

Aim of the study: Thyroid carcinoma is the most common malignancy of endocrine organs. The prognosis varies. Factors such as age, sex, size of the tumor, stage of disease, presence of extrathyroidal spread, and completeness of resection have been found to significantly influence prognosis. We aimed to evaluate clinical features of our patients with thyroid carcinoma, prospectively.

Material and methods: We evaluated total 178 patients treated between 2010 and 2011 at the Department of Endocrinology, İzmir Atatürk Training Hospital, retrospectively. Data on patients, tumors, and therapeutic approaches were collected. All results are shown as mean \pm standard deviation (SD). *P* values were based on two-sided tests with a cutoff for statistical significance of 0.05 and 95% confidence interval.

Results: There were no differences between female and male patients according to histopathological subtypes, demographic data and prognostic findings of thyroid cancer. The assessment of tumor size and other prognostic factors revealed that there was a correlation between tumor size and capsular and/or vascular invasion. In the post-operative evaluation we detected a correlation between metastases and vascular invasion and/or capsular invasion but there was no significant relation between focus (solitary/multifocal) and metastases.

Conclusion: There was no significant difference in terms of gender and age (< 45 years of age and \geq 45 years of age) among the patient groups (low risk/intermediate risk/high risk). By multiple regression analysis among metastasis and prognostic factors it was observed that vascular invasion and thyroglobulin levels affect development of metastases.

Key words: differentiated thyroid carcinoma, papillary thyroid carcinoma, thyroglobulin, TNM, tumor, node, metastases.

Clinical experience of thyroid carcinoma: a study of 178 cases

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Introduction

Although thyroid cancer is a rare disease, its incidence increases with age and use of diagnostic methods such as ultrasound guided fine needle aspiration biopsy. In countries with sufficient iodine supply or only moderate iodine deficiency, papillary thyroid cancer is the dominant histopathological form and accounts for more than 70%. Differentiated thyroid cancers are two to four times as common in females as in males; however, the female preponderance decreases in prepubertal and postmenopausal ages, which suggests that sex hormones might play some role in the pathogenesis.

Prognosis of thyroid cancer is good in general and patients with differentiated thyroid cancer have 10-year cancer-specific mortality rates of less than 10% [1]. On the other hand, prognostic factors may affect survival of patients. The most important prognostic factors in well-differentiated thyroid carcinoma are age (older than 45 years) and gender (male patients). The recurrence rates are reported in the vicinity of 8% to 23% [2, 3]. The AMES (age, distant metastasis, tumor extent, and size), AGES (age, tumor size, histological grade, tumor extent, distant metastasis) and MACIS (distant metastasis, age, completeness of primary tumor resection, local invasion, and tumor size) prognostic systems for well-differentiated thyroid carcinoma are well known [4].

Histopathological variants of papillary thyroid cancer may also affect the prognosis of the disease. In fact, tall cell variant of papillary thyroid cancer is a more aggressive variant than classical papillary thyroid cancer and has a poor prognosis. The diffuse sclerosing variant of papillary thyroid cancer predominantly observed in young patients is a rare aggressive tumor that requires intensive treatment [5].

The approach to risk assessment of thyroid cancer is very important. American Thyroid Association (ATA) guidelines are used for evaluation of these cases [6]. Three risk groups (low, intermediate and high risk) have been reported according to ATA guidelines.

In this study we aimed to investigate clinical characteristics and prognostic factors of all thyroid cancer cases, prospectively.

Material and methods

Patients

This study was carried out in İzmir Atatürk Training Hospital, Department of Endocrinology. All patients with thyroid cancer ($n = 178$) between 2010 and 2011 were enrolled in the study prospectively and respectively.

Methods

All data about risk status such as age, sex, tumor data (pathological diagnosis, size, multifocal/solitary, stage, extrathyroidal spread), metastasis

(locoregional, distant), mode of detection (clinical, imaging, thyroglobulin estimation), and treatment modalities (surgery, iodine 131 therapy) were recorded. Treatment success was determined on the basis of undetectable thyroglobulin estimation under TSH elevation (after withdrawal of thyroid hormone over the course of 4–6 weeks) and/or normalization of imaging modalities including thyroid ultrasonography (USG), thyroid scintigraphy, thorax computed tomography (CT), whole body scintigraphy, and abdominal USG.

Diagnosis of thyroid cancer

Ultrasound-guided fine needle aspiration biopsy was performed in all 178 patients. 112 patients were diagnosed with FNAB; and the remaining 66 patients were diagnosed post-operatively, although they were benign ($n = 13$), suspicious cytology ($n = 51$) and non-diagnostic cytology ($n = 2$) in FNAB.

Biochemical analysis

Biochemical parameters (TSH, FT3 and FT4 hormones) were evaluated with chemiluminescence analyzers by Advia Centaur XR Hormone Analyzer. Calcitonin and thyroglobulin levels were detected with chemiluminescence analyzers by Immulate 2000 Hormone Analyzer.

Statistical analysis

All results are shown as mean \pm standard deviation (SD). P values were based on two-sided tests with a cutoff for statistical significance of 0.05 and 95% confidence interval. The Kolmogorov-Smirnov test, χ^2 test, Fisher's exact test, Mann-Whitney U test, independent sample t test and analysis of covariance test (ANOVA) were used to evaluate values. All statistical analyses were performed with MedCalc Statistical Software Version 10.16.0 (Licensed to MedCalc Turkey 020931118117) and SPSS (Statistical Package for Social Sciences) version 15.0.

Results

Demographic data and prognostic findings of the patients

Our patients had a clear female preponderance (85.4% vs. 14.6%, $p = 0.001$). Mean age of all patients was 48.5 ± 24.0

years, and 48.2 ± 25.4 years in female and 50.1 ± 12.4 in male patients, respectively. Mean age of female and male patients was similar. In terms of poor prognostic parameters such as focus, capsular invasion, metastases and tumor size, there were no significant differences between male and female patients. Of 178 patients, 85 patients had macrocarcinoma (> 10 mm) and 93 patients had microcarcinoma (< 10 mm). We detected that 18 patients had distant metastases (hepatic metastasis in 1 patient, pulmonary metastases in 16 patients, bone metastasis in 1 patient), 30 patients had vascular invasion, and 63 patients had capsular invasion. All data of demographic and prognostic findings are shown in Table 1.

In our study, there were no differences between female and male patients in terms of histopathological subtypes of thyroid cancer (Table 2). Two of the 16 patients with thyroid medullary cancer had metastases and significantly high serum calcitonin levels were detected ($p < 0.05$). There were normal serum calcitonin levels in the patients who had thyroid medullary carcinoma without metastases. Similarly, there were normal serum calcitonin levels in the patients with papillary cancer + medullary cancer (mix). We detected pheochromocytoma and primary hyperparathyroidism in 2 female patients with medullary cancer. They were diagnosed as MEN II A syndrome.

Assessment of relationship between tumor size and the other prognostic findings

We evaluated the relationship between tumor size and poor prognostic factors and as a result we found that there was a positive correlation between tumor size and capsular and/or vascular invasion (capsular invasion, $r = 0.54$, $p < 0.05$; vascular invasion, $r = 0.44$, $p < 0.05$). In addition, we detected a statistically significant relation between focality (solitary/multifocal) and capsular invasion, similarly between vascular invasion and capsular invasion (Table 3). In evaluation of patients with metastases, there was no significant correlation between metastases and focus (solitary/multifocal) but there was a statistically significant relation between metastases and tumor size, capsular invasion, and vascular invasion ($p < 0.05$).

Table 1. Demographic data and prognostic findings of the patients

		Male ($n = 26$)	Female ($n = 152$)	Total ($n = 178$)	p value
Focus	solitary	19 (73.1%)	119 (78.3%)	138 (77.5%)	NS
	multifocal	7 (26.9%)	33 (21.7%)	40 (22.5%)	
Capsular invasion	+	9 (34.6%)	54 (35.5%)	63 (35.4%)	NS
	-	17 (65.4%)	98 (64.5%)	115 (64.6%)	
Vascular invasion	+	6 (23.1%)	24 (15.8%)	30 (16.9%)	NS
	-	20 (76.9%)	128 (84.2%)	148 (83.1%)	
Metastases	+	4 (15.4%)	14 (9.2%)	18 (10.1%)	NS
	-	22 (84.6%)	138 (90.8%)	160 (89.9%)	
Tumor size	≤ 10.0 mm	12 (46.2%)	81 (53.3%)	93 (52.2%)	NS
	> 10.0 mm	14 (53.8%)	71 (46.7%)	85 (47.8%)	

Table 2. Histopathological analysis of female and male patients

Histopathological diagnosis	Female (n = 152)	Male (n = 26)	Total (n = 178)	P-value*
papillary microcancer	66 (43.4%)	11 (42.3%)	77 (43.3%)	NS
papillary cancer follicular variant	16 (10.5%)	2 (7.7%)	18 (10.1%)	NS
papillary cancer oncocytic variant	1 (0.7%)	0 (0.0%)	1 (0.6%)	NS
papillary cancer classical variant	38 (25.0%)	6 (23.1%)	44 (24.7%)	NS
minimally invasive follicular carcinoma	5 (3.3%)	0 (0.0%)	5 (2.8%)	NS
follicular carcinoma	4 (2.6%)	2 (7.7%)	6 (3.3%)	NS
thyroid medullary cancer	13 (8.6%)	3 (11.5%)	16 (9.0%)	NS
hurthle cell carcinoma	1 (0.7%)	0 (0.0%)	1 (0.6%)	NS
follicular adenoma	1 (0.7%)	0 (0.0%)	1 (0.6%)	NS
papillary cancer + thyroid medullary cancer (mix)	2 (1.3%)	0 (0.0%)	2 (1.1%)	NS
follicular cancer oncocytic variant	2 (1.3%)	1 (3.8%)	3 (1.7%)	NS
papillary cancer + follicular cancer (mix)	1 (0.7%)	1 (3.8%)	2 (1.2%)	NS
undifferentiated thyroid cancer	2 (1.3%)	0 (0.0%)	2 (1.1%)	NS

*NS – non-significant

Table 3. Relationship between tumor size and the other prognostic findings

	Focus		Capsular invasion	Vascular invasion	Total
	Solitary	Multifocal			
< 10 mm tumor size	75 (80.6%)	18 (19.4%)	10 (10.8%)	1 (1.1%)	93 (52.2%)
> 10 mm tumor size	63 (74.1%)	22 (25.9%)	53 (62.4%)	29 (34.1%)	85 (47.8%)
total	138 (77.5%)	40 (22.5%)	63 (35.4%)	30 (16.9%)	178 (100%)
p-value	$p > 0.05$	$p > 0.05$	$P < 0.05^*$	$P < 0.05^*$	

Distribution of patients according to risk group

All patients were divided into 3 groups according to their risk level based on ATA guidelines as low risk (group I), intermediate risk (group II) and high risk (group III) [6]. There were 161 patients in group I [138 female (85.7%), 23 male (14.3%)], 15 patients in group II [12 female (80%), 3 male (20%)] and only 2 patients in group III (1 female, 1 male). Gender distribution in all risk groups was similar to the whole patient population. Significant differences could not be detected in terms of gender and age (< 45 years of age and \geq 45 years of age) among groups I, II and III.

Postoperative screening and evaluation

We detected residual thyroid tissue in 55 patients, residual thyroid tissue with recurring thyroid nodule in 4 patients, and residual tissue with lymphadenopathy in 19 patients by ultrasonographic examination. Tg levels between the patients with and without residual thyroid tissue were significantly different (respectively, $n = 87$, $tg = 3.74 \pm 5.89$; $n = 91$, $tg = 1.47 \pm 2.62$; $p = 0.01$). In postoperative scanning (ultrasonography, thyroid scintigraphy, computed tomography, whole body scintigraphy), we detected 18 patients with metastases (hepatic metastasis in 1 patient, pulmonary metastases

in 16 patients, bone metastases in 1 patient). In terms of thyroglobulin levels there was a significant difference between the patients with and without metastases (respectively, $n = 18$, $tg = 2.51 \pm 3.54$; $n = 160$, $tg = 2.58 \pm 4.75$; $p > 0.05$).

Discussion

Thyroid cancer is one of the fastest growing cancer diagnoses worldwide. It is 2.9 times more common in women than men (female : male ratio 16.3 : 5.7) [7]. In our study, we observed that our patients had a clear female preponderance too. The cause of this gender discrepancy is not clear yet. Many factors have been evaluated in terms of dominance by gender in thyroid cancer. The fluctuation of sex hormones during women's menstrual cycle and pregnancy has been hypothesized as the reason for gender disparity in papillary thyroid cancer. In particular, the peak incidence of papillary thyroid cancer has been observed in women aged 40–49 years, this being the age group at which most women approach or enter menopause [7–9]. There were also several studies looking at the association of papillary thyroid cancer with reproductive factors such as age of menarche, menopause, number of pregnancies and other parameters [9–14]. Effects of sex hormone are mediated by hormone-specific nuclear receptors and the

effects of estrogen on thyroid cancer cell lines are dependent on the type of thyroid cancer, and estrogen dramatically increases estrogen receptor α levels in papillary thyroid cancer, whereas in anaplastic thyroid cancer and follicular thyroid cancer the receptor levels are not significantly altered [15–17]. In this study, mean age of female and male patients was similar. We can claim that there is no difference between male and female patients in terms of age. In females, the age-specific incidence rate rises sharply at the beginning of the reproductive years, with increasing age peaking at 40–49 years, while in the men the peak is at 60–69 years. It was shown that the incidence rates equalize by 85 years of age [7, 8].

It was reported that less aggressive histological subtypes of thyroid cancer were more common in women, whereas the more aggressive types of thyroid cancer, anaplastic thyroid cancer and medullary thyroid cancer, have similar rates of incidence in men and women. In contrast we could not determine any significant difference between female and male patients in terms of histopathological subtypes of thyroid cancer. We served as a reference hospital and our patients were selected and referred patients. This situation may be responsible for this result.

It was detected that male sex, advanced initial stage, and presence of extrathyroidal spread within the primary tumor are the most significant independent predictors of developing multiple recurrences in patients with well-differentiated thyroid cancer [18]. Factors such as age, sex, size of the tumor, stage of disease, presence of extrathyroidal spread, and completeness of resection have also been found to significantly influence prognosis [19]. However, in our study we could not find any significant difference in terms of gender and age (< 45 years of age and \geq 45 years of age) in the patients with poor prognostic factors.

We detected 93 patients with microcancer (< 10 mm). There were solitary cancer ($n = 75$) and multifocal cancer ($n = 18$). In these patients with thyroid microcarcinoma, 10 patients had capsular invasion, 1 patient had vascular invasion, and 2 patients had metastasis. Among the patients with thyroid micropapillary cancer ($n = 83$) we detected capsular invasion ($n = 5$), vascular invasion ($n = 1$), solitary cancer ($n = 67$), multifocal cancer ($n = 16$), and metastases ($n = 2$). In accordance with these results we can claim that thyroid microcarcinomas may not be as innocent as they say. An increasing proportion of newly diagnosed thyroid carcinomas have a small size: when no larger than 1.0 cm in diameter, they are classified as microcarcinomas. Many microcarcinomas may remain occult and become diagnosed as an incidental finding during surgery for goiter or other benign thyroid disorders. Microcarcinomas in multicentric papillary thyroid cancer should be treated as high-risk tumors [20]. In autopsy series the rate of papillary microcancer (PMC) varies from 1% to 35% [21]. In some studies, it was reported that 20% of patients had PMC [21]. Patients with PMC ($n = 203$) were investigated retrospectively and it was found that the disease-related mortality rate was 1.0%, lymph node recurrence was 5.0%, and the distant metastases rate was 5.0% [22]. In our study, there were 85 patients with thyroid macrocancer (> 10 mm). Among these patients we detected multifocal cancer ($n = 22$), solitary cancer ($n = 63$), capsular invasion ($n = 53$), vascular invasion ($n = 29$), and metastases

($n = 15$). In the patients with papillary macrocancer ($n = 56$) we found solitary cancer ($n = 40$), multifocal cancer ($n = 16$), capsular invasion ($n = 31$), vascular invasion ($n = 17$), and metastases ($n = 11$).

We found that there was a positive correlation between tumor size and capsular and/or vascular invasion. In addition, we detected a statistically significant relation between focality and capsular invasion. In evaluation of patients with metastases, there was no significant correlation between metastases and focus (solitary/multifocal) but there was a statistically significant relation between metastases and tumor size, capsule invasion, and vascular invasion.

Generally, it was reported that there were distant metastases for patients with tumors greater than 1.5 cm [2]. In one study, there was no relation between tumor size and distant metastases [23]. Some authors emphasized that bilateral foci were associated with tumor size larger than 1.0 cm. In the same study, extrathyroidal invasion was found to be significantly associated with male sex, vascular invasion, lymph node metastases, and tumor size larger than 1.0 cm. Moreover, there were significant relations between lymph node metastases and other prognostic factors (patient age above 45 years, extrathyroidal invasion) [24]. A clear association was identified between extrathyroidal spread and the development of both locoregional and distant recurrence [25, 26].

In this study, there were no differences between female and male patients in terms of prognostic factors. A significant difference was not detected according to age (< 45 years of age and \geq 45 years of age) among risk groups. There was a significant relation between extrathyroidal spread and distant metastases. The tumor size were found to be significantly large in the patients with distant metastases and lymph node metastases. Furthermore, in terms of histopathological assessment, there was no significant statistical difference between the ones with or without metastases. The most commonly used risk stratification systems, such as MACIS (metastases, age, completeness of resection, invasion, and size) and the TNM system of the American Joint Committee on Cancer (AJCC), were designed to predict disease-specific mortality rather than risk of recurrence [27, 28]. This has resulted in the recognition of low- and high-risk patient categories and allowed meaningful comparison of a variety of treatment approaches. Tuttle et al. stratified risk of death into four categories: very low risk, low risk, intermediate risk, and high risk. High-risk features are age > 45 years, larger tumors (> 4 cm) or worrisome histology, incomplete resection, distant metastases, and cervical lymph node metastases. Low-risk features are young age, classical histology, smaller tumors, complete resection, no distant metastases, and no cervical lymph node involvement (in patients < 45 years of age, lymph node involvement did not correlate with increased risk of death). Intermediate-risk disease includes young patients with classic papillary tumors > 4 cm, microscopic extrathyroidal disease, more aggressive histology or vascular invasion, or older patients with classic papillary histology with a size < 4 cm, or extrathyroidal extension, aggressive histology < 1 cm to 2 cm but with complete resection and without distant metastases [29]. Thus, the treatment plan must be created after the risk assessment is done. For each individual patient, the physician must rely on clinical judg-

ment and consider the disease and the patient's wishes before deciding on the management strategy.

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