The efficiency of elastography in the diagnostics of follicular lesions and nodules with an unequivocal FNA result

Porównanie skuteczności elastografii w diagnostyce zmian pęcherzykowych tarczycy i ognisk z jednoznacznym wynikiem BAC

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Abstract

Introduction: The aim was to assess the usefulness of strain elastography (SEG) in the diagnostics of two groups of thyroid nodules (TNs): follicular lesions (FL) with low malignancy risk (< 20.0%) and low percentage of papillary carcinomas (PTCs) among cancers as well as TNs with unequivocal cytology (UC) and high percentage of PTCs among cancers.

Material and methods: 168 TNs were analysed and eventually surgically treated: 100 UC (50 benign and 50 malignant — 90.0% PTCs) and 68 FL (60 benign, 8 malignant — 50.0% PTCs). Elasticity score (ES) and strain ratio (SR) were evaluated, and their effectiveness was compared with the evaluation of the number of ultrasound malignancy risk features (NoUMRFs).

Results: In the UC group the evaluation of mean values of SR and ES in both sections (meanSR, meanES) was more efficient than NoUMRFs analysis (AUC: 0.903 and 0.869 vs. 0.754, p < 0.05). The following thresholds: meanSR ≥ 2.01, meanES ≥ 2.5, NoUMRFs ≥ 2, were related to the increased malignancy risk in nodules (OR: 45.0; 23.2; 5.4, respectively), but only meanSR ≥ 2.01 was an independent risk factor (OR: 20.3; SEN: 86.0%, SPC: 88.0%). In the FL group, only the evaluation of tSR (SR assessed in transverse section) had the value of AUC > 0.7, and only the set of features: tSR ≥ 1.7 and NoUMRFs ≥ 1 increased the malignancy risk in nodules (OR: 12.0; SEN: 75.0%, SPC: 75.0%).

Conclusions: SEG is more reliable than conventional US in the diagnostics of TNs. The efficacy of SEG decreases with lowering percentage of PTCs among cancers. But in FL nodules SEG may support the selection of nodules for surgical treatment. **(Endokrynol Pol 2017; 68 (6): 610–622)**

Key words: *elastography, thyroid, follicular lesion, fine-needle aspiration biopsy, thyroid cancer*

Streszczenie

Wstęp: Celem pracy była ocena przydatności elastografii uciskowej (SEG) w diagnostyce 2 grup guzków tarczycy (TNs): zmian pęcherzykowych (FL) z niskim ryzykiem złośliwości (< 20,0%) i niskim odsetkiem raków brodawkowatych (PTCs) wśród nowotworów złośliwych oraz TNs z jednoznaczną cytologią (UC) i wysokim odsetkiem PTCs wśród nowotworów złośliwych.

Materiał i metody: Analizowano 168 TNs, wszystkie ostatecznie były leczone operacyjnie, 100 UC: 50 łagodnych i 50 złośliwych (90,0% PTCs) i 68 FL: 60 łagodnych i 8 złośliwych (50,0% PTCs). Oceniano klasę elastogramu (ES) i wskaźnik odkształcenia (SR) oraz porównywano ich skuteczność z oceną liczby ultrasonograficznych cech ryzyka złośliwości (NoUMRFs).

Wyniki: W grupie UC ocena średnich wartości SR i ES (*meanSR* i *meanES*) z obu przekrojów była bardziej skuteczna niż ocena NoUMRFs (AUC: 0,903 i 0,869 *v.* 0,754, < 0,05). Przekroczenie progów: *meanSR* ≥ 2,01, *meanES* ≥ 2,5, NoUMRFs ≥ 2 powodowało istotny wzrost ryzyka złośliwości zmiany (odpowiednio OR: 45,0; 23,2; 5,4), ale tylko meanSR ≥ 2,01 był niezależnym czynnikiem ryzyka złośliwości (OR: 20,3; SEN: 86,0%, SPC: 88,0%). W grupie FL tylko dla tSR (SR analizowane na przekroju poprzecznym) stwierdzono wartość AUC > 0,7. Jednoczesne występowanie tSR ≥ 1,7 i NoUMRFs ≥ 1 istotnie zwiększało ryzyko złośliwości zmiany (OR: 12,0; SEN: 75,0%, SPC: 75,0%).

Wnioski: SEG jest bardziej wiarygodna niż klasyczna ultrasonografia w diagnostyce TNs. Skuteczność SEG spada z obniżaniem się odsetka PTCs wśród nowotworów złośliwych. Ale także w grupie FL SEG może pomóc wyodrębnianiu TNs, które powinny być leczone chirurgicznie. **(Endokrynol Pol 2017; 68 (6): 610–622)**

Słowa kluczowe: *elastografia, tarczyca, zmiany pęcherzykowe, biopsja aspiracyjna cienkoigłowa, rak tarczycy*

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Introduction

The preoperative diagnostics of thyroid nodules (TNs) is a challenge because it requires the detection of cancers among many non-neoplastic lesions. Ultrasonography (US) and fine-needle aspiration biopsy (FNA) are the preferred diagnostic methods, but both procedures have serious limitations. These limitations are especially serious in the case of nodules with equivocal FNA results, which can constitute up to 30% of all examined nodules. They are particularly related to follicular lesions (FL) [1, 2]. The current Bethesda classification of cytological diagnoses distinguishes two categories among FL: III — follicular lesion of undetermined significance (FLUS) and IV — suspicious for follicular neoplasm (SFN). In the case of category IV the risk of malignancy in a nodule is usually over 15% and a surgical treatment is recommended [1]. But in areas of iodine deficiency or in post-endemic areas that risk may be lower (due to non-neoplastic hyperplastic follicular nodules outnumbering follicular neoplasms), and then the decision on the surgical treatment becomes less obvious [3, 4]. The risk of malignancy of category III is more diverse and it ranges from 5% to as much as 50% [5–9] among various centres. This is in contrast to the assumptions that were made when that category was created. According to them, category III should isolate nodules with lower risk of malignancy from other FL. The management of those nodules should be based on repeated FNA [2]. Unfortunately, both in centres reporting low and high malignancy risk in FLUS nodules, the repeated FNAs are inconclusive in 20–30% of cases — because of recurrent FLUS result or non-diagnostic smears [7, 8, 10]. Molecular diagnostics performed with repeated FNA is neither efficient nor easily accessible [1, 11]. Analysis of classic ultrasound malignancy risk features (UMRFs) usually does not improve cancer detection in FL nodules either. Our previous studies showed that the efficiency of UMRFs analysis decreases with the lowering percentage of papillary cancers (PTCs) among malignant tumours [12]. This should not be surprising because the identification of UMRFs was particularly based on the analysis of the most common PTCs [13, 14]. Ultrasound images of these cancers differ from the images of follicular cancers (FTC) [15], which are more common among malignant FL than among other nodules, especially in iodine deficient populations.

The aforementioned limitations of US and FNA are sought to be overcome by finding new US parameters. Elastography is thought to be a promising technique in this area. This method, depending on its type and the employed image analysis technique, may provide a qualitative or quantitative assessment of the nodule stiffness/hardness, which is the accepted malignancy risk feature of a tumour. The most popular and widely used elastography technique is strain elastography (SEG), which allows analysis of a colour map of the nodule stiffness and assessment of the relative nodule stiffness in comparison to its surroundings. Elastography was successfully applied to the thyroid gland in 2005 [16]. Since then, several studies on the usefulness of elastography in the diagnosis of TNs have been reported; however, clear conclusions have not been established yet. The majority of authors state that elastography may assist conventional methods in the diagnostics of thyroid nodules [17–22], and it may be helpful in diagnosing thyroiditis [23], especially in the differentiation of nodules in patients with chronic thyroiditis [23, 24]. Nevertheless, in the opinion of some authors the usefulness of SEG is limited [25–27], especially in patients with multinodular goitre [28]. In such cases shear wave elastography may be a useful tool for quantitative elastographic measurements [29]. Some reports confirmed SEG efficiency in relation to FL [30–32]. However, most of them indicate that further studies are still required [33–35]. In the majority of those studies the influence of particular types of thyroid cancer on the obtained results was not considered. The ratio of PTCs to other cancers in FL nodules differed among reporting centres.

Therefore, the aim of our study was to establish the usefulness of SEG in two groups of TNs: nodules with unequivocal cytology (UC), where PTCs dominate, and nodules in FL group, where the percentage of PTCs is markedly lower.

Material and methods

SEG was performed in patients with TNs subjected to FNA in our centre in the years 2013–2015. The examined nodules had at least one malignancy risk factor (ultrasonographic or clinical), or they were the largest nodules in the thyroid, while no other lesion was more suspicious. A detailed description of the FNA procedure was presented in our earlier report [8]. Results of FNA were classified into six groups defined in the Bethesda system [2]. SEG was performed in all of the nodules with the FNA outcome corresponding to FL, i.e. categories III (FLUS) or IV (SFN) in the Bethesda system, and in UC nodules: all of the nodules with category VI (malignant neoplasm — MN) and similar number of subsequent nodules with an FNA result of category II (benign lesion — BL). The exclusion criteria were as follows: the nodule diameter wider than the width of the transducer, the presence of eggshell calcifications, more than 50% of the cystic content, another superficially located nodule, and absence of surrounding reference thyroid tissue (free of pathological lesions). Additionally,

the following clinical exclusion criteria were used: prior treatment for thyroid cancer, radioiodine therapy, thyroid surgery, neck irradiation, and a massive thyroid fibrosis in the course of Hashimoto disease. Eventually, the analysis included only TNs with the available postoperative histopathological result. It was the basis for the selection of malignant and benign nodules in both groups (FL and UC). Patients with the cytological outcome SFN or MN were routinely referred for surgical treatment. The decision on the surgical treatment in the patients with FLUS or BL result was based on the patient's preferences (in the majority of cases) or on the presence of clinical risk features (e.g. the nodule enlargement).

In total, 68 FL nodules were analysed: 34 SFN and 34 FLUS. Cancers were found in 11.8% of FLs, including two FLUS nodules (5.9%) and six SFN nodules (17.6%). Among the revealed cancers there were four (50.0%) PTCs, two (25.0%) FTCs, including one case of oxyphylic type (FTC-O), and two (25.0%) medullary cancers (MTC). The UC group included 100 nodules: 50 subsequently examined, cytologically and histopathologically benign nodules, as well as 50 cancers, including 45 (90.0%) PTCs (p = 0.018 vs. FL group), four (8.0%) MTC, and one (2.0%) FTC-O. There were no differences in the mean age of patients between the groups: FL group — 54.3 ± 12.8 years; UC group — 52.9 ± 13.8 years (p = 0.523). In the UC group the patients with cancers were significantly younger than the patients with benign nodules: 49.0 ± 15.3 vs. 56.7 ± 11.2 years (p = 0.005), while in the FL group such differences were not observed: 59.0 ± 15.5 vs. 53.7 ± 12.5 years, respectively (p = 0.271). The percentage of males in both groups was similar: FL — 10.3%, UC — 12.0% (p = 0.731). The mean nodule volume was also similar: FL — 2.5 ± 3.5 mm^3, UC — 1.7 ± 3.4 mm^3 (p = 0.079).

Conventional US and SEG were accomplished using an Aloka Prosound Alpha 7 sonograph, ALOKA co. Ltd., Tokyo, Japan with a 7.5–14 MHz linear transducer, power Doppler functionality, and Hitachi software for the elastography. Elastography examinations were performed using the real-time compression method. Freehand, delicate compression was applied to the neck. The pressure level and its regularity were controlled by a five-point scale — the applied pressure was kept between levels 3 and 4. The colour map of tissue stiffness — the elastogram — was analysed and classified using the four-grade elasticity scale (*elasticity score* — ES) developed by Asteria et al. [36]: score 1 — elasticity in the whole nodule (entirely green), score 2 — elasticity in a large part of the nodule (mostly green with some blue parts), score 3 — no elasticity in a large part of the nodule (mostly blue with some green parts), score 4 — no elasticity in the whole nodule (entirely blue). Furthermore, the strain ratio (SR) was measured as the relative nodule stiffness compared to the reference thyroid area (shown in the same image, with no pathological lesions). This area was kept similar in size to the examined nodule and had a similar distance from the skin (Fig. 1–3). The measurements were performed in transverse (tES and tSR) and longitudinal (lES and lSR) sections. Mean (meanES, meanSR) and maximal values (maxES and maxSR) of those variables in both sections were also analysed. The results of SEG were compared with the analysis of the number of conventional UMRFs (NoUMRFs) present in the nodule (ranging from 0 to 5), which included: 1) hypoechogenicity or marked hypoechogenicity (compared with the surrounding thyroid or strap muscles) of a solid nodule (< 25% cystic), 2) more-tall-than-wide shape (measured on the transverse view), 3) pathological vascularisation — chaotic intra-nodular vascular spots, 4) suspicious margins — irregular or blurred or suggesting extra-thyroidal extension, and 5) microcalcifications. Such a design was related to the fact that current recommendations concordantly admit that none of the single UMRF has sufficient accuracy. There is also a diversity of suggested sets of UMRFs, and none of them is widely accepted [1, 13, 37, 38]. The only non-disputable point is that the higher number of UMRFs in the nodule, the higher risk of its malignancy.

The efficacy of examined elastographic parameters (tES, tSR, lES, lSR, meanES, mean SR, max ES, and max SR) and of the NoUMRFs in the differentiation between benign lesions and cancers was assessed by analysis of the receiver operating characteristics curve (ROC) and the area under the ROC (AUC) value. That method was also applied to calculate the cut-off values of examined parameters characterised by optimal sensitivity (SEN) and specificity (SPC), meant as the highest possible sum of SEN and SPC. The thresholds were determined for the ES and SR parameters which showed the highest AUC values on the condition that AUC was above 0.7. The effectiveness of the determined thresholds in both groups was presented as SEN, SPC, the accuracy (ACC), the positive predictive value (PPV), the negative predictive value (NPV), and the positive likelihood ratio (LR+). The odds ratio (OR) for the established cut-off values and the efficacy of combinations of ES, SR, and NoUMRFs were assessed with the use of logistic regression analysis. The comparison of frequency distributions was performed with the χ^2 test (with suitable modifications according to the number of analysed cases), and the Kruskal-Wallis test was used for comparison of continuous variables between groups. The statistical analysis was performed with Statistica version 10 statistical software. The value of 0.05 was assumed as
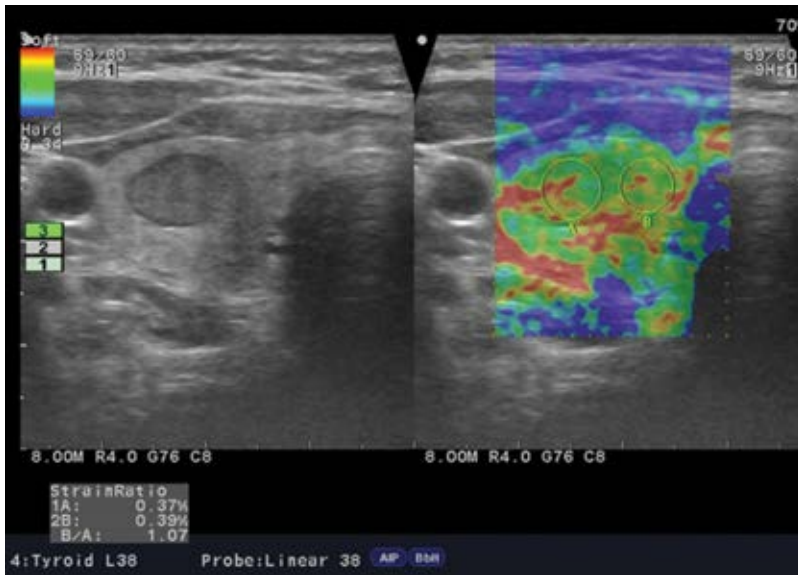
Figure 1. *Benign lesion: B-mode and elastographic image, NoUMRFs — 1 (hypoechogenicity), ES — 2, SR — 1.07*

Rycina 1. *Zmiana łagodna: obraz w prezentacji B i elastogram, NoUMRFs — 1 (hipoechogeniczność), ES — 2, SR — 1,07*
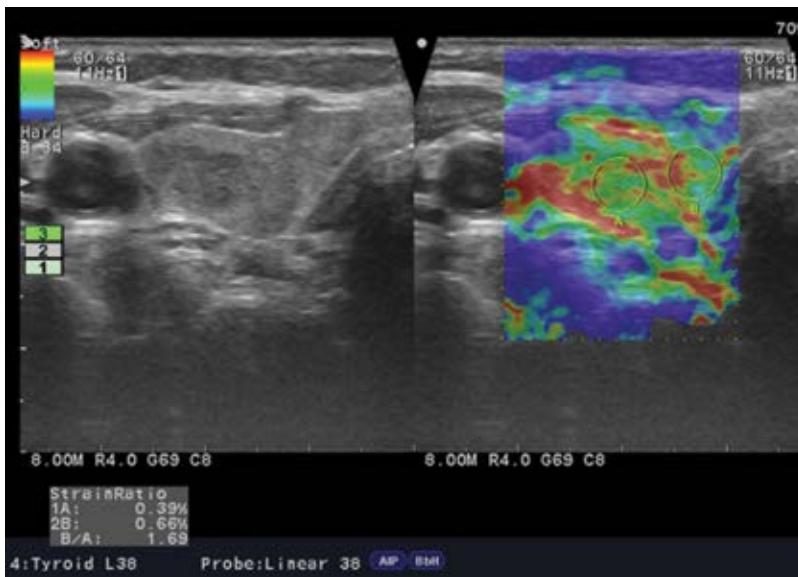
Figure 2. *Follicular lesion of undetermined significance: B-mode and elastographic image; NoUMRFs — 2 (hypoechogenicity, irregular margin), ES — 2, SR — 1.69*

Rycina 2. *Zmiana pęcherzykowa bliżej nieokreślona: obraz w prezentacji B i elastogram; NoUMRFs — 2 (hipoechoegeniczność, nieregularne granice), ES — 2, SR — 1,69*
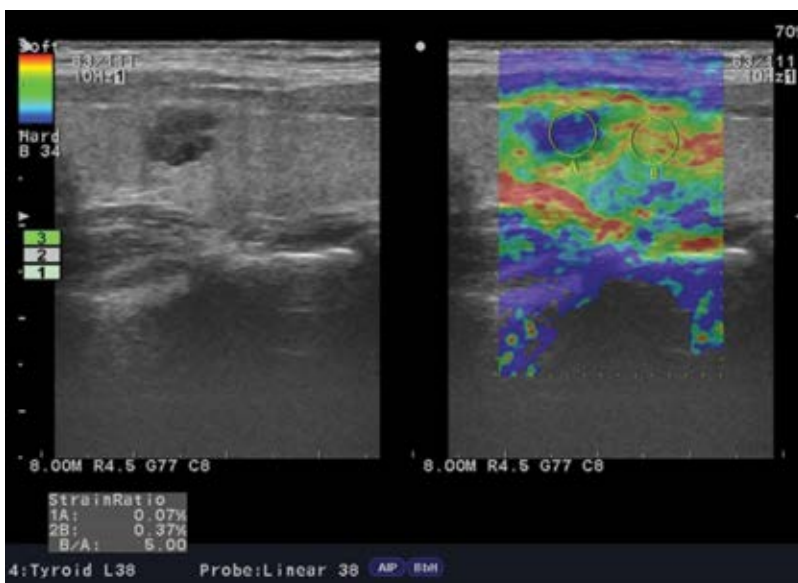
Figure 3. *Malignant neoplasm: B-mode and elastographic image; NoUMRFs — 3 (hypoechogenicity, irregular margin, taller-than-wide shape), ES — 4, SR — 5.0*

Rycina 3. *Nowotwór złośliwy: obraz w prezentacji B i elastogram; NoUMRFs — 3 (hipoechoegeniczność, nieregularne granice, kształt wyższy niż szerszy), ES — 4, SR — 5,0*

the level of significance. The study protocol had been approved by the local Bioethics Committee. All the patients gave their informed consent.

Results

Table I shows the distribution of particular ES as well as the mean and the median SR in patients in UC and FL groups in relation to the result of the postoperative histopathological examination. In the UC group the nodules were soft (ES1 or ES2) less often among cancers than among benign lesions and were hard (ES3 or ES4) more often (only in the case of lES1 the difference was insignificant — p = 0.074). In the FL group, no significant differences were found in the distribution of ES between cancers and benign lesions. Cancers in the FL group showed ES3 or ES4 less often than cancers in the UC group (32.5% vs. 88.0% in the transverse section, p = 0.004 and 25.0% vs. 82.0% in the longitudinal section, p = 0.003), and none of the cancers in the FL group showed ES4. Normal elasticity (meant as ES1) was found concomitantly in both sections in a single cancer (2.0%) of the UC group and in no cancer of the FL group. The mean value of SR was significantly higher in cancers than in benign lesions in the UC group, while in the FL group no such difference was observed. In the longitudinal section the cancers of the FL group showed significantly lower mean SR than cancers of the UC group (lSR: p = 0.007)

Table II shows the distribution of the NoUMRFs in examined groups. In the UC group, cancers showed 3 UMRFs and above 2 UMRFs (p < 0.001) more often than benign lesions, and 1 UMRF and under 2 UMRFs (p < 0.001) less often than benign lesions. The FL group did not show similar regularity. The distribution of the NoUMRFs in benign lesions in both groups was similar, but it differed between cancers: above 2 UMRFs were found in 44.0% of cancers in the UC group, but in none cancer of the FL group (p = 0.047).

Table III shows the comparison of the classification value of particular SEG parameters and the NoUMRFs in both groups. In the UC group, AUC values for all elastographic parameters were higher than 0.8 and did not differ significantly. In the analysis of both ES and SR, the highest AUC was noted for meanES and meanSR, respectively. The AUC value for both of those parameters was significantly higher than for the NoUMRFs (meanSR: p = 0.006, meanES: p = 0.029). The thresholds determined for those parameters with the use of ROC curves were: 2.5 for meanES, 2.01 for meanSR, and 2 for the NoUMRFs (Fig. 4). In the FL group the highest AUC values were found for tSR and tES, but the value of AUC exceeded 0.7 only for tSR. The threshold determined for tSR was 1.7 (Fig. 4).

Table IV shows the values describing the diagnostic efficacy of the determined thresholds in both groups. In the UC group the analysis based on meanSR ≥ 2.01 showed significantly higher SPC (p = 0.027), ACC (p = 0.003), PPV (p = 0.030), and NPV (p = 0.048) and a lower percentage of FP results (p = 0.038) in comparison to the NoUMRFs ≥ 2 criterion. Nearly significant differences were observed for SEN (p = 0.054) and the percentage of FN results (p = 0.070). The analysis based on meanES ≥ 2.5 showed significantly higher SEN (p = 0.027) and ACC (p = 0.047) and a lower percentage of FN results (p = 0.038) in comparison to the NoUMRFs ≥ 2 criterion. The difference was nearly significant for NPV (p = 0.057). No statistically significant differences were found for SEN, SPC, ACC, PPV, or NPV between meanES ≥ 2.5 and meanSR ≥ 2.01 criteria, but the LR+ value was nearly two-fold higher for meanSR ≥ 2.01 than for meanES ≥ 2.5 (7.2 vs. 3.7). The logistic regression analysis confirmed that all of the analysed criteria were significantly related to thyroid malignancy in the UC group, but only meanSR ≥ 2.01 was an independent malignancy risk factor. The addition of other criteria to meanSR did not improve the diagnostic efficiency of the test as measured with AUC (Tables V and VI). OR values slightly higher than those noted for the isolated meanSR ≥ 2.01 criterion were observed only in two models: the conjunction of both elastographic criteria, i.e. meanES ≥ 2.5 and meanSR ≥ 2.01 (Table V) as well as the inclusive disjunction of the NoUMRFs ≥ 2 and meanSR ≥ 2.01 criteria (Table VI). The former model had values of SEN and SPC similar to the single criterion of meanSR ≥ 2.01. The inclusion of the NoUMRFs ≥ 2 criterion to this model markedly lowered SEN — to 60.0%, but increased SPC to 92.0%. High SPC could be also obtained with the conjunction of the NoUMRFs ≥ 2 and meanSR ≥ 2.01 criteria, while the inclusive disjunction of the criteria led to maximal SEN (96.0%). The model with maximal SEN was connected with a need for biopsy of twice as many nodules compared to the model with maximal SPC (65.0% vs. 34.0%, p < 0.001).

In the FL group the models based on meanES ≥ 2.5, meanSR ≥ 2.01, and NoUMRFs ≥ 2 criteria were not efficient (LR+ in the range of 1.2–1.4, SEN did not exceed 50%). The model based on tSR ≥ 1.7 criterion also had low LR+ (2.5), but with SEN: 75.0% and PPV: 24.0%. The tSR ≥ 1.7 criterion was related to the increased risk of malignancy in FL nodules in a nearly significant way (OR: 8.6, p = 0.065) (Table IV), similarly to the model based on conjunction of tSR ≥ 1.7 and NoUMRFs ≥ 2 criteria (OR: 6.6, p = 0.071) (Table V). That combination showed higher SPC than models based on single tSR ≥ 1.7 or single NoUMRFs ≥ 2 criterion (respectively,
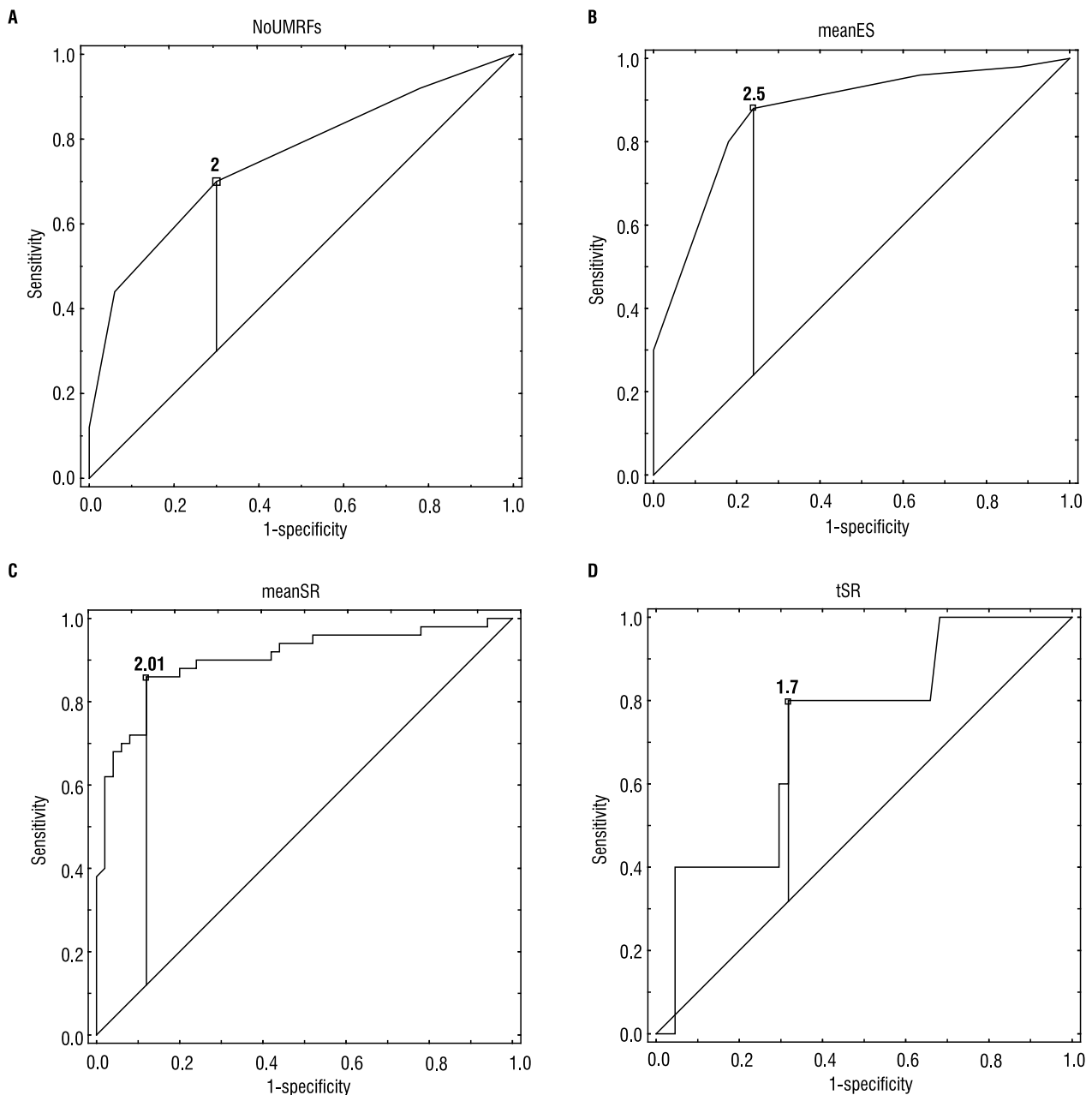
Figure 4. *ROC curves for the classification of benign and malignant lesions using analysis of:* **A.** *number of ultrasound malignancy risk features (NoUMRFs);* **B.** *mean values of elasticity score in both sections (meanES);* **C.** *mean values of strain ratio in both sections (meanSR);* **D.** *strain ratio measured in transverse section (tSR)*

Rycina 4. *Krzywe ROC w różnicowaniu zmian łagodnych i złośliwych wyznaczone dla wartości:* **A.** *liczby ultrasonograficznych cech ryzyka złośliwości (NoUMRFs) w grupie UC;* **B.** *średniej wartości w punktowej skali oceny klasy elastogramu z obu przekojów (meanES) w grupie UC;* **C.** *średniej wartości wskaźnika odkształcenia z obu przekojów (mean SR) w grupie UC;* **D.** *wartości wskaźnika odkształcenia na przekroju poprzecznym (tSR) w grupie FL*

85.0% vs. 68.3% and 58.3%, p = 0.031 and p = 0.001), but the SEN of that combination was low (37.5%). The inclusive disjunction of those criteria did not improve the SEN of the model in comparison to isolated tSR ≥ 1.7 criterion and had lower SPC (41.7% vs. 68.3%, p = 0.003). Optimal SEN and SPC at the level of 75.0% were simultaneously observed in the model based on the conjunction of tSR ≥ 1.7 and UMRFs ≥ 1 criteria. These criteria were matched by 30.9% of the nodules that should be potentially diagnosed by FNA. The logistic regression analysis confirmed that the risk of malignancy of those nodules was significantly higher (OR: 12.0, p = 0.034). The inclusive disjunction of those criteria led to SEN reaching 100.0%, but was accompanied with low SPC (16.7%) and a very high percentage of nodules matching any of the criteria (85.3%).

Table I. *Results of elastographic evaluation of the nodules in FL and UC groups in relation to the eventual histopathological diagnosis*

Tabela I. *Wyniki badania elastograficznego ognisk z grup FL i UC w zależności od ostatecznego rozpoznania histopatologicznego*

Parameters		The category of FNA					
		UC (100)			FL (68)		
		Histopathological results					
		Benign (50) No/%	Malignant (50) No/%	p	Benign (60) No/%	Malignant (8) No/%	p
ES							
Transverse section	tES1 [n/%]	15/30.0	1/2.0	**0.005**	15/25.0	0/0.0	0.251
	tES2 [n/%]	23/46.0	5/10.0	**< 0.001**	27/45.0	5/62.5	0.579
	tES3 [n/%]	12/24.0	36/72.0	**< 0.001**	18/30.0	3/32.5	0.981
	tES4 [n/%]	0/0	8/16.0	**0.009**	0/0	0/0	–
	tES [Me (Q:25–75)]	2.0 (1.0–2.0)	3.0 (3.0–3.0)	**< 0.001**	2.0 (2.0–2.0)	2.0 (2.0–3.0)	0.231
Longitudinal section	lES1 [n/%]	10/20.0	3/6.0	0.074	9/15.0%	1/12.5%	0.731
	lES2 [n/%]	30/60.0	6/12.0	**< 0.001**	36/60.0%	5/62.5%	0.804
	lES3 [n/%]	10/20.0	29/58.0	**< 0.001**	14/23.3%	2/25.0%	0.734
	lES4 [n/%]	0/0.0	12/24.0	**< 0.001**	1/1.7%	0/0.0%	0.232
	lES [Me (Q:25–75)]	2.0 (2.0–2.0)	3.0 (3.0–3.0)	**< 0.001**	2.0 (2.0–2.0)	2.0 (2.0–2.5)	0.893
SR							
Transverse section	tSR [x ± SD]	1.4 ± 0.6	3.6 ± 1.7	**< 0.001**	1.7 ± 1.3	2.8 ± 1.8	0.102
	tSR [Me (Q:25–75)]	1.3 (1.0–1.6)	3.3 (2.3–4.7)		1.3 (0.8–2.1)	1.8 (1.7–4.5)	
Longitudinal section	lSR [x ± SD]	1.5 ± 0.8	3.3 ± 1.7	**< 0.001**	1.6 ± 1.2	1.8 ± 1.4	0.478
	lSR [Me (Q:25–75)]	1.2 (1.0–1.9)	3.3 (2.1–4.0)		1.3 (0.9–1.7)	1.4 (1.2–1.6)	

Table II. *Number of UMRFs in the nodules of FL and UC groups in relation to the eventual histopathological diagnosis*

Tabela II. *Liczba UMRFs w ogniskach z grup FL i UC w zależności od ostatecznego rozpoznania histopatologicznego*

NoUMRFs	The category of FNA					
	UC (100)			FL (68)		
	Histopathological results					
	Benign (50) No/%	Malignant (50) No/%	p	Benign (68) No/%	Malignant (8) No/%	p
0 [n/%]	11/22.0	4/8.0	0.093	13/21.7	0/0	0.324
1 [n/%]	24/48.0	11/22.0	**0.006**	22/36.7	4/50.0	0.733
2 [n/%]	12/24.0	13/26.0	0.817	19/31.7	4/50.0	0.527
3 [n/%]	3/6.0	16/32.0	**0.002**	6/10.0	0/0	0.785
4 [n/%]	0/0	5/10.0	0.066	0/0	0/0	—
5 [n/%]	0/0	1/2.0	1.0	0/0	0/0	—
Me (Q:25–75)	1.0 (1.0–2.0)	2.0 (1.0–3.0)	**< 0.001**	1.0 (1.0–2.0)	1.5 (1.0–2.0)	0.494

Table III. *Comparison of the classification value of elastographic parameters and of the number of UMRFs in FL and UC groups*
Tabela III. *Porównanie wartości klasyfikacyjnej kolejnych parametrów elastograficznych oraz liczby UMRFs w grupach FL i UC*

Parameter	The category of FNA							
	UC				FL			
	AUC	SE	95% CI	p	AUC	SE	95% CI	p
NoUMRFs	0.754	0.049	0.658–0.849	**< 0.001**	0.571	0.085	0.404–0.737	0.404
ES								
tES	0.845	0.040	0.766–0.924	**< 0.001**	0.622[c]	0.088	0.449–0.795	0.167
lES	0.823	0.044	0.737–0.909	**< 0.001**	0.513	0.107	0.303–0.723	0.904
meanES	0.869[a]	0.036	0.798–0.940	**< 0.001**	0.568	0.096	0.380–0.758	0.479
maxES	0.856	0.038	0.783–0.932	**< 0.001**	0.532	0.100	0.337–0.728	0.746
SR								
tSR	0.898[a]	0.039	0.822–0.974	**< 0.001**	0.725[d]	0.112	0.505–0.945	**0.045**
lSR	0.860	0.038	0.784–0.935	**< 0.001**	0.578	0.087	0.407–0.749	0.371
meanSR	0.903[b]	0.032	0.840–0.965	**< 0.001**	0.597[e]	0.091	0.419–0.774	0.285
maxSR	0.893[a]	0.033	0.828–0.958	**< 0.001**	0.536	0.105	0.330–0.743	0.729

[a]$p < 0.05$ — vs. NoUMRFs; [b]$p < 0.01$ — vs. NoUMRFs; [c]$p < 0.0001$ — vs. maxES; [d]$p < 0.005$ — vs. tES, maxES; [e]$p < 0.05$ — vs. maxSR

Discussion

For the last decade, interest in applying elastography to thyroid diagnostics has been increasing. The current recommendations indicate elastography as an optional method that needs further studies [1, 4, 36]. An important obstacle is the lack of standardisation of elastographic measurements, which makes it impossible to adopt common thresholds for both ES and SR values. Our data show that the necessity of local thresholds for ES and SR is also related to the specificity of examined nodules. Specific criteria are necessary especially for FL that are characterised by low risk of malignancy and relatively low percentage of PTC among cancers.

We found that in the UC group (with a high percentage of PTC among cancers) the elastography had higher diagnostic efficacy than the assessment of NoUMRFs, both ES and SR. The efficacy of SEG in longitudinal and transversal sections is similar, but the evaluation of mean ES and SR values of both sections is the most effective. The criterion of meanSR ≥ 2.01 is an independent risk factor of malignancy in the nodule. However, in the case of lack of a suitable reference area the criteria based on ES evaluation can be used. These criteria also indicate significantly increased risk. The determined threshold for meanES, i.e. meanES ≥ 2.5, leads to the conclusion that ES4 found in any section is a malignancy risk factor regardless of the value measured in the other section (similarly to the ES3 accompanied by any score >1 in the other section).

Similar observations that indicate the advantage of SR evaluation over UMRFs analysis were made in the studies carried out in populations with a high percentage of PTCs among thyroid cancers. Xing et al. [21] indicated that both SEG parameters, but especially SR, were more reliable than the analysis of single UMRFs. The advantage of SR and ES was shown also by Ning et al. [39], Wang et al. [40], as well as in the meta-analysis by Sun et al. [41], but it was not confirmed by Chong et al. [42]. Less coherent observations were made on the effectiveness of ES analysis. Azizi et al. [17] showed that the ES analysis stratifies the malignancy risk of thyroid nodules with the PPV equal to microcalcifications and higher than other UMRFs. The high usefulness of ES analysis in the differentiation between benign and malignant thyroid nodules was also reported by Hong at al. [20]. Interestingly, Mehrorta et al. [43] showed that the ES measurement might be helpful in the selection of benign nodules only due to high NPV and SPC, but it was related to low PPV. Shuzhen [44] demonstrated higher NPV, SPC, and ACC but lower SEN for ES in comparison with UMRFs analysis. Our study also showed higher NPV of ES evaluation than of NoUMRF analysis, with similar SPC, but higher SEN and ACC. It should be remembered that the direct comparison of PPV and NPV values originating from various centres is difficult because these parameters depend on the general risk of cancer in thyroid nodules in the examined population. On the other hand, Unlütürk et al. [27] did not find any superiority of ES over classic US. Moon et al. [26] even showed that URMF analysis had a distinct advantage over ES evaluation in diagnosing thyroid cancers. In spite of these discrepancies some authors underline the significance of the lowest elasticity score (ES1) in

Table IV. *Indexes of the diagnostic efficacy of the determined thresholds for the number of UMRFs and elastographic parameters — comparison between UC and FL*

Tabela IV. *Wartości wskaźników opisujących skuteczność diagnostyczna ustalonych progów odcięcia dla liczby UMRFs oraz parametrów elastograficznych — porównanie grup UC i FL*

		The category of FNA							
		UC			FL				
		NoUMRFs ≥ 2	meanES ≥ 2.5	meanSR ≥ 2.01	NoUMRFs ≥ 2	meanES ≥ 2.5	meanSR ≥ 2.01	tSR $\geq 1,7$	NoUMRFs ≥ 1
TP [n/%]		35/35.0	44/44.0	43/43.0	4/5.9	3/4.4	2/2.9	6/8.8	8
TN [n/%]		35/35.0	38/38.0	44/44.0	35/51.5	39/57.4	49/72.1[a]	41/60.3	13
FP [n/%]		15/15.0	12/12.0	6/6.0[a]	25/36.8	21/30.9	11/16.2[a, c]	19/27.9	47
FN [n/%]		15/15.0	6/6.0[a]	7/7.0	4/5.9	5/7.4	6/8.8	2/2.9	0
SEN [%]		70.0	88.0[a]	86.0	50.0	37.5	25.0	75.0	100.0
SPC [%]		70.0	76.0	88.0[a]	58.3	65.0	81.7[b]	68.3	21.7
ACC [%]		70.0	82.0[a]	87.0[b]	57.4	61.8	75.0	69.1	30.9
PPV [%]		70.0	78.6	87.8[a]	13.8	12.5	15.4	24.0	14.5
NPV [%]		70.0	86.4	86.3[a]	89.7	88.6	89.1	95.3	100.0
LR+		2.3	3.7	7.2	1.2	1.2	1.4	2.5	1.3
OR (95% CI) P	Univariate analysis	5.4 (2.3–12.8) **< 0.001**	23.2 (8.0–67.8) **< 0.001**	45.0 (14.0–144.9) **< 0.001**	1.4 (0.3–6.3) 0.655	1.1 (0.2–5.3) 0.889	1.5 (0.3–8.6) 0.654	8.6 (0.8–89.2) 0.065	—
	Multivariate analysis	2.7 (0.8–9.3) 0.103	2.3 (0.5–11.4) 0.294	20.3 (4.3–96.1) **< 0.001**	—	—	—	—	—

[a]p < 0.05 — vs. NoUMRFs; [b]p < 0.01 — vs. NoUMRFs; [c]p < 0.05 — vs. meanES

Table V. *Analysis of selected conjunctions of the elastographic parameters and the number of UMRFs in differentiation between benign and malignant lesions in UC and FL groups*

Tabela V. *Analiza koniunkcji parametrów elastograficznych i liczby UMRFs w różnicowaniu zmian łagodnych i nowotworów złośliwych w grupach UC i FL*

	The category of FNA					
	UC				FL	
	NoUMRFs ≥ 2 & meanES ≥ 2.5	NoUMRFs ≥ 2 & meanSR ≥ 2.01	meanES ≥ 2.5 & meanSR ≥ 2.01	NoUMRFs ≥ 2 & meanES ≥ 2.5 & meanSR ≥ 2.01	NoUMRFs ≥ 1 & tSR ≥ 1.7	NoUMRFs ≥ 2 & tSR ≥ 1.7
SEN [%]	64.0	60.0	84.0	60.0	75.0	37.5
SPC [%]	88.0	92.0	90.0	92.0	75.0	85.0
ACC [%]	76.0	76.0	87.0	76.0	75.0	79.4
PPV [%]	84.2	88.2	89.4	88.2	28.6	25.0
NPV [%]	71.0	69.7	84.9	69.7	95.7	91.1
LR+	5.3	7.5	8.4	7.5	3.2	2.5
OR (95% CI) p	13.0 (4.7–36.5) **< 0.001**	17.3 (5.4–55.5) **< 0.001**	47.3 (14.3–155.9) **< 0.001**	17.3 (5.4–55.5) **< 0.001**	12.0 (1.1–119.1) 0.034	6.6 (0.8–55.4) 0.071
% of all nodules	38.0	34.0	47.0	34.0	30.9	17.7

Table VI. *Analysis of the selected inclusive disjunctions of elastographic parameters and the number of UMRFs in the differentiation between benign and malignant lesions in UC and FL groups*

Tabela VI. *Analiza alternatywnych kombinacji parametrów elastograficznych i liczby UMRFs w różnicowaniu zmian łagodnych i nowotworów złośliwych w grupach UC i FL*

	The category of FNA					
	UC			**FL**		
	NoUMRFs ≥ 2 or meanES ≥ 2.5	**NoUMRFs ≥ 2 or meanSR ≥ 2.01**	**meanES ≥ 2.5 or meanSR ≥ 2.01**	**NoUMRFs ≥ 2 or meanES ≥ 2.5 or meanSR ≥ 2.01**	**NoUMRFs ≥ 1 or tSR ≥ 1.7**	**NoUMRFs ≥ 2 or tSR ≥ 1.7**
SEN [%]	94.0	96.0	90.0	96.0	100.0	75.0
SPC [%]	58.0	66.0	74.0	56.0	16.7	41.7
ACC [%]	76.0	81.0	82.0	76.0	26.5	45.6
PPV [%]	69.1	73.8	77.6	68,6	13.8	14.6
NPV [%]	90.6	94.3	88.1	93.3	100.0	92.6
LR+	2.2	2.8	3.5	2.2	1.2	1.3
OR (95% CI) p	21.6 (5.9–79.0) **< 0.001**	46.6 (10.1–215.3) **< 0.001**	25.6 (8.4–78.5) **< 0.001**	30.5 (6.7–139.8) **< 0.001**	—	3.3 (0.3–34.3) 0.298
% of all nodules	68.0	65.0	58.0	70.0	85.3	60.6

the identification of benign nodules [27, 43], which is concordant with our results.

Few reports are related to the usefulness of SEG in the nodules with an equivocal FNA result. The comparison of the studies on this group of nodules is difficult because of epidemiological differences between the examined populations, mainly in the iodine supply. These differences are particularly important in such nodules because iodine supply not only modifies the malignancy risk in FL but also influences the relation between the numbers of PTCs and FTCs. Another issue is related to the discrepancies in the qualification of nodules into the FLUS category. In our population the incidence of malignancy in FL nodules, as determined with histopathological examinations, is low (below 20%) [4]. As a consequence of the long-term iodine deficiency (successfully corrected for the last 20 years), non-neoplastic lesions still dominate among FL, while FTCs constitute a significant fraction of cancers. Such a profile of cancers in FL is also a consequence of the conservative attitude to the FLUS category. In our country, this diagnosis is formulated mainly in the case of smears located on the border between follicular neoplasms and non-neoplastic lesions [4]. In many other centres the FLUS category includes similar numbers of smears from the border between a suspected malignancy and a non-diagnostic specimen. Therefore, the risk of malignancy in FLUS nodules increases up to 50% and the percentage of PTCs among revealed cancers is higher [5, 9].

In our study, both SEG and classic US parameters showed lower diagnostic efficacy in the FL group than in the UC group. Only SR evaluation in the transverse section might be potentially useful (AUC > 0.7), and tSR values ≥ 1.7 increased nearly twice the risk of malignancy in that group. The SEG criteria determined in the UC group showed very low SEN in FL nodules. This was because of differences in the elastographic image of cancers between FL and UC groups. These observations are concordant with some reports suggesting that the stiffness of PTCs may differ from the stiffness of other thyroid cancers (including FTC and MTC) on the basis of ES evaluation [19, 27, 43, 44] or — less often — SR evaluation [45]. We did not find any differences between benign lesions in both groups. Consequently, the elastographic criteria determined in the UC group (especially meanSR ≥ 2.01) showed only slightly lower SPC in the FL group, and may be utilised to identify benign nodules among FL. The ES1 can be used for the same purpose just like in UC nodules. This conclusion is concordant with the results of the meta-analysis by Veer and Puttagunta [46], which led to the statement that in the case of the low malignancy risk in nodules with an equivocal or non-diagnostic cytology a normal elastogram should indicate conservative treatment.

Other reports on the effectiveness of SEG and especially of ES evaluation in the group of nodules with equivocal cytology (including FL) are not coherent. Rago et al. [31] showed that ES analysis is more useful than the UMRFs examination in indeterminate

nodules. On the other hand, Lippolis et al. [33] and Vidal-Casariego et al. [34] did not confirm the diagnostic usefulness of the elastogram assessment in such nodules. The meta-analysis by Trimboli et al. [47] came to the conclusion that ES analysis alone should not be used for selecting patients for surgery, which is concordant with our observations. There is a dominating opinion on the advantage of SR analysis over ES evaluation also in the group of nodules with equivocal cytology. Cakir et al. [30] showed that SR examination allowed the detection of cancers with higher ACC than ES analysis in patients with FNA outcomes "atypia of undetermined significance" (AUS — a subgroup of FLUS with nuclear atypia and higher risk of cancer than classic FLUS, as well as higher percentage of PTCs among cancers). Cantisani et al. [32] reported that SR evaluation significantly increased the ACC of US examination, both in comparison with particular UMRFs and their number. Conversely, Seong et al. [48] found that neither ES evaluation nor SR analysis was useful in the diagnostics of nodules with indeterminate cytology.

The last question is related to the studies on the combination of SEG and classic US. In our study, we found that their combination showed no substantial advantage over isolated SR evaluation as measured with AUC. However, the model based on the inclusive disjunction of SR criterion and the NoUMRFs gives a test with maximal SEN, while the conjunction of these criteria results in maximal SPC. When the SR analysis is impossible (no suitable reference area) similar effects may be obtained with analogical combinations of ES analysis and the NoUMRF. In the FL group the optimal SEN and SPC (75.0% both) can be accomplished with the conjunction of at least 1 UMRF with the suspected SR value. Such a model was the only one that increased the risk of malignancy in a nodule of the FL group to a level suggesting surgical treatment.

The comparison of the studies with regard to the combination of SEG and US criteria is difficult because of various ways of their combination. In the study on nodules with both unequivocal and equivocal cytology (but with PTC domination and without FL nodules) Moon et al. [26] did not find any positive effect of the combination of UMRFs and ES examination. They analysed the number of malignancy risk features including both US and SEG analysis. Shao et al. [49] found that the combination of ES and the NoUMRFs significantly improved the discriminating value of each (their study included nodules with PTC predominating among cancers). Unlütürk et al. [27] reported that the combination of ES and single UMRF slightly increased SEN and PPV of SEG as well as SPC and ACC of UMRF analysis in the group of non-preselected nodules (with PTCs > 90% of all cancers). Trimboli et

al. [50] also analysed non-preselected thyroid nodules (PTC > 90.0% of all cancers) and stated that the analysis of the presence of at least 1 UMRF or ES ≥ 3 increased SEN and NPV of the test, but significantly decreased SPC, ACC, and PPV in comparison to the isolated analysis of those parameters. The increase in SEN and the decrease in SPC should be expected in such model, and the authors did not assess simultaneous occurrence of the analysed parameters. In FL nodules with 63.6% of PTCs among all cancers, Garino et al. [51] showed that the presence of at least two suspicious features either in US or SEG (they also evaluated ES) increased the risk of malignancy of the nodule to the level implying the surgical treatment.

The evaluation of SR was connected with UMRF analysis less often. Russ at al. [52] found that in nodules with unequivocal cytology the model based on the presence of suspected SR or suspected NoUMRFs improved SEN, but worsened SPC in comparison with the analysis of the NoUMRFs alone. Friedrich-Rust et al. [53] analysed non-preselected nodules and found that optimal SEN and SPC (85% and 68%) can be achieved in the model expecting the presence of at least four of the following features: ES ≥ 3, SR > 2.66, microcalcifications, macrocalcifications, no halo, irregular margins, and pathological pattern of the blood flow. According to our knowledge, none of the published reports assessed the combination of SR and the NoURMFs in FL nodules, which was examined in our study.

There are some limitations related to the design of our study, which should be considered while interpreting its results. First, it is the way of selecting nodules for the analysis on the basis of the postoperative histopathological examination. It was necessary to establish a reliable diagnosis in FL nodules in which neither the control FNA nor the clinical follow-up allows to answer the diagnostic uncertainty. But the drawback of such a model is the nodule selection bias. To assure uniform design, the surgical treatment was mandatory in all of the nodules with unequivocal cytology. As was mentioned before, the elastographic evaluation is performed in various, non-uniform ways. Thus, in our study, following published data [16, 21, 27, 31, 36, 44, 45, 53], and on the basis of our own experience, we specified the exclusion criteria and described precisely the applied measurement technique. Because the study included the comparison of the efficacy of ES and SR in both sections, it was limited to the nodules with a suitable reference area available in both sections at similar depth. A simple four-grade scale was employed for the classification of elastograms because it is characterised with good reproducibility [54]. It makes it unnecessary to perform sometimes difficult interpretation of the localisation of stiff regions (e.g. central vs. peripheral),

or to visualise the whole area around the lesion (which would exclude some nodules from the measurements). A limitation of our study is the low number of cancers in the FL group, but this number reflects the low risk of malignancy in such nodules in our population. It is indicated to confirm our observations in a higher number of malignant FL nodules.

Conclusions

Concluding, in UC nodules, with a predomination of PTCs among cancers, SEG (especially SR evaluation) shows a higher diagnostic efficacy than the analysis of NoUMRFs. The most effective parameter is the mean value of SR of both sections, but also SR and ES analysis performed in any section may be successfully used. The conjunction of a suspicious elastographic parameter (especially SR) with the presence of at least 2 UMRFs provides the maximum SPC, while the inclusive disjunction of the elastographic parameter with the NoUMRFs leads to maximal SEN.

In FL nodules with a low risk of malignancy and a low percentage of PTCs among cancers, SEG is less effective but still better than NoUMRFs analysis. Suspected SR values speak in favour of the surgical treatment, which allows us to obtain a certain diagnosis. On the other hand, low SR values and normal ES may be used to identify nodules with a very low risk of malignancy and to limit the number of so-called diagnostic surgeries performed when the clinical image is equivocal.

Authors contributions
MWN, DSK, MK: study concept and design; acquisition of data, analysis and interpretation of data, writing of the manuscript; SS: discussion and critical revision of the manuscript; BP, KK, LP, KK, JS: acquisition of data.

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