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Efficacy of Multidisciplinary Approach in Thyroid Nodules: Analysis of Factors Used for Predicting Malignancy

ABSTRACT

Objective: To date, numerous molecular tests have been developed for preoperative evaluation of thyroid nodules. Nevertheless, these tests cannot be administered in many centers due to their imprecise diagnoses and high costs. The present study aimed to investigate the effect of making surgical decisions in a panel through a multidisciplinary approach after clinical, ultrasonographic, and pathological evaluation of nodules on the accuracy of the decisions.

Methods: The retrospective study included patients with thyroid nodules who underwent preoperative ultrasonography followed by fine-needle aspiration biopsy, which was confirmed by postoperative pathological examinations between January 2017 and January 2019. The relationship between ultrasonography features of nodules and malignancy was analyzed. A comparison was performed between patients who were referred for surgery through the multidisciplinary versus non-multidisciplinary approach.

Results: A total of 255 nodules in 211 patients were evaluated in the study. The prevalence of malignancy was 100% in nodules with hypoechogenicity + microcalcification + margin irregularity ($P < .001$). The likelihood of malignancy was significantly higher in dual combinations of these 3 adverse conditions ($P < .001$ for all). Margin irregularity was found to be the most predictive model for malignancy (CI: 1.9-13.8, odds ratio: 5.249, $P < .001$). The multidisciplinary approach was superior to the non-multidisciplinary approach in the detection of malignancy ($P = .008$).

Conclusion: Margin irregularity had the highest predictive value for the detection of malignancy. Employing the multidisciplinary approach in preoperative evaluation of thyroid nodules can be highly effective in detecting malignancy and preventing unnecessary surgery.

Keywords: Fine-needle aspiration, irregular margin, multidisciplinary approach, risk of malignancy, thyroid cancer, thyroid nodules

Introduction

Thyroid nodules constitute the most common disease group of the thyroid gland.[1] The incidence of thyroid nodules increases with age and can be seen in almost 1 out of every 3 people in our region.[2]

In our country, the American Thyroid Association (ATA) criteria are used for the ultrasound (USG) risk assessment of thyroid nodules and the Bethesda system is used for the classification of thyroid nodule cytology in fine-needle aspiration biopsy (FNAB).[1]

Although the majority of thyroid nodules have a benign character,[3] patients detected with a nodule on USG examination may become anxious and apply to the endocrinology department. Subsequently, due to the anxiety of the patients and the concerns of the physicians about the possibility of delayed diagnosis of malignancy, many patients can be referred for unnecessary surgery.

The present study aimed to investigate the effect of making surgical decisions in a panel through a multidisciplinary approach after clinical, ultrasonographic, and cytological evaluation of nodules on the accuracy of the decisions.

Materials and Methods

The study protocol was approved by Karadeniz Technical University, Faculty of Medicine, Ethics Committee (approval date: December 11, 2019; No: 24237859-785). The Institutional Review Board waived the need for informed consent given the retrospective nature of the

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research. The study was conducted in accordance with the principles laid out by the 18th World Medical Assembly (Helsinki, 1964) and all its subsequent amendments (up to 2013) and with the International Society for Pharmacoepidemiology guidelines for Good Pharmacoepidemiology Practice and local regulations, including local data protection regulations.

Patients

The retrospective study included patients with thyroid nodules who underwent preoperative USG followed by FNAB, which was confirmed by postoperative pathological examinations between January 2017 and January 2019.

Patients with a thyroid-stimulating hormone level of <0.1 mIU/L and those who underwent surgical treatment due to toxic nodules were excluded from the study. Patients who received head and neck radiation and pregnant patients were not included in the study. Regardless of the presence of autoimmune thyroid disease, patients with nodules without radioactive iodine uptake on scintigraphy were included in the study.

Thyroid Ultrasonography and Fine-Needle Aspiration Biopsy

Detailed ultrasonographic evaluation is performed before the FNAB procedure, and FNAB is performed by interventional radiology specialists. Both thyroid USG and USG–FNAB were performed using 5-12 MHz linear array transducers (GE LOGIQ 7) by 2 specialized radiologists with more than 10 years' experience in thyroid imaging and biopsy. Biopsies performed other than interventional radiology specialists were not evaluated. Ultrasonographic features included nodule size, echo structure (solid and mixed), echogenicity (hypoechogenicity, isoechogenicity, or hyperechogenicity, mixed echogenicity, solid, mixed solid-cystic, spongiform, cystic), margin (regular or irregular), halo (none, circumscribed, or non-circumscribed), and presence or absence of microcalcifications. A mixed solid-cystic nodule was defined as a nodule containing areas of cystic degeneration in less than 50% of the nodule. A nodule of mixed echogenicity was defined as a nodule containing both hypoechoic and isoechoic areas.

The flow pattern of the nodule was divided into 3 types: type I: none, type II: presence of perinodular flow, type III: presence of intra- and/or perinodular flow.

The FNAB procedure was performed with antiseptic conditions after the induction of local anesthesia. Sampling was performed by making at least 10 needle passes with only a single capsular puncture using a 25-gauge needle and syringe (10 mL) if necessary. At least 2 punctures were made for each nodule, and the specimens were air-dried. Smears prepared from each nodule were either air-dried and stained with May–Grünwald–Giemsa stain without fixation or were fixed in alcohol and then stained with Papanicolaou stain. In nodules with cystic and solid components, both components were sampled.

Cytology and Histology

All the histopathological examinations were performed by 2 cytopathologists. Based on the 2017 Bethesda System for Reporting Thyroid Cytopathology (F), the cytology results were classified as follows: (i) non-diagnostic or unsatisfactory, (ii) benign, (iii) atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS), (iv) follicular neoplasm or suspicious for a follicular neoplasm, (v) suspicious for malignancy, and (vi) malignant. In the presence of more than 1 cytology result, the most suspicious cytology result was taken into consideration (vi>v>iv>iii>ii>i).

All the thyroid specimens were fixed in 10% neutral-buffered formalin, and all the nodules present on the thyroid tissues were embedded in paraffin and stained with hematoxylin and eosin staining. Histological analysis was performed on all surgically excised lesions. The FNAB results were compared with those of histopathological examination, which is the gold standard in the diagnosis of thyroid nodules. Thyroid cancer classification was performed according to the 2017 World Health Organization classification.

Multidisciplinary Approach

As a rule, endocrinology residents do not make surgical decisions on their own, and these decisions are made by the panel. All patients evaluated by endocrinology residents in our hospital's endocrinology outpatient clinic were brought to the panel for a final decision. Except for endocrinology residents, patients presented in the panel were not included in the evaluation. A multidisciplinary approach by a panel that consisted of at least 3 endocrinologists and included other specialists such as radiologists, pathologists, general surgeons, and nuclear medicine specialists was needed. In the panel approach, in case of inconsistency between the ultrasonographic appearance of the thyroid nodule and the cytology result, it was requested to reevaluate the ultrasonography and cytology. Rebiopsy was performed when necessary. In the non-multidisciplinary approach, surgical decisions were made by only 1 of the specialists including endocrinologist, general surgeon, or otorhinolaryngologist.

Statistical Analysis

The study was planned as a retrospective descriptive study. Statistical Package for the Social Sciences 22.0 statistical package program (IBM Corp.; Armonk, NY, USA) was used for the analysis of the data. By using the G-Power 3.1 program, it was aimed to reach 197 people with 0.25 design effect, 0.05 margin of error and 95% power, and the study was completed with 211 people. Descriptive statistics of evaluation results; numbers and percentages for categorical variables, mean and standard deviation for numerical variables are given. Chi-square test was used to compare qualitative data. Multiple logistic regression analysis was performed to predict independent predictors of thyroid malignancy. Statistical alpha significance level was accepted as $P < .05$

Results

A total of 255 nodules in 211 patients were evaluated in the study. While 16 (8%) patients underwent lobectomy or lobectomy plus isthmustectomy, 195 (92%) patients underwent total thyroidectomy.

MAIN POINTS

- Margin irregularity had the highest predictive value for the detection of malignancy.
- The multidisciplinary approach in preoperative evaluation of thyroid nodules can be highly effective in detecting malignancy and preventing unnecessary surgery.
- The multidisciplinary approach in preoperative evaluation of thyroid nodules can be highly effective in preventing unnecessary surgery.

Although the number of biopsied nodules was higher in female patients, malignancy rates were similar in both genders ($P = .561$). There were no pregnant patients among the operated patients. Mean age of the patients was 49.86 ± 12.52 years. There were 149 female patients and 62 male patients. Histological evaluation was appropriate for most of the nodules of patients aged between 40 and 59 (n = 118) years, while it was used in a limited fashion in nodules of patients aged under 20 (n = 1) and over 80 (n = 1) years. Moreover, the tendency for malignancy gradually decreased from the second decade to the end of the sixth decade.

Malignancy was detected in 22% of mixed solid-cystic nodules. No significant relationship was found between malignancy and the presence and absence of halo ($P = .684$ and $P = .684$, respectively) (Table 1). Hypoechogenicity was found to increase the likelihood of malignancy ($P < .001$). The significance of the relationship between hypoechogenicity and malignancy disappeared in nodules with a diameter of over 20 mm ($P = .178$) (Table 1).

Margin irregularity was found to be the most predictive model for malignancy (Table 2). The prevalence of malignancy was significantly higher in nodules detected with margin irregularity along with macrocalcification, microcalcification, hypoechogenicity, and central vascularity ($P < .05$ for all). Of note, the prevalence of malignancy was 100% in nodules with hypoechogenicity + microcalcification + margin irregularity ($P < .001$). Additionally, the likelihood of malignancy was significantly higher in dual combinations of these 3 adverse conditions ($P < .001$ for all) (Table 3).

Figures 1 and 2 present postoperative histological results and the subtypes of papillary carcinoma detected in our patients. Accordingly, 4 (1.6%) patients were detected with non-invasive follicular thyroid neoplasm with papillary-like nuclear features, 2 (0.8%) patients were detected with medullary thyroid cancer, 1 (0.4%) patient was detected with follicular thyroid cancer, 1 (0.4%) patient was detected with anaplastic thyroid cancer, and 2 (0.8%) patients were detected with a tumor with uncertain malignant potential. The preoperative calcitonin value of the patient who was sent to the operation by the panel was 237 pg/mL, the other patient was not evaluated by the panel, and the preoperative calcitonin level was not measured. Tumor diameters of both patients were 18 mm and 25 mm, respectively, and no lymph node metastasis was detected. In the postoperative follow-up of both patients, the calcitonin value decreased to <2 pg/mL.

Significant relationship was found between multidisciplinary approach and postoperative histological results ($P < .008$).

In 2 patients, 3 FNAB were made and cytology was reported as benign, non-diagnostic, and AUS/FLUS, respectively. These 2 patients were included in the "AUS/FLUS" category (Table 3) and not included in the "1 bx non-diagnostic + 1 bx AUS/FLUS" category (Table 4). Additionally, postoperative histological result of both patients was also reported as benign.

In 6 patients who had benign preoperative cytology and were operated on due to patient-related factors (cosmetic, compression effect), postoperative histology was unexpectedly malignant. In patients whose cytology was reported as "suspicious for malignancy," postoperative cytology was mostly malignant (92.9%). In the non-multidisciplinary group, on the other hand, 36 patients who had non-diagnostic cytology underwent surgery and only 5 (13.5%) of them were detected with malignancy. In patients who underwent surgery with FNAB for non-diagnostic cytology, 97.3% of them were operated on through the non-multidisciplinary approach and most of them (86.5%) were detected with a benign histology.

Discussion

Fine-needle aspiration biopsy has become more popular in line with the advancements in USG. Moreover, numerous molecular tests have been developed to reduce the anxiety and hesitation of both patients and physicians in indeterminate cytology results. Nevertheless, these tests cannot be administered in many centers due to their imprecise diagnoses and high costs.[4-5] In the present study, we investigated the effect of extensive evaluation of ultrasonographic and cytological features through the multidisciplinary approach to making accurate preoperative decisions.

In our study, although the prevalence of malignancy was higher in women, female gender did not increase the likelihood of malignancy ($P = .561$). Moreover, there was a female preponderance in our study, which could be attributed to the estrogen sensitivity of the thyroid gland and the higher incidence of nodules and thyroid cancer in female patients.[6-8] In line with the literature, the prevalence of thyroid nodules in our patients was found to increase with age. Nevertheless, although the prevalence of thyroid nodules in our region (East Black Sea Region) has been reported to increase with age,[2] our findings indicated a remarkable decrease in the number of biopsied nodules after the sixth decade, which suggests that physicians avoid biopsy due to the life expectancy and preoperative risks of such patients.

Among the high-risk features of thyroid nodules, hypoechogenicity, microcalcification, and margin irregularity were found to have significantly higher predictive values in detecting malignancy (Table 2). Similar findings have been reported by Gülçelik et al,[9] Mohammadi et al,[10] and Yoon et al,[11] However, unlike in the studies by Gülçelik et al[9] and Mohammadi et al,[10] we found that margin irregularity had the highest predictive value among all parameters, which could be attributed to the fact that it is often difficult for radiologists to differentiate nodules with blurred margins and those with irregular margins.[12] In our study, blurred margins were not accepted as a high-risk USG criterion, which, in turn, could have led to a lower predictive value for blurred margins. Additionally, the likelihood of malignancy was significantly higher in dual combinations of hypoechogenicity, microcalcification, and margin irregularity (Table 3).

In our study, relationship between cytological and histological evaluation was found to be consistent with literature.[3,13] Our findings indicated that the multidisciplinary approach was superior to the non-multidisciplinary approach in the detection of malignancy. In the non-multidisciplinary approach, unlike in the multidisciplinary approach, patients who had non-diagnostic cytology underwent surgery despite their low risk of malignancy, and postoperative histology of the patients was reported as benign (Table 4). Among these, 4 patients with a nodule size of 40-45 mm were operated on due to subjective health concerns. Of these 4 patients, 1 patient was detected with a thyroid lesion with a SUVmax of 3.5 on positron emission tomography-computed tomography and another patient underwent total thyroidectomy following parathyroid adenoma excision. The remaining 2 patients were operated on due to the large size of the nodules despite the lack of compression on neck magnetic resonance imaging and 1 of these patients developed hoarseness

Table 1. Frequency Distribution of Ultrasound Features in Benign and Malignant Thyroid Nodules Relationship Between Nodule Diameters and Nodule Histology

	Benign Nodules	Malign Nodules	
Ultrasound Features	**n (%)**	**n (%)**	***P***
Internal components			
Solid (n = 163)	83 (53.9)	80 (80.8)	<.001
Mixed (n = 90)	71 (46.1)	9 (19.2)	
Echogenicity			<.001
Hypoechogenity (n = 103)	42 (27.3)	61 (61.6)	<.001
Isoechogenity or hyperechogenity (n = 23)	14 (9.1)	9 (9.1)	1.000
Mixed echogenity solid (n = 37)	27 (17.5)	10 (10.1)	.147
Mixed solid-cystic (n = 81)	63 (40.9)	18 (18.2)	<.001
Spongioform and cystic (n = 9)	8 (5.2)	1 (1.0)	.094
Margin			
Margin (n = 216)	149 (95.5)	67 (67.7)	<.001
Irregular (n = 39)	7 (4.5)	31 (32.3)	
Calcifications			<.001
Microcalcifications (n = 66)	24 (15.4)	42 (42.4)	<.001
Macrocalcifications (n = 17)	15 (9.6)	2 (2.0)	.035
Microcalcifications + macrocalcifications (n = 22)	10 (6.4)	12 (12.1)	.176
None (n = 150)	107 (68.6)	43 (43.4)	<.001
Vascularity			.052
Type I (n = 67)	33 (25.0)	34 (40.5)	.017
Present (n = 149)	99 (75.0)	50 (59.5)	.017
Type II (n = 81)	55 (41.7)	26 (31.0)	.113
Type III (n = 68)	44 (33.3)	24 (28.5)	.559
Halo			-------
None (n = 220)	133 (85.3)	87 (87.9)	.684
Present (n = 35)	23 (14.7)	12 (12.1)	.684
Circumscribed (n = 31)	22 (14.1)	9 (9.1)	.319
Non-circumscribed (n = 4)	1 (0.6)	3 (3.0)	.302
Lesions ≤ 10 mm (n= 37)			-------
Hypoechogenity (n = 27)	7 (50.0)	20 (83.3)	.061
Isoechogenity or hyperechogenity (n = 5)	2 (15.4)	3 (12.5)	1.000
Mixed echogenity solid (n = 3)	3 (23.1)	------	.037
Mixed solid-cystic (n = 2)	1 (7.7)	1 (4.2)	1.000
Spongioform and cystic (n = 0)	------	-------	-------
Lesions > 10 mm (n = 216)			<.001
Hypoechogenity (n = 76)	35 (24.8)	41 (54.7)	<.001
Isoechogenity or hyperechogenity (n = 18)	12 (8.5)	6 (8.0)	1.000
Mixed echogenity solid (n = 34)	24 (17.0)	10 (13.3)	.608
Mixed cystic nodule (n = 76)	62 (44.0)	17 (22.7)	.002
Spongioform and cystic (n = 9)	8 (5.7)	1 (1.3)	.167
Lesions ≤ 20 mm (n = 135)			------
Hypoechogenity (n = 81)	29 (42.6)	52 (77.6)	<.001
Isoechogenity or hyperechogenity (n = 12)	6 (8.8)	6 (9.0)	1.000
Mixed echogenity solid (n = 18)	13 (19.1)	5 (7.5)	.082
Mixed cystic nodule	17 (25.0)	3 (4.5)	.002
Spongioform and cystic (n = 4)	3 (4.4)	1 (1.5)	.619
Lesions > 20 mm (n = 118)			-------
Hypoechogenity (n = 22)	13 (15.1)	9 (28.1)	.178
Isoechogenity or hyperechogenity (n = 11)	8 (9.3)	3 (9.4)	1.000
Mixed echogenity solid (n = 19)	14 (16.3)	5 (15.6)	1.000
Mixed cystic nodule (n = 11)	46 (53.5)	15 (46.9)	.666
Spongioform and cystic (n = 5)	5 (5.8)	------	.321

Table 2. Multiple Logistic Regression Analysis for Independent Factors for Predicting Thyroid Malignancy

Ultrasound Features	Beta Coefficient	Odds Ratio	95% CI	*P*
Hypoechogenicity	1.336 ± 0.329	3.804	1.996, 7.250	<.001
Irregüler margin	1.658 ± 0.495	5.249	1.989, 13.856	.001
Microcalcifications	0.998 ± 0.358	2.713	1.344, 5.476	.005
Macrocalcifications	−0.268 ± 0.470	0.671	0.335, 1.343	.569
Type III vascularity	−0.399 ± 0.354	0.765	0.305, 1.923	.260

Table 3. Diagnostic Performance of Nodule Ultrasound Feature Combinations and Malignancy Risk and Bethesda Classification

	Benign Nodules	Malign Nodules	
	n (%)	n (%)	*P*
Hypoechogenicity + irregular margin (n = 26)	1 (3.8)	25 (96.2)	<.001
Hypoechogenicity + microcalcifications (n = 48)	11 (22.9)	37 (77.1)	<.001
Hypoechogenicity + macrocalcifications (n = 12)	4 (33.3)	8 (66.7)	.065
Hypoechogenicity + type III vascularity (n = 31)	16 (51.6)	15 (48.4)	.330
Irregular margin + type III vascularity (n = 11)	1 (9.1)	10 (90.9)	<.001
Irregular margin + microcalcifications (n = 29)	4 (13.8)	25 (86.2)	<.001
Irregular margin + macrocalcifications (n = 4)	-------	4 (100.0)	.022
Microcalcifications + macrocalcifications (n = 22)	10 (45.5)	12 (54.5)	.176
Microcalcifications + type III vascularity (n = 25)	10 (40.0)	15 (60.0)	.037
Macrocalcifications + type III vascularity (n = 11)	7 (63.6)	4 (36.4)	1.000
Hypoechogenicity + microcalcifications + Irregular margin (n = 18)	------	18 (100.0)	<.001
Non-diagnostic I (n = 37)	31 (83.8)	6 (16.2)	
Benign II (n = 78)	72 (92.3)	6 (7.7)	
AUS/FLUS III (n = 67)	44 (65,7)	23 (34.3)	
Follicular neoplasm IV (n = 11)	7 (63.6)	4 (36.4)	
Suspicious of malignancy V (n = 28)	2 (7.1)	26 (92.9)	
Malignancy VI (n = 34)	-------	34 (100.0)	
1 bx non-diagnostic (n = 28)	24 (85.7)	4 (14.3)	
1 bx AUS/FLUS (n = 38)	22 (57.9)	16 (42.1)	
2 bx non-diagnostic (n = 9)	7 (77.8)	2 (22.2)	
2 bx AUS/FLUS (n = 18)	12 (66.7)	6 (33.3)	
1 bx non-diagnostic + 1 bx AUS/FLUS (n = 9)	7 (78.8)	2 (22.2)	

AUS, atypia of undetermined significance; FLUS, follicular lesion of undetermined significance.

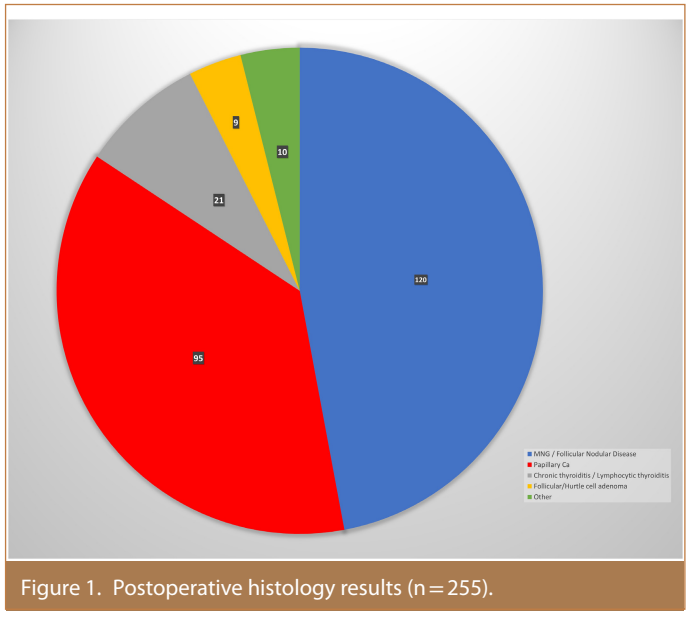

Figure 1. Postoperative histology results (n = 255).

and shortness of breath on exertion following surgery. In the multidisciplinary approach, 1 patient with non-diagnostic cytology was operated on due to compression and the possible benefits of right lobectomy. Subsequently, complementary total thyroidectomy was performed after postoperative histological diagnosis was reported as malignant.

Multidisciplinary approach is commonly preferred in the treatment of postoperative thyroid cancer.[14,15] However, we consider that this approach is highly essential for preoperative evaluation processes in endocrinology practice. Kang et al[16] showed that the administration of repeat USG and cytology in patients who are referred to reference centers due to cytology-biopsy discrepancy can prevent unnecessary surgery. We consider that this procedure can be performed in all centers through adequate communication among the centers.

In a recent study, Suh and Choi suggested that the Thyroid Imaging Reporting and Data System 5 classification and the $BRAF^{V600E}$ genetic

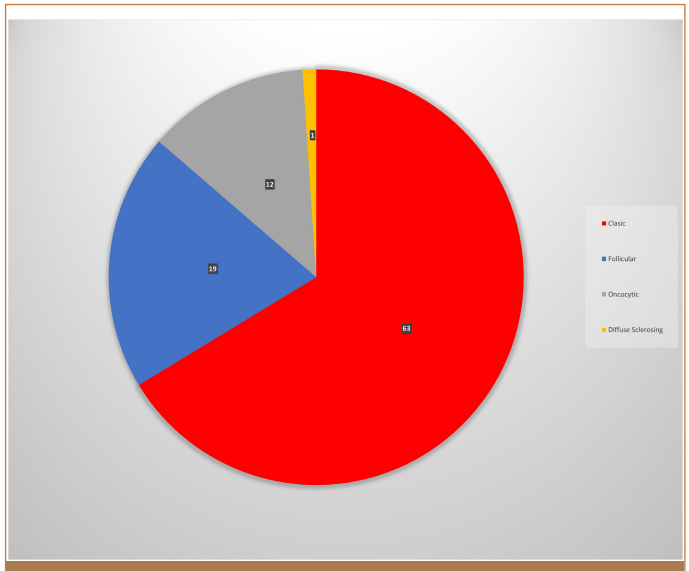

Figure 2. Papillary thyroid cancer subtype (n = 95).

Table 4. Comparison of Multidisciplinary Approach and Non-Multidisciplinary Approach

	Multidisciplinary Approach		Non-Multidisciplinary Approach	
	Benign Histology	Malignant Histology	Benign Histology	Malignant Histology
	n (%)	n (%)	n (%)	n (%)
Non-diagnostic I	------	1 (100.0)	31 (86.5)	5 (13.5)
Benign II	8 (88.9)	1 (11.1)	64 (92.8)	5 (7.2)
AUS/FLUS III	7 (43.8)	9 (56.2)	37 (72.5)	14 (27.5)
Follicular neoplasm IV	2 (66.6)	1 (33.3)	5 (62.5)	3 (37.5)
Suspicious of malignancy V	------	8 (100.0)	2 (10.0)	18 (90.0)
Malignancy VI	------	4 (100.0)	------	30 (100.0)

test are important parameters that should be administered to reduce unnecessary surgery in patients with an AUS/FLUS cytology.[16] Nevertheless, the $BRAF^{V600E}$ genetic test is not performed in many centers and a negative test result has a remarkably low predictive value.[17] Therefore, we suggest that re-evaluation of nodules with indeterminate ultrasonographic features and cytology by an experienced pathologist and radiologist through a multidisciplinary approach will be highly beneficial. Moreover, surgical decisions made by the surgeon alone may create a financial conflict of interests. Accordingly, surgical decisions made by multidisciplinary panel will reduce the error margin and also will distribute the responsibility among physicians, thereby resulting in more accurate decisions.

Conclusion

Margin irregularity had the highest predictive value for the detection of malignancy. Employing the multidisciplinary approach in preoperative evaluation of thyroid nodules can be highly effective in detecting malignancy and preventing unnecessary surgery and may also help reduce patient anxiety, particularly in current issues such as partial thyroidectomy.

Ethics Committee Approval: The study protocol was approved by Karadeniz Technical University, Faculty of Medicine, Ethics Committee (approval date: December 11, 2019; No: 24237859-785).

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.V.K.; Design – S.V.K., H.A.; Supervision – H.O.E.; Resources – E.Ç., Ş.O.; Materials – E.Ç., Ş.O.; Data Collection and/or Processing – E.Ç., S.V.K., H.A.; Analysis and/or Interpretation – S.K., S.V.K; Literature Search – S.V.K.; Writing Manuscript – S.V.K.; Critical Review – H.O.E.

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