Submitted: 09.11.2021
Accepted: 04.01.2022
Early publication date: 13.04.2022

Endokrynologia Polska
DOI: 10.5603/EP.a2022.0027
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 73; Number/Numer 2/2022

The role of thyroid sonographic malignancy risk features when the fine needle aspiration biopsy result is indeterminate

Agnieszka Kotecka-Blicharz[1], Marcela Krzempek[2], Alexander Jorge Cortez[2], Małgorzata Oczko-Wojciechowska[3], Agnieszka Czarniecka[4], Ewa Nożyńska[5], Ewa Chmielik[5], Barbara Jarząb[1], Jolanta Krajewska[1]

[1]*Department of Nuclear Medicine and Endocrine Oncology, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland*
[2]*Department of Biostatistics and Bioinformatics, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland*
[3]*Department of Genetic and Molecular Diagnostics of Cancer, M. Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland*
[4]*The Oncologic and Reconstructive Surgery Clinic, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland*
[5]*Tumor Pathology Department, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland*

Abstract

Introduction: Although the role of the thyroid ultrasound is well established in the initial thyroid nodule work up, it is still equivocal whether the thyroid ultrasound pattern could have an impact on refining malignancy risk after an indeterminate cytopathology result. We aim to assess the possible supportive role of the thyroid nodule ultrasound malignancy risk features listed in the Polish guidelines when a biopsy result is indeterminate.

Material and methods: We retrospectively reviewed thyroid ultrasound scans from 175 adult patients with thyroid nodules and indeterminate cytopathology results, who underwent thyroid surgery. Sonographic malignancy risk features were reported in accordance with the guidelines of the Polish National Societies Diagnostics and Treatment of Thyroid Carcinoma and included the following: solid structure, hypoechogenicity, microcalcifications, taller than wide shape, irregular margins, features of extrathyroidal expansion, suspicious cervical lymph nodes.

Results: The malignancy risk in relevant cytological categories, estimated on the basis of histological verification, was 10.9% for Bethesda III category, 12.1% for Bethesda IV, and 71.4% for Bethesda V. The predominant type of thyroid malignancy was papillary thyroid carcinoma (79%). Thyroid nodules sonographic malignancy risk features provided high specificity but low sensitivity in selected groups of indeterminate thyroid nodules. Microcalcifications was the only characteristic that solely had a clinically relevant positive likelihood ratio (> 10) to suggest malignancy in the analysed cohort, but it was not observed in thyroid nodules eventually verified as follicular thyroid carcinoma. An accumulation of more than one sonographic risk feature yielded significant increase in malignancy risk only in Bethesda V category thyroid nodules.

Conclusions: The impact of sonographic malignancy risk features on refining post-biopsy probability of thyroid cancer in thyroid nodule with indeterminate cytopathology, may be inadequate to sort patients (without any doubt) between those who require thyroid surgery and those who only require surveillance. There is an urgent need to search for new tools in the diagnostics of indeterminate thyroid nodules and to standardize thyroid ultrasound reports. **(Endokrynol Pol 2022; 73 (2): 316–324)**

Key words: *indeterminate thyroid nodule; thyroid nodule; Bethesda system; thyroid ultrasonography; fine needle aspiration biopsy*

Introduction

Ultrasonography of the thyroid nodules has made a huge progress from the late 1970s, when it served only as a tool to identify, localize, and measure focal thyroid lesions, to the present day, when it is used as an easily accessible, non-invasive tool to predict the probability of malignancy in thyroid nodules and triage thyroid nodules for further management, i.e. fine needle aspiration biopsy (FNAB) [1–5]. In 2002 Kim et al. reported 4 ultrasound malignancy attributes: microcalcifications, irregular margins, marked hypoechogenicity, and taller than wide shape, which, with an accuracy 72.9–77.4% of each sign, differentiated malignant from benign thyroid nodules [6]. Since then, many studies have analysed the diagnostic performance of these and other sonographic malignancy risk features, noting their high specificity but rather low sensitivity [7]. This stimulated research-

Agnieszka Kotecka-Blicharz, Department of Nuclear Medicine and Endocrine Oncology, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Wybrzeże Armii Krajowej 15, 44–102 Gliwice, Poland, tel: (+48) 32 278 99 32; e-mail: agnieszka.kotecka-blicharz@io.gliwice.pl

ers to create systems of ultrasound risk stratification in thyroid nodules, based on matching specific ultrasound patterns to the expected risk of malignancy, as a guide for thyroid nodule triage for surveillance or FNAB. Some of these systems were named with the acronym TIRADS (thyroid imaging reporting and data system), and some were constructed as guidelines. Although, the diagnostic performance of the different thyroid ultrasound risk stratification systems varies between studies, some suggest that discrepancies are mostly influenced by the various size thresholds proposed for biopsy referral [8-11]. Unfortunately, the multiplicity of systems impedes universal use worldwide.

To the authors' knowledge, none of the published thyroid ultrasound risk stratification systems is widely implemented in Poland. In the recommendations of the Polish National Societies Diagnostics and Treatment of Thyroid Carcinoma, none of the systems is imposed and sonographic features of increased malignancy risk are listed as single characteristics, which should be taken under consideration when managing patients with thyroid nodules [12]. However, it should be noted, that these features coincide with the sonographic risk features listed in the highest risk categories of different ultrasound systems.

Although the role of thyroid ultrasound is well established in initial thyroid nodule work up, it is still equivocal whether the thyroid ultrasound pattern could have an impact on refining the malignancy risk after FNAB with an indeterminate result. According to the widely accepted Bethesda System for Reporting Thyroid Cytopathology, the indeterminate cytopathology results contain Bethesda III category — atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), Bethesda IV category — follicular neoplasm/suspicious for follicular neoplasms (FN/SFN), and Bethesda V category — suspicious for malignancy (SM). The indetermined character of the aforementioned categories results from the wide range of malignancy risk assigned to them, being not low enough to just ignore or not high enough to strongly recommend surgery, especially in the AUS/FLUS category, in which it ranges from 6 to 30%, and in the FN/SFN category with 10% to 40%. The estimated risk for the SM category is higher, ranging from 45% to 75%, being high enough to refer a patient for surgery, although the extent of surgery may remain debatable [13].

Obviously, management of thyroid nodules with indeterminate cytopathology should be a continuous pathway of diagnostic steps, playing a supportive role in malignancy risk stratification. A thorough investigation of the patient's medical history and a careful search for symptoms, which may indicate thyroid malignancy and the ultrasonographic assessment of the neck area, are not to be overestimated. Nevertheless, in the era of "thyroid incidentaloma epidemic" we must face the patients usually with no complaints and no positive family history. Furthermore, data regarding supportive role of ultrasound pattern in the aforementioned clinical situation are divergent. Recently a comprehensive study from another Polish centre, appraising the diagnostic performance of 6 different TIRADS in a subgroup of 540 cytologically indeterminate thyroid nodules in the Polish population, showed a limited role of ultrasound risk stratification systems in this particular group of thyroid nodules [14].

In our analysis, we aimed to assess the possible supportive role of thyroid nodule ultrasound malignancy risk features listed in the Polish recommendations, when the FNAB result is indeterminate. Our attempt focused on determining the extent to which the sonographic risk characteristics, found in cytologically indeterminate thyroid nodules, may dispel uncertainty about malignancy risk and influence further management in this group of patients.

Material and methods

We retrospectively reviewed thyroid ultrasound imaging from 175 adult patients with 175 thyroid nodules, who underwent fine needle aspiration thyroid biopsy, as part of the project STRATEGMED2/267398/4/NCBR/2015 between 2014 and 2016, with indeterminate cytopathology result falling in one of three categories: Bethesda III (AUS/FLUS), Bethesda IV (SFN/FN), or Bethesda V category (SM), who underwent thyroid surgery. All patients provided informed consent. The project was approved by the Local Bioethical Commission. The analysed cohort was part of the larger series of thyroid nodules previously analysed by the authors [submitted].

Fine needle aspiration biopsies of thyroid nodules were performed using capillary ultrasound-guided technique with 25–27-gauge needle, by an experienced pathologist. The cytopathology results were classified accordingly to the Bethesda System for Reporting Thyroid Cytopathology and confirmed by 2 independent pathologists. The AUS/FLUS diagnosis in the analysis herein was always the result of repeated biopsy.

The clinical decision to refer a patient for surgery was made by the attending physician according to the clinical circumstances.

The final diagnosis was determined on the basis of the histopathological analysis, obtained after thyroid surgical procedure, performed in our Institute or in external hospitals. 122 patients were operated on at our Institute. In 25 of 53 surgeries performed in external centres, histological analysis of our pathologists was available, encompassing all malignant lesions. Hence, the central histopathological analysis from our institute was available for 147 (84%) postoperative specimens. Each histopathology report was matched to a cytopathology one, to verify the location and character of the index thyroid nodule.

The ultrasound features of thyroid nodules were reviewed retrospectively by one experienced endocrinologist on the basis of the description and digital image, if available, of the last ultrasound scan preceding the fine needle aspiration biopsy. The ultrasound was performed using a Philips HDI 5000 Ultrasound System (Philips Healthcare, Netherlands) with a linear 5–12 mHz probe or Samsung Medison HS70A (Samsung Healthcare, South Korea) with a linear 3–12 mHz probe, in real time, by an endocrinologist or a radiologist trained in thyroid ultrasound.

Sonographic malignancy risk features were reported for each index thyroid nodule, in accordance with the recommendations of the Polish National Societies Diagnostics and Treatment of Thyroid Carcinoma, and it included the following: solid structure, hypoechogenicity, microcalcifications, taller than wide shape (assuming ratio of height to width above 1.0 as positive), irregular margins, features of extrathyroidal expansion, and suspicious cervical lymph nodes. Regarding the inconsistency in available descriptions, thyroid nodule vascularity was not assessed in the analysis herein.

Statistical analysis

Categorical variables were summarized as frequencies and percentages unless otherwise stated. Pairwise comparisons between patient subgroups were performed by Fisher's exact test for nominal variables. For continuous variables comparisons between 2 groups were made using the Wilcoxon rank sum test, and for more than 2 patient subgroups we used the Kruskal-Wallis H test. Effect size was assessed with odds ratio and proportion difference. All analyses were performed using R environment for statistical computing version 4.0.3 "Bunny-Wunnies Freak Out" released on 10 October 2020 (R Foundation for Statistical Computing, Vienna, Austria). We considered a 2-sided p-value < 0.05 as statistically significant.

Results

The analysis included 175 adult patients with 175 thyroid nodules with indeterminate cytopathology, 46 nodules in Bethesda III category, 66 in Bethesda IV category, and 63 in Bethesda V category (Tab. 1). The median patient's age was 52 years with female preponderance (86%). Patients from the Bethesda V cohort were significantly younger. Only 6.3% of patients presented with symptoms, and in 3.4% of them clinical risk factors were present. The median nodule size in the whole group was 16 mm. Thyroid nodules in the Bethesda V category were significantly smaller than in the Bethesda III and IV category. All analysed

Table 1. *Cohort characteristics*

	All (n = 175)	Bethesda III (n = 46)	Bethesda IV (n = 66)	Bethesda V (n = 63)	p value
Age					
Median [years]	52	52	57	49	0.010
IQR	41.5–63.0	46.0–58.7	45.0–67.0	35.0–59.0	
Gender					
Female [no. (%)]	150 (85.7%)	39 (84.8%)	59 (89.4%)	52 (82.5%)	0.540
Male [no. (%)]	25 (14.3%)	7 (15.2%)	7 (10.6%)	11 (17.5%)	
Clinical risk factors [no. of patients]	6 (3.4%)	1 (2.2%)	2 (3.0%)	3 (4.8%)	0.769
Symptoms [no. of patients]	11 (6.3%)	4 (8.7%)	4 (6.1%)	3 (4.8%)	0.679
Nodule size					
Median [mm]	16	19	18	13	
IQR	11.0–27.0	13.2–29.7	11.0–27.0	10.0–22.5	
≤ 10mm [no. (%)]	41 (23.4%)	6 (13.0%)	15 (22.7%)	20 (31.7%)	0.034
11–20 mm [no. (%)]	72 (41.1%)	20 (43.5%)	26 (39.4%)	26 (41.3%)	
21–39 mm [no. (%)]	45 (25.7%)	14 (30.5%)	20 (30.3%)	11 (17.5%)	
≥ 40 mm [no. (%)]	17 (9.7%)	6 (13.0%)	5 (7.6%)	6 (9.5%)	
Sonographic features [nodules no. (%)]					
Hypoechogenicity	114 (65.1%)	27 (58.7%)	46 (69.7%)	41 (65.1%)	0.500
Microcalcifications	7 (4%)	1 (2.2%)	0 (0.0%)	6 (9.5%)	0.013
Taller than wide shape	17 (9.7%)	1 (2.2%)	10 (15.2%)	6 (9.5%)	0.069
Irregular margins	19 (10.9%)	2 (4.3%)	3 (4.5%)	14 (22.2%)	0.002
Extrathyroidal extension	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000
Suspicious cervical lymph nodes	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0.623
Solidity	175 (100%)	46 (100%)	66 (100%)	63 (100%)	1.000
Malignant thyroid nodules [no. (%)]	58 (33.1%)	5 (10.9%)	8 (12.1%)	45 (71.4%)	< 0.001
Malignant histology subtypes [no. (%of malignant)]					0.003
Papillary thyroid cancer	46 (79.3%)	2	4	40	

Table 1. *Cohort characteristics*

	All (n = 175)	Bethesda III (n = 46)	Bethesda IV (n = 66)	Bethesda V (n = 63)	p value
Follicular thyroid cancer	6 (10.3%)	2	4	0	< 0.001
Others:					
Poorly differentiated thyroid cancer	2 (3.4%)	0	0	2	1.000
Medullary thyroid cancer	3 (5.2%)	1	0	2	0.283
Thyroid lymphoma	1(1.7%)	0	0	1	1.000
Benign thyroid nodules [no. (%)]	117 (66.9%)	41 (89.1%)	58 (87.9%)	18 (28.6%)	< 0.001
Benign histology subtypes [no. (% of benign)]					
Nodular hyperplasia	62 (53.0%)	27	23	12	0.018
Follicular adenoma	47 (40.2%)	12	31	4	0.014
Trabecular hyalinizing tumour	4 (3.4%)	0	2	2	0.102
FTUMP	2 (1.7%)	1	1	0	1.000
NIFTP	1 (0.9%)	1	0	0	0.504
Thyroiditis	1 (0.9%)	0	1	0	1.000

IQR — interquartile rate; FTUMP — follicular tumour of uncertain malignant potential; NIFTP — noninvasive follicular tumour with papillary-like nuclear features

nodules were solid on ultrasound examination. The majority of nodules were hypoechoic (65.1%). There were no features of extrathyroidal extension in the analysed thyroid nodules. In one case suspicious cervical lymph nodes were reported. Microcalcifications were observed in 7 nodules (6.0%), taller than wide shape in 17 nodules (9.7%), and irregular margins in 19 nodules (10.9%). Microcalcification and irregular margins were seen significantly more often in the Bethesda V cohort. Histological analysis identified 58 (33.1%) malignant lesions. The malignancy risk in relevant cytological categories, estimated on the basis of histological verification was 10.9% for the Bethesda III category, 12.1% for Bethesda IV, and 71.4% for Bethesda V. The predominant type of thyroid malignancy was papillary thyroid cancer (79%), with most cases (87%) in the group of Bethesda V category. Concurrently, papillary thyroid carcinoma accounted for 40% of all malignancies in Bethesda III category, for 50% in Bethesda IV category, and for 89% in Bethesda V. Whereas follicular thyroid carcinoma was diagnosed in 10% of malignant thyroid nodules with all cases preoperatively assigned to cytological categories Bethesda III and IV exclusively. The remaining 10% of malignancies included medullary thyroid carcinoma, poorly differentiated thyroid carcinoma, and lymphoma. Among benign nodules, besides nodular hyperplasia, follicular adenoma was the most prevalent diagnosis, accounting for about 40% of all benign lesion.

The comparative characteristics of benign and malignant thyroid lesions are shown in Table 2. Patients with malignant thyroid nodules were significantly younger and the median diameter of malignant lesions was significantly smaller. Microcalcifications and irregular margins were seen significantly more often in the cohort of malignant thyroid nodules. Simultaneously, it is worth noting that these 2 features were not observed in the follicular thyroid carcinoma, and the microcalcifications were absent in the cohort of the follicular variant of papillary thyroid carcinoma. The prevalence of sonographic risk features regarding the type of thyroid cancer is depicted in Figure 1. Nevertheless, the observed differences between papillary thyroid carcinoma, its classic and follicular variants, and follicular carcinoma did not reach statistical significance.

The diagnostic performance of singular ultrasonographic risk features is shown in Table 3. Taller than wide shape, microcalcifications, and irregular margins yielded high specificity of more than 90% with simultaneously very low sensitivity. Hypoechogenicity showed sensitivity of about 70% with specificity slightly below 40%. The highest odds ratio and positive likelihood ratio were observed for microcalcifications, with scores of 13.38 and 12.1, respectively. Lower values were observed for irregular margins: respectively, 5.34 and 4.37. The odds ratio and positive likelihood ratio for hypoechogenicity were around 1.0.

Assuming the pre-test probability of malignancy in thyroid nodules with indeterminate cytopathology result as 10.9% for Bethesda III category, 12.1% for Bethesda IV category, and 71.4% for Bethesda V category, as calculated from histology outcomes, we

Table 2. *Comparative characteristics between benign and malignant thyroid nodules (Note: row percentages are shown)*

	Benign nodule (n = 117)	Malignant nodule (n = 58)	p value
Median age [years]	54	47.5	0.029
IQR	45.0–63.0	35.25–60.5	
Gender			
Females [no. (%)]	100 (66.7%)	50 (33.3%)	1
Males [no. (%)]	17 (68%)	8 (32%)	
Clinical risk factors [no. of patients (%)]	3 (50%)	3 (50%)	0.399
Symptoms [no. of patients (%)]	7 (63.6%)	4 (36.4%)	1
Median nodule size [mm]	18	14	0.041
IQR	12.0–28.0	10–22.75	
Bethesda III [no. (%)]	41 (89.1%)	5 (10.8%)	< 0.001
Bethesda IV [no. (%)]	58 (87.9%)	8 (12.1%)	
Bethesda V [no. (%)]	18 (28.6%)	45 (71.4%)	
Solid structure [no. (%)]	117 (66.9%)	58 (33.1%)	1.000
Hypoechogenicity [no. (%)]	74 (64.9%)	40 (35.1%)	0.503
Microcalcifications [no. (%)]	1 (14.3%)	6 (85.7%)	0.006
Taller than wide shape [no. (%)]	8 (47.1%)	9 (52.9%)	0.101
Irregular margins [no. (%)]	6	13	0.001
Extrathyroidal extension [no. (%)]	0	0	1.000
Suspicious cervical lymph nodes [no. (%)]	0 (0%)	1 (100%)	0.331

IQR — interquartile rate

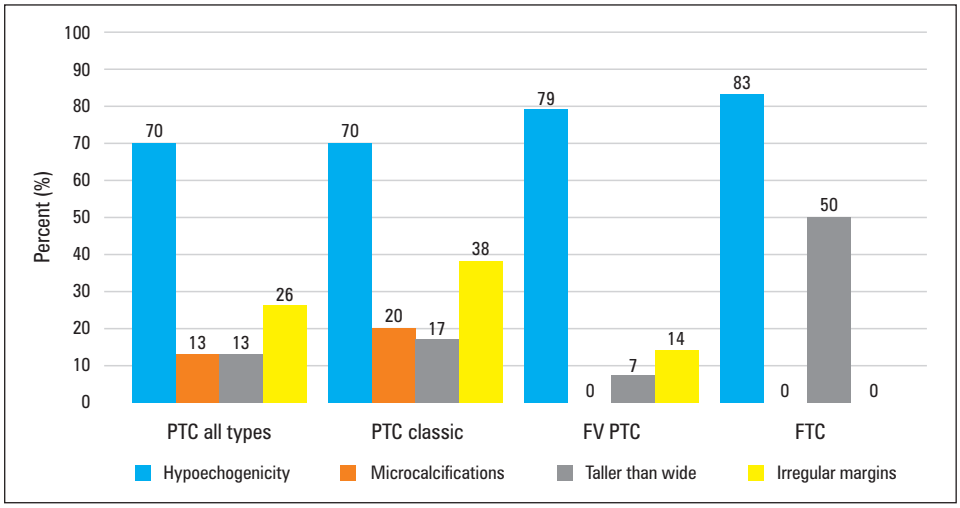

Figure 1. *Comparison of ultrasonographic malignancy risk features among classic variants of papillary thyroid carcinoma, follicular variant of papillary thyroid carcinoma, and follicular thyroid carcinoma. PTC — papillary thyroid carcinoma; FV — follicular variant; FTC — follicular thyroid carcinoma*

analysed how identification of one or more additional sonographic risk features in solid thyroid nodules would modify the estimated malignancy risk (Tab. 4). Only in Bethesda V category of thyroid nodules, the cumulation of more than one sonographic risk feature yielded a significantly increased risk of malignancy. In Bethesda IV category, we observed a rise in the estimated risk of malignancy, in line with the increase in the number of sonographic risk features but without statistical significance. In Bethesda III category there was no solid thyroid nodule with more than one sonographic risk feature apart from solid structure.

Table 3. *Diagnostic performance of single ultrasonographic malignancy risk features in thyroid nodules with indeterminate cytopathology*

	Taller than wide shape	Irregular margins	Microcalcifications	Hypoechogenicity
Sensitivity	15.52%	22.41%	10.34%	68.97%
95% CI	7.35–27.42%	12.51–35.27%	3.89–21.17%	55.46–80.46%
Specificity	93.16%	94.87%	99.15%	36.75%
95% CI	86.97–97.00%	89.17–98.10%	95.33–99.98%	28.03–46.16%
PPV	52.94%	68.42%	85.71%	35.09%
95% CI	27.81–77.02%	43.45–87.42%	42.13–99.64%	26.38–44.59%
NPV	68.99%	71.15%	69.04%	70.49%
95% CI	61.15–76.10%	63.37–78.12%	61.47–75.94%	57.43–81.48%
Odds ratio	2.50	5.34	13.38	1.29
95% CI	0.91–6.87	1.91–14.93	1.57–114.00	0.66–2.53
Likelihood ratio+	2.27	4.37	12.10	1.09
95% CI	0.92–5.58	1.75–10.91	1.49–98.20	0.87–1.36

CI — confidence interval; PPV — positive predictive value; NPV — negative predictive value

Table 4. *Risk of malignancy in particular cytological categories according to the presence of ultrasonographic malignancy risk features*

	Risk of malignancy estimated on FNAB result	Solid structure with no other risk feature	Solid structure with one risk feature	Solid structure with two risk features	Solid structure with three or more risk features	p-value
Bethesda III (n = 46)	5/46	2/18	3/25	0/3	–	1.000
	10.9%	11.1%	12%	0%		
Bethesda IV (n = 66)	8/66	2/18	3/37	3/11	–	0.252
	12.1%	11.1%	8.1%	27.3%		
Bethesda V (n = 63)	45/63	14/21	13/24	13/13	5/5	0.008
	71.4%	66.7%	54.2%	100%	100%	

Discussion

The group of patients with indeterminate results of fine needle aspiration thyroid biopsy is the most challenging in clinical practice. Realizing that a lot of these thyroid lesions prove to be benign after histopathological analysis, guiding directly to surgery will expose the patient to possible life-long complications dealing with eventually benign lesion, which probably would never have any impact on patient's morbidity. On the other hand, leaving indetermined thyroid nodules for surveillance may cause fear of failing to omit clinically significant thyroid malignancies. This cumbersome clinical situation may become a problem even for experienced clinicians. Unfortunately, our analysis suggests that the supportive role of sonographic malignancy risk features is suboptimal in refining malignancy risk, estimated due to an indeterminate cytopathology result, and it may be insufficient to drive clinical decision-making for further management. Among the analysed ultrasound malignancy risk features, microcalcifications were the only characteristics that achieved a clinically relevant positive likelihood ratio (> 10) to suggest malignancy in the analysed cohort. Although we observed an odds ratio of 13.38 for microcalcifications and 5.34 for irregular margins, no microcalcifications or irregular margins were observed in indeterminate thyroid nodules, eventually verified as follicular thyroid carcinoma. Although differences in the frequency of sonographic risk features occur between papillary thyroid carcinoma classic and follicular variants and follicular carcinoma, it did not reach statistical significance in our study, which may be due to the relatively low number of malignant thyroid nodules in the analysed cohort. According to the literature data, follicular thyroid carcinoma frequently corresponds, in ultrasound assessment, to low-risk patterns without well-known ultrasound risk features [15, 16]. Moreover, a lot of studies assessing the thyroid ultrasound risk stratification systems exclude cytologically indeterminate thyroid nodules, which results in lower

prevalence of follicular thyroid carcinoma [17]. In our analysis, follicular thyroid carcinoma was exclusively within the Bethesda III and IV groups and accounted for, respectively, 40 and 50% of all malignancies in these categories, as well as for 10% of all malignancies in the whole cohort. By comparison, in one of the studies on unselected thyroid nodules the prevalence of follicular thyroid carcinoma did not exceed 6.0% [18]. In the metanalysis of Brito et al., the type of thyroid cancer influenced the diagnostic odds ratio for echogenic features of the thyroid nodules; in studies in which more than 90% of cancers were papillary, the OR was higher in comparison to studies in which less than 90% of cancers were papillary. Moreover, they demonstrated the poorer diagnostic performance of sonographic risk features in the subgroup of exclusively indeterminate thyroid nodules as compared to the unselected ones [19]. Likewise, Remonti et al. in their metanalysis showed a positive likelihood ratio of 3.26 for microcalcifications and 1.66 for hypoechogenicity in unselected thyroid nodules with significant decline to 2.52 for microcalcifications and to 1.12 for hypoechogenicity in indeterminate thyroid nodules [20].

In our study, the highest odds ratio and positive likelihood ratio were observed for microcalcifications, contrary to the aforementioned meta-analyses of unselected thyroid nodules, in which taller than wide shape was the most robust malignancy risk feature with odds ratio of above 10.0 and positive likelihood ratio of about 8.0. In our analysis, the feature "taller than wide shape" was not as clinically significant with OR = 2.5 (95% CI: 0.91–6.87). This might be due to the specified selected group of exclusively indeterminate thyroid nodules in our analysis. Similarly in the meta-analysis of Borowczyk et al., concerning only thyroid follicular neoplasms, taller than wide shape did not play an important role in the case of follicular thyroid carcinoma, with OR 2.73 (95% CI, 1.02-5.86) [21]. The assumed definition of this particular sonographic feature, i.e. an excess of anteroposterior diameter (AP) in relation to transverse (T) diameter, without specifying any minimum magnitude, may also be relevant. If so, even an excess of 1 mm could constitute a positive result. The intra- and interobserver variability in reporting thyroid nodule diameters seen in the literature might be a crucial issue in these circumstances [22]. In the report by Grani G. et al., application of the definition of taller than wide shape as the AP/T ≥ 1.2 contributed to the increased odds ratio of this sonographic feature, as compared to the definition applied in our analysis [23].

In our study, microcalcifications, irregular margins, and taller than wide shape yielded a high specificity above 90% but with a relatively low sensitivity of below 30%. In the meta-analysis of Remonti et al., including unselected thyroid nodules, the authors reported also a high specificity of these sonographic malignancy risk features of above 80% with sensitivity as low as 26.7% for taler than wide shape, 39.5% for macrocalcifications as well as 50.5% for irregular margins [20]. These results indicate that the presence of some sonographic risk features identifies thyroid nodules with increased risk of malignancy, but none of the sonographic characteristics in isolation is capable to sufficiently diagnose malignancy, especially in indeterminate thyroid nodules. The idea of the malignancy risk increasing with the increase in the number of sonographic features was applied in a risk stratification system named Kwak-TIRADS published in 2011 [24]. Conducted by Migda et al., a metanalysis on the use of Kwak-TIRADS for the diagnostic assessment of indeterminate nodules showed that the cut-off point between risk category 4a, corresponding to the presence of one risk feature, and 4b, denoting 2 risk features, was characterised by increased specificity but decreased sensitivity compared with the cut-off in which a single risk feature was regarded as a positive test [25]. In our analysis, we observed an increase in malignancy risk in line with an increasing number of sonographic features in Bethesda IV and V categories, but the rise was statistically significant only in the Bethesda V category. We did not observe accumulation of more than one sonographic risk feature in Bethesda III category thyroid nodules.

Due to continued implementation of new thyroid ultrasound stratifications systems, for about the last 10 years we have observed a rising number of reports investigating the dilemma of their supportive role in the management of thyroid nodules with indeterminate cytopathology. Słowińska Klencka et al. assessed the diagnostic performance of 6 TIRADS in 540 cytologically equivocal thyroid nodules in the Polish population. In the mentioned report, only the assignment of the thyroid nodule to the highest risk TIRADS category increased the estimated malignancy risk, but significant differences were observed only in the Bethesda III category [14].

Drawing unequivocal conclusions from studies is hampered by differences in used methods and estimated risk of malignancy in indeterminate thyroid nodules in different populations. Undoubtedly, the limitations of our analysis also imply the need for careful drawing of conclusions. In our study ultrasound examination preceding FNAB was done by several endocrinologists and radiologists, and we did not explore the interobserver variability. Existing data indicate possible substantial interobserver variation in the assessment and reporting of some ultrasound features and patterns [26,27]. Thus, the risk of misclassifying the sonographic features must be taken under

consideration. Moreover, cytopathology analyses were conducted by experienced pathologists from a highly specialized centre, which does not reflect everyday clinical practice. According to the report of Cibas et al., interobserver concordance between local and central pathologists was the lowest in Bethesda III and V category — 34.9% and 36.8%, respectively [28]. Furthermore AUS/FLUS diagnosis in the analysis herein was the result of repeated FNAB, which might influence the decision about referring patients for surgery and modifying the final risk of malignancy assigned to this category when estimated exclusively upon histologic reports. In addition, the low malignancy rates, especially in Bethesda III and IV categories, observed in our cohort result in a low number of malignant lesions, in particular follicular thyroid carcinoma, which may contribute to underpowered conclusions. Finally, a notable limitation is the retrospective nature of the study.

The role of thyroid ultrasound in the initial thyroid nodule work up is well established and was thoroughly assessed by other Polish centres experienced in this field [29–32]. Our aim was to establish the role of ultrasound features after fine needle aspiration biopsy, when its result is indeterminate. The presented results indicate that the impact of sonographic malignancy risk features on refining the post-biopsy probability of thyroid cancer in thyroid nodules with indeterminate cytopathology may be not sufficiently robust. Undoubtedly, there is an urgent need for additional tools in the diagnostic work up of indeterminate thyroid nodules in Polish clinical practice. Reports concerning the use of molecular tests in the diagnostic pathway are encouraging [32, 33]. Unfortunately, the use of commercially available ones, mainly created in the United States, is limited by extremely high costs. Studies conducted in Poland regarding the diagnostic performance of molecular tests in indeterminate thyroid nodules are currently limited to clinical trials and single-centre studies, but this might be the first step to their use in everyday practice [34, 35].

Conclusions

Single sonographic malignancy risk features provide high specificity but low sensitivity in the selected group of indeterminate thyroid nodules. Follicular thyroid carcinoma, which often preoperatively falls in indeterminate cytological categories, may present an ultrasound pattern without known risk characteristics. The impact of sonographic malignancy risk features on refining post-biopsy probability of thyroid cancer in thyroid nodules with indeterminate cytopathology is not sufficient to classify patients as those requiring thyroid surgery and those who may only require surveillance. There is an urgent need to find new diagnostic tools in indeterminate thyroid nodules and to standardize thyroid ultrasound reports.

Conflict of interest

Not declared.

Funding

The study was supported by the National Centre for Research and Development project under the program "Prevention practices and treatment of civilization diseases" STRATEGMED (STRATEGMED2/267398/4/NCBR/2015). The author AJC was co-financed by the European Union through the European Social Fund (grant no. POWR.03.02.00-00-I029).

ORIGINAL PAPER

References

1. Scheible W, Leopold GR, Woo VL, et al. High-resolution real-time ultrasonography of thyroid nodules. Radiology. 1979; 133(2): 413–417, doi: 10.1148/133.2.413, indexed in Pubmed: 582856.
2. Katz JF, Kane RA, Reyes J, et al. Thyroid nodules: sonographic-pathologic correlation. Radiology. 1984; 151(3): 741–745, doi: 10.1148/radiology.151.3.6718735, indexed in Pubmed: 6718735.
3. Shen Y, Liu M, He J, et al. Comparison of Different Risk-Stratification Systems for the Diagnosis of Benign and Malignant Thyroid Nodules. Front Oncol. 2019; 9: 378, doi: 10.3389/fonc.2019.00378, indexed in Pubmed: 31139568.
4. Migda B, Słapa R, Bierca J, et al. Differentiation of thyroid nodules in multinodular goiter with the application of technical ultrasound advances - initial results. Endokrynol Pol. 2016; 67(2): 157–165, doi: 10.5603/EP.a2016.0026, indexed in Pubmed: 26884295.
5. Migda B, Migda M, Migda AM, et al. Evaluation of Four Variants of the Thyroid Imaging Reporting and Data System (TIRADS) Classification in Patients with Multinodular Goitre - initial study. Endokrynol Pol. 2018; 69(2): 156–162, doi: 10.5603/EP.a2018.0012, indexed in Pubmed: 29334119.
6. Kim EK, Park CS, Chung WY, et al. New sonographic criteria for recommending fine-needle aspiration biopsy of nonpalpable solid nodules of the thyroid. AJR Am J Roentgenol. 2002; 178(3): 687–691, doi: 10.2214/ajr.178.3.1780687, indexed in Pubmed: 11856699.
7. Russ G, Leboulleux S, Leenhardt L, et al. Thyroid incidentalomas: epidemiology, risk stratification with ultrasound and workup. Eur Thyroid J. 2014; 3(3): 154–163, doi: 10.1159/000365289, indexed in Pubmed: 25538897.
8. Maino F, Forleo R, Martinelli M, et al. Prospective Validation of ATA and ETA Sonographic Pattern Risk of Thyroid Nodules Selected for FNAC. J Clin Endocrinol Metab. 2018; 103(6): 2362–2368, doi: 10.1210/jc.2018-00274, indexed in Pubmed: 29672763.
9. Castellana M, Castellana C, Treglia G, et al. Performance of Five Ultrasound Risk Stratification Systems in Selecting Thyroid Nodules for FNA. J Clin Endocrinol Metab. 2020; 105(5), doi: 10.1210/clinem/dgz170, indexed in Pubmed: 31690937.
10. Yim Y, Na DG, Ha EJu, et al. Concordance of Three International Guidelines for Thyroid Nodules Classified by Ultrasonography and Diagnostic Performance of Biopsy Criteria. Korean J Radiol. 2020; 21(1): 108–116, doi: 10.3348/kjr.2019.0215, indexed in Pubmed: 31920034.
11. Ha SuM, Baek JH, Na DG, et al. Diagnostic Performance of Practice Guidelines for Thyroid Nodules: Thyroid Nodule Size versus Biopsy Rates. Radiology. 2019; 291(1): 92–99, doi: 10.1148/radiol.2019181723, indexed in Pubmed: 30777805.
12. Jarząb B, Dedecjus M, Słowińska-Klencka D, et al. Guidelines of Polish National Societies Diagnostics and Treatment of Thyroid Carcinoma. 2018 Update. Endokrynol Pol. 2018; 69(1): 34–74, doi: 10.5603/EP.2018.0014, indexed in Pubmed: 29442352.
13. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. Thyroid. 2017; 27(11): 1341–1346, doi: 10.1089/thy.2017.0500, indexed in Pubmed: 29091573.
14. Słowińska-Klencka D, Wysocka-Konieczna K, Klencki M, et al. Diagnostic Value of Six Thyroid Imaging Reporting and Data Systems (TIRADS) in Cytologically Equivocal Thyroid Nodules. J Clin Med. 2020; 9(7), doi: 10.3390/jcm9072281, indexed in Pubmed: 32709122.
15. Jeh Sk, Jung SoL, Kim BS, et al. Evaluating the degree of conformity of papillary carcinoma and follicular carcinoma to the reported ultrasonographic findings of malignant thyroid tumor. Korean J Radiol. 2007; 8(3): 192–197, doi: 10.3348/kjr.2007.8.3.192, indexed in Pubmed: 17554185.
16. Kim DS, Kim Jh, Na DG, et al. Sonographic features of follicular variant papillary thyroid carcinomas in comparison with conventional papillary thyroid carcinomas. J Ultrasound Med. 2009; 28(12): 1685–1692, doi: 10.7863/jum.2009.28.12.1685, indexed in Pubmed: 19933483.

17. Trimboli P, Castellana M, Piccardo A, et al. The ultrasound risk stratification systems for thyroid nodule have been evaluated against papillary carcinoma. A meta-analysis. Rev Endocr Metab Disord. 2021; 22(2): 453–460, doi: 10.1007/s11154-020-09592-3, indexed in Pubmed: 32959174.
18. Angell TE, Maurer R, Wang Z, et al. A Cohort Analysis of Clinical and Ultrasound Variables Predicting Cancer Risk in 20,001 Consecutive Thyroid Nodules. J Clin Endocrinol Metab. 2019; 104(11): 5665–5672, doi: 10.1210/jc.2019-00664, indexed in Pubmed: 31310316.
19. Brito JP, Gionfriddo MR, Al Nofal A, et al. The accuracy of thyroid nodule ultrasound to predict thyroid cancer: systematic review and meta-analysis. J Clin Endocrinol Metab. 2014; 99(4): 1253–1263, doi: 10.1210/jc.2013-2928, indexed in Pubmed: 24276450.
20. Remonti LR, Kramer CK, Leitão CB, et al. Thyroid ultrasound features and risk of carcinoma: a systematic review and meta-analysis of observational studies. Thyroid. 2015; 25(5): 538–550, doi: 10.1089/thy.2014.0353, indexed in Pubmed: 25747526.
21. Borowczyk M, Woliński K, Więckowska B, et al. Sonographic Features Differentiating Follicular Thyroid Cancer from Follicular Adenoma-A Meta-Analysis. Cancers (Basel). 2021; 13(5), doi: 10.3390/cancers13050938, indexed in Pubmed: 33668130.
22. Lee HJ, Yoon DY, Seo YL, et al. Intraobserver and Interobserver Variability in Ultrasound Measurements of Thyroid Nodules. J Ultrasound Med. 2018; 37(1): 173–178, doi: 10.1002/jum.14316, indexed in Pubmed: 28736947.
23. Grani G, Lamartina L, Ramundo V, et al. Taller-Than-Wide Shape: A New Definition Improves the Specificity of TIRADS Systems. Eur Thyroid J. 2020; 9(2): 85–91, doi: 10.1159/000504219, indexed in Pubmed: 32257957.
24. Kwak JY, Han KH, Yoon JH, et al. Thyroid imaging reporting and data system for US features of nodules: a step in establishing better stratification of cancer risk. Radiology. 2011; 260(3): 892–899, doi: 10.1148/radiol.11110206, indexed in Pubmed: 21771959.
25. Migda B, Migda M, Migda MS. A systematic review and meta-analysis of the Kwak TIRADS for the diagnostic assessment of indeterminate thyroid nodules. Clin Radiol. 2019; 74(2): 123–130, doi: 10.1016/j.crad.2018.09.009, indexed in Pubmed: 30482561.
26. Lam CA, McGettigan MJ, Thompson ZJ, et al. Ultrasound characterization for thyroid nodules with indeterminate cytology: inter-observer agreement and impact of combining pattern-based and scoring-based classifications in risk stratification. Endocrine. 2019; 66(2): 278–287, doi: 10.1007/s12020-019-02000-0, indexed in Pubmed: 31300961.
27. Persichetti A, Di Stasio E, Coccaro C, et al. Inter- and Intraobserver Agreement in the Assessment of Thyroid Nodule Ultrasound Features and Classification Systems: A Blinded Multicenter Study. Thyroid. 2020; 30(2): 237–242, doi: 10.1089/thy.2019.0360, indexed in Pubmed: 31952456.
28. Cibas ES, Baloch ZW, Fellegara G, et al. A prospective assessment defining the limitations of thyroid nodule pathologic evaluation. Ann Intern Med. 2013; 159(5): 325–332, doi: 10.7326/0003-4819-159-5-201309030-00006, indexed in Pubmed: 24026318.
29. Skowrońska A, Milczarek-Banach J, Wiechno W, et al. Accuracy of the European Thyroid Imaging Reporting and Data System (EU-TIRADS) in the valuation of thyroid nodule malignancy in reference to the post-surgery histological results. Pol J Radiol. 2018; 83: e579–e586, doi: 10.5114/pjr.2018.81556, indexed in Pubmed: 30800196.
30. Dobruch-Sobczak K, Adamczewski Z, Szczepanek-Parulska E, et al. Histopathological Verification of the Diagnostic Performance of the EU-TIRADS Classification of Thyroid Nodules-Results of a Multicenter Study Performed in a Previously Iodine-Deficient Region. J Clin Med. 2019; 8(11), doi: 10.3390/jcm8111781, indexed in Pubmed: 31731455.
31. Szczepanek-Parulska E, Wolinski K, Dobruch-Sobczak K, et al. S-Detect Software vs. EU-TIRADS Classification: A Dual-Center Validation of Diagnostic Performance in Differentiation of Thyroid Nodules. J Clin Med. 2020; 9(8), doi: 10.3390/jcm9082495, indexed in Pubmed: 32756510.
32. Steward DL, Carty SE, Sippel RS, et al. Performance of a Multigene Genomic Classifier in Thyroid Nodules With Indeterminate Cytology: A Prospective Blinded Multicenter Study. JAMA Oncol. 2019; 5(2): 204–212, doi: 10.1001/jamaoncol.2018.4616, indexed in Pubmed: 30419129.
33. Patel KN, Angell TE, Babiarz J, et al. Performance of a Genomic Sequencing Classifier for the Preoperative Diagnosis of Cytologically Indeterminate Thyroid Nodules. JAMA Surg. 2018; 153(9): 817–824, doi: 10.1001/jamasurg.2018.1153, indexed in Pubmed: 29799911.
34. Kowalska A, Kowalik A, Pałyga I, et al. The usefulness of determining the presence of BRAF V600E mutation in fine-needle aspiration cytology in indeterminate cytological results. Endokrynol Pol. 2016; 67(1): 41–47, doi: 10.5603/EP.2016.0006, indexed in Pubmed: 26884114.
35. Oczko-Wojciechowska M. Assessment of the use of a molecular classifier in the diagnosis of thyroid nodules in the minimum amount of material collected by fine-needle biopsy. Polish Endocrine Cancer Group, Gliwice 2019.