



Submitted: 10.12.2023
Accepted: 29.01.2024
Early publication date: 02.04.2024

Endokrynologia Polska
DOI: 10.5603/ep.98488
ISSN 0423-104X, e-ISSN 2299-8306
Volume/Tom 75; Number/Numer 2/2024

Ultrasound and cytopathological characteristics of thyroid tumours of uncertain malignant potential — from diagnosis to treatment

Agnieszka Żyłka¹, Katarzyna Dobruch-Sobczak², Hanna Piotrkowska-Wróblewska³, Maciej Jędrzejczyk⁴, Piotr Góralski¹, Jacek Gałczyński¹, Elwira Bakula-Zalewska⁵, Marek Dedecjus¹

¹Department of Endocrine Oncology and Nuclear Medicine, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland

²Radiology Department II, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland

³Institute of Fundamental Technological Research, Polish Academy of Sciences, Warsaw, Poland

⁴Department of Ultrasound and Mammography Diagnostics, Mazovian Brodnowski Hospital, Warsaw, Poland

⁵Department of Pathology, Maria Skłodowska-Curie National Research Institute of Oncology, Warszawa, Poland

Abstract

Introduction: The latest World Health Organization (WHO) classification from 2022 distinguishes the division of low-risk thyroid neoplasms such as non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), follicular tumour of uncertain malignant potential (FT-UMP), and well-differentiated tumour of uncertain malignant potential (WDT-UMP). The final diagnosis is made postoperatively according to histopathologic results. The aim of the study was the assessment of ultrasonographic and cytopathological features of borderline lesions to predict low-risk tumours preoperatively and plan the optimal treatment for that group of patients.

Material and methods: A total of 35 patients (30 women; 5 men), aged 20–81 years with a mean age of 49 years, were enrolled in the study. The study evaluated 35 focal lesions of the thyroid gland, classified as low-risk neoplasms according to the WHO 2022 classification: FT-UMP (n = 21), NIFTP (n = 7), and WDT-UMP (n = 7). Ultrasonographic features of nodules including contrast-enhanced ultrasound (CEUS) and elastography were assessed by 2 specialists, and the risk of malignancy was evaluated according to EU-TIRADS-PL classification.

Results: Of the 35 focal thyroid lesions, most were categorised as low or intermediate risk of malignancy according to EU-TIRADS-PL, with dominant category 3 (n = 13 [37.2%]) and category 4 (n = 15 [42.8%]). High-risk category 5 was assessed in 7 lesions (20%). In cytopathology nodules were categorised as follows (Bethesda System TBSRTC 2023): Bethesda II (n = 4), Bethesda III (n = 2), Bethesda IV (n = 25), Bethesda V (n = 3), and Bethesda VI (n = 1). In the CEUS study, contrasting patterns dominated compared to the surrounding parenchyma, such as enhancement equal to the parenchyma (66.6%) or intense (28.5%), heterogeneous (61.9%), centripetal (42.8%), or diffuse (57.1%) with fast (33.3%) or compared to parenchyma contrast wash-in (42.8%) and its fast (33.3%) or comparable to thyroid parenchyma wash-out (52.3%).

Conclusions: The study indicates that lesions with uncertain malignant potential typically present features suggesting low to intermediate risk of malignancy based on EU-TIRADS-PL classification, with dominant cytopathologic Bethesda IV category. However, 20% of lesions were assessed as EU-TIRADS-PL category 5. Low-risk tumours, including NIFTP, FT-UMP, and WDT-UMP, require careful observation and monitoring post surgical treatment due to their potential for recurrence and metastasis. The preoperatively prediction of borderline tumour may play an important role in proper treatment and follow-up. (*Endokrynol Pol* 2024; 75 (2): 170–178)

Key words: thyroid tumour; ultrasound; thyroid cancer; contrast-enhanced-ultrasound

Introduction

In 2009, a novel classification of thyroid tumours, encompassing changes with borderline (uncertain) malignant potential, referred to as borderline tumours, was introduced by Kakudo et al., marking a significant development in the literature [1]. This group comprises tumours that pose challenges for pathologists, clinicians, and diagnosticians [1]. Pathologists often encounter uncertainties when diagnosing these tumours due to their ambiguous nature. This is primarily attributed

to the subjective nature of pathologists' assessments and the complexities associated with alterations in tumours following numerous fine-needle aspiration biopsies (FNA).

Numerous updates, including the latest from the World Health Organisation (WHO) from 2022, distinguish the following division of low-risk neoplasms – thyroid tumours of uncertain malignant potential: follicular tumour of uncertain malignant (FT-UMP) potential; well-differentiated tumour of uncertain malignant potential (WDT-UMP); and noninvasive fol-



Agnieszka Żyłka, Department of Endocrine Oncology and Nuclear Medicine, Maria Skłodowska-Curie National Research Institute of Oncology, Roentgena 5 Street, 02-781 Warsaw, Poland; e-mail: agnieszka.zylka.edu@gmail.com

licular thyroid neoplasm with papillary-like nuclear features (NIFTP) and hyalinising trabecular tumour [2]. Diagnosing the aforementioned tumours requires histopathological evaluation as opposed to cytopathological assessment. Among the borderline tumours, the existing literature predominantly focuses on NIFTP. Incidence rates vary between 0.4% and 25.0% depending on the studied population, with discrepancies stemming from revisions in the nomenclature of papillary thyroid carcinoma (PTC) [3, 4]. Morphologically, FT-UMP manifests as a tumour with characteristics of both adenoma and cancer. WDT-UMP is characterised by nuclear features resembling papillary carcinoma alongside uncertain capsular or vascular invasion traits. NIFTP corresponds to a noninvasive variant of follicular papillary carcinoma (FVPTC) previously described. According to a meta-analysis by Bongiovani, borderline tumours are commonly classified as Bethesda IV category (follicular neoplasm or suspicious for follicular neoplasm (FN/SFN) [5]. Ultrasound findings, predominantly applicable to NIFTP, describe these lesions as oval, well-circumscribed, variably echogenicity, and often solid [6, 7]. Interestingly, co-occurrence of malignant changes within the gland is relatively high, ranging from 14.9% to 46.5%. Instances of microcalcifications are infrequent, and a mixed vascular pattern is observed, resembling changes in FVPTC. In the study by Rosario et al. it was indicated that most ultrasound NIFTP features align with American College of Radiology Thyroid Image Reporting and Data System 3 (ACR-TIRADS3) (mildly suspicious) or T4 (moderately suspicious) criteria [8]. Conversely, a comprehensive study involving 257 focal thyroid lesions with indeterminate fine-needle biopsy (FNA) outcomes found no substantial differences in ultrasound assessments between malignant, benign, and NIFTP [7]. While traditional B-mode ultrasound is crucial in the differential diagnosis of thyroid lesions, it faces limitations stemming from operator experience, inter-operator agreement, transducer resolution, and access to advanced ultrasound technologies. Novel technologies such as sonoelastography for assessing stiffness and contrast-enhanced ultrasonography (CEUS) for evaluating tumour perfusion appear promising for distinguishing lesion characteristics. In the treatment of borderline tumours, surgical options include lobectomy or total thyroidectomy for patients who decline moni-

toring of the remaining thyroid gland. Prospective studies monitoring progression risk, growth dynamics, and active surveillance of these lesions face challenges due to their reliance on histopathological evaluation for diagnosis. Additionally, borderline tumours introduce a new direction for clinicians to estimate malignancy risk using the various TI-RADS classifications. This study aims to analyse ultrasound features and assess the utility of novel techniques like sonoelastography and CEUS in conjunction with FNA results for selecting patients suitable for active monitoring or surgery.

Material and methods

A total of 35 patients, aged 20–81 years with a mean age of 49 years, were enrolled in the study. The majority were women (30 [85.7%]), while men constituted a smaller proportion (5 [14.3%]). The study evaluated 35 focal lesions of the thyroid gland, classified as low-risk neoplasms according to the WHO 2022 classification: FT-UMP [n = 21 (60%)], NIFTP (n = 7 (20%)), and WDT-UMP [n = 7 (20%)]. Preoperative ultrasound examinations were conducted using a Philips Epiq 5 device with an 18 MHz linear transducer. US features were assessed by 2 experienced radiologists with a minimum of 10 years of clinical experience. The EU-TIRADS-PL classification, a modification of EU-TIRADS, was used to stratify malignancy risk of thyroid lesions based on size criteria [9]. Semi-qualitative assessment of strain elastography (SE) was conducted to evaluate lesion stiffness using the 4-point Asteria scale. Additionally, CEUS was performed on 21 patients to assess contrast patterns. Contrast medium (SonoVue) was administered intravenously, and its distribution within the lesion was evaluated in real-time or retrospectively in comparison with surrounding thyroid parenchyma. Cytopathological assessment following the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC 2023) categorised lesions from I to VI based on increasing malignancy risk [10]. All patients underwent surgical treatment at the Department of Oncological Endocrinology and Nuclear Medicine, National Institute of Oncology, Warsaw.

Results

Of the 35 focal thyroid lesions, most were categorised as low or intermediate risk of malignancy according to EU-TIRADS-PL, with 13 (37.2%) falling into category 3 and 15 (42.8%) into category 4. High-risk category 5 was assessed in only 7 (20%) lesions (Tab. 1). There were no lesions classified as unsuspected category 2 according to EU-TIRADS-PL. Lesion size averaged 28.7 mm (\pm 14.2 mm), with hypo- or isoechoogenicity [n = 16 (45.7%)] and solid structure [n = 27 (77.1%)] being the predominant features. Most lesions displayed an oval shape

Table 1. EU-TIRADS-PL classification of thyroid lesions of uncertain malignancy potential

EU-TIRADS-PL category	EU-TIRADS-PL classification			
	2	3	4	5
Number of patients	0	13	15	7
Percentage	0%	37.2%	42.8%	20%

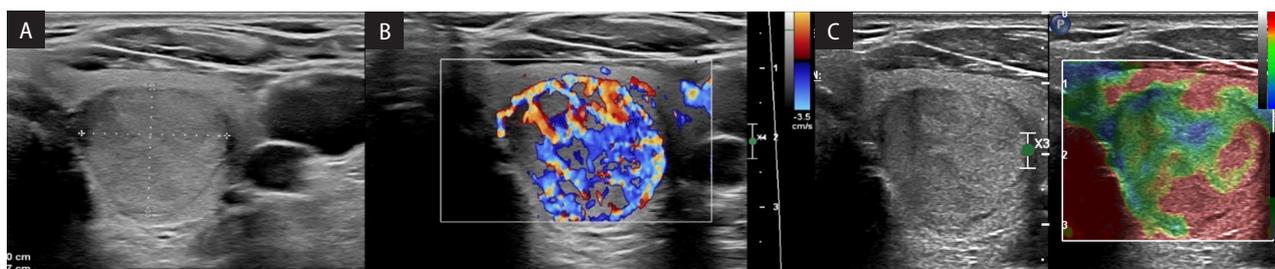


Figure 1A–C. A 74-year-old patient — a thyroid lesion of the left thyroid lobe: oval, solid, hypoechoic, with smooth margins (A), with increased mixed vascularity (B), Asteria 2 in strain sonoelastography (C), EU-TIRADS-PL 4, fine needle aspiration biopsy (FNA) — category IV according to Bethesda, result of histopathological examination: non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)

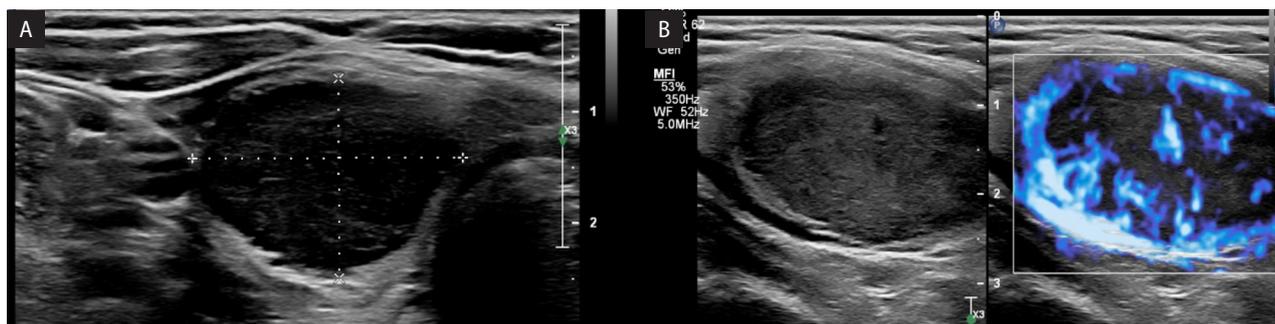


Figure 2A–B. A 33-year-old patient — a thyroid lesion of the right lobe of the thyroid gland: solid, markedly hypoechoic, with irregular margins (A), with increased mixed vascularity in the examination with the function of superb microvascular imaging [SMI] (B), EU-TIRADS-PL 5, fine needle aspiration biopsy (FNA) — category IV according to Bethesda, result of histopathological examination: follicular tumour of uncertain malignant potential (FT-UMP)

[n = 33 (94.2%)], parallel orientation [n = 33 (94.2%)], smooth margins [n = 26 (74.2%)], and a mixed vascular pattern [n = 30 (85.7%)] (Fig. 1A–C). Most nodules were partially deformable in SE elastography, resulting in Asteria 2 for 16 lesions (45.7%) and Asteria 3 for 11 tumours (31.4%). Several patients had high-risk US features, including marked hypoechoicity [n = 4 (11.4%)], non-parallel orientation [n = 2 (5.7%)], irregular margins [n = 2 (5.7%)], and the presence of microcalcifications in one lesion (2.9%) (Fig. 2A–B).

There were no features of extrathyroidal expansion; only capsule modelling was observed in 2 cases (5.7%). In the CEUS study, some dominating contrasting patterns were evaluated, compared to the surrounding parenchyma, such as enhancement equal to the parenchyma (66.6%) or intense (28.5%), heterogeneous (61.9%), centripetal (42.8%), or diffuse (57.1%) with fast (33.3%) or compared to parenchyma contrast wash-in (42.8%) and its fast (33.3%) or comparable to thyroid parenchyma wash-out (52.3%) (Tab. 2A–B; Fig. 3A–C).

Table 2a. Qualitative contrast enhancement features in contrast-enhanced ultrasound (CEUS) of thyroid lesions

CEUS examination								
A. Assessment of contrast enhancement of the thyroid lesion in comparison with the thyroid parenchyma								
	Intensity			Homogeneity		Wash-in rate		
	Higher	Equal	Lower	Homogeneous	Heterogeneous	Slow	Equal	Fast
n (%)	6 (28.5)	14 (66.6)	2 (9.5)	8 (38.0)	13 (61.9)	5 (23.8)	9 (42.8)	7 (33.3)
B. Assessment of contrast enhancement of the thyroid lesion in comparison with the thyroid parenchyma								
	Type of enhancement				Wash-out rate			
	Ring enhancement	Centripetal	Centrifugal	Diffuse	Slow	Equal	Fast	
n (%)	2 (9.5)	9 (42.8)	1 (4.7)	12 (57.1)	7 (33.3)	11 (52.3)	3 (14.2)	

Table 4. Quantitative distribution of borderline tumours according to histopathological classification

Histopathology	Histopathological diagnosis		
	NIFTP	WDT-UMP	FT-UMP
Number of patients/percentage	7 (20%)	7 (20%)	21 (60%)

NIFTP — non-invasive follicular thyroid neoplasm with papillary-like nuclear features; WDT-UMP — well-differentiated tumour of uncertain malignant potential; FT-UMP — follicular tumour of uncertain malignant potential

Bethesda most often as lesions with an intermediate risk of malignancy [14]. This includes category III (atypia of undetermined significance — AUS, 29.8%), category IV (follicular neoplasm — FN, 28.0%), and to a lesser extent, category V (suspicious for malignancy — SM, 21.2%) and II (benign, — BN, 10.2%). It is also important to note that category VI (malignant — ML) can be diagnosed in 8.4% of these lesions, and non-diagnostic biopsies (category I) occur in 1.8% of cases. These findings were similarly reflected in 2 subsequent meta-analyses conducted by Bongiovanni et al. and Ruanpeng et al. [5, 15]. In our study group, most lesions were classified as category IV according to Bethesda (71.4%), and fewer tumours were classified as category II (11.4%) and III (5.7%). Three lesions were assessed as category V (8.6%; there were no FT-UMP lesions in this group), and one nodule with category VI (2.9%; histopathologically diagnosed as NIFTP) (Fig. 4A–B). The obtained data are consistent with the results of the study published by Ito et al. on the clinical characteristics of FT-UMP lesions, in which 60% of 339 nodules were classified as Bethesda category IV after FNA, and only 1% of lesions were classified as high-risk tumors, category V or VI [16].

Ultrasound examination is the basic tool in the pre-operative diagnosis of focal lesions of the thyroid gland. Its limitation is subjectivity and the lack of a single US feature that would allow the determination of the risk of malignancy. Based on the literature data, a significant number of borderline tumours are defined by ultrasonography as low or intermediate risk [8]. In the study published by Ito et al., 339 lesions with histopathological diagnosis of FT-UMP were analysed, identifying 232 intermediate-risk tumours (68%), 89 low-risk lesions (26%), and high-risk malignancy in 16 patients (5%) [16]. A much larger number of studies concern the characteristics of NIFTP tumours, indicating certain tendencies in ultrasound images in this group, defining them as well-circumscribed lesions with smooth margins, round or oval shape, heterogeneous echogenicity, with the very rare occurrence of calcifications and increased mixed type of vascularisation [17–21]. These lesions are usually classified as low or intermediate risk of malignancy according to the ATA classification, and as intermediate (TR3)

or moderate (TR4) risk assessed in ACR-TI-RADS [8, 20, 22, 23]. In the paper published by Song et al. US features of 87 NIFTP lesions were assessed, defining them as solid (81.8%), with increased vascularity (93.8%), without calcifications (86.5%), hypoechoic (44.9%), or isoechoic (38, 8%) [18]. In a study by Hahn et al., US features of NIFTP were compared with the follicular variant of papillary carcinoma (FVPTC), determining those more common in NIFTP, such as hyper or isoechogenicity ($p = 0.043$), well-defined margins ($p = 0.001$), or lack of calcifications ($p = 0.031$) [24]. Moreover, significantly fewer cases of high-risk category 5 lesions according to K-TIRADS in the NIFTP group were observed [24]. Subsequent studies identified certain trends in US images in the group of NIFTP lesions, including iso- or hyperechogenicity, smooth margins, peripheral or central vascular pattern, and lack of calcifications [19, 25]. In our study, we also observed reproducible ultrasound features for borderline lesions of NIFTP, FT-UMP, and WDT-UMP, which is consistent with the literature data. Among the dominant features, we noted solid lesion structure (77.1%), oval shape (94.2%), parallel orientation (94.2%), well-defined margins (74.2%), and mixed vascular pattern (85.7%), including increased vascularity (31.4%) and disordered pattern (45.7%). Most lesions were determined based on the EU-TIRADS-PL scale as low or intermediate risk (TR3 37.2% and TR4 42.8%, respectively). Noteworthy is the fact that 7 nodules (20%) with a high risk of malignancy (TR5) were identified. In this group, there were thyroid lesions diagnosed as NIFTP ($n = 2$), FT-UMP ($n=4$), and WDT-UMP ($n=1$), with a maximum dimension between 8.5 and 34 mm in women aged 31–48 years. Among the US features of increased malignancy risk in this group, markedly hypoechogenicity ($n = 4/7$), non-parallel orientation ($n = 2/7$), irregular margins ($n = 2/7$), disordered distribution of vessels ($n = 3/7$), increased vascularity ($n=1/7$), and stiffness in grade 4 according to the Asteria scale in SE ($n = 1$) were observed. Based on the Polish guidelines, the use of elastography (both SE, and shear wave elastography – SWE) is not required for the routine assessment of thyroid lesions, but it is recommended to use in the qualification for FNA and further follow-up [9].

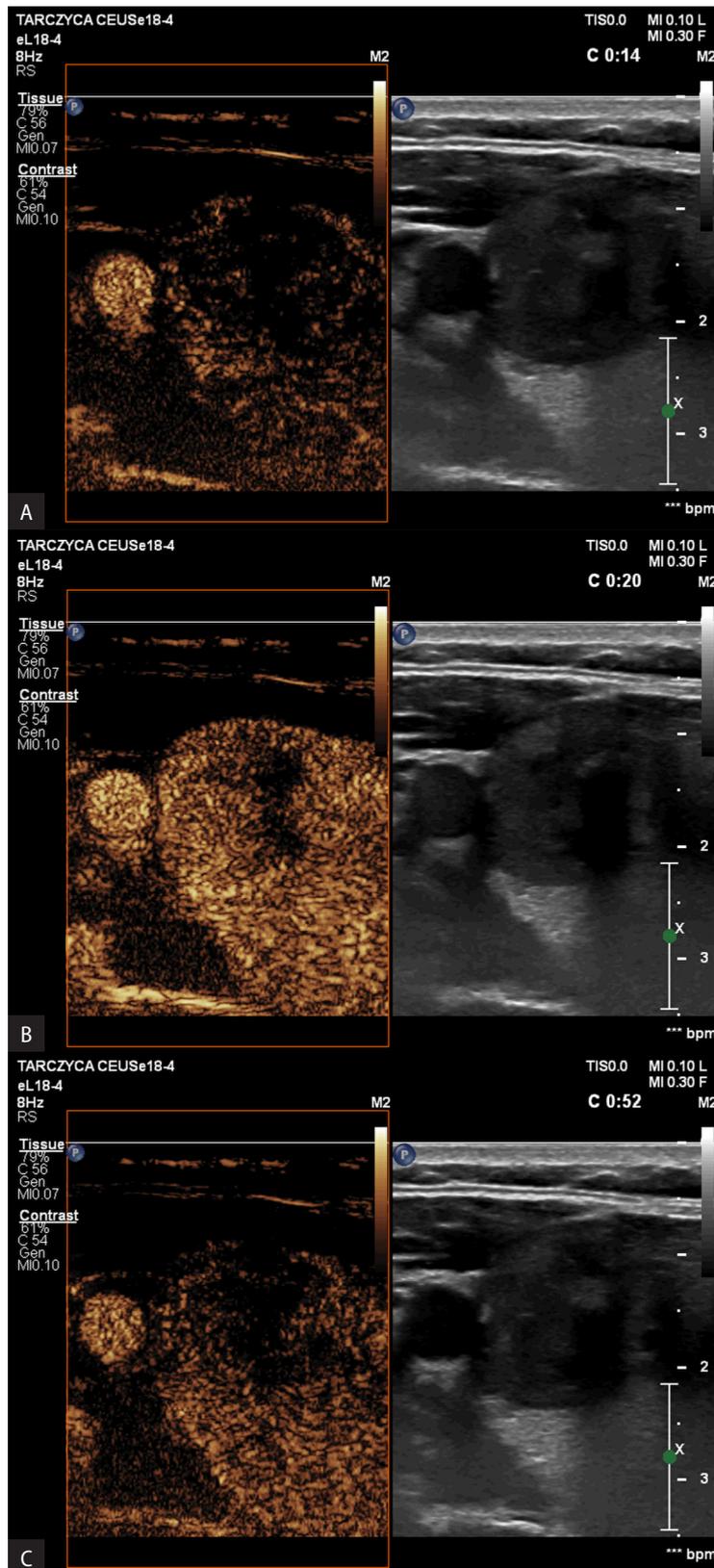


Figure 4A–C. A 60-year-old patient — a thyroid lesion of the right thyroid lobe: solid-fluid, hypoechoic, with irregular margins, in the CEUS examination - contrast enhancement from the periphery (A), with intensity comparable to the surrounding parenchyma and heterogeneous (B), with a fast wash-out phase (C), EU-TIRADS-PL 5, fine needle aspiration biopsy (FNA) — category II according to Bethesda, result of histopathological examination: follicular tumour of uncertain malignant potential (FT-UIMP)

A similar position is taken by European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) in the 2018 guidelines [26]. So far, there are not enough studies on the use of elastography in the differential diagnosis of borderline lesions. However, in the study of Garino et al., a significant usefulness of the use of semi-qualitative assessment using SE of thyroid nodules with an intermediate risk of malignancy, based on the cytopathological result, was found to be significant [27]. Moreover, in another original paper, the clinical utility of the implementation of SE in the differential diagnosis of lesions assessed as category III according to Bethesda was evaluated [28]. In our study, borderline lesions were also subjected to the assessment in SE using the Asteria scale. The majority of nodules were characterised by partial stiffness in Asteria grades 2 (45.7%) and 3 (31.4%), and only 3 tumours were assessed with complete lack of elasticity (Asteria grade 4; 8.5%). Further studies on the assessment of borderline tumours in SE and SWE should be performed, with the possibility of implementing this method in the EU-TIRADS-PL classifier in the future.

Currently, new diagnostic methods such as CEUS are being considered to optimise ultrasound images of thyroid lesions. This method is not recommended for routine clinical use, while the EFSUMB guidelines from 2017 indicate the possibility of using it in the differential diagnosis of thyroid nodules [29]. The available data indicates a very high accuracy of CEUS, which is the subject of many studies conducted on almost all continents [29]. Despite the lack of standardised contrast patterns in the CEUS examination, both in qualitative and quantitative assessment, the guidelines indicate 2 main features that may be predictors of a malignant lesion, such as heterogeneous and hypointense contrast enhancement, and ring enhancement as a strong predictor of benign tumours [29]. Since 2017, many papers have been published on the use of CEUS in the diagnosis of thyroid cancer. In a meta-analysis by Trimboli et al., covering 14 studies with a total of 1515 tumours, CEUS was found to have high sensitivity and specificity in the differential diagnosis of thyroid lesions [85% (95% CI: 83–88) vs. 82% (95% CI 77–87%)] [30]. Moreover, in the study of Xu et al., several CEUS contrast features as predictors of thyroid cancer were distinguished, including heterogeneous enhancement (88.4%), with irregular shape (78.3), ill-defined margins (83.3%), and slow wash-in phase (74.8%) [31]. Many studies indicate that the combination of diagnostic methods, such as the assessment of lesions in B-mode US with the use of elastography and CEUS, significantly increase the sensitivity and specificity of ultrasound in the differential diagnosis of thyroid nod-

ules [32]. So far, there are no studies on the possibility of differential diagnosis of borderline lesions such as NIFTP, FT-UMP, or WDT-UMP. In our study group, in a significant number of patients, we used CEUS with the qualitative assessment of contrast patterns, both in real-time and in retrospective assessment, with the participation of 2 experienced radiologists. Several features dominant in borderline lesions were identified, including contrast enhancement of intensity comparable to that of the surrounding thyroid parenchyma (66.6%), heterogeneous (61.9%), diffuse (57.1%), or centripetal (42, 8%), with a rate of contrast wash-in and wash-out comparable to the parenchyma (42.8% and 52.3%, respectively). It is noteworthy that a ring enhancement, as a predictor of benign nodules, was found only in 2 cases, while other features that may be evidence against malignancy, such as hyperenhancement or fast wash-in and slow wash-out phase, were found in, respectively, 28.5%, 33.3%, and 14.2% of nodules. It is necessary to continue studies on a more representative group assessing the use of CEUS in the diagnosis of low-risk neoplasms to determine the contrast patterns that might differentiate borderline tumours from malignant and benign thyroid lesions.

In the absence of an ultrasound consensus for tumours of uncertain malignancy potential, the issue of the use of molecular tests in this group remains the subject of numerous studies. The concept of low-risk neoplasm is confirmed by the common occurrence of molecular agents characteristic of both benign and malignant lesions, although one of the features, which is the presence of the BRAF V600E mutation, is an exclusion criterion for the diagnosis of NIFTP [33]. The usefulness of immunohistochemical or molecular assessment of borderline tumours remains the subject of ongoing multicentre studies.

One of the limitations of the study is the lack of a representative group of patients diagnosed with borderline thyroid tumours. Moreover, it is necessary to continue a prospective study in order to observe patients postoperatively in terms of the metastatic disease and make the correlation of ultrasound features of thyroid tumours with their malignant potential. The main advantage of the study is the fact that the diagnosis of thyroid nodules was performed by experienced ultrasonographers and pathologists in one reference centre. Secondly, the authors used new diagnostic methods, that allow the optimisation of ultrasound images of thyroid lesions, including contrast-enhanced ultrasound. The presented preliminary results of the assessment of low-risk thyroid tumours are consistent with the literature data, and the authors plan to continue the study with the participation of a more representative group of patients diagnosed in the clinic.

Conclusions

Our study demonstrates that lesions with uncertain malignant potential tend to exhibit features associated with low to intermediate malignancy risk, according to EU-TIRADS-PL classification. This observation is crucial for guiding biopsy decisions and determining observation strategies. The majority of our cytopathological assessments fell within Bethesda IV category, underscoring the need for vigilant follow-up at specialised centres. Notably, low-risk tumours such as NIFTP, FT-UMP, and WDT-UMP from our study cohort necessitate meticulous post-surgical monitoring because they present a risk of recurrence and metastasis, setting them apart from benign thyroid lesions. Future research should explore the potential of emerging technologies, including elastography and CEUS, to enhance the differentiation of these low-risk neoplasms from other thyroid lesions.

Data availability statement

Data were collected in the Department of Endocrine Oncology and Nuclear Medicine, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland and referred to ultrasound examinations performed in patients who underwent thyroidectomy in the clinic.

Ethics statement

Positive opinion of Bioethical Commission in Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland; number 83/2021.

Author contributions

Collecting data, statistical analysis, interpreting the statistical analysis, writing the manuscript, supervising the teamwork, and substantive worth of the paper.

Funding

No funding.

Conflict of interest

Authors declare no conflict of interest.

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