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Consensus

Treatment of adult Graves' disease

Traitement de la maladie de Basedow de l'adulte

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Abstract

Treatment strategy in Graves' disease firstly requires recovery of euthyroid status by antithyroid therapy. Treatment modalities, precautions, advantages and side-effects are to be discussed with the patient. No particular treatment modality has demonstrated superiority. Pregnancy or pregnancy project affects choice of treatment and monitoring. Graves' orbitopathy is liable to be aggravated by iodine-131 treatment and requires pre-treatment assessment. Iodine-131 treatment aims at achieving hypothyroidism. Thyroid surgery for Graves' disease should preferably be performed by an expert team. In case of recurrence of hyperthyroidism, the various treatment options should be discussed with the patient. Empiric treatment of thyroid dermopathy uses local corticosteroids in occlusive dressing.

Keywords: Graves' disease; Surgery; Antithyroid drugs; Radioiodine; Orbitopathy; Pregnancy; Thyroid dermopathy

Résumé

La stratégie thérapeutique de la maladie de Basedow comporte, en premier lieu, le retour à l'euthyroïdie par un traitement antithyroïdien. Les modalités, précautions, avantages et effets indésirables du traitement doivent être discutés avec le patient. Il n'y a pas de preuve de la supériorité d'une modalité de traitement sur les autres. Une grossesse, ou un projet de grossesse, oriente le choix thérapeutique et les modalités de surveillance. Une orbitopathie basedowienne peut être aggravée par un traitement par iode 131, et nécessite une évaluation préthérapeutique. Le traitement par iode 131 vise à obtenir une hypothyroïdie. La chirurgie thyroïdienne pour maladie de Basedow doit être réalisée préférentiellement par une équipe experte. En cas de récidive d'hyperthyroïdie, les différentes options thérapeutiques doivent être rediscutées avec le patient. Le traitement empirique du myxœdème prétibial fait appel aux corticoïdes locaux en pansement occlusif.

Mots clés : Maladie de Basedow ; Chirurgie ; Radioiode ; Antithyroïdien ; Orbitopathie ; Grossesse ; Myxœdeme prétibial

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Hyperthyroidism in Graves' disease can be treated in 3 ways:

- by antithyroid drugs;
- by radioiodine destruction of the gland;
- by thyroidectomy [1–3].

The choice depends on objective medical criteria (risk of recurrence, indications and contraindications for each option) and on the patient's preference: i.e., expectations and fears. The pros and cons of each option should therefore be explained [1–6] (Table 1).

In recent years, treatment strategy has been improved by better assessment of the efficacy of the options and adaptation to the individual patient, partly thanks to active involvement of patients in the choice of treatment. However, strategy still remains influenced by local cultural and medical traditions [7,8]. Treatment acting on etiopathogenesis (i.e., on the autoimmune process) is lacking, leaving two approaches, both targeting the thyroid gland: blocking hormone synthesis by means of antithyroid drugs, or destroying the gland by radioiodine or surgery. Antithyroid drugs are presently the only means of cure not requiring long-term definitive treatment. Surgery always requires long-course thyroid hormone replacement therapy, as usually does iodine-131 treatment. The risk of recurrence after 12–18 months' drug treatment is around 50%, and theoretically higher in certain sub-populations: male gender, smoker, severe hyperthyroidism, large goiter and elevated anti TSH-R antibodies. These factors are significant at sub-population level, but usually insufficiently predictive at individual level, except in the case of goiter > 80 mL [4].

Table 1
Comparison of the three possible therapeutic options.

Treatment	Advantages	Drawbacks
Antithyroid drugs	Avoids risks related to radioiodine	Risk of recurrence
	Avoids risks related to surgery and anesthesia	Requires frequent biologic control
	Lower risk of permanent hypothyroidism	Mild but frequent side-effects
	Outpatient treatment	Rare but possible severe side-effects
Radioiodine	Definitive treatment of hyperthyroidism	Radiation-related risks
	Avoids risks related to surgery and anesthesia	Possible aggravation of orbitopathy
	Short outpatient treatment	Adherence to radioprotection rules
	Fairly quick definitive control of hyperthyroidism	Less effective in large goiters
	Low cost	May require second course
	Side-effects are rare, mild and transient	Very frequent induction of hypothyroidism
	Thyroid volume often normal by 1 year	
Surgery	Definitive treatment of hyperthyroidism	High cost
	Avoids risks related to radioiodine	Requires hospital admission
	Thyroid function very quickly normal	Anesthesia risks
	Histologic diagnosis possible	Risk of secondary hypoparathyroidism (1–2%) and recurrent nerve lesion (1–2%)
	Very effective for compression syndrome	Risks of bleeding, infection and esthetic blemish
		Definitive hypothyroidism

Choice of treatment strategy is a major element of management. As none of the 3 options shows clear superiority [3], the feasibility, advantages and drawbacks of each should be discussed in detail with the patient and family [5]. Where there are no specific contraindications, the patient's fears and expectations can be taken fully into account. Antithyroid drug treatment will tend to be chosen by patients for whom possible remission is important and who wish to avoid long-course thyroid hormone treatment; however, they will have to accept the necessity of biological monitoring and a risk of recurrence. Radioiodine will tend to be chosen by patients seeking relatively rapid definitive control of hyperthyroidism but not wishing to undergo surgery, and who are willing to accept irradiation and the need for long-course thyroid hormone treatment. And surgery will tend to be chosen by patients seeking very rapid definitive control of hyperthyroidism but not wishing to be exposed to radiation and who are not unduly worried about the risks inherent to surgery – and for whom an experienced medical and surgical team is available [1,2,4,5,7,8].

A famous prospective study compared the 3 options. Patients were informed volunteers with equivalent clinical presentation of Graves' hyperthyroidism, and were randomized between treatment groups. Follow-up was greater than 10 years. More than 90% of patients were satisfied with their treatment, with no significant differences according to option [9].

> Recommendation 1. Choice of treatment for Graves' disease should be made in discussion with the patient, after explanation of the respective advantages and drawbacks of the three classical options. Specialist opinion is needed to choose the appropriate treatment and determine the monitoring program.
> 1/++.

1. Medical treatment of Graves' disease

1.1. Role of antithyroid drugs in the treatment strategy for Graves' disease

In the treatment strategy plan for Graves' disease, antithyroid drugs feature in 2 indications:

- they are recommended in first line in the vast majority of cases, to restore euthyroid status within a few weeks. This is essential, enabling the patient to discuss the various treatment options while under euthyroid conditions. Recovery of euthyroid status is in any case preferable prior to surgery or iodine 131-therapy;
- they are used as long-course treatment, lasting 12 to 18 months, when the "medical" option is chosen, in hope of obtaining final remission.

Recommendation 2. Whichever treatment option is chosen, an adapted dose of antithyroid drugs should be prescribed in first line to restore euthyroid status.
1/++.

1.2. Antithyroid drugs in the treatment of Graves' disease

Thionamide-class antithyroid drugs have been used in Graves' disease for more than 60 years. The class comprises 2 families: imidazolines, with carbimazole and its active metabolite thiamazole (also known as methimazole), and thiouracil derivatives, with propylthiouracil (PTU) and benzylthiouracil. After almost total digestive absorption, thionamides are taken up and concentrated by the thyroid cells, blocking thyroid hormone synthesis. PTU, when at high dose, also blocks deiodination of T4 into T3. Antithyroid treatment reduces blood thyroid hormone levels [10]. In most cases, there is reduction or abolition of blood TSH-R antibody levels, with remission of Graves' disease in about 50% of cases, defined as maintained euthyroid status for at least 1 year after treatment termination [11]. Questions remain regarding a real immunomodulation effect and the nature of the observed remission, the mechanism of which is not understood.

Four antithyroid drugs are available in France: thiamazole (methimazole), carbimazole, PTU and benzylthiouracil. It is generally agreed that carbimazole 10 mg shows the same efficacy as 6 mg thiamazole. For practical reasons, the French Society of Endocrinology suggests the following equivalences: 1 tab. carbimazole 20 mg is equivalent to 15 mg thiamazole and 200 mg PTU.

Thiamazole or carbimazole are preferable to PTU, which shows rare but potentially severe toxicity and is now restricted to 2 situations: 1st trimester of pregnancy, or in case of thiamazole intolerance with refusal, contraindication or impossibility of alternative treatment. Thiamazole has 2 advantages over PTU: its pharmacokinetics requires a single dose per 24 h, versus 3 for PTU [12], and side-effects are generally less severe. Resistance to antithyroid drugs, if any, is exceptional; most cases of apparent resistance turn out rather to be pseudo-resistance due to defective adherence [13].

Recommendation 3. To control hyperthyroidism, thiamazole and carbimazole are preferable to propylthiouracil, except in the first trimester of pregnancy or in case of pregnancy project.
1/++ [14,15].

1.2.1. Tolerance of antithyroid treatment

Antithyroid treatments show toxicity, with frequency and mechanisms not always perfectly known. "Minor" toxicity may cause discomfort but is generally not serious, while "major" toxicity may require treatment termination.

1.2.1.1. Minor toxicity. Skin reactions such as rash or urticaria occur in 5–10% of patients, and are generally well-controlled by antihistamines [14,15]. Joint or muscle/tendon pain occurs in 1–5% of cases and, although not serious, can be disabling and may also be the inaugural symptom of vasculitis, which is a major but fortunately rare complication [14,15].

Moderate biological hepatitis was found in 14–28% of patients in series in which liver transaminase assay was systematic and regular, mainly during the first 2 months of treatment [16,17]. Spontaneous normalization is the rule, even when treatment is prolonged at low dose. Clinical hepatitis (icterus, pruritus, pale stools) is found in 1–1.2% of patients, and necessitates treatment termination.

In analyzing biological findings, it is necessary to take account of abnormalities induced by hyperthyroidism as such: it is progression and severity that implicate the antithyroid treatment in transaminase elevation.

After antithyroid treatment termination for minor side-effects, the probability of side-effects under a different antithyroid drug is unchanged, with no extra risk except for liver toxicity when thiamazole is replaced by PTU [15].

1.2.1.2. Major toxicity. There are 3 major complications associated with antithyroid treatment.

Agranulocytosis (polymorphonuclear neutrophils (PMN) $< 500/mm^3$) occurs during 0.15–0.45% of antithyroid treatments. It is thought to be immune-allergic, and hence relatively unpredictable. Absolute neutrophil count on systematic monitoring is normal in more than 60% of patients during the 2 weeks prior to onset of agranulocytosis, making monitoring scarcely contributive. Risk factors are genetic, with results varying between study populations (e.g., HLA-B27:05, specifically in Caucasian subjects) [18]. High-dose antithyroid drugs are also associated with increased risk. Most cases of agranulocytosis have onset within the first 3 months of treatment.

Patients need to be informed of this risk and of how to respond. Treatment should be stopped in case of PMN $< 1{,}000/mm^3$, although a lower threshold of $800/mm^3$ has been suggested due to the high rate of spontaneous pre-treatment moderate neutropenia in hyperthyroidism.

If systematic complete blood-count monitoring is implemented, it should begin before antithyroid treatment given the above-mentioned risk of neutropenia in Graves' disease.

Antithyroid treatment should be stopped in case of onset of agranulocytosis. Use of granulocyte colony-stimulating factors is debated. Risk of recurrence of agranulocytosis on introducing a different antithyroid drug is estimated at 50% (based on the frequency of cross allergy); it is therefore strictly contraindicated to reintroduce thionamides after agranulocytosis. There are also some very rare cases of anemia or pancytopenia associated with antithyroid treatment.

Recommendation 4. Despite the summary of product characteristics for antithyroid drugs, there is no strong evidence for or against systematic blood-count monitoring during treatment. If such monitoring is implemented, it should begin with a pre-treatment blood count.
2/++.

Recommendation 5. Emergency blood count should be performed in case of any symptoms of infection or onset of pharyngitis during antithyroid drug treatment. Polymorphonuclear neutrophil count < 800/mm^3 requires termination of antithyroid treatment and definitively contraindicates reintroduction of thionamides.
1/+++.

1.2.1.2.1. Severe to fulminant hepatitis and hepatocellular failure. Clinical hepatitis occurs in 1–1.2% of patients under PTU [16]. Fulminant hepatitis and hepatocellular failure rates are estimated at 1/10,000 in adults and (probably more reliably) 1/1,000 in children [14,19]. Fulminant forms are mainly if not exclusively associated with PTU. It should be borne in mind that the largest prospective series concerned Asian populations, and extrapolation to Caucasian populations may be hazardous.

A study with systematic monitoring of transaminases in a Chinese population found that moderate hepatitis nevertheless requiring hospital admission was more often associated with thiamazole or carbimazole (3/1000 versus 1.2/1000), and severe forms involving liver failure with PTU; cholestasis was associated in the same proportions with both [16,20].

There are probably several different liver toxicity mechanisms operating between simple moderate transaminase elevation and severe clinical hepatitis, probably involving immuno-allergic reaction and free radical detoxification defect. There seems to be female predominance, which probably induces bias against PTU, which is frequently prescribed for women of child-bearing age. Most treatment terminations for hepatotoxicity are made within 3 months of treatment initiation. Systematic transaminase monitoring probably does not ensure against fulminant forms. Pregnancy, however, is a particular situation, with more frequent impairment of liver function.

Recommendation 6. Given the risk of severe hepatitis, PTU should be reserved for cases of pregnancy or pregnancy project, minor thiamazole allergy and some situations of iodine overload. There is no strong evidence for or against systematic transaminase monitoring. Onset of clinical and/or severe hepatitis (transaminase > 3 times upper normal limit) requires termination of antithyroid treatment.
1/++.

1.2.1.2.2. Vasculitis. One complication of antithyroid treatment that can sometimes be extremely serious is onset of vasculitis, manifesting as joint pain, fever and skin lesions, or multi-organ failure. Simple positive findings for anti-neutrophil antibodies, which are frequent in antithyroid treatment and more frequent at baseline in Graves' disease than in the general population, do not in themselves indicate vasculitis [21–23]. Systematic screening for anti-neutrophil antibodies in antithyroid treatment cannot be recommended, as significance is unknown in this context (i.e., poor predictive value).

Recommendation 7. There is no strong evidence in favor of systematic anti-neutrophil antibody monitoring.
2/+.

Recommendation 8. The patient should be informed, ideally in writing, about possible minor and major side-effects of antithyroid treatment, inaugural signs and the procedure to be followed in case of onset.
1/++.

1.2.2. Antithyroid drug dose as primary treatment for Graves' hyperthyroidism

Primary antithyroid drug treatment aims to normalize thyroid function rapidly, whatever the definitive treatment option. Initial daily dose is usually around 20–40 mg carbimazole or 15–30 mg thiamazole. There have been few studies correlating biological intensity of hyperthyroidism and initial antithyroid drug dose efficacy. Several studies showed that time to normalization of thyroxinemia is shorter with 40 than 10 mg thiamazole (83% vs 68% of patients at 3 weeks) [24,25]. This greater efficacy of higher doses is especially clear in severe hyperthyroidism. In a Japanese study, 40% of patients with FT4 > 7 ng/dl

(90 pmol/l) receiving 30 mg thiamazole recovered euthyroid status by 4 weeks, versus 15% of those receiving 15 mg and 13% of those receiving 300 mg PTU [26]. Likewise, another study showed that, with 20 mg carbimazole daily, most patients with total T4 > 21 μg/dl remained hyperthyroid at 4 weeks' treatment, unlike those receiving 40 mg [27]. In mild hyperthyroidism, on the other hand, 30 mg thiamazole seemed no more effective than 15 mg [26].

Initial dose should therefore be adapted to biological severity. We recommend an initial dose of 40 mg carbimazole or 30 mg thiamazole if FT4 concentration is 3 to 4 times the upper limit of normal; for lower FT4 levels, 20–30 mg carbimazole or 15–20 mg thiamazole is probably sufficient. At usual dose, PTU is clearly less powerful than thiamazole, which is another reason why it should not be used in first line (see Recommendation 6). Other than in the very particular case of iodine contamination, euthyroid status classically recovers more slowly in case of high iodine intake. Azizi reported that recovery was faster in Teheran, where moderate iodine deficiency is prevalent, than in Boston, where iodine intake is normal [28]. A European study conducted in several countries likewise found that subjects with ioduria > 100 μg/g creatinine responded more slowly to antithyroid treatment than those with < 50 μg/g creatinine [25]. The main lesson of these studies is that literature data on thyroid pathology should always be interpreted according to iodine intake in the geographical study region; in France, there is persistent moderate iodine deficiency [29,30]. Large goiter also slows recovery of euthyroid status.

Recommendation 9. Initial antithyroid drug dose should be adjusted to hyperthyroidism severity. Recommended initial doses are 40 mg daily for carbimazole and 30 mg daily for thiamazole if FT4 concentration is > 3–4 times the upper limit of normal; at lower concentrations, doses are 20–30 mg carbimazole or 15–20 mg thiamazole.
1/++.

1.2.3. Subsequent antithyroid drug treatment: the "medical" option

After recovery of euthyroid status, two medical protocols are available.

- isolated antithyroid drugs: dose should be adjusted to the minimum needed to maintain euthyroid status, and reassessed according to each biological control;
- "Combined" (block-replace) treatment: blocking dose of antithyroid drugs (usually 30 mg carbimazole or 20 mg thiamazole) associated to levothyroxine on recovery of euthyroid status. Initial levothyroxine dose is usually about 1.6–1.7 μg/kg/day, reassessed according to each biological control.

There is presently no evidence for superiority of one protocol or the other. A 2010 Cochrane review found no difference in recurrence [31]; there were significantly more side-effects in combined treatment, but mainly in patients receiving much higher antithyroid drug doses than nowadays recommended. The theoretic advantage of combined treatment is to improve thyroid function stability. A 2014 retrospective study, however, reported no significant differences in onset of hyper- or hypo-thyroidism according to protocol [32].

There is thus no evidence recommending one protocol rather than the other, and the choice is mainly a matter of the clinician's habits.

Recommendation 10. The "adapted" and "combined" treatment protocols show equal efficacy. The choice is up to the clinician and his or her usual practice, taking account of the patient's preference.
No recommendations. No evidence in favor of one or other protocol.

1.2.4. Optimal treatment duration to limit recurrence

Few high-quality studies have focused on treatment duration impact on recurrence within 1 year of treatment termination. The above-mentioned Cochrane review recommended a minimum 12 months, based on just 4 studies, 1 of which used isolated antithyroid drugs and another combined treatment [31,33,34]; the strength of the recommendation came mainly from the isolated antithyroid drug study [33]. Other studies are needed to determine whether less than 12 months' treatment can be sufficient in some cases. No studies have reported benefit for durations exceeding 18 months.

Recommendation 11. Whichever the treatment protocol, standard duration is 12–18 months.
1/++.

1.2.5. Monitoring and follow-up of antithyroid drug treatment

During treatment initiation, dose is adapted according to FT4 and/or FT3 concentrations. TSH concentration may remain below normal for several weeks after normalization of thyroid function, and is not relevant at this stage. In the initial treatment phase, FT3 should be assayed in case of Graves' disease with normal FT4 and elevated FT3 [35,36]. Thyroid hormone assay should be performed 3 to 4 weeks after treatment initiation, then monthly until recovery of euthyroid status.

During the 12–18 months' treatment, control frequency depends on the protocol and on stability of results: once every 2–3 months for treatment by adapted doses, and once every

3–4 months for combined treatment. The objective is to maintain euthyroid status throughout treatment while avoiding iatrogenic hypothyroidism. In case of Graves' orbitopathy, it is especially important to avoid iatrogenic hypothyroidism, which can aggravate the orbitopathy.

Recommendation 12. During the euthyroid recovery phase, hormonal monitoring of antithyroid treatment mainly consists in FT4 ± FT3 assay. It should be at least monthly until recovery of euthyroid status, defined as normalized FT4 ± FT3. TSH may remain below normal for 1 month or more after normalization of thyroid function, and thus serves to assess euthyroid status only secondarily.
1/++.

Recommendation 13. After recovery of euthyroid status and normalization of TSH, hormonal monitoring of antithyroid treatment consists in TSH and FT4 assay at appropriate intervals: at least every 2 months in adapted dose treatment, and every 4 months for combined treatment. Intervals may be shortened in case of change in dose or unstable results.
1/++.

1.2.6. Treatment termination modalities

Before terminating antithyroid drug treatment, recurrence risk needs assessing. As seen above, the risk of relapse or recurrence of hyperthyroidism is generally higher in smokers and males, but failure to reduce goiter volume, persistent thyroid gland hypervascularization and significant anti-TSH-R antibody levels at end of treatment are also predictive of high risk of recurrence. Likewise, in the "adapted dose" protocol, the need to maintain fairly high antithyroid drug doses after several months' treatment suggests continued thyroid hyperfunction and is therefore a major risk factor for recurrence at end of antithyroid drug treatment. Anti-TSH-R antibodies should be assayed at end of treatment to assess recurrence risk. Thyroid volume and vascularization are assessed on ultrasound, but this examination need not be systematic unless ultrasound findings at start of treatment require control at 1 year (e.g., for nodular thyroid). Antithyroid drugs and any concomitant levothyroxine should be stopped completely at the end of the 12–18 month course; persistence of recurrence risk factors does not mean treatment should not be terminated. If, however, the patient so wishes for personal reasons, antithyroid drugs may be continued for a few months. In case of high recurrence risk, treatment options in case of recurrence should be discussed with the patient.

1.2.7. Monitoring after end of treatment

Recurrence is usually within 3–6 months of end of treatment. Risk then diminishes and plateaus after 1 or 2 years. Special attention should be paid to postpartum women: 70%

Recommendation 14. Anti-TSH-R antibody assay is recommended at the end of the standard treatment course to assess recurrence risk at end of treatment.
1/++.

of women in remission of Graves' disease show recurrence or thyroiditis postpartum. In all cases, thyroid function should be monitored systematically for 1 year: at 3–4 weeks after end of treatment, then every 3 months or in case of clinical recurrence. The patient can be considered to be in remission if thyroid function remains normal 1 year after termination of antithyroid drugs. Thereafter, monitoring should be clinical, to detect recurrence of hyperthyroidism. Yearly or 2-yearly biological follow-up is recommended, to diagnose progression toward hypothyroidism, which may occur spontaneously even without radioiodine treatment or thyroidectomy in 5–20% of cases [37–39].

1.2.8. Procedure in case of recurrence

Recurrence of hyperthyroidism is defined by return to elevated FT4 associated with below-normal TSH. Predominant or exclusive FT3 elevation is more frequent in recurrence. When recurrence is proven, the various options should be discussed again with the patient [40]. If not contraindicated, impossible or refused by the patient, in most cases radical radioiodine or surgical treatment should be chosen. However, a second course of antithyroid drugs is also a valid option; 2 possibilities have been studied: second antithyroid treatment conducted classically as described above, or long-course low-dose treatment. Very few studies have analyzed whether the chances of remission are different after a second classical antithyroid drug treatment. A recent Chinese study reported more than 75% remission 48 months after a second classical antithyroid course in monotherapy [41]; but it remains to be determined whether these findings apply in other geographical regions. There have been no studies of remission after a second course of combined treatment. Maintaining low-dose antithyroid drugs for several years is another option in some cases, especially for patients refusing radical treatment, and compares favorably to radioiodine in terms of thyroid function stability and progression of orbitopathy [42–44]. However, even if antithyroid drugs are not contraindicated, a long-course low-dose regimen requires good adherence, regular follow-up and a low effective dose ($\leq$ 5 mg thiamazole daily) able to maintain stable euthyroid status and normalized TSH and FT4 levels. The option moreover is not applicable in case of significant or large goiter.

1.3. Role of β-blockers

Beta-blockers are useful in initial treatment of Graves' disease before thyroid function has been normalized. They reduce the adrenergic symptoms of hyperthyroidism: trembling, palpitation, tachycardia, intolerance of heat. Some decrease T4 conversion into T3 in peripheral tissue, but only at high dose

Recommendation 15. In case of recurrence of hyperthyroidism after termination of antithyroid drug treatment, treatment options (second classical antithyroid course or radical treatment by radioiodine or surgery) should be discussed again with the patient in the light of the clinical data; in particular cases, long-course low-dose antithyroid drug treatment is an option.
2/+.

(> 160 mg propranolol). There is no evidence of superiority of one compound over another. Classic doses are 40–160 mg propranolol or 25–100 mg atenolol. The usual contraindications for β-blockers apply; notably, caution should be taken in case of asthma, congestive heart failure, bradycardia and Raynaud's phenomenon. There is no interest in continuing treatment after recovery of euthyroid status.

Recommendation 16. If not contraindicated, β-blockers can be used in elderly patients with symptomatic hyperthyroidism and any patient with resting heart rate > 90–100/min. They may be considered in all symptomatic subjects.
1/++.

1.4. Does iodide have a role in medical treatment of "common" Graves' disease?

Until the advent of antithyroid drugs in the 1940s, iodide, in the form of saturated potassium or sodium iodide solution or Lugol's iodine-iodide solution, was a widespread remedy for hyperthyroidism in Graves' disease. High thyroid iodine concentration inhibits thyroid secretion and T4 and T3 synthesis, the latter by blocking thyroperoxidase by Wolff-Chaïkoff effect. These effects have rapid onset. However, synthesis inhibition is transient, due to physiological diminution of the Wolff-Chaïkoff effect within 3 to 6 weeks after blockage. Obviously, the advent of antithyroid drugs made iodide obsolete in this indication, unlike in the treatment of thyrotoxic storm and acute hyperthyroid episodes. Recently, however, several studies, mainly in Japan and also in South Korea demonstrated efficacy for potassium iodide in hyperthyroidism in common Graves' disease [1,45].

At 10–400 mg daily, either alone or especially associated with thiamazole 15 mg daily, iodide restores biological euthyroidism more quickly than isolated thiamazole [46–48].

Prolonged potassium iodide treatment, for 1 year or longer, is possible, but remission rates do not differ between thiamazole and iodide. Tolerance is good; iodide is indicated basically in case of thiamazole intolerance [49].

A study conducted during the first trimester of pregnancy, which is another indication, demonstrated efficacy and safety for both mother and fetus [50].

Three important points need to be made:

- all of these studies were conducted in geographical regions with particularly high iodine intake (ioduria, 300–700 μg/day) [51]; extrapolation to regions with lower intake is hazardous;
- at least as far as isolated iodide is concerned, the studies concerns relatively mild hyperthyroidism;
- in Europe, and in France in particular, lack of experience of the use of iodide in common Graves' hyperthyroidism argues against clinical application; if it seems important to introduce it, prospective randomized controlled trials will be necessary. The only certain role of iodide is in surgical preparation in Graves' disease in patients showing severe side-effects contraindicating antithyroid drugs to normalize thyroid function ahead of surgery.

1.5. Immunosuppression treatment

Although Graves' disease is an autoimmune pathology, mediated by B-cell deregulation with the involvement of a pathogen (anti-TSH-R antibodies), it has yet, unlike systemic autoimmune diseases, to find an effective means of treatment by immunomodulation. A few very limited corticosteroid trials have not been sufficiently convincing to justify more systematic studies [52,53].

In Graves' orbitopathy, on the other hand, some studies reported a certain response to conventional immune-suppressors and, more recently, to rituximab, an anti-CD20 monoclonal antibody targeting B cells. Collaterally, without any large-scale dedicated prospective randomized studies, some light was shed on the possible impact of rituximab on Graves' disease itself; in a series of 20 patients, 4 of the 10 receiving rituximab were in remission at 1 year, versus none of the 10 not treated by rituximab [54].

In a study of 9 patients with orbitopathy treated by rituximab, thyroid function at 1 year was not specifically affected by rituximab treatment, whatever the baseline thyroid status [55]. And a prospective study, although with only 13 patients with relapsed Graves' disease, found a lower rate of subsequent recurrence with rituximab [56].

Studies of the effect of rituximab on circulating anti-TSH-R antibody levels, despite certain differences in results, reported no change or else slight reduction. Series comparing glucocorticoids versus rituximab found no significantly greater effect of rituximab than of corticosteroids or antithyroid drugs on anti-TSH-R antibody levels [57–59]. This may be because plasmocytes not expressing the CD20 marker are not depleted by rituximab.

Finally there also seems at present to be no clear impact of rituximab on the process of Graves' disease itself. However, as suggested above, results from the limited studies conducted so far suggest that rituximab might reduce recurrence risk in Graves' disease. The question at this point is whether prospective

randomized controlled studies testing the hypothesis would be worthwhile, biologically and also in terms of cost-effectiveness and risk/benefit [60].

2. Radioiodine treatment in Graves' hyperthyroidism

2.1. Indications

In Europe, radioiodine is mainly indicated in case of failure of well-conducted medical treatment, but may also be used in first line. The physician's choice should take account of absolute and relative contraindications.

Treatment indications in adults are dealt with as a whole alongside contributions to treatment in general at the beginning of the present article.

Here we simply detail contraindications and precautions.

Absolute contraindications:

- pregnancy or project for the coming 4–6 months (being the minimal time to recovery of euthyroid status while respecting radioprotection criteria);
- breast-feeding;
- thyroid nodule suggesting thyroid cancer on cytology;
- patient unable to adhere to radioprotection rules.

Relative contraindications:

- urinary incontinence;
- dialysis;
- compressive goiter;
- risk of treatment failure: low thyroid fixation on scintigraphy, or goiter > 60–80 g;
- severe and/or active orbitopathy (clinical activity score ≥ 3);
- pregnancy project for the 2 years following treatment, due to anti-TSH-R antibody elevation following radio-isotope treatment.

2.2. Preparation

Radio-isotope treatment can cause early transient aggravation of hyperthyroidism due to the cytolytic effect of radiation [61–64]. Depending on the report, this occurs in 10–15% of cases, and is usually moderate, without clinical impact. Severe thyrotoxic forms are rare: 0.3–0.5% of cases [65].

In symptomatic forms and/or significant hyperthyroidism, beta-blocker preparation should be systematic if not contraindicated, to improve comfort and prevent aggravation by treatment [66]. Medical preparation by antithyroid drugs accelerates recovery of euthyroid status and improves treatment tolerance by avoiding complications during the phase of transient aggravation of hyperthyroidism. Antithyroid drug treatment associated to the radioiodine treatment is recommended if not contraindicated or poorly tolerated, especially in fragile patients (elderly, or with cardiovascular history) and/or patients with hyperthyroid complications (notably cardiothyreosis) or in case of very symptomatic or severe thyrotoxicosis. Antithyroid drugs, however, are liable to impair the efficacy of radioiodine by reducing iodine uptake and free radical production, thus delaying recovery of euthyroid status and increasing the rate of failure [67–70]. In a meta-analysis by Walter et al. [70], radioiodine efficacy was reduced when antithyroid drugs were administered in the 7 days preceding or following radioiodine administration, with no difference between thiouracil derivatives and imidazole derivatives (carbimazole/thiamazole). It is therefore generally recommended to interrupt treatment for 3 to 7 days around radioiodine administration, although there is no consensus as to optimal interruption. The alternative in fragile or highly symptomatic patients is to continue antithyroid drug treatment with increased radioactive dose.

When antithyroid drugs are contraindicated, lithium has been proposed; its action mechanism enhances treatment efficacy, allowing lower radioactivity [61,71–73]. Tolerance is satisfactory if contraindications are respected and overdosing is avoided.

Recommendation 17

- 17a. Before administration of radioiodine, beta-blocker treatment should be systematic in symptomatic hyperthyroidism, due to the risk of transient aggravation of hyperthyroidism following treatment, or when antithyroid drugs are contraindicated or poorly tolerated. 1/++.
- 17b. Medical preparation by antithyroid drugs is helpful when not contraindicated or poorly tolerated, especially in fragile patients (elderly, highly symptomatic, with thyroid hormone elevation or cardiovascular history). When prescribed, antithyroid treatment should be interrupted during 3–7 days around radioiodine treatment, although there is no consensus on optimal interruption duration. 2/++.

2.3. Dosage and administration modalities

Radioiodine has been widely used in Graves' disease for more than 60 years, with proven efficacy and safety [74]. Yet, even after all this time, treatment modalities, and dosage in particular, remain controversial.

Two dosage methods are generally used: (i) ablative, by standardized activity estimate, with fixed activity for all patients or approximate adaptation to thyroid volume and estimated fixation; or (ii) adjusted, with dosage based on uptake at 4 and 24 hours after test-dose administration, combined with estimated thyroid volume.

Many randomized and non-randomized studies have addressed this issue [75–83]. The theoretic interest of dose adjustment is to obtain euthyroid status with an "ALARA" (as low as reasonable achievable) radiation dose. Most of

these studies were included in a relatively old systematic review [84], which found no significant difference between the two approaches, whether in terms of achieving euthyroid status (44 ± 19%) or of curing hyperthyroidism (euthyroidism or hypothyroidism: 73 ± 14%). Even so, high-dose ablation (> 10–15 mCi) achieved success rates exceeding 80% [83,85]. With the dose-adjustment method, euthyroid status is rarely achieved and diminishes over follow-up, as incidence of post-radioiodine hypothyroidism increases year on year [86]. These results are probably due to calculation methods, which vary between studies and, if they are to provide an exact estimate of the radiation dose absorbed by the gland, take account of several factors: age, gender, disease severity and inter- and intra-subject variation in thyroid metabolism under Graves' disease [87]. Moreover, the dose-adjustment method does not always result in a lower administered dose, which can sometimes be even higher than the fixed ablative dose [76,79,80,82]. In the fixed-dose ablative strategy, it is generally agreed that hypothyroidism rates are greater with higher doses [77,85,88,89]; however, some studies showed that, above a threshold of 550–600 MBq (15 mCi), there is no obvious benefit with increased dose [90–92], even when thyroid volume is large [90].

Recommendation 18

- 18a. In Graves' disease, an "ablative" strategy is more appropriate than a "dose-adjustment" strategy. The administered radioiodine dose should be such as to achieve hypothyroidism. 1/++.
- 18b. There is no preferable method for determining radioiodine dose: fixed or adjusted dose methods may both be used. However, fixed or semi-fixed dose methods have the advantage of simplicity. (No recommendation; no grade).
- 18c. Whichever method is chosen, thyroid ultrasound and scintigraphy imaging assessment should be performed. Ultrasound characterizes any nodules, and measures thyroid volume. Scintigraphy, with iodine-123 or technetium-99^{m}, measures fixation under the same conditions as actual treatment (with interruption of antithyroid drugs if necessary). 1/++.

2.4. Precautions and radioprotection

2.4.1. Specific precautions for pregnancy and breast-feeding

Pregnancy and breast-feeding are the only absolute contraindications to iodine-131 treatment [66,93–95]. Depending on the country, pregnancy testing in women of child-bearing age is recommended between 24 and 72 hours ahead of administration [66,94,95]. Breast-feeding should be definitively terminated 4–6 weeks ahead of treatment, to minimize mammary irradiation and to protect the infant [96]. A recent study confirmed the findings of many previous case reports, with very high iodine-131 concentrations in breast milk due to sodium/iodide symporters (Na+/I−: NIS) in mammary gland cells [96,97]; activity level in the breast milk averaged 30% of the administered dose, with 29 mSv received by the infant per MBq administered to the mother, well above the recommended ceiling of 1 mSv per year [96,97]. Treatment should also be followed by 6 months' effective contraception, to ensure stable euthyroid status before any pregnancy is considered. Paternity projects should likewise be postponed for at least 4 months to allow spermatozoid turnover [66].

Recommendation 19

- 19a. Pregnancy testing should be performed at most 72 hours before iodine-131 treatment in women of child-bearing age. 1/++.
- 19b. Breast-feeding should be definitively terminated at least 4 weeks before treatment. 1/++.
- 19c. Treatment should be followed by 6 months' effective contraception. 1/++.

2.4.2. Patient information on precautions and radioprotection

In line with the French January 21, 2004 Decree on information to persons exposed to ionizing radiation in nuclear medicine, patient information should comprise:

- treatment objective (euthyroidism or eradication of hyperthyroidism) and strategy (ablative or adjusted dose);
- list of medication to be suspended, foods and vitamin supplements to be avoided, and duration of such adjustment;
- risk of treatment failure and strategy in case of failure;
- risk of onset or aggravation of ophthalmopathy, role of smoking, and procedure in case of ocular symptoms;
- early side-effects (increased hyperthyroidism, increased thyroid volume) and long-term side-effects (hypothyroidism);
- specific precautions for pregnancy and breast-feeding (see above);
- specific precautions for radioprotection of family and public (see below);
- specific precautions to minimize non-thyroid irradiation of patient (see below).

2.4.3. Specific precautions for radioprotection of family and public

These precautions are in line with Decree n^{o} 2003-2070 of March 24, 2003 on protection of persons exposed to ionizing radiation for medical and medico-legal purposes, setting a 1 mSv ceiling on irradiation of the general public. This implies certain life-style recommendations for patients receiving radioiodine treatment, to minimize irradiation of

those living under the same roof, or encountered in the workplace or in public transport, especially as concerns young children and pregnant women. Adhering to these recommendations, the 1 mSv ceiling requires administered doses < 20 mCi (740 Mbq), and any need for higher doses entails hospital admission. The 1998 European Directive [93] by the European Atomic Energy Commission (EURATOM) identifies two main categories of persons at risk of exposure to ionizing radiation from patients treated with radioiodine: family and close friends, and third parties (general public) (https://ec.europa.eu/energy/sites/ener/files/documents/097_en.pdf); this allows some flexibility for those directly involved in providing support and comfort to the patient. Specific radioprotection precautions were based on dosimetric studies of patients' families [98–102]. They should be specific to hyperthyroidism, as distinct from thyroid cancer; in the latter, patients have undergone prior total or subtotal thyroidectomy [103,104] and, despite high administered doses, the patient's dose rate is lower and the iodine-131 half-life much shorter. In patients' families, 5 subgroups are distinguished: pregnant women, children under 2 years of age, 3–10 year-olds, spouses, and spouses over 60 years of age. Under-10 year-olds are more sensitive to ionizing radiation, and this goes for fetuses in the womb. Under-2 year-olds are liable to be in closer contact with their parents [99], and may sometimes be put under the care of a third party. As for over-60 year-olds, their shorter life expectancy reduces the risk of radiation-induced cancer. The dose ceiling may thus be increased to 3 mSv for 10-to-60 year-olds, who have a theoretic risk of radiation-induced cancer 2–3-fold lower than fetuses and under-10 year-olds, while still allowing a mean dose of 5 mSv over 5 consecutive years not to be exceeded, and increased to 15 mCi for over-60 year-olds, whose risk is 3–10-fold lower [93]. The French Society of Nuclear Medicine (SFMN) has detailed restricted contact duration according to dose: http://www.sfmn.org/index.php/accueil/70-societe/guides-des-procedures/traitements/213-le-traitement-des-hyperthyroidies-par-l-iode-131?showall=1&limitstart=.

2.4.4. *Specific precautions to minimize non-thyroid irradiation of patients*

Hyperthyroidism is a risk factor for morbidity, and notably for long-term cardiovascular and cerebrovascular morbidity [105]. On the other hand, cardiovascular and oncogenic risk for radioiodine treatment of hyperthyroidism has never been clearly demonstrated [105–111]. A recent large-scale prospective study in Denmark [112] reported that excess overall and cardiovascular mortality was found in hyperthyroidism only in patients not controlled by treatment. Oncologically, no extra risk of leukemia or thyroid cancer has been shown [107–110]. It is nevertheless important to minimize irradiation of other organs, the most exposed being the stomach, intestines, salivary glands, lacrimal glands and bladder. The patient should be informed of appropriate precautions, basically involving adapted hydration.

2.4.5. *Specific precautions to prevent environmental contamination*

Radioactive waste, including gloves, capsule goblet, etc., should be treated in line with current legislation in departments administering radioiodine. In outpatient treatment, which is by far the most frequent case, the main source of contamination comprises protections worn for urinary incontinence; except in very particular cases such as antithyroid drug intolerance associated with contraindications for surgery and severe hyperthyroidism, urinary incontinence contraindicates radioiodine treatment in Graves' disease [94].

> Recommendation 20
> The physician administering radioiodine should inform the patient, orally and in writing, of the precautions to be taken following iodine-131 treatment.
> 1/+++.

2.5. *Follow-up after radioiodine treatment*

Most patients progress to hypothyroidism after a variable time and with risk increasing over time [85,92]. With fixed-dose ablative strategies, most patients reach hypothyroidism by 3 months [34]. More rarely, hypothyroidism may be merely transient, with secondary recovery of thyroid function and of euthyroid status, or even recurrence of hyperthyroidism [113]; this requires both early and prolonged biological monitoring. Onset of hypothyroidism may, in a non-negligible number of cases, be early, within the first month after treatment [92]. If untreated, it may induce a range of symptoms (asthenia, weight gain, depression, etc.), impaired quality of life [114,115] and, even more importantly, onset or aggravation of Graves' ophthalmopathy [116,117]. A recent study showed that, in ablative treatment, systematic early levothyroxine therapy to prevent secondary hypothyroidism improved quality of life, but did not reduce onset or aggravation of ophthalmopathy, which was found in only a very few cases [118]. The hypothalamus–pituitary axis may take some weeks to recover, and TSH often remains inhibited for 4–6 weeks [113]. During early follow-up, TSH assay should be associated to FT4 assay, to prevent misinterpretation; later, monitoring can be limited to TSH.

2.6. *Failure of iodine-131 treatment*

Apart from underdosing, risk factors for persistent hyperthyroidism (TSH undetectable, with or without thyroid hormone elevation) after radioiodine treatment comprise: young age, male gender, large thyroid (generally, > 60 g), poor thyroid iodine retention, and antithyroid medication [83,85]. Efficacy is

Recommendation 21

- 21a. After ablative radioiodine treatment, TSH and FT4 should be assayed at 4 weeks then every 4–6 weeks for 6 months. Specialist consultation should be scheduled for adapted hormone replacement therapy, to avoid complications due to severe hypothyroidism; this consultation can also assess orbital status. 1/+++.
- 21b. Once hormonal balance has been achieved, annual TSH assay is mandatory, without limit in time. 1/+++.

generally apparent within 4–6 months of administration; thus it is necessary to await late effects before considering second treatment.

Recommendation 22

- 22a. Treatment failure is defined by persistent hyperthyroidism 6–12 months after radioiodine treatment. 1/+++.
- 22b. In case of failure, a second treatment may be administered, avoiding excessively low doses (< 5–10 mCi, 185–370 MBq). 2/++.

2.7. Radioiodine and orbitopathy

Radioiodine treatment increases the risk of onset or aggravation of orbitopathy [116,119–125]. A recent Cochrane meta-analysis, in 2016 [126], included 2 randomized trials with 425 adults with Graves' disease, treated either by radioiodine or medically by antithyroid drugs, with 2 years' follow-up. Risk of onset or aggravation of orbitopathy was 38% in the radioiodine arm and 19% in the medical arm (RR = 1.94; 95%CI: 1.4–2.7).

Risk seems to be intrinsic, mainly involving antigen release due to the cytolytic impact of radiation [127,128]. Risk factors also include delayed treatment of iatrogenic hypothyroidism and TSH-R antibody level, but most importantly smoking [129–131]. In smokers, orbitopathy is more frequent, more severe and more resistant to treatment, often with onset after radioiodine administration [117,129].

In well-selected patients (mild or moderate non-inflammatory Graves' ophthalmopathy: CAS score, 0 or 1) with close specialist follow-up, risk is < 2%.

Orbitopathy thus does not formally contraindicate radioiodine treatment, but precautions are to be taken: patient information, strong encouragement to stop smoking, specialist ophthalmologic opinion, and close follow-up to avoid hypothyroidism [66,132].

Associated corticosteroids are recommended, to prevent aggravation [117,121,133,134]. Efficacy was confirmed in two recent meta-analyses [119,135]. Shiber et al. [135] reviewed 8 trials with 850 patients; 0.4–0.5 mg/kg/day corticosteroids for 3 months was highly effective in mild to moderate pre-existing orbitopathy (RR = 0.14; $p < 0.01$). Low doses of 0.2–0.3 mg/kg/day for 6 weeks were helpful in mild orbitopathy or in case of risk factors for orbital involvement (RR = 0.20; $P < 0.004$). However, corticotherapy was non-contributive in the absence of orbitopathy or risk factors. Preventive corticotherapy may be considered in case of risk factors without actual orbitopathy (elevated TSH-R antibodies, smoking) [136].

Likewise, the benefit of early thyroxine treatment at 2 weeks after administration is unproven [116,118,137]. By preventing post-treatment thyroid failure, it might reduce the risk of aggravating orbitopathy [137], but this was not confirmed in a recent French multicenter study, which nevertheless found improved quality of life under levothyroxine-4 [118]; however, in this study, patients were carefully selected and orbital events were few.

Recommendation 23

- 23a. Radioiodine incurs a risk of aggravating pre-existing orbitopathy or of inducing orbitopathy, especially in smokers. Radioiodine is not formally contraindicated by orbitopathy. However, indications are restricted to mild or moderate relatively inactive orbitopathy, with certain precautions: patient information, strong encouragement to stop smoking, specialist ophthalmologic opinion, oral corticotherapy and close follow-up to prevent onset of hypothyroidism. 1/+++.
- 23b. Evidence is lacking for systematic post-treatment levothyroxine replacement therapy in the in patients with risk factors (smoking, very high TSH-R antibody level) but no orbitopathy.
- In patients at high risk of orbitopathy or showing mild or inactive orbitopathy, thyroid function should be assessed on free T4 and TSH assay within 2 weeks of radioiodine administration. 1/++.

2.8. Nodules

Prevalence of nodules in Graves' disease is estimated at 10–15% on palpation, and 35–50% on ultrasound, close to rates in euthyroid goiter [138,139]. The risk of malignancy is not higher in Graves' disease than for nodules in general [140]. Radioiodine does not increase the risk of thyroid cancer. Prognosis for thyroid cancer arising in Graves' disease is debated: some authors reported that recurrence risk and mortality were

increased by the impact of TSH-R antibodies on oncogenic processes [141,142], while other more recent studies found no difference in prognosis whether thyroid cancer was associated with Graves' disease or not, although with a strong prevalence of microcarcinoma [143,144]. Death from cancer under Graves' disease was studied in 30,000 patients, and did not differ from that in the general population [109]. Therapeutic attitude should be as for any nodule, notably with fine-needle aspiration for nodules > 1 cm, suspect on ultrasound [66,139,145], as certain cytomorphologic particularities have been described, oncocytic aspects are frequent, and diagnosis may be difficult (e.g., in nodules with onset during thyroiditis) [139].

Recommendation 24

- 24a. Before radioiodine treatment, fine-needle aspiration should be performed in any nodule >1 cm and suspect on ultrasound. 1/+++.
- 24b. Radioiodine treatment may be performed in cytologically benign nodules. 1/++.
- 24c. Follow-up is as for thyroid nodule. 1/++.

Recommendation 25

- 25a. Surgery is not the first-line treatment in Graves' disease. 1/+.
- 25b. Surgery is indicated after failure of medical treatment or complications. 2/+.

Recommendation 26
Surgery should be performed under euthyroid status. 1/++.

Recommendation 27
Surgery should be performed in an expert center or center with high-volume thyroid surgery. 1/++.

3. Surgical treatment in graves' disease

3.1. Indications for surgery in Graves' disease

Indications for surgery in Graves' disease comprise contraindications, adverse effects or failure of medical treatment, contraindications for radioiodine, patient preferences, and physician's habits.

In Europe, surgery is often performed in second line after failure of medical treatment [1,146].

Surgery should preferably be performed under euthyroid status: free T4 below upper limit of normal, to avoid postoperative acute thyrotoxic episode [1,66]. Expert centers with high volume of thyroid surgery show no extra risk of recurrent nerve or parathyroid lesion with total than subtotal thyroidectomy [66].

Radioiodine achieves euthyroidism within 3–6 months, whereas surgery does so immediately, rapidly resolving symptoms related to hyperthyroidism. Radioiodine, like antithyroid drugs, requires a follow-up that can be made difficult by the patient's social situation. Thyroidectomy is therefore sometimes preferable [1].

Graves' disease incurs several complications: ocular (exophthalmia), cardiac, and psychological. These often require speedy resolution, as they induce many disabling symptoms [1,147,148]. Surgery has the advantage of rapidly resolving secondary symptoms in hyperthyroidism.

The relative risk of developing a thyroid nodule is 2.5 compared to the general population; depending on the study, thyroid cancer is found in 0–21% of cases (papillary microcarcinoma) [149]. Surgery is preferable to radioiodine treatment in orbitopathy and in case of suspicious thyroid nodule on ultrasound and/or fine-needle aspiration.

3.2. Type of surgery in Graves' disease, and extension

Two procedures are currently used in Graves' disease: total and subtotal thyroidectomy [150].

Both should be performed in expert centers with high volumes of thyroidectomy and in which recurrent nerve and parathyroid morbidity are regularly assessed [66,151].

Total thyroidectomy, removing the entire gland, precludes risk of recurrence. It rapidly resolves hyperthyroidism, but not always the autoimmune disease itself (Graves' disease). Moreover, in 20% of cases cancer is found in the thyroidectomy specimen, usually with one or several papillary microcarcinomas. Total thyroidectomy thus allows appropriate management in case of associated thyroid cancer that was overlooked preoperatively.

Complications of total thyroidectomy comprise inferior laryngeal or recurrent nerve lesion, superior laryngeal nerve lesion to a lesser degree, and postoperative hypocalcemia due to parathyroid gland devascularization [1], or from metabolic causes (hemodilution, calcitonin, osteodystrophy repair).

Subtotal thyroidectomy conserves about 4–5 grams of thyroid tissue at the 2 superior poles, limiting the risk of superior parathyroid gland involvement and of recurrent nerve lesion where it enters the larynx.

In expert centers with high-volume thyroid surgery, the risk of recurrent nerve or parathyroid involvement is no greater with total than subtotal thyroidectomy [66,149]. However, the volume and functionality of the residual thyroid tissue in the subtotal procedure is hard to judge intraoperatively. Subtotal thyroidectomy moreover incurs a risk of recurrence [152,153] and, according

to pathology findings, of failing to resect a papillary microcarcinoma.

There is a correlation between surgical turnover and post-thyroidectomy complications: recurrent nerve and parathyroid morbidity and hemorrhage. A threshold of 25 thyroidectomies per year was suggested by the American Thyroid Association, with 51% extra risk of complications for lower-volume centers [1]. Thus, if thyroid surgery is indicated, the patient should be referred to a thyroid surgery specialist performing a number of procedures per week.

When rigorously assessed, rates of definitive recurrent nerve and parathyroid morbidity at 1 year post-thyroidectomy are between 2 and 3% [154]. Immediate postoperative morbidity, on the other hand, is 5–9% for the recurrent nerve and 15–25% for hypocalcemia. Intermittent or continuous vagus and/or recurrent neuromonitoring tracks recurrent nerve function in real time. Intraoperative parathyroid hormone assay can assess the risk of postoperative hypocalcemia. These are 2 means of controlling surgical quality in real time, but there is no strong evidence that in themselves they reduce recurrent nerve or parathyroid morbidity.

Recommendation 28

- 28a. Total thyroidectomy is the first-line attitude. 1/+.
- 28b. Alternatively, if dissection of the first thyroid pole is difficult, subtotal thyroidectomy may be performed in the hope of reducing recurrent nerve and parathyroid risk. 2/+.

3.3. Surgical preparation by Lugol's iodine

Graves' disease patients undergoing surgery have to be operated on under euthyroid status to avoid acute thyrotoxic episodes. Lugol's iodine is sometimes used preoperatively to this effect [1,155,156], although beta-blockers are now more common [66].

In Graves' disease, the thyroid is very richly vascularized [155]. Excessive intraoperative bleeding or hemorrhage can lead to complications [157]. It has been suggested that Lugol's iodine reduces thyroid vascularization and hyperemia [31], thereby reducing the risk of postoperative complications involving the recurrent nerve or parathyroid. No prospective randomized controlled studies, however, have demonstrated this, and some have cast doubt [158,159].

The reduction in complications rate is above all correlated with the surgeon's experience, whence the importance of referral to an expert center or center with high thyroid surgery volume [149,155].

Surgery for Graves' disease should be performed in an expert center.

Recommendation 29

- 29a. There are no indications for preoperative application of Lugol's iodine to reduce complications rates. 2/+.
- 29b. Use of Lugol's iodine is at the surgeon's discretion. 2/+.

4. Extrathyroid manifestations of Graves' disease

4.1. Assessment and treatment of orbitopathy

Assessment and treatment of orbitopathy are dealt with in a dedicated article.

4.2. Treatment of thyroid dermopathy (pretibial myxedema)

In about 5% of cases of Graves' disease, there may be skin lesions, known as "pretibial myxedema" for their most frequent location [160].

This form of dermopathy shows late onset during the course of Graves' disease, usually in severe forms, more often in smokers, and often in association with moderate to severe orbitopathy, sometimes following radioiodine therapy. In all cases, anti-TSH-R antibodies are elevated. Pretibial myxedema associates skin redness without pain but with a sensation of local irritation, and typically "orange peel" cutaneous and subcutaneous thickening, with an aspect of non-pitting edema. More rarely, the lesion may be nodular, hypertrophic or even elephantiasis-like. Diagnosis is usually clinically obvious; biopsy is rarely needed, and not indicated due to the risk of trauma-related aggravation [160,161].

Treatment is effective if certain rules are followed. It must be as early as possible, as soon as the dermopathy is identified as such. A strong-activity class 4 topical steroid (with good skin penetration and absorption) should be applied in an occlusive dressing covering the treated area with a plastic seal; application should be once daily at first, for a long period of 4–10 weeks, preferably for the whole night. Only once there is clear resorption of the lesion can treatment be spaced out, although even so continued for several weeks, or even months in severe forms from the point of view of intensity or extent. Preliminary studies have investigated replacing topical steroids by local subcutaneous corticosteroid injection, mesotherapy techniques seeming optimal [162,163].

In hypertrophic diffuse extensive forms, other options should be considered: decompression physiotherapy, general-route corticotherapy, immunomodulation, or surgical resection of local lesions. Treatment of longstanding and complicated forms, however, is difficult [160].

Disclosure of interest

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B. Corvilain, A. Hamy, L. Brunaud, F. Borson-Chazot, J. Orgiazzi, L. Bensalem Hachmi, M. Semrouni declare that they have no competing interest.

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