



The Influence of Remnant Size, Antithyroid Antibodies, Thyroid Morphology, and Lymphocyte Infiltration on Thyroid Function After Subtotal Resection for Hyperthyroidism

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The influence of thyroid remnant size, antithyroid antibody titre, thyroid morphology, and lymphocyte infiltration on postoperative thyroid function was studied in 179 patients undergoing subtotal thyroidectomy because of hyperthyroidism. The surgical procedure was strictly standardized and included determination of the thyroid remnant size. The preoperative medication used was beta-adrenoceptor blocking agents in 101 patients and antithyroid drugs and thyroxine in 78. With remnant size adjusted to 6–10 g (or, in goiters less than 20 g, to 25–30% of initial gland weight), the overall recurrence rate after 2–8 years (mean 5.3 ± 2.0) of follow-up was 1.7% and the incidence of thyroid hypofunction was 29.6%.

In toxic nodular goiter (TNG; $n = 63$), a significant negative correlation was found between TSH and remnant size after 12 months as well as a significantly lower remnant weight in patients developing postoperative hypothyroidism. In toxic diffuse goiter (TDG; $n = 116$), there was no difference in remnant size between euthyroid and hypothyroid patients. For patients with TDG treated preoperatively with beta-blockers, the incidence of autoantibodies against thyroid cytoplasm was increased in patients who postoperatively developed thyroid dysfunction. Within the group of TDG developing hypofunction, we found increased titre of autoantibodies and “presence of lymphoid tissue” more often in patients treated preoperatively with beta-blockers compared to thyrostatics. In toxic nodular goiter, the remnant size was considered the parameter most helpful to the surgeon in predicting postoperative thyroid function.

The choice between surgery and radioiodine treatment for hyperthyroidism is a matter of controversy. One advantage of surgery is that it leaves a remnant of thyroid tissue unaffected by radiation, thereby increasing the patient's chance of remaining euthyroid without supplementation. The objections voiced against surgery are that, in addition to the risk of complications, there is a relatively high incidence of postoperative dysfunction. Toxic recurrence has been reported to occur in 9–12% [1–3] and postoperative hypofunction in 27–49% of the cases [4–6]. If surgical treatment is to be justified, the incidence of complications and of postoperative dysfunction must be kept low. The surgeon can influence both factors—the complication

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rate, by an accurate surgical technique and, as shown in the present study, the postoperative function, by adjustment of the thyroid remnant.

Many factors other than the total size of the thyroid remnant may, however, influence postoperative thyroid function. Such factors are the morphology of the gland (diffuse or nodular goiter, relative amount of pathologic tissue in the remnant, lymphocyte infiltration), presence of autoantibodies against thyroid tissue [7–11], and the type of preoperative treatment [11–13]. Knowledge of how and to what extent these factors influence the postoperative results are of value to the surgeon in determining the amount of tissue to be resected.

The present investigation is aimed at elucidating the relationship between postoperative thyroid function and remnant size (total and relative to original weight of the gland), thyroid morphology, antithyroid antibodies, lymphocyte infiltration, and preoperative medication (beta-blockade or antithyroid drugs).

Material and Methods

The study comprised 179 patients who underwent a subtotal bilateral thyroid resection for hyperthyroidism, using a strictly standardized surgical procedure, at Linköping University Hospital from 1977 to 1982. The female:male ratio was 4.2:1. The age range for all patients was 18–78 years (mean 46.7 ± 13.0). The mean age of the patients with toxic diffuse goiter was 42.8 ± 12.2 and of those with toxic nodular goiter, 52.4 ± 12.4 years. The mean follow-up time was 5.3 ± 2.0 years. Patients operated on during the same time with hemithyroidectomy because of toxic adenoma or patients who had previously undergone thyroid or parathyroid surgery were not included.

Preoperative Medication

Beta-adrenoceptor-blocking agents were the only preoperative treatment given to 101 of the 179 patients, as propranolol (Inderal®) 120–640 mg daily or metoprolol (Seloken®) 200–400 mg daily until euthyroidism. The 78 remaining patients received antithyroid drugs, i.e., carbimazole (Neomercazole®), propyl-

thiouracil (Tiotil®), or thiamazole (Thacapzole®) combined with l-thyroxine (Levaxin®) in accordance with earlier presented principles [13]. Preoperative treatment with antithyroid drugs and thyroxine was started by general practitioners or other clinics submitting patients for operation, which made the comparison between these otherwise identical groups of patients possible.

Surgical Procedure

The surgical technique was strictly standardized [14]. Most of the operations were performed by one of the authors (S.L.), and the others by a few surgeons, with even distribution between the various patient groups. The technique of subtotal thyroid resection included extensive mobilization of the thyroid lobe, with routine identification of the recurrent laryngeal nerve and parathyroid glands. The superior pole vessels and the inferior thyroid artery were ligated and the isthmus divided, so that the lobe could be mobilized also from the medial aspect before resection. The parathyroid glands were, when necessary, dissected down below the line of resection.

The size of the thyroid remnant on both sides was estimated by resecting a segment of tissue and simultaneous palpation of the remnant, adjusting the segment to the size of this residual tissue (Fig. 1). The segment was then weighed, and if the weight indicated the remnant to be too large, further tissue was resected [15].

In this way, total remnant size was adjusted to 6–10 g or, in small goiters (≤ 20 g) to 25–30% of the original weight. The relative remnant size was calculated as the ratio between total thyroid remnant and total original weight of the gland.

Postoperative Follow-Up

All patients were postoperatively followed up from the Department of Surgery for periods of 2–8 years. They were seen routinely at 3 and 9 weeks, 6 months, and 1 year after thyroid surgery and then annually. On each occasion, the patient was clinically examined and the serum levels of thyroxine, tri-iodothyronine, and thyroid-stimulating hormone (TSH) in peripheral blood were determined. A tri-iodothyronine uptake test was also made. When laboratory signs of hypothyroidism (rise in the TSH level, subnormal levels of thyroxine, tri-iodothyronine, FT₄-index, FT₃-index) were combined with clinical signs of hypothyroidism, thyroxine was administered and the patient was classified as postoperatively hypothyroid. Recurrence of hyperthyroidism was confirmed by thyrotropin-releasing hormone (TRH)-stimulation test.

Laboratory Methods

The resected tissue was fixed in 4% formaldehyde and embedded in paraffin wax. Sections, 5 μ m thick, were stained with hematoxylin-eosin and hematoxylin-van Gieson. All specimens were examined by the same pathologist and classified according to the type of goiter and occurrence of "significant lymphocyte infiltration" [16].

In fact, 3 types of goiters were distinguished: (a) diffuse changes in parenchyma with no nodules, consistent with toxic diffuse goiter; (b) diffuse changes in extranodular parenchyma

in a thyroid gland containing 1 or more nodules, consistent with toxic nodular goiter with diffuse hyperplasia; and (c) hyperplasia in nodules only, consistent with toxic nodular goiter with nodular hyperplasia. Based on results in previous studies [16], we combined the first and second types, which were designated toxic diffuse goiter (TDG), whereas the third type was named toxic nodular goiter (TNG). Lymphoid tissue with a germinal center present in the thyroid tissue was considered "significant lymphocyte infiltration." We made no further quantification of lymphocyte infiltration.

Serum antibodies to thyroid epithelial cell cytoplasm were determined according to Coons and Kaplan [17]. Antibodies to thyroglobulin (TG) were detected with tanned sheep erythrocyte agglutination methods [18].

Thyroxine in serum (S-T₄) was determined with a competitive protein-binding technique [19], a tri-iodothyronine by radioimmunoassay [20] modified for double-antibody technique. Thyrotropin in serum (S-TSH) was also radioimmunoassayed [21]. Free thyroxine index was calculated according to Clark and Horn [22] and free tri-iodothyronine index (F-T₃) according to Pain [23].

Statistical Methods

Linear regression analysis, chi-squared test, and Student's *t*-test were used in the statistical analyses, with 2-tailed and (when indicated) 1-tailed tests. Results are stated in the text and tables as mean \pm standard deviation (M \pm SD).

Results

Postoperative Thyroid Function

After 2–8 years of observation, 123 (68.7%) of the 179 patients were euthyroid without medication (Table 1). Three patients (1.7%) had recurrence of hyperfunction and 53 (29.6%) required thyroxine treatment because of hypofunction according to the aforementioned criteria.

All 3 patients with recurrent hyperthyroidism had diffuse hyperplasia. In 2 of the patients, the preoperative medication had consisted of beta-blockers and the third had received antithyroid drugs. In 1 of the patients (given beta-blocker preoperatively), the remnant size was at the upper limit (10 g), whereas the other 2 had relatively small thyroid remnants (Table 2). Preoperative thyroid antibody titres were analyzed in 2 of these patients. Cytoplasmatic thyroid antigen exceeded 1:400 and 1:25, respectively. In all 3 patients with recurrence, the gland showed "significant lymphocyte infiltration."

Thirty-seven (32%) and 16 (25%) patients in the TDG and TNG groups, respectively, developed postoperative dysfunction (Table 1). There were no significant differences in the frequency of hypofunction either between the TDG and TNG groups, or within the groups with regard to type of preoperative treatment with adrenoceptor-blocking drugs or thyrostatics.

Remnant Size

The mean thyroid remnant size in the total patient series was 7.0 \pm 2.0 g. The corresponding figures for TDG and TNG were 6.5 \pm 1.7, and 7.9 \pm 2.3 g, respectively.

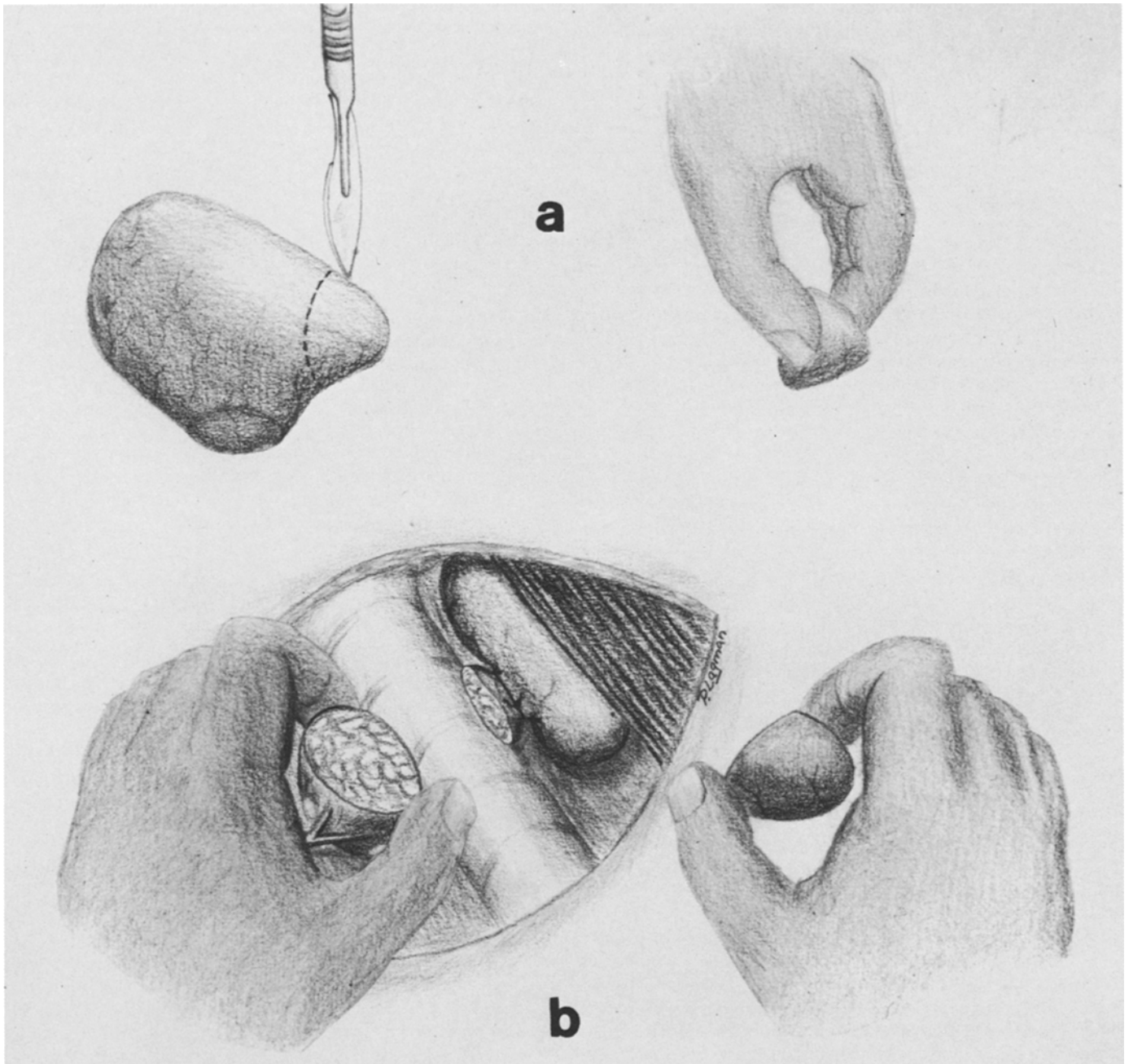


Fig. 1. Perioperative estimation of the thyroid remnant size: (a) A segment of tissue is cut off from the resected part of the gland. (b) By simultaneous palpation, this segment is adjusted to the size of the thyroid remnant and then weighed.

The size of the thyroid remnant in the euthyroid and hypothyroid patients is shown in Table 3. Significantly smaller remnants were observed in the TNG group with postoperative dysfunction as compared to euthyroid TNG patients ($p \leq 0.05$, 1-tailed test). No difference in size was found between hypothyroid and euthyroid TDG patients. No difference between the relative size of the remnants was found in the euthyroid and hypothyroid groups of patients.

Thyroid Antibody Titres

Significantly increased titres of cytoplasmatic antibodies were observed in TDG patients developing postoperative dysfunction ($p \leq 0.05$). Within the TDG group, this increase was correlated to postoperative hypofunction in patients preoperatively treated with adrenoceptor-blocking drugs ($p \leq 0.05$) but not with antithyroid drugs. No difference in cytoplasmic anti-

Table 1. Postoperative results in relation to goiter type and preoperative medication.

Postoperative result	Toxic diffuse goiter (n = 116)		Toxic nodular goiter (n = 63)	
	Beta-blocker (n = 59)	Antithyroid agent (n = 57)	Beta-blocker (n = 42)	Antithyroid agent (n = 21)
Euthyroid	37	39	31	16
Toxic recurrence	2	1	–	–
Thyroid hypofunction	20 (33.9%)	17 (29.8%)	11 (26.2%)	5 (23.8%)

Table 2. Patients (n = 3) with postoperative recurrence of toxic goiter.

Type of toxic goiter	Preoperative medication	Remnant size	
		Weight (g)	% of total gland
Diffuse	Beta-blocker	5.9	–
Diffuse	Beta-blocker	10	17
Diffuse	Antithyroid agent	6.8	21

bodies was found between euthyroid and hypothyroid patients in the TNG group.

No difference in antithyroglobulin antibodies was found in the TDG and TNG groups either between euthyroid and hypothyroid patients or with regard to preoperative treatment.

Presence of Lymphoid Tissue with Germinal Center

There was no increased incidence of "significant lymphocyte infiltration" in the tissue in patients developing postoperative dysfunction as compared to the euthyroid patients in any of the groups. In TDG patients developing postoperative dysfunction, a significantly higher incidence of "significant lymphocyte infiltration" was observed in those treated with adrenoceptor-blocking agents as compared to thyrostatics ($p \leq 0.05$). The same result was observed in the whole TDG group ($p \leq 0.01$). In the TNG group, the incidence of "significant lymphocyte infiltration" was low and no difference was found in tissues from postoperatively euthyroid and hypothyroid patients. Calculated on the total series, TDG showed markedly more "significant lymphocyte infiltration" than TNG ($p \leq 0.0005$).

Postoperative TSH Levels in Euthyroid Patients

The TSH level was significantly higher 3 and 9 weeks and 6 months postoperatively in the patients given antithyroid agents preoperatively than in the beta-blocked group ($p \leq 0.001$, $p \leq 0.01$, and $p \leq 0.05$, respectively). No intergroup differences in TSH level between TDG and TNG patients was found, except at 6 months postoperatively, when the TSH was significantly ($p \leq 0.01$) lower in the TDG group.

Regression analysis showed a significant negative correlation between the remnant size and TSH level at 12 months for euthyroid patients in the TNG group ($p \leq 0.01$, 1-sided test) and TDG group ($p \leq 0.05$, 1-sided test). If, however, patients developing postoperative dysfunction were included in the

Table 3. Total (g) and relative (%) thyroid remnant size in relation to postthyroidectomy status and preoperative medication.

Type of goiter preoperative medication	Postoperative status			
	Euthyroid		Hypothyroid	
Diffuse				
Beta-blockade	6.6 ± 1.8 g	22 ± 7.2%	6.1 ± 1.1 g	22 ± 9.7%
Antithyroid drugs	6.5 ± 1.8 g	23 ± 7.8%	7.0 ± 1.6 g	28 ± 13%
Nodular				
Beta-blockade	8.2 ± 2.1 g	12 ± 8.5%	6.9 ± 2.7 g	11 ± 6.8%
Antithyroid drugs	7.8 ± 2.0 g	13 ± 8.2%	6.6 ± 2.6 g	8.2 ± 3.1%

calculation, no significant correlation was found in the TDG group, but remained ($p \leq 0.01$, 1-sided test) in the TNG group.

Surgical Complications

No bleeding and no infections complicated the thyroid surgery. There was no lasting damage to the recurrent laryngeal nerve (vocal cord function was routinely checked by laryngoscopy). Mild, persistent hypocalcemia in 2 patients required substitution medication with alphacalcidol.

Discussion

In a recent article, we reported the postoperative course and late results in patients surgically treated for hyperthyroidism after pretreatment with either adrenoceptor-blocking agents or thyrostatics [24]. No significant difference in relative number of patients with postoperative thyroid dysfunction was found with regard to type of preoperative treatment. In the present study, the case series is homogenous with regard to type of operation (bilateral resection only) and other factors that might be of importance for the thyroid function have been evaluated. We found it important to differentiate the 2 main histopathological types of goiter in the present study since these entities probably have different etiologies [7–9, 25–28]. In these 2 types, remnant size, antibody titres, and lymphocyte infiltration might be of varying importance for remnant function.

Size of Thyroid Remnant

In the present series of patients, a standard surgical procedure was used, with adjustment of the remnant to a size within prospectively determined limits. The method for assessing thyroid remnant size was previously evaluated in cadavers, when the postresection remnant was removed and weighed. Close correlation was found between true and estimated remnant size [15] indicating that, in experienced hands, the method is accurate for determining the size of the thyroid remnant (Fig. 1). The present analysis indicates that the size of the remnant, within the weight range used in the present study, is more directly related to the postoperative thyroid function in patients operated on for toxic nodular goiter than for toxic diffuse goiter. This conclusion is sustained by the observed significant negative correlation between postoperative TSH level and remnant size in the TNG patients.

Antithyroid Antibodies

Preoperatively raised titres of antithyroid antibodies were previously shown to increase the risk of postoperative thyroid dysfunction [29]. Our study similarly showed significantly greater incidence of titre elevation of cytoplasmic antibodies in TDG patients with subsequent hypofunction. Postoperative dysfunction, however, was found both in patients preoperatively treated with adrenoceptor-blocking drugs with high antibody titres and in those treated with thyrostatics in which no elevated titres were present. Information of cytoplasmic antibody titres is available at the time for operation and could possibly assist the surgeon's choice of strategy by leaving a larger remnant in patients with high antibody titres. This information is, however, to the full extent only present in cases preoperatively treated with adrenoceptor-blocking drugs. It is not known if high antibody titre also increases the risk of toxic recurrence and, because so few of our patients had recurrence, no conclusions in this respect are permissible from our study.

Lymphocyte Infiltration

Earlier studies showed presence of lymphoid tissue to be of value in histologic evaluation of thyroid tissue [29]. With the criteria used in the present study, this was not confirmed. No significant difference was found between euthyroid patients and those developing postoperative dysfunction. The results indicate that the incidence of lymphocyte infiltration in thyroid tissue preoperatively treated with antithyroid drugs might be underestimated.

Thyroid Morphology

Apart from mild thyrotoxic symptoms at the onset of Hashimoto's thyroiditis [30], increased concentrations of circulating thyroid hormone are caused by diffuse or nodular toxic goiter. These are 2 separate entities. In diffuse toxic goiter, the follicle cells are stimulated to hypersecretion by an immunoglobulin G fraction [7, 9]. In toxic nodular goiter, the gradually intensifying toxicosis is assumed to be caused by a slowly increasing fraction of autonomously functioning follicles [25–28]. A previous report from this hospital suggested a close relationship between postoperative thyroid function and the morphological type of goiter, and that postoperative thyroid dysfunction is rare in patients with nodular hyperplasia [16]. Our study did not confirm these observations, although the same pathologist examined all the tissue specimens in both studies. The earlier investigation, however, comprised a series of patients, almost half of whom were preoperatively treated with iodine and the rest with antithyroid drugs. The follow-up time was shorter than in our investigation. In the present study, the mean age of the TDG and TNG groups was slightly lower, and the female:male ratio was slightly higher.

The present study indicates that the postoperative function of the remnant is correlated to its size in TNG whereas other factors may add their influence in case of TDG; hence, the morphological type could conceivably be useful for identifying potential risk groups as regards postoperative hypofunction. A macroscopically nodular goiter can, however, contain diffuse hyperplasia [16], and clearly the histopathological pattern is as a rule not apparent at the time of operation.

Conclusion

Although postoperative thyroid function obviously is influenced by many factors other than the amount of residual thyroid tissue, the present study indicates that accurate adjustment of the size of the thyroid remnant is a valuable contribution to avoidance of postoperative dysfunction. In toxic nodular goiter, adjustment of the remnant size to 6–10 g would lead to postoperative euthyroidism in the majority of the patients. In patients with toxic diffuse goiter, the size of the remnant is less predictive with regard to postoperative function. High cytoplasmic antibody titres, which can only be detected during preoperative treatment of TDG with adrenoceptor-blocking drugs, may indicate that a larger remnant would reduce the incidence of postoperative dysfunction. With resection to remnant size according to the principles here described, more than 98% of goiter operations can give definitive cure, with only slightly more than one-fourth of the patients possibly requiring future thyroxine supplementation.

Presence of lymphoid tissue in this study seems not to be the determining factor for the postoperative function. We found that preoperative treatment with beta-adrenoceptor-blocking agents, although advantageous in other respects [31], did not reduce the risk of postoperative thyroid dysfunction. Finally, our study demonstrated that surgery not only leads to rapid and definite cure of goiter in the overwhelming majority of patients, but can also be a safe procedure, with very low risk of surgical complications.

Résumé

L'influence de la taille du parenchyme thyroïdien restant, du taux de l'anticorps anti-thyroïdien, de la morphologie thyroïdienne, de l'infiltration lymphocytaire sur la fonction post-opératoire de la thyroïde a été étudiée chez 179 malades qui ont subi une thyroïdectomie subtotale pour hyperthyroïdie. La technique opératoire a été uniforme prenant en compte la taille du parenchyme thyroïdien laissé en place. La préparation à l'intervention a été réalisée en employant des bêta-bloquants chez 101 malades, des médicaments anti-thyroïdiens et de la thyroxine chez 78 patients. Pour un moignon de parenchyme thyroïdien de 6–10 g (ou lorsque le goitre pesait moins de 20 g, un moignon thyroïdien représentant 25–30% du poids initial de la glande), le taux global de récurrence après 2–8 ans (moyenne 5.3 ± 2.0) a été de 1.7% et le taux d'hypothyroïdie de 29.6%.

En cas de goitre nodulaire toxique ($n = 63$) une corrélation négative significative a été observée après 12 mois entre le taux de TSH et la taille du moignon thyroïdien ainsi qu'une diminution du poids du parenchyme restant chez les malades accusant un hypothyroïdisme post-opératoire. En cas de goitre toxique diffus ($n = 116$), il ne fut pas constaté de différence dans la taille du parenchyme restant, que l'opéré fut euthyroïdien ou hypothyroïdien. Chez les malades porteurs d'un goitre toxique diffus préparés avant l'intervention par des bêta-bloquants, le taux des auto-anticorps contre le cytoplasme thyroïdien s'est montré plus élevé lorsque les opérés ont développé une hypothyroïdie. Chez les malades porteurs d'un goitre toxique diffus qui ont accusé une hypofonction thyroïdienne, il a été constaté une augmentation du taux des auto-anticorps et l'existence de tissu lymphoïde plus souvent chez les patients

qui avaient été préparés par un bêta-bloquant que chez ceux préparés par un médicament thyroïdostatique. En cas de goitre nodulaire toxique la taille du parenchyme restant a représenté le paramètre le plus utile pour prédire la fonction post-opératoire thyroïdienne.

Resumen

La influencia del volumen del remanente tiroideo, del título de anticuerpos antitiroideos, de la morfología tiroidea, y de la presencia de infiltración linfocítica sobre la función tiroidea postoperatoria fue estudiada en 179 pacientes sometidos a tiroidectomía subtotal por hipertiroidismo. El procedimiento quirúrgico fue estrictamente estandarizado e incluyó la determinación del tamaño del remanente tiroideo. La medicación preoperatoria utilizada fue con agentes bloqueadores de beta-adrenoreceptores en 101 de los pacientes y con tiroxina en 78. Con remanentes tiroideos limitados a 6–10 g (o, en bocios de menos de 20 g, a 25–30% del peso inicial de la glándula), la tasa general de recurrencia a los 2–8 años (promedio 5.3 ± 2.0) de seguimiento fue 1.7% y la incidencia de hipofunción tiroidea 29.6%.

En el bocio nodular tóxico (BNT; n = 63), se halló una significativa correlación negativa entre TSH y el tamaño del remanente a los 12 meses, así como un remanente de peso significativamente menor en los pacientes que desarrollaron hipotiroidismo postoperatorio. En el bocio difuso tóxico (BDT; n = 116), no se halló diferencia en cuanto al tamaño del remanente entre los pacientes eutiroideos y los hipotiroideos. Entre los pacientes con BDT tratados preoperatoriamente con betabloqueadores, se encontró aumento en la incidencia de autoanticuerpos contra el citoplasma tiroideo en aquellos que desarrollaron disfunción tiroidea postoperatoria. En el grupo con BDT que desarrolló hipofunción, encontramos aumento en el título de autoanticuerpos y la "presencia de tejido linfoide" con mayor frecuencia en aquellos tratados preoperatoriamente con betabloqueadores en comparación con los que recibieron tratamiento con tirostáticos. En el BNT, el remanente tiroideo fue considerado como el parámetro de mayor utilidad para el cirujano en cuanto a la predicción de la función tiroidea postoperatoria.

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