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Definition of Clinical Risk Factors for Differential Thyroid Cancers in Patients with Nodular Goiter

Clinical Risk Factors in Thyroid Cancer

Lutfi CETINTEPE*[1], Tugba CETINTEPE[2], Mehmet Sercan ERTURK[3], Baris AKINCI[4]

[1]Department of Nephrology, Karaburun State Hospital Ankara, Türkiye.
[2]Department of Hematology, Izmir Katip Celebi University, Ataturk Training and Research Hospital, Izmir, Türkiye.
[3]Department of Endocrinology and Metabolism, Izmir Katip Celebi University, Ataturk Training and Research Hospital, Izmir, Türkiye.
[4]Department of Endocrinology and Metabolism, Faculty of Medicine, Dokuz Eylul University, Izmir Türkiye.

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ABSTRACT

Objective: This study aimed to evaluate the clinical, radiological, and laboratory risk factors for differentiated thyroid cancers in patients with nodular thyroid disease and to investigate the relationship between these findings and the cytopathological features of the nodules.
Materials and Methods: Demographic data, laboratory and imaging findings, and fine-needle aspiration pathology results of 323 patients with incidentally detected thyroid nodules during clinical or radiological examination at the Endocrinology Clinic were retrospectively evaluated and recorded.
Results: Fine-needle aspiration biopsy of the dominant nodules revealed that 309 (95.6%) patients had benign nodules, while 14 (4.33%) had malignant nodules. Among patients with benign nodules, microcalcifications were detected in 274 (88.7%) cases, and macrocalcifications were observed in 18 (5.8%). In the malignant group, irregular nodule margins were noted in 1 (7.1%) patient, and multinodular goiter was present in 8 (57.1%). On thyroid ultrasound imaging, 8 (57.1%) patients with malignant nodules exhibited hypoechoic nodules, and 4 (28.6%) displayed microcalcifications. The internal structure of malignant dominant nodules was heterogeneous in 10 (71.4%) cases.
Conclusion: This study examined the relationship between histological results and various nodule characteristics, including echogenicity, diameter, calcification type, edge irregularity, autoimmunity, thyroid hormone levels, and cystic content. No significant associations were identified in the analyses, including the presence of microcalcifications (p = 0.074). Broad-spectrum prospective studies with larger patient cohorts are needed to provide further insights and contribute to the existing literature.

Nodüler Guatrli Hastalarda Diferansiye Tiroid Kanserleri için Klinik Risk Faktörlerinin Tanımlanması

Tiroid Kanserlerinde Klinik Risk Faktörleri

Makale Bilgisi

Makale Geçmişi
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ÖZET

Amaç: Çalışmamızda, nodüler tiroid hastalarda diferansiye tiroid kanserleri için klinik, radyolojik ve laboratuar risk faktörlerinin değerlendirilmesi ve bu bulguların nodüllerin sitopatolojik özellikleri ile ilişkisinin saptanması amaçlanmıştır.
Gereç ve Yöntemler: Endokrinoloji Polikliniğine başvuran, muayene ile veya radyolojik tetkik sırasında tesadüfi olarak tiroid nodülü saptanan 323 hastanın demografik verileri, laboratuvar ve görüntüleme bulguları, ince iğne aspirasyon patoloji sonuçları retrospektif olarak değerlendirildi ve kaydedildi.
Bulgular: Olguların dominant nodüllerinden yapılan ince iğne aspirasyon biyopsisi sonucunda 309(%95,6) hastanın benign, 14(%4,33) hastanın ise malign nodüle sahip olduğu saptanmıştır. Benign nodüle sahip olguların 274'ünde(%88,7) mikrokalsifikasyon, 18'inde(%5,8) makrokalsifikasyon saptandı. Malign nodüllü olguların 1 (%7.1) inde nodül sınırları düzensiz, hastaların 8(%57,1) inde multinodüler guatr tespit edildi. Tiroid ultrason görüntülemesinde 82(%57,1) hastanın nodülleri hipoekoik iken 4(%28,6) hastada mikrokalsifikasyon mevcuttu. Malign dominant nodülün iç yapısı 10(%71,4) olguda heterojen izlendi.
Sonuç: Histolojik sonuçlarla nodüllerin yapısı, ekojenitesi, çapı, kalsifikasyon içeriği, kenar düzensizliği, eşlik eden otoimmunite, tiroid hormon düzeyi, kistik içeriği arasında ilişki araştırılmış ancak yapılan analizlerde ilişki saptanmamıştır. Mikrokalsifikasyon varlığı açısından tüm gruplarda anlamlı fark izlenmemiştir (p=0.074). Bu konuda literatüre katkı amaçlı daha çok hasta içeren geniş spektrumlu prospektif çalışmaların dizayn edilmesine ihtiyaç vardır.

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***Corresponding Author:** Lutfi Cetintepe,
Department of Nephrology, Karaburun State Hospital, Izmir, Türkiye.
lutficetintepe@gmail.com

Introduction

Thyroid diseases are increasingly prevalent worldwide, including in our country. Thyroid nodules are typically benign and clinically asymptomatic lesions, observed in approximately 65% of the population, largely due to advancements in diagnostic imaging methods (1). Nodular thyroid disease is a condition of the endocrine system characterized by the presence of one or more nodules within the thyroid gland, with iodine deficiency being the most common cause (2). Thyroid cancer is detected in 7–15% of all thyroid nodules (3). However, it affects only 0.1% of the population, accounting for less than 1% of all cancers (2).

Thyroid nodules are often diagnosed incidentally during physical examinations or radiologic evaluations and are usually asymptomatic. While thyroid function tests, scintigraphy, and ultrasonography provide valuable information in the clinical and diagnostic approach to thyroid nodules, these methods alone cannot reliably differentiate between benign and malignant lesions. Fine-needle aspiration biopsy (FNAB), when combined with other diagnostic tools, offers more accurate insights into the pathology of thyroid nodules. FNAB is particularly significant for the early detection of malignant nodules and for avoiding unnecessary surgical procedures for benign nodules (3).

In this study, we aimed to evaluate the clinical, radiologic, and laboratory risk factors for differentiated thyroid cancers in patients with nodular goiter and to investigate the relationship between these findings and the cytopathologic features of the nodules.

Materials and Methods

The records of 323 male and female patients aged 18–80 years, who were admitted to the Endocrinology and Metabolic Diseases Outpatient Clinic and incidentally diagnosed with thyroid nodules during examination or radiologic evaluation, were retrospectively analyzed and recorded.

Patient characteristics such as gender, age, comorbidities, and autoimmunity status were documented. Laboratory tests included the evaluation of sT3, sT4, TSH, and thyroid autoantibodies (anti-TPO, anti-Tg). Serum levels of sT3 (2.8–7.1 pmol/L), sT4 (12–22 pmol/L), and TSH (0.35–5.0 µIU/mL) were measured using the electrochemiluminescence method in the Biochemistry Laboratory. Patients with a TSH level <0.35 µIU/mL and elevated sT3 and sT4 levels were classified as having overt hyperthyroidism, while those with normal sT3 and sT4 levels were classified as having subclinical hyperthyroidism. Patients with a TSH level >5 µIU/mL were classified as having overt hypothyroidism if sT3 and sT4 levels were low, and as having subclinical hypothyroidism if sT3 and sT4 levels were within normal limits. Patients with TSH and sT4 levels within normal reference ranges were considered euthyroid.

Thyroid ultrasonography (USG) was performed using a GE-Logic 9 USG device equipped with a 12 MHz multifrequency linear probe in the Radiology or Endocrinology and Metabolic Diseases Ultrasonography Unit. Sonographic features of each nodule were recorded during

the examination.

Fine-needle aspiration biopsies (FNABs) were performed under USG guidance by specialist physicians in the Radiology Unit using 0.70 × 32 mm (25-gauge) needles, with patients positioned supine and without anesthesia. Nodules larger than 1 cm in size or smaller nodules with suspicious ultrasonographic features were biopsied. Each nodule underwent 2–4 aspirations, and biopsy materials were evaluated in the hospital's pathology laboratory.

Statistical analyses were performed using the SPSS 20.0 software package. Descriptive statistics were used for demographic data. The Student's t-test and one-way ANOVA with post-hoc tests were employed to compare continuous variables, while the Chi-square test was used for categorical variables. A p value <0.05 was considered statistically significant.

This study was approved by the local Ethics Committee and conducted in accordance with the Declaration of Helsinki. The authors declare no conflict of interest.

Results

Among the 323 patients included in the study, 283 (87.6%) were female, and 40 (12.4%) were male. The mean age of all patients was 48.16 ± 12.96 years (range: 17–84). Laboratory analysis showed a mean FT3 value of 3.17 ± 0.63 pmol/L (range: 0.9–5.93), a mean FT4 value of 1.11 ± 0.19 pmol/L (range: 0.41–2.13), and a mean TSH value of 2.51 ± 7.24 µIU/mL. Patients with TSH levels <0.35 µIU/mL were classified as hyperthyroid, with a total of 48 (14.9%) cases in this group. TSH levels >5 µIU/mL were considered indicative of hypothyroidism, with 26 (8%) cases in this group. The remaining 249 (77.1%) patients, whose TSH and thyroid hormone levels fell within reference ranges, were classified as euthyroid (Table 1).

Thyroid ultrasound (USG) of the 323 patients revealed multinodular goiter (MNG) in 198 (61.3%) cases and a solitary nodule in 125 (38.7%) cases. The mean diameter of the dominant nodule was 19.14 mm (range: 6–70 mm). Autoimmune thyroiditis was not detected in 274 (84.8%) cases but was present in 49 (15.2%) cases. The borders of the nodules were regular in 283 (87.6%) cases and irregular in 40 (12.4%) cases. Regarding echogenicity, 167 (51.7%) nodules were isoechoic, 139 (43%) were hypoechoic, and 17 (5.3%) were hyperechoic. Microcalcifications were present in 39 (12.1%) nodules, while the remaining 284 (87.9%) nodules lacked microcalcifications. Macrocalcifications were observed in 19 (5.9%) nodules. Cystic content was detected in 91 (28.2%) nodules, with one case (0.3%) exhibiting purely cystic content.

Fine-needle aspiration biopsy (FNAB) of the dominant nodules revealed 309 (95.6%) benign cases and 14 (4.33%) malignant cases. The mean age of patients with benign nodules was 48.08 years, with 270 (87.4%) females and 39 (12.6%) males. Among these patients, 240 (77.7%) were euthyroid, 25 (8.1%) were hypothyroid, and 44 (14.2%) were hyperthyroid. MNG was found in 190 (61.5%) cases, while solitary nodules were observed in 119 (38.5%) cases. The dominant nodule was

located in the isthmus in 6 (1.9%) cases, the right lobe in 185 (59.9%) cases, and the left lobe in 118 (38.2%) cases. Autoimmune thyroiditis accompanied 48 (15.5%) cases of benign nodular goiter. Among benign nodules, 161 (52.1%) were isoechoic, 131 (42.4%) were hypoechoic, and 17 (5.5%) were hyperechoic. Microcalcifications were present in 35 (11.3%) cases, while macrocalcifications were detected in 18 (5.8%) cases. Cystic content was identified in 88 (28.5%) benign nodules, with heterogeneous internal structures observed in 176 (57%) cases and homogeneous structures in 133 (43%) cases.

In the malignant group, the mean age of the 14 patients was 49.92 years, with 13 (92.9%) females and 1 (7.1%) male. Among these patients, 9 (64.3%) were euthyroid, 1 (7.1%) was hypothyroid, and 4 (28.6%) were hyperthyroid. MNG was found in 8 (57.1%) cases, and solitary nodules in 6 (42.9%) cases. The dominant nodule was located in the right lobe in 10 (71.4%) cases and the left lobe in 4 (28.6%) cases. Autoimmune thyroiditis accompanied 1 (7.1%) case with malignant nodular goiter. Regarding nodule borders, 13 (92.9%) had regular borders, while 1 (7.1%) had irregular borders. Among malignant nodules, 6 (42.9%) were isoechoic, 8 (57.1%) were hypoechoic, and none were hyperechoic. Microcalcifications were present in 4 (28.6%) cases, while macrocalcifications were observed in 1 (7.1%) case. Cystic content was identified in 3 (21.4%) malignant nodules, and the internal structure was heterogeneous in 10 (71.4%) cases and homogeneous in 4 (28.6%) cases (Tables 2 and 3).

FNAB results revealed 5 (1.54%) cases with follicular lesions, 10 (3.09%) with suspicious cytology, and 7 (2.16%) with malignant cytology. In 301 (93.18%) cases, FNAB reported benign results; cases with insufficient material were excluded from the study (Table 4).

Among the 323 patients, 25 (7.73%) underwent surgery. Pathological examination of the surgical material revealed malignancy in 14 (4.33%) cases and benign results in 11 (3.40%) cases. Of the malignant cases, 12 (3.71%) were papillary thyroid carcinomas, and 2 (0.61%) were follicular thyroid carcinomas.

The relationship between histological results and nodule characteristics, including structure, echogenicity, diameter, calcification content, edge irregularity, autoimmunity, TSH level, and cystic content, was analyzed. However, no significant associations were found, including the presence of microcalcifications ($p = 0.074$).

Discussion

Nodular thyroid disease is the most common endocrine pathology and continues to rise rapidly. Studies have shown that 4–7% of thyroid nodules can be detected by careful physical examination in the general population (4). The introduction of thyroid ultrasonography (USG) into clinical practice has enabled the detection of nodules that were previously undetectable during physical examination. It has been reported that the prevalence of thyroid nodules in the general population ranges from 30–50%, with 5–6.5%

of these nodules being malignant when evaluated by USG (5). In our study, the frequency of malignancy among all thyroid nodules was found to be 4.33%, consistent with the literature.

Although factors such as medical history, age, gender, radiation exposure, and family history are useful in evaluating thyroid nodules, there are no definitive ultrasonographic or scintigraphic markers for distinguishing malignant thyroid nodules. Fine-needle aspiration biopsy (FNAB) is crucial due to its simplicity, low complication rate, cost-effectiveness, and ability to provide cellular-level information. By distinguishing benign from malignant nodules, FNAB helps prevent unnecessary surgical interventions and guides surgical techniques.

Similar to nodular thyroid diseases, thyroid cancers are 3–4 times more common in females than males (6). In our study, 283 cases (87.6%) were female, and 40 cases (12.4%) were male, with a female-to-male ratio of 7:1. Of the 14 cancer cases, 13 (92.9%) were female, and 1 (7.1%) was male. Studies by El-Gammal et al. and Witczak et al. similarly found malignant nodules to be more common in female patients (7, 8). However, other studies have suggested that malignant thyroid nodules are more prevalent in males and individuals over 45 years of age (9). In our study, while malignant nodules were more common in females, no significant correlation was observed with age.

In our patient group, no correlation was found between nodule size and TSH levels or between elevated TSH levels and malignancy. Most patients, regardless of whether they had benign or malignant nodules, were euthyroid, consistent with the literature (10).

FNAB results were categorized as benign (e.g., regressive changes, nodular hyperplasia, colloidal goiter), suspicious, or malignant (e.g., papillary carcinoma, follicular carcinoma). In a 2020 study by Al-Hakami et al., papillary thyroid carcinoma accounted for 85% of all thyroid malignancies, a finding consistent with our study (11). Nodules with suspicious cytology carry a high risk of malignancy (12, 13). For example, Hamad Ahmed et al. reported malignancy in 33.3% of 81 suspicious specimens, 21% of which were compatible with papillary carcinoma (14). Similarly, Maighan A. Seagrove-Guffey et al. found a 33% malignancy rate in patients with suspicious cytology in a study of 893 patients (15). In our study, 12 cases were diagnosed with papillary carcinoma and 2 with follicular carcinoma among nodules classified as malignant or suspicious. In addition, malignancy was found in 50% of operated cases with suspicious cytology, a rate similar to the literature. Suspicious nodules should therefore be surgically removed.

The increasing use of USG has made it essential for radiologists and clinicians to identify features suggestive of malignancy in thyroid nodules. Many USG findings, such as nodule size, internal structure (solid/cystic), echogenicity, vascularity, margins, hypoechoic halos, and the presence of microcalcifications, have been studied to differentiate benign from malignant nodules. These studies aim to determine which nodules should undergo further evaluation via biopsy, thus reducing unnecessary procedures for

benign nodules.

Most studies have not demonstrated a significant relationship between nodule size and malignancy. However, nodule size remains important for clinicians in deciding on follow-up, biopsy, or surgery. Nodules ≥10 mm require careful evaluation, and nodules with an anteroposterior-to-transverse diameter ratio >1 are considered more likely to be malignant (16). In our study, there was no statistically significant association between nodule size and malignancy (p = 0.24).

Hypoechogenicity is considered more suggestive of malignancy compared to iso- or hyperechogenicity. Jeh et al. reported high rates of hypoechogenicity in papillary cancers (72%) but lower rates in follicular cancers (35%), attributing this to lower intra-nodular colloid levels in follicular cancers (17). In our study, 42.4% of benign nodules and 57.1% of malignant nodules were hypoechoic, while no hyperechoic nodules were found in the malignant group. However, no statistically significant relationship was observed between echogenicity and malignancy (p = 0.43).

Numerous studies have established a strong association between microcalcifications and malignancy. For instance, Serdal Uğurlu et al. identified microcalcifications as a critical predictor of malignancy in a study of 1004 cases (10). Similarly, Carlo Capelli et al. reported higher microcalcification rates in malignant nodules compared to benign ones (18). In our study, microcalcifications were found in 28.6% of malignant nodules and 11.3% of benign nodules. Although this difference did not reach statistical significance (p = 0.074), one-way regression analysis indicated that the presence of microcalcifications increased the likelihood of malignancy 3.285-fold (p = 0.059, CI 0.955–11.303). While not statistically significant, this finding may still hold clinical relevance.

Conclusion

In conclusion, the relationship between histological results and nodule structure, echogenicity, diameter, calcification content, margin irregularity, autoimmunity, thyroid hormone levels, and cystic content was investigated, but no significant associations were found. Broad-spectrum prospective studies with larger patient cohorts are required to further contribute to the literature.

Limitations

The main limitation of our study is its relatively small sample size. Additionally, as a retrospective file review, the study had access to limited patient data. Larger prospective studies are needed to provide more robust and meaningful subgroup analyses.

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Ethics Approval: This study was approved by the local Ethics Committee and conducted in accordance with the Declaration of Helsinki (23.06.2010/4/3).

Author contributions
Concept: L.C, S.E.
Design: L.C, S.E.
Supervision: İ.E.G.
Resources: İ.E.G.
Data Collection and Procesing: T.C, L.C.
Analysis and Interpretation: T.C, S.E, B.A .
Literature Search: T.C, S.E, B.A .
Writing Manuscript: L.C, S.E.
Critical Review: T.C, S.E, B.A .

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Table 1. Laboratory results

Laboratory Result	Figure
Euthyroid	249 (77.1%)
Hypothyroidism	26 (8%)
Hypertrophy	48 (14.9%)

Table 2. Distribution of nodules

Conclusion	Figure
Benign	309 (95.6%)
Malignant	14 (4.33%)

Table 3. Distribution of benign and malignant nodules according to USG features

Result	Hypothyroid	Irregular outlines	Microcalcification
Benign	25(8.1%)	39 (12.6%)	35 (11.3%)
Malignant	1(7.1%)	1 (7.1%)	4 (28.6%)

Table 4. Distribution of FNAB results

FNAB result	Figure
Benign	301(93.18%)
Suspicious	10 (3.09%)
Malignant	7 (2.16%)
Follicular lesion	5 (1.54%)