Evaluation of Strain Elastography for Differentiation of Thyroid Nodules: Results of a Prospective DEGUM Multicenter Study

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

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Abstract
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Purpose: Many patients with thyroid nodules are presently referred to surgery for not only therapeutic but also diagnostic purposes. The aim of noninvasive 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 for the differentiation of thyroid nodules in a prospective multicenter study.

Materials and Methods: The study was registered at clinicaltrials.gov and was approved by the local ethics committees of all participating centers. All patients received an ultrasound (US) of the thyroid gland including color Doppler US. In addition, all nodules were evaluated by SE (Hitachi Medical Systems) using qualitative image interpretation of color 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. The sensitivity, specificity, NPV, PPV, +LR were 21 %, 73 %, 86 %, 11 %, 0.8, respectively, for color Doppler US; 69 %, 75 %, 94 %, 30 %, 2.9, respectively, for SE-ES; 56 %, 81 %, 92 %, 32 %, 2.9, respectively, for SE-strain value; and 58 %, 78 %, 92 %, 30 %, 2.6, respectively, for SE-strain ratio. The diagnostic accuracy was 71 % for both strain value and strain ratio of nodules.

Conclusion: 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.

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Zusammenfassung
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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 Elastografie (SE) ermöglicht die Ultraschall-basierte Messung der Gewebeelastizität. Das Ziel der vorliegenden Studie war es den Stellenwert der SE in einer prospektiven Multizenter-Studie für die Differenzierung von Schilddrüsenknoten zu evaluieren.

Material und Methoden: 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.

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

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Introduction

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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 an excellent method, but it only has 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 ≥ 10 mm 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 – 7]. However, besides high specificities (60 – 98 %), varying sensitivities (54 – 90 %) have been reported for FNAB for the diagnosis of malignant thyroid nodules [8 – 11]. 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 [12].

A classic criterion of malignancy upon palpation or US probe pressure is a hard or firm consistency [3, 13]. 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 [14, 15]. Meta-analyses of SE reported mean sensitivities of 82 – 92 % and mean specificities of 67 – 92 % for the diagnosis of malignant thyroid nodules [16 – 18]. However, SE was also challenged and criticized for its operator dependency in studies [19].

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

Materials and Methods

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The multicenter study was approved by the lead ethics committee at the University of Frankfurt with local approval from the ethics committees of the other study centers. The study was registered with Clinicaltrials.gov with the registration number NCT01 609 946.

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 ≥ 5 mm, normal values of thyroid-stimulating hormone (TSH ≥ 0.35 µU/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 a US scan of the thyroid gland including color Doppler US followed by SE (Hitachi Medical Systems) using qualitative image interpretation of color distribution (SE-ES), strain value and strain ratio in real-time.

An online case report form was used for data collection.

Reference method – cytology/histology

Cytology with a 6 – 12-month follow-up US scan (showing absence of lesion growth – increase in diameter of less than 20 % or increase in volume of less than 50 %) or histology was used as the reference method for the diagnosis of benign thyroid nodules [3, 7].

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 [20]. The Bethesda system was used to report thyroid cytopathology [21]. 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.

One to two investigators (all physicians) were involved in ultrasound scanning at each center. The same investigator performed all US and SE measurement in the same patient and interpreted the results. No change in examiners was done in between. The investigators at all centers had at least 10 years of experience in thyroid US and at least 6 months in elastography. The investigators were blinded to the results of cytology and histology.

Conventional ultrasound (B-mode, Doppler)

All patients received a US examination of the thyroid gland using a transducer at 9 MHz (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. Thyroid nodules were evaluated for size, volume, echogenicity, echotexture, presence/absence of halo sign, presence/absence of microcalcification (hyperechoic spots < 1 mm) and/or macrocalcification (> 1 mm). After B-mode US, power Doppler and duplex imaging were performed. Vascularization of thyroid nodules was classified using five different patterns as described previously [22]: pattern 0: no visible flow; pattern 1: minimal internal flow without a peripheral ring; pattern 2: peripheral ring of flow but minimal or no internal flow; pattern 3: peripheral ring of flow and moderate amount of internal flow; pattern 4: extensive internal flow with or without a peripheral ring.

In patients with a goiter and multiple nodules, up to 4 nodules per patient, which fulfilled at least 2 ultrasound criteria of malignancy, could be included. If more than 4 nodules fulfilled these criteria, hierarchically the nodules with the most ultrasound criteria of malignancy were selected. Each nodule was characterized independently.

Strain Elastography (SE)

Strain elastography was performed with a Hitachi Systems (Hitachi HI Vision Preirus, HI Vision Avius, EUB 900 HV and EUB 7500 HV, Hitachi Medical Corporation, Japan). The machines at the different centers were all standardized to the elastography parameters: frame rejection/noise rejection: 4 – 4, persistence: 6, blending: 32, E.-Dyn: 4, density: 3, smoothing: 3, elastofreq.: low, frame rate: mid., color: fineflow: 500 Hz; color Doppler: 800 Hz, loops of 30 seconds. 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 [23, 24]. 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 [25 – 27]:

► 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 a transverse and longitudinal position. SE was performed in real-time and images and/or clips were stored. Directly after storing of a representative SE image, the strain value calculation of the elasticity within an ROI was performed using the auto-correlations method (values of 1.0 indicate maximum elasticity) and the strain ratio (ratio of the strain value in the surrounding thyroid tissue and strain value in thyroid nodule) was calculated. The size of the ROI within the nodule was chosen to be as large as possible to include the nodule only, and 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 the 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 the sensitivity and specificity. Based on the results of a previous meta-analysis on SE [16], a sensitivity and specificity of at least 90 % were 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. The sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV), and positive likelihood ratio (LR) were calculated for the diagnosis of malignant nodules for all ultrasound criteria and SE. Malignancy criteria were defined as follows for this purpose: hypoechogenicity, irregular margin, absent halo sign, pattern 3&4 vascularization, presence of microcalcification, elastography ES score 3&4. All tests were two-sided and use a significance level of $\alpha = 5$ %. 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 the prediction of malignancy. The statistical program R (R Foundation for Statistical Computing, Vienna, Austria), particularly the R package pROC [28] was used to obtain an optimal combination of ultrasound criteria with respect to the Youden criteria consisting of microcalcification, macrocalcification, hypoechogenicity, absent halo sign, irregular margins, pattern 3 – 4 vascularization, ES 3 – 4 transverse and longitudinal and strain value < 0.17, strain ratio > 2.66.

Results
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646 patients with 701 thyroid nodules were prospectively enrolled at 7 centers in this multicenter study. 36 patients were excluded due to missing data on SE results or cytology/histology. Additionally 8 patients with malignant cytology who did not receive surgery within the study period were excluded. Therefore, 602 patients with 657 thyroid nodules were available for final analysis. In 47 patients with a goiter, 2 nodules per patient were included and in 4 patients 3 nodules per patient were included. Patient characteristics are shown in ◗ **Table 1**. Thyroid hormone values were within normal range in all patients.

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 Bethesda-III-V, as well as 15 patients with nodules with Bethesda-II and a 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 on. The final diagnosis of benign histology was papillary adenoma in 29 nodules, follicular adenoma in 79, microfollicular adenoma in 53, oncocytic adenoma in 4, thyroid hyperplasia in 6 and goiter in 251 evaluated nodules. The final diagnosis of malignant histology was papillary carcinoma in 77 patients with 78 nodules, medullary carcinoma in 10 patients/nodules, follicular carcinoma in 1 patient/nodule, and anaplastic carcinoma in 1 patient/nodule. Therefore, in total 567 benign nodules from 515 patients and 90 malignant nodules from 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 2.66 for strain ratio (strain value thyroid tissue/strain value nodule) 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 color classification. The diagnostic value of different combinations of US criteria as well as combinations of US with SE is shown in ◗ **Table 3, 4** and supplementary Table 1. Overall, 185 benign and 61 malignant nodules had irregular margins; 129 benign and 39 malignant nodules were round, 397 benign and 28 malignant nodules were oval, and 31 benign and 22 malignant nodules were polycyclic. Depending on the combination of US criteria, 12 – 51 malignant nodules misclassified by B-mode/Doppler ultrasound could be correctly diagnosed by elastography. To estimate the optimal combination of imaging criteria, sum scores l to optimize the Youden index were calculated including (1) B-mode criteria only, (2) B-mode and power Doppler US, and (3) B-mode, power Doppler and SE:

(1) For B-mode criteria the optimal sum score consisted of the two criteria: microcalcification and absent halo sign. This score results in a sensitivity of 54.5 %, specificity of 91.8 %, NPV of 92.7 %, PPV of 51.6 %, +LR of 6.7, and –LR of 0.5.

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 Hospital 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[1]				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				< 0.001
transverse				
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				< 0.001
longitudinal				
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.
[1] Scintigraphy of nodule available in 429 patients with 474 nodules.

(2) Including power Doppler US did not change the optimal sum score. Power Doppler was not selected itself.

(3) For the combination of US criteria and SE, the optimal sum score consisted of: microcalcifications, macrocalcification, absent halo sign, irregular margins, pattern 3 – 4 vascularization, ES 3 – 4 longitudinal, strain ratio > 2.66. Each fulfilled criterion adds one point to the sum score. If 4 or more of these criteria indicate malignancy, the score results in a sensitivity of 68.2 %, specificity of 85.1 %, NPV of 94.1 %, PPV of 43.6 %, +LR of 4.6 and –LR of 0.4. (○ **Fig. 1, 2**)

Discussion
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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 [14 – 18]. 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, histograms of color pixels and ECI index [14, 15, 29 – 34]. 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 [19, 35, 36].

The aim of the present study was to evaluate high-quality conventional US performed by physicians with significant experience in ultrasound 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 multicenter study in patients referred for work-up of thyroid nodules. Overall, 602 patients with 657 thyroid nodules were analyzed and the negative predictive
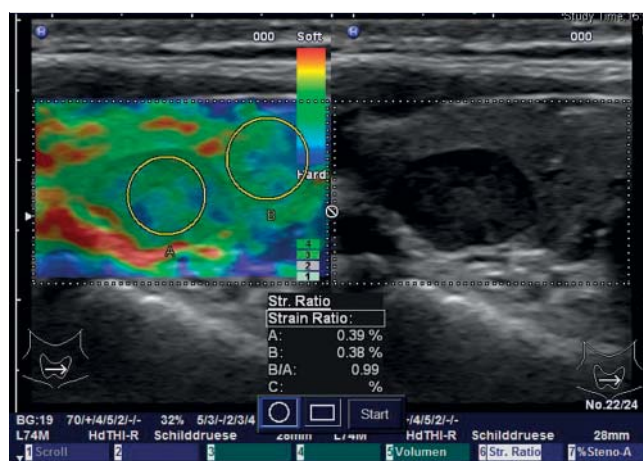
Table 2 Diagnostic value of US and SE for the diagnosis of malignant thyroid nodules.

criteria	benign	malig-nant	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 vascularization								
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 > 2.66								
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)

Not all criteria were recorded for each nodule. Therefore, the numbers in each column do not always total 567 benign and 90 malignant nodules.
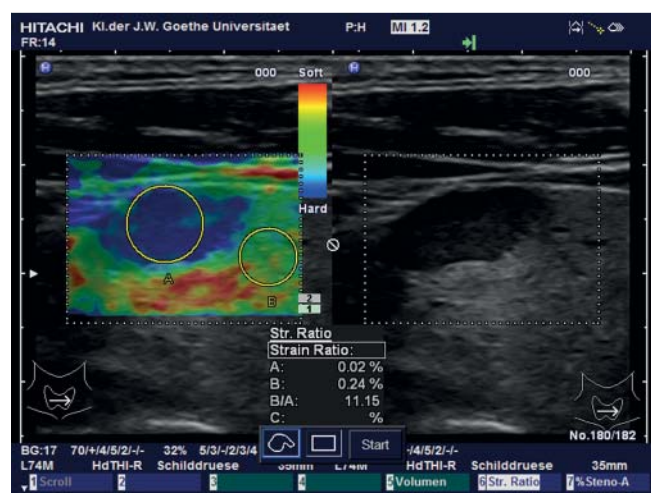
Fig. 1 Example of SE of papillary carcinoma: An 8 × 12 mm nodule in the right thyroid gland classified as SE ES-4 (completely blue = hard; consistent with malignancy) with strain ratio of 11.15. Histology revealed a papillary T2 carcinoma.

Fig. 2 Example of SE of thyroid adenoma: An 8 × 12 mm 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.

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

US pattern	benign	malignant	sensitivity (%)	specificity (%)	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)

Not all criteria were recorded for each nodule. Therefore, the numbers in each column do not always total 567 benign and 90 malignant nodules.

value (NPV) of the different SE methods was > 90 %. These results are in accordance with previously published studies reporting NPV of 88 – 99 % [25, 27, 33, 37 – 43]. Meta-analyses of SE reported mean sensitivities of 82 – 92 % and mean specificities of 67 – 92 % for the diagnosis of malignant thyroid nodules [16 – 18]. In the present study the sensitivity of SE was 69 – 70 % and the specificity was 72 – 75 %. SE was recorded in a transverse and longitudinal position in the present study to evaluate any influence of positioning. The results support taking the best access since no significant difference was observed.

While in a recent meta-analysis [18] the semi quantitative analysis had a slightly higher sensitivity than the qualitative analysis, no significant difference was observed in the present study. Only performing qualitative analysis is time-saving and can be recommended if the examination is performed by examiners with substantial ultrasound experience like in the present study. However, semi-quantification with strain value and strain ratio might be helpful for more novice examiners. This assumption

has to be evaluated in future studies. The optimal strain ratio cut-off was 2.66. This is in accordance with previously published strain ratios calculating the strain value of the thyroid gland divided by the strain value of the thyroid nodule ranging from 1.5 – 4.2 [18]. In the present study only SE from the company Hitachi was used. However, other strain elastography methods have been evaluated with excellent diagnostic accuracy and interobserver agreement [44]. However, the strain elastography methods of different companies might not be directly comparable and might influence the calculation of strain value and strain ratio. Recently shear-wave elastography methods have been evaluated for the diagnosis of thyroid nodules. The results are comparable to the results of SE [45].

The combination of B-mode US criteria and SE could improve the noninvasive diagnosis of malignant thyroid nodules in the present study. A sum score including B-mode and SE increased sensitivity by 14 % and NPV by 2 % as compared to B-mode/Doppler US alone. Depending on the combination of US criteria, 12 – 51 ma-

Table 4 Diagnostic value of US in combination with SE for the diagnosis of malignant thyroid nodules (dual combination).

US pattern	benign	malignant	sensitivity (%)	specificity (%)	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)

Not all criteria were recorded for each nodule. Therefore, the numbers in each column do not always total 567 benign and 90 malignant nodules.

lignant nodules misclassified by B-mode/Doppler ultrasound could be correctly diagnosed by elastography. This additive value has also been reported in previously published studies [43]. Therefore, SE should be used in addition to conventional US in the diagnostic work-up of thyroid nodules. For example, in patients with suspicious signs on conventional ultrasound but soft elastography values (ES1 – 2), FNAB should be performed. If cytology reveals a benign non-follicular lesion, follow-up can be recommended.

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 centers with an average of even 30 % of malignant thyroid nodules [16]. Cytology without lesion growth was accepted as the reference method for benign lesions as suggested by international guidelines [3, 7]. However, it might not be the perfect reference. Yet, only including histology would have a relevant bias and further increase the number of malignant lesions. And the aim of the study was to evaluate thy-

roid nodules referred for further diagnostic work-up according to present guidelines. In addition, only one case of follicular carcinoma was included in the present study. Therefore, no statement on the diagnostic accuracy of SE for follicular carcinoma can be made. Previous studies have reported that both FNA and SE have difficulties in the diagnosis of follicular carcinoma [3, 16, 27, 38, 46]. In a meta-analysis on SE including 8 studies, 44 % of follicular carcinoma were not detected as malignant thyroid nodules using SE. Gross anatomy and cellular patterns of follicular carcinoma overlap with those of benign follicular adenoma and might be an explanation [16, 46]. Nodules < 5 mm were excluded from the present study, so no statement can be made regarding this lesion size. Another limitation is that no minimum case number per center was proposed in the study design. However, the examination was performed in high volume centers with experienced examiners. For the calculation of strain value and ratio, the ROI size was adapted to the size of the nodule to obtain an overall elasticity value of the nodule. However, the size of the ROI might influ-

ence the elasticity results. The inter-observer variability was not assessed in the present manuscript since each patient was only examined by one examiner.

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.

Supplement Tables see online.

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