid cancers. It usually occurs in patients above the age of 50 with a goitre or a thyroid nodule and has a peak incidence around 70 years of age. The tumour is rapidly invasive and metastasizes readily to the lung, bone, brain and liver.

The tumour is composed of giant fusiform or polygonal cells at histopathology. There is often a mixture of several cell types, along with keratinised, osteoblastic or sarcomatous cells. Epithelial structures are often present. Immunohistochemical studies have to be performed systematically. Keratin is the most useful epithelial marker and is present in 40-100% of the cases. Other antibodies will enable discrimination between lymphoma or more rarely a poorly differentiated follicular carcinoma, and a medullary carcinoma or an intrathyroid metastasis.

Survival is not modified by surgery, radiotherapy or chemotherapy, averages 2-6 months and rarely beyond 12 months.

3.3. *Other malignant tumours*

These consist mainly of sarcomas, lymphomas, histiocytosis, teratomas and metastases from the breast, kidney, lung, colon or a melanoma (see Table 1).

4. Management of a thyroid nodule[3,6,8,9,15,16]

– Anamnesis is essential, taking into account family history, gender, age (under 20, above 60 years of age), any past medical history of irradiation to

Table 1
TNM classification of thyroid carcinomas

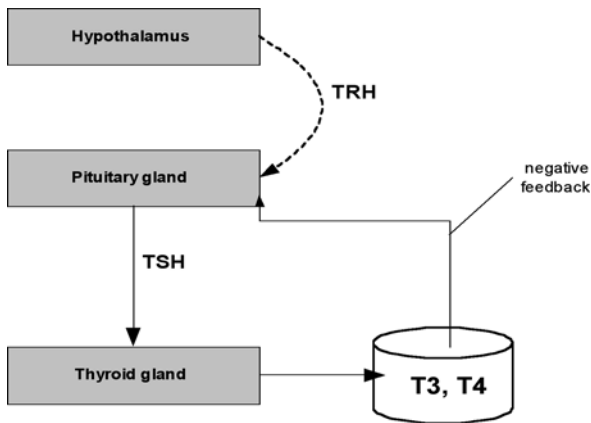| **TNM classification of thyroid carcinomas:[28]** |
| --- |
| **TX:** Primary tumour cannot be assessed |
| **T0:** No evidence of primary tumour |
| **T1:** The tumour is 2 cm (slightly less than an inch) or smaller |
| **T2:** Tumour is between 2 cm and 4 cm (slightly less than 2 inches) |
| **T3:** Tumour is larger than 4 cm or has extended slightly outside the thyroid gland |
| **T4a:** Tumour of any size and has grown beyond the thyroid gland to invade adjacent tissues of the neck |
| **T4b:** Tumour has grown either back to the spine or into adjacent large blood vessels |
| |
| The values for **N** are: |
| |
| **NX:** Regional (nearby) lymph nodes cannot be assessed |
| **N0:** No regional lymph node spread |
| **N1:** Spread to lymph nodes |
| **N1a:** Spread to lymph nodes in the neck (cervical lymph nodes) |
| **N1b:** Spread to lymph nodes in the upper chest (upper mediastinal lymph nodes) |
| |
| The values for **M** are: |
| |
| **MX:** Presence of distant metastasis (spread) cannot be assessed |
| **M0:** No distant metastasis |
| **M1:** Distant metastasis is present, involving non-regional lymph nodes, internal organs, bones, etc. |
| Separate stage groupings are recommended for papillary or follicular, medullary, and anaplastic (undifferentiated) carcinomas according to the age of the patient (under or above 45 years of age) (see association for online resources). |

Figure 1

Regulation of thyroid hormone synthesis. TRH: thyrotropin releasing hormone, TSH: thyroid stimulating hormone (thyrotropin), T3: tri-iodothyronine, T4: thyroxine.

the cervical area, the presence of any pain, rapid nodular growth and compression symptoms.

– Clinical examination: by palpation, the size of the nodule can be assessed along with the presence of tenderness, induration, glandular fixation, plunging goitre, or lymphadenopathy.

– Paraclinical examinations have to be focused if only from an economical point of view.

– Biological assessment (TSH, T3 and T4) will enlighten the clinician about the functional state of the gland and on the eventual presence of a toxic adenoma.

– TSH: thyrotropin or thyroid stimulating hormone (TSH) stimulates thyroid secretion and is released by the thyrotropic cells of the pituitary gland. Its secretion is in turn regulated by the circulating levels of the thyroid hormones (see Figure 1).

The new ultra-sensitive measurement technique of TSH levels is currently available everywhere in Belgium. As TSH levels are low in almost all hyperthyroid conditions linked to a primary pathology, this measurement alone should theoretically indicate the diagnosis of hyperthyroidism.

– Antibodies: anti-thyroglobulin and anti-peroxidase antibodies, when present, direct the diagnosis towards an auto-immune pathology.

– Calcitonin and carcino-embryonic antigen are measured when there is a suspicion of medullary carcinoma of the thyroid. When positive, a phaeochromocytoma should be excluded by measuring urinary catecholamines. Pentagastrin tests are only useful in infraclinical familial medullary carcinoma or in the postoperative follow-up of patients.

– Thyroid ultrasonography is the most common examination performed and enables the study of the morphology of the thyroid, the description of a nodule that had been found by palpation, the distinction between solid and cystic nodules, whether it is isolated or associated with other nodules, its situation within the gland and enables the search for cervical lymph nodes. Ultrasonography enables the visualisation of solid nodules measuring at least 3 mm and fluid-filled nodules of at least 1 mm in diameter. Hypo-echogenicity and an irregular shape increase the probability of a nodule being malignant. Its wider use has enabled the discovery of a large number of micronodules. When these are smaller than 1.5 cm, conservative management is proposed to the patient, whilst when the nodule size is above 5 mm, ultrasound guided fine-needle biopsy will be recommended.[17,18]

– Fine-needle aspiration (FNA) results will greatly depend on the experience of the operator as well as that of the pathologist. On average, two to three punctures will be performed on each nodule in order to get 5 to 6 glass slides. FNA is the most reliable and least invasive examination for the distinction between a benign and malignant nodule, and enables a better selection of patients requiring surgery.

The FNA is reliable in 85-95% of the cases and has a 1-11% false negative and 1-8% false positive rate. The lesions are benign in 69% of FNA, are suspect in 10%, malignant in 4% and indeterminate in 17%.[14,19-22]

– Scintigraphy: This examination reflects mainly the functional aspect of the thyroid gland and does not distinguish between benign and malignant nodules with sufficient specificity. This functional evalua-

tion enables the distinction between cold nodules with low fixation from hot nodules that are hyperfixating. The majority of cold nodules is benign but 10% are malignant; only 4% of hot nodules are malignant.[23] Moreover, 33% of the echographic nodules, including the infracentimetric nodules, are not visible at scintigraphy.

Hyperfixating hot nodules will show up toxic adenomas as well as hyperthyroidism, toxic adenomas with preclinical hyperthyroidism, and Hürthle cell adenomas. The risk of malignancy in these is 4%. Hypofixating cold nodules represent 80% of thyroid nodules. As 10% of cold thyroid nodules are malignant, scintigraphy is recommended if TSH is low.

The most commonly used isotopes are iodine I[131] and technetium Tc[99]. Technetium is currently the main isotope used for the initial exploration of thyroid pathology. Results obtained by Tc[99] are comparable to those from I[131] in 98% of the cases. This examination is not routinely proposed to the patient in several European countries, although it is part of daily practice in Belgium.

– <u>The CT scan</u> is only useful when complex surgery is planned or in cases of major tissue invasion. The use of iodinated contrast medium is contra-indicated in cases of hyperthyroidism. An NMR is preferred though rarely performed.
– <u>The PET-scan</u> is used for searching for distant metastases.
– <u>Genetic studies</u>: a 6-gene array-based predictor model has recently been developed to diagnose benign versus malignant thyroid lesions. Due to its high sensitivity and specificity, this technique may prove useful to diagnose the malignant potential of thyroid nodules preoperatively.[24,25]

4.1. *Medical treatment*

Thyroxine

– <u>For cold nodules</u>: thyroxine is very often prescribed when surgery is not indicated, and most often when there is an associated goitre. It has little effect on the size of the nodules but decreases the size of the goitre as a whole and may prevent the apparition of further nodules, by rducing the metabolic activity of the thyroid gland. The dose has to be adapted so as to achieve low-normal TSH levels, taking into account tolerance and eventual associated pathologies. It is unnecessary if TSH is already inhibited. Thyroxine is also prescribed postoperatively in order to maintain euthyroidism and prevent the occurrence of new nodules in the remaining thyroid parenchyma, in cases of partial thyroidectomy. The aim is again to maintain low-normal TSH levels.
– <u>For hot nodules</u>: thyroxine is usually not indicated, and it is unnecessary if TSH is low or inhibited. In case of surgery (often a unilateral lobectomy), its prescription is recommended to ensure euthyroidism and to avoid hypertrophy of the residual lobe or hypothyroidism if the remaining lobe is too small.
– <u>For carcinomas</u>: thyroxine is frequently given to the patient following a surgical intervention. Should a treatment with radio-iodine be necessary, thyroxine should only be given at the end of the treatment. In case of a papillary carcinoma, the dose of thyroxine has to be adapted so as to obtain TSH levels just above the minimal levels. TSH levels must be reduced in case of a follicular carcinoma and normal but rather low in cases of medullary of anaplastic carcinomas. It is important not to give too much thyroxine in cases of carcinoma in order to prevent osteoporosis that could set in after several years of treatment.

Radio-iodine I[131]

– This treatment is unnecessary in cases of medullary or anaplastic carcinomas.
– It is indicated in papillary and mainly follicular carcinomas although this is still a matter of debate.
– It is unnecessary when the papillary carcinoma is <1 cm, if it is localised and non-invasive and treated by a simple lobectomy. However, although its use is absolutely classic in case of follicular carcinoma, it is a little more controversial in papillary carcinoma treated by total thyroidectomy.
– It is usual to wait for one month prior to prescribing I[131], as TSH levels have to be >30 µU/ml. The usual dose is 100 mC.
– For papillary carcinomas, a single dose is usually sufficient.
– For follicular carcinomas, treatment has to be repeated every six months and always follows a weaning-off period of thyroid hormones. This con-

tinues until there is no fixation on a Total Body Scan.

– Thereafter, monitoring can be limited to thyroglobulin levels (with or without a Total Body Scan) following stimulation by TSH-rh (Thyrogen), which should enable continued treatment with L-Thyroxine (more comfortable but expensive).

Ideally this treatment should be repeated at six months, then after a year, two years and five years. Thyroglobulin levels must remain <1 ng/ml. If it is above 1 ng/ml, one should repeat the I^{131} Total Body Scan with a view to complementing the treatment.

Follow-up with cervical ultrasonography should also be performed.

It is important to note that I^{131} is also used in case of toxic nodules (with inhibited TSH and raised T3 levels) that do not require an operation (<3 cm, not causing any discomfort) and particularly when the patient is elderly or has too high an operative risk.

Calcium

– Calcium is indicated in cases of postoperative hypoparathyroidism and is either given per os or is depending on the severity. Hypoparathyroidism becomes persistent in +/- 2% of total thyroidectomies and calcium is often needed in association with vitamin D (Rocaltrol). This is constraining and expensive as calcium therapy is not reimbursed by the INAMI.

Fine-needle biopsy

– in the case of a cyst: the FNA procedure is often therapeutic, particularly when the cyst is haemorrhagic. It also yields a diagnosis on cytological exam-

ination. Should the cyst not disappear, ultrasonography should follow and a decision regarding surgery has to be made. Surgery is always indicated in cases of suspicious or positive cytology.

– In case of a cold nodule: ultrasound-guided fine-needle biopsy has become the most important examination in therapeutic management (see above).

External Radiotherapy

This treatment is reserved for anaplastic carcinomas, certain lymphomas and sarcomas as well as very particular cases of extensive differentiated carcinomas that do not fix I^{131}.

4.2. *Surgical management*

It is mandatory to obtain frozen sections of the tumour during the surgical intervention.

Total lobectomy plus isthmusectomy with recurrent nerve dissection and parathyroid gland exposure is the basic treatment of benign nodules.
It can also be performed for small unifocal papillary carcinomas as well as for minimal invasion follicular carcinomas.

Total thyroidectomy with careful dissection of the recurrent nerves and parathyroid glands (respecting vascularisation) is recommended in cases of multicentric papillary carcinomas either with lymphadenopathy or a poor prognosis as well as in follicular carcinomas that are either invasive or larger than 1.5 cm in diameter. A decrease in the recurrence risk within the contra-lateral lobe and easy patient follow-up will play in favour of total thyroidectomy.[26,27]

The morbidity of total thyroidectomy is low when it is performed by an experienced surgeon.

However, complications include recurrent nerve palsy and hypoparathyroidism, both of which can be either transient or permanent (approximately 2% for both).

In both medullary carcinoma and Hürthle cell carcinoma, total thyroidectomy is paramount.

In anaplastic carcinoma, surgery will depend on tumour size, since survival won't be modified by the procedure.

When reoperation is envisaged at a later stage, such as in toxic multi-nodular goitres and particularly in the presence of recurrent nerve palsy or hypoparathyroidism, it is well worth considering radio-iodine as a satisfactory alternative. Indeed, the risk of complications such as recurrent nerve palsy is doubled at reoperation.

Lymph node clearance

In follicular carcinoma, functional clearance is performed if lymphadenopathy is present.

In papillary carcinoma, homolateral lymph node clearance is performed if lymphadenopathy is found peroperatively (recurrent nerve chain, pre- and latero-tracheal lymph nodes and the inferior part of the homolateral jugulo-carotid chain).

In medullary carcinoma, functional bilateral lymph node clearance, including the recurrent and jugulo-carotid chains is mandatory.

Conclusions

Rapid, efficient and financially sustainable diagnostic procedural steps are essential for the benefit
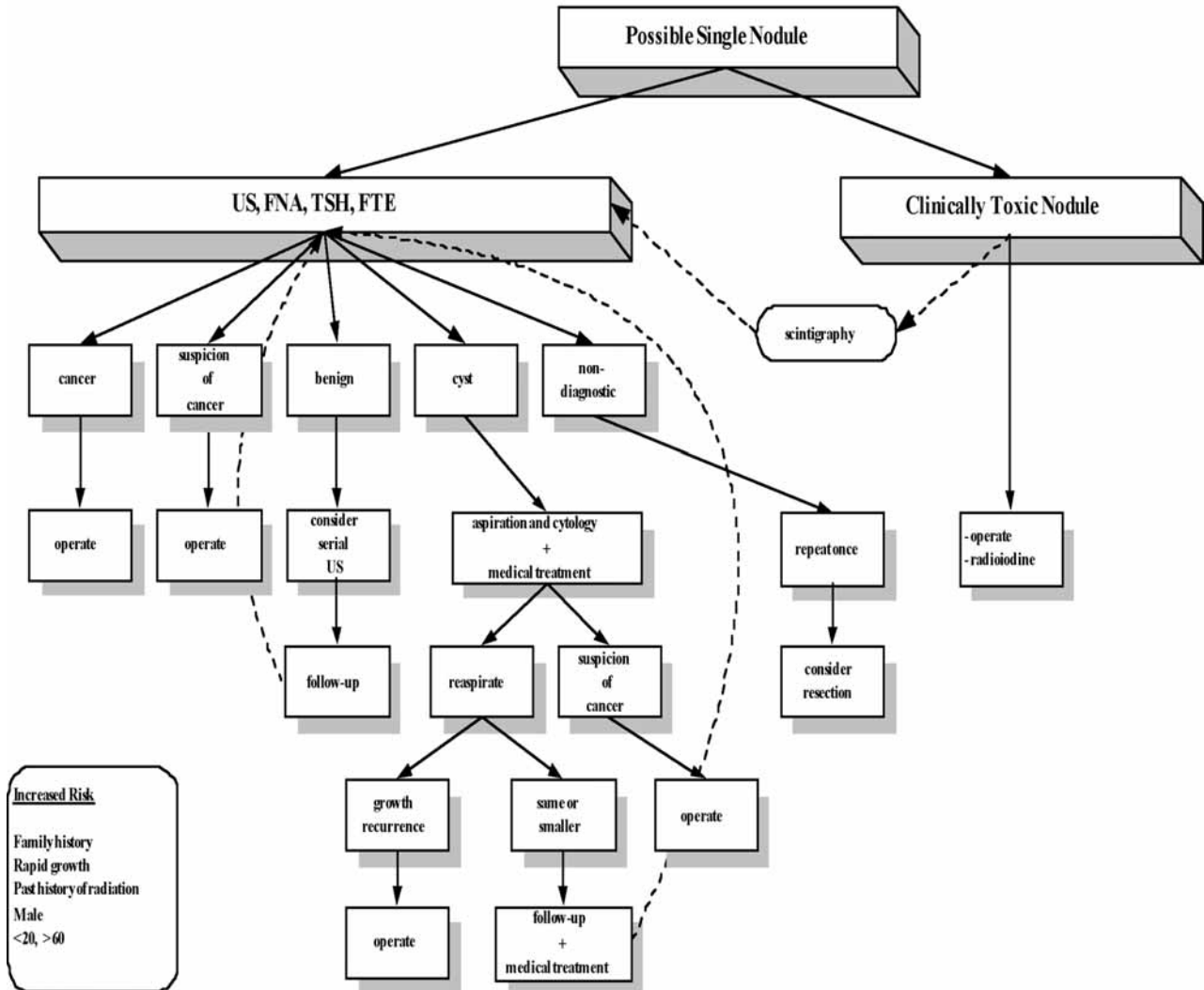
THYROID NODULE MANAGEMENT

Figure 2
Management flow-chart of the thyroid nodule

of the patient and should consist of biological tests including TSH, T4, ultrasound and fine-needle aspirate (see Figure 2). In case of an uncertain diagnosis, a fine-needle aspirate can be repeated in order to decide on the most appropriate treatment. Only in a few particular cases should the other technical procedures (scintigraphy, further histological techniques,…) be proposed to the patient with a view to optimizing management.

Therapeutic management should be installed and followed-up by an endocrinologist. Surgical treatment should be performed by a cervical surgeon, ENT or other surgeon, whereas radiotherapy will usually be managed by the various disciplines involved.

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CME questions

1. What percentage of the population will present with a thyroid nodule on palpation of the thyroid gland?

    A – 1%
    B – 5%
    C – 10%
    D – 20%
    E – 50%

2. What percentage of a solitary thyroid nodule will be an adenoma?

    A – 10%
    B – 20%
    C – 50%
    D – 70%
    E – 90%

3. Which is the most common type of thyroid carcinoma?

    A – Papillary
    B – Follicular
    C – Insular
    D – Anaplastic
    E – Medullary

4. Which type of thyroid carcinoma has the most favourable prognosis?

    A – Papillary
    B – Follicular
    C – Insular
    D – Anaplastic
    E – Medullary

5. The Hürthle cell carcinoma is usually classified among which type of thyroid carcinoma?

    A – Papillary
    B – Follicular
    C – Insular
    D – Anaplastic
    E – Medullary

6. What is the first test that should be performed when facing a patient with a thyroid nodule?

    A – Limited biological assay
    B – Complete biological assay
    C – Fine-needle aspiration
    D – Ultrasound examination
    E – Scintigraphy

7. What percentage of "cold" nodules are malignant tumours?

   A – 2%
   B – 5%
   C – 10%
   D – 15%
   E – 25%

8. The risk of developing a recurrent nerve palsy following reoperation increases by:

   A – 10%
   B – 25%
   C – 50%
   D – 75%
   E – 100%

9. Should the fine-needle aspiration cytology report be non-diagnostic, one has to:

   A – Operate
   B – Treat medically
   C – Re-aspirate
   D – Perform a scintigraphy
   E – Perform a CT-scan

10. In the presence of a thyroid nodule, which of the following presents a greater risk of having a carcinoma?

    A – A woman aged 20 to 60 years
    B – A man aged 20 to 60
    C – A multi-nodular goitre
    D – A hot nodule
    E – Hashimoto's thyroiditis

Answers: 1B; 2E; 3A; 4A; 5B; 6A; 7C; 8E; 9C; 10B