Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Research Article

J Exp Clin Med
2022; 39(3): 749-754
doi: 10.52142/omujecm.39.3.30

Malignancy rates and risk factors in Bethesda category IV thyroid nodules: Is lobectomy enough in an endemic region?

Ali ÖZDEMİR, Mikail UYAN*, Süleyman KALCAN, Muhammed Kadri ÇOLAKOĞLU, Ahmet PERGEL

Department of General Surgery, Faculty of Medicine, Recep Tayyip Erdoğan University, Rize, Türkiye

Received: 23.02.2022 • **Accepted/Published Online:** 05.06.2022 • **Final Version:** 30.08.2022

Abstract

In this paper, we determined the rates of Bethesda IV thyroid nodules and calculated the malignancy rates of these nodules in a university hospital located in an endemic area for thyroid diseases. We aimed to define the predictive factors for malignancy to select patients who need surgery. We included in the study 221 patients who had a preoperative biopsy for follicular neoplasm or because of suspicion for follicular neoplasm and underwent thyroidectomy between January 2012 and December 2018. We evaluated the data about patient characteristics, preoperative ultrasound results, indications for operation and postoperative pathological valuation results and calculated ratio of Bethesda Category IV nodules and incidental malignancy rates. The malignancy rate of Bethesda Category IV nodules was 48.9 %, while the incidental malignancy rate was 30.7 %. There was no statistical difference between patients with benign and malignant pathology results in terms of gender, age, preoperative diagnosis, size of the index nodule, number and results of biopsies and the thyroidectomy performed. The most important risk factor among all parameters was hypoechogenicity of the nodule. The solid structure increases this risk. Ultrasonographic hypoechogenicity is the most important risk factor for preoperative malignancy risk assessment for Bethesda Category IV thyroid nodules. Centers should determine their malignancy rates with particular risk factors and surgical approaches in endemic regions.

Keywords: thyroidectomy, follicular neoplasm, thyroid nodules, Bethesda Category

1. Introduction

Thyroid nodules are a common clinical problem, especially in endemic areas, and constitute a significant risk for thyroid cancer. Although some authors think there is more to it than that, the incidence of thyroid nodules increases in parallel with the improvement of imaging modalities and increased follow-up frequency (1, 2). As the rate of detected thyroid nodules increases, hesitations on the clinical approach to these nodules also increase. This situation augments the importance of understanding the malignancy risk of detected nodules in the preoperative period.

The primary method used to diagnose and treat thyroid nodules is fine needle aspiration biopsy (FNABx), and it is the standard of care for evaluation (3). Although FNABx can help distinguish malignant and benign nodules, indeterminate results create clinical dilemmas, and about 30% of thyroid nodules cannot be diagnosed clearly by pathologists for various reasons (4). To standardize pathological interpretations, the National Cancer Institute introduced a system named Bethesda System for Reporting Thyroid Cytopathology (Bethesda) in 2009 (5). According to this system, thyroid FNABx results are classified into six diagnostic categories (Bethesda I-VI). Bethesda category IV is defined as follicular neoplasm or suspicion for follicular neoplasm lesions, and 22-42% of thyroid nodules are diagnosed as Bethesda category IV by FNABx (6). This category is one of the most controversial groups in the system, and the malignancy rate of Bethesda category IV is found in a wide range of 10-40% (7). The recommended treatment for Bethesda Category IV thyroid nodules is surgical excision with hemithyroidectomy (or lobectomy) or risk assessment with molecular testing before surgery. Furthermore, the American Thyroid Association (ATA) guidelines recommend surgery for Bethesda Category IV thyroid nodules (3). However, when a large number of these nodules (60-90%) are observed to be benign after surgical excision, this group of patients are considered to be at risk of unnecessary surgical morbidity. Even if the final pathology is malignant, a second surgery may be required for the opposite side. This controversial situation and uncertainty lead to the investigation of the preoperative evaluation criteria that can be used to determine the malignancy risk of these nodules or the

*Correspondence: drmikailuyan@gmail.com

medical centers own risk rates, thus enabling them to give their patients treatment under the light of these ratios (8-10).

In this study, we determined the rates of Bethesda IV thyroid nodules and calculated the malignancy rates of these nodules in a university hospital located in an endemic area for thyroid diseases. Initially, we aimed to define the predictive factors for malignancy to select patients who need surgery. Afterwards, we tried to establish a treatment approach for Bethesda Category IV thyroid nodules considering these predictive factors and incidental malignancy rates in endemic areas for thyroid diseases such as our own region.

2. Materials and Methods

Due to various indications, 1583 thyroid surgeries were performed between January 2012 and December 2018 in our institution, Rize, Turkey. We obtained Institutional Review Board approval (2021/42). We then examined the records of these patients retrospectively. We included in the study 221 patients who had preoperative FNABx for follicular neoplasm or because of suspicion for follicular neoplasm (Bethesda Category IV) and underwent thyroidectomy. These patients constituted our study group.

We obtained the data about patient characteristics, preoperative ultrasound (USG) results (including nodule size, margin status, structure, echogenicity, vascularization and microcalcification), indications for operation and postoperative pathological evaluation results from the center's digital patient records of the center. Since the region is endemic for thyroid diseases, the approach to thyroid nodules is carried out under a certain standard. Experienced radiology specialists performed all preoperative fine needle aspiration biopsies under ultrasound guidance, and a single pathologist also specialized in thyroid diseases interpreted all preoperative biopsies and postoperative pathology results.

After FNABx, we called the nodule reported as Bethesda Category IV as the index nodule. We excluded the patients who underwent biopsies for diseases other than index nodules. If the index nodule was reported malign at the final pathology report, we included it in actual malignancy rates, but in case of a malignancy other than the index nodule, we called it incidental cancer and calculated it separately.

We used the Statistical Package for Social Sciences (SPSS) version 20.0 (SPSS Inc.; Chicago, IL, USA) for statistical analysis and the Kolmogorov-Smirnov test to classify variables according to normal distribution. We then evaluated demographic, preoperative and postoperative data and pathological features after surgery through the parametric and non-parametric Mann-Whitney U test, t-test, chi-square and frequency analyses. We conducted a logistic regression analysis to correlate thyroid malignancy and USG findings in terms of risk factors and defined statistical significance as $p<0.05$.

3. Results

A total of 1583 patients underwent thyroid surgery during the study period. 13.9% (221/1583) of these patients had a preoperative Bethesda Category IV FNABx result and constituted the study group. The majority of patients were female (177/80.7% vs 44/19.9% female and male ratios, respectively), and the mean age was 50.98±11.7 (15-81) for the whole group. As well as fine needle biopsy results, the most common cause of surgical indications was multinodular goiter (83.7%), but thyroiditis, Graves' disease, toxic multinodular goiter, recurrence of multinodular goiter, solitary nodule and nodule size alone also created additional indications. The mean size of the radiologist biopsied index nodules was 20.9±12.5 mm (6-80). Most of the patients underwent total thyroidectomy (84.6%). Others underwent hemithyroidectomy (9.5%) or complementary thyroidectomy (5.9%). We determined the type of operation per the surgeon and patient's decision depending on the patient's laboratory, biopsy and imaging results.

Among the 221 patients who underwent biopsy, one hundred and eight of Bethesda IV nodules had malignancy associated with after the surgery. Thus, our study group's actual malignancy rate of Bethesda Category IV nodules was 48.9%. The remaining 113 patients had benign histopathology in Bethesda IV nodules in the final pathology, but in 68 of these patients, we detected malignancy incidentally in a different thyroid gland area. So, the incidental malignancy rate was 30.7%, while the total malignancy rate was as high as 79.6%. Table 1 represents the malignancy rates and other characteristics of index nodules. As evident, there was no statistical difference between patients who had benign or malignant pathology results in terms of gender, age, preoperative diagnosis, size of the index nodule, number of preoperative FNABx, result of FNABX and the operation performed.

We also compared preoperative ultrasound results to detect a predictive factor for malignancy in the preoperative period. Table 2 and Table 3 represent ultrasonographic risk factors differences between benign and malignancy associated with Bethesda IV nodules with odds ratios and p values. We evaluated vascularization, margins, structure, echogenicity and microcalcification. Due to the structure of a retrospective analysis, as shown in Table 2, it became clear that vascularization, margin and microcalcification data were not wholly reported in each ultrasound report. We did not evaluate these factors statistically due to the high number of unspecified data while evaluating only the structure and echogenicity for index nodules. Univariate analysis and multivariate logistic regression analysis demonstrated that the most important risk factor among these two parameters was echogenicity ($p= 0.041$). Index nodules with hypoechogenicity tended to be malign. The solid structure also increased the risk of malignancy for nodules ($p=0.004$).

Table 1. Patient characteristics, preoperative diagnosis, number of FNABx and results and operations performed for Bethesda Category IV index nodules

	Benign	Malign	P values
Gender			
-Female	91 (41.1%) [56 incidental malign]	86 (38.9%)	0.867
-Male	22 (9.9%) [12 incidental malign]	22 (9.9%)	
-Total	113 (51.1%)	108 (48.9%)	
Age (years)			
	51.11±11.06	50.84±12.54	0.934
Preoperative Diagnosis			
- MNG*	92 (41.6%)	93 (42%)	0.395
- MNG, thyroiditis	2 (0.9%)	4 (1.8%)	
- Recurrent MNG	12 (5.4%)	2 (0.9%)	
- MNG with subclinical hyperthyroidism	1 (0.4%)	2 (0.9%)	
- Toxic MNG	3 (1.3%)	1 (0.4%)	
- MNG, Graves' Disease	1 (0.4%)	1 (0.4%)	
- Solitary nodule	2 (0.9%)	5 (2.2%)	
Size of the index nodule (mm)			
	20.92±11.25	20.90±13.81	0.370
Number of FNABx performed			
- 1	73 (33%)	74 (33.4%)	0.550
- 2	38 (17.1%)	32 (14.4%)	
- 3	2 (0.9%)	2 (0.9%)	
FNABx result			
- SFN**	57 (25.7%)	53 (23.9%)	0.371
- SFN oncocytic type	26 (11.7%)	16 (7.2%)	
- FN***	23 (10.4%)	27 (12.2%)	
- FN oncocytic type	7 (3.1%)	12 (5.4%)	
Operation			
- Total thyroidectomy	91 (41.1%)	96 (43.4%)	0.063
- Lobectomy	11 (4.9%)	10 (4.5%)	
- Complementary thyroidectomy	11 (4.9%)	2 (0.9%)	

*MNG: Multinodular goiter, **SFN: Suspicious for a follicular neoplasm, ***FN: Follicular neoplasm

Table 2. Frequencies of ultrasonographic risk factors among benign and malign index nodules

	Benign Index Nodule (n=113)	Malign Index Nodule (n=108)	P values
Vascularization			
-Not increased	6	6	0.912
-Increased	41	42	
-Not specified	66	60	
Margin			
-Irregular	25	33	0.249
-Regular	11	13	
-Not specified	77	62	
Structure			
-Cystic	3	1	0.124
-Solid	62	73	
-Mixed	48	34	
Echogenicity			
-Isoechoic	14	13	0.058
-Hyperechoic	6	1	
-Mixed	58	45	
-Hypoechoic	35	49	
Microcalcification			
-Absent	7	4	0.669
-Present	53	50	
-Not specified	53	54	

Table 3. Statistical differences between ultrasonographic risk factors

Risk Factor	Odds ratio (%95 confidence interval)	P Values
Echogenicity		
- Iso/hyper/mixed	1	**0.041**
- Hypo	1.64 (0.44-6.15)	
Structure		
- Cystic/mixed	1	**0.004**
- Solid	8.4 (3.5-69.8)	

Table 4 represents the pathological differences for incidental malign nodules and index malign nodules. The most common malignancy in index nodules was oncocytic type papillary carcinoma, while oncocytic type papillary microcarcinoma for incidental nodules. The risk of follicular carcinoma was very low (0.9%). Patients with malignant index nodules were more likely to have poor prognostic markers after surgery than patients with incidental lesions.

Table 4. Differences between pathological results among incidental and index malign nodules

	Incidental malign nodule	Malignancy in Bethesda IV nodules	P
Final pathology results			
- Papillary carcinoma	-	9 (8.3%)	**<0.001**
- Papillary microcarcinoma	9 (13.2%)	4 (3.6%)	
- Follicular carcinoma	-	1 (0.9%)	
- Medullary carcinoma	-	-	
- Medullary microcarcinoma	3 (4.5%)	-	
- Oncocytic type papillary carcinoma	1 (1.5%)	61 (56.7%)	
- Oncocytic type papillary microcarcinoma	55 (80.8%)	32 (29.6%)	
- Papillary+Medullarycarcinoma	-	1 (0.9%)	
Tumor size (mm)			
	3.70 ±3.11	18.13±12.95	**<0.001**
Lymph node metastasis			
- No	27 (39.7%)	33 (30.6 %)	**0.380**
- Yes	-	4 (3.7 %)	
- Not specified	41 (60.3%)	71 (65.7 %)	
Extra capsular invasion			
- No	35 (51.5%)	13 (12%)	**<0.001**
- Yes	33 (48.5%)	95 (88%)	
Parenchymal invasion			
- No	44 (64.7%)	86 (79.6%)	**0.021**
- Yes	24 (35.3%)	22 (20.4%)	
Extra thyroidal spread			
- No	68 (100%)	102 (94.4%)	**0.071**
- Yes	-	6 (5.6%)	
Positive surgical margin			
- No	68 (100%)	97 (89.8%)	**0.010**
- Yes	-	11 (10.2%)	
Multifocality			
- No	34 (50%)	41 (37.9%)	**0.129**
- Yes	34 (50%)	67 (62.1%)	
Lymphovascular invasion			
- No	67 (98.5%)	105 (97.3%)	**0.560**
- Yes	1 (1.5%)	3 (2.7%)	

4. Discussion

In this paper, we attempted to determine the malignancy and incidental malignancy rates of patients who were operated after Bethesda Category IV thyroid nodule biopsy diagnosis and investigated the factors that could predict the risk of malignancy. We found that the cancer rates in Bethesda Category IV nodules were high in an endemic region and the risk of incidental cancer was also high. We also demonstrated the relationship of some ultrasonographic risk factors with these rates.

As Acar et al. suggested in their paper, the Bethesda system allows for more accurate predictions for suspicious and malignant lesions (11). Although this is true, the rates of malignancy of indeterminate lesions vary, and the factors that can predict the risks of malignancy of indeterminate nodules to avoid unnecessary thyroidectomies are being investigated (12, 13). This effort is also valid for patients suspected of a follicular neoplasm or follicular neoplasm, which is reflected as Bethesda Category IV in the classification system. Malignancy rates of Bethesda category IV are found in a wide range of 10-40%. This suggests that predictive factors may prevent high unnecessary thyroidectomy rates. The results of studies on predictive factors are also controversial. Lee KH et al. suggested that tumor size (>2.5cm), malignant ultrasonography diagnoses are predictive factors (14), while Lee SH et al. revealed that only high thyroglobulin levels and the presence of calcification on ultrasonography are significant predictive factors (10). Najafian A et al. added that male sex, family history of thyroid cancer and history of head and neck radiation were associated with malignancy for follicular neoplasms of the thyroid (15). We believe that all of this confusion was due to the heterogeneity of the study groups. The most compact and recent study on this subject belongs to Kuru B and Kefeli M (16). They suggested a predictive risk index and recommended surgery for patients with one or more predictive risk factors. We obtained similar results in our study; nodules with hypoechogenicity tended to be malign, and this result was significant. The nodule being also solid increased the risk of malignancy. We presented vascularity, margin and microcalcification status as frequency only due to the excess of unspecified data. We could not detect a relationship between tumor size and malignancy for Bethesda Category IV nodules.

The appropriate surgical approach for Bethesda Category IV thyroid nodules is not clear. Some centers offer total thyroidectomy to appropriate patients by taking into account the risk factors, while others recommend hemithyroidectomy (or lobectomy) to reduce surgical morbidity, especially nerve damage (17, 18). However, this leads to the risk of a second

operation in malignant patients. In this regard, we recommend that centers manage the process by considering the risk factors and determining their regional malignancy rates. In this study, the malignancy rate of index nodules was 48.9%, which constituted nearly half of the patients. This incidence increased to 79.6% by adding incidental malignant nodules, and this rate is relatively high. There may be two reasons for this result. Firstly, suspicious nodules other than index nodules were not evaluated. However, the size of the incidental cancers varied between 1-6 mm, which made radiologic evaluation difficult. Secondly, the region is endemic to thyroid diseases, and total thyroidectomy is recommended to most patients as a surgical reflex for malignancy risk, increasing the incidental malignancy ratios. However, it should be kept in mind that most of the incidental malignancies are microcarcinoma and their clinical significance is still uncertain even if half of them are multifocal, as seen in Table 4. There is still a question that needs to be answered: Does each pathology result as incidental microcarcinomas evaluated retrospectively suggest an indication for the extent of surgery?

Although there are studies showing the rates of incidental malignancy, we could not find a study comparing the incidence and index nodules (19, 20). In our study, the rate of incidental malignancy was found to be high, and a significant difference was found between the incidental malignant nodule and the malignant Bethesda IV nodule in terms of tumor diameter and capsule invasion (Table 4). It should be kept in mind that the high rate of incidental malignancy may have a survival effect and new regulations may be needed in the preoperative evaluation process. There are also limitations to this study. The most common malignancy among index nodules was papillary thyroid carcinoma. In 2016, the definition of noninvasive follicular variant papillary thyroid cancer was changed into follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), which is not cancer (21). Even if we consider that the effect will be low, this will undoubtedly decrease malignancy rates. Furthermore, we did not evaluate thyroid function tests, thyroglobulin or thyroglobulin antibody levels or molecular pathological examinations. We believe that these may be important in preoperative risk assessment. Another limitation was that all five factors determined for ultrasonographic risk were not evaluated wholly on ultrasonography and the excess of lost data in each report. We conducted statistical studies with the available data only.

Our results revealed that ultrasonographic hypoechogenicity and solidity of the nodules were significant risk factors for preoperative malignancy risk assessment of Bethesda Category IV thyroid nodules. Surgeons should be careful in this respect and inform patients about the risk of malignancy and decide the extent of surgery. Tumor size did not affect malignancy in our study. The high incidence of malignancy and the high incidental malignancy rates of these patients in endemic regions may alter the surgical approach for Bethesda Category IV nodules. For this reason, we recommend that centers should determine their malignancy rates with particular risk factors and determine their surgical approaches accordingly.

Conflict of interest

We have no financial and personal relationships with persons or organizations that could have inappropriately influenced our work.

Funding

No funding was used for the study.

Acknowledgments

The authors thank Bekir Kuru from the Ondokuz Mayıs University in Samsun for advice and comments.

Authors' contributions

Concept: A.Ö., M.U., S.K., Design: A.Ö., M.U., Data Collection or Processing: S.K., M.K.C., Analysis or Interpretation: M.U., S.K., A.P., Literature Search: A.Ö., M.K.C., A.P., Writing: A.Ö., M.U.

References

1. Dal Maso L, Panato C, Franceshi S, Serraino D, Buzzoni C, Busco S, et al. The impact of overdiagnosis on thyroid cancer epidemic in Italy, 1998-2012. Eur J Cancer 2018; 94: 6-15.
2. Horn-Ross PL, Lichtensztajn DY, Clarke CA, Dosiou C, Oakley-Girvan I, Reynolds P, et al. Continued rapid increase in thyroid cancer incidence in California: trends by patient, tumor and neighborhood characteristics. Cancer Epidemiol Biomarkers Prev 2014;23:1067-79.
3. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2016; 26: 1–133.
4. Wong LQ, Baloch ZW. Analysis of the bethesda system for reporting thyroid cytopathology and similar precursor thyroid cytopathology reporting schemes. Adv Anat Pathol 2012; 19: 313-19.
5. Cibas ES, Ali SZ. The Bethesda System for Reporting Thyroid Cytopathology. Am J Clin Pathol 2009; 132: 658–65.
6. Seiberling KA, Dutra JC and Gunn J. Ultrasound-guided fine needle aspiration biopsy of thyroid nodules performed in the office. Laryngoscope 2008; 118: 228-31.
7. Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. Thyroid 2017; 27: 1341-46.
8. Gulcelik NE, Gulcelik MA, Kuru B. Risk of malignancy in patients with follicular neoplasm: predictive value of clinical and ultrasonographic features. Arch Otolaryngol Head Neck Surg 2008;134:1312–15.
9. Kiernan CM, Solorzano CC. Bethesda Category III, IV and V. Thyroid Nodules Can nodule size help predict malignancy? J Am Coll Surg 2017; pii: S1072–7515(17)30178-3.
10. Lee SH, Baek JS, Lee JY, Lim JA, Cho SY, Lee TH, et al. Predictive factors of malignancy in thyroid nodules with a cytological diagnosis of follicular neoplasm. Endocr Pathol 2013;24:177–83.
11. Acar Y, Dogan L, Güven HE, Aksel B, Karaman N, Özaslan C, et al. Bethesda made it clearer: A review of 542 patients in a single institution. Oncol Res Treat 2017;40:277-80.
12. Rosenblum RC, Shtabsky A, Marmor S, Trejo L, Yaish I, Barnes

S, et al. Indeterminate nodules by the Bethesda system for reporting thyroid cytopathology in Israel: Frequency and risk of malignancy after reclassification of follicular thyroid neoplasm with papillary-like features. Eur Surg Oncol 2019; doi:10.1016/j.ejso.2019.03.015.

13. Thewjitcharoen Y, Butadej S, Nakasatien S, Chotwanvirat P, Porramatikul S, Krittiyawong S, et al. Incidence and malignancy rates classified by the Bethesda system for reporting thyroid cytopathology (TBSRTC) – An 8-year tertiary center experience in Thailand. J Clin Transl Endocrinol 2018;16:100175.

14. Lee KH, Shin JH, Ko ES, Hahn SY, Kim JS, Kim JH, et al. Predictive factors of malignancy in patients with cytologically suspicious for Hurthle cell neoplasm of thyroid nodules. Int J Surg 2013;11:898-902.

15. Najafian A, Olson MT, Schneider EB, Zeiger MA. Clinical presentation of patients with a thyroid follicular neoplasm: are there preoperative predictors of malignancy? Ann Surg Oncol 2015;22:3007-13.

16. Kuru B, Kefeli M. Risk factors associated with malignancy and with triage to surgery in thyroid nodules classified as Bethesda category IV (FN/SFN). Diagn Cytopathol 2018;46:489-94.

17. Conzo G, Calo PG, Gambardella C, Tartaglia E, Mauriello C, Pietra CD, et al. Controversies in the surgical management of thyroid follicular neoplasms. Retrospective analysis of 721 patients. Int J Surg 2014;1:29-34.

18. Conzo G, Avenia N, Ansaldo GL, Calò P, Palma MD, Dobrinja C, et al. Surgical treatment of thyroid follicular neoplasms: results of a retrospective analysis of a large clinical series. Endocrine 2017;55:530-38.

19. Maturo A, Tromba L, De Anna L, Carbotta G, Livadoti G, Donello C, et al. Incidental thyroid carcinomas. A retrospective study. G.Chir 2017;38(2), 94-101.

20. Vlassopoulou V, Vryonidou A, Paschou SA, Ioannidis D, Koletti A, Klonaris N, et al. No considerable changes in papillary thyroid microcarcinoma characteristics over a 30-year time period. BMC Research Notes 2016; 9(1), 1-9.

21. Nikiforov YE, Seethala RR, Tallini G, Baloch ZW, Basolo F, Thompson LD, et al. Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm shift to reduce overtreatment of indolent tumors. JAMA Oncol 2016;2:1023-29.