Original Research
Turk J Endocrinol Metab 2018;22:64-71

Analysis of Risk Factors of Neck Nodal Metastasis in Patients with Papillary Thyroid Microcarcinoma

Tiroid Papiller Mikrokarsinom Tanısı Alan Hastalarda Boyun Lenf Nodu Metastazlarının Risk Faktörlerinin Analizi

Barış Tırman, Mahmut Başoğlu, Kaan Karabulut

Ondokuz Mayıs University Faculty of Medicine, Department of General Surgery, Samsun, Turkey

Abstract

Objective: The aim of this study was to evaluate the risk factors of neck nodal metastasis on papillary thyroid microcarcinoma patients.

Material and Methods: About 123 patients diagnosed with thyroid papillary microcarcinoma, who had undergone total thyroidectomy, between January 2012 and December 2014, were analyzed retrospectively for neck nodal metastasis and distant metastasis risk factors. Laboratory and surgical data were collected for these patients. Other factors such as gender, age, levels of anti-thyroid peroxidase and anti-thyroglobulin antibodies, thyroid stimulating hormone, level of thyroglobulin on thyroid stimulating hormone suppression, size of tumor, presence of capsular invasion, extrathyroidal extension, metastasis of central neck lymph node, vascular invasion, multifocality, bilateral involvement, size of preoperative node, duration of the disease, radioactive iodine therapy, metastasis of lateral neck lymph node and histopathological type were investigated.

Results: Among the cases that were studied, there were 104 (84.6%) females and 19 (15.4%) males. Their average age was 48.60±12.05 years and the mean tumor size was 6.06±2.63 mm. In patients with lateral neck lymph node metastasis and capsular invasion, the thyroglobulin levels after thyroid stimulating hormone suppression were higher. The rate of total neck lymph node metastasis was found to be higher in patients with capsular invasion. Furthermore, the Anti-thyroid peroxidase levels were higher in thyroid papillary microcarcinoma patients who did not have lateral lymph node metastasis.

Conclusion: The thyroglobulin levels after thyroid stimulating hormone suppression and capsular invasion are important risk factors for neck nodal metastasis, in papillary thyroid microcarcinoma patients.

Keywords: Thyroid papillary microcarcinoma; TSH; capsular invasion; lateral neck lymph nodal metastasis

Özet

Amaç: Bu çalışmada, papiller tiroid mikrokarsinomlu hastalardaki boyun lenf nodu metastazlarının risk faktörlerinin incelenmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışmamızda, 2012 Ocak-2014 Aralık tarihleri arasında, kliniğimizde total tiroidektomi yapılmış tiroid papiller mikrokarsinomu tanılı 123 hastada, boyun lenf nodu metastazlarının ve uzak metastazların risk faktörleri retrospektif olarak analiz edilmiştir. Hastaların laboratuvar ve cerrahi bilgileri toplanmıştır. Hastaların cinsiyetleri, yaşları, anti-tiroid peroksidaz antikoru ve anti-tiroglobulin antikoru, tiroid stimüle edici hormon, tiroid stimüle edici hormon süpresyonda iken tiroglobulin değeri, tümör çapı, kapsüler invazyon, ekstratiroidal yayılım, santral boyun lenf nodu metastazı, vasküler invazyon varlığı, multifokalite, bilateral tutulum varlığı, preoperatif nodülün büyüklüğü, hastalık süresi, radyoaktif iyot tedavisi, lateral boyun lenf nodu metastazı ve histopatolojik tiplere ait veriler toplanmıştır.

Bulgular: Vakaların 104 (%84,6)'ü kadın, 19 (%15,4)'u erkek hastalardan oluşmaktadır. Ortalama yaş 48,60±12,05 yıl'dır. Hastalarımızın tümör çapı ortalama olarak 6,06±2.63 mm'dir. Lateral boyun lenf nodu metastazı ve kapsüler invazyonu olan hastalardaki tiroid stimüle edici hormon süpresyonda iken tiroglobulin değerleri daha yüksek saptanmıştır. Kapsüler invazyonu olan hastalardaki total boyun lenf nodu metastazı oranı daha yüksek bulunmuştur. Anti-tiroid peroksidaz antikoru değerinin, lateral boyun lenf nodu metastazı olmayan Tiroid papiller mikrokarsinomlu hastalarda daha yüksek olduğu belirlenmiştir.

Sonuç: Papiller tiroid mikrokarsinomlu hastalarda, tiroid stimüle edici hormon süpresyonda iken tiroglobulin değerleri ve kapsüler invazyon boyun lenf nodu metastazı için önemli birer risk faktörü oluşturmaktadır.

Anahtar kelimeler: Tiroid papiller mikrokarsinom; TSH; kapsüler invazyon; lateral boyun lenf nodu metastazı

Address for Correspondence: Barış Tırman, Ondokuz Mayıs University Faculty of Medicine, Department of General Surgery, Samsun, Turkey
Phone: 0362 312 19 19 **E-mail:** mdbaristirman@gmail.com **Received:** 25/10/2017 **Accepted:** 06/04/2018

DOI: 10.25179/tjem.2017-58632

Introduction

Malignant neoplasms of the thyroid gland constitute nearly one percent of all known cancers. They are the most common tumors that arise from endocrine organs and are usually encountered in both young and middle-aged adults. Approximately 122,000 new cases are diagnosed every year (1), among which, the most common type of thyroid carcinoma is papillary carcinoma (2). The prevalence of this carcinoma varies based on both environmental and genetic factors. Thyroid papillary microcarcinoma is classified as a subgroup of thyroid papillary cancers, with largest tumor size of one centimeter or smaller. Though some researchers have reported that this size can also be about one and a half centimeter (3).

In 2004, the classification by the World Health Organisation (WHO), narrowed down this definition, to include the incidental tumors that were smaller than one centimeter and exclude the small-sized thyroid papillary microcarcinoma with clinical signs (1,4).

Although thyroid papillary microcarcinoma, which is the most common form of thyroid papillary cancers, is clinically silent, the patients of this type rarely present with lymph node metastasis and distant metastasis (1, 4-6).

In our study, we retrospectively analyzed 123 patients having thyroid papillary microcarcinoma for the risk factors of neck nodal metastasis and distant metastasis.

Material and Methods

A total of 123 patients with microcarcinoma of thyroid papillary, who had undergone total thyroidectomy at our clinic, between January 2012 and December 2014, were retrospectively analyzed for the risk factors of neck nodal metastasis and distant metastasis. Only the patients showing pathological findings of thyroid papillary microcarcinoma were included in this descriptive study. The exclusion criteria were, age younger than 18 years, pregnancy, and tumor with a diameter exceeding one centimeter.

The patient's laboratory and surgical data were collected for this study. Factors like gender, age, levels of Anti-Thyroid Peroxidase (Anti-TPO) and anti-thyroglobulin (Anti-Tg) antibodies, Thyroid Stimulating Hormone (TSH), level of thyroglobulin after TSH suppression, tumor size, presence of capsular invasion, extrathyroidal extension, metastasis of central neck lymph node, vascular invasion, multifocality, bilateral involvement, preoperative node size, duration of the disease, RAI (radioactive iodine therapy), metastasis of lateral neck lymph node and histopathological type were investigated.

Dependent and Independent Variables

The dependent variables in this study were lymph node metastasis, thyroglobulin level after TSH suppression, Anti-TPO values and Anti-TG values and the independent variables were a capsular invasion, age, sex and RAI therapy.

Data Pooling and Statistical Analysis

Data summary is represented in numbers and percentages for qualitative variables and arithmetic mean and standard deviations for quantitative variables (in case of normal dispersion). The groups were evaluated using the Likelihood Ratio tests and Logistic Regression analysis. The Mann-Whitney U and Wilcoxon W test for variance were employed when no difference between the groups in terms of quantitative variables was found. Independent variables were tested with the help of T-test, Pearson's Chi-Square Test and Fisher's Exact Test, when assumptions were made. A p-value <0.05 was considered to be statistically significant.

Results

A total of 123 patients having thyroid papillary microcarcinoma were analyzed retrospectively to identify the risk factors for neck nodal metastasis and distant metastasis. Among the patients studied, 104 (84.6%) were female and 19 (15.4%) were male, with an F/M ratio of 5.49 and mean age of 48.6±12.05 years. From the whole group, 11.4% had metastasis of total neck lymph node while 88.6% did not have any metastasis of total neck lymph node. The median value of TSH was 0.09 mIU/mL (0.02-3.09) and the mean value of thyroglobulin after TSH suppression was 8.56±40.52 ng/mL. The mean level of anti-TPO antibody was 21.26±40.53 IU/mL. The mean tumor size in our study group was found to be 6.06±2.63 mm and the median duration of the disease was 32 (20.75-38) months. The mean anti-Tg value was observed to be 30.13±49.76 IU/mL (Table 1).

The study of the relationship between the presence of total neck lymph node metastasis and capsular invasion revealed that, in patients with capsular invasion, the rate of total neck lymph node metastasis was 37.5%, in contrast to the rate of 6.6% among those without capsular invasion. Therefore, a statistically significant rela-

Table 1. Characteristics of the patients with papillary thyroid microcarcinoma.

		Thyroid papillary microcarcinoma patients (n=123)
Mean age (years)		48.60±12.05
Gender	Female	104 (84.6%)
	Male	19 (15.4%)
Tumor size (mm)		6.06±2.63
Tumor focality	Multifocal	63 (51.2%)
	Unifocal	60 (48.7%)
Median value of disease duration (month)		32 (20.75-38)
Tumor laterality	Bilateral	30 (24.3%)
	Unilateral	93 (75.6%)
Radioactive iodine therapy		100 (100%)
Capsular invasion		16 (13%)
Extrathyroidal extension		5 (4.0%)
Central neck lymph node metastasis		8 (6.5%)
Lateral neck lymph node metastasis		12 (9.7%)
Total neck lymph node metastasis		14 (11.4%)
Vascular invasion		8 (6.5%)
Mean value of anti-Tg value (mL)		30.13±49.76
Mean value of anti-TPO antibodies (IU/mL)		21.26±40.53
In supressed TSH, mean value of thyroglobulin (ng/mL)		8.56±40.52
Median value of TSH (mIU/mL)		0.09 (0.02-3.09)

Data presented as mean±SD, median (IQR) or n (%).

tionship was found between the presence of capsular invasion and metastasis to the neck lymph nodes (p=0.020) (Table 2).

The relationship between the level of thyroglobulin after TSH suppression and the presence of capsular invasion was also examined. It was found that the mean level of thyroglobulin after TSH suppression was 27.10±72.36 ng/mL in the group with capsular invasion while in the group without capsular invasion it was 1.80±7.62 ng/mL. Thus, the level of thyroglobulin after TSH suppression was higher in patients with capsular invasion, indicating the presence of a significant relationship between the level of thyroglobulin values after TSH suppression and capsule invasion (z=-2.379, p=0.017) (Table 2).

Anti-TPO values and the presence of lateral neck lymph node metastasis in patients were compared. The mean Anti-TPO value in patients with and without lateral neck lymph node metastasis was 10.52±8.26 IU/mL and 22.48±42.53 IU/mL, respectively. The Anti-TPO values were higher in patients who did not have lateral lymph node metastasis, suggesting that there existed a significant relationship between the presence of lateral neck lymph node metastasis and Anti-TPO values (z=-2.510, p=0.012) (Table 2).

The levels of thyroglobulin after TSH suppression were evaluated in relation to the presence of lateral neck lymph node metastasis. It was found that the median thyroglobulin value on TSH suppression in the group with and without lateral neck lymph node metastasis was 0.59 (0.04-18.59) ng/mL and 0.04 (0.04-0.04) ng/mL, respectively. Thus, a statistically significant relationship was seen between the levels of the thyroglobulin after TSH suppression and the presence of lateral neck lymph node metastasis (z=-3.022, p=0.003) (Table 2).

The logistic regression analysis indicated that gender, age, Anti-TPO, TSH, and additionally RAI (radioactive iodine therapy) variables were not risk factors for total neck lymph node metastasis in patients with microcarcinoma of papillary thyroid, moreover, statistically significant relationship could not be determined with respect to the other parameters (Table 3).

Variable (s) entered on step 1: Gender, Age, Anti-TPO, TSH, TSH Suppressed Tg, RAI therapy.

Table 2. Results of the patients.

	Thyroid papillary microcarcinoma patients (n=123)	p value
The mean age of patients of the group with central lymph node metastasis (years)	51.71±3.67	0.481
The mean tumor size of the group with central neck lymph node metastasis (mm)	5.42±2.50	0.434
The number of male patients of the group with central neck lymph node metastasis [n(%)]	2 (28.6%)	0.299
The number of female patients of the group with central neck lymph node metastasis [n(%)]	5 (71.4%)	0.299
The mean anti-Tg values in patients of the group with lateral neck lymph node metastasis (IU/mL)	21.87±15.13	0.745
The mean age of patients of the group with lateral neck lymph node metastasis (years)	45.08±3.61	0.292
The mean anti-TPO values in patients with lateral neck lymph node metastasis (IU/mL)	10.52±8.26	0.012*
The mean TSH values in patients with lateral neck lymph node metastasis (mIU/mL)	0.49±0.21	0.071
The median thyroglobulin value on TSH suppression with lateral neck lymph node metastasis (ng/mL)	0.59 (0.04-18.59)	0.003*
The mean tumor size of the group with lateral neck lymph node metastasis (mm)	6.27±0.87	0.649
The number of male patients of the group with lateral neck lymph node metastasis [n(%)]	2 (10.5%)	1
The number of female patients of the group with central neck lymph node metastasis [n(%)]	10 (9.6%)	1
The mean age of patients with capsular invasion (years)	47.25±9.70	0.421
The mean anti-Tg values in patients with capsular invasion (mL)	49.26±21.89	0.356
The number of lateral neck lymph node metastasis in patients with capsular invasion [n(%)]	2 (18.2%)	0.637
The number of total neck lymph node metastasis in patients with capsular invasion [n(%)]	6 (37.5%)	0.020*
The mean anti-TPO values in patients with capsular invasion (mIU/mL)	17.27±4.31	0.896
The mean TSH values in patients with capsular invasion (mIU/mL)	20.02±9.12	0.438
The mean thyroglobulin value on TSH supression in the group with capsular invasion (ng/mL)	27.10±72.36	0.017*
The mean tumor size of the group with capsular invasion (mm)	7.09±2.23	0.060
The number of male patients of the group with capsular invasion [n(%)]	1 (5.3%)	0.462
The number of female patients of the group with capsular invasion [n(%)]	15 (14.6%)	0.462
The number of central neck lypmh node metastasis in patients with capsular invasion [n(%)]	1 (14.3%)	1
The mean age of patinets with total lymph node metastasis (years)	50.21±11.90	0.827
The mean anti-Tg values in patients with total neck lymph node metastasis (IU/mL)	32.10±11.30	0.993
The mean anti-TPO values in patients with total neck lymph node metastasis (IU/mL)	9.66±1.45	0.011*
The mean TSH values in patients with total neck lymph node metastasis (mI/mL)	5.35±4.76	0.317
The mean thyroglobulin value on TSH suppression with total neck lypmh node metastasis (ng/mL)	31.07±88.04	0.164
The mean tumor size of the group with total neck lymph node metastasis (mm)	6.46±0.73	0.619
The number of male patients of the group with total neck lymph node metastasis ([n(%)]	1 (5.3%)	0.690
The number of female patients of the group with total neck lymph node metastasis ([n(%)]	13 (12.5%)	0.690

Data presented as mean±SD, median (IQR) or n (%).
*p<0.05, **p<0.01, considered statistically significant.

Table 3. Logistic regression analysis of gender, age, anti-TPO, TSH, RAI therapy variables with total neck lypmh node metastasis.

Variables in the Equation

						95.0% C.I. for Exp (B)	
		B	S.E.	Sig.	Exp (B)	Lower	Upper
Step 1	Female (1)	0.496	1.328	0.709	1.642	0.122	22.167
	Age	0.068	0.036	0.058	1.071	0.998	1.149
	Anti-TPO	0.024	0.039	0.541	1.024	0.949	1.106
	TSH	1.227	1.080	0.256	3.411	0.411	28.340
	TSH Suppressed Tg	-0.019	0.012	0.096	0.981	0.959	1.003
	RAI therapy (1)	19.662	17625.951	0.999	3E+008	0.000	
	Constant	7.926	8812.976	0.999	2768.654		

a. Variable (s) entered on step 1: Gender, Age, Anti-TPO, TSH, TSH Suppressed Tg, RAI therapy.

Dependent variables in this study were lymph node metastasis, the values of thyroglobulin after TSH suppression, Anti-TPO, and Anti-TG values while the independent variables were a capsular invasion, age, sex and RAI therapy.

Discussion

The medical records of 123 patients, diagnosed with papillary thyroid microcarcinoma, were evaluated retrospectively.

The number of male and female patients was 19 and 104, respectively, resulting in an F/M ratio of 5.49. In a multicentre study in Denmark by Rossing et al. in 2012, there were 282 females out of 340 patients (7), while a study conducted in Spain by Mantinan et al. in 2012, reported, 71 females out of 95 patients (8). All these findings are consistent with our results.

Most of the patients in this study were young and their age distribution was found to be similar to that of other studies conducted in Europe (7,8).

The average age of the patients (calculated in mean) with total neck lymph node metastasis was 50.21±11.90 years when compared to the mean age of 54 years in the study of Lin et al. (9).

The gender distribution of patients with respect to the total neck lymph node metastasis was examined and it was found that out of the 19 male patients, only one (5.3%) had total neck lymph node metastasis, while the remaining 18 (94.7%) did not have total neck lymph node metastasis at all. Similarly, out of the 104 female patients, 13 (12.5%) had total neck lymph node metastasis, while the remaining 91 (87.5%) did not show total neck lymph node metastasis. Moreover, no significant relationship was observed between the two groups in terms of gender and total neck lymph node metastasis (p=0.690). A study conducted in China that was published in the year 2016, reported the presence of a significant relation between total neck lymph node metastasis and male gender (10). Our results were incompatible with this literature, probably due to the small number of patients that were examined.

During our analysis, we detected total neck lymph node metastasis in 14 (11.4%) patients and no total neck lymph node metastasis in 109 (88.6%) patients. This was in contrast to the study conducted by the Mayo Clinic wherein total neck lymph node metastasis was found in 98% of the patients (11).

The mean tumor size, of thyroid papillary microcarcinoma, in our patients, was 6.06±2.63 mm when compared to the average tumor size of 7 mm as reported by a multi-center study in the US, that was published in the year 2012 (12).

The association between patient age and the presence of capsular invasion were evaluated, and the mean ages of patients with and without capsular invasion were found to be 47.25±9.70 years and 48.66±12.35 years, respectively. The presence of capsular invasion was found to be independent of patient's age (z=-0.804, p=0.421). A study published in 2013, in a series of 1979 patients in Heraklion hospital in Greece, evaluated the association between patient age and the presence of capsular invasion and found no significant relationship (13).

As for the link between tumor size and the presence of capsular invasion, it was observed that the mean tumor sizes of the group with and without capsular invasion were 7.09±2.23 mm and

5.91±2.35 mm, respectively. The presence of capsular invasion did not seem to affect the tumor size (z=-1.880, p=0.060).

The levels of Anti-TPO were analyzed with respect to the presence of total neck lymph node metastasis. The mean levels of Anti-TPO in patients with and without total neck lymph node metastasis were 9.66±5.44 IU/mL and 22.82±42.92 IU/mL, respectively. The Anti-TPO levels were significantly higher (z=-2.53, p=0.011) in the absence of total neck lymph node metastasis. A study conducted in 2016 in China, found the levels of Anti-TPO to be higher in thyroid papillary microcarcinoma patients when total lymph node metastasis was present (14). Once again our study was noted to be incompatible with the literature due to the small number of patients studied. Haymart et al. in 2008, reported the existence of a relationship between thyroid autoimmunity and thyroid malignancy (15), which needs to be investigated in further studies.

No correlation was found between the tumor size and the presence of central lymph node metastasis. The mean tumor size among the patients with central lymph node metastasis was 5.42±2.50 mm and the presence of central lymph node metastasis did not affect the tumor size (z=-0.782, p=0.434). Our results are compatible with those of the study conducted in Spain, in the year 2012, where it was found that the central neck lymph node metastasis does not affect the tumor size (8).

The rate of total neck lymph node metastasis in patients with capsular invasion was 37.5% and the relationship between the presence of capsular invasion and the total neck lymph node metastasis was significant (p=0.020). Page et al. in 2009, reported that 24 out of a group of 41 thyroid papillary microcarcinoma patients, having neck lymph node metastasis, were found to have a capsular invasion. These findings are in accordance with the results of our analysis (16, 17).

When the thyroglobulin values on TSH suppression were evaluated with respect to the presence of capsular invasion, the mean levels of thyroglobulin after TSH suppression in the groups with and without capsular invasion were observed to be 27.10±72.36 ng/mL and 1.80±7.62 ng/mL, respectively. Hence it can be inferred that the levels of thyroglobulin on TSH suppression were higher in patients with capsular invasion and the difference between thyroglobulin values on TSH suppression and capsular invasion was statistically significant (z=-2.379, p=0.017). A published study by Girelli et al. in 429 patients with well-differentiated thyroid carcinoma, reported that the levels of thyroglobulin after TSH suppression was higher in the group with capsular invasion than in the group without capsular invasion (18). Our study was found similar results when compared to this report.

The levels of thyroglobulin after TSH suppression were examined with respect to the presence of total neck node metastasis. The average levels of thyroglobulin after TSH suppression in all the patients with and without total neck lymph node metastasis were 31.07±88.04 ng/mL and 5.18±27.44 ng/mL, respectively. There was no significant relationship between the levels of thyroglobulin after TSH suppression and total neck lymph node metastasis (z=-1.392, p=0.164). Girelli et al. (1985) studied 429 patients with well-differentiated thyroid cancers and found that there were higher levels of thyroglobulin after TSH suppression in the total neck lymph node metastasis group compared to the non-metastasized group (18-20). Our study is not compatible with this study, again due to the smaller number of cases.

Anti-TPO and Anti-Tg levels were compared in patients with and without lateral neck lymph node metastasis. In the presence of lateral neck lymph node metastasis, the mean anti-TPO and the mean AntiTg levels were 10.52±8.26 IU/mL and 21.87±15.13 IU/mL, respectively, whereas in its absence the levels were 22.48±42.53 IU/mL and 31.07±52.22 IU/mL, respectively. Thus, higher mean Anti-TPO values were evident in thyroid papillary microcarcinoma patients who did not have lateral lymph node metastasis. The relationship between the presence of lateral neck lymph node metastasis and the Anti-TPO values was statistically significant (z=-2.510, p=0.012) whereas the relationship between the lateral neck lymph node metastasis and Anti-Tg values was non-significant (z=-0.326, p=0.745). A Chinese study conducted in 2016 reported that the mean Anti-TPO and Anti-Tg values were higher in thyroid papillary microcarcinoma patients with lateral neck lymph node metastasis than in the ones without lateral metastasis of the neck lymph node (14).

Logistic regression analysis confirmed that gender, age, Anti TPO, TSH, and the RAI variables did not constitute a risk factor for total neck lymph node metastasis in papillary thyroid mi-

crocarcinoma patients. Furthermore, no statistically significant relationship was found with respect to the other parameters.

There are no data the on mortality of thyroid papillary microcarcinoma, either in any previous or in our study. Distant metastases were not detected in any of our patients during their follow-up between the years 2012 and 2014.

In conclusion, the values of thyroglobulin after TSH suppression were higher in patients exhibiting lateral neck lymph node metastasis and capsular invasion. The rate of total neck lymph node metastasis was also seen to be higher in patients with capsular invasion. The Anti-TPO values were higher in thyroid papillary microcarcinoma patients who did not have lateral lymph node metastasis.

These findings indicate that the levels of thyroglobulin after TSH suppression and capsular invasion are important risk factors for neck nodal metastasis in papillary thyroid microcarcinoma patients. In a research regarding thyroid papillary carcinoma performed in Colombia between the years 2006 and 2012, 78% of patients with tumor size greater than 20.8 mm exhibited capsular invasion (21). However, the p-value calculated in our study was noted to be at the border. Our results were incompatible with this literature, probably due to the small number of patients that were examined.

Source of Finance: During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest: No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Barış Tırman; Design: Barış Tırman; Control/Supervision: Mahmut Başoğlu; Data Collection and/or Processing: Barış Tırman; Analysis and/or Interpretation: Kağan Karabulut; Literature Review: Kağan Karabulut; Writing the Article: Barış Tırman; Critical Review: Barış Tırman; Materials: Barış Tırman.

References

1. DeLellis RA, Williams ED. Tumours of the Thyroid and Parathyroid. In: DeLellis RA, Lloyd RV, Heitz PU, Eng C, eds. The WHO Classification of Tumours of Endocrine Organs (3rd ed). Lyon: IARC Press; 2004:51-133.
2. Maitra A. The Endocrine System. In: Kumar V, Abbas AK, Fausto N, Aster J, eds. Pathologic Basis of Disease (8th ed). Philadelphia; Elsevier Saunders; 2010:1107-1126.
3. Christopher DM. Fletcher. Diagnostic Histopathology of Tu- mors (3rd ed). Philadelphia; Churchill Livingstone Elsevier; 2010;997-1015.
4. Rosai J. Thyroid gland. Ackerman's Surgical Pathology (9th ed). Edinburgh; Mosby Elsevier; 2004;317-1335.
5. Mills SE. Stenberg's Diagnostic Surgical Pathology (5th ed). Philadelphia; Wolters Kluwer Health, Lipincott Williams & Wilkins; 2010;493-507.
6. Braga M, Graf H, Ogata A, Batista J, Hakim NC. Aggressive behavior of papillary microcarcinoma in a patient with Graves' disease initially presenting as cystic neck mass. J Endocrinol Invest. 2002;25:250-253.
7. Rossing M, Nygaard B, Nielsen FC, Bennedbæk FN. High prevalence of papillary thyroid microcarcinoma in danish patients: a prospective study of 854 consecutive patients with a cold thyroid nodule undergoing fine-needle aspiration. Eur Thyroid J. 2012;1:110-117.
8. Mantinan B, Rego-Iraeta A, Larrañaga A, Fluiters E, Sánchez-Sobrino P, Garcia-Mayor RV. Factors influencing the outcome of patients with incidental papillary thyroid microcarcinoma. J Thyroid Res. 2012;2012:469397.
9. Lin KD, Lin JD, Huang MJ, Huang HS, Jeng LB, Chao TC, Ho YS. Clinical presentations and predictive variables of thyroid microcarcinoma with distant metastasis. Int Surg. 1997;82:378-381.
10. Lin DZ, Qu N, Shi RL, Lu ZW, Ji QH, Wu WL. Risk prediction and clinical model building for lymph node metastasis in papillary thyroid microcarcinoma. Onco Targets Ther. 2016;9:5307-5316.
11. Liu Z, Wang L, Yi P, Wang CY, Huang T. Risk factors for central lymph node metastasis of patients with papillary thyroid microcarcinoma: a meta-analysis. Int J Clin Exp Pathol. 2014;7:932-937.
12. Creach KM, Siegel BA, Nussenbaum B, Grigsby PW. Radioactive iodine therapy decreases recurrence in thyroid papillary microcarcinoma. ISRN Endocrinol. 2012;2012: 816386.
13. Karatzas T, Vasileiadis I, Kapetanakis S, Karakostas E, Chrousos G, Kouraklis G. Risk factors contributing to the difference in prognosis for papillary versus micropapillary thyroid carcinoma. Am J Surg. 2013;206:586-593.
14. Li C, Yu W, Fan J, Li G, Tao X, Feng Y, Sun R. Thyroid functional parameters and correlative autoantibodies as prognostic factors for differentiated thyroid cancers. Oncotarget. 2016;7:49930-49938.

15. Haymart MR, Repplinger DJ, Leverson GE, Elson DF, Sippel RS, Jaume JC, Chen H. Higher serum thyroid stimulating hormone level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage. J Clin Endocrinol Metab. 2008;93:809-814.
14. Romero-Rojas A, Cuervo-Martínez J, Osorio-Arango K, Olaya N. Histological variants and prognostic factors of papillary thyroid carcinoma at the Colombian Instituto Nacional de Cancerología, 2006-2012. Biomedica. 2015;35:429-436.
16. Page C, Biet A, Boute P, Cuvelier P, Strunski V. 'Aggressive papillary' thyroid microcarcinoma. Eur Arch Otorhinolaryngol. 2009;266:1959-1963.
17. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Sherman SI, Tuttle RM; American Thyroid Association Guidelines Taskforce. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2015;25:109-142.
18. Girelli ME, Busnardo B, Amerio R, Scotton G, Casara D, Betterle C, Piccolo M, Pelizzo MR. Serum thyroglobulin levels in patients with well-differentiated thyroid cancer during suppression therapy: study on 429 patients. Eur J Nucl Med. 1985;10:252-254.
19. Zhang L, Wei WJ, Ji QH, Zhu YX, Wang ZY, Wang Y, Huang CP, Shen Q, Li DS, Wu Y. Risk factors for neck nodal metastasis in papillary thyroid microcarcinoma: a study of 1066 patients. J Clin Endocrinol Metab. 2012;97:1250-1257.
20. Qu N, Zhang L, Ji QH, Chen JY, Zhu YX, Cao YM, Shen Q. Risk factors for central compartment lymph node metastasis in papillary thyroid microcarcinoma: a meta-analysis. World J Surg. 2015;39:2459-2470.
21. Romero-Rojas A, Cuervo-Martínez J, Osorio-Arango K, Olaya N. Histological variants and prognostic factors of papillary thyroid carcinoma at the Colombian Instituto Nacional de Cancerología2,006-2012. Biomedica. 2015;35:429-436.