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**Iodine 131 in the treatment of large goiters.**

**L'Iode 131 dans le traitement des volumineux goitres.**

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## **Abstract**

The treatment of large, complicated goiters with iodine 131 constitutes an interesting alternative to surgery. It is minimally invasive, safe, and effective in most cases, and is particularly valuable in elderly, fragile patients with multiple co-morbidities. Also, it does not preclude the possibility of surgery, should it become a necessary alternative, for whatever reason in the future. The precise pre-treatment evaluation includes thyroid scintigraphy, calculation of thyroid volume and tracheal surface measurement. Patients who are most at risk of acute complications (very small cross sectional tracheal area, underlying respiratory pathology, and hyperthyroidism) should be managed during hospitalization for possible respiratory distress, or rhythm disturbances induced by hormone release. The choice of the iodine 131 activity depends on individual routine practice, either standardized or modulated by thyroid mass. Administration may be repeated depending on the effect obtained and the cumulative dose. Efficacy in terms of volume reduction is practically constant at an early stage. Its effectiveness is difficult to predict, often less in the case of large size goiters. It can be improved by increasing iodine fixation, for example, using synthetic antithyroid drugs. Permanent hypothyroidism is the most frequent and minor complication of the treatment. It involves biological monitoring in order to introduce hormone replacement therapy to avoid thyroid growth stimulation and negate the benefits of radioiodine treatment.

*thyroid, treatment, iodine 131, goiter.*

## **Résumé**

Le traitement par iode 131 des goitres volumineux, compliqués, constitue une alternative tout à fait intéressante à la chirurgie. Peu invasif, sûr, et efficace dans la majorité des cas, il est particulièrement précieux chez les patients âgés, fragiles, avec de multiples comorbidités. Il ne coupe pas du recours possible un jour ou l'autre à la chirurgie, si celle-ci s'avérait souhaitable pour quelque raison que ce soit. L'évaluation préthérapeutique rigoureuse comporte notamment la scintigraphie thyroïdienne, la mesure du volume thyroïdien et de la surface trachéale. Les patients les plus à risque de complications aiguës (surface trachéale très diminuée, pathologie respiratoire sous-jacente, hyperthyroïdie) doivent recevoir le traitement par iode 131 cours d'une hospitalisation pour prendre en charge une éventuelle détresse respiratoire, ou des troubles du rythme induits par la libération hormonale. Le choix de l'activité d'iode 131 est fonction des habitudes, soit modulée par la masse, soit standardisée. L'administration peut être répétée selon l'effet obtenu et la dose cumulée. L'efficacité en termes de réduction de volume est pratiquement constante, précoce. Son importance est difficilement prévisible, souvent moindre en cas de goitres très volumineux. Elle peut être améliorée par l'augmentation de la fixation iodée par exemple sous antithyroïdien de synthèse. L'hypothyroïdie définitive est la complication la plus fréquente et la plus véniale du traitement. Elle implique une surveillance biologique en vue d'introduire une hormonothérapie substitutive pour ne pas favoriser à nouveau la croissance du parenchyme thyroïdien et altérer le bénéfice du traitement par Iode 131.

*thyroïde, traitement, iode 131, goitre.*

## **1 Introduction**

A goiter is a diffuse hypertrophy of the thyroid gland. Despite international programs for the correction of iodine deficiency, its prevalence remains high, close to 10% in adults, affected by genetic predisposition, female gender, pregnancy, smoking, medication (i.e. lithium) etc. [1]. Initially diffuse and homogenous, clinically latent or responsible for a slight esthetic deformity, goiters are organized in the form of nodules and increase by 0 to 20% per year [2]. It is often from the fifth decade that its volume exceeds 100 cm<sup>3</sup> [3], and that multinodular goiter becomes symptomatic and at risk of complications: compression, hyperthyroidism, or cancer.

At this stage a total thyroidectomy is considered as first-line treatment [2,4,5]. It is sometimes debated or rejected in elderly, fragile patients with comorbidities that make anesthesia and surgery excessively risky. Levothyroxine suppressive therapy is then practically ineffective, exposing patients to the risk of fracture and atrial fibrillation [6]. In the case of toxic goiter, long-term treatment with synthetic anti-thyroid drugs could be proposed, but the normalization of TSH increases the volume of the goiter and its compressive risk [7].

Treatment with iodine 131 has been an alternative treatment used since the 1950s in Germany, then widely promoted in the Benelux and Nordic countries [8, 9]. It has also been adopted in Lille for almost 30 years [10]. It allows both thyroid volume reduction and hyperfunctional nodules eradication.

The aim of our study was to specify the indications for radioisotopic treatment of bulky goiters, the practical modalities (in particular the measures likely to increase thyroid iodine 131 fixation), the constraints, the efficacy and possible complications.

## 2 Which patients could benefit from radioisotopic treatment?

Typically, iodine 131 treatment concerns:

- Patients with bulky goiters requiring therapeutic management because they are progressive, plunging, complicated by compressive signs and thyroid hyperfunction,
- Subjects for whom the risks of surgery and anesthesia appear excessive (i.e. elderly subjects, cardiac and respiratory insufficiency, anticoagulant treatment, etc.),
- Patients who refuse surgery,
- Recurrences of nodular goiter after partial thyroidectomy, due to an increased risk of operative complications in cases of new surgery.

In addition to the standard contraindications of iodine 131, the suitability of radioisotopic treatment should be questioned in the following situations:

- presence of a thyroid nodule on ultrasound and cytologically suspected of being an epithelioma,
- coincidence of primary hyperparathyroidism when its operative indication appears evident (symptomatic forms, serum calcium > 110 mg/L or 2.75 mmol/L)
- Need for a rapid halting of tracheal compression.

**Table 1**, based on recent articles [11,12], summarizes the therapeutic direction based on patients' data.

### **3 How should the practical modalities of treatment be considered?**

Before scheduling radioisotopic treatment, the patient should undergo routine evaluation: clinical, biological (thyroid, phosphocalcic, and calcitonin measurement), morphological and scintigraphic tests.

#### **3.1 Clinical evaluation**

The clinical examination assesses the importance of the compression of nearby organs [1] and will search in particular for:

- Phonation disorders (fragile, muffled or bitonal voice, by recurrent paralysis),
- Dysphagia (trouble swallowing liquids or solids),
- Respiratory discomfort (inspiratory dyspnea, wheezing, due to tracheal compression [9]),
- Venous compression (collateral circulation, jugular turgescence, facial erythrosis triggered by a Pemberton maneuver: raised arms pressed firmly against the ears for one minute).

The clinical examination also evaluates the general and especially cardiovascular repercussions of a possible associated hyperthyroidism.

At the end of this evaluation and before administration of the isotope:

- In the case of multiple comorbidities, attention should be paid to the risk of iodine overload, either transient due to the iodinated contrast agent injection [5], or prolonged with amiodarone,
- Dysphagia should be taken into account. An ingestion test with a placebo capsule should then be proposed. If necessary, iodine 131 can be administered in liquid form

(injectable iodine 131 will not be available in France until September 2020 at the earliest),

- The usual radiation protection guidelines and a low iodine diet are specified so as not to reduce thyroid uptake of iodine 131.

### **3.2 Morphological and scintigraphic evaluation**

Prior to the validation of iodine 131 treatment, several points should be considered:

- Screening for nodules suspected of epithelioma,
- Evaluate thyroid volume, and if necessary the impact on the surrounding structures,
- Measure the tracheal surface in its smallest dimensions, i.e. where the reduction by the goiter is most significant,
- Assess the quality of iodine fixation by the thyroid parenchyma (intensity and homogeneity).

This evaluation must at least include a cervical ultrasound, possibly supplemented by cytological study of suspected thyroid nodules (growing nodules, EuTIRADS 4 or 5, and nodules > 2 cm EuTIRADS 3), thyroid scintigraphy, cervico-thoracic tomodensitometry (without injection of contrast agent), which can be performed either by hybrid imaging during thyroid scintigraphy (SPECT-CT) or on dedicated equipment.

In the case of intrathoracic extension, MRI is recommended to determine the thyroid volume and its relationship to the surrounding structures [2,12].

#### **4 How can the therapeutic activity of iodine 131 be envisaged?**

There is no universal approach as to how the scintigraphic protocol should be performed, or as to the method of determining iodine 131 activity to be administered [9].

As regards scintigraphy, iodine 123 is often preferred to  $^{99m}\text{Tc}$  for the following reasons [4,5]:

- It permits molecular and functional imaging, reflecting both the process of cell uptake and organification of iodine, and the creation of a binding curve,
- $^{99m}\text{Tc}$  has only cell uptake that can lead to nodules incorrectly considered as autonomous.

The French Society of Nuclear Medicine [5] has issued several recommendations concerning scintigraphic explorations in patients with goiter:

- increase the diagnostic activity administered (20 MBq of  $^{123}\text{I}$  or 110 MBq of  $^{99m}\text{Tc}$ ),
- perform an additional acquisition on the neck and thorax with a parallel collimator to specify the endothoracic extension of the goiter. This avoids underestimating the thyroid volume in cases of ultrasound evaluation alone,
- perform multimodal imaging : computed tomography scan associated with tomoscintigraphy (SPECT-CT) to assess the anatomical ratios of plunging goiters, evaluate tracheal caliber and specify the volume.

In the literature, and in European recommendations [4], the feasibility of the treatment is validated by measuring the uptake rate 24 hours (TF24) after administration of a tracer dose of iodine 131 (from 0.6 to 3.7 MBq, no longer marketed in France). A TF24 of less than 20 % leads to reject treatment with iodine 131 alone, or to consider methods to increase iodine fixation.

The choice of the therapeutic activity of iodine 131 can be determined in several ways:

- In case of dosimetry calculation, it is necessary to perform at least one further measurement of the uptake rate (at best at 96 hours [13]), which is more constraining for the patient. The target absorbed dose (AD) to the thyroid is estimated from 100 to 150 Gy for non Grave disease goiters, whether toxic or not.
- The most commonly used alternative is the calculation of activity taking into account thyroid mass to deliver between 3.7 and 4.44 MBq per gram of thyroid tissue (i.e. between 1 and 1.2 mCi/g), corrected for the uptake rate (TF<sub>24</sub> in the majority of publications).
- Finally, in an even simpler way, it is possible to alternatively choose a fixed dose of iodine 131 (555 to 925 MBq), in a single or repeated dose, depending on the volume of the goiter and the observed efficacy.

## **5 What are the expected benefits of iodine 131 treatment?**

Treatment with iodine 131 reduces thyroid volume and compressive symptoms for the vast majority of patients, whether the goiter is basically cervical or intra-thoracic [12]. The volume reduction is on average 30-50% in the year following treatment, and may continue beyond [14,15] (**figure 1**).

Individual response is not necessarily predictable. However, in most surveys, it appears that the larger the goiter, the more limited the volume reduction [12,17]. The response is also influenced by the presence of a hyperfunctional dominant nodule due to the lower irradiation of the rest of the thyroid [14,17], or the low dose of iodine 131 delivered [9,17].

Although the data are heterogeneous in terms of dose, thyroid volumes, proportion of hyperthyroidism, and iodine binding rate, the overall results appear satisfactory and show similar volume reductions (**Table 2**).

In the case of a normally functioning goiter, the administration of 4 fixed doses of iodine 131 every 3 months [14], can produce results equivalent at one year to the use of a single capsule of iodine 131, adjusting the activity to the mass and the uptake rate. With repeated fixed doses the volume reduction predominates 3 months after the first treatment; thereafter the therapeutic effect of the other doses is more limited. These data suggest that for normally functional goiters, it would be preferable to carry-out an initial treatment with a standard activity (800 MBq for example). Secondly if the iodine binding and the 3 months morphological response are sufficient, radioiodine treatment can be repeated according to the evolution of the symptomatology.

The benefit usually obtained is the improvement or disappearance of compressive symptoms. In Baczyk et al.'s study [14], in which all patients had a goiter of more than 100 ml, dyspnea had decreased by 50 to 75% after one year and at two years 90% of initially symptomatic patients had noted a disappearance of dysphagia and/or local discomfort. Globally, studies indicate that approximately 75% of patients experience an improvement in compressive symptomatology [8, 19].

These data are in agreement with the increase in tracheal surface area and inspiratory capacity using spirometry measurement. In Bonnema et al. 1999 study [13], one year after treatment, the tracheal surface area had increased by 17.9% on average (37.5-126 mm<sup>2</sup> before versus 53-

164.5 mm<sup>2</sup> at one year) and inspiratory capacity by 21.7%. In Huysmans et al. survey [8], the smallest tracheal surface area increased by 36% ( $\pm 38\%$ ) on average one year after irradiation. Quality of life questionnaires also show a significant improvement in the overall health status of patients one year after treatment, with a lower degree of satisfaction in the older subjects. At the same time, dyspnea, respiratory signs and cervical discomfort improved, without a correlation with the extent of goiter size reduction and initial goiter size [20].

## **6 Can iodine binding be increased?**

Iodine uptake by the thyroid parenchyma depends on the iodine load, the state of stimulation of the thyroid parenchyma, and the degree of autonomy of nodular formations.

When iodine uptake is insufficient, treatment activity can be potentiated either by stimulating uptake (rhTSH, synthetic antithyroid drugs) or by increasing iodine retention within the thyroid follicles (Lithium salt).

### **6.1 Lithium salts**

Lithium salts, particularly in its carbonate form, increases iodine retention by reducing thyroglobulin proteolysis and the release of iodothyronines into the blood flow [21].

They are particularly used in cases of severe thyrotoxicosis to achieve a rapid (usually transient) reduction in hyperhormonemia prior to radical treatment (total thyroidectomy or iodine 131), or in the treatment of metastatic differentiated thyroid cancers to increase the effectiveness of radiotherapy with iodine 131.

Only one study evaluated the interest of associating lithium salts with iodine 131 treatments for euthyroid nodular goiters [21]. In 62 patients with thyroid volume between 20 and 128.1 mL, the reduction in thyroid volume was equivalent in a group treated with iodine 131 alone, and in a similar group receiving iodine 131 + lithium salt for 6 days. The addition of lithium was found to prevent early radiation-induced thyrotoxicosis, which is potentially dangerous in cases of cardiovascular fragility.

This advantage must be weighed against the specific risks of lithium overdosage, increased in low-salt diet and drug interactions (diuretics, enzyme conversion inhibitors, non-steroid anti-inflammatory drugs, etc.). Lithium is therefore an adjunctive therapy rarely used for the treatment of large goiters by iodine 131 in elderly, polymedicated subjects.

## **6.2 rh-TSH**

Recombinant human recombinant TSH (rh-TSH) is a thyrostimulin which, at a dose of 0.9 mg, increases iodine 131 binding by a factor of 2 to 4 and makes its distribution more homogeneous within the thyroid parenchyma (**Figure 2**) [11,12]. It therefore appears likely to accentuate the decrease in size of benign goiters submitted to radiiodine.

In fact, the combined treatment with rh-TSH and iodine 131 generally produces an equivalent or superior efficacy to the treatment with iodine 131 alone, depending on the dose of recombinant TSH, which has been demonstrated in several studies [11,12,23,24]. In a comparative survey in 2012 [23], 42 patients were treated with 0.3 mg rh-TSH + <sup>131</sup>I and 44 patients with placebo + <sup>131</sup>I: one year after treatment the reduction in goiter volume was significantly greater in the rh-TSH + <sup>131</sup>I group ( $59.2 \pm 2.4\%$ ) than in the <sup>131</sup>I group alone

( $43.2 \pm 3.7\%$ ); the degree of satisfaction and improvement of compressive signs was greater in the first group.

However rh-TSH doses above 0.3-0.45 mg increase the risk of acute adverse effects: local pain, cervical edema, tracheal compression and cardiac symptoms requiring glucocorticoids and/or beta blockers. Premedication with recombinant TSH increases the risk of thyroid hyperhormonemia and acute rise of goiter volume after iodine 131 [25], so that the American Thyroid Association has advised against its use in hyperfunctional bulky goiters in the elderly.

For this reason, mrh-TSH, a modified-release form of rh-TSH, that delays and reduces the TSH peak, has been developed. A randomized multicenter study compared 3 groups of patients with goiter volumes ranging from 31.9 to 242.2 mL [26]. Patients received either placebo +  $^{131}\text{I}$  or 0.01 mg mrh-TSH +  $^{131}\text{I}$  or 0.3 mg mrh-TSH +  $^{131}\text{I}$ . At 6 months the mean volume reduction was  $23.1\% \pm 8.8$  in Group 1,  $32.9\% \pm 20.7$  in Group 3; this significant reduction did not appear in Group 2. At 36 months, the reduction was  $44 \pm 12.7\%$  in group 1 and  $53 \pm 18.6\%$  in group 3, without reaching significance.

In contrast, hypothyroidism was 3 to 4 times more frequent in patients pretreated with recombinant TSH. In the study of Fast et al. [23] after 0.3 mg of rh-TSH +  $^{131}\text{I}$ , 43% of hypothyroidism was observed at one year, and 52% after 5 years after treatment. For patients treated with  $^{131}\text{I}$  alone (at an equivalent dose) there was 9% and 16% of hypothyroidism respectively. In the protocol with mrh-TSH [26], 13% of patients treated with  $^{131}\text{I}$  alone developed hypothyroidism, compared to 33% and 45% of patients who received 0.01 mg and 0.03 mg mrh-TSH before iodine 131, respectively.

Thus rh-TSH was shown to achieve a better reduction of bulky goiters, at the cost of an increased risk of hypothyroidism. This treatment is not recommended in patients with hyperthyroidism, especially if they have cardiac comorbidities and in cases of severe tracheal compression.

In other situations, the best compromise recommended by Bonnema et al. [12] is a single injection of 0.1-0.3 mg rh-TSH 24h before iodine 131. In France recombinant TSH is not approved for this indication and is marketed only in its 0.9 mg form.

### **6.3 Synthetic antithyroid drugs**

Synthetic antithyroid drugs reduce the synthesis and serum concentration of thyroid hormones, thereby increasing endogenous TSH levels. Studer et al. have shown that prolonged treatment with antithyroid drugs can restore initially impaired iodine binding [27]. For these reasons, this treatment could be used to reinforce the action of iodine 131, whether or not the subjects are hyperthyroid, but there is currently very little data reported in the literature to rely on.

In 2020, [28] the effect on thyroid volume and the risk of hypothyroidism were compared in 16 patients treated for 6 weeks with 10 mg methimazole (MMI) followed by iodine 131 four days after stopping MMI, and 15 patients treated with placebo followed by iodine 131. The activity of iodine 131 was set at 800 MBq; one or more additional treatments of 800 MBq were delivered every 6 months as long as the thyroid volume remained above 40 mL (mean initial thyroid volume =  $61.9 \pm 19.8$  mL in the MMI group,  $68.3 \pm 12.3$  mL in the placebo group). For patients treated with MMI + Iodine 131 binding rates at 24 and 48 hours were

doubled. The difference of average volume reduction between the two groups was 34% at 6 months and 22% at 2 years, in favor of the MMI group. In the MMI group, 4 patients received more than one dose of iodine 131, compared to 10 patients in the <sup>131</sup>I group alone. The number of patients who developed hypothyroidism was equivalent in both groups, approximately 30%.

Premedication with synthetic antithyroid drugs is an attractive alternative, since these drugs are available in France, with a modest and manageable risk of undesirable effects (particularly hematological). However, its interest and tolerance still remain to be assessed in patients with larger goiters than those in the previously reported study.

## **7 Are there any side effects?**

Acute or subacute adverse reactions are quite rare.

In less than 25% of patients, particularly those with a very bulky goiter, an early and transient increase in thyroid volume up to +25% of the initial volume can be observed, usually without any clinical consequences (**Figure 3**) [13,29].

In one study [13], five out of 23 patients experienced early worsening of dyspnea requiring glucocorticoid treatment. These were patients with the lowest tracheal surfaces. A Danish team recommended combined corticosteroid therapy with iodine 131 in patients with a tracheal surface area lower than 50-60 mm<sup>2</sup> [13]. In these patients with marked tracheal narrowing or respiratory insufficiency, it is preferable to deliver the treatment during an in-patient stay of at least 48 hours to ensure monitoring and early management of possible worsening.

Transient hyperthyroidism may occur within the first 15 days after treatment. It often appears to be clinically moderate, with an increase in the order of 20% for FT4 and 13% for FT3 [29], but careful clinical monitoring should be performed if there is a history of heart disease.

Later in life, there is a risk of autoimmune hyperthyroidism associated with the development of autoantibodies stimulating TSH receptors. These radio-induced Graves diseases generally occur within 3 to 6 months following the IRAtreatment. Their risk is estimated to be just below 5% in patients treated for toxic goiter [30]. These situations occur more frequently in patients with initially increased titers of antithyroperoxidase antibodies or even TSH receptor antibodies. The treatment is most often medical using temporary and adapted prescription of a synthetic antithyroid drug, to avoid any TSH release. Though a new therapeutic dose of iodine 131 should be avoided in the acute phase because of the increased risk of orbitopathy, it is possible to resort to it subsequently.

Hypothyroidism is finally the most frequent undesired effect. It occurs in 20-50% of patients (Table II) and most often appears within 2 years after treatment. Its incidence increases over the years, but is less frequent than in Graves disease [31]. Small volume goiters, increased antithyroid antibody titers and a family goiter context are the main predisposing factors for radiation-induced hypothyroidism [17]. This risk implies prolonged thyroid biological monitoring and the introduction of hormone replacement therapy if necessary, especially to avoid the re-increase in thyroid volume by the trophic effect of TSH.

Finally, for these multinodular goiters, reduced but not eradicated by radio-isotopic treatment, there is still a risk of revealing a malignant tumor (even malignant degeneration or anaplastic

dedifferentiation of an unknown papillary or vesicular epithelioma). This is a theoretical risk that has long led to prefer surgery. It is minimized by the extensive preoperative morphological evaluation, as well as by clinical and ultrasound monitoring, which should be maintained for a long time. Blood calcium levels should also be monitored, because of a theoretical risk of radiation-induced late primary hyperparathyroidism [32]. These are the reasons that lead the medical community to reject iodine 131 in the treatment of simple goiter in young adults. Whereas Danish teams who use radioiodine more frequently have shown that the best morphological results are obtained at the stage of homogeneous goiter [2].

## **8 Conclusion**

Reduction in the size of large, benign, symptomatic, possibly hyperfunctioning goiters can be effectively achieved with iodine 131, and should be considered for the treatment of elderly, frail, surgically at risk patients. Prior clinical and morpho-functional evaluations have to be extensive to validate the indication and to select patients to monitor more closely. Post-treatment follow-up is important to ensure functional benefit and to detect hypothyroidism.

The efficacy of iodine 131 could be enhanced by prior treatment with synthetic antithyroid drugs if preliminary data are confirmed and demonstrate their usefulness in the cases of large goiters.

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## **Conflict of Interest:**

**Béron A:** Conferences: Invitations in the capacity of an auditor (travel and accommodation expenses paid by a company on his behalf) for Genzyme.

**Wémeau J-L:** No conflict of interest.

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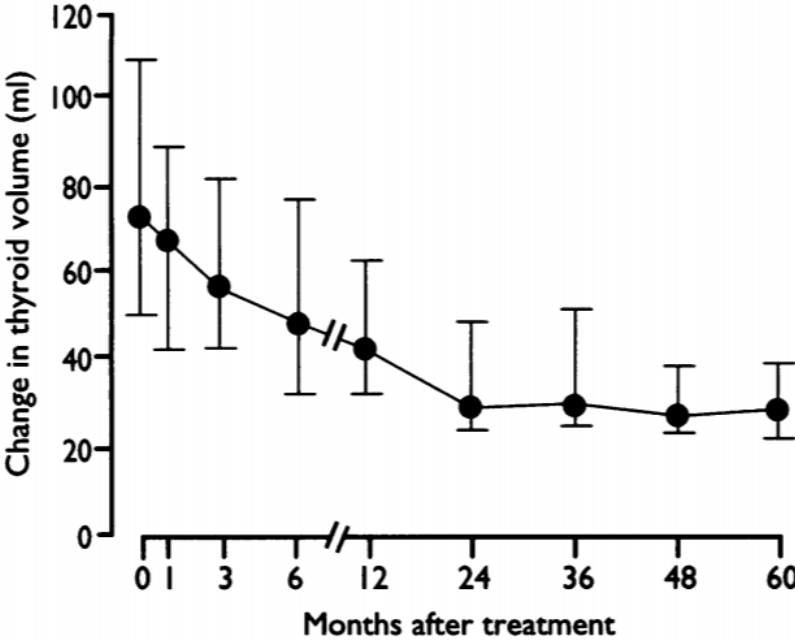
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Figure 1



**Figure 2**

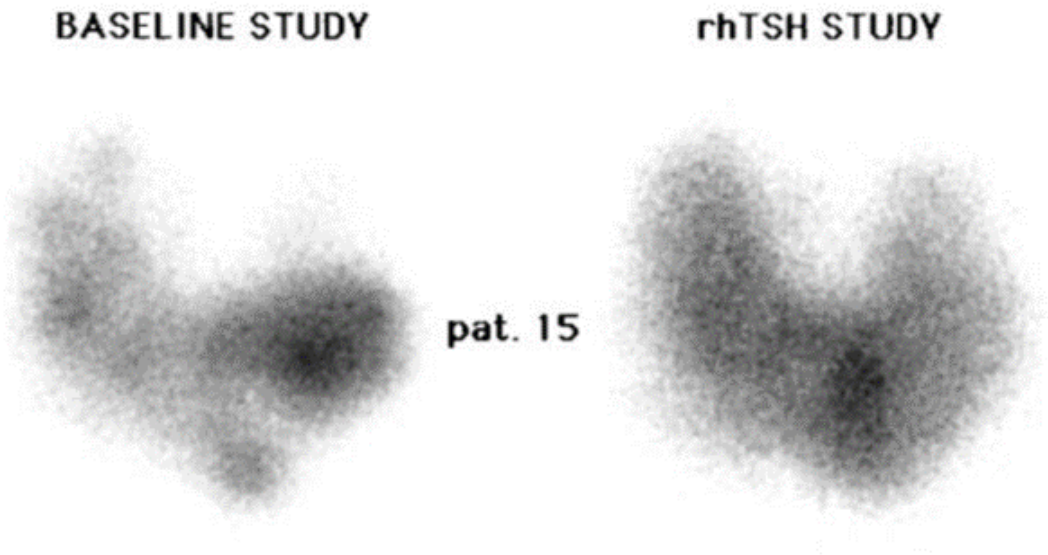
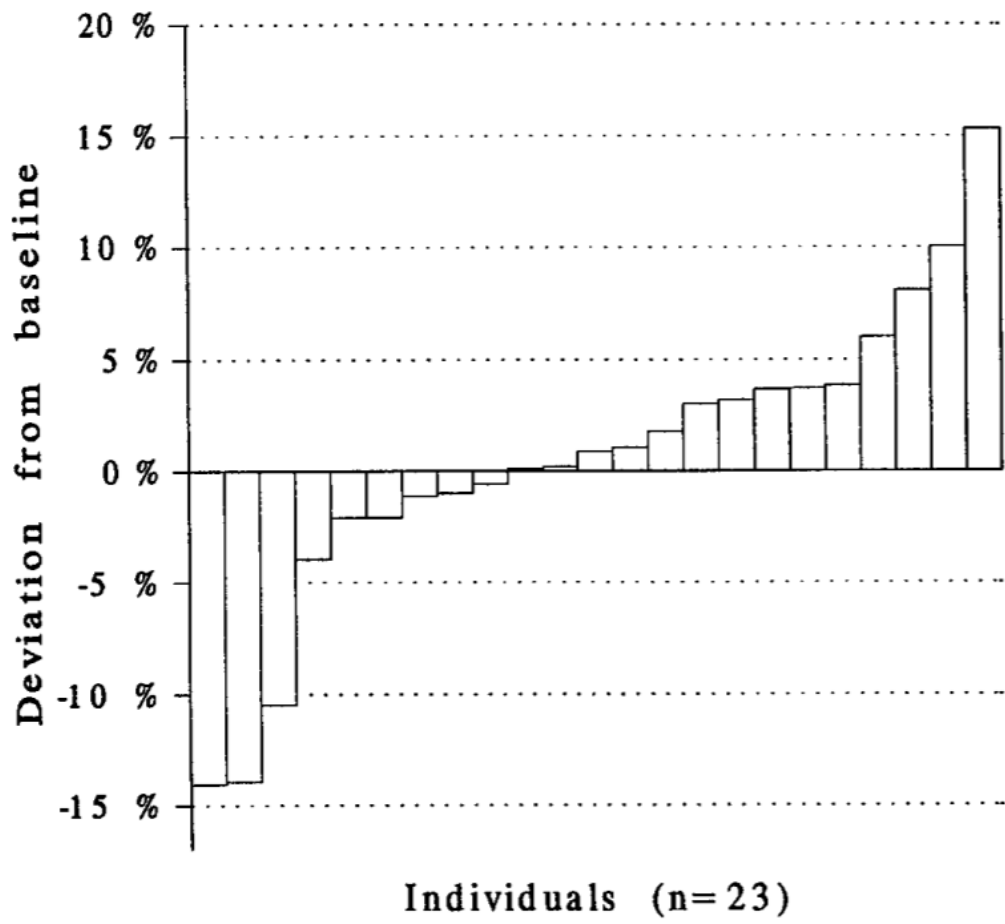


Figure 3



**Tableau 1**

	<b>Iodine 131</b>	<b>Surgery</b>
Previous thyroidectomy	++	+
Hyperthyroidism due to nodular autonomy	++	+
Severe co-morbidity	++	-
Plunging goiter	++ (a)	+
Suspicion of thyroid malignancy	-	++
Severe tracheal compression	+	++
Need of rapid relief of thyroid compression	+	++
symptomatic HPT, or calcemia > 110 mg/L	-	++
Insufficient iodine thyroid binding	+(b)	++
Insufficient response to Radioiodine treatment	+(c)	++

++ = First choice; + = Second choice; - = no option

a: Radioiodine treatment can be proposed to reduce volume before surgery

b: consider prior stimulation of iodine binding by rh-TSH or antithyroid drugs

c: a second radioiodine treatment may lead satisfaction

HPT = hyperparathyroidism

++ = 1<sup>ère</sup> intention ; + = 2<sup>ème</sup> intention ; - = non indiqué

a : un traitement par iode 131 peut être proposé à visée néoadjuvante de réduction de volume avant chirurgie ; b : envisager une stimulation préalable par rhTSH ou antithyroïdiens de synthèse ; c : un deuxième traitement peut entraîner un résultat satisfaisant

HPT = hyperparathyroïdie

**Tableau 2**

Author Year	Number of patients (pts)	Calculation of <sup>131</sup> I activity	<sup>131</sup> I administered activity in MBq Mean $\pm$ 2DS (Range)	Thyroid volume mean $\pm$ 2DS (Range)	Average of volume reduction (%) $\pm$ 2DS (Range)	Rate of hypothyroidism (%)
<b>HUYSMANS 1994 [8]</b>	21	3,7 MBq/ g, corrected for TF	2,6 $\pm$ 1 GBq	269 $\pm$ 153 mL	40 % $\pm$ 15 %	NC
<b>LE MOLI 1999 [17]</b>	68	3 – 5 MBq/ g corrected for TF	(444 – 3330 MBq)	82 mL (17- 325 mL)	49 % at 2 years	48 % at 2 years
<b>BONNEMA 1999 [13]</b>	23	Dosimetry (DA = 100 Gy)	2281 MBq (988 – 4620 MBq)	311 $\pm$ 28 mL (100 - 703 mL)	33,9 % at 1 year (13,5 – 61,4 %)	22 % at 1 year
<b>VELAYOUDOM 2005 [10]</b>	38	Dosimetry: 30 pts Standardized dose: 8 pts	Dosimetry (111- 1110 MBq) Fixed dose: 740 or 925 MBq	20 pts / 38 53 $\pm$ 70 cm <sup>3</sup>	33,5 % (18 – 82 %)	13 % at 1 year
<b>BACZYK 2008 [14]</b>	34	Repeated fixed dose every 3 months 4 x 800 MBq	3,2 GBq	145 cm <sup>3</sup> (100 -368)	TG :28 % at 3 months 41 % at 2 years NTG: 40 % (3 months) 76 % (2 years)	40 % at 1 year
<b>BACHMANN 2009 [15]</b>	88	Dosimetry (DA = 150 Gy)	1721 $\pm$ 440 MBq (714- 2395 MBq)	127 $\pm$ 38,56 mL (80-250 mL)	41,9 % (3 months) 65,9 % (2 years)	50 % at 5 years
<b>KANIUKA 2015 [18]</b>	35	4,44 MBq/g, corrected for TF	1806 MBq (800-4000 MBq)	104,36 mL (36,23- 301,09)	43,2 % at 1 year	42,9 %

TF = iodine uptake rate, DS = standard deviation, NC = unknown

TF = *taux de fixation*, DS = *déviati on standard*, NC = *non connu*