

## The Evaluation of Malignancy Rates of Nondiagnostic Cases in Thyroid Fine-Needle Aspirations

Zeynep Betül ERDEM\*, Şenay ERDOĞAN DURMUŞ\*\*, Hamit Yücel BARUT\*\*\*

### Abstract

**Aim:** In this study, it was aimed to investigate the malignancy rates of nondiagnostic (ND) thyroid fine-needle aspiration cytology (FNAC) material by evaluating either the result of the second FNAC or resection/biopsy materials.

**Method:** Among the 1165 thyroid FNAC cases evaluated in the Pathology Department of Başakşehir Çam and Sakura City Hospital within 9 months (October 2020-June 2021), 102 cases (8,7%) diagnosed with ND were included in the study. At the end of the 6-15 months follow-up period after the diagnosis of ND, the results of the second FNAC or resection (thyroidectomy, lobectomy)/biopsy of the cases were evaluated. Diameter and sonographic features of thyroid nodules (solid, cystic, mixed) were also noted.

**Results:** 49% of the cases (n:50) had a second FNAC. Resection/biopsy was performed in only 12 (11,8%) cases. Of these 62 cases, 39 were diagnosed by second FNAC and 7 by resection/biopsy as benign (74,1%), and 5 cases were diagnosed as malignant by resection/biopsy. 7 cases were diagnosed as nondiagnostic again after the second FNAC. Final diagnosis (by resection) of the case whose second FNAC result was reported as suspicious for malignancy was papillary microcarcinoma. This case was included in the group 'diagnosed as malignant only by resection/biopsy. In other words, malignancy was detected in 5 of 62 patients who underwent a second FNAC or resection/biopsy. The risk of malignancy was found to be 8% in the patient population included in the study with the diagnosis of ND.

**Conclusion:** A low rate of NE results were found in this ultrasound-guided thyroid series (8,7%). After the second FNAC or resection, malignancy rates was found to be 8%. Although this result is compatible with the results of some studies, it is considerably lower than others. It would be appropriate to follow up on ND

---

### Özgün Araştırma Makalesi (Original Research Article)

**Geliş / Received:** 09.08.2022 & **Kabul / Accepted:** 16.12.2022

**DOI:** <https://doi.org/10.38079/igusabder.1157491>

\* MD., Basakşehir Cam and Sakura City Hospital, Department of Pathology, Istanbul, Türkiye.

E-mail: [zberdem@gmail.com](mailto:zberdem@gmail.com) [ORCID](https://orcid.org/0000-0002-0840-4689) <https://orcid.org/0000-0002-0840-4689>

\*\* Assoc. Prof., MD., Prof. Dr. Cemil Tascioglu City Hospital, Department of Pathology, Cytopathology Division, Istanbul, Türkiye. E-mail: [senayerdgn@gmail.com](mailto:senayerdgn@gmail.com) [ORCID](https://orcid.org/0000-0003-3388-9312) <https://orcid.org/0000-0003-3388-9312>

\*\*\* MD., Basakşehir Cam and Sakura City Hospital, Department of Radiology, Istanbul, Türkiye,

E-mail: [yucelbarut@yahoo.com](mailto:yucelbarut@yahoo.com) [ORCID](https://orcid.org/0000-0002-6004-9194) <https://orcid.org/0000-0002-6004-9194>

---

**ETHICAL STATEMENT:** This study was found appropriate ethically according to the Ethical Committee of the Basakşehir Cam and Sakura City Hospital on 24<sup>th</sup> November 2021 with its decision number 2021-249.

nodules with their clinical/sonographic features. Additional studies with large series will be more helpful in determining the malignancy rates of the ND group.

**Keywords:** Thyroid cancer, papillary, biopsy, fine-needle, cytology.

## **Tiroid İnce İğne Aspirasyonlarında Tamsal Olmayan Olguların Malignite Oranlarının Değerlendirilmesi**

### **Öz**

**Amaç:** Çalışmada nondiagnostik (ND) tiroid ince iğne aspirasyon sitolojisi (İİAS) materyalinin malignite oranlarının araştırılması (ikinci İİAS sonucu veya rezeksiyon/biyopsi materyalleri değerlendirilerek) amaçlandı.

**Yöntem:** Başakşehir Çam ve Sakura Şehir Hastanesi Patoloji Bölümü'nde 9 ay (Ekim 2020-Haziran 2021) içinde değerlendirilen 1165 tiroid İİAS olgusundan ND tanısı alan 102 olgu (%8,7) çalışmaya dahil edildi. ND tanısı konulduktan sonra 6-15 aylık takip süresi sonunda olguların ikinci İİAS veya rezeksiyon (tiroidektomi, lobektomi)/biyopsi sonuçları değerlendirildi. Tiroid nodüllerinin (solid, kistik, mikst) çap ve sonografik özellikleri de kaydedildi.

**Bulgular:** Vakaların %49'unda (n:50) ikinci bir İİAS yapıldı. Sadece 12 (%11.8) olguda rezeksiyon/biyopsi yapıldı. İkinci İİAS ile AUS tanısı alan üç olguda rezeksiyon/biyopsi yapılmadı. Bu 62 olgunun 39'una ikinci İİAS, 7'sine rezeksiyon/biyopsi ile benign (%74,1), 5 olguya ise rezeksiyon/biyopsi ile malign tanısı konuldu. 7 olgu ikinci FNAC sonrası yeniden nondiagnostik tanısı aldı. İkinci İİAS sonucu malignite şüpheli olarak bildirilen olgunun kesin tanısı (rezeksiyon ile) papiller mikrokarsinom olarak belirlendi. Bu olgu 'sadece rezeksiyon/biyopsi ile malign olarak teşhis edilen' gruba alındı. Yani ikinci İİAS veya rezeksiyon/biyopsi yapılan 62 hastanın 5'inde malignite saptandı. ND tanısı ile çalışmaya alınan hasta popülasyonunda malignite riski %8 olarak bulundu.

**Sonuç:** Ultrason rehberliğinde tiroid İİAS serimizde düşük oranda ND sonuçları bulunmuştur (%8,7). İkinci İİAS veya rezeksiyon sonrası malignite oranları %8 olarak bulundu. Bu sonuç bazı çalışmaların sonuçları ile uyumlu olsa da diğerlerine göre oldukça düşüktür. ND nodüllerin klinik/sonografik özellikleri ile takip edilmesi uygun olacaktır. Geniş serili ek çalışmalar, ND grubunun malignite oranlarının belirlenmesinde daha fazla yardımcı olacaktır.

**Anahtar Kelimeler:** Tiroid kanser, papiller, biyopsi, ince-iğne, sitoloji.

### **Introduction**

Fine needle aspiration cytology (FNAC) is a widely used important process for diagnosing thyroid nodules and managing their treatments. FNAC is an initial diagnostic test because of its simplicity, safety, and cost-effectiveness<sup>1</sup>. FNAC results are categorized in six groups according to the Bethesda system for reporting thyroid cytopathology (TBSRTC), such as; nondiagnostic (ND), Benign, Atypia of undetermined significance/follicular lesion of undetermined significance

(AUS/FLUS), Follicular neoplasm/Suspicious for follicular neoplasm (FN/SFN), Suspicious for malignancy (SFM) and Malignancy<sup>2-4</sup>.

There were malignancy rates and proper managements for each category in TBSRTC and these rates were updated in TBSRTC II<sup>2,3</sup>. Although the expected risk of malignancy (ROM) in ND category was 1-4% in previous studies and updated to 1-5% in TBSRTC II, risk of malignancy varies between 0.4% to 51% in different studies<sup>3,5-9</sup>. And also the risk of malignancy varies with the type/structure of the nodule. ND diagnosis from solid nodules are associated with a higher risk of malignancy as compared to cystic nodules ( $\geq 50\%$  cystic change) with low-risk ultrasonographic features<sup>2,5</sup>.

In this study, it was aimed to investigate the malignancy rates of ND thyroid FNAC material by evaluating either the result of the second FNAC or resection/biopsy materials.

### **Material and Method**

This study was found appropriate ethically according to the ethical committee of the Basakşehir Cam and Sakura City Hospital on 24<sup>th</sup> November 2021 with its decision number 2021-249.

Among the 1165 thyroid FNAC cases evaluated in the Pathology Department of Başakşehir Çam and Sakura City Hospital within 9 months (October 2020-June 2021), 102 cases (8,7%) diagnosed with ND re-evaluated retrospectively and included in the study. At the end of the 6-15 months of follow-up period after the diagnosis of ND, the results of the second FNAC or resection (thyroidectomy, lobectomy)/biopsy of the cases were evaluated. Diameter and sonographic features of thyroid nodules (solid, cystic, mixed) were also noted.

### **Cytological Preparation**

All FNAC specimens of cases were prepared with a liquid-based cytology technique. BD SurePath PAP test kit (BD Diagnostics-tripath, Burlington, NC, USA®) was used as liquid-based cytology examination technique. Samples in ethanol-based fixative were centrifuged 2 times. Then cellular sample was mixed with a vortex homogeneously; 40  $\mu$ l of the sample was pulled out with a micropipette and spread as a thin layer in a circular area of a microscope slide.

### **Cytological Examination**

The PAP-stained LBC slides and H&E slides of cell blocks were evaluated under the light microscope.

The material was diagnosed as ND if it did not fulfill the adequacy criteria of the TBSRTC, such as; a specimen containing at least six well-preserved and well-stained follicular groups, including at least 10 cells; abundant thick colloid which is suggestive of colloid nodule; and, solid nodules

with inflammation that is suggestive of thyroiditis. Thyroid cysts containing histiocytes but with little or no follicular cells are interpreted as ND. In contrast, a solid nodule with an atypia does not have a requirement for a minimum number of follicular cells<sup>2</sup>.

Fifty cases out of 102 cases underwent a second FNAC and histological follow-up was available in 12 cases. Results of the second FNAC and resection/biopsy were noted.

### Statistical Analysis

SPSS.25 program was used for statistical evaluation. A descriptive analysis was carried out in which nominal variables were shown as number of cases and the percentage (%).

### Results

79,4% of the cases were female and 29,6% were male, and the mean age was  $48,3 \pm 14,0$  (8-80 years). 49% of the cases had a second FNAC. The distribution of the results of the second FNAC evaluation is given in Table 1.

**Table 1.** Distribution of second FNAC results

		Frequency	Percent	Valid Percent
<b>Valid</b>	<b>None</b>	52	51,0	51,0
	<b>ND</b>	7	6,9	6,9
	<b>Benign</b>	39	38,2	38,2
	<b>AUS</b>	3	2,9	2,9
	<b>SFM</b>	1	1,0	1,0
	<b>Total</b>	102	100,0	100,0

ND: Nondiagnostic, AUS: Atypia of undetermined significance, SFM: Suspicious for malignancy

Resection/biopsy was performed in only 12 (11,8%) cases (Table 2). Resection/biopsy was not performed in three cases diagnosed as AUS with the second FNAC. Of these 62 cases, 39 were diagnosed by second FNAC and 7 by resection/biopsy as benign (74,1%), and 5 cases were diagnosed as malignant by resection/biopsy. 7 cases were diagnosed as nondiagnostic again after the second FNAC. Final diagnosis (by resection) of the case whose second FNAC result was reported as suspicious for malignancy was papillary microcarcinoma. This case was included in the group "diagnosed as malignant only by resection/biopsy". In other words, malignancy was detected in 5 of 62 patients who underwent second FNAC or resection/biopsy. The risk of malignancy was found to be 8% in the patient population included in the study with the diagnosis of ND.

**Table 2.** Distribution of surgical resection/biopsy results

		Frequency	Percent	Valid Percent
<b>Valid</b>	<b>None</b>	90	88,2	88,2
	<b>Benign (AN, LT)</b>	7	6,9	6,9
	<b>Malignant (PTC, mikroPTC)</b>	5	4,9	4,9
	<b>Total</b>	102	100,0	100,0

AN: Adenomatoid nodule, LT: Lymphocytic thyroiditis, PTC: Papillary thyroid carcinoma

The mean diameter of the thyroid nodules diagnosed as ND was 17,8±10,7 mm (5-60 mm), and 51% were cystic or mixed (Table 3).

**Table 3.** Sonographic features of the cases

		Frequency	Percent	Valid Percent
<b>Valid</b>	<b>Solid</b>	50	49,0	49,0
	<b>Cystic</b>	14	13,7	13,7
	<b>Mix</b>	38	37,3	37,3
	<b>Total</b>	102	100,0	100,0

Nodules were solid in 4 of 5 (80%) cases diagnosed as malignant by resection/biopsy (Table 4). However, nodules were also solid in 6 of 7 (85,7%) cases with benign resection/biopsy results.

**Table 4.** Distribution of resection/biopsy results according to sonographic features of nodules

		Solid		Cystic		Mix		Total	
		n	%	n	%	n	%	n	%
<b>Resection / Biopsy</b>	<b>None</b>	40	44,4	14	15,6	36	40,0	90	100,0
	<b>Benign (AN, LT)</b>	6	85,7	0	0,0	1	14,3	7	100,0
	<b>Malignant (PTC, mikroPTC)</b>	4	80,0	0	0,0	1	20,0	5	100,0

AN: Adenomatoid nodule, LT: Lymphocytic thyroiditis, PTC: Papillary thyroid carcinoma

The distribution of the second FNAC and resection/biopsy results of the cases by gender is given in Table 5.

**Table 5.** Distribution of second FNAC and resection results by gender

		<b>Gender</b>			
		<b>Female</b>		<b>Male</b>	
		<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>
<b>Second FNAC</b>	<b>None</b>	42	51,9%	10	47,6%
	<b>ND</b>	5	6,2%	2	9,5%
	<b>Benign</b>	31	38,3%	8	38,1%
	<b>AUS</b>	2	2,5%	1	4,8%
	<b>SFM</b>	1	1,2%	0	0,0%
	<b>Total</b>	81	100,0%	21	100,0%
<b>Resection / Biopsy</b>	<b>None</b>	72	88,9%	18	85,7%
	<b>Benign (AN, LT)</b>	4	4,9%	3	14,3%
	<b>Malignant (PTC, mikroPTC)</b>	5	6,2%	0	0,0%
	<b>Total</b>	81	100,0%	21	100,0%

ND: Nondiagnostic, AUS: Atypia of undetermined significance, SFM: Suspicious for malignancy, AN: Adenomatoid nodule, LT: Lymphocytic thyroiditis, PTC: Papillary thyroid carcinoma

## Discussion

The risk of malignancy for ND cases is difficult to calculate exactly, because most of the ND nodules does not undergo surgery. There are highly variable malignancy rates for surgically excised nodules initially reported as ND. In a meta-analysis the malignancy rate was found to be 9–32%<sup>10</sup>. Baloch et al. found the malignancy rate as 51% after surgery in a series of 237 patients whose initial FNAC were ND<sup>6</sup>. In another study, which compares malignancy rates of ND and diagnostic thyroid FNAC cases, a statistically significant higher rate of thyroid cancer was found on repeated FNAC or on histology in ND group<sup>11</sup>. On the other hand, Ferreira MA et al. found a malignancy rate as 0,4% after repeated FNAC whose initial FNAC smears were ND<sup>8</sup>. In this study malignancy rate was 8% in ND cases. This may be a relatively low rate when compared to the literature.

In TBRST, it is recommended to repeat the FNAC under ultrasound guidance after the first ND result<sup>2</sup>. Repeated FNAC may be very helpful because it provides a relatively high rate of diagnostic results.<sup>8,11</sup> In this study, FNAC was repeated in 50 out of 102 ND cases. After the second FNAC, only 7 cases (14%) were diagnosed as ND again. Forty-three cases (86%) received a diagnosis after the second FNAC.

Surgically resected nodules in the ND category, represent a selected subset of nodules that were repeatedly diagnosed as ND or had worrying clinical or sonographic features. Thus, surgically resected ND nodules have higher malignancy rates compared to the entire cohort of ND nodules<sup>12</sup>. In this study malignancy rate was 8%. All malignant cases were diagnosed in resected nodules (5 of 12 resected nodules).

In centers that use the conventional technique, on-site adequacy evaluation and, if necessary, multiple interventions are recommended in the second FNAC to be performed after the first ND diagnosis<sup>13</sup>. In centers using the LBC method, making an additional LBC slide helps with achieving a diagnosis in cases classified as ND initially. This procedure is particularly helpful for meeting the adequacy criteria<sup>1</sup>. Furthermore, performing a cell block from the residual LBC sample can convert some initially ND LBC FNACs into a satisfactory sample<sup>14</sup>.

After two ND specimens, close clinical and sonographic follow-up or surgery should be considered, depending on the clinical findings. Because the risk of malignancy in cystic lesions is low, re-aspiration of most cystic nodules with an initial ND result should be performed only if the ultrasound findings are suspicious<sup>2</sup>. The malignancy rates are also variable in nodules containing a cystic component. Güney G et. al. found malignancy rates in cystic content and ND-other group, 0% and 17,6, respectively<sup>5</sup>. In another study that compare malignancy rates in between patients who were diagnosed as ND due to cystic content and those who were diagnosed as ND due to other causes, malignancy rates in the cystic content group were 14,3%, whereas it was 6,6% in the other group<sup>15</sup>. In this study, 80% of the nodules diagnosed as malignant after resection were solid, while 20% of nodules were mix (Table 4). No resection was performed in pure cystic nodules. therefore, the malignancy rate could not be given for pure cystic nodules.

There were limitations of this study. First, the number of ND cases were restricted (In a suitable cytology laboratory, it is not desired to be too much.). And secondly, although the number of patients who underwent a second FNAC was not low, the number of patients who underwent resection was quite low. So malignancy rates were given according to a small group.

## **Conclusion**

Found a low rate of ND results in this series of ultrasound-guided thyroid FNAC (8.7%). After the second FNAC or resection, malignancy rates was found to be 8%. Although this result is

compatible with the results of some studies, it is considerably lower than others. However, it would be appropriate to follow up on ND nodules with their clinical/sonographic features. Additional studies with large series will be more helpful in determining the malignancy rates of the ND group.

## REFERENCES

1. Rossi ED, Morassi F, Santeusano G, Zannoni GF, Fadda G. Thyroid fine needle aspiration cytology processed by ThinPrep: An additional slide decreased the number of inadequate results. *Cytopathology*. 2010;21(2):97-102.
2. Ali SZ, Cibas ES, ed(s). *The Bethesda System for Reporting Thyroid Cytopathology*. 2nd ed. Switzerland: Springer; 2018.
3. Cibas ES, Ali SZ. The bethesda system for reporting thyroid cytopathology. *Thyroid*. 2009;19:1159–1165.
4. Cibas ES, Ali SZ. The 2017 bethesda system for reporting thyroid cytopathology. *Thyroid*. 2017;27:1341-1346.
5. Güney G, Şahiner İT. Malignancy rates of thyroid cytology: Cyst fluid benign or non-diagnostic? *Med Sci Monit*. 2017;21(23):3556-3561. doi:10.12659/msm.905718.
6. Baloch Z, LiVolsi VA, Jain P, et al. Role of repeat fine-needle aspiration biopsy (FNAB) in the management of thyroid nodules. *Diagn Cytopathol*. 2003;29:203–206.
7. MacDonald L, Yazdi HM. Nondiagnostic fine needle aspiration biopsy of the thyroid gland: A diagnostic dilemma. *Acta Cytol*. 1996;40:423–428.
8. Ferreira MA, Gerhard R, Schmitt F. Analysis of nondiagnostic results in a large series of thyroid fine-needle aspiration cytology performed over 9 years in a single center. *Acta Cytol*. 2014;58(3):229-234.
9. Gunes P, Canberk S, Onenerk M, et al. A different perspective on evaluating the malignancy rate of the non-diagnostic category of the bethesda system for reporting thyroid cytopathology: A single institute experience and review of the literature. *PLoS One*. 2016;11(9):e0162745.
10. Bongiovanni M, Spitale A, Faquin WC, Mazzucchelli L, Baloch ZW. The bethesda system for reporting thyroid cytopathology: A meta-analysis. *Acta Cytol*. 2012;56(4):333–339.



11. Coorough N, Hudak K, Jaume JC, et al. Non-diagnostic fineneedle aspirations of the thyroid: Is the risk of malignancy higher? *J Surg Res.* 2013;184:746–750.
12. Haugen BR, Alexander EK, Bible KC, et al. 2015 american thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The american thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid.* 2016;26(1):1-133.
13. Naïm C, Karam R, Eddé D. Ultrasound-guided fine-needle aspiration biopsy of the thyroid: Methods to decrease the rate of unsatisfactory biopsies in the absence of an on-site pathologist. *Can Assoc Radiol J.* 2013;64(3):220–225.
14. 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. *Am J Clin Pathol.* 2010;134(3):450–456.
15. García-Pascual L, Barahona MJ, Balsells M, et al. Complex thyroid nodules with nondiagnostic fine needle aspiration cytology: Histopathologic outcomes and comparison of the cytologic variants (cystic vs. acellular). *Endocrine.* 2011;39(1):33–40.