Predictive Factors of Malignancy in Residual Thyroid Tissue after Partial Thyroidectomy in Patients with Differentiated Thyroid Cancer

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Abstract

Although partial thyroidectomy has lower operative risk, it potentially caries the risk of leaving residual malignancy. The aim of this study was to establish malignancy rate in residual thyroid tissue in patients with differentiated thyroid cancer (DTC) who underwent partial thyroid surgery and subsequently had completion thyroidectomy. We also investigated a number of clinical and biochemical factors that may anticipate the presence of malignancy in the thyroid remnant. Data of 58 patients with DTC who underwent completion thyroidectomy were retrospectively analyzed. Patients were divided into 2 groups based on the residual tissue pathology after completion thyroidectomy; the first group consisted of patients with malignant residual tissue, and the second group consisted of patients with benign residual tissue. Tumor histopathology type and serum thyroglobulin levels before completion thyroidectomy were compared between the two groups. Among 58 patients, 13 (22.4%) patients were found to have malignant residual tissue after completion thyroidectomy. No significant differences were found between the groups with respect to age, serum thyroglobulin level before completion thyroidectomy, primary tumor type, tumor size, bilateralism, multifocality, arterial invasion, thyroid capsular invasion, and extrathyroidal invasion. Residual thyroid volume was higher in patients with malignant residual tissue. In binary logistic regression analysis, residual thyroid volume was the only predictor factor for the presence of malignancy in the thyroid remnant. Malignancy in residual thyroid tissue is not uncommon. Thyroid remnant volume may be predictive of malignancy in residual thyroid tissue.

Keywords: Thyroid cancer, completion thyroidectomy, residual thyroid tissue

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Introduction

Thyroid cancer accounts for 90% of all endocrine system cancers and 0.2% of deaths related to cancer with a worldwide prevalence of 1% [1]. General approach for the management of differentiated thyroid cancer (DTC) in high-risk patients is radioactive iodine (RAI) therapy after total or subtotal thyroidectomy and thyroid stimulating hormone (TSH) suppression with thyroid hormone replacement [2].

The main target in DTC therapy is complete removal of primary tumor by keeping complication risk at a minimum level and to provide better quality of life. The residual thyroid tissue carries recurrence risk for the cases in whom total thyroidectomy cannot be performed [3]. Therefore, in patients with residual tissue, completion thyroidectomy or RAI ablation therapy should be performed. But it is still controversial that these patients should have a completion thyroidectomy or should have a more conservative approach, such as RAI ablation. Awareness of whether or not cancerous tissue presents in residual thyroid tissue can help us in determining the treatment approach.

Thyroglobulin (Tg) is a glycoprotein secreted by normal or neoplastic follicular cells of thyroid gland. Measurable level of Tg after total thyroidectomy indicates the presence of residue, recurrence, or metastasis [4].

The aim of the present study was to establish the rate of malignancy in residual thyroid tissue in patients with DTC as well as to investigate whether or not some factors such as serum Tg level before completion thyroidectomy and histopathologic characteristics of the tumor could anticipate the presence of malignancy in residual tissue.

Material and Methods

The present retrospective study was approved by the Ethics Committee of Ankara Numune Training and Research Hospital.

Study Design and Participants: The medical records of 58 patients with DTC who had partial thyroid surgery and subsequently underwent completion thyroidectomy between 2006 and 2012 in Ankara Numune Training and Research Hospital were reviewed. The demographic characteristics of patients, histopathological features of primary tumor (size, multifocality,

bilateralism, extrathyroidal invasion, thyroid capsular invasion, and vascular invasion), serum TSH, Tg, and anti-Tg levels before completion thyroidectomy were recorded.

Patients were divided into 2 groups according to the pathological findings of residual tissue following completion thyroidectomy; the first group consisted of the patients with malignant residual tissue, and the second group consisted of the patients with benign residual tissue. The study groups were compared with respect to demographic characteristics of patients, serum Tg levels before completion thyroidectomy, and histopathological characteristics of the primary tumor. There were no thyroid nodules in residual thyroid tissue in any of the patients. Being under the age of 18, receiving RAI therapy before completion thyroidectomy, having distant metastases, high anti-Tg levels, and presence of Hashimoto's thyroiditis were the exclusion criteria.

Laboratory Assays: Serum free triiodothyronine (fT3), free thyroxine (fT4), TSH, Tg, and anti-Tg concentrations were measured using paramagnetic particle, chemiluminescence immunoassays (Unicel DxI 800, Beckman Coulter, Brea, CA, USA). The normal reference range was 0.34-4.25 μIU/mL for TSH level, 2.5-3.9 pg/mL for fT3 level, 0.61-1.2 pg/mL for fT4 level, <2 ng/mL for Tg level, and 0-115 IU/mL for anti-Tg level.

In patients receiving levothyroxine, the treatment was stopped 4 weeks before the measurements of Tg and TSH. Before the completion thyroidectomy, ultrasonographic examination of the neck was performed using a high-resolution ultrasound device (Loqic 3, General Electric, USA). Residual thyroid volume of the patients was calculated using the following formula: width (cm) x depth (cm) x height (cm) x π/6 [5].

Statistical Analysis: Data analysis was performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 13.0. Kolmogrov–Smirnov test was used to test the normality of distribution of the measurable parameters. Data were expressed as mean ± standard deviation for normally distributed continuous variables, whereas continuous variables which did not distribute normally were shown as median (minimum-maximum). Percentages were used for categorical variables. When comparing the groups Student t Test was used for the normally distributed subset, and Mann-Whitney U test was used for the abnormally distributing subset. Logistic regression analysis was used to determine the

predictive factors of malignancy in thyroid remnant. A p-value of less than 0.05 was considered indicative of statistical significance.

Results

Patient characteristics and the first surgery: The mean age of the patients (81% female, 19% male) was 41.9±11.1 years. Preoperative fine needle aspiration biopsy results are given in Table 1. All of the patients had residual thyroid tissue after a planned total thyroidectomy (55.2%), total thyroidectomy+bilateral central lymph node dissection (10.3%), or lobectomy (34.5%) (Table 1). 53 (91.4%) patients had papillary thyroid cancer, and 5 (8.6%) had follicular thyroid cancer. The primary tumor was micro carcinoma in 63.8% of the patients and macrocarcinoma in 36.2%. The median tumor size was 0.8 cm (range, 0.1-5.5 cm). Multifocality was detected in 27.6% of the patients, thyroid capsular invasion in 27.6%, vascular invasion in 12.1%, and perithyroidal invasion in 6.9%.

Table 1. General features of the patients

Variables	**n (%)**
Age > 45 years	27 (46.6)
Gender	
Female	47 (81)
Male	11 (19)
Preoperative fine-needle aspiration cytology	
Not applied	34 (58.6)
Benign	7 (12.1)
Malign	4 (6.9)
Suspect of malignancy	2 (3.4)
Cellular microfollicular lesion	5 (8.6)
Hurthle cell lesion	4 (6.9)
Nondiagnostic	2 (3.4)
Initial operation procedure	
Total thyroidectomy	32 (55.2)
Total thyroidectomy+ CLND	6 (10.3)
Lobectomy	20 (34.5)

CLND, Central lymph node dissection

Residual thyroid volume and laboratory results before completion surgery: The median residual thyroid volume was 2.6 mL (range, 0.3-20 mL), the median TSH level was 24 μIU/mL (range, 0.4-100 μIU/mL), and the median Tg level was 10 ng/mL (range, 0.2-421 ng/mL). Tg level was <2 ng/mL in 17.2%, between 2-10 ng/mL in 31%, and >10 ng/mL in 51.7% of the patients.

Results of Completion Thyroid Surgery and Predictive Factors: The median time for completion thyroidectomy was 5 months (range, 1-17 months). After completion thyroidectomy, 13 (22.4%) patients had malignant residual tissue and 45 (77.6%) patients had benign residual tissue. In all patients, tumor type in residual thyroid tissue was the same with the primary tumor type. Other tumor features such as multifocality, thyroid capsular invasion, vascular invasion, and perithyroidal invasion were not available in the pathological examinations of remnant tissue.

There were no significant differences between the two groups with respect to age, primary tumor type, tumor size, presence of bilateralism, multifocality, thyroid capsular invasion, vascular invasion, and perithyroidal invasion ($p>0.05$ for all). Female/male ratio was significantly lower in malignant residual tissue group (Table 2). There were no significant differences between the study groups in terms of the time interval for completion thyroidectomy, as well as TSH, Tg, and Tg subgroups (Table 3). Residual thyroid volume was higher in malignant residual tissue group than in benign residual tissue group (5.4.±2.8 vs. 2.8±2.8, respectively; $p=0.014$) (Table 3). In multivariate binary logistic regression analysis, only residual thyroid volume could independently predict the existence of residual malignancy (Table 4).

Table 2. Comparison of demographic features and tumor characteristics between the study groups

Variables	Patients with malignant residual tissue (n=13)	Patients with benign residual tissue (n=45)	p-value
Female/male	8/5 (61.5/38.5)	39/6 (86.7/13.3)	**0.042**
Mean age (year)	40.1±12.4	42.4±10.8	0.510
Age >45 years, n(%)	6 (46.2)	21 (46.7)	0.974
DTC type (PTC/FTC), n(%)	12/1 (92.3/7.7)	41/4 (91.1/8.9)	0.892
Tumor size (cm)	0.8 (0.1-5.5)	0.8 (0.2-5.5)	0.844
Bilateralism n(%)	1 (7.7)	8 (17.8)	0.376
Multifocality, n(%)	2 (15.4)	14 (31.1)	0.264
Thyroid capsular invasion, n(%)	5 (38.5)	11 (24.4)	0.319
Vascular invasion, n(%)	1 (7.7)	6 (13.3)	0.582
Perithyroidal invasion, n(%)	2 (15.4)	2 (4.4)	0.170

Data are mean ± SD or median (minimum-maximum) or number (percentage) of subject, Bold p-values indicate statistically significant ($p<0.05$), DTC: differentiated thyroid cancer; FTC: follicular thyroid cancer; PTC: papillary thyroid cancer

Table 3. Comparison of time interval for completion thyroidectomy, residual thyroid volume, and TSH and Tg prior to completion thyroidectomy between the study groups

Variables	Patients with malignant residual tissue (n=13)	Patients with benign residual tissue (n=45)	p-value
Time interval for completion thyroidectomy (months)	5 (2-97)	5 (1-60)	0.587
Residual thyroid volume (mL)	5.4 ±2.8	2.8±2.8	**0.014**
TSH level (µIU/mL)	25 (0.4-100)	22 (0.4-100)	0.695
Tg level (ng/mL)	12 (1-61)	10 (0.2-421)	0.450
Tg (ng/mL) subgroups, n(%)			0.549
<2	1 (7.7)	9 (20)	
2-10	5 (38.5)	13 (28.9)	
>10	7 (53.8)	23 (51.1)	

Data are mean ± SD or median (minimum-maximum) or number (percentage) of subject, Bold p-values indicate statistically significant (p<0.05), Tg: thyroglobulin; TSH: thyroid stimulating hormone

Table 4. Variables to predict the existence of thyroid cancer in residual thyroid tissue in binary logistic regression analysis

Variables	B	S.E.	p-value	OR	95 % CI for OR
Age (years)	.010	.031	.750	1.010	.950-1.074
Sex (Female/male)	-.271	.899	.763	.763	.131-4.442
Tumor type (PTC/FTC)	.399	1.320	.762	1.491	.112-19.827
Tumor size (cm)	-.097	.257	.707	.908	.707-.908
Bilaterality present	.799	.799	.563	2.223	.149-33.234
Multifocality present	.159	.131	.224	1.172	.907-1.515
Thyroid capsular invasion present	1.141	.954	.231	3.131	.231-3.131
Vascular invasion present	-.622	1.280	.627	.537	.044-6.606
Perithyroidal invasion present	.625	1.437	.663	1.869	.112-31.221
TSH(µIU/mL)	.011	.012	.376	.376	.987-1.036
Tg(ng/mL)	-.005	.007	.443	.995	.981-1.008
Residual thyroid volume (mL)	.277	.277	**.039**	1.320	1.008-1.727

Bold p-values indicate statistically significant (p<0.05), CI: confidence interval; FTC: follicular thyroid cancer; PTC: papillary thyroid cancer; OR: odds ratio; Tg: thyroglobulin; TSH: thyroid stimulating hormone

Discussion

In the present study, we investigated the predictor factors for the presence of thyroid cancer in residual thyroid tissue of patients with DTC after partial thyroidectomy. The mean age, primary tumor size, tumor type, presence of bilateralism, multifocality, thyroid capsular invasion, vascular invasion, and perithyroidal invasion, serum TSH and Tg levels before completion thyroidectomy were similar between malign and benign residual tissue groups whereas residue volume and the number of male patients were higher in patients with malignant residual tissue. Additionally, residue volume was the only factor to predict presence of thyroid cancer in residual thyroid tissue.

The extend of thyroid surgery in patients with DTC is a controversial issue. Total thyroidectomy is associated with a higher operative risk whereas partial thyroidectomy has the risk of leaving residual malignancy. Additionally, complete surgery improves the patient outcome and makes follow-up with serum Tg and RAI scanning more reliable [6,7]. In previous studies, the rate of tumor detection in residual tissue after completion thyroidectomy has been reported between 20-77% [8-12]. In the present study, 22.4% of the patients had tumor in the residual tissue.

Completion thyroidectomy is recommended within 5 days after the first operation or after waiting for 3-4 months to diminish scar, inflammation, and edema [13-15]. In the present study, the median time to completion thyroidectomy was 5 months. The variability of time for completion thyroidectomy in our study was due to the fact that the initial operation of the patients was performed in different centers and patients were admitted to our clinic in variant periods after initial thyroidectomy.

Kim et al. [16] assessed a number of clinical and pathological variables for their ability to predict the presence of malignancy in the opposite residual lobe after hemithyroidectomy. Among all factors studied, only presence of multifocal disease at initial surgery was found to be a significant predictor for the presence of malignancy in opposite lobe. Similarly, in another study [17], multifocality was a significant predictor of tumor presence in the residual tissue with a rate of 57.7%. Age, gender, tumor histology, tumor size, thyroid capsular invasion, vascular invasion, and categorized serum Tg levels (Tg <2ng/mL, 2-10 ng/mL, and >10 ng/mL) were not significant predictive factors in that study. In the study by Alzahrani et al. [11] conducted in 101 patients with DTC undergoing completion thyroidectomy, predicting factors for malignancy were evaluated. They found that multifocality and serum Tg level >20 ng/mL were significant predictors for malignancy in residual thyroid tissue. In the present study, age, sex, primary tumor type, tumor size, bilateralism, multifocality, thyroid capsular invasion, vascular invasion, perithyroidal invasion, serum TSH and Tg levels before completion thyroidectomy could not predict the tumor presence in residual thyroid tissue. When we categorized the Tg levels (<2 ng/mL, 2-10 ng/mL, and >10 ng/mL), no significant differences were detected between benign and malign residue groups with respect to Tg subgroups. Our study, for the first time, showed that residue volume was a predictor factor for malignancy in residual thyroid tissue.

In conclusion, residue volume seems to a predicting factor for malignancy in residual thyroid tissue. However, further large scale studies are needed for clinical application of our results.

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