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Investigation of pre-operative demographic, biochemical, sonographic and cytopathological findings in low-risk thyroid neoplasms

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Abstract

Objective: The present article analyses pre-operative demographic, biochemical, sonographic and histopathological characteristics of low-risk thyroid neoplasms (LRTNs), with a focus on four subgroups, "well-differentiated carcinoma-not otherwise specified" (WDC-NOS), "non-invasive follicular thyroid neoplasm with papillary like nuclear features" (NIFTP), "well-differentiated tumours of uncertain malignant potential" (WDT-UMP) and "follicular tumour of uncertain malignant potential" (FT-UMP).

Methods: The study retrospectively analyzed the histopathology of 2453 malignant thyroids and the final analyses included 99 cases diagnosed with LRTNs. The demographic and clinical features, pre-operative thyroid function, ultrasonography results, cytopathology results, histopathology results and prognostic classifications were assessed.

Results: The groups were similar demographic characteristics and the majority of clinical data, including comorbidities, thyroid function tests, thyroid cancer/neck radiotherapy history. NIFTPs represented 69.7% of all LRTNs. All (100%) WDT-UMPs had solitary nodules. Index nodule volume differed among the groups ($p = .036$), it was the lowest in WDC-NOS [0.68 (0.63–0.72 cc)] and highest in FT-UMP [12.6 (0.5–64 cc)]. Echogenicity findings were similar. Index nodule TIRADS demonstrated a significant difference ($p = .021$) but index nodule halo sign and BETHESDA scores were similar in all groups. The diameter, localisation and multicentric structure of LRTNs were again similar for all groups. Finally, prognostic scores suggested similar outcomes in all groups.

Conclusion: The majority of LRTNs were NIFTPs in our population and all WDT-UMPs were solitary lesions. Index nodule volume was the most essential discriminating sonographic finding but further research must be performed before discriminatory potential can be described.

Level-III, Retrospective Observational Study.

KEYWORDS
follicular tumour of uncertain malignant potential, low-risk thyroid neoplasms, non-invasive follicular thyroid neoplasm with papillary-like nuclear features, well-differentiated carcinoma-not otherwise specified, well-differentiated tumours of uncertain malignant potential

1 | INTRODUCTION

Thyroid nodules and tumours are common clinical problems encountered by endocrinologists and pathologists worldwide.[1] These thyroid lesions range from benign to malignant, with varying degrees of clinical significance and potential for progression.[2] The diagnostic evaluation and management of thyroid nodules and tumours have evolved significantly in recent years, with a greater emphasis on molecular testing to guide clinical decision-making.[3] Despite the advances, there are still challenges in accurately understanding thyroid nodules and tumours.

There is increasing recognition of borderline thyroid tumours, which have features of both benign and malignant lesions and pose challenges in diagnosis, treatment and clinical management.[2,4] These tumours are characterised by histological features that fall between benign and malignant categories, making it difficult to classify them as either.[5] This subset of thyroid nodules is classified as "low-risk thyroid neoplasms" (LRTNs) due to the lack of definitive evidence of invasive growth or metastatic potential.[6]

Although LRTNs have been described for several decades, their clinical and histopathological characteristics and optimal management are still topics of research.[7] Recent studies have shed light on the molecular mechanisms and genetic alterations of these tumours, leading to better understanding of their pathogenesis, potentially improving diagnostic accuracy and patient outcomes. The development of new diagnostic tools, such as molecular testing and imaging modalities, has provided additional options for managing these challenging lesions.[8] Given the variability of LRTN, a multidisciplinary approach involving pathologists, surgeons and endocrinologists is necessary for proper management.[6]

The present study aimed to analyze the demographic, clinical, laboratory, imaging and histopathological characteristics of LRTNs, defined as "well-differentiated carcinoma-not otherwise specified" (WDC-NOS), "non-invasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP), "well-differentiated tumours of uncertain malignant potential" (WDT-UMP) and "follicular tumour of uncertain malignant potential" (FT-UMP).

2 | MATERIALS AND METHODS

2.1 | Study design

The present study was conducted in Ankara Bilkent City Hospital from March 2019 to February 2021 and retrospectively reviewed 2453 patients with malignant thyroid histopathology for the potential for inclusion in the analyses. Approval was received from the Institutional Ethics Committee (Date: October 2021: Approval ID: E1-21-2063) and informed consent was waived due to the retrospective design. All steps of the study were conducted with respect to the Helsinki Declaration. Participants' demographic features, pre-operative thyroid functions, autoantibodies, Ultrasonography (USG) findings and fine-needle aspiration biopsy (FNAB) results were drawn from electronic databases and compared between the subgroups (NIFTP, WDC-NOS, WDT-UMP and FT-UMP).

2.2 | Participants

After all cases who underwent thyroidectomy were analyzed, we included 99 patients diagnosed with LRTN in the study. Sixty-nine were evaluated as NIFTP, 3 as WDC-NOS, 17 as WDT-UMP and 10 as FT-UMP. The diagnosis of NIFTP in this study is based on revised diagnostic criteria published in 2018.[3] These criteria consist of primary and secondary criteria. While primary criteria are indispensable, secondary criteria are not obligatory but are helpful in diagnosis. The primary criteria are as follows: Encapsulation or clear demarcation, follicular growth pattern with (no well-formed papillae, no psammoma bodies, <30% solid/trabecular/insular growth pattern), nuclear score 2–3, no vascular or capsular invasion, no tumour necrosis or high mitotic activity (<3 mitoses per 10 high-power fields) and the secondary criteria are as follows: lack of BRAF V600E mutation detected by molecular assays or immunohistochemistry, lack of BRAF V600E-like mutations or other high-risk mutations (TERT, TP53). In our study, DNA was obtained with DNA FFPE isolation kit and using Diatech EasyPGX EGFR kit, in real time PCR study with positive and negative controls, mutation in both BRAF (BRAF V600E/K/D/R) gene RAS (NRAS codon 12–13, 59–61, 61, 117 and 146) gene were studied in 6 of 69 patients with NIFTP and isolated mutation in the BRAF gene was studied in one patient. No mutation investigation was required as molecular method in other patients. Participants with insufficient clinical data or histopathological reports, those with other variants of papillary thyroid cancers, tumour diameter ≤2 mm of NIFTP, follicular thyroid carcinoma, medullary thyroid carcinoma or poorly differentiated thyroid carcinoma were excluded. Thyroid USG was performed by the same endocrinologist using a routine ultrasound device (Toshiba Aplio 500).

2.3 | Diagnosis and data collection

Fine needle aspiration biopsy (FNAB) had been performed in all patients and histopathology analyses had been carried out by

experienced pathologists in a routine setting. Multiple biopsies were performed in some patients in some thyroid nodule groups because the initial FNAB was BETHESDA classification I or III. In these patients, re-biopsy was performed after 3 months. The pathology department evaluated individual types of nodules from the post-operative samples or pre-operative FNAB-cytopathology. During the study, histopathological specimens of patients with LRTNs were re-evaluated by a different group of experienced pathologists and all cases included in the study ultimately received the same diagnosis. Prognostic assessment systems were used to evaluate patients' prognosis. These included the TNM, STAGE, AMES and MACIS scores/classifications.

2.4 | Laboratory analyses

A Mindray-BC6400 autoanalyzer was used for complete blood counts. Biochemical results, thyroid hormones and thyroid-related antibodies were analyzed by the same biochemistry autoanalyzer (Siemens ADVIA-2400 biochemistry-analyzer/CENTAUR-XPT device) with the original kits. Hematological and thyroid parameters were analyzed within 1 h after blood withdrawal. All whole blood samples were drawn on the morning of the second day of hospitalisation into routine sampling tubes after 8 h of fasting.

2.5 | Statistical analysis

All data, including demographics, thyroid function tests, clinical findings and other analyses were collected and entered into a data base created with the IBMSPSS v24 software. The GraphPad Prism v9.4.3 software was used to draw scatter plots or column bar graphs. Categorical data were summarised as frequency and percentage (after analyzing between groups with Chi-square tests), while continuous data were expressed as mean ± standard deviation. We used the Kruskal–Wallis H if continuous data were distributed abnormally (pre-operative thyroid nodule count, index nodule volume and the anterior-posterior diameter/transverse diameter (AP/T; for the index nodule) values; whereas, the one-way analysis of variance test was used to compare continuous variables with normal distribution (age, free T_3 and free T_4). The present study accepted a p value of <.05 as the significance threshold.

3 | RESULTS

Analysis of demographic data showed that all groups were similar in terms of age ($p = .892$) and sex distribution ($p = .178$). Similarly, there were no differences between the groups in terms of systemic disease ($p = .801$), thyroid cancer history ($p = .565$), neck radiotherapy history ($p = .932$), thyroid parenchyma findings ($p = .522$), thyroid volume ($p = .223$) or thyroid function status ($p = .772$). The majority of comparisons concerning laboratory findings also demonstrated non-significant results, including free T3 ($p = .356$), free T4 ($p = .437$), TSH ($p = .099$), thyroglobulin ($p = .845$), Anti-TPO ($p = .248$), and calcitonin >2 pg/mL ($p = .147$), the exception being Anti-TG values ($p = .021$) (Table 1).

The average pre-operative thyroid nodule count was similar for all the groups ($p = .343$). In the NIFTP group, the frequency of having multiple thyroid nodules was higher compared to single nodules [61 (88.4%) vs. 8 (11.6%)]. While all 3 cases had multiple thyroid nodules in the WDC-NOS group, in the FT-UMP group ($n = 10$), half of the patients had solitary nodules while the other half had multiple nodules. In WDT-UMP ($n = 17$), all nodules were solitary. There was no significant difference between the groups in terms of solitary or multiple nodule presence ($p = .375$) (Table 2).

Index nodule volume demonstrated a significant difference between the groups ($p = .036$). The lowest value was in patients with WDC-NOS [0.68 (0.63–0.72 cc)], while the highest value was in the FT-UMP group [12.6 (0.5–64 cc)]. Index nodule AP/T values were similar in all groups ($p = .394$). Isoechoic and iso-hypoechoic echogenicity were the most commonly recorded echogenicity findings in all groups and no significant differences were noted ($p = .128$). Calcification of the index nodule was seen in 8 of the 69 NIFTP patients and in 3 of the 17 WDT-UMP patients while this feature was entirely absent in the WDC-NOS and FT-UMP groups ($p = .608$). There was a significant difference between the groups in terms of index nodule TIRADS result ($p = .021$), but index nodule halo sign did not differ groups ($p = .402$). In terms of localisation, the most common were the right (54.5%), inferior (35.3%) and posterior (55.2%).

BETHESDA scoring showed similar results in all groups. The diameter ($p = .832$), localisation ($p = .981$) and multicentric structure ($p = .314$) of LRTNs were similar for all the groups. Side of thyroidectomy ($p = .197$), frequency of complementary thyroidectomy ($p = .021$), PTC presentation ($p = .514$), localisation ($p = .667$) and PTC diameter ($p = .193$) did not significantly differ among the groups. While history of RAI treatment was present in all 3 cases in the WDC-NOS group, the next highest frequency was in the WDT-UMP group (41.2%) ($p = .028$) (Table 3).

As shared in Table 4, the results from the prognostic classification systems were similar in all groups, including the TNM ($p = .462$), STAGE ($p = .712$), AMES ($p = .069$), and MACIS ($p = .887$).

4 | DISCUSSION

The present study evaluated LRTNs, which are rare and difficult to distinguish histopathologically, by dividing them into four borderline groups. Demographic, laboratory, pre-operative sonographic and cytopathological comparison of these subgroups can provide crucial information about LRTNs, strengthen the ability to distinguish these rare diseases, and help to analyze these borderline diseases.

In recent analyses of thyroid masses, well-circumscribed masses with encapsulation and extensive growth were reported by investigators as essential indicators of a favourable prognosis for thyroid

TABLE 1 Demographical features and laboratory data of low-risk thyroid neoplasms.

Variables	NIFTP (*n*: 69)	WDC-NOS (*n*: 3)	FT-UMP (*n*: 10)	WDT-UMP (*n*: 17)	*p* value
Age, year	45 (22–61)	45 (38–51)	47 (35–58)	47 (34–57)	.892
Gender					
Male	14 (20.3)	1 (33.3)	4 (40)	1 (5.9)	.178
Female	55 (79.7)	2 (66.7)	6 (60)	16 (94.1)	
Systemic disease					
No	45 (65.2)	2 (66.7)	6 (60)	13 (76.5)	.801
Yes	24 (34.8)	1 (33.3)	4 (40)	4 (23.5)	
Thyroid cancer history					
No	61 (88.4)	3 (100)	10 (100)	16 (94.1)	.565
Yes	8 (11.6)	0	0	1 (5.9)	
Neck radiotherapy					
No	68 (98.6)	3 (100)	10 (100)	17 (100)	.932
Yes	1 (1.4)	0	0	0	
Thyroid parenchyma					
Heterogenic	66 (95.6)	3 (100)	9 (90)	17 (100)	.522
Homogenic	3 (4.4)	0	1 (10)	0	
Thyroid function status					
Hyperthyroid	11 (15.9)	1 (33.3)	2 (20)	3 (17.7)	.772
Hypothyroid	8 (11.5)	0	3 (30)	4 (22.6)	
Euthyroid	50 (72.4)	2 (66.7)	5 (50)	10 (59.7)	
Thyroid volume, cc	29.2 ± 29.7	83.5 ± 8.41	26.4 ± 28.2	27.7 ± 22.9	.223
Free T_3, pg/mL	3.2 ± 0.49	3.6±	3.24 ± 0.51	3.02 ± 0.47	.356
Free T_4, pg/mL	1.14 ± 0.17	1.12 ± 0.06	1.02 ± 0.21	1.13 ± 0.2	.437
TSH, µIU/mL	1.76 ± 1.61	2.74 ± 1.33	3.6 ± 2.07	3.07 ± 4.4	.099
Thyroglobulin, ng/mL	437 ± 1014	–	704 ± 1129	1200 ± 1423	.845
Anti-TG, IU/mL	21 (1–71)	13 (10–15)	28 (11–41)	76 (1–122)	.021
Anti-TPO, IU/mL	665 ± 3125	14.7 ± 11.6	333 ± 383.2	538 ± 915.6	.248
Calcitonin					
Normal	61 (88.4)	2 (66.7)	10 (100)	17 (100)	.147
High	8 (11.6)	1 (33.3)	0	0	

Note: In group comparison; age, free T3 and free T4 were analyzed with ANOVA, while other continuous data were analyzed with the Kruskal–Wallis H test. The Chi-square test analyzed categorical data. Continuous data are given as mean ± standard deviation or median (range), while categorical are given as frequency (percentage).

Abbreviations: ANOVA, analysis of variance; Anti-TG, anti-thyroglobulin; Anti-TPO, anti-thyroid peroxidase; FT-UMP, follicular tumour of uncertain malignant potential; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; TSH, thyroid stimulating hormone, T3, Triiodotironin; T4, ve Tiroxin; WDC-NOS, well differentiated carcinoma-not otherwise specified; WDT-UMP, well-differentiated tumours of uncertain malignant potential.

carcinoma.[9,10] In the thyroid follicular cell tumour classification by Kakudo et al.,[6] the scope of borderline tumours included encapsulated tumours (WDT-UMP and FT-UMP). Liu et al.[11] reported the incidence of WDT-UMP as 1.1% (30/2648), while Hofman et al.[12] reported the frequency as 1.5% (16/1078). A study by Piana et al.[10] reported 0.5% (5/1009 cases). In our population ($n = 2453$), frequencies were 0.4% ($n = 10$) for FT-UMP and 0.7% for ($n = 17$) for WDT-UMP. Of note, all WDT-UMP cases presented with solitary nodular findings and index nodule volume was a notable difference compared to other LRTNs. This difference may have allowed WDT-UMP nodules to encompass most of the lobe, possibly contributing to the differences in localisation. According to Kakudo et al.,[6] a new

TABLE 2 Preoperative sonographic findings.

Variables	NIFTP (*n*: 69)	WDC-NOS (*n*: 3)	FT-UMP (*n*: 10)	WDT-UMP (*n*: 17)	*p* value
Pre-operative thyroid nodule number, average	4.7 ± 2.1	4.5 ± 1.6	4.5 ± 0.7	3.8 ± 1.8	.343
Thyroid nodule					
STN	8 (11.6)	0	5 (50)	17 (100)	.375
MTN	61 (88.4)	3 (100)	5 (50)	0	
Index nodule volume, cc	1.7 (0–80)	0.68 (0.63–0.72)	12.6 (0.5–64)	4 (0.6–55.9)	.036
Index nodule AP/T	0.72 ± 0.23	0.75 ± 0.25	0.85 ± 0.23	0.76 ± 0.32	.394
Index nodule localisation (1)					
Right	39 (56.5)	1 (33.3)	6 (60)	8 (47.1)	.74
Left	27 (39.1)	1 (33.3)	3 (30)	9 (52.9)	
İsthmus	3 (4.3)	1 (33.3)	1 (10)	0	
Index nodule localisation (2)					
Superior	7 (10.1)	0	0	1 (5.9)	.356
Middle	22 (31.9)	1 (33.3)	5 (50)	5 (29.4)	
İnferior	27 (39.1)	1 (33.3)	4 (40)	3 (17.6)	
Completely	13 (18.8)	1 (33.3)	1 (10)	8 (47.1)	
Index nodule localisation (3)					
Anterior	25 (44.6)	1 (50)	2 (22)	7 (77)	.244
Middle	4 (7.1)	0	2 (22)	1 (11.1)	
Posterior	27 (48.2)	1 (50)	5 (52)	1 (11.1)	
Index nodule echogenicity					
Anechoic	3 (4.3)	0	0	0	.128
Hypoechoic	9 (13)	1 (33.3)	1 (10)	1 (5.9)	
Hyperechoic	1 (1.4)	1 (33.3)	0	0	
Isoechoic	41 (59.4)	0	7 (70)	12 (70.6)	
Iso-hypoechoic	14 (20.3)	1 (33.3)	2 (20)	4 (23.5)	
Mixed	1 (1.4)	0	0	0	
Index nodule calcification					
No	61 (88.4)	3 (100)	10 (100)	14 (82.4)	.608
Macro	3 (4.3)	0	0	3 (17.6)	
Micro	5 (7.2)	0	0	0	
Index nodule Halo sign					
No	50 (72.5)	3 (100)	8 (80)	15 (88.2)	.402
Yes	19 (27.5)	0	2 (20)	2 (11.8)	
Index nodule TIRADS					
1	0	1 (33.3)	1 (10)	4 (23.5)	.021
2	3 (4.3)	2 (66.7)	0	0	
3	43 (62.3)	0	7 (70)	8 (47.1)	
4	16 (23.2)	0	2 (20)	4 (23.5)	
5	7 (10.1)	0	0	1 (5.9)	

Note: In group comparison, index nodule volume and index nodule AP/T were analyzed the Kruskal–Wallis H test. The Chi-square test analyzed categorical data. Continuous data are given as mean ± standard deviation or median (range), while categorical data are given as frequency (percentage).

Abbreviations: Anti-TG, anti-thyroglobulin; Anti-TPO, anti-thyroid peroxidase; FT-UMP, follicular tumour of uncertain malignant potential; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; TSH, thyroid stimulating hormone, T3, Triiodotironin; T4, ve Tiroxin; WDC-NOS, well differentiated carcinoma-not otherwise specified; WDT-UMP, well-differentiated tumours of uncertain malignant potential.

TABLE 3 Analysis of fine needle aspiration biopsy and histopathology results.

Variables	NIFTP (*n*: 69)	WDC-NOS (*n*: 3)	FT-UMP (*n*: 10)	WDT-UMP (*n*: 17)	*p* value
Index nodule BETHESDA[a]					
1	33 (33.0)	2 (66.7)	5 (31)	5 (29.4)	.638
2	5 (5.0)	0	2 (12.5)	2 (11.8)	
3	40 (40.0)	1 (33.3)	7 (44)	7 (41.2)	
4	9 (9.0)	0	2 (12.5)	2 (11.8)	
5	9 (9.0)	0	0	1 (5.9)	
6	4 (4.0)	0	0	0	
Side of TDx					
Right TDx	8 (11.5)	1 (33.3)	2 (20)	2 (11.7)	.197
Left TDx	5 (7.25)	0	2 (20)	3 (17.6)	
Total TDx	56 (81.1)	2 (66.6)	6 (60)	12 (70.5)	
Complementary thyroidectomy	4 (5.8)	1 (33.3)	2 (20)	2 (11.7)	.201
LRTNs diameter, *mm*	16 (2–85)	19 (4–54)	24 (3–20)	17 (3–58)	.832
LRTNs localisation					
Right	36 (52.2)	3 (100)	6 (60)	6 (35.3)	.981
Left	24 (34.8)	1 (33.3)	3 (30)	10 (58.8)	
İsthmus	9 (13)	0	1 (10)	1 (5.9)	
Multicentric					
No	48 (69.6)	2 (66.7)	9 (90)	15 (88.2)	.314
Yes	21 (30.4)	1 (33.3)	1 (10)	2 (11.8)	
PTC present					
Yes	27 (39.1)	1 (33.3)	2 (20)	4 (23.5)	.514
No	42 (60.9)	2 (66.7)	8 (80)	13 (76.5)	
PTC localisation					
Right	17 (24.6)	0	1 (10)	3 (17.6)	.667
Left	7 (10.1)	2 (66.7)	0	2 (11.8)	
İsthmus	3 (4.3)	0	1 (10)	0	
PTC diameter, mm	4 (1–30)	5 (5–5)	9 (4–15)	9.5 (7–30)	.193
RAI treatment					
No	52 (75.4)	0	6 (60)	10 (58.8)	.028
Yes	17 (24.6)	3 (100)	4 (40)	7 (41.2)	

Note: In group comparison, LRTNs and PTC Diameter were analyzed with the Kruskal–Wallis H test. The Chi-square test was used to analyze categorical data. Continuous data are given as mean ± standard deviation or median (range), while categorical data are given as frequency (percentage).

Abbreviations: FT-UMP, follicular tumour of uncertain malignant potential; LRTN, low-risk thyroid neoplasms; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; TDx, thyroidectomy; WDC-NOS, well differentiated carcinoma-not otherwise specified; WDT-UMP, well-differentiated tumours of uncertain malignant potential.

[a]In some cases, more than one biopsy may be taken.

terminology to replace the cancer terminology for this lesion was NIFTP.[13] After further evidence, the World Health Organisation (WHO) added UMP and NIFTP as subsections to other encapsulated follicular pattern thyroid tumours.[14] In our analysis, the general incidence of NIFTP was 2.8% (69/2453) and it was the primary neoplasm in the LRTN (70%, 69/99). The presence of sonographically-detected microcalcification resembles psammoma in PTC; therefore, it was interesting to detect this feature in NIFTPs. Nonetheless, potential presence of simultaneous PTC can explain this situation.

TABLE 4 AMES, MACIS and TNM prognostic classification in low-risk thyroid neoplasm.

Variables	NIFTP (*n*: 69)	WDC-NOS (*n*: 3)	FT-UMP (*n*: 10)	WDT-UMP (*n*: 17)	*p* value
TNM					
T1a(m)N_0M_0	8 (11.6)	0	2 (20)	1 (5.9)	.462
T1a(s)N_0M_0	17 (24.6)	0	2 (20)	2 (11.8)	
T1b(m)N0M_0	5 (7.2)	0	0	1 (5.9)	
T1b(s)N_0M_0	14 (20.3)	0	2 (20)	7 (41.2)	
T1b(s)$N_{1b}M_1$	1 (1.4)	0	0	0	
T2(m)N_0M_0	3 (4.3)	1 (33.3)	1 (10)	0	
T2(s)N_0M_0	11 (15.9)	1 (33.3)	1 (10)	4 (23.5)	
T3a(s)N_0M_0	8 (11.6)	1 (33.3)	2 (20)	2 (11.8)	
T3a(m)N_0M_0	2 (2.9)	0	0	0	
STAGE					
1	66 (95.7)	3 (100)	9 (90)	16 (94.1)	.712
2	2 (2.9)	0	1 (10)	1 (5.9)	
3	0	0	0	0	
4	1 (1.4)	0	0	0	
AMES					
Low risk	67 (97.1)	2 (66.6)	10 (100)	16 (94.1)	.069
High risk	2 (2.9)	1 (33.3)	0	1 (5.9)	
MACIS	4.5 (3.2–10.7)	4.5 (3.9–5.7)	4.4 (3.7–5.9)	4.2 (3.5–6.2)	.887

Note: In group comparison: MACIS score was analyzed with the Kruskal–Wallis test, while the Chi-square test was used to analyze categorical data. Continuous data are given as mean ± standard deviation or median (range), while categorical data are given as frequency (percentage).

Abbreviations: FT-UMP, follicular tumour of uncertain malignant potential; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; WDC-NOS, well differentiated carcinoma-not otherwise specified; WDT-UMP, well-differentiated tumours of uncertain malignant potential.

High anti-Tg levels and the heterogeneity of the thyroid parenchyma on pre-operative USG in WDT-UMP suggest the presence of chronic autoimmune thyroiditis. Additionally, although pre-operative thyroid volumes were similar in all four subgroups, index nodule volume was observed to be relatively greater in the WDT-UMP group. Most of the index nodules in the NIFTP, FT-UMP and WDT-UMP were isoechoic in echogenicity and did not contain microcalcifications. Therefore, these nodules were classified as TIRADS 3. LRTNs are expected to demonstrate low-risk findings when assessed via USG. In this context, most index nodules in had a mean AP/T value o f<1, which is characteristic of benign thyroid nodules. The majority of index nodules were either BETHESDAI or III. However, there were nine cases of BETHESDA-V and four cases of BETHESDA-VI in the NIFTP group, suggesting that pre-operative malignancy predictivity may be more effective in this subset of patients compared to the other subgroups.

Since a significant portion of newly-diagnosed cases are LRTNs with relatively lower risk, it would be reasonable to apply a different approach to these patients. This can be summarised as reducing the utilisation of surgery and RAI in favour of close follow-up. There is already a trend showing reduced use of RAI, mostly due to the increase in surgically-cured patients as a result of early diagnosis. Related to this issue, the study by Canini et al.[15] enroled 68 NIFTPs. In 41 of these cases (60.1%), similar to our results, multinodular background was observed. The diagnosis was incidental in 12 cases and the pre-operative FNAB was performed on a different target. They did not observe any recurrence or disease progression in radioiodine-treated NIFTPs.[15] Xu et al.[16] reported no disease recurrence detected in 37 patients who did not receive RAI therapy with NIFTP and had nodules of over 4 cm in size. NIFTPs with a diameter greater than 4 cm are also characterised by having an indolent course after surgical treatment alone which can, therefore, be the treatment of choice without the need for radioiodine administration. In our analyses, there were 17 cases in the NIFTP, three cases in the WDC-NOS, four cases in the FT-UMP and 7 cases in the WDT-UMP groups which we treated with RAI.

The diameter (p = .832) of LRTNs was similar for all the groups. However, I want to draw attention to an important point that NIFTP cases over 2 mm were included in our study. Because it's almost impossible to be certain that tumours ≤2 mm are non-invasive and

have <1% true papilla. Therefore, NIFTP cannot be diagnosed in tumours ≤2 mm.[17,18]

TNM staging, which illustrates an association between mortality and nodal spread, is widely assessed to classify disease stage.[19] In thyroid staging, TNM also considers patient age.[20] Another system that endocrinologists widely prefer is the MACIS evaluation system,[21] described by the Mayo Clinic. It divides thyroid patients into four prognostic categories and calculates their scores. AMES assesses the curability potential of primary tumour resection and distant metastasis.[22] It can distinguish high-risk patients from low-risk patients because it defines mortality-related risk. In the present research, we evaluated these prognostic systems for LRTNs; however, all groups were similar in terms of prognostic results. Despite being an expected result due to the well-established variations in the degree of clinical significance in LRTNs, our findings also show that these scoring systems cannot differentiate between LRTN subgroups.

The present study had limitations that must be noted alongside its strengths. The main strength is that the LRTNs investigated in this study are rarely observed; thus, to the best of our knowledge, such a detailed study including and comparing all of these groups has not been performed. As a main limitation, due to the retrospective nature, some histopathological data were not available, which hindered the analysis of other pathological factors. Our study was conducted between 2019 and 2021 and was based on the revised diagnostic criteria published in 2018 for NIFTP. According to these criteria, the percentage of papillae was 0. In the 2022, WHO classification of thyroid tumours, the percentage of papillae was accepted as <1 in the NIFTP diagnostic criteria. For this reason, patients with a 0–1 papillae percentage may have been overlooked. This is one of the important limitations of the study. Another limitation is that the very low number of WDC-NOS and FT-UMP cases, which limits the conclusions that can be drawn from statistical analyses, particularly in terms of defining the characteristics of the mentioned LRTNs. However, this is an unavoidable limitation caused by the rarity of these pathologies and the challenges encountered in their diagnosis. In addition, the number of molecular data could have been more in the study.

5 | CONCLUSION

The present study aimed to investigate and describe LRTNs, which are rare and difficult to distinguish histopathologically, by dividing them into four borderline groups. The great majority of LRTNs were found to be NIFTPs. The WDT-UMP cases were clearly characterised by solitary nodular lesions and had relatively large index nodules. Although many sonographic findings were similar among the LRTNs, index nodule volume appeared to be the most essential discriminating sonographic finding in our population with LRTNs. Most patients with LRTNs did not have a family history of thyroid cancer which suggests limited inheritance. Although these tumours are low risk, various factors such as size, presence of PTC, histopathology/behaviour of PTC, post-operative residual tissue size and thyroglobulin values may be important in determining treatment strategy.

AUTHOR CONTRIBUTIONS

The author confirms equal responsibility for study conception and design, data collection, analysis and interpretation, and manuscript preparation.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data supporting this study's findings are available from the corresponding author upon reasonable request.

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