

The frequency of malignancy and the relationship between malignancy and ultrasonographic features of thyroid nodules with indeterminate cytology

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Abstract Various approaches are available for the management of nodules that are evaluated to be indeterminate according to the results of thyroid fine needle aspiration biopsy. The present study aimed to determine the rate of malignancy and the ultrasonographic features that could be used as predictor of malignant pathologies at the nodules with indeterminate cytology. A total of 201 patients who underwent total thyroidectomy and whose fine needle aspiration biopsy results were evaluated to be Hurthle cell lesion ($n = 99$), follicular neoplasm ($n = 61$) or suspicious for malignancy ($n = 41$) were enrolled in this study. Of these patients, 178 were females (88.6 %) and 23 were males (11.4 %). The rates of malignancy were found to be 33.3 % in the Hurthle cell lesion group, 23.0 % in the follicular

neoplasm group and 53.7 % in the suspicious for malignancy group ($p = 0.006$). The comparison of the ultrasonographic characteristics of the malignant and benign nodules revealed hypoechogenicity and microcalcification to be more common in malignant nodules (34.3 vs. 16.9 %, $p = 0.005$; 27.1 vs. 13.1 %, $p = 0.014$; respectively). While 92.3 % of the malignant nodules were ≥ 1 cm, 82.9 % of the benign nodules were ≥ 1 cm ($p = 0.042$). In the current study, malignancy was observed in 33.3 % of the Hurthle cell lesion group, 23 % of the follicular neoplasm group and 53.7 % of the suspicious for malignancy group. In addition, we detected that microcalcification and benign hypoechoic at patients with indeterminate cytology can be related with increased risk of malignancy. We believe that as the patients at Hurthle cell lesion group have higher risk of malignancy than the patients with Follicular Neoplasia, total thyroidectomy will be suitable for these patients.

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Introduction

Thyroid diseases are common clinical problems in Turkey as in worldwide. After the employment of high resolution ultrasonography (US) in the evaluation of thyroid nodules, the incidence of thyroid nodules has reached up to 30–50 % of the population [1, 2]. While the overall rate of malignancy in thyroid nodules is about 5 %, recent studies have reported that the malignancy rates are 12 % in incidental thyroid nodules and 28 % in nonpalpable thyroid nodules [3]. Thyroid fine needle aspiration biopsy (FNAB) is the first step in the evaluation of thyroid nodules. FNAB plays a critical role in avoiding unwarranted surgery that is performed to

differentiate benign thyroid nodules from malignant thyroid nodules. Thus, FNAB is the gold standard in establishing accurate information regarding the pathology of thyroid nodules. Thyroid FNAB has a mean sensitivity of 83 % and a mean specificity of 92 % [4]. On the other hand, if the nodules have malignant ultrasonographic features, then there are publications in the literature, which mention that the FNAB must be done twice to increase the sensitivity and specificity of the FNAB although the first FNAB is benign [5]. A number of classification systems are used in the evaluation of the results of FNAB. In the guideline published in 2006 by American Thyroid Association (ATA) and American Association of Clinical Endocrinologists (AACE), cytologic findings that are suspicious for malignancy as well as follicular lesions and follicular neoplasms (FN) were classified under the heading of “indeterminate” [4, 6]. The guideline was revised by ATA in 2009, and indeterminate group was redefined as consisting from follicular and Hurthle cell neoplasm (HLN) and follicular lesion of undetermined significance [6]. However, Hurthle cell lesion was described as a subtype of FN in the 2010 Bethesda FNAB classification system [7]. Thus, in our study, we aimed to find out an answer to the question of whether the Hurthle cell neoplasm must be accepted as a different class or must be act as a subgroup of FN by comparing the malignancy risk between the FN and HLN because of the classification chaos at the Hurthle cell lesions.

We also aimed to add benefit to the type and wideness of the surgical treatment preoperatively by determining the ultrasonographic features that can be predictive for malignant pathology at HLN, FN, and at the nodules that are in the suspicious cytologic groups for malignancy.

Materials and methods

Study design and patients

Thyroid FNABs that were done to the patients, who were referred to the endocrinology outpatient clinic of the Ankara Numune Research and Training Hospital of the Ministry of Health between January 2008 and January 2010, were evaluated according to the 2007 Bethesda classification. According to these evaluations, 99 patients with suspicion of HLN (Bethesda 4), 61 patients with suspicion of follicular neoplasm (Bethesda 5), and 41 patients with suspicion of malignancy (Bethesda 6) were included in the study. All patients underwent total thyroidectomy in our hospital.

Thyroid ultrasonography, fine needle aspiration biopsy and cytological examinations

Ultrasonographic examinations and FNABs of the patients were performed in our clinic by endocrinologists (YA, DB,

SI) using the LOGIQ 3 US system (General Electric Healthcare, Waukesha, WI, USA) with a linear probe of 11 MHz. Dimensions of thyroid lobes, features of thyroid parenchyma and nodules structure, echogenicity, halo features, spheric structure (anterior/transverse ratio being >1 and long axis/short axis being $\leq 1,5$), regularity of the edges, calcification pattern, vascularization pattern of the nodules that are detected at ultrasonography of all of the patients were recorded. Nodule structure is defined as solitary if the nodule is solely solid; as mixed if it contains both solid and cystic components; and as cystic nodule if its appearance is cystic.

The color Doppler pattern of the thyroid nodules was evaluated on PACS and classified as follows: scant type (only a few vascular spots), peripheral type (the vascular signal in the peripheral portion was higher than that in the central portion), central type (the vascular signal in the central portion was higher than that in the peripheral portion), and mixed type (the vascular signal in the peripheral portion was similar to that in the central portion).

FNAB were performed with accompanying ultrasonography using either a 22-gage needle attached to a 10-mL disposable plastic syringe or an aspirator. Samples were stained with hematoxylin and eosin (H&E) and Giemsa, and were evaluated by the Pathology Department of our institution. Patients for whom cytology results were reported as suspicious for malignancy, FN or HLN was included in the study. All patients underwent total thyroidectomy in our hospital. The risk of malignancy was determined for each group by evaluating the postoperative histopathology results. The association between the ultrasonographic features of the nodules and histopathologic results were evaluated to investigate if nodule characteristics were predictive for malignancy.

Laboratory measurements

The serum levels of thyroid-stimulating hormone (TSH), free triiodothyronine (FT₃), free thyroxine (FT₄), anti-TSH receptor antibody (TR-Ab), anti-thyroperoxidase antibody (TPO-Ab), and anti-thyroglobulin antibody (Tg-Ab) were analyzed. Serum levels of TSH, FT₃ and FT₄ levels were measured by using the Abbott Architect 2000 device (Abbott Diagnostics Division, IL, USA) and chemiluminescence microparticle immunoassay method.

Statistical analysis

The statistical analyses of the data were performed using Statistical Program for Social Sciences (SPSS, Inc., Chicago, IL, USA) version 13 for windows. Continuous variables were expressed as mean \pm standard deviation (SD), or median (minimum–maximum), whereas categorical

variables were expressed as number of observations or percentages. The differences between the groups in terms of measured parameters were analyzed using Mann–Whitney *U* test. Chi square test or Fisher's exact test were used for the comparisons of categorical variables. The risk factors significantly affecting malignancy according to the univariate analysis were analyzed using multivariate logistic regression analysis. A *p* value of <0.05 was considered statistically significant.

Results

General characteristics of the patients and comparison of the groups

A total of 201 patients whose FNAB results indicated HLN (*n* = 99), FN (*n* = 61), or suspicion for malignancy (*n* = 41) were included in the study. Of the patients, 178 were females (88.6 %) and 23 were males (11.4 %). The mean age of the patients was 47.7 ± 13.6 years (range, 17–79 years). The groups were similar in terms of age and gender distribution. Although the rate of male patients was higher in the FN group (19.6 %) when compared with the HLN (8.1 %) and SUSP (7.3 %) groups, the difference was not statistically significant (*p* = 0.066). No significant difference was observed between the groups in terms of thyroid function test results or Tg-Ab or TPO-Ab levels.

Comparison of the groups in terms of ultrasonographic features

The ultrasonographic features of the cytological groups are presented in Table 1. No significant differences were observed between the groups in terms of nodule echogenicity, structure of nodules, absence of halo sign, margin irregularity, and the incidence of having an A/T ratio of ≥ 1 . While the groups were comparable in terms of the rate of nodules with no vascularization, the FN group had a higher incidence of nodules with mixed type vascularization when compared with the other groups (*p* = 0.009). Similarly, microcalcification was significantly more common in the SUSP group when compared with the other groups (*p* = 0.005). The LA/SA ratio of the SUSP group was also significantly higher than that of the other groups (*p* = 0.002).

Evaluation of histopathologic results

In the patients undergoing surgery due to indeterminate cytology, histopathologic examination revealed 113 (70.6 %) benign and 47 (29.4 %) malignant cases (Fig. 1), whereas in the suspicion for malignancy group, histopathologic

examinations revealed 19 benign and 22 malignant (53.7 %) cases. When the indeterminate cytology results were separately evaluated, no statistically significant difference was found between the HLN and FN groups in terms of malignancy incidence [33/99 (33.3 %) and 14/61 (23.0 %), respectively; *p* = 0.211]. However, a statistically significant higher incidence of malignancy [22/41 (53.5 %)] was observed in the suspicion for malignancy group when compared with the HLN and FN groups. The patients with malignant and benign nodules were comparable in terms of age and gender distribution (Table 2). No significant differences were observed between the groups in terms of thyroid function test results as well as Tg-Ab or TPO-Ab levels.

At histopathologic evaluation, in the HLN group 25 papillary carcinomas (20 classic type, 4 follicular variant and oncositic variant), 4 follicular carcinomas, one medullary cancer, 1 Hurthle cell carcinoma, 1 well-differentiated tumor of uncertain malignant potential; and at 1 patient both follicular carcinoma and papillary carcinoma; and 9 papillary carcinoma (6 classic type and 3 follicular variant), 4 follicular carcinomas, and 1 well-differentiated tumor of uncertain malignant potential were detected in the FN group. Of the patients undergoing surgery due to suspicion of malignancy, papillary carcinoma was detected in 20, whereas 2 had well-differentiated tumors of uncertain malignant potential.

The relationship between the histopathologic results and the ultrasonographic features

All groups

The ultrasonographic features of the malignant and benign nodules (all of the nodules that are included in the study) were evaluated. Of the malignant nodules, 33.3 % were hypoechoic, 24.6 % were isoechoic, 2.9 % were hyperechoic and 39.1 % were of mixed echogenicity. Of the benign nodules, 17.4 % were hypoechoic, 28.0 % were isoechoic, 3.0 % were hyperechoic and 51.5 % were of mixed echogenicity. Hypoechoicity was observed to be significantly more common in malignant nodules than in benign nodules (*p* = 0.011) [odds ratio (OR), 2.370; 95 % CI: 1.209–4.644].

A significant difference was noted in the HLN group in terms of malignancy rates between nodules that were ≥ 4 and < 4 cm in size (*p* = 0.013). No significant differences were observed in terms of malignancy rates between the nodules that were ≥ 4 and < 4 cm in the FN and SUSP groups (*p* = 0.310 and *p* = 0.207, respectively). There were no significant differences between the nodules that were ≥ 1 and < 1 cm regarding the rate of malignancy in the HLN, FN, and SUSP groups (*p* = 0.674, *p* = 0.222 and *p* = 0.207, respectively, Fig. 2).

Table 1 Comparison of the ultrasonographic features of groups

Variables	HLN group (<i>n</i> = 99)	FN group (<i>n</i> = 61)	SUSP group (<i>n</i> = 41)	<i>p</i>
Echogenicity (%)				
Hypoechoic	25 (25.3)	11 (18.0)	10 (24.4)	0.707
Isoechoic	25 (25.3)	19 (31.1)	10 (24.4)	
Hyperechoic	4 (4.0)	1 (1.6)	1 (2.4)	
Mixed echogenicity	45 (45.5)	30 (49.2)	20 (48.8)	
Structure (%)				
Solid	69 (69.7)	44 (72.1)	31 (75.6)	0.501
Cystic	3 (3.0)	1 (1.6)	1 (2.4)	
Mixed	27 (27.3)	16 (26.2)	9 (22.0)	
Vascularization (%)				
Absent	59 (59.6)	32 (52.5)	24 (58.5)	0.009
Intranodal	10 (10.1)	0 (0)	3 (7.4)	
Peripheral	30 (30.3)	15 (24.5)	14 (34.1)	
Intranodal + peripheral	0 (0)	14 (23.0)	0 (0)	
Microcalcification (%)	14 (14.1)	5 (8.2)	13 (31.7)	0.005
No halo sign (%)	83 (83.8)	51 (83.6)	34 (82.9)	0.899
Margin irregularity (%)	11 (11.1)	5 (8.2)	2 (4.9)	0.486
A/T ratio ≥ 1	25 (25.3)	22 (36.1)	8 (19.5)	0.151
LA/SA ratio, mean \pm SD	1.5 \pm 0.5	1.3 \pm 0.5	1.7 \pm 0.7	0.002

HLN Hurthle cell lesion, FN follicular neoplasm, SUSP suspicion for malignancy, A/T the ratio of the anteroposterior diameter to the transverse diameter, LA/SA the ratio of long axis to short axis

Bold values indicate $p < 0.05$

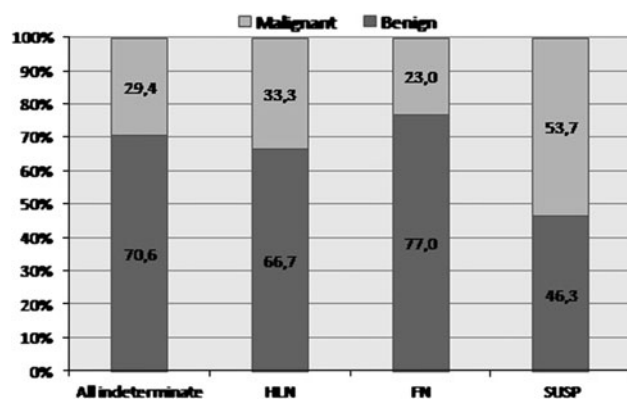


Fig. 1 Comparison of the histopathologic results of the groups

Ultrasonographic features of malignant and benign nodules in groups are presented in Table 3

Group with Hurthle cell lesions (HLN group)

In the HLN group, the mean ages of the patients with malignant and benign nodules were similar (49.8 ± 12.6 years and 49.4 ± 13.1 years, respectively; $p = 0.772$). In this group, microcalcification was significantly more common in malignant nodules compared with the

benign nodules (24.2 versus 9.1 %, $p = 0.041$). The OR for microcalcification was 3.200 (95 % CI, 1.006–10.175).

Group with follicular neoplasms (FN group)

Although the mean age of the patients with malignant nodules was higher than that of those with benign nodules, the difference was not statistically significant (49.8 ± 11.4 years and 44.7 ± 15.0 years, respectively; $p = 0.180$). In this group, hypoechoogenicity was more frequent in malignant nodules than in benign nodules; however, the difference was not statistically significant (35.7 versus 12.8 %, $p = 0.05$). The OR for hypoechoogenicity was 3.796 (95 % CI, 0.947–15.225).

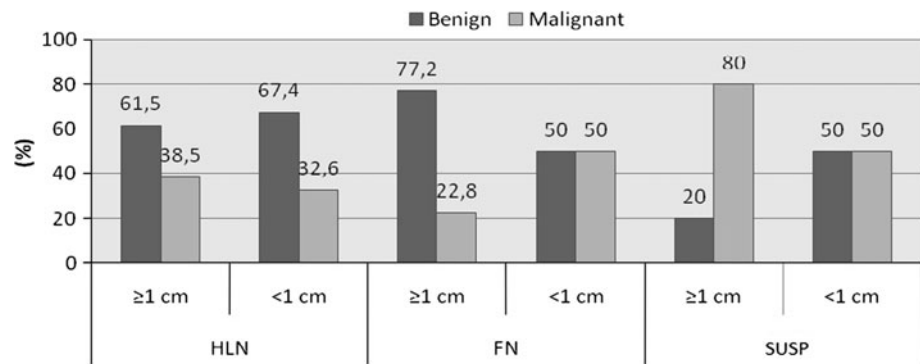
Group with suspicion for malignancy (SUSP group)

Although the mean age of the patients with malignant nodules were higher than that of those with benign nodules, the difference was not statistically significant (47.8 ± 13.9 years and 43.9 ± 14.9 years, respectively; $p = 0.374$). The frequency of the nodules with solid nodül and mixed-type vascularity was higher in malignant nodules than in benign nodules in this group (90.9 versus 57.9 %, $p = 0.014$; 40.9 versus 10.5 %, $p = 0.038$, respectively). The OR for solid

Table 2 Comparison of the patients with malignant and benign nodules in terms of age, gender and laboratory results

Variables	Benign (<i>n</i> = 132)	Malign (<i>n</i> = 69)	<i>p</i>
Age (years)	47.1 ± 14.1	48.9 ± 12.8	0.365
Gender (F/M)	118/14	60/9	0.361
TSH (μIu/mL)	2.3 ± 3.8	3.1 ± 6.1	0.272
FT ₃ (pg/mL)	3.0 ± 0.6	3.3 ± 1.9	0.163
FT ₄ (ng/dL)	1.0 ± 0.5	1.0 ± 0.4	0.644
TPO-Ab (Iu/mL)	71.5 ± 157.9	24.7 ± 34.5	0.289
Tg-Ab (Iu/mL)	41.1 ± 83.7	43.5 ± 107.6	0.946

F female, *M* male, *TSH* thyroid-stimulating hormone, *FT₃* free triiodothyronine, *FT₄* free thyroxine *TR-Ab* anti-TSH receptor antibody, *TPO-Ab* anti-thyroperoxidase antibody, *Tg-Ab* anti-thyroglobulin antibody

Fig. 2 Distribution of supracentimeter and subcentimeter nodules according to histopathologic results

nodül was 7.273 (95 % CI, 1.308–40.424). The mixed nodül and central-type vascularity were observed to be more common in benign nodules. The OR for peripheral vascularity was found to be 4.857 (95 % CI, 0.884–26.676). The OR for mixed type vascularity was calculated to be 5.885 (95 % CI, 1.082–32.014).

Discussion

We found the risk of malignancy to be 33.3 % in the HLN group and 23 % in the FN group. Although the rate of malignancy was higher in the HLN group when compared with the FN group, the difference was not statistically significant. In another study similar to this study, which is conducted with 216 FN and 87 HLN cases, malignancy risk is found to be 28 and 41 %, respectively [8]. In another study that included, 108 FN and 37 HLN patients although the malignancy risk was reported as 24 and 41 % respectively, any statistically significant difference was not detected [9]. A study including 73 FN and 10 HLN cases reported the rate of malignancy to be 15 % for the cases with FN and 20 % for the cases with HLN [10]. Similar to this study, in the study of Sorrenti et al., [11] malignancy risk is found to be 17.3 % in the FN group while it is found to be 18.6 % in the HLN group. In light of our study and

others, as the malignancy rate is higher in the HLN group when compared with the FN group, it is obviously clear that the patients with HLN must be evaluated more seriously. As mentioned in the section “Introduction”, so far different classification systems were used for FNAB evaluation. We believe that HLN can be classified in the same group with FN; however, we also believe that the total thyroidectomy will be suitable for the HLN group because of the high probability of malignancy.

In the studies evaluating patients with thyroid nodules, malignancy risk was found to be increased with age [12]. In the studies evaluating Hurthle cell lesions and FN, the rate of malignancy was observed to be higher in patients older than 50 years [13, 14]. However, there are also studies reporting the malignancy risk for HLN and FN groups to be independent of age [15]. In the present study, although the patients with malignant pathologies in the FN and SUSP groups were older, there were no significant differences between the mean ages of the patients with malignant and benign pathologies in all three groups.

While hypoechogenicity was reported to be associated with malignancy in certain studies evaluating echogenicity of the nodules, others failed to demonstrate a correlation between hypoechoic appearance and malignancy [16–19]. In a study performed in patients with FN alone, the hypoechogenicity was identified in 18.1 % of the malignant

Table 3 Evaluation of ultrasonographic features of the benign and malignant nodules in the groups

Variables (%)	HLN group			FN group			SUSP group		
	Benign (n = 132)	Malign (n = 69)	p	Benign (n = 47)	Malign (n = 14)	p	Benign (n = 132)	Malign (n = 69)	p
Echogenicity									
Hypoechoic	21.2	33.3	0.224	12.8	35.7	0.05	15.8	31.8	0.233
Isoechoic	24.2	27.3	0.808	31.9	28.6	0.813	31.6	18.2	0.319
Hyperechoic	4.5	3.0	0.718	2.1	0	0.582	0	4.5	0.347
Mixed echogenicity	50.0	36.4	0.284	53.2	35.7	0.363	52.6	45.5	0.647
Structure									
Solid	68.2	72.7	0.817	74.5	64.3	0.456	57.9	90.9	0.014
Cystic	3.0	3.0	1.000	0	7.1	0.065	5.3	0	0.276
Mixed	28.8	24.2	0.811	25.5	28.6	0.820	36.8	9.1	0.032
Vascularization									
No	69.7	60.6	0.376	66.0	42.9	0.135	31.6	18.2	0.319
Central type	4.5	15.2	0.068	6.4	21.4	0.097	47.4	4.5	0.001
Peripheral type	25.8	24.2	1.000	14.9	28.6	0.243	10.5	36.4	0.055
Mixed type	0	0	–	12.8	7.1	0.562	10.5	40.9	0.038
Spherical structure									
A/T ≥ 1	22.7	30.3	0.466	36.2	35.7	1.000	10.5	27.3	0.177
LA/SA ≥ 1.5	47.0	42.4	0.831	31.9	42.9	0.449	57.9	36.4	0.217
Microcalcification	9.1	24.2	0.041	6.4	14.3	0.344	36.8	27.3	0.737
No halo sign	86.4	78.8	0.390	80.9	92.9	0.287	89.5	77.3	0.301
Margin irregularity	10.6	12.1	0.821	8.5	7.1	0.870	10.5	0	0.119

HLN Hurthle cell lesion, FN follicular neoplasm, SUSP suspicion for malignancy, A/T the ratio of the anteroposterior diameter to the transverse diameter, LA/SA the ratio of long axis to short axis

Bold values indicate $p < 0.05$

nodules, and no relationship was found between malignancy and hypoechoogenicity [13]. Similarly, the evaluation of 505 patients with HLN and FN, cytological examinations revealed that hypoechoogenicity of the nodule was not associated with malignancy [15]. In the present study, no significant correlation was found between hypoechoogenicity and malignancy in the HLN and SUSP groups; on the other hand, malignancy at hypoechoic nodules are more at the FN group (35.7 %), but it is not statistically significant ($p = 0.058$). However, in the follicular neoplasia group the malignancy risk was found to be 3.79-fold if the nodule was hypoechoic.

A number of studies have demonstrated a correlation between the presence of a solid nodule and that of malignancy [16–20]. There are also certain studies suggesting that the presence of a solid nodules could not be one of the criteria for malignancy [21, 22]. In a few studies at which indeterminate nodules were evaluated, solid or cystic characteristics of the nodules were not significantly correlated with malignancy [13, 23]. Similar to these studies, in our study, a significant correlation was also not found between solid or cystic characteristics of the nodules and

malignancy in the HLN and FN groups. However, the presence of a solid nodule in the nodules was found to be significantly correlated with malignancy in the SUSP group.

Another possible sign of malignancy in thyroid nodules is the presence of microcalcification within the nodules [16, 21, 22, 24]. In a study investigating FN and HLN, the presence of microcalcification within the nodules was demonstrated to be significant in terms of malignancy [15]. However, in another study in which patients with FN were evaluated, none of the ultrasonographic features was found to be associated with malignancy [13]. In the present study, while the presence of microcalcification was not found to be correlated with malignancy in the FN and SUSP groups, microcalcification was observed in 24.2 % of the malignant nodules and 9.1 % of the benign nodules in the HLN group. The presence of microcalcification within the nodules in the HLN group increased the risk of malignancy by 3.2 times.

Another ultrasonographic feature suggesting malignancy in thyroid nodules is the margin irregularity. No correlation was established between irregular margins and malignancy

in a study performed in with HLN and FN cases [13, 15]. Consistent with the results reported in these previous studies, we found no correlation between irregular margins and malignancy in the present HLN, FN, and SUSP groups. On the contrary, irregular margins were reported to be more common in malignant nodules in a study evaluating patients with FN [25].

Evaluation of the nodules in all our three groups in terms of having a LA/SA ratio of ≥ 1.5 and A/T ratio of ≥ 1 revealed no correlation between this ratio and malignancy. Although there are studies similar to our study, which suggest that A/T ratio of ≥ 1 and LA/SA ratio of ≥ 1.5 is not predictive for malignancy [26–28], in contrast, there are studies that suggest that these criteria are predictive for malignancy [29].

Central-type vascularization was demonstrated to be a predictive criterion in terms of malignancy in FN [30, 31]. In contrast to these studies, Choi et.al. [13] and Sippel et.al [23] showed in their studies that there was no any correlation between the central type vascularization and malignancy. Similar to these studies, we showed in our study, no significant correlation was found between the vascularization patterns of nodules and malignancy in the HLN and FN groups. On the other hand, mixed-type vascularization was found to be associated with higher risk of malignancy in SUSP group.

The relationship between nodule size and malignancy is the most commonly investigated issue in patients with HLN and FN [23, 32–35]. The risk of malignancy was reported to be 65 % in the patients with HLN having nodules greater than 4 cm [16, 36]. Although the rate of malignancy is rather high in nodules greater than 3 cm, nodules smaller than 1 cm have also been observed with malignancy. Thus, nodule size cannot be utilized alone to eliminate malignancy [23]. Although a number of studies have reported a strong correlation between nodule size and malignancy, in a study evaluating the patients with FN and HLN, no correlation was reported between nodule size and malignancy [11, 13, 15]. In the current study, a significant correlation between nodule size of ≥ 4 cm and malignancy was found only in the HLN group. However, as we observed malignancy in 38.5 % of the nodules < 1 cm as well, we concluded that size could not be used alone to eliminate malignancy.

Elastosonography (USE) is a new ultrasonographic evaluation method with 90 % specificity and sensitivity up to 92 % in the malignant and benign discrimination of the thyroid nodules [37, 38]. Rago et al. [39] reported that they can perform discrimination of malignant and benign with the ratio of 92.9 % by using real time USE in the indeterminate nodules. However, Lippopis et al. [37] could not confirm this ratio at their study at which they included 102 patients. Cantisani et al. [40] reported in their study at which they used Q-USE that USE have high sensitivity and

specificity in prediction of malignancy in indeterminate nodules. Çakır et al. [41] made strain index (SI) measurement with USE as it is an objective parameter in the differentiation of malignant and benign nodules and showed that the SI measurements have higher sensitivity against and same specificity with the USE scoring.

Also, a new procedure called thin core biopsy can help in taking the surgery decisions and at the classification of the indeterminate nodules. With this procedure, it is reported that 1/3 of the indeterminate nodules are resulted as benign, and it also must be kept in the mind that it is an alternative diagnostic test that can be done before the decision of surgery as it allows to make detailed immunohistochemical evaluation [42].

Conclusion

In the current study, malignancy was observed in 33.3 % of the HLN group, 23 % of the FN group, and 53.7 % of the SUSP group. Although the patients in the HLN group can be considered in the same group with Follicular neoplasm group, we believe that the total thyroidectomy will be better for this group of patients because of the high rates of malignancy.

Because of the considerable rates of malignancy in this group of nodules, thorough preoperative US evaluation is warranted; it is recommended to perform total thyroidectomy for the nodules, which contains microcalcification, which are hypoechoic and greater than 4 cm. However, we believe that larger immunohistochemical and molecular studies are required to find out more precise factors to predict malignancy.

Conflict of interest The authors declare that they have no conflict of interest.

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