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Nodule and cancer assessment following thyroid surgery: a cohort of 460 patients

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Abstract. – OBJECTIVE: Thyroid nodule formation and the cancer risk of these nodules have recently become widely researched topics. Developments in diagnosis and treatment options have correlated with an increased number of diagnosed patients. However, such a high number of malignant patients in a single center is rare, and this advantage is able to assess the patients in reverse by reviewing nodularity in the malignant patient population. In this study, we retrospectively reviewed nodularity and malignancy following thyroid surgery in a high-risk population with high thyroid cancer rates.

PATIENTS AND METHODS: Out of 1,007 thyroid patients either referred to or operated on at Ankara Oncology Training and Research Hospital between January 1995 and December 2003, 460 patients with readily available data were included in the study.

RESULTS: Of the 460 patients, 74.9% were female and 25.1% were male. The mean age of female patients operated on due to thyroid nodules was 43.7 years (SD: 14.7; range: 12-81) and 47.1 years for males (SD: 14.6; range: 14-80) (p = 0.02). The mean age of patients with a solitary thyroid nodule (STN) was 40.57 years (SD: 13.65) and 45 years (SD: 14.49) for multinodular cases, with the number of nodules increasing with age (p = 0.0008). Malignancy was seen in 78% of STN cases and 73% of multinodular goiter (MNG) cases (p = 0.554). Comparing genders, 74.2% of female patients and 79.6% of male patients with an STN showed malignancy (p = 0.556). Similarly, 73.4% of females and 75.7% of males with MNG showed malignancy (p = 0.694). Multicentric malignancy was detected in 65.2% of MNG cases and 26.6% of STN cases (p < 0.001). This was especially prominent in papillary carcinomas, which had multicentric malignancy rates of 66.6% for MNG and 22.4% for STN (p < 0.001).

CONCLUSIONS: The females tended to develop nodules at an earlier age than the males, the MNG risk increased with age, and multicentric malignancy was prominent in MNG in papillary carcinomas.

Key Words:
Thyroidectomy, Cancer, Multinodular goiter, Solitary thyroid nodules.

Introduction

Thyroid nodules, with both benign and malignant causes, are quite common. In a large population study, about 6.4% of females and 1.5% of males showed clinically significant thyroid nodules, and about 4%-6% of thyroid nodules were due to malignancy[1-4].

The incidence rate of thyroid cancer has increased rapidly over the last three decades due to advances in diagnostic tools and their widespread use in the population. One of the main reasons for this increase is the higher detection rate of early-stage thyroid tumors with slow progression. However, mortality rates due to thyroid cancers have been stable or decreased[5-9].

Many studies[10-14] have reported different results for solitary thyroid nodules (STNs) and multinodular goiter (MNG) and their relation to age and gender. Because reviews found in the literature mainly present data about incidental cancer found in thyroid nodules, we wanted to determine nodularity and malignancy results following thyroid surgery in a center with high oncology surgery turnover rates.

Patients and Methods

This retrospective study was undertaken in the Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital following approval from the Training Planning Committee and Yüksek İhtisas University Ethical Commit-

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tee. A total of 1,007 patients who had been operated on in our hospital or referred to our endocrinology, general surgery, nuclear medicine, radiation oncology, and medical oncology clinics for further diagnosis and treatment following surgery at other hospitals between January 1995 and December 2003 were assessed. Of these, 460 patients who had readily available data were included in the study.

All the patients' files were retrospectively reviewed for age; gender; physical examination findings; ultrasonography (USG) and thyroid scintigraphy results; preoperative thyroid hormone, thyroglobulin (Tg) and antithyroglobulin values; thyroid fine-needle biopsy (TFNB) and frozen reports; surgical notes; pathology reports; multicentric findings (i.e., multifocal cancer), and nodularity. According to the pathology reports, 95 patients had a STN; however, to assess nodularity, USG, scintigraphy, and pathology reports were subsequently reviewed; if any of those showed a multinodular presence, the patient was included in a multinodular group. In this case, there were 100 patients with a "true" solitary nodule. The patients were then divided into two groups according to the presence of either a solitary or multiple nodules. The patients' age, decade, gender, scintigraphy results, USG results, malignancy incidence, and malignancy types were statistically compared and reviewed.

Statistical Analysis

Patient data were assessed using SPSS 18.0 software (SPSS Inc., Chicago, IL, USA). Spread and variances and non-homogeneous age were reviewed using the Mann-Whitney U test, and categorical variables were assessed using the chi-square test. The statistical significance level was set as $p < 0.05$.

Results

Out of the 460 patients included in the study, 74.9% (344) were females and 25.1% (116) were males. The mean age for females operated on for thyroid nodules was 43.7 years (SD: 14.7; range: 12-81), and the mean age for males was 47.1 (SD: 14.6; range: 14-80), with significantly advanced age ($p = 0.02$). The mean age for an STN was 40.57 years (SD: 13.65), whereas the mean age for a multinodular goiter was 45.00 years (SD: 14.49), with MNG more frequent with advanced age ($p = 0.0008$) (Table I).

A review of the patients' laboratory results indicated that about 62.4% of the patients were clinically euthyroid, 26.8% had hyperthyroidism, and 10.8% had hypothyroidism. Antithyroglobulin levels were normal in 41.1%, low in 35.7%, and high in 23.2% of the patients. Thyroglobulin levels were high in 47.5% of the patients, normal in 38.8%, and low in 13.7%. When the surgeries were reviewed, 35.6% (165) received a bilateral subtotal thyroidectomy (BST), 36.3% (167) a BST complementary thyroidectomy, and 28% (129) a total thyroidectomy. Thyroid fine-needle biopsy (TFNB) was undertaken in 130 patients; the results showed as benign in 69.2% of the patients (90), as malignant in 23.8% (31), and as suspicious in 6.9% (9) (Table II).

Seventy-six percent (76) of STN and 73% (252) of MNG cases showed malignancy, and there was no significant difference between the groups ($p = 0.554$). When genders were compared in terms of malignancy, females with STN had a malignancy rate of 74.2% (49) and males had a rate of 79.6% (27), without any significant difference ($p = 0.556$). Malignancy was detected in 73.4% (196) of female patients with MNG and 75.7% (56) of male patients with MNG, without a significant difference ($p = 0.694$) (Table I).

Reviewing the post-op pathology reports for all the patients, 75.4% (347) of the patients showed malignancy, whereas 24.6% (113) were benign. Histopathological assessment of STN revealed the most common types of carcinoma as papillary in 49% of the patients (49), follicular in 15% (15), and anaplastic in 6% (6). The same type of review of MNG patients revealed the most common types of carcinoma as papillary in 53.7% of the patients (183), follicular in 9.4% (32), and anaplastic in 6.2% (21) (Table III). A review of multicentricity in MNG showed multicentricity in 66.6% (124) of papillary carcinoma patients, 55.9% (19) in follicular carcinoma, and 90.5% (19) in anaplastic carcinoma. Multicentricity in STN was detected in 22.4% (11) of papillary carcinoma patients, 13.3% (2) in follicular carcinoma, and 83.3% (5) in anaplastic carcinoma. Multicentric malignancy was detected in 65.2% (165) of MNG patients and 26.6% (20) of STN patients, with a significant difference ($p < 0.001$). Significantly increased multicentricity was seen, especially in papillary carcinoma: 66.6% (124) in MNG patients and 22.4% (11) in STN patients ($p < 0.001$). However, the numerical value of the multicentricity was higher for anaplastic carcinoma for both STN and MNG patients (Table IV).

Table I. General features (SD; Standard Deviation).

		p-value
Age-Mean (Standard deviation, Range)	44.5 (SD: 14.7, Range: 12-81)	0.02
Male	47.1 (SD: 14.6, Range: 14-80)	
Female	43.7 (SD: 14.7, Range: 12-81)	
Gender		0.01
Female	344 (74.9%)	
Male	116 (25.1%)	
Total	460 (100%)	
Age according to nodule presence (Mean, SD)		0.008
Single nodule	40.57 ± 13.65	
Multiple nodule	45.00± 14.49	
Single nodule		0.556
Female		
Benign	17 (25.8%)	
Malign	49 (74.2%)	
Male		
Benign	7 (20.6%)	
Malign	27 (79.6%)	
Multiple nodule		0.694
Female		
Benign	71 (26.6%)	
Malign	196 (73.4%)	
Male		
Benign	18 (24.3%)	
Malign	56 (75.7%)	
Single nodule		0.554
Benign	24 (24%)	
Malign	76 (76%)	
Multinodular		
Benign	92 (27%)	
Malign	252 (73%)	

Discussion

Because reviews in the literature mainly contain data about incidental cancer rates in removed thyroid nodules, we wanted to present nodularity and malignancy results following thyroid surgery at a center with high oncology surgery turnover rates. In the literature, the incidence rates of cancer in thyroid nodules range between 4% and 42%, according to cancer frequency, incidental nature, a wide population base, and the presence of an endemic region[1-3,10-16]. In our work, about 75.4% of the patients had malignant nodules; this series with high malignancy rates was clearly not a normal population sample, but the nodularity incidence rate and the malignancy development of those nodules could not be assessed. However, such a high number of malignant patients in a single center is rare, and the advantage of this is being able to assess the patients in reverse by reviewing nodularity in the malignant patient population.

The literature reports that thyroid disorders in females are diagnosed three times more often than for men[1-3]. In our study, 74.9% of the patients were females and 25.1% were males. We also found that nodular thyroid disorders develop relatively earlier in females (43.7 years) compared to males (47.1 years).

A study[17] that assessed the relationship between age, nodule, and cancer using a wider series than that in the current study revealed that nodularity increased with age, but differentiated thyroid cancers usually developed at earlier ages. Our paper results comply with these findings; we found that the mean ages for the development of STN and MNG were 40.5 and 45 years, respectively.

Malignancy risk in assessments using TFNAB and thyroid USG is reported as ranging from 3%-5%[1-2]. However, from the literature, TFNAB shows benign results for about half of malignant patients, especially in endemic regions[13,14]. In our study, patients' TFNAB data showed malignancy

Table II. Laboratory and surgical features.

	N: 460
Preoperative Thyroid Function	
Hyperthyroidism	77 (26.8%)
Hypothyroidism	31 (10.8%)
Euthyroid	179 (62.4%)
Total	287 (100%)
Thyroglobulin	
Low	19 (13.7%)
High	66 (47.5%)
Normal	54 (38.8%)
Total	139 (100%)
Antithyroglobulin	
Low	40 (35.7)
High	26 (23.2%)
Normal	46 (41.1%)
Total	112 (100%)
Surgery	
Bilateral Subtotal Thyroidectomy (BST)	164 (35.6%)
BST + Complementary Thyroidectomy	167 (36.3%)
Total Thyroidectomy	129 (28%)
Total	460 (100%)
Preoperative FNAB	
Benign	90 (69.2%)
Malign	31 (23.8%)
Suspicious	9 (6.9%)
Total	130 (100%)
USG Nodularity Results	
Single nodule	74 (23.2%)
Multiple nodule	235 (73.7%)
Diffused goiter	10 (3.1%)
Total	319 (100%)
Thyroid Scintigraphy Nodularity	
Single nodule	65 (32.7%)
Multiple nodule	108 (54.3%)
Diffused	26 (13.1%)
Total	199 (100%)
Pathology Nodularity	
Single nodule	95 (23.1%)
Multinodular	315 (76.9%)

in 23.8% and suspicious histology in 6.9% of the patients, which is higher than the rates reported in the literature.

Another study[12] with a wider series that assessed malignancy following thyroidectomy reported MNG in 17.5% of cancer patients, toxic nodular goiter in 18.3%, and Graves' disease in 6.1%. Multivariate analysis in the same study indicated that the most significant parameter in cancer development was nodularity. Reviewing the literature, we found that although euthyroid nodular goiter was more frequently related to malignancy, patients with hyperthyroidism were also at a higher risk of malignancy. Moreover, malignancy was reported at earlier ages in patients with hyperthyroidism. A retrospective series that assessed incidental papillary thyroid cancer reported 26% for Graves' disease, whereas the euthyroid nodular disease rate was 28%[11]. Another study[15] reported the malignancy rate in patients with Graves' disease as 18%. Some studies[18-20] reported that hyperthyroidism, thyroiditis, goiter, and adenoma increase the risk of differentiated thyroid cancer in patients. In our patient series, we saw hyperthyroidism in 26.8% of the patients, euthyroid in 62.4%, and hypothyroidism in 10.8%. We found that antithyroglobulin levels caused by thyroiditis were higher than normal in 23.2% of the patients.

Miccoli et al[13] assessed results following thyroidectomy for benign reasons and reported that gender, age, thyroid size, and the time from diagnosis to surgery did not affect malignancy frequency. Another MNG study that included 1,791 patients reported a relationship between age, female gender, nodule diameter, and the number of nodules with malignancy[14]. However, Ergin et al[11] did not show a relationship between nodule size and malignancy frequency. In our study, we were also unable to detect a significant difference between STN and MNG in terms of malignancy frequency. Again, there was no difference between genders in terms of malignancy frequency. In our study group, the number of MNG patients was three times greater than STN patients and, in parallel, the malignancy rate was also reported as three times greater.

Table III. Distribution of thyroid cancer by nodule status.

	Single nodule	Multiple nodule	Diffused other	Total
Papillary carcinoma	49 (49%)	183 (53.7%)	4	236 (52.5%)
Follicular carcinoma	15 (15%)	32 (9.4%)	4	51 (10.9%)
Hurtle-Cell carcinoma	3 (3%)	7 (2.1%)	1	11 (2.3%)
Anaplastic carcinoma	6 (6%)	21 (6.2%)	8	35 (6.1%)
Medullar carcinoma	2 (2%)	9 (2.6%)	2	13 (2.5%)
Lymphoma	1 (1%)	–	–	1 (0.2%)
Benign	24 (24%)	89 (26.1%)	–	113 (24.5%)

Table IV. Distribution of thyroid cancer by nodule and focal status.

	Single nodule		Multiple nodule		
	Single focus	Multicentric	Single focus	Multicentric	*p*-value
Papillary carcinoma	38 (77.5%)	11 (22.4%)	62 (33.3%)	124 (66.6%)	< 0.001
Follicular carcinoma	13 (86.6%)	2 (13.3%)	15 (44.1%)	19 (55.9%)	0.0554
Hurtle-Cell carcinoma	2 (66.6%)	1 (33.3%)	3 (60%)	2 (40%)	0.850
Anaplastic carcinoma	1 (16.6%)	5 (83.3%)	2 (9.5%)	19 (90.5%)	0.623
Medullar carcinoma	1 (50%)	1 (50%)	6 (85.7%)	1 (14.3%)	0.283
Total	55 (73.3%)	20 (26.6%)	88 (34.7%)	165 (65.2%)	< 0.001

Ninety-five percent of thyroid cancers comprise differentiated thyroid cancers (i.e., papillary, follicular, and turtle-cell carcinomas), whereas 1%-2% are medullar carcinomas and less than 1% are anaplastic carcinomas[3]. In our study, the histopathological results of the STN patients indicated that the most frequent cancer types were papillary (49%), follicular (15%), and anaplastic (6%). For the MNG patients, 53.7% were papillary, 9.4% were follicular, and 6.2% were anaplastic carcinomas. In our patient population, the frequency of anaplastic carcinoma was higher than that reported in the literature. Because our hospital is a multidisciplinary oncology center, the main reason for our reported higher malignancy rates is that most of the sampled patients had received a subtotal thyroidectomy in other clinics, and when malignancy was detected, the majority of these patients were referred to our center for either a complementary thyroidectomy, radioactive iodine treatment, or further assessment in the case of patients with a high malignancy risk. This is reflected in 36.3% of the sample comprising patients who had received a complementary thyroidectomy following bilateral subtotal thyroidectomy.

Bilateral lobe involvement and multicentric spreading are closely related to papillary micro cancers[21-23]. In our study, we found that papillary carcinomas, especially those found in MNG, were significantly multicentric. Differentiated thyroid cancers also had an affinity to being single centered in STN cases and multicentric in MNG cases. However, even though the number of patients included in this study was low, multicentric affinity was higher for anaplastic carcinomas in both STN and MNG cases.

Limitations

Being a retrospective study, the patients were not randomly selected from the population, and this could have created bias. In addition, the patients included in the study consisted of patients with surgical indications due to a high malignancy risk for thyroid cancer. Moreover, those patients were selected from an oncology hospital, so the rates for oncology patients are expected to be higher than the general population. Another limitation is that we were unable to directly statistically assess the relationship between thyroiditis, hyperthyroidism, Graves' disease, and cancer rates; being unable to access some data, we were unable to make a thorough assessment for those subjects.

Conclusions

The population sample used in this study allowed us to review the nodularity spread across a population with high malignancy rates. Females tend to develop nodules at an early age, the MNG risk increases with age, and multicentric malignancy is prominent in MNG in papillary carcinomas. We were unable to find a significant difference in malignancy development rates between STN and MNG cases; however, female patients were three times more than males. Although the malignancy rates were numerically three times greater, we did not see any more malignancy developments compared to the present nodularity.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

This study was conducted following approval from the Yüksek İhtisas University Ethical Committee to access archived patients' records.

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