Should Subtotal Thyroidectomy Be Abandoned in Multinodular Goiter Patients From Endemic Regions Requiring Surgery?

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The most convenient surgical procedure for benign thyroid diseases is still controversial. The aim of this study is to determine the recurrence rate and risk factors for recurrence after different thyroidectomy procedures in multinodular goiter patients. Patients were separated into two groups according to the detection of a recurrent nodule or not after thyroidectomy. Of the 748 patients, 216 (29%) had recurrence, while 532 had no recurrent nodule. The difference between surgical procedures described as subtotal (ST), near total (NT) and total thyroidectomy (TT) was statistically significant. Transient hypoparathyroidism was significantly higher in NT and TT, when compared to ST patients ($P < 0.05$). Young age, bilateral multinodular goiter and insufficient surgery are risk factors affecting recurrence for benign nodular thyroid disease. Currently, subtotal procedures should be discontinued and total or near total procedures should be preferred. Meanwhile, the probability of a higher risk of hypoparathyroidism should be kept in mind.

Key words: Multinodular goiter – Thyroidectomy – Recurrence classification description: Endocrinology

Goiter, affecting almost 6% of the population, is the leading neck endocrine disease in Turkey, as is true in the rest of the world.[1] Thyroidectomy, which remains an important option for treating multinodular goiter, is one of the most performed operations by general surgeons in our country.

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Turkey is an endemic region, where most goiters present with multinodular disease.[1] Recently, surgery for benign goiter has been recognized as an acceptable and safe treatment modality, which has low surgical risk and mortality rates. Despite the improvement in diagnosis and treatment of thyroid diseases in the last two decades, there remains controversy in the literature concerning which procedure is superior for this benign disease.[2] Previously, subtotal thyroidectomy for multinodular thyroid disease was regarded as a gold standard treatment, due to decreased laryngeal nerve and parathyroid complications and decreased requirement for life-long hormone replacement therapy.[3,4] However, it is widely reported that during long-term follow-up after subtotal thyroidectomy in multinodular disease, an increasing recurrence rate of up to 78% should be expected.[5] Meanwhile, a second operation for recurrent nodules is well accepted to result in increased laryngeal nerve and parathyroid morbidity, when compared with an initial approach. Although many centers have changed their operative strategy in favor of total and/or near total thyroidectomy, subtotal thyroidectomy still seems to be the preferred option in daily practice.[6]

Based on these considerations, our aim was to evaluate the outcomes of various operations and postoperative replacement therapy as on recurrence in patients undergoing multinodular goiter surgery in a single center.

Patients and Methods

This study was approved by the institutional local ethics committee and all patients were requested for informed consent in relation to analysis of data. A retrospective analysis was performed on a total of 2020 patients, who had undergone thyroid surgery for benign multinodular disease between June 1996 and November 2005. All cases underwent a subtotal thyroidectomy (ST), a near total thyroidectomy (NT) or a total thyroidectomy (TT), based on the results of preoperative tests, intraoperative exploration, and frozen section analysis, as previously mentioned.[7] For the purposes of the present study, ST is defined as a thyroidectomy with residual bilateral 3-g remnants of thyroid tissue, NT is defined as a thyroidectomy with <1 g of remnant thyroid tissue. Cases with lobectomy, unilateral disease, and thyroid cancer were not analyzed.

Patient demographics including age, gender and family history were examined. Data collection also included L-thyroxine replacement therapy, surgeon experience, and complications. These were collected from clinical records, surgical data, pathology reports, and follow-up surveys. All patients were invited to the hospital via telephone and invitation letters for physical examination, thyroid hormone assessment, and thyroid ultrasonography. A survey that involved questions related to symptoms, pre- and postoperative treatments and a revision surgery had been carried out. Serum thyroid hormone levels as well as the thyroid bed were evaluated. Thyroid ultrasonography was performed by experienced radiologists E.K, S.T and S.O. Interobserver and intra-observer variability had been checked. Siemens Sonoline Elegra Ultrasound Unit with a 7.5 MHz linear probe (Siemens, Munich, Germany) was used to demonstrate the presence and volume of the remaining thyroid tissue and, if present, the characteristics of thyroid nodules. Indications for reoperation of recurrence were presence of a nodule at risk for malignancy, large goiter and compressive symptoms. The rate of recurrences and patients requiring revision surgery were calculated for each surgical procedure. Patients were divided into two groups: Group 1 represented patients without a recurrent disease, while Group 2 was comprised of patients in whom recurrence was detected during follow-up.

Postoperative complications were also examined in detail, which included transient hypocalcemia, permanent hypoparathyroidism, recurrent laryngeal nerve injury, and postoperative neck hematoma. Hypocalcemia was defined as a serum calcium level less than 8.4 mg/dL (normal range: 8.4–10.4 mg/dL). Transient hypocalcemia was defined as postoperative hypocalcemia that resolved within 6 months of thyroidectomy. Permanent hypoparathyroidism was defined as postoperative hypocalcemia that persisted for greater than 6 months after surgery.

SPSS for Windows (SPSS Inc. Chicago IL, USA), version 15.0 software was used for statistical analysis. Results were expressed as mean + standard deviation (SD). The relation between clinical data and recurrence of the disease or the necessity for reoperation were analyzed with the Fisher's exact test (for categorical variables) and Mann–Whitney U test (for continuing variables). Values of $P < 0.05$ were accepted as significant.

Results

Unfortunately, only 748 (37%) out of 2020 patients replied to the follow-up call. All patients provided

Table 1 Comparison of the two groups for demographic data

	Group 1 (n = 532)	Group 2 (n = 216)	P value
Mean age (years)	50.1 ± 9.8	52.6 ± 10.3	NS
Gender (%)			
Female	86.5	85	NS
Male	13.5	15	
Family history (%)			
Yes	47	46	NS
No	53	54	
Replacement therapy (%)			
Yes	81.8	62.1	P < 0.05
No	18.2	37.9	
Surgical technique (%)			
ST	47.9	65.2	P < 0.05
NT	13.3	25.5	
TT	38.8	9.3	
Surgeon experience (%)			
Resident under supervision	36	42	NS
Attending surgeon	64	58	

ST, subtotal thyroidectomy; NT, near total thyroidectomy; TT, total thyroidectomy.

informed consent in relation to the storage, analysis and presentation of the data. The average age of 748 studied patients was 50.3 ± 10.8 years, and 86% were female. Between 1996 and 2000, 68% of patients underwent ST. After 2000, all patients (n = 394) had undergone TT or NT. The change in operative management was made in response to reported high rates of recurrence and to the change in the philosophy of the surgical management of multinodular goiter. The rate of recurrent goiter was 29% (n = 216). The interval between initial surgery and detected recurrence was 6,6 ± 2 years (range 2–11 years). Long term data (>10 years) was available in 86 patients (11.5%). Only 11 patients (5%) in whom a recurrence was developed required further surgical treatment.

There was no statistical difference regarding comparison of age, gender, and family history between the groups ($P > 0.05$). Subtotal thyroidectomy was the initial procedure in 255 cases (47.9%) and a TT in 206 cases (38.8%) in Group 1. In Group 2, there were 141 subtotal thyroidectomies (65.2%) and 20 TT (9.3%). There was a significant difference between groups ($P < 0.05$). There were more patients on L-thyroxine replacement therapy in Group 1 ($P < 0.05$). Surgeon experience (resident under supervision *versus* attending surgeon) had no impact on recurrence rates (Table 1).

There was no operative mortality in the study group. Five (0.6%) patients required urgent re-exploration for hematoma. Rates of permanent hypoparathyroidim and transient or permanent recurrent laryngeal nerve (RLN) palsy were not significantly different between ST, NT, and TT patients ($P > 0.05$), while transient hypoparathyroidism was significantly higher in NT and TT, when compared to ST patients ($P < 0.05$). Postoperative complications for each surgical treatment group are detailed in Table 2.

Discussion

Limits of resection for thyroid surgery have changed over years. Until the end of the 20th century, total thyroidectomy, except for thyroid cancer, was performed very rarely due to high complication rates. Subtotal resections for benign thyroid diseases have been accepted as gold standard therapy during this period.[3,4] However, after long-term follow-up results of subtotal resection, it was obvious that this procedure was involved with increased recurrence rates. Afterwards, discussions on the type of surgery for benign diseases came into question.[8–10]

In most studies investigating recurrence in multinodular goiter, research is done after the 5th postoperative year to detect recurrence. In case of a longer follow-up period, it is no surprise that the rate of recurrence will be increasing and meanwhile many patients will be lost during follow-up. The incidence of recurrence after ST, especially after

Table 2 Postoperative complications

	ST	NT	TT	P value
Transient hypocalcemia	9%	15%	21%	P < 0.05
Permanent hypocalcemia	1%	1.6%	1.5%	NS
Transient recurrent nerve palsy	2.2%	2.3%	1.9%	NS
Permanent recurrent nerve palsy	0.8%	1.2%	1.1%	NS
Neck hematoma	0.7%	0.7%	0.4%	NS

ST, subtotal thyroidectomy; NT, near total thyroidectomy; TT, total thyroidectomy.

follow up over 10 years, reaches 40%. Interestingly, there are no standard criteria to define recurrence.[11–13] Recurrence of benign thyroid diseases has been defined variously in the literature. Physical examination, thyroid ultrasonography, thyroid function tests, scintigraphy, and sometimes computed tomography are tools defined to be used in the diagnosis of recurrence. In some studies, detecting a nodule ultrasonographically or the presence of a thyroid tissue greater than 18 mL in women and 24 mL in men, have been accepted as recurrence.[6,14,15] In this study, a standard follow-up procedure had not been performed. For this reason, the true relapse time of nodules determined via ultrasonography is unknown. Even our recurrence rate was 29%, we suggested reoperation for 11 patients with the above characteristics. Surgery was recommended when there was a suspicion of malignancy, presence of pressure symptoms and/or nodules greater than 30 mm.[14]

The main aim of surgical treatment for thyroid diseases should always be to perform the most effective treatment with minimum complication and recurrence rates. Total thyroidectomy for benign diseases eliminates the disease and prevents the possibility of recurrence.[16] However, the authors, who are against total thyroidectomy in benign disease management, emphasize increased morbidity, including recurrent laryngeal nerve and parathyroid injury. They emphasize that those patients are also sentenced to have a lifelong hormone replacement therapy.[17] In the current study, after the initial surgery, RLN and parathyroid morbidity rates were not higher than reported in the literature. In addition, only the transient hypocalcemia rate was significantly higher in NT and TT, when compared to ST patients.

Surgical dissection around the RLN during reoperations is difficult because of fibrosis due to previous surgery. The morbidity caused by nerve injury is higher in this situation. Development of RLN paralysis in a reoperation is directly associated with the surgeon's experience and rates are between 0 and 14% in the literature.[18–21] Recurrent laryngeal nerve palsy following previous surgery may be masked by contralateral vocal cord compensation and the voice may appear normal. Therefore, preoperative vocal cord examination must be carried out in patients who are candidates for recurrent surgery and when it is not safe, some part of thyroid tissue should be left at the posterior to prevent bilateral nerve injury.[11,23,24]

Before recurrent surgery, assessing the localization and functional status of parathyroid glands is impossible. The isolation of parathyroid glands may be difficult and autotransplantation is recommended in order to prevent permanent hypocalcemia for incidentally removed glands.[11,18,24] Even when reoperations have been performed by experienced surgeons, the risk of parathyroid gland and RLN injury will be higher, when compared to the first surgery.[25] Menegaux et al have done a comparative study between reoperative thyroid surgery and primary thyroid surgery in terms of complication. They observed a significantly higher RLN and parathyroid morbidity in reoperative cases.[18]

Recently, studies concerning recurrence in benign thyroid diseases demonstrate that young age, multinodular or bilobar disease, family history and inadequate surgery are the prominent risk factors for recurrence.[25] To prevent recurrence of benign thyroid disease, a detailed preoperative evaluation is necessary to decide the appropriate surgical procedure. Ultrasonography, which is used for both benign and malignant thyroid diseases, is a user-dependent method. An experienced radiologist guides surgeons to decide the best surgical procedure by reporting micronodules, which have a major impact on early recurrences. Barbier et al found multinodular disease in 30% of the patients during surgery who were reported to have solitary nodules during the preoperative work-up.[4] In multinodular goiter, 40% of nodules are located close to the posterior capsule of the thyroid gland and might be left during a subtotal resection. These nodules may grow independently from TSH and lead to high recurrence rates.[26] Particularly, in endemic goiter regions, procedures like nodule enucleation, subtotal and unilobar resections are not recommended for multinodular bilobar disease, since the unavoidable risk of continuing disease on the remaining tissue.[27,28] Total thyroidectomy is accepted as an increasingly preferable treatment option for nodular disease involving both thyroid lobes in benign goiters.[9,16,29] In our series, total thyroidectomy had been carried out more in Group 1.

The importance of family history in thyroid cancer is clearly reported in the literature.[30] Family history may be considered as an influential factor in the development of recurrence after multinodular goiter surgery. Erbil et al evaluated family history between reoperation and primary surgery in multinodular goiter where no significant differences had been found.[1] Likewise, Gibelin et al reported that the

rate of family history was higher in recurrence surgery patients than those who had undergone primary surgery but the difference was not statistically significant.[25] In our study, there was no significant difference compared family history between groups.

Some studies have expressed that L-thyroxine therapy is protective against relapses and reoperations, by reducing TSH stimulation on the residual tissue. Thus, it is claimed that thyroid hormone supplementation after conservative surgery could effectively protect patients from recurrence.[1,5,14,12] But on the other hand, according to other researchers, despite replacement therapy, long-term postoperative follow-up showed a high recurrence rate after subtotal thyroidectomy.[18] Recent studies indicate that the protective effect of hormone therapy is controversial.[31–33] It has been believed that thyroid tissue continues to grow independently from TSH, under the influence of multiple factors like fibroblast growth factor and insulin-like growth factor. Insulin-like growth factor-1, epidermal growth factor, fibroblast growth factor, anti-TSH receptor antibodies and antithyroid peroxidase antibodies stimulate the growth of follicular cells independently from TSH. Thus, nodular formation will be seen in the remaining tissue, which is regarded as normal after thyroidectomy even though the suppression therapy and recurrence will occur.[17,34–36] Because this process takes a long time period, for young patients, total resection and for elderly patients more limited resections has been suggested so that elderly patients will be able to continue their lives without the need for thyroid replacement.[37] All pathologic tissue should be removed in the presence of bilobar disease in young patients who are expected to have a longer life span.[34] In our study, there was no significant difference in terms of average age between groups. Nevertheless, rate of postoperative thyroid hormone replacement in Group 2 was 62,1%, which was significantly lower than Group 1. This result supports the literature concerning TSH stimulation required for nodule recurrence.

To conclude, to the best of our knowledge this study is the only series examining the recurrence and factors affecting recurrence in multinodular goiter in western Turkey. Recurrence rate after surgery for benign thyroid diseases was 29%. Limited surgical resection, lack of replacement therapies, presence of bilobar disease and young age must be taken into account as related factors for recurrence. The necessity of reoperation for recurrence of benign thyroid diseases is a serious clinical problem due to the high rates of postoperative complications. For this reason, we believe that total or near-total thyroidectomy should be the preferred surgery in multiple bilobar disease to avoid recurrence.

Acknowledgments

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