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In The Presence of Risk Factors High Rate of Incidental Multifocal Microcarcinoma Detection in Solitary Thyroid Nodule and Multinodular Goitre Justifies Total Thyroidectomy

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Abstract

Aim: Thyroid nodules are commonly encountered with increasing age. Majority of them are benign. In the present study, our goal was to identify both the false negative rate (FNR) of preoperative cytology, radiology results, risk factors for malignancy, and the prevalence of thyroid carcinoma in cases to whom operation performed for solitary thyroid nodule (STN) with multinodular goitre (MNG) and the final histopathological report.

Methods: A retrospective study among 141 patients who were operated for suspicion of thyroid cancer between 2019-2022. 118 were women (83.6%) and 23 were men (16.3%). The mean age was 50.2(23.1). Demographic characteristics and factors predicting malignancy were questioned for all patients preoperatively. Preoperative ultrasonography (US), fine needle aspiration cytology (FNAc) results and postoperative histopathology data were collected. Ultrasound features (ACR-TIRADS), FNAc results, histopathology records, risk factors and malignancy rates was registered. Statistical analysis was done with Fisher's precision and Mann-Whitney U tests.

Results: 141 patients underwent total thyroidectomy for STN (n=28, 19.8%) and MNG (n=113, 80.1%). The correlation of FNAc with final histopathology revealed that FNR in MNG was more often than that of STN (33.3% vs 66.6%, p<0.001). Malignancy was detected in 43 of 141 patients with total thyroidectomy due to STN and MNG (30.4%).Family history and previous radiotherapy were risk factors in patients with STN (25%). The histopathology results of 129 patients were compatible with ACR-TIRADS in ultrasound (91.4%).

Conclusion: Although multinodular goiter (MNG) is generally believed to have a lower risk of malignancy compared to solitary thyroid nodules (STN), the prevalence of malignancy is significantly higher in STN and MNG. Optimal patient management depends on a good interaction between radiologist, pathologist and surgeon to decrease false negative and false positive cases.

Keywords: Cytology, solitary thyroid nodule, multinodular goitre, malignancy

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Risk Faktörlerinin Varlığında SoliterTiroid Nodülü ve Multinodüler Guatrda Tesadüfi Multifokal Mikrokarsinom Saptanmasının Yüksek Oranı Total Tiroidektomiyi Haklı Çıkarır

Öz

Amaç: Tiroid nodüllerine yaş ilerledikçe sıkça rastlanır. Bunların büyük çoğunluğu benindir. Bu çalışmada amacımız multinodüler guatr (MNG) ile birlikte soliter tiroid nodülü (STN) nedeniyle ameliyat edilen olgularda ameliyat öncesi sitoloji, radyoloji sonuçları, malignite için risk faktörleri ve tiroid karsinomu prevalansının hem yanlış negatiflik oranını (FNR) hem de nihai histopatolojik raporunu belirlemektir.

Yöntemler: 2019-2022 yılları arasında tiroid kanseri şüphesiyle ameliyat edilen 141 hasta üzerinde yapılan retrospektif çalışmadır. 118'i kadın (%83,6), 23'ü erkek (%16,3) idi. Ortalama yaş 50,2(23,1) idi. Tüm hastaların ameliyat öncesi demografik özellikleri ve maligniteyi öngören faktörler sorgulandı. Ameliyat öncesi ultrasonografi, ince iğne aspirasyon sitoloji (FNAc) sonuçları ve ameliyat sonrası histopatoloji verileri toplandı. Ultrasonografi özellikleri (ACR-TIRADS), FNAc sonuçları, histopatoloji kayıtları, risk faktörleri ve malignite oranları kaydedildi. İstatistiksel analiz Fisher'in kesinliği ve Mann-Whitney U testleri ile yapıldı.

Bulgular: STN (n=28, %19,8) ve MNG (n=113, %80,1) nedeniyle 141 hastaya total tiroidektomi uygulandı. FNA'in son histopatoloji ile korelasyonu, MNG'deki FNR'ın STN'ye göre daha sık olduğunu ortaya çıkardı (%33,3 vs %66,6, p<0,001). STN ve MNG nedeniyle total tiroidektomi yapılan 141 hastanın 43'ünde (%30,4) malignite tespit edildi. STN'li hastalarda aile öyküsü ve daha önce radyoterapi uygulanmış olması risk faktörleriydi (%25). 129 hastanın histopatoloji sonucu ultrasonda ACR-TIRADS ile uyumluydu (%91,4).

Sonuç: Multinodüler guatrın (MNG) genellikle soliter tiroid nodüllerine (STN) kıyasla daha düşük malignite riski taşıdığına inanılsa da, malignite prevalansı STN ve MNG'de önemli ölçüde daha yüksektir. Optimal hasta yönetimi, yanlış negatif ve yanlış pozitif vakaları azaltmak için radyolog, patolog ve cerrah arasındaki iyi bir etkileşime bağlıdır.

Anahtar kelimeler: İnce iğne aspirasyonu, soliter tiroid nodülü, multinodüler guatr, malign.

INTRODUCTION

Thyroid nodules are frequently come acrossed in the clinic with advancing age. More than 50% of people in the world have at least one nodule. Most of these are benign, but the likelihood of them becoming malignant is estimated to be between 7% and 15%, depending on factors such as age, gender, radiation exposure, family history, and whether the individual is in an endemic region[1]. It is essential to distinguish between benign and malignant nodules to determine the appropriate course of treatment.

The risk of malignancy in assessments using FNAc and thyroid ultrasound is reported to range from 3% to 5%[2]. However, according to the literature, FNAc shows benign results in about half of the patients with malignancies, particularly in endemic regions[2]. The incidental carcinoma detection rate in the terminal histological evaluation of patients undergoing surgery for MNG was previously reported to be approximately 5 to 10%[1].The majority of previous studies have shown that the risk of cancer is lower in patients with MNG compared to solitary thyroid nodule (STN)[1]. But, some of the latest surgical studies have reported similar risk of thyroid carcinoma in STN and MNG and also significantly higher risk than previously reported[1].

High-frequency ultrasonography (US) is widely used to differentiate malignant from benign thyroid nodule, and US-guided FNAc is the most popular method used to identify thyroid cancer worldwide[3,4]. In addition, an US-based risk arrangement of thyroid nodules with the Thyroid Imaging Reporting and Data System (ACR TI-RADS) is now offered to have a higher accuracy in decision making[4,5]. Because the incidence of malignancy in STN and MNG and the FNR in cytological examination are quite high, examining additional risk factors related

to malignancy in endemic regions is crucial for accurate decision-making.

While surgery for all indeterminate cases can help accurately diagnose and treat thyroid cancer, it is important to weigh the risks and benefits of surgery in each individual case. In this study, our goal was to find both the FNR of preoperative FNA biopsy and the currency of thyroid carcinoma in patients operated for STN and MNG and to look at all malignancy risk factors particularly with TI-RADS and final histopathological report.

METHODS

The study protocol was confirmed by our institution's Ethics' Committee (E-10840098-202.3.02-2053). All the procedures in the study carefully followed the ethical principles and were consistent with Declaration of Helsinki. This study was a single center study conducted retrospectively on 141 patients who underwent total thyroidectomy between 2019-2022. This study has received no financial support and no conflict of interest was declared by the authors. Written informed consent was obtained from the patients for inclusion of their information in this study.

In the present study, our aim was to analyze the false negative rate of preoperative FNA biopsy, the likelihood of thyroid carcinoma in surgical cases, and factors that could influence the accuracy of preoperative assessments of STN and MNG along with final histopathological result. To address cytology-histology incompatibility, it's essential to investigate additional sampling techniques, interpretation errors, and strategies to reduce the FNR. Analyzing the correlation between incidental carcinomas discovered postoperatively and the decision for total thyroidectomy can provide insights into the appropriateness of surgical interventions. Additionally, examining differences in malignancy risk between MNG and STN patients based on final pathology results can help tailor treatment approaches.

All patients had preoperative FNA biopsy reports as benign, indeterminate, suspicious, or malignant, and all underwent total thyroidectomy. Our clinical protocol for thyroid disorders dictates total thyroidectomy for all bilateral MNG (one nodule should be larger than 4 cm if cytology is benign) and for STN based on multiple risk factors (endemic area, previous radiation exposure to the neck region) and patient preference. Patients with toxic thyroid disease and patients who underwent lobectomy for STN were excluded. Demographics, results of surgery, cyto- and histopathological association, histopathological subtypes of carcinomas, and incidence of malignancy were listed in an Excel file (Office 2017, Microsoft, USA).

A thorough screening and evaluation process for thyroid cancer were done for all patients. Screening for risk factors such as previous radiation exposure, family history, genetic disorders, endemic geographical origin, iodine deficient diet, etc. and using high-resolution US using the Thyroid Imaging Reporting and Data System (ACR TI-RADS) for risk stratification of thyroid nodules are important steps in early detection. Performing US-guided FNAc and evaluating cytological results according to the Bethesda classification system were standard practices for diagnosing thyroid nodules. Routine diagnostic criteria for interpreting FNAc results to ensure consistency and accuracy in diagnosis were done6.

A standard transverse cervical incision 2 cm above the sternal notch and just below cricoid cartilage was used to explore thyroid gland. Intraoperative nerve monitoring (IONM, nim response 3. version, Medtronic, U.S.) and harmonic focus shears instrument (Ethicon, U.S.) were used in all cases. Standard total thyroidectomy was performed by the same

surgical oncologist, after identification and electrical stimulation of recurrent laryngeal nerve (RLN) bilaterally. Patients with final pathology report showing malignancy were referred to Nuclear Medicine for further evaluation and follow-up.

A senior Cytopathologist involved in a process of evaluating discrepant cases in cytology-histology and reviewed the sampling or interpretation errors, and a senior Radiologist re-evaluated the US findings using the ACR TI-RADS calculator that is planned by American College of Radiology7. By systematically reviewing the five main criteria (composition, echogenicity, shape, margin, and echogenic foci) on the previous images to identify any potential issues or areas that require further attention. This structured approach to evaluating cases with a team of experienced specialists will help in improving the accuracy and reliability of the diagnoses and treatment decisions.

Statistical Analysis

Statistical analyses were conducted by using IBM SPSS Statistics version 19 for Windows. Fisher's exact test was used for categorical variables and the Mann-Whitney U test for continuous variables to evaluate associations between predictive variables and thyroid cancer. It's important to note that a P-value of less than 0.05 was considered statistically significant in our analysis.

RESULTS

Of the 141 patients who underwent total thyroidectomy for STN (n=28, 19.8%) and MNG (n=113, 80.1%) with different Bethesda categories (benign, indeterminate, suspicious/malign; 66.6% vs 19.1% vs 14.1%, respectively, shown in Table I. 118 were women (83.6%) and 23 were men (16.3%). In both groups, most of the patients were women (85.7% and 83.1%, Table I). The mean age was 50.2 years. Male patients with STN was significantly younger (34.0(6.3) vs 53.9(19.6) years, $p<0.001$). Of the 141 patients to whom total thyroidectomy applied for STN and MNG, forty-three (30.4%) were detected to have malignancy (Table I). Among the patients with thyroid carcinoma, 48.8% had incidentalomas(n=21). The prevalence of carcinoma was higher in STN compared to MNG (39.2% vs 28.3%, respectively, $p<0.001$). Incidental cancers were more common in MNG compared to STN(56.2% vs 27.2%, $p<0.001$). Macrocarcinomas (>1cm) were more frequent and larger in STN (63.6% vs 21.8%, $p<0.001$, Table I; 2. 4(1.9) cm vs 1.2(0.8) cm in diameter, respectively, $p<0.001$Table II, while microcarcinomas (≤1 cm) were more common in MNG (56.2% vs 27.2%, $p<0.001$, Table 1); 0.48(0.34) cm vs 0.64(0.3) cm, $p<0.05$, Table II). Half of the macro carcinomas in MNG were found alongside micro carcinomas(Table I). Multifocality was more significant in MNG compared to STN(43.7% vs 18.1%, $p<0.001$).

Table I: Demographics, predictor factors of malignancy, preoperative cytology and final histopathology of patients with solitary thyroid nodule and multinodular goitre (MNG)

	Total(n=141)	STN(n=28)	MNG(n=113)	P value
Demographics				
Women	118(83.6%)	24(85.7%)	94(83.1%)	0.60
Men	23(16.3%)	4(14.2%)	19(16.8%)	0.40
Age(mean years, SD)	50.2±23.1	46.2±21.2**	51.9±22	<0.001**
W	50.8±21.3	49.1±17	51.9±22	0.10
M	52±15	34±6.3	53.9±19.6	<0.001**
Demographics(malign cases)				
Women	32(74.4%)	8(72.7%)	24(75%)	0.60
Men	11(25.5%)	3(27.2%)	8(25%)	<0.001
Age(mean years, SD)	44.9±20.7	42.2±17**	48.9±14	<0.001
W	49.1±21.3	47±15	49.9±20	0.10
M	40.9±18	30±5.3**	47±14**	<0.001
Other predictors of malignancy				
Family history	11(7.8%)	7((25%)**	4(3.5%)	<0.001
Previous radiation treatment	5(3.5%)	3(10.7%)	2(1.7%)	<0.001
Genetic disorders	0	0	0	1.00
Body mass index(kg/m^2)	28.9	27*	29.9	<0.05*
Diabetes mellitus	11(7.8%)	3(10.7%)	8(7%)	0.40
Iodine deficient diet	3(2.1%)	1(3.5%)*	2(1.7%)	<0.05
Origin from The Black Sea Region++	109(77.3%)	16(57.1%)**	93(82.3%)**	<0.001
Preoperative cytology				
Benign	94(66.6%)	16(57.1%)	78(69%)**	<0.001
Indeterminate	27(19.1%)	4(14.2%)	23(20.3%)**	<0.001
Suspicious/Malign	20(14.1%)	8(28.5%)	12(10.6%)	<0.001
Final histopathology				
Benign	98(69.5%)	17(60.7%)	81(71.6%)**	<0.001
Malign	43(30.4%)	11(39.2%)**	32(28.3%)	<0.001
Microcarcinoma	21(48.8%)	3(27.2%)	18(56.2%)**	<0.001
Macrocarcinoma	14(32.5%)	7(63.6%)**	7(21.8%)	<0.001
Micro and macrocarcinoma	8(18.6%)	1(9%)	7(6.1%)	<0.001
Malign				
Multifocal	16(37.2%)	2(18.1%)	14(43.7%)**	<0.001
Bilateral	6(13.9%)	0	6(13.9%)	1.00
Incidental	21(48.8%)	3(27.2%)	18(56.2%)	<0.001

**p<0.05: Statistically significant **p<0.001: Statistically very significant *Body mass index(kg/m2): 18-25Normal, 25-30 Overweight, >30 Obez++Origin from The Black Sea Region: A region of Turkey endemic for goitre and mostly affected by Chernobyl nuclear fallout*

Table II: Size, number and distrubition of thyroid nodules, mean diameters of carcinomas and microcarcinomas, and the factors resulting in false negative cytology in our series

	Total(n=141)	STN(n=28)	MNG(n=113)	P value
Diameter of all nodules(cm, mean)	2.4±1.09	3.1±1.7	2.9(1.9)	0.20
Diameter of carcinoma(cm, mean)	1.6±1.4	2.4±1.9	1.2(0.8)**	<0.001**
Diameter of microcarcinoma(mm,mean)	0.62±0.4	0.64±0.3	0.48(0.34)*	<0.005**
Number of nodules	3±2	1	3.6(2.1)	-
Carcinoma in the dominant nodule	29(20.5%)	11(100%)	18(56.2%)	-
Carcinoma in the non-dominant nodule	14(9.9%)	0	14(43.7%)	<0.001
False negative cytology	21(14.8%)	3(10.7%)	18(15.9%)**	<0.001
Sampling errors	16(76.1%)	1(33.3%)	15(83.3%)**	<0.001
-Sampling from the periphery of the nodule	4(19%)	1(33.3%)	3(20%)	0.40
-Sampling a less suspicious nodule	12(57.1%)	0	12(80%)**	<0.001
Over/miss -interpretation	3(14.2%)	1(33.3%)	2(11.1%)	0.90
Inherent nature of nodule	2(9.5%)	1(33.3%)	1(5.5%)	0.60

**p<0.05: Statistically significant **p<0.001: Statistically very significant*

13.9% of patients with MNG had malign lesions in both lobes. FNA was performed on all patients in the preoperative period. The results were evaluated as false negative in 21 of 141 patients (14.8%).Of the patients evaluated as negative, 3 were from the STN group and 18 were from the MNG group. 76.1% of this rate was due to the radiologist (sampling from the periphery of the nodule in 4 patients and sampling from the less suspicious nodule in 12 patients with MNG) (Table II) and the rest related to the pathologist's error (mis-interpretation in 3 and inherent nature of nodule in 2 patients). Among the patients in this group who were operated on due to suspicion of cancer, pressure symptoms, and difficulty in swallowing, a microcarcinoma focus was detected in those whose preoperative FNAc results were evaluated as false negative.

The correlation of preoperative cytology with final histopathology revealed that false negative cytology in MNG was higher compared to STN (33.3% vs 66.6%, p<0.001, Table II).Indeterminate cytology was also more frequent in the MNG group (20.3% vs 14.2%, p<0.001, Table I).Since the preoperative US results of 12 patients were evaluated as compatible with ACR-TIRADS 3 so direct biopsy was performed on these less suspicious slightly hypoechoic nodules greater than 2.5 cm in diameter. When we evaluated in general, the histopathology results of 129 patients were compatible with the the risk-stratification system ACR-TIRADS in US (91.4%). ACR-TIRADS has a high ability to exclude malignant nodules from benign.

The histological findings and subtypes were summarized in Table IV. The most common subtype was papillary carcinoma (83.7%), classic variant (77.7%). The predictive risk factors of malignancy were displayed in Table I and include younger age and male gender for both groups. However, family history providing important genetic predispositions and previous radiation treatment were more important predisposing risk items in cases with STN (25% and 10.7%, respectively). Another noteworthy finding in the present series was the high ratio of patients (77.3%) from The Black Sea Region, an endemic area. There was no important morbidity following surgery, except transient hypocalcemia (n=6, 4.2 %), transient vocal cord paralysis (n=3, 2.1%) and surgical site infections (n=2, 1.4%).

Table III: Preoperative evaluation of nodules with Thyroid Imaging Reporting and Data System (TI-RADS) scores

TI-RADS Definition	Total(n=141)	STN(n=28)	MNG(n=113)	P value
1-Normal thyroid gland	0	0	0	1.00
2-Benign nodule	56(39.7%)	15(28.5%)	41(36.2%)*	<0.05*
3-Highly probable benign nodule	75(53.1%)	16(57.1%)	59(52.2%)	0.60
4a-Low suspicious for malignancy	7(5%)	3(10.7%)*	4(3.5%)	<0.05
4b-High suspicion for malignancy	4(2.8%)	1(3.5%)	3(2.6%)	0.60
5-Malignant nodule with more than two criteria of high suspicion	9(6.3%)	3(10.7%)*	6(5.3%)	<0.05

*Mean TI-RADS scores for each: 3,*p<0.05: statistically signifant, **P<0.001: statistically highly significant*

Table IV: The histopathologic characteristics of patients

Final histopathology	Total(n=141)	STN(n=28)	MNG(n=113)	P value
Benign	98(69.5%)	17(60.7%)	81(71.6%)	<0.001*
Malign	43(30.4%)	11(39.2%)	32(28.3%)	<0.001**
M-Hurtle cell carcinoma (HC)	5(11.6%)	4(36.3%)**	1(3.1%)	<0.001**
M-Follicular carcinoma(FC)	2(4.6%)	1(9%)	1(3.1%)	0.20
M-Papillary carcinoma(PC)	36(83.7%)**	6(54.5%)**	30(93.7%)**	<0.001**
PC-Classical variant	28(77.7%)	3(50%)*	25(83.3%)**	<0.001**
PC-Follicular variant	2(5.5%)	1(16.6%)	1(3.3%)	0.20
PC-Follicular and classic variant	3(8.3%)	1(16.6%)	2(6.6%)	0.10
PC-Oncocytic variant	1(2.7%)	0	1(3.3%)	0.60
PC-Oncocytic and classic variant	2(5.5%)	1(16.6%)	1(3.3%)	0.20

** P<0.05: Statistically significant, ** P<0.001: Statistically very significant*

DISCUSSION

Most common nodular thyroid disease is MNG. The extent of surgery is still controversial since its most frequent presentation is bilateral involvement[1,2]. Although the majority of thyroid nodules are benign, the aim is to differentiate the nodule from benign to malignant in the preoperative period in the patient for whom the operation will be planned. The risk of thyroid cancer in indeterminate cases of fine-needle aspiration cytology (FNAC) can vary depending on several factors, such as the characteristics of the nodule and the patient's medical history. Traditionally, STN has been known to carry a higher risk of malignancy than multiple nodules, and in the presence of an indeterminate Bethesda cytology, diagnostic lobectomy can often be used[1,2,8]. Studies indicate that about 15% to 30% of thyroid nodules with indeterminate FNAc outcomes are found to be cancerous following surgery[9]. Thus, it is important to accurately identify these nodules to prevent unnecessary surgeries and associated complications.

Diagnosis cannot be made with a single noninvasive method. While surgery for all indeterminate cases can help accurately diagnose and treat thyroid cancer, it is important to weigh the risks and benefits of surgery in each individual case.

Thyroid cancer is relatively uncommon when compared to other types of cancer, making up less than 1% of all new cancer cases in the United States. However, the number of diagnosed cases has been rising recently. This increase is believed to be largely due to advancements in detection techniques, such as ultrasound imaging and fine needle aspiration biopsy. The American Cancer Society has projected that around 44280 new cases of thyroid cancer were expected to be diagnosed in the United States in 2021. It is more prevalent in women than in men and can occur at any age, although it is most frequently diagnosed in individuals between the ages of 25 and 65. The overall survival rate for thyroid cancer is high, with most patients experiencing a positive prognosis and successful treatment outcomes. Overall occurrence of thyroid cancer in this study group was high (30.49%) compared to similar studies on the subject[6-8]. The incidence of thyroid cancer was significantly higher in STN group according to MNG group (39,2% vs. 28,3% respectively, p<0,001). Young male gender was identified as a risk factor for thyroid cancer in STN. The pathology of the young men in the STN group was evaluated as malignant in our study group. Our results was similar to that of Smith et al.[10] and Rago et al. who identified male gender and young age as independent risk factors for thyroid carcinoma[11].

It's interesting that the incidence of cancer post-thyroid surgery has increased over the years (from 14% to over 50%), highlighting the need for accurate diagnosis and appropriate management. ACR TI-RADS is indeed a valuable tool in evaluating thyroid nodules based on

ultrasonographic characteristics to help guide clinical decisions and reduce unnecessary biopsies. Proper evaluation of clinical history, physical examination, radiological findings, and cytomorphological features is crucial for making a definitive diagnosis and determining the best course of treatment. The advancements in diagnostic technologies and guidelines like ACR TI-RADS and FNAc play a vital role in improving the accuracy of thyroid nodule assessment and management. The American College of Radiology (ACR) Thyroid Imaging Reporting and Data System (ACR TI-RADS) was designed in 2017 to reduce biopsies of benign nodules and increase overall diagnostic accuracy (Table III).

The five ultrasound features of thyroid nodules include composition, echogenicity, shape, margin and punctate echogenic foci. Malignant characteristics of nodules on ultrasonographic examination include irregular margins, microcalcifications, an absent halo, the lesion is taller than its width in the transverse dimension, and increased vascularity. According to Frates et al., there is a 15% risk of missing a thyroid carcinoma if only the largest nodule is biopsied12. Therefore, it's important to be aware of these characteristics when evaluating thyroid nodules for potential malignancy. According to ACR-TIRADS there is 5 types of nodule present with a risk of malignancy 0.3%, 1.5%, 4.8%, 9.1% and 35% respectively. Ultrasound-guided FNAc is recommended as the most accurate and cost-effective method for evaluating thyroid nodules with Bethesda classification (Table II). The Bethesda classification system is an important tool in interpreting FNAc results and guiding further management decisions. For cases with non-diagnostic interpretations (2-20%), a repeat FNAc with US guidance is typically recommended, as it can often provide a definitive diagnosis. In our study, 19.14% of the preoperative cytology results were indeterminate.

Our results suggest that a negative finding does not exclude the possibility of cancer (14.8%). The success of FNAc depends on the experience of radiologist who evaluates nodule size and suspicious features on US.

There are challenges and limitations associated with using preoperative diagnostic tools such as FNAc in cases where there are multiple nodules present in the thyroid gland[13]. The presence of multiple nodules can decrease the diagnostic accuracy of these tools, leading to higher rates of indeterminate and false negative results in both STN and MNG[14,15]. Additionally, some studies have shown that many thyroid carcinomas may be multifocal or originate from non-dominant nodules, further complicating the diagnostic process. In our series, a significant percentage (43%) of carcinomas were found in non-dominant nodules, with most being microcarcinomas with a mean diameter of 0.4 mm in MNG and 0.6 mm in STN. Having an experienced cytopathologist involved in the interpretation of FNAc results is crucial for achieving more accurate and reliable diagnostic outcomes in these complex cases. Their expertise can help navigate the challenges posed by coexisting nodules and improve the diagnostic accuracy in identifying thyroid carcinomas.

It's important to consider the various factors that may contribute to the increased incidence of thyroid cancer, particularly the papillary subtype with the highest multifocality feature[13,16]. The occurrence of multifocal thyroid microcarcinoma (MTMC) ranges from 15% to 36.1% of all thyroid microcarcinoma (TMC), and some authors suggest that it might be on the rise. So et al.[17]determined that when multifocal TMC is localized within one lobe, there is a higher likelihood of bilateral involvement. Consequently, they suggested more extensive surgery for cases of MTMC.

Family history, genetic disorders, past radiation exposure, low iodine intake, diabetes, and obesity all play a role in the development of thyroid cancer and should be taken into account when determining the appropriate course of treatment, including the extent of surgery[18]. Monitoring and addressing these risk factors can help in better managing and treating thyroid cancer.

However, a completion thyroidectomy is required in most cases[19,20]. On the other hand, the recently published data caused a reasonable suspicious approach to the results of FNA cytology, since most of these studies suggested that a negative finding does not exclude the possibility of cancer[1,21]. Furthermore, recent surgical series have shown that MNG have an incidence of cancer that approaches that of STN[1,13]. In a study of Ajarma et al, the prevalence of thyroid cancer was 41.1% in STN compared to 29.2% in MNG ($p < 0.01$)[1]. Similarly, Luo et al have reported that malignancy was present in nearly a third of patients with a MNG in their study[13]. The authors concluded that their current methods for the detection of malignancy pre-operatively were not adequate. In the present study, of the 141 patients who underwent total thyroidectomy for STN and MNG, the prevalence of thyroid carcinoma was higher in STN (39%) in comparison with MNG (28%) (Table I).

However incidental microcarcinomas and multifocality are more common in MNG compared to other conditions (MNG 56.2% vs STN 27.2%, $p<0.001$) (Table I), (MNG 43.7% vs 18.1%, $p<0.001$ respectively). This information could be important for understanding the characteristics and potential risks associated with MNG.

Only10% of patients with MNG had a suspicious or malign FNA cytology preoperatively (Table I), and cancer was not suspected preoperatively in 15.9% (Table II) of patients that were ultimately found to have malignancy on the final histopathology. Furthermore, the rate of indeterminate cytology was higher (20%) in MNG (Table I).

In this study thyroid nodules in preoperative ultrasound (US) evaluations of cytology-histology discrepant cases also evaluated by the Thyroid Imaging Reporting and Data System (TI-RADS) with a mean score 3 in both groups. The findings indicate that TI-RADS was effective in detecting sampling errors, with some cases showing FNAs taken from less suspicious nodules in multinodular goiter (MNG)(80%). Other reasons for discrepancies (14.2%) included missing the core of the lesion during FNA(33.5% in STN vs 20% in MNG), as well as over and misinterpretations by cytopathologists(2%)In some cases, discrepancies were attributed to the inherent nature(9.5%) of the thyroid nodule as in our 2 patients. It's important to consider these factors when evaluating thyroid nodules preoperatively, as they can impact diagnostic accuracy and treatment decisions.

Since TI-RADS and FNA have limitations and may skip smaller microcarcinomas or may give false negative results, we need to look for other predictors of malignancy in detail. There are some well-known risk factors for thyroid carcinoma, such as young age, male gender, family history, previous radiation treatment, iodine-deficient diet, obesity, diabetes et.[1,13,18,22]. However, while some studies emphasize the importance of one or two of these predictors, others highlight the remaining factors[1,13]. Therefore, we evaluated all of the known risk factors in detail, and found that younger age and male gender are important predictors in both diseases, but especially in STN. Family history(25%), previous radiation treatment(10%), and iodine-deficient diet(3.5%) are all significant risk factors for developing thyroid nodules. Additionally, living in the Black Sea Region, which is known to be an endemic area for thyroid disorders, increases

the likelihood of developing thyroid nodules. 77% of our patients were from this region. This geographic region was also affected Chernobyl nuclear power plant explosion in 1986, and it caused a major release of nuclear radioactive material into the atmosphere[23-25]. Radionuclides were scattered in the vicinity of the plant and over much of Europe[26]. Even we have no exact evidences to accuse the accident of increasing thyroid malignancy, we also can not ignore the radiation effect as a significant risk factor. Therefore, when we consider all of these risk factors along with preoperative FNAc study indicating either indeterminate or suspicious/malign cytology, we could say that almost all of the patients with STN are in risk.

The incidence of papillary carcinoma, the histological subtype of thyroid carcinomas associated with a highest incidence of multifocality according to latest trends[9,12]. Discussing all surgical options with patients who have multiple risk factors is crucial in ensuring they receive appropriate treatment. Recent research suggests that patients with multifocality of thyroid cancer have a higher likelihood of recurrence or persistence even after undergoing more aggressive treatments, compared to those with unifocal lesions[27]. This may be attributed to the higher rates of lymph node metastases, soft tissue invasion, and distant metastases at the time of diagnosis and treatment in patients with multifocal thyroid cancer[27]. As a result, some experts advocate for total aggressive thyroidectomy and postoperative radioiodine ablation therapy for cases of multifocal thyroid cancer[27]. Since it is only possible to detect the presence of capsular invasion in the presence of multifocal microcarcinoma in paraffin sections, it is more appropriate to perform total thyroidectomy in large nodules in order not to put the patient at risk and to avoid complications that may be caused by a second surgery. Individualized discussions with patients will help determine the most suitable approach for each case. Recurrence risk and the possible need for a completion thyroidectomy and its consequences should also be mentioned in case of a non-total surgery would be chosen. In our opinion, in appropriate cases with high risks, total thyroidectomy is a safe procedure in centers experienced in endocrine surgery. However, a dedicated radiologist-cytopathologist team seems to be more important in decreasing FNR.

It is crucial to be vigilant about the possibility of malignancy in seemingly benign thyroid diseases, particularly in regions where the prevalence is high. Given the relatively high false negative rates of cytology and the prevalence of malignancy in solitary thyroid nodules (STN) and multinodular goiter (MNG), it is important to consider other factors that may predict malignancy. Collaborative efforts between radiologists, pathologists, medical endocrinologists, and endocrine surgeons are key in optimizing patient management and reducing the rates of false negatives and false positives. In cases where malignancy is confirmed, complete resection during the initial thyroid surgery tends to yield positive outcomes.

It appears that the study highlights differences in the characteristics of thyroid carcinomas in patients with STN and MNG, such as tumor size, prevalence, and multifocality by incorporating TI-RADS and analyzing final histopathological reports. Our study can contribute valuable insights to the field of thyroid cancer diagnosis and treatment.

Ethics Committee Approval: The study protocol was confirmed by our instution's Ethics' Committe (E-10840098-202.3.02-2053). All the procedures in the study carefully followed the ethical principles and were consistent with Declaration of Helsinki.

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REFERENCES

1. Ajarma KY, Al-Faouri AF, Al Ruhaibeh MK, et al. The risk of thyroid carcinoma in multinodular goiter compared to solitary thyroid nodules: A retrospective analysis of 600 patients. Med J Armed Forces India. 2020;76(1): 23–9. doi: 10.1016/j.mjafi.2018.05.001

2. Alyanak A, Aslan F. Nodule and cancer assessment following thyroid surgery: a cohort of 460 patients. Eur Rev Med Pharmacol Sci. 2020;24(18):9565-70. doi: 10.26355/eurrev_202009_23042.

3. Mohammadi M, Betel C, Burton KR, et al. Retrospective application of the 2015 American Thyroid Association Guidelines for ultrasound classification, biopsy indications, and follow-up imaging of thyroid nodules: Can improved reporting decrease testing? AssocRadiol J 2019;70(1):68-73. doi: 10.1016/j.carj.2018.09.001

4. Pezzolla A, Lattarulo S, Madaro A, et al. What really is an indeterminate FNA thyroid nodule? Ann Ital Chir2017;88:275–81.

5. Tessler FN, Middleton WD, Grant EG, et al. ACR Thyroid Imaging, Reporting and Data System (TI-RADS): White Paper of the ACR TI-RADS Committee. J Am CollRadiol 2017;14(5):587–95.doi: 10.1016/j.jacr.2017.01.046.

6. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. Thyroid 2017;27(11):1341–6. doi: 10.1089/thy.2017.0500

7. RadioGyan, TI-RADS online calculatorhttps://radiogyan.com/tirads-calculator/#tirads-calculator 2020.

8. Tessler FN, Middleton WD, Grant EG. Thyroid Imaging Reporting and Data System (TI-RADS): A user's guide. Radiology 2018;287(3):29–36. doi: 10.1148/radiol.2017171240

9. Popoveniuc G, Jonklaas J. Thyroid Nodules. Med Clin North Am. 2012;96(2):329–49.

10. Smith JJ, Chen X, Schneider DF, et al. Cancer after thyroidectomy: a multiinstitutional experience with 1,523 patients. J Am Coll Surg. 2013;216(4):571–7. http://dx. doi.org/10.1016/j.jamcollsurg.2012.12.022.

11. Rago T, Fiore E, Scutari M, et al. Male sex, single nodularity, and young age are associated with the risk of finding a papillary thyroid cancer on fine-needle aspiration cytology in a large series of patients with nodular thyroid disease. Eur J Endocrinol. 2010;162(4):763–70. http://dx.doi.org/ 10.1530/EJE-09-0895.

12. Frates MC, Benson CB, Doubilet PM, et al. Prevalence and distribution of carcinoma in patients with solitary and multiple thyroid nodules on sonography. J ClinEndocrinolMetab. 2006;91(9):3411–7.

13. Luo J, McManus C, Chen H, Sippel RS. Are there predictors of malignancy in patients with multinodular goiter? J Surg Res 2012;174(2):207-10. doi: 10.1016/j.jss.2011.11.1035.

14. Rossi ED, Adeniran AJ, Faquin WC. Pitfalls in Thyroid Cytopathology. SurgPatholClin 2019;12(4):865–81. doi: 10.1016/j.path.2019.08.001

15. Renshaw AA, Gould EW. Characteristics of False-Negative Thyroid Fine-Needle Aspirates. ActaCytol 2018;62(1):12–8. doi: 10.1159/000481722.

16. Evranos B, Polat SB, Cuhaci FN, et al. A cancer of undetermined significance: Incidental thyroid carcinoma. DiagnCytopathol 2019;47(5):412–6. doi: 10.1002/dc.24117.

17. So YK, Kim MW, Son YI: Multifocality and bilaterality of papillary thyroid microcarcinoma. ClinExpOtorhinolaryngol 2015; 8(2):174–8. doi: 10.3342/ceo.2015.8.2.174.

18. Zupunski L, Ostroumova E, Drozdovitch V, et al. Thyroid Cancer after Exposure to Radioiodine in Childhood and Adolescence: 131I-Related Risk and the Role of Selected Host and Environmental Factors. Cancers (Basel) 2019;11(10):1481. doi: 10.3390/cancers11101481

19. DiMarco AN, Wong MS, Jayasekara J, et al. Risk of needing completion thyroidectomy for low-risk papillary thyroid cancers treated by lobectomy. BJS Open 2019;3(3):299–304.doi: 10.1002/bjs5.50137.

20. Li YJ, Wang YZ, Yi ZB, Chen LL, Zhou XD. Comparison of completion thyroidectomy and

primary total surgery for differentiated thyroid cancer: A meta-analysis. Oncol Res Treat 2015;38(10):528–31. doi: 10.1159/000440690.

21. Dalquen P, Rashed B, Hinsch A, et al. Feinnadelaspiration (FNA) der Schilddrüse: Analysediskrepanterzytologischer und histologischerDiagnosen [Fine-needle aspiration (FNA) of the thyroid gland: Analysis of discrepancies between cytological and histological diagnoses]. Pathologe 2016;37(5):465–72. doi: 10.1007/s00292-016-0172-x.

22. Zimmermann MB, Boelaert K. Iodine deficiency and thyroid disorders. Lancet Diabetes Endocrinol 2015;3(4):286–95. doi: 10.1016/S2213-8587(14)70225-6.

23. Weiss W. Chernobyl thyroid Cancer: 30 years of follow-up overwiew. RadiatProt Dosimetry 2018;182(1):58–61. doi: 10.1093/rpd/ncy147

24. Tronko M, Brenner AV, BogdanovaT,et al. Thyroid neoplasia risk is increased nearly 30 years after the Chernobyl accident. Int J Cancer 2017;141(8):1585–8. doi: 10.1002/ijc.30857.

25. Fridman M, Krasko O, Lam AK. Optimizing treatment for children and adolescents with papillary thyroid carcinoma in post-Chernobyl exposed region: The roles of lymph node dissections in the central and lateral neck compartments. Eur J SurgOncol 2018;44(6):733–43.doi: 10.1016/j.ejso.2017.12.004.

26. Cahoon EK, Nadyrov EA, Polyanskaya ON, et al. Risk of Thyroid Nodules in Residents of Belarus Exposed to Chernobyl Fallout as Children and Adolescents. J ClinEndocrinolMetab 2017;102(7):2207–17. doi: 10.1210/jc.2016-3842

27. Kaliszewski K, Zubkiewicz-Kucharska A, Wojtczak B, Strutynska-Karpinska M. Multi- and Unifocal Thyroid Microcarcinom: Are there any differences? AdvClinExp Med 2016;25(3):485-92. Doi: 10.17219/acem/62327