ORIGINAL ARTICLE

Thyroid nodules with indeterminate cytopathology: a constant challenge in everyday practice. The effectiveness of clinical decisions using diagnostic tools available in Poland

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KEY WORDS

Bethesda category, indeterminate thyroid nodule, risk stratification in thyroid nodule, thyroid ultrasonography

EDITORIAL

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ABSTRACT

INTRODUCTION A crucial issue in the management of thyroid nodules is an accurate estimation of their malignancy risk. The key tool for risk stratification is fine-needle aspiration biopsy. Unfortunately, approximately 20% of biopsy results are indeterminate. The malignancy risk assigned to these categories does not allow unequivocal further management.

OBJECTIVES We aimed to assess the malignancy risk in indeterminate thyroid nodules in the Polish population, and to analyze the effectiveness of clinical decisions after an indeterminate cytological diagnosis in Polish clinical practice.

PATIENTS AND METHODS This retrospective analysis included 222 indeterminate thyroid nodules in 222 patients. The ultrasound features were assessed based on scans preceding a thyroid biopsy. Cytology results were classified according to the Bethesda system. The nature of the thyroid nodule was determined on the basis of histopathological analysis or follow-up.

RESULTS The analyzed cohort comprised 82 lesions in Bethesda category III, 75 in Bethesda category IV, and 65 in Bethesda category V. The malignancy risk, estimated on the basis of histological verification and surveillance was 6.7% for Bethesda III, 11.3% for Bethesda IV, and 70.3% for Bethesda category V. An ultrasound pattern was not sufficient enough to refine the malignancy risk after obtaining an indeterminate cytopathology result. In surgically treated nodules, postoperative hypoparathyroidism was significantly more frequent following more extensive surgical procedures.

CONCLUSIONS The majority of Polish patients with thyroid nodules assigned to Bethesda III and IV cytological categories are overtreated based on the use of diagnostic tools currently available in Poland.

INTRODUCTION Nodular goiter is an extremely common disorder in clinical practice. In the era of high-resolution ultrasonography, the clinician must be prepared for numerous patients with this diagnosis, as it may involve as much as 70% of the adult population.[1,2] Currently, a thyroid nodule corresponds to a structurally distinct lesion in the thyroid parenchyma, rather than to a palpable

WHAT'S NEW?

The study proves a low malignancy risk in Bethesda category III and IV thyroid nodules in the Polish population (6.7% and 11.3%, respectively). Universal referral for surgery of these indeterminate thyroid nodules leads to overtreatment, with patients being unjustifiably exposed to possible life-long complications. A concurrent analysis of the clinical risk factors and thyroid nodule ultrasound pattern may not be sufficiently effective in terms of refining the malignancy risk in patients with thyroid nodules after obtaining an indeterminate cytopathology result. The analysis points to the urgent need for new tools to be created for the management of thyroid nodules with indeterminate cytopathology results in the Polish population in order to minimize the number of redundant thyroid surgical procedures and to optimally determine the extent of the primary surgical procedure, if necessary.

nodule, as was observed formerly. Though the diagnosis of a thyroid nodule is prevalent, thyroid carcinoma concerns only 5% of cases.[3] With this in mind, the crucial issue in the management of thyroid nodules is to estimate, as accurately as possible, the risk of malignancy in particular thyroid lesion in order to select those that warrant surgery. The key tool for the diagnosis of a malignant thyroid nodule is fine-needle aspiration biopsy (FNAB) with cytopathological analysis.[3-6] Cytological reports are based on the widely accepted Bethesda System for Reporting Thyroid Cytopathology, with an estimated sensitivity of 97% and a specificity of 50.7%, and with a very low percentage of false-negative and false-positive results—3% and 0.5%, respectively.[5] Unfortunately, approximately 20% of biopsy results are indeterminate; the cytological features are inconclusive and fail to provide a definitive diagnosis. The indeterminate cytological categories include Bethesda category III, defined as atypia of undetermined significance / follicular lesion of undetermined significance, Bethesda category IV, which encompasses follicular neoplasm / suspicion of follicular neoplasm, and Bethesda category V—suspected malignancy. The Bethesda categories differ in the risk of thyroid cancer diagnosis in the case of postoperative histopathological verification. Total malignancy risk in Bethesda category III ranges between 6% and 30%, in Bethesda IV, between 10% and 40%, and in Bethesda V, between 45% and 75%.[6] Such a wide-ranging risk of malignancy usually causes a high degree of physician uncertainty in the management of patients with this kind of thyroid nodule and may lead to overtreatment due to fear of cancer omission. Furthermore, clinician uncertainty usually goes with a permanent psychological burden on the patient after facing the diagnosis of indeterminate cytopathology. It is generally acceptable to follow thyroid lesions with an assigned malignancy risk below 5%, which we observe in Bethesda category II, and to refer for surgery in the case of a malignancy risk above 90%, as in Bethesda category VI.[5-8] However, a malignancy risk assigned to the aforementioned indeterminate cytological categories, especially Bethesda III and IV, does not provide clear guidance for further management. Due to the defined limitations associated with the management of indeterminate thyroid nodules, medical communities have sought out novel diagnostic methods or possible benefits of the diagnostic tools accessible in clinical practice that would allow to refine the malignancy risk estimated on the basis of cytopathology. This has promoted the development of thyroid molecular tests, though unfortunately, these remain not widely available. On the other hand, the idea of incorporating ultrasound features of thyroid nodule in the malignancy risk estimation, together with the elevated risk associated with an indeterminate cytopathology result, has been considered. Since there is no single ultrasound feature unequivocally pointing to a diagnosis of thyroid cancer in a scanned thyroid nodule, various medical societies from all over the world have tried to create ultrasound reporting data systems linking particular ultrasound patterns of thyroid nodules to a potential risk of malignancy.[4,9-12] Undoubtedly, the role of thorough ultrasound scanning of the thyroid gland and cervical lymph nodes, along with an analysis of clinical risk factors and symptoms, are crucial in the initial workup of the thyroid nodules and selecting these warranting FNAB.[3,4] Universal referral of all incidentally discovered thyroid lesions for FNAB would be an unacceptable approach and would lead to an overwhelming number of diagnostic procedures.[13] Nevertheless, the role of thyroid ultrasound patterns being reused after an indeterminate cytology result in order to modify the estimated malignancy risk is less clear, with divergent data concerning their effectiveness in deciding about the referral of a patient for surgery. However, apart from selecting a candidate for surgery, there is also an issue of deciding on the extent of the surgical procedure. If the thyroid surgery is too extensive or unjustified, the patient may experience overtreatment, with the risk of life-long complications. Postoperative hypothyroidism, hypoparathyroidism, and recurrent nerve injury, if they appear, all require permanent medical attention. On the other hand, the extent of the thyroid surgery may be insufficient in the case of postoperative diagnosis of thyroid carcinoma, exposing the patient to subsequent surgical procedures.

Considering these limitations in this particular population of patients, we aimed to analyze the effectiveness of clinical decisions after a cytological diagnosis of Bethesda categories III, IV, V thyroid nodules, with a simultaneous assessment of the malignancy risk in indeterminate thyroid nodules in the Polish population.

PATIENTS AND METHODS Medical records of patients with nodular goiter requiring a differential diagnosis of thyroid nodules and participating in the STRATEGMED 2/267398/4/NCBR/2015 project were retrospectively analyzed. All patients

provided informed consent. The study was approved by the local Bioethics Committee. Under the project, FNABs were performed in 1456 thyroid lesions, providing material for cytological and molecular analyses. A total of 222 thyroid lesions in 222 patients with indeterminate cytopathology results (Bethesda III, IV, or V) were included in the analysis.

The clinical risk factors were assessed on the basis of data available in medical records, data collected by the endocrinologist, and through interviewing the patient on the first visit in our center.

Ultrasound examination of the thyroid gland was performed by an experienced endocrinologist or radiologist using Philips HDI 5000 Ultrasound System (Philips Healthcare, the Netherlands) with a linear 5- to 12-mHz probe or Samsung Medison HS70A (Samsung Healthcare, Seoul, South Korea) with a linear 3- to 12-mHz probe. Ultrasound features of the thyroid nodules were assessed on the basis of the last ultrasound examination preceding FNAB. The ultrasound pattern of each thyroid nodule was classified according to the European Thyroid Imaging and Reporting Data System (EU-TIRADS), which includes 5 categories. EU-TIRADS category 1 denotes a normal thyroid examination. The benign category EU-TIRADS 2 corresponds to pure / anechoic cysts and entirely spongiform nodules. EU-TIRADS 3 is a low-risk category, including oval-shaped iso- or hyperechoic lesions with smooth margins. EU-TIRADS 4, an intermediate-risk category, also encompasses oval thyroid nodules with smooth margins, but mildly hypoechoic. The highest-risk category, EU-TIRADS 5, includes solid thyroid nodules characterized by at least one of the following risk features: taller-than-wide shape, irregular margins, microcalcification, or significantly reduced echogenicity compared with the adjacent strap muscles. The EU-TIRADS categories were retrospectively scored, based on the description of the ultrasound examination and the digital image, if available.

FNAB was performed by an experienced pathologist using the capillary ultrasound-guided technique with a 25 to 27 gauge needle. The cytology results were classified according to the Bethesda system and were confirmed by 2 independent pathologists.

Patients with indeterminate cytopathology results were managed individually by the providing physician, with referral for thyroid surgery in selected patients.

The nature of the thyroid nodule was determined on the basis of histopathological analysis carried out after the surgical procedure performed in the place of the patient's residence or in our center. A histopathological confirmation was available for 175 thyroid lesions. Of these, 122 patients were operated on at our center and 53 in external centers. In 25 cases of surgeries in external centers, our expert histopathological opinion was available, encompassing all malignant thyroid lesions. Thus, the number of expert histopathological opinions was 147 and these included all malignant lesions.

In the absence of a histopathological confirmation, patient follow-up for at least 24 months with at least a single thyroid ultrasound examination proving a stable image of the lesion classified the lesion as benign. The nature of nodules lost to follow-up before 24 months was considered undetermined.

Postoperative complications were assessed based on data from medical records. Persistent hypoparathyroidism was diagnosed if it lasted longer than 24 months after the surgery.

Statistical analysis Categorical data were summarized as numbers and percentages. Continuous data were presented as medians and interquartile ranges (IQRs). Categorical variables were compared using the Fisher exact test. In the case of post-hoc pairwise comparisons, the Benjamini–Hochberg correction was used. Comparisons of continuous variables were performed using the 2-tailed Mann–Whitney test or the Kruskal–Wallis test. Univariable and multivariable Firth bias-reduced logistic regression analyses were carried out to determine the factors associated with the development of hypoparathyroidism. The results of logistic regression were summarized as odds ratios (ORs) and 95% CIs. All variables with significant associations in univariable analyses were entered into the multivariable model. In all analyses, *P* values of less than 0.05 were considered significant. Statistical analyses were performed using the R software, version 3.6.2, tableone package, version 0.11.1, logistf package, version 1.24, and fmsb package, version 0.7.0 (the R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The analysis included 222 thyroid lesions with indeterminate cytopathology results; 82 lesions in Bethesda category III, 75 in Bethesda category IV, and 65 in Bethesda category V (TABLE 1). In most cases, the thyroid lesions were incidentally revealed. Only in 12 cases (5.4%), patients presented symptoms. In 2 cases, compression symptoms were observed and in 10, a palpable neck tumor was the first manifestation. Clinical risk factors were found in 6 cases (2.7%) and comprised a positive family history (1 patient), a confirmed lymph node metastasis (1 patient), distant metastasis (1 patient), and a significant increase in lesion size (3 patients). The study group was dominated by women (86%). The median age in the whole group was 54 years. The median thyroid nodule size was 16 mm. There was a significant association between the EU-TIRADS and Bethesda classifications. Thyroid lesions scored as EU-TIRADS 4 were more frequent in Bethesda categories III and IV than in Bethesda V, while EU-TIRADS 5 was more frequent in Bethesda category V.

Histopathological confirmation was available for 175 (79%) of 222 thyroid lesions.

TABLE 1 Characteristics of the analyzed cohort

Parameter	All (n = 222)	Bethesda III (n = 82)	Bethesda IV (n = 75)	Bethesda V (n = 65)	*P* value
Female sex	191 (86)	72 (87.8)	66 (88)	53 (81.5)	0.48
Age, y, median (IQR)	54 (41.3–63.8)	53.5 (43–62)	59 (45–68)	49 (35–59)	0.002
Thyroid nodule size, mm, median (IQR)	16 (10.3–25)	17 (11–25)	18 (11–27)	14 (10–23)	0.35
Patients with symptoms	12 (5.4)	5 (6.1)	4 (5.3)	3 (4.6)	>0.99
Patients with clinical risk factors	6 (2.7)	1 (1.2)	2 (2.7)	3 (4.6)	0.45
EU-TIRADS 3	70 (32.6)	28 (35)	20 (28.2)	22 (34.4)	0.01
EU-TIRADS 4	73 (34)	33 (41.2)	28 (39.4)	12 (18.8)	
EU-TIRADS 5	72 (33.5)	19 (23.8)	23 (32.4)	30 (46.9)	
Operated on	175 (78.8)	46 (56.1)	66 (88)	63 (96.9)	<0.001
Malignant lesions, n (% of operated on)	58 (33.1)	5 (10.9)	8 (12.1)	45 (71.1)	<0.001
Operated on or followed up for ≥24 months	210 (94.6)	75 (91.5)	71 (94.7)	64 (98.5)	0.17
Malignant lesions, n (% of operated on or followed up)	58 (27.6)	5 (6.7)	8 (11.3)	45 (70.3)	<0.001

Data are presented as number (percentage) unless otherwise indicated.

Abbreviations: EU-TIRADS, European Thyroid Imaging and Reporting Data System; IQR, interquartile range

TABLE 2 Distribution of histological subtypes among thyroid nodules treated surgically

Subtype	All (n = 175)	Bethesda III (n = 46)	Bethesda IV (n = 66)	Bethesda V (n = 63)	*P* value
Malignant	58 (33.1)	5 (10.9)	8 (12.1)	45 (71.4)	<0.001
PTC	46 (26.3)	2 (4.3)	4 (6.1)	40 (63.5)	<0.001
FTC	6 (3.4)	2 (4.3)	4 (6.1)	0	0.17
MTC	3 (1.7)	1 (2.2)	0	2 (3.2)	0.37
PDTC	2 (1.1)	0	0	2 (3.2)	0.2
Benign	117 (66.9)	41 (89.1)	58 (87.9)	18 (28.6)	<0.001
NHP	62 (35.4)	27 (58.7)	23 (34.8)	12 (19.0)	<0.001
FA	47 (26.9)	12 (26.1)	31 (47.0)	4 (6.3)	<0.001
THT	4 (2.3)	0	2 (3.0)	2 (3.2)	0.56
FTUMP	2 (1.1)	1 (2.2)	1 (1.5)	0	0.73
NIFTP	1 (0.6)	1 (2.2)	0	0	0.26
TI	1 (0.6)	0	1 (1.5)	0	>0.99

Data are presented as number (percentage).

Abbreviations: FA, follicular adenoma; FTC, follicular thyroid carcinoma; FTUMP, follicular tumor of uncertain malignant potential; MTC, medullary thyroid carcinoma, NHP, nodular hyperplasia; NIFTP, noninvasive follicular tumor with papillary-like nuclear features; PDTC, poorly differentiated thyroid carcinoma; PTC, papillary thyroid carcinoma, THT, trabecular hyalinizing tumor; TI, thyroiditis

The postoperative material included 117 benign lesions and 58 malignant ones. The malignancy risk in relevant cytological categories, estimated on the basis of the histological verification was 10.9% for Bethesda category III, 12.1% for Bethesda IV, and 71.4% for Bethesda V. The malignancy risk differed significantly between Bethesda V and both Bethesda III (P <0.001) and IV (P <0.001) categories but the difference between Bethesda III and IV was not statistically significant (P >0.99). The distribution of histological subtypes among the operated tumors is presented in TABLE 2. The predominant type of thyroid malignancy was papillary thyroid cancer (79.3%), with most cases (40 out of 46 [87%]) contained within the group of Bethesda category V. Follicular thyroid cancer was diagnosed in 10.3% of malignant thyroid nodules, with all cases preoperatively assigned exclusively to Bethesda III and IV cytological categories.

Bilateral thyroid surgery was performed in 103 patients, while 70 individuals underwent unilateral procedures (TABLE 3). In a single case, it was not possible to obtain information on the extent of the procedure, and in another case, only wide tumor tissue excision was performed, in light of a significant suspicion of lymphoma, which was confirmed by a histological examination. There were no significant differences between the Bethesda categories according to the extent of surgical procedures. Completion thyroid surgery was carried out in 12 patients (6.9% of

TABLE 3 The extent of surgery in particular cytological categories

Parameter	Total (n = 175)	Bethesda III (n = 46)	Bethesda IV (n = 66)	Bethesda V (n = 63)	*P* value
Bilateral	103 (59.2)	27 (58.7)	38 (58.5)	38 (60.3)	0.98
Unilateral	70 (40.2)	19 (41.3)	27 (41.5)	24 (38.1)	0.92
Tissue excision	1 (0.6)	0	0	1 (1.6)	0.63
Completion surgery	12 (6.9)	2 (4.3)	2 (3.1)	8 (12.7)	0.11
Lack of data	1	0	1	0	–

Data are presented as number (percentage) or number.

TABLE 4 Distribution of adverse effects according to the type of thyroid surgery

Parameter	Overall (n = 173)[a]	Unilateral without completion surgery (n = 59)	Unilateral with completion surgery (n = 11)	Bilateral without completion surgery (n = 102)	Bilateral with completion surgery (n = 1)	*P* value
Hypoparathyroidism	23 (13.5)	0	1 (9.1)	21 (21)	1 (100)	<0.001[b]
Laryngeal nerve palsy	2 (1.2)	1 (1.7)	0	1 (1)	0	>0.99

Data are presented as number (percentage).

a Two surgically treated patients (a patient with an unknown extent of surgery and a patient with wide tumor tissue excision) were not included in the analysis.

b In the comparison of hypoparathyroidism frequency between bilateral surgery (without completion surgery) and unilateral surgery (without completion surgery), a *P* value <0.001 was obtained

TABLE 5 Factors contributing to the development of hypoparathyroidism: univariable and multivariable logistic regression analysis

Variables	Univariable		Multivariable	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Thyroid surgery (bilateral vs unilateral)	13.11 (3.25–119.84)	<0.001	10.49 (2.55–96.48)	<0.001
Age, y	1.01 (0.98–1.04)	0.47	–	–
Sex (male vs female)	0.11 (0.001–0.83)	0.03	0.14 (0.001–1.15)	0.07
Clinical risk factors (present vs absent)	0.47 (0.004–4.17)	0.57	–	–
Symptoms (present vs absent)	2.82 (0.65–10.05)	0.15	–	–
Thyroid nodule size, mm	1.00 (0.96–1.04)	1.00	–	–
Thyroid nodule character (malignant vs benign)	3.02 (1.26–7.43)	0.01	2.72 (1.07–7.04)	0.03

Abbreviations: OR, odds ratio

the surgically treated ones). It was more often required in patients with thyroid lesions in Bethesda category V (12.7%); however, the difference between Bethesda categories III, IV, and V did not reach statistical significance.

Postoperative hypothyroidism requiring substitution with levothyroxine developed in all operated patients. Postoperative adverse effects according to the known extent of the surgical procedure are summarized in TABLE 4. In 2 operated patients (1.2%), unilateral laryngeal nerve injury occurred. There were 23 confirmed cases (13.5%) of postoperative hypoparathyroidism. Persistent hypoparathyroidism was observed in 9 patients (5.3%), whereas transient hypoparathyroidism and hypoparathyroidism of unknown duration were observed in seven patients (4.1%) each. Hypoparathyroidism occurred more often after bilateral than unilateral thyroid surgery (21% vs 0%; *P* <0.001). In both univariable and multivariable logistic regression analyses, more extensive surgical procedure and malignant nature of the thyroid lesion were risk factors for hypoparathyroidism, with odds ratio above 10 for bilateral surgery compared with the unilateral procedure (TABLE 5).

There were 47 (21%) thyroid lesions that remained without histopathological verification, 36 in Bethesda category III, 9 in Bethesda category IV, and 2 in Bethesda category V. The median follow-up time was 38 months (range, 1–156 months). Of the thyroid nodules not subjected to surgery, 35 (74.5%) were under surveillance for at least 24 months and remained stable throughout the follow-up period, which allowed to classify them as benign.

Most patients with thyroid lesions in Bethesda categories IV and V were operated on or referred for surgery. Active surveillance was offered to 1

TABLE 6 Characteristics of patients with lesions classified as Bethesda category III according to the recommended management

Parameter	All (n = 82)	Recommended for surgery (n = 54)	Recommended for follow-up (n = 28)	*P* value
Age, y, median (IQR)	53.5 (43–62)	51.5 (43–59)	55 (46.8–62.5)	0.29
Nodule size, mm, median (IQR)	17 (11–25)	18.5 (13.3–29)	12 (9–17)	<0.001
Patients with symptoms	5 (6.1)	4 (7.4)	1 (3.6)	0.66
Patients with clinical risk factors	1 (1.2)	1 (1.9)	0	>0.99
EU-TIRADS 3[a]	28 (35)	20 (37.7)	8 (29.6)	0.6
EU-TIRADS 4[a]	33 (41.2)	22 (41.5)	11 (40.7)	
EU-TIRADS 5[a]	19 (23.8)	11 (20.8)	8 (29.6)	
EU-TIRADS, lack of data	2	1	1	–

Data are presented as number (percentage) or number unless otherwise indicated.

a Percentages are calculated for the group of patients with known EU-TIRADS

Abbreviations: see TABLE 1

TABLE 7 Characteristics of patients with thyroid lesions classified as benign or malignant based on histopathological analysis and long-term follow-up (note: row percentages are shown)

Parameter		All (n = 210)	Benign (n = 152)	Malignant (n = 58)	*P* value
Sex	Female	181	131 (72.4)	50 (27.6)	>0.99
	Male	29	21 (72.4)	8 (27.6)	
Age, y, median (IQR)		53.5 (42–63)	54.5 (45–64)	47.5 (35.3–60.5)	0.015
Thyroid nodule size, mm, median (IQR)		16 (11–25)	17 (11–25)	14 (10–23)	0.11
EU-TIRADS 3		66	48 (72.7)	18 (27.3)	<0.001[a]
EU-TIRADS 4		70	61 (87.1)	9 (12.9)	
EU-TIRADS 5		67	37 (55.2)	30 (44.8)	
Bethesda III		75	70 (93.3)	5 (6.7)	<0.001
Bethesda IV		71	63 (88.7)	8 (11.3)	
Bethesda V		64	19 (29.7)	45 (70.3)	

Data are presented as number/number (percentage) unless otherwise indicated.

a The following results were obtained in post-hoc tests for malignancy risk: EU-TIRADS 3 vs 4, $P = 0.052$; EU--TIRADS 3 vs 5, $P = 0.052$; EU-TIRADS 4 vs 5, $P < 0.001$; Bethesda III vs IV, $P = 1$; Bethesda III vs V, $P < 0.001$; Bethesda IV vs V, $P < 0.001$.

Abbreviations: see TABLE 1

(1.5%) out of 65 patients with lesions in Bethesda category V and 3 (4%) out of 75 patients with lesions in Bethesda category IV. Thyroid surgery was abandoned in an 81-year-old patient with a lesion classified as Bethesda category V with coexisting relevant cardiac disorders. Due to a stable image of the 28-mm lesion in the 13-year follow--up as well as cytological verification as Bethesda category II in subsequent biopsies, the lesion was classified as benign. Among individuals with lesions classified as Bethesda category IV, follow--up was recommended for 3 patients with thyroid lesions 9 to 12 mm in diameter, without symptoms or clinical risk factors.

In the group of Bethesda category III, surveillance was recommended for 28 (34%) of 82 thyroid nodules (TABLE 6). Thyroid lesions referred for surgical treatment were significantly larger, but no differences in the coexisting clinical risk factors, symptoms, ultrasound pattern, or patient age were observed.

Twelve patients with nodular goiter were lost to follow-up before 24 months had elapsed. The nature of these thyroid lesions was regarded as undetermined.

Comparative characteristics of the thyroid nodules eventually classified as benign and malignant, including also the lesions followed up for at least 24 months, are presented in TABLE 7. Patients with malignant lesions were significantly younger. There was a significant difference in the frequency of malignant lesions between EU-TIRADS categories. The malignancy rates in particular Bethesda categories were 6.7% for Bethesda III, 11.3% for Bethesda IV, and 70.3% for Bethesda V. The malignancy rates in different Bethesda categories according to ultrasound patterns are shown in TABLE 8. The estimated risk in particular EU-TIRADS categories was significantly different only in Bethesda category III thyroid nodules. The low-risk ultrasound category EU--TIRADS 3 was associated with a lower risk of

TABLE 8 Risk of malignancy in particular Bethesda categories according to the ultrasound pattern in all 210 lesions classified as benign and malignant based on histopathological analysis and long-term follow-up

Parameter	All	EU-TIRADS 3	EU-TIRADS 4	EU-TIRADS 5	*P* value
Bethesda III					
Participants	75	25	31	17	–
Malignant lesions	5 (6.7)	1 (4.0)	0	3 (17.6)	0.029
Bethesda IV					
Participants	71	20	27	20	–
Malignant lesions	8 (11.3)	3 (15.0)	2 (7.4)	3 (15.0)	0.71
Bethesda V					
Participants	64	21	12	30	–
Malignant lesions	45 (70.3)	14 (66.7)	7 (58.3)	24 (80.0)	0.30

Data are presented as number (percentage) or number.

Abbreviations: see **TABLE 1**

malignancy (<5%). In EU-TIRADS 5, the malignancy risk was significantly higher, reaching 18%. There were no significant differences in terms of the calculated risk of malignancy in Bethesda categories IV and V with regards to the ultrasound pattern.

DISCUSSION Our results clearly show that in the Polish population, thyroid nodules assigned to Bethesda III (atypia of undetermined significance / follicular lesion of undetermined significance and Bethesda IV (follicular neoplasm / suspicious for follicular neoplasm) cytological categories are associated with a low malignancy risk. In a combined group of Bethesda III and IV, the risk of malignancy was 11.6% among patients that were operated on and 8.9% among those who were operated on or followed up for at least 24 months after diagnosis. Due to the fact that postoperative histological analysis did not confirm malignancy in 88.4% of Bethesda III and IV cases, referral of almost all thyroid nodules classified to these categories for surgery results in overtreatment in the majority of patients with these diagnoses.

The low malignancy risk in Bethesda categories III and IV observed in our study—10.9% and 12.1%, respectively, considering only lesions with histopathological verification, and 6.7% and 11.3%, respectively, including also the nodules recommended for follow-up—is similar to that reported recently by another Polish center. The authors only analyzed thyroid nodules with histological results and estimated the risk of malignancy of 10.6% in lesions classified as Bethesda III and 11.6% in those classified as Bethesda IV.[14] Moreover, the previously reported risk of malignancy in Bethesda category III in Poland was even lower, ranging between 2.8% and 6.4%.[15,16] The malignancy risk associated with these cytological categories varies widely around the world, depending on the analyzed population and the method of lesion verification. A French study by Chaigneau et al[17] analyzed thyroid nodules after surgical treatment and reported a malignancy risk of 23.2% in lesions classified as Bethesda category III and 13.8% in those assigned to Bethesda category IV. Ho et al[18] assessed the malignancy risk in thyroid lesions classified as Bethesda category III treated at the United States Oncology Center; the malignancy rates were 37.8% in thyroid lesions treated surgically and 26.6% considering also the lesions under surveillance.[18] In a multicenter study conducted in the United States, based on 265 lesions with indeterminate cytological results undergoing surgical treatment, the malignancy risk was 24% in Bethesda category III and 24.7% in Bethesda category IV.[19] In studies analyzing populations from Asia, the malignancy risk in lesions classified as Bethesda category III and verified histologically ranged between 28.7% an 35.5%, whereas in those classified as Bethesda category IV, it was 44.4%.[20,21] Undoubtedly, one of the most important factors associated with the declining malignancy rates in the Polish population compared with other countries is iodine deficiency observed in Poland until the late 1990s.[22] This relevant discrepancy in the malignancy risk highlights that the management of Polish patients with nodular goiter must be guided by recommendations adapted to Polish epidemiological conditions.

Moreover, our study confirms that we live in the era of widespread thyroid ultrasound screening, in which an overwhelming number of thyroid lesions are discovered incidentally and the possibility of using identifiable clinical risk factors and symptoms as an additive tool is limited to a small number of patients. In the study cohort, this situation concerned only 18 (8.1%) of 222 patients. Nevertheless, if clinical risk factors and worrisome symptoms are recognized, they must be strongly considered in malignancy risk stratification.[3,4] Furthermore, in our study there were no significant differences in the calculated malignancy risk in Bethesda categories IV and V with respect to the EU-TIRADS score. Only in Bethesda category III co-occurring with an EU--TIRADS 5 ultrasound pattern, the malignancy risk was significantly higher (reaching 18%), although still not high enough to allow classification of patients with such lesions as warranting surgery. In a study by Słowińska-Klencka et al[14] conducted in another Polish center, the malignancy risk in Bethesda III thyroid nodules with EU-TIRADS 3 and 4 scores was not significantly different compared with the risk of malignancy based only on cytology results. Similar to our findings, the authors also observed a significant increase in the malignancy risk (up to 25%) when EU-TIRADS 5 was scored in Bethesda category III.[14] Nevertheless, this still indicates that about 70% to 80% of patients might be overtreated in the case of surgery. Chaigneau et al[17] reported a limited value of the French TIRADS score (similar to EU-TIRADS) in predicting the malignancy risk in thyroid nodules with indeterminate cytopathology. In their study, the TIRADS score was

positively correlated with the malignancy rate; however, only in Bethesda category V there was a significant difference in the risk of malignancy among different TIRADS scores.[17] Maia et al[23] assessed the diagnostic performance of TIRADS, a score analogous to the French system but also including vascularity in the risk estimation of thyroid nodules with indeterminate cytopathology. The authors observed a negative predictive value of 90% only in thyroid nodules with Bethesda category III and a low-risk TIRADS pattern, with a pretest malignancy risk of 8.7% in this cytological category. At the same time, they reported a high risk of malignancy in nodules with a high-risk TIRADS pattern classified as Bethesda IV and V (75% and 76.9%, respectively), which was significantly higher than the risk of malignancy according to the cytological result alone. However, the pretest malignancy risk in these lesions was high, especially in Bethesda category IV (51.3%).[23] In addition, data on the use of ultrasound-based risk stratification systems other than EU-TIRADS in the decision-making process regarding the management of thyroid nodules with indeterminate cytopathology are confounding.[24-29] Existing data suggest that stratification systems based on thyroid ultrasound were designed mainly to recognize papillary thyroid carcinoma, whereas follicular thyroid cancer frequently corresponds to low-risk patterns in ultrasound assessment, without well-known ultrasound risk features such as marked hypoechogenicity, irregular margins, microcalcifications, and a taller-than-wide shape.[30,31] Furthermore, a lot of studies assessing thyroid ultrasound risk stratification systems exclude thyroid nodules with indeterminate cytological results, which results in low prevalence of follicular thyroid carcinoma in analyzed cohorts.[8,32] In our study, follicular thyroid carcinoma was diagnosed in 10% of malignant thyroid nodules, and all cases were preoperatively assigned exclusively to Bethesda III and IV cytological categories.

Our study indicates that the size of the thyroid lesion, rather than the ultrasound pattern, was the main factor influencing the decision of a providing clinician to refer a patient with Bethesda category III thyroid nodules for surgery.

In the group of patients with thyroid nodules classified as Bethesda category IV, nearly all were referred for thyroid surgery. Only 3 patients with this cytological diagnosis, with lesion size between 9 and 12 mm and without any symptoms and clinical risk factors were triaged for follow-up. Such management is generally in line with Polish recommendations, but still results in diagnostic surgical procedures in the majority of patients, whereas 87.9% of these thyroid nodules turn out to be benign.

In contrast, in patients with thyroid nodules classified as Bethesda category V, the estimated malignancy risk is high enough to recommend surgical treatment. In our cohort, postoperative malignancy risk was 71.4% in this cytological category. The risk reported in the literature is similar, ranging between 45% and 75%.[5,17]

In all cases of indeterminate thyroid nodules, triaging the patient for surgery in lieu of a follow-up requires decision about the extent of the surgical procedure. In our analysis, bilateral thyroid surgery was performed in 59.2% of operated patients, without significant differences regarding the extent of surgery in particular cytological categories. Bilateral thyroid surgeries resulted in hypoparathyroidism in 13.5% of patients, which was not observed after less extensive surgical procedures. This is consistent with the published data, which emphasize significantly less frequent calcium metabolism complications after hemithyroidectomies.[4,33] These data, along with the low malignancy risk, especially in Bethesda categories III and IV (6.7% and 11.3%, respectively), indicate that hemithyroidectomy is unreasonably avoided by clinicians in these groups of patients. Furthermore, even in the case of a postoperative diagnosis of thyroid carcinoma, especially a low-risk one, hemithyroidectomy may be a sufficient treatment, without risk of prognosis deterioration.[34] On the other hand, high-risk thyroid cancers revealed after histopathological analysis may require subsequent thyroid surgery. In our analysis, the need for subsequent surgery was the most prevalent in the group of patients with nodules classified as Bethesda category V (12.7% of cases), which points to the urgent need for more precise tools in preoperative risk stratification to plan the extent of surgery more accurately.

According to the recommendations of the American Thyroid Association, the extent of thyroid surgery, as well as the decision about the management of thyroid nodules with indeterminate cytopathology, may be modified by the results of molecular tests, which may allow for surgical treatment to be abandoned in favor of follow-up.[4] Molecular tests require a small amount of cell material, usually obtained from an additional pass during FNAB of a thyroid nodule. Duick et al[35] reported a significant, almost 10-fold reduction in the number of surgical procedures performed in the group of patients with thyroid nodules with indeterminate cytopathology after implementing molecular tests in preoperative diagnosis in the United States (7.6% vs 74%). At the same time, the study pointed to a more frequent application of hemithyroidectomies in lieu of total thyroid excision in this group of patients.[35] According to a report by Celik et al,[36] molecular assessment during FNAB may be valuable in the diagnostic workup of thyroid tumors with uncertain malignant potential.[36] Unfortunately, the molecular tests that are now commercially available were developed and mostly validated in the American population, which, apart from the price (USD 2000–USD 5000), limits their application in Polish clinical practice due to significant differences in the malignancy risk in indeterminate thyroid nodules in the Polish population.[37]

Moreover, a meta-analysis by Borowczyk et al[38] points out some limitations in the available molecular tests. In another analysis, Borowczyk et al[39] show a high genetic heterogeneity of indeterminate thyroid nodules.[39] Therefore, there is an urgent need to create new tools for the Polish population that would guide the management of thyroid nodules with indeterminate cytopathology. Such tools would help minimize the number of redundant thyroid surgical procedures as well as optimally determine the extent of the primary surgical procedure in cases where it is necessary.

ARTICLE INFORMATION

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CONTRIBUTION STATEMENT AKB conceived the concept and design of the study and was responsible for data analysis and interpretation, writing the manuscript, and final approval of the version to be submitted; AP was responsible for statistical analysis and data interpretation; AC was responsible for data analysis and interpretation; MOW was responsible for study design and supervision of the project; EC and EN participated in data analysis and interpretation; MJ was responsible for study design and revising the manuscript; BJ participated in study design, supervision of the project, and data interpretation; JK participated in study design and supervision of the project. All authors edited and approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

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