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ENDOCRINE SURGERY

Long-term sequelae of the less than total thyroidectomy procedures for benign thyroid nodular disease

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Abstract

Introduction Nodular goiter is the most common disorder of the thyroid gland. Less than total thyroidectomy procedures are considered the gold standard in the surgical management of nodular thyroid disease despite its propensity for recurrence. The aim of the study was to assess long-term sequelae of the less than total thyroidectomy procedures.

Material and methods In this single-center retrospective study, records of 154 patients that underwent less than total thyroidectomy, for nodular disease and/or hyperthyroidism between 1998 and 2013, were reviewed. Patients with malignant findings in the histology report and a follow-up of less than 5 years were excluded.

Results The mean age of the recorded patients was 65.1 ± 12.91 years of which 132 were females. Subtotal thyroidectomy was performed in 45.5% of the study population, 22.1% underwent partial thyroidectomy, while the remaining 32.5% underwent lobectomy. Long-term thyroxine supplementation was administered in 138 patients (89.6%). Recurrence of clinically important nodules (>1 cm) was observed in 68.2% of patients but only 11% of the population underwent completion thyroidectomy. In the univariate analysis, the duration of follow-up ($p = 0.00005$, C.I.: 0.903–0.965) as well as the type of operation ($p = 0.035$, C.I.: 1.031–2.348) appeared to have a significant correlation with nodular recurrence. The multivariate analysis identified the duration of follow-up ($p = 0.0005$, C.I.: 0.908–0.973) as the only significant predictive factor of nodular recurrence.

Conclusion This is the first study with such a long duration of post-operative follow-up. The high rate of nodular recurrence in less than total thyroidectomy procedures along with the lifelong need for thyroxine supplementation suggest that a more conservative surgical approach is needed. When surgery is recommended, we suggest total thyroidectomy as the treatment of choice to avoid the recurrence of disease, the high cost associated with frequent follow-ups by means of sonography as well as thyroxine replacement therapy.

Keywords Thyroid nodules · Thyroid lobectomy · Nodular recurrence

Introduction

Nodular goiter is the most common disorder of the thyroid gland. In the last decades, the frequency is rising due to the increased availability of sensitive and specific radiological, cytological, and biochemical diagnostic tests [1, 2]. Recent advances in ultrasonography screening and fine-needle aspiration biopsy (FNAB) have facilitated the detection and diagnosis of thyroid cancer [3]. Procedures such as less than total thyroidectomy (defined as lobectomy, partial or subtotal thyroidectomy) [4] were used mainly to treat thyroid nodules, and/or hyperthyroidism. In recent years, the surgical interest is focused on less extensive thyroid surgery; even in cases of differentiated thyroid cancer [5]. Serious complications related to total thyroidectomy, such as recurrent laryngeal nerve (RLN) injury and postoperative hypocalcemia, favor the practice of such techniques, especially in cases of benign thyroid disease [6]. The lifetime needs for thyroxine supplementation and, as a result, the

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increased overall healthcare cost may be another limitation in the use of total thyroidectomy.

The main indication for surgical treatment of thyroid nodules is malignancy. Surgery is also recommended in the cases of toxic nodules, compressive symptoms, growing nodules, or patient anxiety concerning the nodule. American Association of Clinical Endocrinologists (AACE), Associazione Medici Endocrinologi (AME), and American College of Endocrinology (ACE) guidelines published in 2016, recommend lobectomy as the preferred surgical method for uninodular benign goiter and suggest lobectomy plus isthmusectomy or near total thyroidectomy for multinodular goiter, depending on the clinical presentation and patient's preference [7]. American Thyroid Association (ATA) guidelines endorse lobectomy for solitary, indeterminate nodules, but they state that total thyroidectomy may be preferred for nodules cytologically suspicious for malignancy, nodules >4 cm or nodules associated with high-risk of malignancy in sonographic or molecular testing findings [8].

Taking into consideration the lack of consensus in the treatment of thyroid nodules disease, as well as the scarcity of available data regarding the efficacy of less than total thyroidectomy in the treatment of benign thyroid nodular disease, we designed this study to evaluate the effectiveness of this surgical approach as a therapeutic model for nodular disease, multinodular goiter as well as for hyperthyroidism. In particular, the aim of our study was to assess the long-term sequelae of less extensive surgical procedures with emphasis on the nodular recurrence rate and to identify potential predictive factors of recurrence. We also analyzed the need of thyroxine supplementation postoperatively, since maintaining normal thyroid function is one of the main advantages of less than total thyroidectomy, as well as the frequency of re-operations.

Materials and methods

This is a single-center retrospective study of an endocrinology outpatient clinic at the Tertiary, General, University Hospital. Records of 154 patients that underwent less than total thyroidectomy for nodular disease and/or hyperthyroidism between 1998 and 2013, were reviewed. These patients were identified using the endocrinology department database. Less than total thyroidectomy was defined as any surgical procedure on thyroid gland (lobectomy, partial or subtotal thyroidectomy) resulting in postoperative thyroid remnant of more than 1 ml [4]. Inclusion criteria for less than total thyroidectomy were: (1) single nodule, (2) multinodular goiter, or (3) recurrent Graves' disease. Exclusion criteria were: (1) malignant histology report, (2) a follow-up less than 5 years, and (3) thyroidectomy due to less than 1 ml in volume remnant.

All patients included in the study had TSH levels in the normal range (0.4–4.5 μIU/ml).

All pre- and post-operative ultrasound imagines were reviewed by a single investigator (G.B.). The remaining lobe, in patients who underwent lobectomy, was pre-operatively tested and was sonographically normal. Development of new thyroid nodules, size of nodules as well as the dates of ultrasound reports were recorded. Reoperations for nodule recurrence were also noted. Recurrence was defined as the occurrence of new nodule(s) >1 cm in the remaining lobe(s) for lobectomy or partial thyroidectomy and for subtotal thyroidectomy the occurrence of nodule(s) of any size in the thyroid remnant >1 ml on at least one postoperative ultrasound. Follow-up time was defined as the time interval between surgery and the most recent recorded endocrinological examination. Time to recurrence was defined as the time interval between surgery and the first positive postoperative thyroid ultrasound (new nodule occurrence, as previously reported). The decisions for the need of postoperative levothyroxine supplementation, or the need of reoperation for nodular recurrence were also recorded.

The population was divided into two groups based on the presence of recurrence. Characteristics of the population that had been recorded were age, gender, and body mass index (BMI).

The study followed the 1975 Helsinki guidelines and was approved by the Ethical Committee of LAIKO General Hospital.

Assays

The serum TSH levels were measured by a sensitive two-site chemiluminescent immunometric assay with normal values 0.4–4.5 μU/ml with analytical sensitivity 0.004 μIU/ml.

Statistical analysis

The comparison between the subgroups was carried out using Chi-squared test corrected by Fisher's exact test when appropriate for non-continuous variables, while the continuous variables were analyzed by Student's *t*-test for parametric and Mann–Whitney *U* test for non-parametric variables. The impact of age, gender, type of operation (1 = lobectomy; 2 = partial; 3 = subtotal thyroidectomy), duration of follow-up, thyroxine replacement need after surgery was assessed by logistic regression analysis. Non-parametric variables were submitted to logarithm transformation in order to be used in logistic regression analysis. A p-value < 0.05 was considered statistically significant. SPSS software (SPSS 16. Inc. Chicago, IL) was used for the statistical analysis.

Results

One hundred fifty-four (154) patients, 132 of whom females (85.7%), were included in the study. The mean age of the patients was 65.1 ± 12.91 years (median: 66 years, range: 30–97). Subtotal thyroidectomy was performed in 34 patients (22.1%), 70 patients (45.5%) underwent partial thyroidectomy while the remaining 50 patients (32.5%) underwent lobectomy (Table 1).

The mean follow-up time was 26.89 ± 13.1 years. All patients suffered from benign thyroid disease, as confirmed by the histology. The majority of patients, 138 out of 154 patients (89.6%), needed long-term thyroxine supplementation. The target TSH levels with thyroxine supplementation were between 0.4 and 4.5 μIU/ml.

Recurrence of nodules was observed in 68.2% of patients but only 11% underwent completion thyroidectomy. Reoperation for nodules recurrence in the remnant gland was performed mostly due to anxiety of the patients, despite benign cytology on repeated FNABs. The nature of the recurrent nodules after surgery was confirmed by a single pathologist. All nodules after reoperation were also benign on histology.

The prevalence of surgical complications in primary surgery was a low 1.3% (2/154). One patient with permanent hypocalcemia and the other with damage of the RLN. In the re-operated patients there was not any surgical complication (0/17).

In the univariate analysis, the duration of follow-up ($p = 0.00005$, C.I.: 0.903–0.965) as well as the type of operation ($p = 0.035$, C.I.: 1.031–2.348) were significantly associated with nodular recurrence. Furthermore, in the multivariate analysis, the duration of follow-up ($p = 0.0005$, C.I.: 0.908–0.973) was the only independent predictive factor of nodule recurrence (Table 2).

Table 1 Patients characteristics ($N = 154$)

Women (*n*, %)	132 (85.7)
Age (years) (mean, SD)	65 (12.9)
Follow-up (years) (mean, SD)	26.8 (13.1)
Type of operation	
1. Lobectomy (*n*, %)	50 (32.5)
2. Partial thyroidectomy (*n*, %)	34 (22.1)
3. Subtotal thyroidectomy (*n*, %)	70 (45.5)
Re-operation (*n*, %)	17 (13.3)

Discussion

Less than total thyroidectomy procedures are considered the gold standard in the surgical management of nodular thyroid disease in the Western World; even in cases of differentiated thyroid cancer. Conversely, the use of total thyroidectomy for the treatment of nodular thyroid disease is very limited due to major post-operative complications, such as RLN injury and permanent hypocalcemia, which are associated with this type of operation. Nevertheless, in the present study, we found a high rate of nodular recurrence (68.2%) in patients who underwent less than total thyroidectomy procedures. Moreover, majority of these patients need a lifelong thyroxine supplementation.

Most thyroid conditions, including differentiated thyroid cancer, carry excellent prognosis [5]. Therefore, given the fact that, in many cases treatment involves surgery, understanding and minimizing surgical morbidity has been the focus. One of the basic arguments against total thyroidectomy is the increased surgical morbidity of this procedure in comparison to less than total thyroidectomy. In contrast, the complication rates of total thyroidectomy seem to be decreased due to the advance of surgical technique and surgical expertise. The use of technological devices such as neurostimulators to reduce the complications are not so clear, especially in primary surgery for benign diseases.

Agarwal et al. as well as Moalem et al. in two evidence-based reviews of literature demonstrate that the rates of transient and permanent RLN palsy are not significantly different after total thyroidectomy compared to lobectomy [6, 9]. On the contrary, transient hypocalcemia is more frequent in patients after total thyroidectomy [6, 9]. Moreover, a surgeon's volume in thyroid surgery plays a crucial role in complication rates. High-volume surgeons (>40 cases per year) had fewer readmitted patients and improved patient safety [10]. A cross-sectional analysis by Gourin et al. showed that surgeon volume is significantly associated

Table 2 Statistics results (logistic regression analysis) regarding predictive factors of nodular recurrence in less than total thyroidectomy

Parameters	Crude		Mutually adjusted	
	OR (95% C.I.)	*p*-Value	OR (95% C.I.)	*p*-Value
1. Thyroxine supplementation (1 = no; 2 = yes)	0.79–16.6	0.098	0.41–10.2	0.38
2. Type of operation (1 = lobectomy; 2 = partial thyroidectomy; 3 = subtotal thyroidectomy)	1.031–2.348	0.035	0.8–1.9	0.37
3. Duration of follow-up (years)	0.903–0.965	0.00005	0.908–0.973	0.00005

with complication rates [11]. Furthermore, re-operative thyroid surgeries carry a higher risk of complications compared to primary surgeries, even in experienced hands, due to technical difficulties from the distorted region's anatomy [11]. In a previous study conducted by Sandonato et al. on 697 patients undergoing surgery for benign thyroid disease, a comparison was made regarding the safety between primary total thyroidectomy ($n = 545$) for benign multinodular goiter and completion thyroidectomy for recurrence of multinodular disease, following an earlier subtotal thyroidectomy ($n = 34$) [12]. The authors reported a significantly higher complication rate in patients undergoing completion thyroidectomy for recurrence than in those who underwent total thyroidectomy from the beginning. The author stated total thyroidectomy as the procedure of choice for benign multinodular goiter because of its low incidence of complications and the radical control of the disease.

Another disadvantage of total thyroidectomy, according to literature, is the risk of postoperative thyroid dysfunction. Stoll et al. showed that after thyroid lobectomy, approximately only 1 in 7 patients experience hypothyroidism requiring thyroid hormone treatment [13]. Furthermore, Lee et al. demonstrated that patients with preoperative TSH > 2.5 mIU/L showed a high risk of requiring postoperative levothyroxine supplementation [14]. In our study, 89.6% of the patients who underwent less than total thyroidectomy, experienced hypothyroidism. This observation is being confirmed by a recently published study investigating the efficacy of lobectomy in the treatment of unilateral nodular benign disease, and demonstrating that, despite the residual thyroid gland mass, patients were still in need of thyroxine supplementation. This study showed a high prevalence of levothyroxine replacement, up to 87.3% (213/244) in patients who underwent thyroid surgery and were in need for postoperative thyroxine supplementation [5].

The risk of nodular recurrence, and therefore the need for a completion reoperation, is the main disadvantage of less than total thyroidectomy. There are limited data concerning nodular relapse after less radical thyroid surgery for benign thyroid disease. The heterogeneity of studied populations, the different iodine intake status, the inconsistency in follow-up duration as well as the lack of clear definition of nodular recurrence, render extremely difficult the comparison between the results of several studies. In reports with clear definition and ultrasound imaging of the recurrent disease, nodular recurrence rates varied from 1.2 to 60% [15–25]. The rate of nodular recurrence in our study was 68.2% and concerns clinically identified nodules, meaning more intensive follow-up, more neck ultrasounds as well as any eventual FNAB. A recent study by Tuttle et al. showed that even the rates of tumor growth for malignant nodules less than 15 mm were low, an indication similar to that of benign nodules [26]. Therefore, we excluded patients with a follow up of less than 5 years from our study; as a minimum time for nodular recurrence. This is the first study including patients with such an extensive follow-up duration. Interestingly, the only predictive risk factor for nodular recurrence in this multivariate analysis was the duration of follow-up, suggesting that recurrence of thyroid nodules after less than total thyroidectomy procedures is a matter of time.

Finally, a recent prospective study showed that total thyroidectomy leads to significant benefit among patients with benign nontoxic goiters by restoring the quality of life equal to that in the general population [27]. On the other hand, for the case of less than total thyroidectomies, recurrence of clinically important nodules is "the price to pay". Thus, the psychological as well as the financial cost for these patients, resulting from the need for long-term surveillance and repeated FNAB, should be taken into consideration. Moreover, patients who underwent total thyroidectomy with benign nodular disease have no need for lifelong ultrasound assessment.

In conclusion, thyroid surgery and especially total thyroidectomy is nowadays proven to be a safe procedure in high volume surgeons, with much lower complication rates than completion thyroidectomy. The present study demonstrated a high rate of nodular recurrence in less than total thyroidectomy procedures, as well as a lifetime need for thyroxine supplementation for many patients. The psychological and economic cost of nodular recurrence in the remnant gland is a huge burden to the patient. Considering the multifactorial complexities, we conclude that, when bilateral surgery is required for thyroid disease (regardless of indication), total thyroidectomy is preferable than less than total thyroidectomy, with several benefits for the patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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