ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

Med J SDU / SDÜ Tıp Fak Derg ▶ 2022:29(2):213-222 doi: 10.17343/sdutfd.1100450

ANALYSIS OF FINE NEEDLE ASPIRATIONS OF THE THYROID: CYTOLOGICAL-HISTOPATHOLOGICAL CORRELATION AND OUTCOMES OF THE BETHESDA SYSTEM

TİROİD İNCE İĞNE ASPİRASYONLARININ ANALİZİ: SİTOLOJİK-HİSTOPATOLOJİK KORELASYON VE BETHESDA SİSTEMİNİN SONUÇLARI

Ayça TAN[1]

[1] Manisa Celal Bayar University, Faculty of Medicine, Department of Pathology, Manisa, TÜRKİYE

Cite this article as: Tan A. Analysis of Fine Needle Aspirations of the Thyroid: Cytological-Histopathological Correlation and Outcomes of The Bethesda System. Med J SDU 2022; 29(2): 213-222.

Öz

Amaç
Bethesda sistemi, tiroid nodüllerinin aspirasyonunu değerlendirmek için yaygın olarak kullanılmaktadır. Çalışmanın amacı sitoloji ve histopatoloji sonuçları arasındaki korelasyonun ışığında sistemin kullanılabilirliğini değerlendirmek ve literatür eşliğinde gözden geçirmektir.

Gereç ve Yöntem
Bethesda sistemi kullanılarak raporlanan tiroid nodüllerinin ince iğne aspirasyon sonuçları analiz edildi. Tiroidektomi sonuçlarına göre malignite oranları hesaplandı. Bethesda sisteminin gücünü analiz etmek için altı farklı alt grup tasarlandı. Duyarlılık, özgüllük, pozitif prediktif değer, negatif prediktif değer ve tanısal doğruluk bu alt gruplarda ayrı ayrı hesaplandı. Veriler, Windows için SPSS 20 kullanılarak analiz edildi.

Bulgular
Tiroid nodüllerin Bethesda'ya göre dağılımı sırasıyla 2212 (%33,5), 3163 (%47,9), 720 (%10,9), 67 (%1), 361 (%5,5) ve 75 (%1,1) idi. Tiroidektomi yapılan 873 nodülün 254'ü (%29.9) malignite tanısı aldı. Tiroidektomilere göre tanı kategorileri sırasıyla 233 (%26,7), 277 (%31,7) 137 (%15,7), 23 (%2,6), 163 (%18,7) ve 40 (%4,6) idi. Her Bethesda kategorisinin malignite oranları %14,5, %6,8, %32,8, %52,1, %66,8 ve %97,5 idi. İnce iğne aspirasyonunun sensitivitesi, spesifisitesi, pozitif prediktif değeri (PPV), negatif prediktif değeri (NPV), doğruluğu hesaplandı ve sırasıyla %61,8 ile %89,3, %79,6 ile %99,6, %70,4 ile %97,5, %84,5 ile %93,1 ve %79,5 ila %93,6 arasında değişmekteydi.

Sonuç
Bu çalışmanın sınırlılığı B1 kategorisinin çok yüksek olmasıdır. Ancak verilerin sadece bir patolog tarafından değerlendirilmesi ve en fazla vaka sayısına sahip ilk üç çalışmadan biri olması nedeniyle B1 dışındaki diğer kategoriler açısından literatüre önemli bir katkı sağlamaktadır. Bethesda sistemi, klinisyene uygun klinik takip ve doğru tedavi yaklaşımı sağlayan ve patologlar için gözlemciler arası uyumun yüksek olduğu bir sınıflandırmadır.

Anahtar Kelimeler: Tiroid, İnce iğne, Tiroidektomi, Bethesda

Abstract

Objective
The Bethesda system is widely used to evaluate aspiration of thyroid nodules. The aim of the study is to

Sorumlu yazar ve iletişim adresi /Corresponding author and contact address: A.T. / draycatan@gmail.com
Müracaat tarihi/Application Date: 08.04.2022 • Kabul tarihi/Accepted Date: 31.05.2022
ORCID IDs of the authors: A.T: 0000-0003-4450-5425

evaluate the usability of the system by the correlation between cytology and final histopathology results and to review the literature.

Materials and Methods
Fine needle aspiration of thyroid nodules reported using Bethesda system were analyzed. Malignancy rates were calculated by the results of thyroidectomies. To analyze the power of the Bethesda system six distinct subgroups were designed. The sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were calculated separately in these subgroups. The data were analyzed using SPSS 20 for Windows.

Results
The distribution of thyroid nodules according to the Bethesda was 2212 (33.5%), 3163 (47.9%), 720 (10.9%), 67 (1%), 361 (5.5%) and 75 (1.1%), respectively. Of 873 nodules that underwent thyroidectomy, 254 (29.9%) were diagnosed as malignant. The diagnostic categories according to thyroidectomies were 233 (26.7 %), 277 (31.7%), 137 (15.7%), 23 (2.6%), 163 (18.7%) and 40 (4.6%), respectively. The malignancy rates of each Bethesda category were 14.5%, 6.8%, 32.8%, 52.1%, 66.8% and 97.5%. The sensitivity, spesifity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of fine needle aspiration was calculated and ranged from 61.8% to 89.3%, 79.6% to 99.6%, 70.4% to 97.5%, 84.5% to 93.1% and 79.5% to 93.6%, respectively.

Conclusion
The limitation of this study is that the B1 category is very high. However, since the data are evaluated by only one pathologist and it is one of the first three studies with the highest number of cases, it makes a significant contribution to the literature in terms of all categories except B1. The Bethesda system is a classification that provides the clinician with appropriate clinical follow-up and the accurate treatment approach, and a high interobserver agreement for pathologists.

Keywords: Thyroid, Fine-needle, Thyroidectomy, Bethesda

Introduction

Approximately 1 in 20 people have thyroid nodules and the risk of developing malignancy is 5% in these (1, 2). A reliable and feasible test is needed to identify this possibility (1). Fine needle aspiration of thyroid is primary choice and also most useful diagnostic tool. It has a critic role to distinguish benign and malignant nodules to avoid unnecessary surgery (3). The sensitivity and spesificity of the test are 57 to 99% and 45 to 99% in the literature, respectively (1).

The accepted classification for standardized diagnosis of thyroid nodules is The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) which was created in 2007, published in 2009 and revised in 2017. The system comprises six diagnostic categories which provide to predict the malignancy risk of each nodule and to make decision about clinical management (4, 5).

The aim of this study is to compare the results of the aspirations evaluated according to Bethesda system with the actual diagnoses after surgery and to determine the strength of the test. Also aimed to see the distribution of the data and compare the sensitivity, spesificity, positive predictive value, negative predictive value and accuracy of our data with the other publication's data in the literature.

Materials and Methods

This study was approved by the ethics committee of Manisa Celal Bayar University (18.9.2019, 20.478.486).

From January 2015 to June 2019 (54 months), the patients which have ultrasonography guided fine needle aspiration (FNA) cytology of thyroid were obtained. Conventional smears were prepared for all nodules. All of the slides were stained with May-Grunwald-Giemsa and evaluated by one expert pathologist using TBSRTC which included six diagnostic categories defined as Nondiagnostic (ND) or Unsatisfactory, Benign (BG), Atypia of Undetermined Significance (AUS) or Follicular Lesion of Undetermined Significance (FLUS), Follicular neoplasm (FN) or Suspicious for a Follicular neoplasm (SFN), Suspicious for Malignancy (SFM) and Malignant (MG), respectively. These categories were also abbreviated as B1, B2, B3, B4, B5 and B6, respectively. The patients who underwent thyroidectomy were also recorded and histopathologic diagnoses were noted. The cases diagnosed as FVPTC were reevaluated to determine whether they were noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) or not.

To analyze the power of the system six distinct subgroups were designed. The each subgroup was

categorized as negative and positive. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy were calculated according to each groups.

Results

A total of 6598 thyroid nodules in 4447 pathology reports from 3635 patients were included in this study. The mean age and standard deviation (SD) of aspirations was 52.19±13.44 with a range of 8-94 years. The mean of age was 51.58±13.67 for pathology reports (n=4447) and 51.31±13.88 for patients (n=3635). The female/male ratio was 3.44 (F/M=5114/1484) for all aspirations, 3.38 (F/M=3665/1082) for pathology reports and 3.53 (F/M=2834/801) for patients. 3240 (49.1%) of the nodules were located in the right lobe, 3050 (46.2%) of the nodules were located in the left lobe, 246 of (3.8%) nodules were in the isthmus and pyramidal lobe and 62 of them have unknown localization. The mean nodule size was 19.06 ± 10.86 mm and the range was 5-112 mm in 4972 nodules with known diameters.

The distribution of nodules according to the Bethesda category was 2212 (33.5%), 3163 (47.9%), 720 (10.9%), 67 (1%), 361 (5.5%) and 75 (1.1%), respectively. Overall, 594 (15.48%) patients underwent surgery for 873 (13.23%) nodules, and malignancies were identified in 254 nodules (29.09% of nodules

Table 1 The cytological diagnosis and cytological-histopathological correlation

CYTOLOGICAL DIAGNOSIS			BETHESDA CATEGORIES						
			ND	BG	AUS/FLUS	FN/SFN	SFM	MG	Total
			2212 (33.5%)	3163 (48%)	720 (10.9%)	67 (1%)	361 (5.5%)	75 (1.1%)	6598
HISTOPATHOLOGICAL DIAGNOSIS	BENIGN	FND/NG	182 (78.1%)	246 (88.8%)	69 (50.4%)	5 (21.7%)	28 (17.2%)	0	**530**
		HT	12 (5.2%)	10 (3.6%)	17 (12.4%)	0	13 (8%)	0	52
		FA/HCA	3 (1.3%)	1 (0.4%)	4 (2.9%)	6 (26.1%)	9 (5.6%)	0	23
		Others	2 (0.9%)	1 (0.4%)	2 (1.4%)	0	4 (2.4%)1	1 (2.5%)	10
	Total		**199 (85.5%)**	**258 (93.2%)**	**92 (67.2%)**	**11 (47.8%)**	**54 (33.2%)**	**1 (2.5%)**	**615**
	MALIGNANT	PTC	31 (13.3%)	17 (6.1%)	43 (31.4%)	10 (43.5%)	104 (63.8%)	38 (95%)	243
		FTC	1 (0.4%)	2 (0.7%)	1 (0.7%)	1 (4.3%)	1 (0.6%)	0	6
		MTC	1 (0.4%)	0	1 (0.7%)	0	2 (1.2%)	1 (2.5%)	5
	Total		**33 (14.1 %)**	**19 (6.9%)**	**45 (37.8%)**	**11 (%47.8)**	**107 (65.6%)**	**39 (97.5%)**	**254**
	NIFTP		1 (0.4%)	0	0	1 (4.4%)	2 (1.2%)	0	4
	Total		**233**	**277**	**137**	**23**	**163**	**40**	**873**

AUS/FLUS: atypia of undetermined significance/follicular lesion of undetermined significance, BG: benign, FA/HCA: follicular adenoma/hurthle cell adenoma, FN/SFN: follicular neoplasm/suspicious for a follicular neoplasm, FND/NG: follicular nodular disease/nodular guatr, FTC: follicular thyroid carcinoma, HT: hashimoto's thyroiditis, MG: malignant, MTC: medullary thyroid carcinoma, ND: nondiagnostic, NIFTP: noninvasive follicular thyroid neoplasm with papillary-like nuclear features, PTC: papillary thyroid carcinoma, SFM: suspicious for malignancy

with surgical resection). The diagnostic categories according to thyroidectomies were 233 (26.7 %), 277 (31.7%), 137 (15.7%), 23 (2.6%), 163 (18.7%) and 40 (4.6%), respectively.

The cytologic diagnosis of nodules which underwent thyroidectomy were described by individual categories and demonstrated in Table 1. The others category in Table 1 is included subacute thyroiditis and diffuse hyperplasia. Five cases which diagnosed as subacute thyroiditis in thyroidectomy were diagnosed as AUS (1 case), SFN (3 case) and MG (1 case). Five cases which diagnosed as diffuse hyperplasia in thyroidectomy were diagnosed as ND (2 case), BG (1 case), AUS/FLUS (1 case) and FN/SFN (1 case).

The malignancy rates of each Bethesda category were calculated. The rates were given in two different forms (without or with NIFTP) and were shown in Table 2.

Six subgroups were classified as FNA negative and FNA positive. In group I “BG (Bethesda 2)” was accepted as FNA-negative, and “MG (Bethesda 6)” was accepted as FNA-positive. The remaining four Bethesda categories (ND, AUS/FLUS, FN/SFN, SFM) were excluded from the evaluations of group I. The division of the other groups was shown in Table 3.

Table 2 The malignancy rates of each Bethesda category

Bethesda category	Prevalance	Tiroidectomies	Malignant diagnosis	NIFTP diagnosis	Malignancy rate without NIFTP	Malignancy rate with NIFTP
B1	2212	233	33	1	14.16%	14.59%
B2	3163	277	19	0	6.85%	
B3	720	137	45	0	32.84%	
B4	67	23	11	1	47.82%	52.17%
B5	361	163	107	2	65.64%	66.87%
B6	75	40	39	0	97.5%	
Total	**6598**	**873**	**254**	**4**		

NIFTP: noninvasive follicular thyroid neoplasm with papillary-like nuclear features

Table 3 The created six new subgroups

	FNA positive	FNA negative
Group I	MG	BG
Group II	SFM + MG	BG
Group III	FN/SFN + SFM + MG	BG
Group IV	SFM + MG	BG + AUS/FLUS
Group V	FN/SFN + SFM + MG	BG + AUS/FLUS
Group VI	FN/SFN + SFM + MG	ND + BG + AUS/FLUS

AUS/FLUS: atypia of undetermined significance/follicular lesion of undetermined significance
BG: benign, FN/SFN: follicular neoplasm/suspicious for a follicular neoplasm,
MG: malignant, ND: nondiagnostic, SFM: suspicious for malignancy

According to the all prepared groups the diagnoses were noted as benign and malignant with or without NIFTP. The sensitivity, spesifity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of fine needle aspiration were calculated and showed in Table 4.

To detect the accuracy and availability of the test, we searched all publications including all metaanalyses. The number of aspirations of 27 publications with full text available was noted. [5-31] Monthly time of the study and number of aspirations per month were calculated for all studies. These data and the Bethesda

Table 4 The histopathological diagnosis, sensitivity, spesificity, PPV, NPV and accuracy of all subgroups

		Histopathologic diagnosis			Sensitivity		Specificity		PPV		NPV		Accuracy	
		Malignant If NIFTP ≠ CA	Malignant If NIFTP = CA	Benign	NIFTP ≠ CA	NIFTP = CA	NIFTP ≠ CA	NIFTP = CA	NIFTP ≠ CA	NIFTP = CA	NIFTP ≠ CA	NIFTP = CA	NIFTP ≠ CA	NIFTP = CA
Group I	FNA positive	39	39	1	67.2	67.2	99.6		97.5	97.5	93.1	93.1	93.6	93.6
	FNA negative	19	19	258										
Group II	FNA positive	146	148	55	88.4	88.6	82.4		72.6	72.9	93.1	93.1	84.5	84.5
	FNA negative	19	19	258										
Group III	FNA positive	157	160	66	89.2	89.3	79.6		70.4	70.7	93.1	93.1	83.0	83.1
	FNA negative	19	19	258										
Group IV	FNA positive	146	148	55	69.5	69.8	86.4		72.6	72.9	84.5	84.5	80.6	80.7
	FNA negative	64	64	350										
Group V	FNA positive	157	160	66	71.0	71.4	84.1		70.4	70.7	84.5	84.5	79.5	79.6
	FNA negative	64	64	350										
Group VI	FNA positive	157	160	66	61.8	62.0	89.2		70.4	70.7	84.9	84.8	81.2	81.3
	FNA negative	97	98	549										

CA: carcinoma, NIFTP: noninvasive follicular thyroid neoplasm with papillary-like nuclear features, NPV: negative predictive value, PPV: positive predictive value

distribution for all series were shown in Table 5. The series with the highest and lowest percentage in the distribution of the series according to the Bethesda categories are marked in bold in Table 5. The numbers of the studies above the mean value in all categories were 10, 14, 12, 14, 10 and 7, respectively.

The malignancy rates of the 24 studies with both Bethesda (first and revised) were shown in Table 6 (1, 6-33). The malignancy rates of Bethesda was shown in the first two rows of Table 6 and the differences between the old and new Bethesda were showed as bold. Also the values above the Bethesda were marked in bold.

Table 5 The number of aspiration and the distribution of the Bethesda categories of each study

	Number of aspiration	Time period (month)	Aspiration per month	B1 %	B2 %	B3 %	B4 %	B5 %	B6 %
Yang et al 2007	4703	132	36	10.4	64.6	3.2	11.6	2.6	7.6
Yassa et al 2007	3589	120	30	7	66	4	9	9	5
Nayar et al 2009	5194	78	67	5	64	18	6	2	5
Theoharis et al 2009	3207	12	267	11.1	73.8	3	5.5	1.4	5.2
Jo et al 2010	3080	204	15	18.6	59	3.4	9.7	2.3	7
Renshaw 2010	7089	156	45	25	54	8	9	2	4
Kim et al 2011	865	36	24	1.8	58.5	16.3	1.2	6.2	16.2
Bohacek et al 2012	1000	130	8	5.6	67.1	0.8	17.2	2.4	6.9
Bongiovanni et al 2012	3724	36	103	3	55.4	6.7	**23.8**	6	5.1
Mufti et al 2012	250	72	3	11.6	77.6	**0.8**	4	2.4	3.6
Wu et al 2012	1382	36	38	20.1	39	**27.2**	8.4	2.6	2.7
Mondal et al 2013	1020	36	28	**1.2**	**87.5**	1	4.2	1.4	4.7
Williams et al 2013	1481	57	30	28.9	45.7	18.8	4.4	1.3	0.9
Naz et al 2014	528	unknown	unknown	4.7	76.3	12.7	2.1	3.4	**0.8**
Park et al 2014	1730	3	577	13.3	40.6	9.1	**0.4**	**19.3**	17.3
Arul et al 2015	603	30	20	2.7	65.2	10	10.6	5.3	6.3
Lee et al 2017	1925	6	321	9.4	57.1	10.7	1	3.5	18.3
Abdullah et al 2018	499	39	13	11.4	54.7	16.2	4	7.2	6.4
Nandedkar et al 2018	606	121	5	4.29	82.67	0.82	9.07	**1.15**	1.98
Paajenen et al 2018	363	12	30	26	49	9	9	5	2
Reuters et al 2018	980	24	41	11	59.8	7.1	8.5	5.1	8.2
Ke et al 2019	13351	68	196	13.5	**32.3**	13.2	2.8	9.5	**28.7**
Ronen et al 2019	287	49	6	21.6	55.1	13.2	4.2	3.8	2.1
Current study	6598	54	122	**33.5**	47.9	10.9	1	5.5	1.1
Total	64054		Mean value	12.52	59.70	9.33	6.94	4.59	6.96

Table 6 The malignancy rates of all the studies

	Number of resected nodules	Final diagnosis: malignant	MALIGNANCY RATES						
			B1 %	B2 %	B3 %	B4 %	B5 %	B6 %	Overall
Cibas 2009	-	-	**1-4**	0-3	**5-15**	**15-30**	**60-75**	97-99	-
Cibas 2017	-	-	**5-10**	0-3	**10-30**	**25-40**	**50-75**	97-99	-
Yang 2007	1052	478	11 (5/46)	1 (18/247)	19 (10/52)	32 (105/326)	65 (68/105)	98 (272/276)	46 (478/1052)
Yassa 2007	1242	433	10 (8/77)	0,3 (6/369)	24 (20/84)	28 (74/268)	60 (173/288)	97 (152/156)	35 (433/1242)
Nayar 2009	1413	334	9 (6/70)	2 (6/357)	6 (25/430)	14 (36/248)	53 (44/97)	97 (217/255)	24 (334/1413)
Theoharis 2009	378	202	32 (8/25)	**10** (8/82)	**48** (13/27)	34 (35/102)	**87** (26/30)	100 (112/112)	53 (202/378)
Jo 2010	892	276	9 (12/135)	3 (20/317)	17 (9/53)	25 (45/177)	70 (39/56)	98 (151/154)	31 (276/892)
Renshaw 2010	1331	425	2 (6/361)	**25** (50/204)	30 (53/179)	33 (27/108)	**99** (72/73)	50 (1/2)	32 (425/1331)
Kim 2011	204	182	NE	0 (0/8)	**76** (32/42)	**50** (4/8)	**100** (34/34)	100 (112/112)	89 (182/204)
Bohacek 2012	451	130	26 (5/19)	7 (12/173)	13 (1/8)	21 (33/160)	58 (14/24)	97 (65/67)	29 (130/451)
Bongiovanni 2012	1358	563	32 (8/25)	3 (4/158)	14 (19/132)	32 (224/698)	75 (137/183)	99 (161/162)	41 (563/1358)
Mufti 2012	84	20	20 (1/5)	**10** (6/60)	**50** (1/2)	20 (1/5)	**80** (4/5)	100 (7/7)	24 (20/84)
Wu 2012	221	64	14 (3/21)	**10** (6/63)	22 (11/51)	27 (13/49)	67 (12/18)	100 (19/19)	30 (64/221)
Mondal 2013	323	75	0 (0/3)	**5** (10/222)	20 (1/5)	31 (11/36)	75 (9/12)	98 (44/45)	23 (75/323)
Williams 2013	388	110	18 unknown	**16** unknown	25 unknown	32 unknown	**94** unknown	100 unknown	28 unknown
Naz 2014	61	16	0 (0/0)	**11** (5/45)	**33** (2/6)	25 (1/4)	**100** (4/4)	100 (2/2)	26 (16/61)
Park 2014	1547	761	35 (41/116)	**6** (39/702)	**69** (87/126)	**50** (2/4)	**99** (310/314)	99 (282/285)	49 (761/1547)
Arul 2015	392	59	0 (0/10)	1 (3/256)	24,4 (10/41)	28,9 (13/45)	70,8 (17/24)	100 (16/16)	15 (59/392)
Gunes 2015	1100	131	4 (4/103)	**5** (37/797)	21 (10/48)	16 (11/68)	68 (27/40)	95 (42/44)	12 (131/1100)
Lee 2017	381	307	27 (3/11)	**20** (9/46)	**56** (28/50)	33 (3/9)	**98** (42/43)	100 (222/222)	80 (307/381)
Abdullah 2018	101	52	100 (1/1)	11 (2/19)	25 (6/24)	27 (3/11)	**76** (16/21)	96 (24/25)	51 (52/101)
Nandedkar 2018	171	21	0 (0/0)	2 (3/142)	0 (0/2)	**50** (9/18)	**100** (3/3)	100 (6/6)	12 (21/171)
Pajanen 2018	78	27	33 (1/3)	0 (0/10)	8 (1/13)	13 (3/24)	71 (15/21)	100 (7/7)	35 (27/78)
Reuters 2018	418	140	26 (9/35)	**6** (10/166)	12 (3/25)	21 (16/77)	73 (29/40)	97 (73/75)	33 (140/418)
Ke 2019	3890	3396	67 (46/69)	**14** (33/233)	**54** (84/157)	30 (19/63)	**82** (586/715)	99 (2628/2653)	87 (3396/3890)
Ronen 2019	53	21	50 unknown	**25** unknown	27 unknown	**50** unknown	**83** unknown	100 unknown	40 (21/53)
Current study	873	258	14.5 (34/233)	**6.8** (19/277)	**32.8** (45/137)	**52.1** (12/23)	66.8 (109/163)	97.5 (39/40)	29 (258/873)
Total	18402	8481							

NE: not evaluated

Discussion

The classification systems provides to use the same terminology which predicts the correct malignancy rates. There were numerous study in the literature about the using TBSRTC (1, 3-14, 16-33).

According to this analyse, this study ranked third in the highest number of cases (Table 5). It was fifth in the number of aspirations evaluated monthly. The results of this series, which has a very high number of cases, will have a significant contribution to the literature.

For B1 category, the average of all series was 12.52%, and 3 of the 9 studies that were above this threshold were the highest series studies (Ke et al., Renshaw et al. and current study) (Table 5) (12, 24). Of the other six studies, only three had aspiration below 500 and B1 rates were 26%, 21.6% and 11.6% (18, 22, 26). The study with the lowest B1 rate belonged to Mondal et al with 1.2% and it's a great experience of aspiration (17). According to this analysis, this study, which is among the top three series with the highest case number, is the study with the highest ND rate. The reason for this is that the diagnostic criteria of Bethesda cannot be met and therefore the application of aspiration is insufficient. Our hospital does not have on-site and this rate can only decrease with routine on-site use.

Mondal et al was the first study in B2 category with 87.5%, B3 category was only 1% and B4 category was 4.2% (17). The B3 and B4 categories in this study were well below the average and the benign category was well above. In this study, when 323 (323/1020 = 31.6%) surgical follow-up was examined, the number of surgical cases in B2, B3 and B4 categories was 222, 5 and 36, respectively. The malignancy rates were 5, 20 and 31, respectively. Since the number of surgeries in the benign category is high, 87.5% was thought to reflect the actual rate. In this study, the B2 ratio is below the average of all studies, this may be because B1 category is well above average.

The average of all studies for the B3 category is 9.33%. In this study, our percentage of B3 is 10.9% and is close to the average. Wu et al. has the highest value with a rate of 27.9% and the benign category is quite low (29). When the number of cells in aspiration is low, the differential diagnosis between categories B2 and B3 can sometimes be difficult (4, 5). In this study, there may be a tendency to make B3 diagnosis in B2 cases. In the B4 category, the study of Bongiovanni et al., Yilmaz et al. and Bohacek et al. which had a significantly higher value than all other studies had a ratio of 23.8%, 17.5% and 17.2% respectively; where the mean was 7.7% (9, 10, 32). Among the other categories of these studies, B1 category was very low in all and B3 category was very low (0.8%) in one of them. Above the mean value there was ten studies in the B5 category but the first one (Yilmaz et al) was significantly higher than the others (21.3%) (32). In this study the authors studied only cases which have thyrodectomies. In the B6 category, Ke et al had a highest value with 28.7% where the B2 category was very low (12). This data shows that the nodules aspirated in these studies are made with more meaningful indications than other studies. In the current study the values of B4, B5 and B6 categories were 1%, 5.5% and 1.1 %, respectively. The B4 and B6 values of the study were below the mean but the malignancy rates were meaningful with 52.1%, 66.8% and 97.5%.

To review the B1 category is unnecessary for malignancy rates because usually its cause is insufficient aspiration not inadequate evaluation. The range of malignancy rates were 0-25% for B2, 0-76% for B3, 13-50% for B4, 45-100% for B5 and 50-100% for B6 in all studies. Today, the expected rates was 0-3% for B2 category and 15 (53.5%) of them above it. 35.7% of them had higher rates for B3, 21.4% of them for B4 and 50% of them for B5. Three of them had lower rates for B3 and seven of them for B4. The remaining of them were in normal rates (1, 4-14, 16-33). The current study's malignancy rates were 6.8% (high), 32.8% (high), 52.1% (high), 66.8% (normal) and 97.5% (normal). Most of the studies had higher rates for B2, this was because of the limited cellularity and difficulty in interpretation of the aspirations. The rate for B3 category is nearly high, it can be ignored. The rate of B4 category is high due to the low number of cases. When aspiration had adequate cellularity the correct diagnosis can be made.

According to the literature, the sensitivity and spesificity of the studies range from 50% to 96.5% and from 62.7% to 100%, respectively (12, 15). The B1 category should not be included for real evaluation. The sensitivity and spesificity of the current study is calculated for each created groups. The group IV is the ordinary evaluation and the results were 71% and 84% which were concordant with the literature. If B4 category was added the positive part, the ratios were changed minimally. If B3 category was extracted from the negative part the sensitivity was rising while the spesificity was falling. Because of the limited number of NIFTP cases in this study, the end results did not significantly different from each other. The PPV was 72% and NPV was 84% in the current study while the

accuracy was 80%. The accuracy ranged from 64.6% to 99% in the literature (12).

The limitation of this study is the high percentage of the B1 category. However, the data will make an important contribution to the literature as it is evaluated by only expert pathologist and is one of the first three studies with the largest number of cases.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
Manisa Celal Bayar University Ethics Committee approval was obtained for the study (No: 20.478.486, Date: 18.9.2019). The study was conducted in line with the principles of the Helsinki Declaration.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of Data and Materials
Data are available on request due to privacy or other restrictions.

Authors Contributions
AT: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft.

References

1. Güneş P, Demirtürk P, Aker F, Tanrıöver Ö, Gönültaş A, Akkaynak Ş. Evaluation of Fine-Needle Aspiration of Thyroid Nodules in a Series of 1,100 Patients: Correlation Between Cytology and Histopathology Original Article. The Indian journal of surgery. 2015;77(Suppl 3):990-5.
2. İnan G, Sert S, Bircan S, Karahan N, Çiriş M, Başpınar Ş, et al. Tiroid lezyonlarında tiroid ince iğne aspirasyon biyopsisi ve histopatoloji sonuçlarının karşılaştırılması. SDÜ Tıp Fak Derg. 2006;13(4):27-31.
3. Abi-Raad R, Prasad M, Baldassari R, Schofield K, Callender GG, Chhieng D, et al. The Value of Negative Diagnosis in Thyroid Fine-Needle Aspiration: a Retrospective Study with Histologic Follow-Up. Endocrine pathology. 2018;29(3):269-75.
4. Cibas ES, Ali SZ. The Bethesda System for Reporting Thyroid Cytopathology. Thyroid : official journal of the American Thyroid Association. 2009;19(11):1159-65.
5. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. Thyroid : official journal of the American Thyroid Association. 2017;27(11):1341-6.
6. Abdullah N, Hajeer M, Abudalu L, Sughayer M. Correlation study of thyroid nodule cytopathology and histopathology at two institutions in Jordan. CytoJournal. 2018;15:24.
7. Arul P, Akshatha C, Masilamani S. A study of malignancy rates in different diagnostic categories of the Bethesda system for reporting thyroid cytopathology: An institutional experience. Biomedical journal. 2015;38(6):517-22.
8. Avior G, Dagan O, Shochat I, Frenkel Y, Tessler I, Meir A, et al. Outcomes of the Bethesda system for reporting thyroid cytopathology: Real-life experience. Clinical endocrinology. 2021;94(3):521-7.
9. Bohacek L, Milas M, Mitchell J, Siperstein A, Berber E. Diagnostic accuracy of surgeon-performed ultrasound-guided fine-needle aspiration of thyroid nodules. Annals of surgical oncology. 2012;19(1):45-51.
10. Bongiovanni M, Crippa S, Baloch Z, Piana S, Spitale A, Pagni F, et al. Comparison of 5-tiered and 6-tiered diagnostic systems for the reporting of thyroid cytopathology: a multi-institutional study. Cancer cytopathology. 2012;120(2):117-25.
11. Jo VY, Stelow EB, Dustin SM, Hanley KZ. Malignancy risk for fine-needle aspiration of thyroid lesions according to the Bethesda System for Reporting Thyroid Cytopathology. American journal of clinical pathology. 2010;134(3):450-6.
12. Ke J, Jianyong L, Ying L, Genpeng L, Linlin S, Zhihui L, et al. The use of The Bethesda System for Reporting Thyroid Cytopathology in a Chinese population: An analysis of 13 351 specimens. Diagnostic cytopathology. 2019;47(9):876-80.
13. Kim SK, Hwang TS, Yoo YB, Han HS, Kim DL, Song KH, et al. Surgical results of thyroid nodules according to a management guideline based on the BRAF(V600E) mutation status. The Journal of clinical endocrinology and metabolism. 2011;96(3):658-64.
14. Lee YB, Cho YY, Jang JY, Kim TH, Jang HW, Chung JH, et al. Current status and diagnostic values of the Bethesda system for reporting thyroid cytopathology in a papillary thyroid carcinoma-prevalent area. Head & neck. 2017;39(2):269-74.
15. Madgar O, Avior G, Shochat I, Joshua BZ, Baraf L, Avidor Y, et al. Thyroid malignancy rates according to the Bethesda reporting system in Israel - A multicenter study. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2021;47(6):1370-5.
16. Mandal S, Barman D, Mukherjee A, Mukherjee D, Saha J, Sinhas R. Fine needle aspiration cytology of thyroid nodules--evaluation of its role in diagnosis and management. Journal of the Indian Medical Association. 2011;109(4):258-61.
17. Mondal SK, Sinha S, Basak B, Roy DN, Sinha SK. The Bethesda system for reporting thyroid fine needle aspirates: A cytologic study with histologic follow-up. Journal of cytology. 2013;30(2):94-9.
18. Mufti ST, Molah R. The bethesda system for reporting thyroid cytopathology: a five-year retrospective review of one center experience. International journal of health sciences. 2012;6(2):159-73.
19. Nandedkar SS, Dixit M, Malukani K, Varma AV, Gambhir S. Evaluation of Thyroid Lesions by Fine-needle Aspiration Cytology According to Bethesda System and its Histopathological Correlation. International journal of applied & basic medical research. 2018;8(2):76-82.
20. Nayar R, Ivanovic M. The indeterminate thyroid fine-needle aspiration: experience from an academic center using terminology similar to that proposed in the 2007 National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference. Cancer. 2009;117(3):195-202.
21. Naz S, Hashmi AA, Khurshid A, Faridi N, Edhi MM, Kamal A, et al. Diagnostic accuracy of Bethesda system for reporting thyroid cytopathology: an institutional perspective. International archives of medicine. 2014;7:46.
22. Paajanen I, Metso S, Jaatinen P, Kholová I. Thyroid FNA diagnostics in a real-life setting: Experiences of the implementation of the Bethesda system in Finland. Cytopathology : official journal of the British Society for Clinical Cytology. 2018;29(2):189-95.
23. Park JH, Yoon SO, Son EJ, Kim HM, Nahm JH, Hong S. Incidence and malignancy rates of diagnoses in the bethesda system for reporting thyroid aspiration cytology: an institutional experience. Korean journal of pathology. 2014;48(2):133-9.

24. Renshaw AA. Should "atypical follicular cells" in thyroid fine-needle aspirates be subclassified? Cancer cytopathology. 2010;118(4):186-9.
25. Reuters KB, Mamone M, Ikejiri ES, Camacho CP, Nakabashi CCD, Janovsky C, et al. Bethesda Classification and Cytohistological Correlation of Thyroid Nodules in a Brazilian Thyroid Disease Center. European thyroid journal. 2018;7(3):133-8.
26. Ronen O, Cohen H, Abu M. Review of a single institution's fine needle aspiration results for thyroid nodules: Initial observations and lessons for the future. Cytopathology : official journal of the British Society for Clinical Cytology. 2019;30(5):468-74.
27. Theoharis CG, Schofield KM, Hammers L, Udelsman R, Chhieng DC. The Bethesda thyroid fine-needle aspiration classification system: year 1 at an academic institution. Thyroid : official journal of the American Thyroid Association. 2009;19(11):1215-23.
28. Williams BA, Bullock MJ, Trites JR, Taylor SM, Hart RD. Rates of thyroid malignancy by FNA diagnostic category. Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale. 2013;42(1):61.
29. Wu HH, Rose C, Elsheikh TM. The Bethesda system for reporting thyroid cytopathology: An experience of 1,382 cases in a community practice setting with the implication for risk of neoplasm and risk of malignancy. Diagnostic cytopathology. 2012;40(5):399-403.
30. Yang J, Schnadig V, Logrono R, Wasserman PG. Fine-needle aspiration of thyroid nodules: a study of 4703 patients with histologic and clinical correlations. Cancer. 2007;111(5):306-15.
31. Yassa L, Cibas ES, Benson CB, Frates MC, Doubilet PM, Gawande AA, et al. Long-term assessment of a multidisciplinary approach to thyroid nodule diagnostic evaluation. Cancer. 2007;111(6):508-16.
32. Yildirim E, Akbas P, Erdogan KO, Bektas S, Gumuskaya PO, Er AM, et al. The comparison of the histopathological results of the thyroid fine-needle aspiration biopsies in the 795 patients with thyroidectomy. Diagnostic cytopathology. 2021;49(6):671-6.
33. Yilmaz N, Cansu GB, Toru S, Sari R, Ocak GG, Arici C, et al. Cytopathology-histopathology correlation and the effect of nodule diameter on diagnostic performance in patients undergoing thyroid fine-needle aspiration biopsy. Journal of cancer research and therapeutics. 2020;16(Supplement):S53-s8.