Evaluation of strain elastography for differentiation of thyroid nodules: results of a prospective DEGUM multicenter study

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Abstract

Purpose: Many patients with thyroid nodules are presently referred to surgery not only for diagnostic but also for therapeutic purposes. The aim of non-invasive diagnostic methods is to optimize the selection of patients for surgery. Strain elastography (SE) enables the ultrasound-based determination of tissue elasticity. The aim of the present study was to evaluate the value of SE in a prospective multicenter study.

Materials and Methods: The study was registered at clinicaltrials.gov and was approved by the local ethical committees of all participating centers. All patients received an ultrasound (US) of the thyroid gland including Colour Doppler US. In addition all nodules were evaluated by SE (Hitachi Medical Systems) using qualitative image interpretation of colour distribution (SE-ES), strain value and strain ratio.

Results: Overall, 602 patients with 657 thyroid nodules (567 benign, 90 malignant) from 7 centers were included in the final analysis. Sensitivity, specificity, NPV, PPV, +LR were 21%, 73%, 86%, 11%, 0.8 for colour Doppler US; 69%, 75%, 94%, 30%, 2.9 for SE-ES; 56%, 81%, 92%, 32%, 2.9 for SE-strain value; 58%, 78%, 92%, 30%, 2.6 for SE- strain ratio, respectively. Diagnostic accuracy was 71% for both strain value and strain ratio of nodules.

Conclusions: SE as an additional ultrasound tool improves the value of ultrasound for the work-up of thyroid nodules. It might reduce diagnostic surgery of thyroid nodules in the future.

Evaluation der Strain Elastographie für die Differenzierung von Schilddrüsenknoten: Ergebnisse einer prospektiven DEGUM Multizenter-Studie

Abstrakt (Deutsch)

Ziel: Viele Patienten mit Schilddrüsenknoten werden nicht nur therapeutisch, sondern auch zu diagnostischem Zweck operiert. Ziel von nicht-invasiven diagnostischen Verfahren ist es daher die Selektion von Patienten zur Operation zu optimieren. Strain Elastographie (SE) ermöglicht die Ultraschall-basierte Messung der Gewebeelastizität. Das Ziel der vorliegenden Studie war es den Stellenwert der SE in einer prospektiven Multizenter-Studie zu evaluieren.

Material und Methode: Die Studie wurde bei clinicaltrials.gov registriert und von den lokalen Ethikkommissionen der teilnehmenden Zentren genehmigt. Alle Patienten erhielten einen Ultraschall (US) der Schilddrüse inklusive Farbduplex-US. Zusätzlich wurden alle Knoten mittels SE (Hitachi Medical System) untersucht und eine Beurteilung der qualitativen Farbverteilung (SE-ES) und eine semiquantitative Messung der Elastizität mittels strain value und strain ratio durchgeführt.

Ergebnisse: Insgesamt wurden 602 Patienten mit 657 Schilddrüsenknoten (567 benigne, 90 maligne) an 7 deutschen Zentren ausgewertet. Sensitivität, Spezifität, NPV, PPV, und +LR betrugen entsprechend 21%, 73%, 86%, 11%, 0,8 für den Duplex-US; 69%, 75%, 94%, 30%, 2.9 für SE-ES; 56%, 81%, 92%, 32%, 2,9 für SE-strain value; 58%, 78%, 92%, 30%, 2,6 für SE- strain ratio. Die diagnostische Genauigkeit betrug 71% sowohl für SE-strain value, als auch SE-strain ratio.

Schlussfolgerungen: Strain Elastographie als zusätzliche Ultraschallfunktion verbessert die Ultraschall-Diagnostik von Schilddrüsenknoten und könnte in Zukunft die Zahl der diagnostischen Operationen von Schilddrüsenknoten reduzieren.

Introduction

In regions with inadequate iodine supply such as in Germany, thyroid nodules are a common finding and are reported in one third of unselected adults (1). For the detection of thyroid nodules ultrasound (US) is a good method, but it only has a low accuracy for differentiation between benign and malignant thyroid nodules (2). Presently fine-needle-aspiration-biopsy (FNAB) is recommended as an additional diagnostic method in the evaluation of thyroid nodules with a size of ≥10mm in patients with normal thyroid stimulating hormone. In addition, FNAB is also advised in nodules smaller than 10 mm with suspicious US findings or suspicious history (3–6). However, besides high specificities (60-98%) varying sensitivities (54-90%) have been reported for FNAB for the diagnosis of malignant thyroid nodules (7–10). Therefore, a relevant number of patients with the final diagnosis of benign thyroid nodules receive thyroid surgery. Surgery is therefore performed more for diagnostic than for therapeutic purposes.

A classical criterion of malignancy upon palpation or US-probe pressure is a hard or firm consistency (3,11). With the introduction of strain elastography (SE) a reproducible qualitative and semi-quantitative assessment of tissue consistency became available. Most US companies now offer elastography as an additional tool integrated in conventional high-end US machines (12,13). Meta-analyses of SE reported mean sensitivities of 82-92% and mean specificities of 67-92% for the diagnosis of malignant thyroid nodules (14–16). However SE was also challenged and criticized for its operator dependency in some studies (17,18).

The aim of the present study was to evaluate strain elastography for the differentiation of thyroid nodules in a prospective multicenter study.

Materials and Methods

The multicenter study was approved by the lead ethical committee at the University of Frankfurt with local approval from the ethical committees of the other study centers. The study was registered with Clinicaltrials.gov with the registration number NCT01609946.

Between May 2012 and October 2014, consecutive patients, who attended the participating hospitals for cytological or histological assessment of thyroid nodules were evaluated for inclusion in the study. The patients were recruited from seven centers in Germany. Written informed consent was obtained from all patients. Inclusion criteria were age 18 and older, the presence of a thyroid nodule ≥ 5mm, normal values of thyroid-stimulating hormone (TSH ≥ 0,35µU/ml), and FNAB of this nodule performed within the last 6-months or FNAB and/or surgery planned at the time of US examination and finally performed within the study period. Exclusion criteria were pregnancy and lactation, cystic lesions of completely liquid nature, no cytology by FNAB or histology by surgery of the thyroid nodule within the study period, indeterminate cytology by FNAB without repeated FNAB, and suspicious or malignant cytology by FNAB without thyroid operation within the study period.

All patients received an US of the thyroid gland including Colour Doppler US. In addition, all nodules were evaluated by SE (Hitachi Medical Systems) using qualitative image interpretation of colour distribution (SE-ES), strain value and strain ratio.

Reference method- Cytology/Histology

Cytology with 6-12 month follow-up US (showing absence of lesion growth-increase in diameter of less than 20% or increase in volume of less than 50%) or histology were used as the reference method for the diagnosis of benign thyroid nodules.

FNAB was performed with a 25 gauge needle attached to a 20 ml syringe. Adequacy of aspirates was defined according to the guidelines of the Papanicolaou society (19). The Bethesda system was used to report thyroid cytopathology (20). Patients with suspicious or

malignant cytology were referred to surgery and were only included in the study if surgery was performed within the study period. Cytology and histology were read by experienced local pathologists with at least 5 years of working experience who were blinded to the results of US and elastography. Histology was used as the reference method for the diagnosis of malignant thyroid nodules

Conventional ultrasound (B-mode, Doppler)

All patients received an US examination of the thyroid gland using a transducer at 9MHz (Hitachi HI Vision Preirus, HI Vision Avius, EUB 900 HV and EUB 7500 HV, Hitachi Medical Corporation, Japan). The patients were positioned in a supine position with dorsal flexion of the head. US was performed by experienced examiners blinded to the results of cytology. Thyroid nodules were evaluated for size, volume, echogenicity, echotexture, presence/absence of halo-sign, presence/absence of microcalcification (<1 mm) and/or macrocalcification. After B-mode-US, power-Doppler and Duplex-imaging were performed. The observers were blinded to the results of cytology and histology. The observers had at least 10 year experience in thyroid US.

Strain Elastography (SE)

Strain elastography was performed with the above Hitachi Systems which were all standardized to the elastography parameters as recommended by the company. Tissue elasticity distribution is calculated by the strain and stress of the examined tissue. The calculation of tissue elasticity distribution was performed in real-time and the examination results were represented as color-coded images over the conventional B-mode image (blue=hard, red & green=soft tissue). Details have been described in previous studies (21,22). The probe was placed on the neck and a light pressure of 3-4 on a scale of 0-6 arbitrary units was applied for measurement. The region-of-interest (ROI) for the elastography examination

was selected by the operator including the nodule and surrounding normal thyroid tissue. Elasticity was classified in four different patterns as described previously (23–25):

- elasticity score (ES)-1: the nodule is displayed homogeneously in green (soft)
- ES-2: the nodule is displayed predominantly in green with few blue areas/spots
- ES-3: the nodule is displayed predominantly in blue with few green areas/spots
- ES-4: the nodule is displayed completely in blue (hard).

SE was recorded in transverse and longitudinal position. In addition, strain value calculation of the elasticity within a ROI using the auto-correlations method (values of 1.0 indicate maximum elasticity) and strain ratio (ratio of the strain value in the thyroid nodule and strain value in surrounding thyroid tissue) were calculated. The size of the ROI within the nodule was chosen as large as possible to include nodule only, the ROI in the healthy thyroid tissue was placed if possible at the same depth as the ROI in the nodule.

Sample Size calculation

The primary study aim was the quantification of sensitivity and specificity of SE for the diagnosis of malignant thyroid nodules with high diagnostic accuracy. As a primary statistical aim, confidence intervals of 95% were calculated for sensitivity and specificity. Based on the results of a previous meta-analysis on SE (14) a sensitivity and specificity of at least 90% was assumed. To obtain intervals with a length of at most 5%, a sample size of 593 patients was calculated.

Statistical analysis

Statistical analysis was performed using BiAS-for-Windows (version-10.03, epsilon-2013, Frankfurt, Germany). Clinical and laboratory characteristics of patients were expressed as mean±SD, median and range. Sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV), and positive likelihood ratio (LR) were calculated using

ES-Score 1 & 2 for benign classification and ES-Score 3 & 4 for malignant classification of thyroid nodules. All tests were two-sided and use a significance level of α=5%. The diagnostic performance of semi-quantitative SE was also assessed by receiver-operating-characteristic (ROC)-curves. The ROC-curve represents sensitivity versus 1-specificity for all possible cut-off values for prediction of malignancy, respectively. The statistical program R (R Foundation for Statistical Computing, Vienna, Austria), particularly the R package pROC (26) was used to obtain an optimal combination of ultrasound criteria with respect to the Youden criteria under the restriction of a sensitivity above 80% consisting of microcalcification, macrocalcification, hypoechogenicity, absent halo sign, irregular margins, pattern 3-4 vascularisation, ES 3-4 and strain ratio>0.3757, strain ratio >0.165.

Results

Six-hundred forty-six patients with 701 thyroid nodules were prospectively enrolled at seven centres in this multicenter study. Thirty six patients were excluded due to missing data on SE results or cytology/histology. Additionally 8 patients were excluded with malignant cytology, which did not receive surgery within the study period. Therefore, 602 patients with 657 thyroid nodules were available for final analysis. Patient characteristics are shown in Table 1. Thyroid hormone values were within normal range in all patients.

Table 1 here

FNAB was performed in 214 nodules of 198 patients. According to the Bethesda System for reporting thyroid cytopathology these were: Bethesda category I in 3 nodules, Bethesda- II (benign) in 160 nodules, Bethesda-III in 19, Bethesda-IV in 27 and Bethesda-V in 5 nodules. 145 of 160 nodules with Bethesda classification II (benign) without growth within 6 months were classified as benign lesions without histology. All patients with nodules with Bethesda I

and III-V, as well as 15 patients with nodules with Bethesda II and goiter received surgery within the study period. In addition, 443 nodules of patients presented to primary surgery.

Finally, 483 patients with 512 nodules were operated. The final diagnosis of benign histology was papillary adenoma in 29, follicular adenoma in 79, microfollicular adenoma in 53, oncocytic adenoma in 4, thyroid hyperplasia in 6 and goiter in 251 evaluated nodules, respectively. The final diagnosis of malignant histology was papillary carcinoma in 77 patients with 78 nodules, medullary carcinoma in 10 patients/nodules, follicular carcinoma in one patient/nodule, anaplastic carcinoma in one patient/nodule, respectively.

Therefore, finally 567 benign nodules from 515 patients and 90 malignant nodules of 87 patients were analyzed.

Imaging

Details on SE-scoring are shown in Table 1. Results of B-mode US, Duplex-US and SE are shown in Table 2. The diagnostic accuracy for the diagnosis of malignant nodules was 71% for strain value (95%-CI: 0.65;0.77) and 71% for strain ratio (0.64;0.77). The optimal cut-off (highest sum of sensitivity and specificity) was 0.17 for strain value and 0.38 for strain ratio for the diagnosis of malignant thyroid nodules. Details are shown in Table 2. No significant difference in diagnostic accuracy was observed between strain value, strain ratio, and SE-colour classification. The diagnostic value of different combinations of US with SE are shown in Table 3 and 4. To estimate the optimal combination of imaging criteria a sum score consisting of the following criteria was found to optimize the Youden index under the restriction of a sensitivity above 80% in our data: macrocalcification, absent halo sign, irregular margin, ES 3-4. If at least 2 of these 4 criteria was present sensitivity, specificity, NPV, PPV, +LR, -LR for the diagnosis of malignant thyroid nodules were 80.46% [95% CI: 70.57%, 88.19%], 65.98% [61.78%, 70.00%], 95.38% [92.71%, 97.29%], 27.89% [22.43%, 33.88%], 2.365 [2.021, 2.768] and 0.296 [0.193, 0.456], respectively.

Table 2-4 here

Discussion

Strain elastography is a qualitative elastography method evaluating changes in US pattern during strain and stress of direct or indirect tissue compression. Meta-analyses of SE reported mean sensitivities of 82-92% and specificities of 67-92% for the diagnosis of malignant thyroid nodules (12,13,15,16,27). Variable scoring categories of SE have been evaluated, qualitative assessment using a 4-scale scoring system (as used in the present study), a 5-scale scoring system and semi-quantitative scoring using strain value, strain ratio and histograms of colour pixels (12,13,28–32). Nevertheless, besides a lot of promising study results studies have also challenged the usefulness of SE in clinical practice by reporting no additional value as compared to qualified B-mode US (17,18,33).

The aim of the present study was to evaluate high quality conventional US performed by experienced sonographers in DEGUM (German Association of Ultrasound in Medicine), as well as SE using a qualitative 4-scale scoring system as well as the semi-quantitative strain value and strain ratio in a prospective multicentre study. Overall 602 patients with 657 thyroid nodules were analysed and the negative predictive value (NPV) of the different SE methods was >90%. These results are in accordance with previously published studies reporting NPV of 88-99% (23,25,32,34–40). Meta-analyses of SE reported mean sensitivities of 82-92% and mean specificities of 67-92% for the diagnosis of malignant thyroid nodules (14–16). In the present study sensitivity of SE was 69-70% and specificity 72-75%. While in a recent meta-analysis (16) the semi quantitative analysis hat a slightly higher sensitivity than the qualitative analysis, no significant difference was observed in the present study. Recently shear-wave elastography methods have been evaluated for the diagnosis of thyroid nodules, the results are comparable to the results of SE (41).

The combination of B-mode US criteria and SE could improve the non-invasive diagnosis of malignant thyroid nodules in the present study. This additive value has also been reported in previously published studies (40). Therefore, SE should be used in addition to conventional US in the diagnostic work-up of thyroid nodules.

A limitation of the present study is the high percentage (14%) of carcinoma. However, this is a general limitation of most studies performed at endocrinology and US centres with an average of even 30% of malignant thyroid nodules (27).

In summary, strain elastography as an additional US tool improves the diagnostic value of US for the exclusion of malignant thyroid nodules. Qualitative and semi quantitative elastography scores are comparably good.

Table 1. Patients characteristics

Characteristics	All 602 Patients With 657 nodules	515 Patients with 567 benign nodules	87 Patients with 90 malignant nodules	p-value
Centers				
University Frankfurt (%)	128 (19.5)	114 (20.1)	14 (15.6)	
Caritas Hospital Bad Mergentheim (%)	138 (21.0)	129 (22.8)	9 (10.0)	
Buergerhospital Frankfurt (%)	234 (35.6)	180 (31.7)	54 (60.0)	
University Hospital Ulm (%)	54 (8.2)	48 (8.5)	6 (6.7)	
Hospital Reutlingen (%)	52 (7.9)	51 (9.0)	1 (1.1)	
Helfenstein Hospital Geislingen (%)	48 (7.3)	42 (7.4)	6 (6.7)	
Sana Hospital Luebeck (%)	3 (0.5)	3 (0.5)	0 (0)	
Patient age (years)				<0.001
Mean ± SD	52.4 ± 13.6	53.5 ± 13.1	45.6 ± 14.2	
Range	18-90	18-90	21-78	
Median	52	53	44	
Male gender, n (%)	209 (31.8)	185 (32.6)	24 (26.7)	<0.20
Single nodule, n (%)	217 (33.0)	177 (31.2)	40 (44.4)	0.018
Goiter, n (%)	377 (57.4)	332 (58.6)	45 (50.0)	
Nodule location				<0.20
Left, n (%)	326 (50.2)	282 (50.4)	44 (48.9)	
Right, n (%)	292 (44.9)	249 (44.5)	41 (45.6)	
Isthmus, n (%)	32 (4.9)	29 (5.2)	3 (3.3)	
Nodule size				<0.001
Mean ± SD	7.4 ± 11.5	7.7 ± 12.1	3.6 ± 5.9	
Range	0.015-101.2	0.015-101.2	0.03-28.6	
Median	3.24	3.6	2.38	
Scintigraphy of nodule*				0.02
Hypofunctioning, n (%)	421 (88.8)	359 (88.0)	62 (93.9)	
Indifferent, n (%)	51 (10.8)	48 (11.8)	3 (4.5)	
Cytology of nodule, n (%)	214 (32.6)	183 (32.3)	31 (34.4)	<0.001
Histology of nodule, n (%)	512 (77.9)	422 (74.4)	90 (100)	<0.001
Real-time elastography Score Transverse				<0.001
ES 1, n (%)	79 (12.0)	77 (13.7)	2 (2.2)	
ES 2, n (%)	373 (57.1)	347 (61.5)	26 (29.2)	
ES 3, n (%)	172 (26.3)	125 (22.2)	47 (52.8)	
ES 4, n (%)	29 (4.4)	15 (2.7)	14 (15.7)	
Real-time elastography Score Longitudinal				<0.001
ES 1, n (%)	77 (11.8)	75 (13.3)	2 (2.2)	
ES 2, n (%)	355 (54.4)	330 (58.7)	25 (27.8)	
ES 3, n (%)	183 (28.1)	138 (24.6)	45 (50.0)	
ES 4, n (%)	37 (5.7)	19 (3.4)	18 (20.0)	

SD = standard deviation

*Scintigraphy of nodule available in 429 patients with 474 nodules

Table 2. Diagnostic value of US and SE for the diagnosis of malignant thyroid nodules

Criteria	Benign	Malignant	Sens (%)	Spec (%)	NPV (%)	PPV (%)	+ LR	- LR
Hypoechogenicity								
Yes	288	64	71,1	47,7	91,0	18,2	1,4	0,6
No	263	26	(60,6;80,2)	(43,5;52,0)	(87,1;94,0)	(14,3;22,6)	(1,2;1,6)	(0,4;0,8)
Microcalcifications								
Yes	116	57	63.3	79.4	93.1	33.0	3.1	0.5
No	447	33	(52.5;73.3)	(75.8;82.7)	(90.5;95.2)	(26.0;40.5)	(2.5;3.9)	(0.4;0.6)
Macrocalcifications								
Yes	118	15	16.9	78.9	85.7	11.3	0.8	1.1
No	442	74	(9.8;26.3)	(75.3;82.2)	(82.3;88.6)	(6.5;17.9)	(0.5;1.3)	(1.0;1.2)
Absent Halo sign								
Yes	183	61	69.3	66.9	93.2	25.0	2.1	0.5
No	370	27	(58.6;78.7)	(62.8;70.8)	(90.3;95.5)	(19.7;30.9)	(1.7;2.5)	(0.3;0.6)
Irregular margins								
Yes	185	61	67.8	66.7	92.7	24.8	2.0	0.5
No	369	29	(57.1;77.3)	(62.6;70.6)	(89.7;95.1)	(19.5;30.7)	(1.7;2.4)	(0.4;0.7)
Oval shape								
Yes	397	28	31.5	28.7	72.4	6.6	0.4	2.4
No	160	61	(22.0;42.2)	(25.0;32.7)	(66.0;78.2)	(4.4;9.4)	(0.3;0.6)	(2.0;2.9)
Pattern 3-4 vascularisation								
Yes	150	19	21.4	73.4	85.5	11.2	0.8	1.1
No	413	70	(13.4;31.3)	(69.5;77.0)	(82.1;88.5)	(6.9;17.0)	(0.5;1.2)	(1.0;1.2)
ES 3-4 transverse								
Yes	140	61	68.5	75.2	93.8	30.4	2.8	0.4
No	424	28	(57.8;78.0)	(71.4;78.7)	(91.2;95.8)	(24.1;37.2)	(2.3;3.4)	(0.3;0.6)
ES 3-4 longitudinal								
Yes	157	63	70.0	72.1	93.8	28.6	2.5	0.4
No	405	27	(59.4;79.2)	(68.2;75.7)	(91.0;95.8)	(22.8;35.1)	(2.1;3.0)	(0.3;0.6)
Strain value nodule <0.17								
Yes	108	50	56.2	80.6	92.0	31.7	2.9	0.5
No	448	39	(45.3;66.7)	(77.0;83.8)	(89.2;47.6)	(24.4;39.5)	(2.3;3.7)	(0.4;0.7)
Strain ratio <0.38								
Yes	121	52	58.4	77.7	92.0	30.1	2.6	0.5
No	422	37	(47.5;68.8)	(74.0;81.2)	(89.1;94.3)	(23.3;37.5)	(2.1;3.3)	(0.4;0.7)

Table 3a. Diagnostic value of US combinations for the diagnosis of malignant thyroid nodules (dual combination)

US-pattern	Benign	Cancer	Sensitivity (%)	Specifity (%)	NPV (%)	PPV (%)	+ LR	- LR
Hypoechogenicity+ absent halo sign								
Yes	113	50	56,8	79,0	91,8	30,7	2,7	0,5
No	425	38	(45,8;67,3)	(75,3;82,4)	(88,9;94,1)	(23,7;38,4)	(2,1;3,5)	(0,4;0,7)
Hypoechogenicity + microcalcification								
Yes	64	47	52,2	88,3	91,9	42,3	4,5	0,5
No	485	43	(41,4;63,9)	(85,4;90,9)	(89,2;94,0)	(33,0;52,1)	(3,3;6,1)	(0,4;0,7)
Microcalcification + absent halo sign								
Yes	45	48	54.6	91.8	92.7	51.6	6.7	0.5
No	504	40	(43.6;65.2)	(89.2;94.0)	(90.1;94.7)	(41.0;62.1)	(4.7;9.3)	(0.4;0.6)
Pattern 4 vasc. + hypoechogenicity								
Yes	26	5	5,6	95,3	86,1	16,1	1,2	1,0
No	521	84	(1,9;12,6)	(93,1;96,9)	(83,1;88,8)	(5,5;33,7)	(0,5;3,0)	(0,9;1,0)
Pattern 4 vasc. + microcalcification								
Yes	11	4	4.5	98.0	86.6	26.7	2.3	1.0
No	548	85	(1.2;11.1)	(96.5;99.0)	(83.7;89.1)	(7.8;55.1)	(0.7;7.0)	(0.9;1.0)
Pattern 4 vasc. + absent halo sign								
Yes	12	3	3.5	97.8	86.5	20.0	1.6	1.0
No	537	84	(0.7;9.8)	(96.2;98.9)	(83.5;89.1)	(4.3;48.1)	(0.5;5.5)	(0.9;1.0)
Irregular margins + hypoechogenicity								
Yes	105	47	52,2	80,6	91,0	30,9	2,7	0,6
No	436	43	(41,4;62,9)	(77,0;83,8)	(88,1;93,4)	(23,7;38,9)	(2,1;3,5)	(0,5;0,7)
Irregular margins + microcalcification								
Yes	50	48	54.6	90.9	92.6	49.0	6.0	0.5
No	500	42	(43.6;65.2)	(88.2;93.2)	(90.1;94.7)	(38.7;59.3)	(4.3;8.3)	(0.4;0.6)
Irregular margins + absent halo sign								
Yes	105	52	59.1	80.7	92.4	33.1	3.1	0.5
No	438	36	(48.1; 69.5)	(77.1;83.9)	(89.6;94.6)	(25.8;41.1)	(2.4;3.9)	(0.4;0.7)
Irregular margins + pattern 4 vasc.								
Yes	14	4	4.5	97.5	86.3	22.2	1.8	1.0
No	536	85	(1.2;11.1)	(95.8;98.6)	(83.4;88.9)	(6.4;47.6)	(0.6;5.2)	(0.9;1.0)

Table 3b. Diagnostic value of US in combination with SE for the diagnosis of malignant thyroid nodules (dual combination)

US-pattern	Benign	Cancer	Sensitivity (%)	Specifity (%)	NPV (%)	PPV (%)	+ LR	- LR
Irregular margins + ES 3-4 transverse								
Yes	60	49	55.1	89.1	92.5	45.0	5.1	0.5
No	491	40	(44.1;65.6)	(86.2;91.6)	(89.9;94.6)	(35.4;54.8)	(3.7;6.9)	(0.4;0.6)
Irregular margins + ES 3-4 longitudinal								
Yes	68	51	56.7	87.6	92.5	42.9	4.6	0.5
No	481	39	(45.8;67.1)	(84.6;90.3)	(89.9;94.6)	(33.8;52.3)	(3.4;6.1)	(0.4;0.6)
Hypoechogenicity + ES 3-4 transverse								
Yes	75	48	53,9	86,3	92,0	39,0	3,9	0,5
No	473	41	(43,0;64,6)	(83,2;89,1)	(89,3;94,2)	(30,4;48,2)	(3,0;5,2)	(0,4;0,7)
Hypoechogenicity + ES 3-4 longitudinal								
Yes	81	49	54,4	85,7	92,2	37,7	3,8	0,5
No	465	41	(43,6;65,0)	(82,6;88,5)	(89,6;94,4)	(29,4;46,6)	(2,9;5,0)	(0,4;0,7)
Microcalcification + ES 3-4 transverse								
Yes	53	47	52.8	90.5	92.4	47.0	5.6	0.5
No	507	42	(41.9;63.5)	(87.8;92.8)	(89.8;94.4)	(36.9;57.2)	(4.0;7.7)	(0.4;0.7)
Microcalcification + ES 3-4 longitudinal								
Yes	57	49	54.4	89.8	92.5	46.2	5.3	0.5
No	502	41	(43.6;65.0)	(87.0;92.2)	(89.9;94.5)	(36.5;56.2)	(3.9;7.3)	(0.4;0.6)
Absent halo sign + ES 3-4 transverse								
Yes	63	46	52.9	88.6	92.2	42.2	4.6	0.5
No	487	41	(41.9; 63.7)	(85.6; 91.1)	(89.6;94.4)	(32.8;52.0)	(3.4;6.3)	(0.4;0.7)
Absent halo sign + ES 3-4 longitudinal								
Yes	69	47	53.1	87.4	92.1	40.5	4.3	0.5
No	480	41	(42.5;64.1)	(84.4;90.1)	(89.5;94.3)	(31.5;50.0)	(3.2;5.7)	(0.4;0.7)
ES 3-4 transverse + pattern 3-4 vasc.								
Yes	42	12	13.6	92.5	87.2	22.2	1.8	0.9
No	518	76	(7.3;22.6)	(90.0;94.5)	(84.3;89.8)	(12.0;35.6)	(1.0;3.3)	(0.9;1.0)
ES 3-4 longitudinal + pattern 3-4 vasc.								
Yes	51	13	14.6	90.9	87.0	20.3	1.6	0.9
No	507	76	(8.0;23.7)	(88.2;93.1)	(84.0;89.6)	(11.3;32.2)	(0.9;2.8)	(0.9;1.0)

Legends of Figures

Figure 1.

Example of SE of papillary carcinoma:

A 8 x 12 mm nodule in the right thyroid gland classified as SE ES-4 (completely blue = hard; consistent with malignancy) with strain ratio of 11.15. Histology revealed a papillary T2 carcinoma.

Figure 2.

Example of SE of thyroid adenoma:

A 8 x 12mm nodule in the right thyroid gland classified as SE 2 (predominantly green = soft; consistent with benign nodule) with strain ratio of 0.99. Histology revealed a benign papillary thyroid adenoma.

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Supplementary Table 1a. Diagnostic value of US combinations with SE for the diagnosis of malignant thyroid nodules (tripple combination)

US-pattern	Benign	Cancer	Sensitivity (%)	Specifity (%)	NPV (%)	PPV (%)	+ LR	- LR
Irregular margins + microcalcification + hypoechogenicity								
Yes	31	41	45,6	94,3	91,2	56,9	7,9	0,6
No	508	49	(35,0;56,4)	(91,9;96,1)	(88,5;93,4)	(44,7;68,6)	(5,3;11,9)	(0,5;0,7)
Hypoechogenicity + microcalcification + absent halo sign								
Yes	33	42	47,7	93,7	91,5	56,0	7,6	0,6
No	493	46	(37,0;58,7)	(91,3;95,6)	(88,8;93,7)	(44,1;67,5)	(5,1;11,3)	(0,5;0,7)
Hypoechogenitcity +Microcalcification +Macrocalcification								
Yes	18	7	7,8	96,8	86,9	28,0	2,5	1,0
No	549	83	(3,2;15,4)	(95,0;98,1)	(84,0;89,4)	(12,1;49,4)	(1,1;5,7)	(0,9;1,0)
Hypoechogenitcity+ Microcalcification + Absent halo sign								
Yes	33	42	46,7	94,2	91,8	56,0	8,0	0,6
No	534	48	(36,1;57,5)	(91,9;96,0)	(89,2;93,9)	(44,1;67,5)	(5,4;11,9)	(0,5;0,7)
Hypoechogenitcity+ Microcalcification + irregular Margins								
Yes	31	41	45,6	94,5	91,6	56,9	8,3	0,6
No	536	49	(35,0;56,4)	(92,3;96,3)	(89,1;93,7)	(44,7;68,6)	(5,5;12,6)	(0,5;0,7)
Hypoechogenitcity+ Microcalcification+ oval shape								
Yes	48	11	12,2	91,5	86,8	18,6	1,4	1,0
No	519	79	(6,3;20,8)	(88,9;93,7)	(83,8;89,4)	(9,7;30,9)	(0,8;2,7)	(0,9;1,0)
Hypochogenity+ Microcalcification+ Pattern 3-4 vasc.								
Yes	12	10	11,1	97,9	87,4	45,5	5,3	0,9
No	555	80	(5,5;19,5)	(96,3;98,9)	(84,6;89,9)	(24,4;67,8)	(2,3;11,8)	(0,8;1,0)
Hypoechogenitcity+ Macrocalcification +absent Halo sign								
Yes	20	5	5,6	96,5	86,6	20,0	1,6	1,0
No	547	85	(1,8;12,5)	(94,6;97,8)	(83,6;89,1)	(6,8;40,7)	(0,6;4,1)	(0,9;1,0)
Hypoechogenitcity+ Macrocalcification+ irregular Margins								
Yes	23	5	5,6	95,9	86,5	17,9	1,4	1,0
No	544	85	(1,8;12,5)	(94,0;97,4)	(83,6;89,1)	(6,1;36,9)	(0,5;3,5)	(0,9;1,0)
Hypoechogenitcity+ Macrocalcification+ oval shape								
Yes	34	4	4,4	94,0	86,1	10,5	0,7	1,0
No	533	86	(1,2;11,0)	(91,7;95,8)	(83,1;88,7)	(2,9;24,8)	(0,3;2,0)	(1,0;1,1)
Hypoechogenitcity+ Macrocalcification+ Pattern 3-4 vasc.								
Yes	15	3	3,3	97,4	86,4	16,7	1,3	1,0

US-pattern	Benign	Cancer	Sensitivity (%)	Specifity (%)	NPV (%)	PPV (%)	+ LR	- LR
No	552	87	(0,7;9,4)	(95,7;98,5)	(83,5;89,0)	(3,6;41,4)	(0,4;4,3)	(1,0;1,0)
Hypoechogenitcity+ absent halo sign+ irregular Margins								
Yes	65	43	47,8	88,5	91,4	39,8	4,2	0,6
No	502	47	(37,1;58,6)	(85,6;91,0)	(88,8;93,6)	(30,5;49,7)	(3,0;5,7)	(0,5;0,7)
Hypoechogenitcity+ absent Halo sign+ oval shape								
Yes	82	12	13,3	85,5	86,2	12,8	0,9	1,0
No	485	78	(11,2;16,6)	(82,4;88,3)	(83,0;88,9)	(6,8;21,2)	(0,5;1,6)	(0,9;1,1)
Hypoechogenitcity+ absent Halo sign+ Pattern3-4 vasc.								
Yes	13	9	10,0	97,7	87,2	40,9	4,4	0,9
No	554	81	(4,7;18,1)	(96,1;98,8)	(84,4;89,7)	(20,7;63,7)	(1,9;9,9)	(0,9;1,0)
Hypoechogenitcity+ Irregular Margins+ oval Shape								
Yes	68	7	7,8	88,0	85,7	9,3	0,6	1,0
No	499	83	(3,2;15,4)	(85,0;90,6)	(82,6;88,5)	(3,8;18,3)	(0,3;1,4)	(1,0;1,1)
Hypoechogenitcity+ irregular Margins+ Pattern 3-4 vasc.								
Yes	15	10	11,1	97,4	87,3	40,0	4,2	0,9
No	552	80	(5,5;19,5)	(95,7;98,5)	(84,5;89,8)	(21,1;61,3)	(1,9;9,1)	(0,8;1,0)
Hypoechogenitcity+ oval Shape+ pattern 3-4 vasc.								
Yes	46	3	3,3	91,9	85,7	6,1	0,4	1,1
No	521	87	(0,7;9,4)	(89,3;94,0)	(82,7;88,4)	(1,3;16,9)	(0,1;1,3)	(1,0;1,1)
Microcalcification+ Macrocalcification+ irregular Margins								
Yes	10	4	4,4	98,2	86,6	28,6	2,5	1,0
No	557	86	(1,2;11,0)	(96,8;99,2)	(83,8;89,2)	(8,4;58,1)	(0,8;7,9)	(0,9;1,0)
Absent Halo sign+ Macrocalcification+ Microcalcification								
Yes	10	4	4,4	98,2	86,6	28,6	2,5	1,0
No	557	86	(1,2;11,0)	(96,8;99,2)	(83,8;89,2)	(8,4,58,1)	(0,8;7,9)	(0,9;1,0)
Microcalcification+ Macrocalcification+ oval shape								
Yes	28	6	6,7	95,1	86,5	17,7	1,4	1,0
No	539	84	(2,5;14,0)	(92,9;96,7)	(83,6;89,1)	(6,8;34,5)	(0,6;3,2)	(0,9;1,0)
Microcalcification+ Macrocalcification+ Pattern 3-4 vasc.								
Yes	15	3	3,3	97,4	86,4	16,7	1,3	1,0
No	552	87	(0,7;9,4)	(95,7;98,5)	(83,5;89,0)	(3,6;41,4)	(0,4;4,3)	(1,0;1,0)
Microcalcification+ absent halo sign+ irregular Margins								
Yes	25	43	47,8	95,6	92,0	63,2	10,8	0,5
No	542	47	(37,1;58,6)	(93,6;97,1)	(89,5;94,1)	(50,7;74,6)	(7,0,16,8)	(0,4;0,7)

US-pattern	Benign	Cancer	Sensitivity (%)	Specifity (%)	NPV (%)	PPV (%)	+ LR	- LR
Microcalcification+ absent halo sign+ oval Shape								
Yes	32	13	14,4	94,4	87,4	28,9	2,6	0,9
No	535	77	(7,9;23,4)	(92,1;96,1)	(84,5;89,9)	(16,4;44,3)	(1,4;4,7)	(0,8;1,0)
Microcalcification+ absent halo sign+ pattern 3-4 vasc.								
Yes	6	10	11,1	98,9	87,5	62,5	10,5	0,9
No	561	80	(5,5;19,5)	(97,7;99,6)	(84,7;90,0)	(35,4;84,8)	(3,9;28,2)	(0,8;1,0)
Microcalcification+ irregular Margins+ oval shape								
Yes	30	10	11,1	94,7	87,0	25,0	2,1	0,9
No	537	80	(5,5;19,5)	(92,5;96,4)	(84,1;89,6)	(12,7;41,2)	(1,1;4,1)	(0,9;1,0)
Microcalcification+ Irregular Margins+ pattern 3-4 vasc.								
Yes	14	10	11,1	97,5	87,4	41,7	4,5	0,9
No	553	80	(5,5;19,5)	(95,9;98,6)	(84,5;89,9)	(22,1;63,4)	(2,1;9,8)	(0,8;1,0)
Microcalcification+ oval shape+ pattern 3-4 vasc.								
Yes	24	5	5,6	95,8	86,5	17,2	1,3	1,0
No	543	85	(1,8;12,5)	(93,8;97,3)	(83,5;89,0)	(5,9;35,8)	(0,5;3,4)	(0,9;1,0)
Macrocalcification+ absent halo sign + irregular Margins								
Yes	24	3	3,3	95,8	86,2	11,1	0,8 (0,2;2,6)	1,0
No	543	87	(0,7;9,4)	(93,8;97,3)	(83,3;88,8)	(2,4;29,2)		(1,0;1,0)
Macrocalcification+ absent halo sign+ oval shape								
Yes	27	3	3,3	95,2	86,1	10,0	0,7	1,0
No	540	87	(0,7;9,4)	(93,2;96,8)	(83,2;88,7)	(2,1;26,5)	(0,2;2,3)	(1,0;1,1)
Macrocalcification+ absent halo sign + pattern 3-4 vasc.								
Yes	8	1	1,1	98,6	86,3	11,1	0,8	1,0
No	559	89	(0,0;6,0)	(97,2;99,4)	(83,4;88,8)	(0,3;48,3)	(0,1;6,2)	(1,0;1,0)
Macrocalcification+ irregular Margins+ oval Shape								
Yes	29	3	3,3	94,9	86,1	9,4	0,7	1,0
No	538	87	(0,7;9,4)	(92,7;96,6)	(83,1;88,7)	(2,0;25,0)	(0,2;2,1)	(1,0;1,1)
Macrocalcification+ irregular Margins+ pattern 3-4 vasc.								
Yes	12	2	2,2	97,9	86,3	14,3	1,1	1,0
No	555	88	(0,3;7,8)	(96,3;98,9)	(83,4;88,9)	(1,8;42,8)	(0,2;4,6)	(1,0;1,0)
Macrocalcification+ oval shape + pattern 3-4 vasc.								
Yes	25	3	3,3	95,6	86,2	10,7	0,8	1,0
No	542	87	(0,7;9,4)	(93,6;97,1)	(83,2;88,8)	(2,3;28,2)	(0,2;2,5)	(1,0;1,1)

US-pattern	Benign	Cancer	Sensitivity (%)	Specifity (%)	NPV (%)	PPV (%)	+ LR	- LR
Absent Halo sign+ Irregular Margins+ oval shape								
Yes	76	11	12,2	86,6	86,1	12,6	0,9	1,0
No	491	79	(6,3;20,8)	(83,5;89,3)	(83,0;88,9)	(6,5;21,5)	(0,5;1,6)	(0,9;1,1)
Absent Halo sign+ Irregular Margins+ pattern 3-4 vasc.								
Yes	17	9	10,0	97,0	87,2	34,6	3,3	0,9
No	550	81	(4,7;18,1)	(95,2;98,2)	(84,3;89,7)	(17,2;55,7)	(1,5;7,3)	(0,9;1,0)
Absent Halo sign + oval shape+ pattern 3-4 vasc.								
Yes	25	3	3,3	95,6	86,2	10,7	0,8	1,0
No	542	87	(0,7;9,4)	(93,6;97,1)	(83,2;88,8)	(2,3;28,2)	(0,2;2,5)	(1,0;1,1)
Absent Halo sign + oval shape+ pattern 3-4 vasc.								
Yes	25	2	2,2	95,6	86,0	7,4	0,5	1,0
No	542	88	(0,3;7,8)	(93,6;97,1)	(83,1;88,6)	(0,9;24,3)	(0,1;2,1)	(1,0;1,1)

Supplementary Table 1b. Diagnostic value of US in combination with SE for the diagnosis of malignant thyroid nodules (tripple combination)

US-pattern	Benign	Cancer	Sensitivity (%)	Specifity (%)	NPV (%)	PPV (%)	+ LR	- LR
ES 3-4 transverse + Pattern 3-4 vasc. + Hypoechogenicity								
Yes	17	8	8,9	97,0	87,0	32,0	3,0	0,9
No	550	82	(3,9;16,8)	(95,2;98,2)	(84,2;89,6)	(15,0;53,5)	(1,3;6,7)	(0,9;1,0)
ES 3-longitudinal + Pattern 3-4 vasc. + Hypoechogenicity								
Yes	22	9	10,0	96,1	87,1	29,0	2,6	0,9
No	545	81	(4,7;18,1)	(94,2;97,6)	(84,2;89,6)	(14,2;48,0)	(1,2;5,4)	(0,9;1,0)
ES 3-4 transverse+ pattern 3-4 vasc. + microcalcification								
Yes	19	10	11,1	96,7	87,3	34,5	3,3	0,9
No	548	80	(5,5;19,5)	(94,8;98,0)	(84,4;89,8)	(17,9;54,3)	(1,6;6,9)	(0,9;1,0)
ES 3-4 longitudinal+ pattern 3-4 vasc. + microcalcification								
Yes	22	11	12,2	96,1	87,3	33,3	3,2	0,9
No	545	79	(6,3;20,8)	(94,2;97,6)	(84,5;89,9)	(18,0;51,8)	(1,6;6,3)	(0,8;1,0)
ES 3-4 tansverse+ pattern 3-4 vasc.+ macrocalcification								
Yes	17	2	2,2	97,0	86,2	10,5	0,7	1,0
No	550	88	(0,3;7,8)	(95,2;98,2)	(83,3;88,8)	(1,3;33,1)	(0,2;3,2)	(1,0;1,0)
ES 3-4 longitudinal+ pattern 3-4 vasc.+ macrocalcification								
Yes	22	3	3,3	96,1	86,2	12,0	0,9	1,0
No	545	87	(0,7;9,4)	(94,2;97,6)	(83,3;88,8)	(2,6;31,2)	(0,3;2,8)	(1,0;1,0)
ES 3-4 transverse+ pattern 3-4 vasc.+ absent halo sign								
Yes	11	7	7,8	98,1	87,0	38,9	4,0	0,9
No	556	83	(3,2;15,4)	(96,6;99,0)	(84,2;89,5)	(17,3;64,3)	(1,6;10,1)	(0,9;1,0)
ES 3-4 longitudinal+ pattern 3-4 vasc.+ absent halo sign								
Yes	13	7	7,8	97,7	87,0	35,0	3,4	0,9
No	554	83	(3,2;15,4)	(96,1;98,8)	(84,1;89,5)	(15,4;59,2)	(1,4;8,3)	(0,9;1,0)
ES 3-4 transverse+ pattern 3-4 vasc.+ irregular margins								
Yes	15	10	11,1	97,4	87,3	40,0	4,2	0,9
No	552	80	(5,5;19,5)	(95,7;98,5)	(84,5;89,8)	(21,1;61,3)	(1,9;9,1)	(0,8;1,0)
ES 3-4 longitudinal+ pattern 3-4 vasc.+ irregular margins								
Yes	18	10	11,1	96,8	87,3	35,7	3,5	0,9
No	549	80	(5,5;19,5)	(95,0;98,1)	(84,4;89,8)	(18,6;55,9)	(1,7;7,3)	(0,9;1,0)
ES 3-4 transverse+ pattern 3-4 vasc.+ oval shape								
Yes	21	3	3,3	96,3	86,3	12,5	0,9	1,0
No	546	87	(0,7;9,4)	(94,4;97,7)	(83,3;88,8)	(2,7;32,4)	(0,3;3,0)	(1,0;1,0)
ES 3-4 longitudinal+ pattern 3-4 vasc.+ oval shape								
Yes	28	4	4,4	95,1	86,2	12,5	0,9	1,0
No	539	86	(1,2;11,0)	(92,9;96,7)	(83,3;88,8)	(3,5;29,0)	(0,3;2,5)	(1,0;1,1)
ES 3-4 transverse+ Hypoechogenicity + microcalcification								

US-pattern	Benign	Cancer	Sensitivity (%)	Specifity (%)	NPV (%)	PPV (%)	+ LR	- LR
Yes	28	39	43,3	95,1	91,4	58,2	8,8	0,6
No	539	51	(32,9;54,2)	(92,9;96,7)	(88,8;93,5)	(45,5;70,2)	(5,7;13,5)	(0,5;0,7)
ES 3-4 longitudinal+ Hypoechogenicity + microcalcification								
Yes	31	41	45,6	94,5	91,6	56,9	8,3	0,6
No	536	49	(35,0;56,4)	(92,3;96,3)	(89,1;93,7)	(44,7;68,6)	(5,5;12,6)	(0,5;0,7)
ES 3-4 transverse+ Hypoechogenicity+ macrocalcification								
Yes	19	3	3,3	96,7	86,3	13,6	1,0	1,0
No	548	87	(0,7;9,4)	(94,8;98,0)	(83,4;88,9)	(2,9;34,9)	(0,3;3,3)	(1,0;1,0)
ES 3-4 longitudinal+ Hypoechogenicity+ macrocalcification								
Yes	23	5	5,6	95,9	86,5	1,4	1,4	1,0
No	544	85	(1,8;12,5)	(94,0;97,4)	(83,6;89,1)	(0,5;3,5)	(0,5;3,5)	(0,9;1,0)
ES 3-4 transverse+ Hypoechogenicity+ absent halo sign								
Yes	44	41	45,6	92,2	91,4	48,2	5,9	0,6
No	523	49	(35,0;56,4)	(89,7;94,3)	(88,8;93,6)	(37,3;59,3)	(4,1;8,4)	(0,5;0,7)
ES 3-4 longitudinal+ Hypoechogenicity+ absent halo sign								
Yes	46	42	46,7	91,9	91,6	47,7	5,8	0,6
No	521	48	(36,1;57,5)	(89,3;94,0)	(89,0;93,7)	(37,0;58,7)	(4,0;8,2)	(0,5;0,7)
ES 3-4 transverse + Hypoechogenicitiy+ Irregular margins								
Yes	36	40	44,4	93,7	91,4	52,6	7,0	0,6
No	531	50	(34,0;55,2)	(91,3;95,5)	(88,8;93,6)	(40,8;64,2)	(4,7;10,4)	(0,5;0,7)
ES 3-4 longitudinal + Hypoechogenicitiy+ Irregular margins								
Yes	36	42	46,7	93,7	91,7	53,9	7,4	0,6
No	531	48	(36,1;57,5)	(91,3;95,5)	(89,2;93,8)	(42,2;65,2)	(5,0;10,8)	(0,5;0,7)
ES 3-4 transverse+ Hypoechogenicity+ Oval shape								
Yes	44	7	7,8	92,2	86,3	13,7	1,0	1,0
No	523	83	(3,2;15,4)	(89,7;94,3)	(83,3;88,9)	(5,7;26,3)	(0,5;2,2)	(0,9;1,1)
ES 3-4 longitudinal+ Hypoechogenicity+ Oval shape								
Yes	52	9	10,0	90,8	86,4	14,8	1,1	1,0
No	515	81	(4,7;18,1)	(88,2;93,1)	(83,4;89,1)	(7,0;26,2)	(0,6;2,1)	(0,9;1,1)
ES 3-4 transverse+ microcalcification+ Macrocalcification								
Yes	21	2	2,2	96,3	86,1	8,7	0,6	1,0
No	546	88	(0,3;7,8)	(94,4;97,7)	(83,2;88,7)	(1,1;28,0)	(0,1;2,5)	(1,0;1,1)
ES 3-4 longitudinal+ microcalcification+ Macrocalcification								
Yes	26	4	4,4	95,4	86,3	13,3	1,0	1,0
No	541	86	(1,2;11,0)	(93,4;97,0)	(83,3;88,9)	(3,8;30,7)	(0,3;2,7)	(1,0;1,1)
ES 3-4 transverse+ microcalcification+ absent halo sign								
Yes	23	41	45,6	95,9	91,7	64,1	11,2	0,6
No	544	49	(35,0;56,4)	(94,0;97,4)	(89,2;93,8)	(51,1;75,7)	(7,1;17,8)	(0,5;0,7)
ES 3-4 longitudinal+ microcalcification+ absent halo sign								

US-pattern	Benign	Cancer	Sensitivity (%)	Specifity (%)	NPV (%)	PPV (%)	+ LR	- LR
Yes	24	42	46,7	95,8	91,9	63,6	11,0	0,6
No	543	48	(36,1;57,5)	(93,8;97,3)	(89,4;94,0)	(50,9;75,1)	(7,0;17,3)	(0,5;0,7)
ES 3-4 transverse + Irregular margins + microcalcification								
Yes	27	41	45,6	95.2	91,7	60,3	9,6	0,6
No	540	49	(35,0;56,4)	(93,2;96,8)	(89,2;93,8)	(47,7;72,0)	(6,2;14,7)	(0,5;0,7)
ES 3-4 longitudinal + Irregular margins + microcalcification								
Yes	33	43	47.8	94,2	91.9	56.6	8,2	0.6
No	534	47	(37.1;58.6)	(91,9;96,0)	(89.4;94,0)	(44.7;67.9)	(5,5;12,2)	(0.5;0.7)
ES 3-4 transverse+ microcalcification+ oval shape								
Yes	27	41	45,6	95,2	91,7	60,3	9,6	0,6
No	540	49	(35,0;56,4)	(93,2;96,8)	(89,2;93,8)	(47,7;72,0)	(6,2;14,7)	(0,5;0,7)
ES 3-4 longitudinal+ microcalcification+ oval shape								
Yes	33	43	47,8	94,2	91,9	56,6	8,2	0,6
No	534	47	(37,1;58,6)	(91,9;96,0)	(89,4;94,0)	(44,7;67,9)	(5,5;12,2)	(0,5;0,7)
ES 3-4 transverse+ macrocalcification+ absent halo sign								
Yes	23	1	1,1	95,9	85,9	4,2	0,3	1,0
No	544	89	(0,0;6,0)	(94,0;97,4)	(83,0;88,6)	(0,1;21,1)	(0,0;2,0)	(1,0;1,1)
ES 3-4 longitudinal+ macrocalcification+ absent halo sign								
Yes	23	2	2,2	95,9	86,1	8,0	0,5	1,0
No	544	88	(0,3;7,8)	(94,0;97,4)	(83,1;88,7)	(1,0;26,0)	(0,1;2,3)	(1,0;1,1)
ES 3-4 transverse+ macrocalcification+ irregular margins								
Yes	23	1	1,1	95,9	85,9	4,2	0,3	1,0
No	544	89	(0,0;6,0)	(94,0;97,4)	(83,0;88,6)	(0,1;21,1)	(0,0;2,0)	(1,0;1,1)
ES 3-4 longitudinal+ macrocalcification+ irregular margins								
Yes	30	3	3,3	94,7	86,1	9,1	0,6	1,0
No	537	87	(0,7;9,4)	(92,5;96,4)	(83,1;88,7)	(1,9;24,3)	(0,2;2,0)	(1,0;1,1)
ES 3-4 transverse+ macrocalcification+ Oval shape								
Yes	25	1	1,1	95,6	85,9	3,9	0,3	1,0
No	542	89	(0,0;6,0)	(93,6;97,1)	(82,9;88,5)	(0,1;19,6)	(0,0;1,8)	(1,0;1,1)
ES 3-4 longitudinal+ macrocalcification+ Oval shape								
Yes	31	4	4,4	94,5	86,2	11,4	0,8	1,0
No	536	86	(1,2;11,0)	(92,3;96,3)	(83,2;88,8)	(3,2;26,7)	(0,3;2,2)	(1,0;1,1)
ES 3-4 transverse+ absent halo sign+ irregular margins								
Yes	40	42	46,7	93,0	91,7	51,2	6,6	0,6
No	527	48	(36,1;57,5)	(90,5;94,9)	(89,1;93,8)	(42,5;63,9)	(4,6;9,6)	(0,5;0,7)
ES 3-4 longitudinal+ absent halo sign+ irregular margins								
Yes	42	43	47,8	92,6	91,8	50,6	6,5	0,6
No	525	47	(37,1;58,6)	(90,1;94,6)	(89,2;93,9)	(39,5;61,6)	(4,5;9,3)	(0,5;0,7)
ES 3-4 transverse+ absent halo sign+ oval shape								

US-pattern	Benign	Cancer	Sensitivity (%)	Specifity (%)	NPV (%)	PPV (%)	+ LR	- LR
Yes	38	9	10,0	93,3	86,7	19,2	1,5	1,0
No	529	81	(4,7;18,1)	(90,9;95,2)	(83,8;89,3)	(9,2;33,3)	(0,7;3,0)	(0,9;1,0)
ES 3-4 longitudinal+ absent halo sign+ oval shape								
Yes	42	10	11,1	92,6	86,8	19,2	1,5	1,0
No	525	80	(5,5;19,5)	(90,1;94,6)	(83,8;89,4)	(9,6;32,5)	(0,8;2,9)	(0,9;1,0)
ES 3-4 transverse+ irregular margins+ oval shape								
Yes	27	7	7,8	95,2	86,7	20,6	1,6	1,0
No	540	83	(3,2;15,4)	(93,2;96,8)	(82,8;89,3)	(8,7;37,9)	(0,7;3,6)	(0,9;1,0)
ES 3-4 longitudinal+ irregular margins+ oval shape								
Yes	35	8	8,9	93,8	86,6	18,6	1,4	1,0
No	532	82	(3,9;16,8)	(91,5;95,7)	(83,7;89,2)	(8,4;33,4)	(0,7;3,0)	(0,9;1,0)