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Is Bethesda classification sufficient to predict thyroid cancer in endemic regions?

Endemik bölgelerde Bethesda sınıflaması tiroid kanserini ön gördürmede yeterli midir?

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Abstract

Aim: Bethesda classification is widely used to determine the risk of malignancy of thyroid nodules and in many guidelines, treatment algorithms are determined according to this classification. We aimed to investigate the accuracy of malignancy predictions of Bethesda classification in patients who underwent surgery.

Methods: In this retrospective cohort study, the medical records of patients who underwent thyroidectomy between 2013 and 2017 were analyzed. Patients' demographic characteristics, fine needle aspiration biopsy (FNAB) results, ultrasonographic findings, number of nodules, diameter of nodules, type of surgeries performed, and the terminal pathology results were recorded. Malignancies that were detected in Bethesda 1-2 patients and in nodules other than the nodule to which FNAB was performed in other Bethesda categories were defined as incidental cancer.

Results: Nine hundred sixty-seven patients were included in the study. The mean age of the patients was 46.9 (12.4) years and 82.4 % (n=797) were female. Mean nodule diameter was 29.7(13.9) mm and 64.3% (n=622) of the patients had 3 or more nodules. In our series, the rate of malignancy was 24.2% for Bethesda 1, 24.7% for Bethesda 2, 35% for Bethesda 3, 52.1% for Bethesda 4, 91.2% for Bethesda 5 and 100% for Bethesda 6. In all categories, the malignancy rate was higher than the expected range, but statistical significance was determined in Bethesda 1, 2, 4 and 5 groups. When compared to the whole series, rate of incidental cancer was 18.2%, whereas the incidental cancer rate was 49.5% of all cancers. The tumor was multicentric in 34.6% of malignant cases.

Conclusion: In endemic regions, higher rates of malignancy are detected than that predicted by the Bethesda classification. Therefore, updates on guidelines in patient selection for surgery and in choosing the surgical technique may be necessary for endemic areas.

Keywords: Bethesda classification, Incidental thyroid cancer, Endemic region, Thyroid nodule

Öz

Amaç: Tiroid nodüllerinin malignite riskinin belirlenmesinde Bethesda sınıflaması yaygın olarak kullanılmakta ve birçok kılavuzda bu sınıflamaya göre tedavi algoritmaları belirlenmektedir. Bethesda sınıflamasının malignite öngörülerinin cerrahi uygulanmış hastalarda doğruluğunu araştırmayı amaçladık.

Yöntemler: Bu retrospektif kohort çalışmada 2013-2017 yılları arasında tiroidektomi uygulanan hastaların dosyaları incelendi. Hastaların demografik özellikleri, İnce İğne Aspirasyon Biyopsisi(İİAB) sonuçları, ultrasonografik bulguları, nodül sayıları, nodül çapları, yapılan ameliyat ve terminal patoloji sonuçları kaydedildi. İİAB sonucu Bethesda 1 ve 2 olan hastalarda saptanan maligniteler ve diğer Bethesda gruplarında İİAB yapılan nodül dışında saptanan maligniteler insidental kanser olarak tanımlandı.

Bulgular: Dokuzyüzaltmışyedi hasta çalışmaya dahil edildi. Hastaların yaş ortalaması 46,9(12,4) saptandı ve hastaların %82,4'ü (n=797) kadındı. Ortalama nodül çapı 29,7(13,9) mm idi ve hastaların %64,3'ünde (n=622) 3 ve üzeri sayıda nodül mevcuttu. Serimizde malignite oranları Bethesda 1 için %24,2, Bethesda 2 için %24,7, Bethesda 3 için %35, Bethesda 4 için %52,1, Bethesda 5 için %91,2 ve Bethesda 6 için %100 olarak saptandı. Tüm kategorilerde malignite oranları beklenen aralıkların üstünde saptanmasına rağmen bu fark Bethesda 1, 2, 4 ve 5 gruplarında istatistiksel olarak anlamlı saptandı. Tüm seriye göre kıyaslandığında insidental kanser oranı %18,2 iken tüm kanserler içinde insidental kanser oranı %49,5 saptandı. Malignite saptanan olguların %34,6'sında tümör multisentrikti.

Sonuç: Endemik bölgelerde Bethesda klasifikasyonun öngörülerinden yüksek oranda malignite saptanabilmektedir. Bu nedenle cerrahi uygulanacak hastaların seçiminde ve cerrahi teknik tercihinde kılavuz önerilerinin güncellenmesi gerekebilir.

Anahtar kelimeler: Bethesda sınıflaması, İnsidental tiroid kanseri, Endemik bölge, Tiroid nodülü

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Introduction

Thyroid nodules are the most common diseases of the thyroid gland [1]. While the prevalence of thyroid nodules varies according to the method of detection, age, gender, and exposure to radiation, it is between 28.3 to 42.4 percent [1,2].

Ultrasound (US) and fine needle aspiration biopsy (FNAB) are used to evaluate the risk of malignancy of thyroid nodules. All relevant guidelines have defined ultrasonographic risk factors and classified FNAB recommendations [1,3].

Cytological evaluation is the gold standard method for detection of risk of malignancy for thyroid nodules. FNAB results have been standardized by the widely used Bethesda classification system which was defined in 2009 and updated in 2017 [1,3,4]. According to this classification, FNAB results have been divided into six categories, for each of which the risk of malignancy was determined. Recommendations for surgery and follow-up are present in national and international guidelines based on ultrasonographic and cytologic results [1,3].

The aim of this study is to compare the cancer predictions of Bethesda classification with terminal pathology results of the patients who were operated according to the recommendations of the guideline and investigate whether the recommendations of the guideline are sufficient.

Materials and methods

Medical records of patients who had undergone thyroidectomy for thyroid nodules between 2013 and 2017 were retrospectively analyzed, after approval of Non-pharmacological Clinical Research Ethics Committee of Haseki Training and Research Hospital (569-2017) was obtained. Patients operated for hyperthyroidism, whose diagnosis of malignancy was definite before surgery and for whom neck dissection was planned, who had undergone secondary surgery for completion thyroidectomy, for whom sufficient clinical data could not be obtained and who had a cancer other than differentiated thyroid cancer in their terminal pathology were excluded from the study. Thyroidectomy indications were based on ATA guidelines in Bethesda group 3-4-5-6 patients. In Bethesda group 1-2 patients, nodule sizes greater than 3 cm in diameter, grade 2-3 multinodular goiter, compression symptoms and patient preference were operation indications.

Demographic characteristics of the patients, ultrasonographic findings, FNAB results, number of nodules, diameters of nodules, the type of surgery performed, and the terminal pathology results were recorded.

The malignancies that were detected in patients whose FNAB result was Bethesda 1 and 2 were defined as incidental cancer. In patients whose FNAB result were consistent with Bethesda 3, 4, 5 and 6, if malignancy was detected in another nodule while the nodule to which FNAB was performed was benign, that case was also defined as incidental cancer. In patients whose FNAB result were consistent with Bethesda 3, 4, 5 and 6 and if malignancy was detected in that nodule, it was defined as non-incidental cancer. Patients were classified into three groups: Benign, incidental cancer and non-incidental cancer. Indications for surgery were divided into 3 groups according to FNAB as Bethesda 1-2, Bethesda 3-4 and Bethesda 5-6.

Statistical analysis

Descriptive statistics were expressed as number and percent for categorical variables, and as mean, standard deviation, minimum and maximum for numerical variables. The ratios in independent groups were compared using the chi-square test. Since multiple group comparisons did not demonstrate a normal distribution, Kruskal Wallis test was used. Frequency analysis, single ratio test and independent double ratio test were used for data analysis. *P*-value less than 0.05 was considered statistically significant. Applications were prepared using R Project (R Core Team, 2019) and IBM SPSS 20 (IBM Corp. 2011).

Results

Medical records of 1132 patients were retrospectively analyzed, and 967 patients were included in the study. Among all, 82.4 percent of the patients were female. Mean age of the patients was 46.97 (12.49) years. Diameter of the largest nodule was 29.7(13.9) mm and the mean tumor diameter was 17(14.6) mm. 64.3% of patients had 3 or more nodules. Rate of malignancy was 36.7 percent in the entire series. Patients' demographic characteristics and related information is summarized in Table 1.

FNAB results demonstrated that 10.2 percent of patients was classified as Bethesda 1, 44.5 percent of patients was classified as Bethesda 2, 22.1 percent of patients, as Bethesda 3, 14.7 percent, as Bethesda 4, 7 percent, as Bethesda 5 and 1.4 percent, as Bethesda 7. The rate of malignancy in each Bethesda group was 24.2%, 24.7%, 35%, 52.1%, 91.2% and 100% respectively. The 2017 Bethesda classification update presented two different cancer risk predictions based on whether noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFT-P) is considered cancer or not. When NIFT-P is considered cancer and the single ratio comparison test is performed by taking the upper limit of risk ratios, there was a statistically significant difference in Bethesda 1,2,4 and 5 groups (Table 2) ($P<0.001$). When NIFT-P is not considered cancer, the difference in Bethesda 3 category is also statistically significant ($P<0.001$).

While the ratio of incidental cancer was 18.2 % in the whole series, incidental cancers made up 49.5 % of patients with malignancy. 34.6 % of all cancers was multicentric. Patients were classified into three groups: Those with incidental cancer, non-incidental cancer, and benign pathology. Comparison of three groups demonstrated that the mean diameter of largest nodule was 29.7 (14) mm in the incidental cancer group, 22.4 (13.7) mm in the non-incidental cancer group and 31.8(13.2) mm in the benign group. The differences between incidental and non-incidental cancer groups ($P<0.001$) and between non-incidental cancer and benign groups were statistically significant ($P<0.001$) (Figure 1). Mean age of the patients in the incidental cancer, non-incidental cancer and benign groups were 47.6 (11.5) years, 44.8 (13.5) years and 47.3 (12.3) years, respectively. The difference between non-incidental cancer and benign groups was statistically significant ($P=0.047$).

Largest nodule diameter and tumor diameter were significantly smaller in incidental cancers compared to non-incidental cancers (P<0.001). The mean age of the patients in the incidental cancer group was significantly higher than those in the non-incidental cancer group (P=0.024).

Incidental cancers and non-incidental cancers were compared according to multicentricity, tumor capsule invasion, lymphovascular invasion, invasion of thyroid capsule and tumor diameter being larger than 10 mm. 40.3% of incidental cancers and 29.1% of non-incidental cancers were multicentric, the difference between which was statistically significant (P=0.026). There was no statistical significance between the two groups in terms of lymphovascular invasion (p>0.05). However, non-incidental cancers had a significantly higher rate of tumor capsule invasion and invasion of thyroid capsule (P<0.001 and P=0.012 respectively). Tumor diameter was ≥10 mm in 48.9% of incidental cancers and in 72.1% in non-incidental cancers. This difference was also statistically significant (P<0.001) (Table 3).

The diameter of the largest nodule in the non-incidental cancer group was significantly smaller than that in the other 2 groups (P<0.001). There was no difference between the incidental cancer and benign groups (Figure 1).

Table 1: Characteristics of the patients

		n	%
Gender	Female	797	82.4
	Male	170	17.6
Mean age(standard deviation)		46.97(12.49)	
Type of Surgery	Bilateral total thyroidectomy (BTT)	606	62.7
	Lobectomy	361	37.3
Pathology	Thyroid Papillary Cancer	206	21.3
	Papillary Microcancer	143	14.8
	Follicular	6	0.6
	Benign	612	63.3
Indication	Bethesda 1-2	529	54.7
	Bethesda 3-4	356	36.8
	Bethesda 5-6	82	8.5
Number of nodules	1	237	24.5
	2	108	11.2
	3 and more	622	64.3
Diameter of the largest nodule (mm) Mean(SD)		29.7(13.9)	
Tumor diameter (mm) Mean(SD)		17(14.6)	

Table 2: Comparison of ratio of malignancy according to Bethesda groups (If NIFT-P is accepted as cancer)

Bethesda	Reference (%)	Ratio (%)	Z-statistic	*P*-value
1	10	24.244	-5.067	<0.001
2	3	24.707	-26.437	<0.001
3	30	35.033	-1.672	0.095
4	40	52.106	-3.191	0.001
5	75	91.254	-3.652	<0.001
6	99	100.000	0.376	0.707

Table 3: Comparison of histopathologic characteristics of incidental cancers and non-incidental cancers

	Incidental cancers	Non-incidental cancers	*P*-value
Multicentricity	40.3%	29.1%	0.026
Tumor capsule invasion	11.9%	27.4%	<0.001
Lymphovascular invasion	4%	8.9%	0.083
Thyroid capsule invasion	4.5%	12.3%	0.012
Tumor diameter ≥10mm	48.9%	72.1%	<0.001

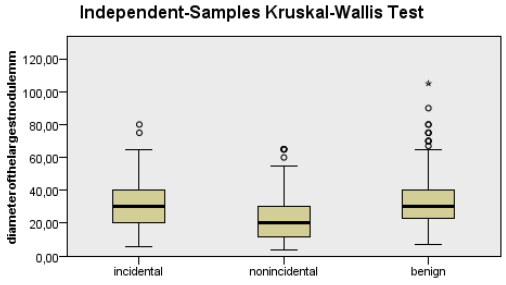

Figure 1: The comparison of three groups according to diameter of the largest nodule

Discussion

Thyroid nodules continue to be the most common disease of thyroid gland. In a patient presenting with thyroid nodule, thyroid function tests, ultrasonography, scintigraphy, fine needle aspiration biopsy are used as indicated to evaluate the nodule. Many guidelines have similar suggestions regarding this approach. For these patients it is important to determine the necessity of surgical treatment and avoid over-treatment. For this purpose, international guidelines have defined certain diagnostic and therapeutic algorithms. According to these algorithms, patients with a thyroid nodule and a normal serum TSH have FNAB indications that are based on ultrasonographic characteristics and size of nodule. FNAB results are widely categorized according to Bethesda classification.

In a meta-analysis performed by Bongiovanni et al. [5], the distribution of patients who had undergone surgery according to different Bethesda categories was 8.3 %, 24.6%, 15%, 28.2%, 7.9% and 16%, respectively and the total rate of cancer was 33.8%. In our series 10.2 % of patients were Bethesda 1, 44.5% were Bethesda 2, 22.1% was Bethesda 3, 14.7% were Bethesda 4, 7% were Bethesda 5 and 1.4% was Bethesda 6 and the total rate of cancer was 36.7%. We believe that the high prevalence of multinodular goiter in our country, the large diameter of nodules and the patients who were treated surgically due to multiple nodules has caused the high rate of patients in benign group. However, in the whole series, the rate of cancer was comparable with the rates reported in the literature.

Bethesda classification was first defined in 2009 and updated in 2017. In the updated classification, malignancy predictions have been determined separately according to whether NIFT-P is considered cancer or not. Accordingly, in cases where NIFT-P is considered cancer, malignancy prediction is 5-10 % for Bethesda 1, 0-3% for Bethesda 2, 10-30% for Bethesda 3, 25-40% for Bethesda 4, 50-75% for Bethesda 5 and 97-99% for Bethesda 6 [4]. In our series, the rate of malignancy was 24.2 % in Bethesda 1 group, 24.7 % in Bethesda 2 group, 35 % in Bethesda 3 group, 52.1% in Bethesda 4 group, 92.1 % in Bethesda 5 group and 100% in Bethesda 6 group. When the rate of malignancy in our series was compared with the upper limits of rates of malignancy where NIFT-P was considered cancer in the 2017 update, the rate of malignancy was significantly higher in our patients in Bethesda 1, 2, 4 and 5 groups. Even though the rate of malignancy in Bethesda 3 group was higher than the predicted upper limit, there was no statistical significance. We used the reference values that considered NIFT-P cancer because our study retrospectively analyzed the data of patients that were treated between 2013 and 2017 and in that period, NIFT-P was not histopathologically reported in our center.

Many studies in the literature report different percentages of malignancy than the rates of cancer that were foreseen in the literature [5-10]. In a meta-analysis by Bongiovanni et al, the percentage of malignancy in Bethesda categories were 16.8%, 3.7%, 15.9%, 26.1%, 75.2 and 98.6% respectively [5]. In 2015 ATA guideline, the actual cancer risk of surgically resected nodules was calculated based on this study and found as 20% (9-32), 2.5% (1-10), 14% (6-48), 25% (14-34), 70% (53-97) and 99% (94-100) respectively [3]. In our series we compared the cancer risk by considering NIFT-P cancer in the

2017 revision of Bethesda classification and by taking the upper limit of predicted cancer risk percentages. There was a statistically significant difference in Bethesda groups 1,2,4 and 5. When evaluated according to actual risk percentages of ATA guideline, the rate of cancer in Bethesda 2 (24.7%) and 4 (52.1%) were above reference values.

In a meta-analysis performed by Huy Gia Vuong et al. [10], the rate of malignancy in Western and Eastern countries was compared according to Bethesda categories. Cancer rates in for Bethesda categories 1, 2,3, 4, 5 and 6 were 13.2 %, 4.1 %, 21.5 %, 27.3%, 75.1% and 99.2%, respectively, in the Western countries, and 26.5%, 13.8%, 45%, 32.8%, 88.1% and 98.6%, respectively, in the Eastern countries. In Eastern countries, the rates of cancer in Bethesda 2, 3 and 5 categories were significantly higher. The malignancy rates in Eastern countries was generally higher. In our series, in all categories, cancer rates were higher than that in the Western countries. When compared with Eastern countries, cancer rates were higher in Bethesda groups 2 and 4 and lower in Bethesda group 3.

Incidental thyroid cancer is reported in up to 12 % of clinical series and in up to 36 % autopsy series in the literature [11]. In our study, rate of incidental cancer was 18.2% of the whole series and 49.5% of all cancers were evaluated as incidental cancer. A study by Evranos et al. detected incidental cancer in 326 (36 %) of 906 patients who were operated and determined to have a malignancy [12].

A study performed by Can et al. [13] compared the incidental and non-incidental thyroid cancers (NITC) according to the histopathologic data and detected findings which demonstrated that NITC could have a more aggressive course. Proximity to surgical margin, positive surgical margin, capsule invasion, lymphovascular invasion, extrathyroidal dissemination, multifocal tumor and lymph node metastasis were significantly higher in NITC. 94.7% bilateral tumors were non-incidental. BRAF V 600 gene mutation was detected in 94 % of NITC. In our series multicentricity was significantly higher in patients with incidental cancer. Tumor capsule invasion, and thyroid capsule invasion were significantly higher in patients with NITC. In our series 48.9 % of incidental cancers were larger than 1 cm, while in NITC, this rate was 72.1%. Incidental cancers are reported to possess less aggressive histopathologic characteristics and our findings are compatible with literature [13,14]. However, nearly half of the incidental cancers are larger than 1 cm and their clinical significance cannot be denied.

In a study that retrospectively analyzed 308 patients with papillary thyroid cancer, 63.6 % of patients that had coexisting chronic lymphocytic thyroiditis in the pathological specimen were incidental. In the same series 88.9 % of patients with multinodular hyperplasia were incidental and 11.1% were non-incidental [13]. Our country is endemic for thyroid diseases, therefore lymphocytic thyroiditis and multinodular hyperplasia are frequently detected. In our series, 64.3% patients had 3 and more nodules, only 24.5 % of patients had a single nodule.

Limitations

The limitations of this study are its retrospective design and that the patients only included those who underwent surgery. Another limitation of this study is that although all patients were operated with an indication according to the guideline recommendations, the study was retrospective and some of the patients had to be excluded from the study due to insufficient data.

Conclusion

Ultrasonographic evaluation and FNAB are gold standard for evaluation of thyroid nodules. Bethesda classification is widely used and a useful and instructive classification. Most guidelines suggest follow-up and treatment algorithms based on this classification. However, in endemic countries such as ours, most of the patients have more than 3 nodules. Guidelines usually make suggestions for a solitary nodule and recommend each nodule to be separately evaluated for risk of malignancy. There are similar studies to our series in the literature. Results of our retrospective study demonstrated higher rates of malignancy than predicted for each Bethesda category. Based on our results we believe that patients in endemic regions should be managed according to the suggestions of guidelines but situations that are unique for endemic regions should also be considered in the decision making. We believe that decisions should be made according to clinical findings, number of nodules, diameter of nodules and radiologic signs, especially for Bethesda 1 and 2 categories. Guidelines recommend lobectomy for Bethesda 3 and 4 categories. In these groups of patients, the dissemination of the disease should be considered and the need for more extensive surgeries should be kept in mind.

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