ORIGINAL ARTICLE

The Advantage of Total Thyroidectomy to Avoid Reoperation for Incidental Thyroid Cancer in Multinodular Goiter

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Hypothesis: To investigate the impact of total thyroidectomy on the rate of completion thyroidectomy for incidentally found thyroid cancer in euthyroid multinodular goiter.

Design: A randomized, prospective clinical trial.

Setting: A tertiary referral center.

Patients: Patients with euthyroid multinodular goiter without any preoperative suspicion of malignancy, history of familial thyroid cancer, or previous exposure to radiation were randomized (according to a random table) to total or near-total thyroidectomy leaving no remnant tissue or less than 1 g (group 1; n=109) or bilateral subtotal thyroidectomy leaving 5 g or more of remnant tissue (group 2; n=109). Patients with preoperative or perioperative suspicion of malignancy were excluded.

Main Outcome Measures: We compared the complication rates and the incidence of thyroid cancer requiring radioactive iodine ablation and completion thyroidectomy between groups.

Results: There were no permanent complications. The rates of temporary unilateral vocal cord dysfunction and hypoparathyroidism showed no significant difference between groups 1 and 2 (0.9% vs 0.9% and 1.8% vs 0.9%, respectively; $P>.05$). Papillary cancer was found in 10 group 1 patients (9.2%) and 8 group 2 patients (7.3%) ($P=.80$). Of the 9 patients requiring radioactive iodine ablation, reoperation was avoided in 5 group 1 patients; the remaining 4 group 2 patients underwent completion thyroidectomy ($P=.007$).

Conclusion: We recommend total or near-total thyroidectomy in multinodular goiter to eliminate the necessity for early completion thyroidectomy in case of a final diagnosis of thyroid cancer.

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TOTAL THYROIDECTOMY IS the procedure of choice in patients with thyroid cancer, Basedow or Graves disease, and toxic multinodular goiter. In recent years, total thyroidectomy has emerged as a surgical option to treat patients with multinodular goiter, especially in endemic iodine-deficient regions.[1-11] Multinodular hyperplasia frequently involves the whole gland in endemic regions, and there is no normal tissue to leave behind. The rate of recurrence is high after subtotal resections for multinodular goiter in long-term follow-up, despite postoperative thyroid hormone supplementation.[2,6,8,12-15] A considerable number of patients undergoing primary treatment with subtotal resection need reoperation for recurrence, which has a higher rate of complication compared with the primary procedures.[6,16-20] The incidence of thyroid cancer varies from 7.5% to 13% in multinodular goiter.[21-23] The presence of multiple nodules decreases the diagnostic value of fine-needle aspiration biopsy, and thyroid cancer is frequently an incidental postoperative histological finding in multinodular goiter. In such patients treated with subtotal thyroidectomy, completion thyroidectomy might be necessary.

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The aim of this study was to investigate whether total or near-total thyroidectomy decreased the rate of completion thyroidectomy for incidentally diagnosed thyroid cancer in multinodular goiter in an endemic iodine-deficiency region.

METHODS

From September 1, 2001, to December 31, 2002, we undertook a prospective study to compare the rates of completion thyroidectomy for

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The Histological Feature of Papillary Cancer in Groups 1 and 2

	Tumor Size, cm	No. of Foci	Thyroid Capsule Invasion	Extrathyroidal Invasion	Indication for Reoperation
Group 1					
Patient 1	0.6	3	+	+	+
Patient 2	1.1	2	+	–	+
Patient 3	0.8	4	+	–	+
Patient 4	0.4	3	+	–	+
Patient 5	1.1	1	+	–	+
Patient 6	0.3	1	–	–	–
Patient 7	0.3	1	–	–	–
Patient 8	0.3	1	–	–	–
Patient 9	0.2	2	–	–	–
Patient 10	0.2	1	–	–	–
Group 2					
Patient 1	1.1	1	+	+	+
Patient 2	0.5	3	+	–	+
Patient 3	2.5	1	+	+	+
Patient 4	1.5	Multiple	+	–	+
Patient 5	0.6	2	–	–	–
Patient 6	0.6	2	–	–	–
Patient 7	0.5	1	–	–	–
Patient 8	0.3	1	–	–	–

Abbreviations: Minus sign, negative finding; plus sign, positive finding.

incidentally found thyroid cancer after total or near-total and subtotal thyroidectomy in multinodular goiter. Two hundred eighteen patients with multinodular goiter were included in the study. All patients were euthyroid and had no history of hyperthyroidism, radiation exposure, or familial thyroid cancer. Thyroid scanning and ultrasonography revealed multinodular hyperplasia of the thyroid gland in all patients. Patients were selected according to the number on the random table for 2 different extensions of surgical procedures. The total amount of remnant thyroid tissue was intended to be none or less than 1 g in group 1 and 5 g or more in group 2. Near-total thyroidectomy was performed by the capsular dissection method, leaving less than 1 g of remnant tissue. The amount of remnant tissue was estimated as 1 cm^3 equals 1 g. Any patient with preoperative or perioperative suspicion of malignancy was excluded. Postoperative complications, thyrotropin (TSH) values, and the incidence of thyroid cancer were assessed in both groups. We investigated whether there was a significant difference in the rate of thyroid cancer requiring radioactive iodine (RAI) ablation and completion thyroidectomy between groups. Histological criteria for RAI therapy included tumor size greater than 1.5 cm, any size of tumor with thyroid capsule or extrathyroidal invasion, or multicentricity (≥3 tumor foci). The departments of general surgery and endocrinology collaborate to maintain the treatment of patients with thyroid cancer at Istanbul Medical Faculty, Istanbul, Turkey. The histological criteria for postoperative RAI ablation (100 mCi [3700 MBq]) was established as a result of this cooperative work and has been our policy for the past 2 decades. The TSH values were required to be more than 30 mIU/L to refer the patient to RAI ablation therapy. Patients who were treated with RAI were verified to have undetectable levels of serum thyroglobulin and no uptake at the thyroid bed or distant sites by iodine I131 (^{131}I)–labeled thyroid and whole body scans after the treatment. These patients received suppressive doses of thyroid hormone, and serum thyroglobulin assays were performed at 6-month intervals. Thyroid and whole body scans labeled with ^{131}I were repeated if serum thyroglobulin levels increased during further follow-up. Patients with noninvasive microcarcinoma who did not receive RAI ablation received suppressive doses of thyroid hormone after thyroidectomy. The follow-up schedule of these patients was similar to that of patients undergoing operation for benign goiter (neck examination and determination of serum TSH values every 6 months for the initial 2 years and then annually). Linear correlation, paired *t* test, and Fisher exact test were used for statistical analysis, and $P<.05$ was accepted as significant. The ethics committee of our institution approved of the study, and informed consent was obtained from all patients participating in the trial.

RESULTS

PREOPERATIVE FINDINGS

The mean±SD age was found to be significantly higher in group 1 (50.3±12.5 years) compared with group 2 (45.7±12.1 years) ($P=.02$). The male-female ratio was 15:94 and 17:92 in groups 1 and 2, respectively ($P=.70$). A coexistent dominant nodule was found in 39 patients (17.9%), including 20 in group 1 and 19 in group 2.

PERIOPERATIVE FINDINGS

Total and near-total thyroidectomy was performed in 19 (17.4%) and 90 (82.6%) patients, respectively, in group 1. Bilateral subtotal thyroidectomy was performed in all 109 patients in group 2. The total amount of remnant tissue was estimated to be 5 g in 77 patients (70.6%), 6 g in 26 (23.9%), and 7 g in 6 (5.5%).

POSTOPERATIVE FINDINGS

Permanent hypoparathyroidism and vocal cord paralysis were not encountered in either group of patients. The rate of temporary unilateral vocal cord dysfunction was the same (0.9%) in both groups. Although not statistically significant, the incidence of temporary hypoparathyroidism was slightly higher in group 1 than in group 2 (1.8% vs 0.9%).

The mean±SD value of the TSH value at the first postoperative month was significantly higher in group 1 compared with group 2 (45.3±17.3 vs 11.5±6.5 mIU/L) ($P<.001$). Papillary cancer was detected in 18 patients (8.2%), of whom 13 (72%) had papillary microcarcinoma (<1 cm). Of 39 patients with a coexistent dominant nodule, papillary cancer was found in only 1. This patient had a papillary microcarcinoma not originating from the dominant nodule and without local invasion or multicentricity. The incidence of papillary cancer was 9.2% (10/109) in group 1 and 7.3% (8/109) in group 2 ($P=.80$) (**Table**). Of 18 patients with papillary cancer, 9 (50%) had microcarcinoma with no local invasion or multicentricity. These patients were scheduled for follow-up only. The remaining 9 patients were found to have the histological criteria for RAI ablation (Table). Of these 9 patients, 5 were in group 1 and 4 in group 2. Five patients in group 1 received RAI ablative therapy directly. The TSH values of the 4 patients in group 2 were below 30 mIU/L, and these patients underwent completion thyroidectomy before ablative therapy. Thus, of 9 patients requiring RAI ablation, reoperation was avoided in 5 group 1 patients; however, 4 patients in group 2 underwent

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completion thyroidectomy ($P = .007$). There were no complications after completion thyroidectomy in those 4 patients.

COMMENT

In the present study, the incidence of incidental thyroid cancer was found to be 8.2% in patients undergoing operation for multinodular euthyroid goiter without any preoperative or perioperative suspicion of malignancy. We documented that performance of total or near-total thyroidectomy instead of subtotal resection as the primary procedure significantly reduced the rate of completion thyroidectomy for incidentally found thyroid cancer in multinodular goiter. Total or near-total thyroidectomy was associated with a slightly higher risk for temporary hypoparathyroidism, but this was not statistically significant.

The goal of surgical treatment in thyroid disease should be to eliminate the disease with low complication rates and to minimize the necessity for reoperative procedures. Reoperations are undertaken for postoperative histological evidence of thyroid cancer or recurrent goiter during further follow-up and are associated with higher complication rates compared with primary procedures.[1,6-20,24,25]

Multinodular goiter is the most common indication for thyroidectomy in endemic iodine-deficient regions. Preoperative evaluation for thyroid cancer by means of fine-needle aspiration biopsy is difficult in multinodular goiter owing to the presence of multiple nodules, and thyroid cancer is frequently an unexpected postoperative finding. The risk for malignancy was thought to be lower in multinodular goiter compared with solitary cold nodules. Recent studies, however, documented that this was not the case. The incidence of thyroid cancer showed no significant difference in solitary cold nodules and in cold nodules of multinodular goiter, and patients with thyroid cancer frequently presented with multinodular goiter.[21,26,27] Reoperation should be performed in patients with incidentally found thyroid cancer if the histological criteria mandate RAI ablation and there is a large volume of thyroid remnant. In the present study, of 9 patients scheduled for RAI ablation, tumor size was smaller than 1.5 cm in 7. Although these patients were considered to be at low risk according to MACIS (*M*etastasis, *A*ge, *C*urative resection, *I*nvasion, *S*ize) classification, histological examination revealed multifocality, thyroid capsule invasion, or extrathyroidial spread. Low-risk patients have a favorable prognosis, but multifocality, thyroid capsule invasion, and extrathyroidial invasion were shown to adversely affect the prognosis.[28-31] Baudin et al[31] analyzed the data of 281 patients with thyroid microcarcinoma (<1 cm) and documented that patients with more than 1 tumor focus had a significantly higher rate of recurrence compared with those with unifocal tumors, and multifocality significantly influenced the prevalence of RAI treatment. The RAI ablation was found to be an important factor in prolonging the disease-free interval and survival in patients with well-diffferentiated thyroid cancer, even low-risk patients.[32] In Turkey, a considerable number of patients undergoing operation for thyroid cancer adher to the postoperative follow-up program; however, patient noncompliance still constitutes a major problem, and some patients undergoing surgery for thyroid cancer delay seeking medical help until the development of serious complications. We prefer to take unfavorable histological findings into account when deciding on RAI treatment, despite the low-risk score. The preferred TSH level is higher than 30 mIU/L for effective RAI ablation.[33] Despite interfering with proper RAI ablation, remnant tissue may contain residual carcinoma in 11% to 53% of patients who undergo subtotal thyroidectomy with no difference in the frequency in high- and low-risk patients.[17,34-39] Thyroid cancer might be detected in approximately 10% of thyroidectomy specimens of recurrent goiter, although the preceding operations were performed for benign goiter.[40] Menegaux et al[40] documented that 20% of such patients had multifocal cancer, lymph node metastasis, or distant metastasis.

Subtotal resections (unilateral or bilateral) have been the preferred surgical treatment for multinodular goiter.[6,23,41] A conservative surgical approach followed by thyroid hormone supplementation has been claimed to efficiently prevent recurrence.[41,42] Reoperation rate for recurrence was low (2%) when all nodules were removed during thyroidectomy, but multinodular goiter was documented to be a risk factor for recurrence.[42] Anderson et al[41] found that postoperative thyroid hormone therapy reduced the rate of recurrence, but that limited unilateral procedures were associated with a high rate of recurrence. Recent studies, however, have documented that the recurrence rate after subtotal resections is high, and that the preventive effect of postoperative thyroxine treatment is highly questionable.[12-15,43,44] The incidence of recurrence has been directly related to a long postoperative follow-up and to large amounts of remnant tissue.[13,41,43-45] Most of the recurrences developed 10 to 20 years after the previous surgery, although some authors recommend 30 years of follow-up to determine the actual outcome.[3,6,13,41,42] Subtotal thyroidectomy in multinodular goiter has resulted in reoperation for recurrence in 13% to 20% of patients, reaching a peak incidence 13 years after the primary operation.[6]

The performance of total thyroidectomy in multinodular disease has been reserved for exceptionally large goiters. Opponents of total thyroidectomy claim that the procedure is not justified in multinodular disease, as the risk for malignancy is low but associated complication rates are high.[46,47] It has been documented that total thyroidectomy can be performed safely in benign nodular goiter, but that reoperations carry greater risk.[5,6,8,9,16] In addition, the relative risk for permanent complications has been found to be higher in reoperations for recurrent disease than in primary operations with extensive resection.[48]

CONCLUSIONS

The incidence of thyroid cancer in multinodular goiter without any previous suspicion of malignancy was found to be 8.2%. Subtotal thyroidectomy resulted in a significantly higher rate of completion thyroidectomy for incidentally diagnosed thyroid cancer compared with total or near-total thyroidectomy. No permanent

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complications occurred, and the extent of surgical resection had no significant effect on the rate of temporary complications. We recommend total or near-total thyroidectomy in multinodular goiter to eliminate the need for completion thyroidectomy in case of a final diagnosis of thyroid cancer.

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