

Advanced Ultrasound Application – Impact on Presurgical Risk Stratification of the Thyroid Nodules

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management

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Aim: Current major guidelines recommend risk stratification of the thyroid nodules, after each diagnostic evaluation, in order to focus attention on potentially risky nodules. The main aim of our study was to evaluate the performance of combined advanced ultrasound techniques in this process, compared with conventional stratification models, in order to reduce unnecessary fine-needle biopsies, respectively, surgery.

Material and Methods: We evaluated 261 cases (261 nodules) using conventional ultrasound (2B), real-time Doppler evaluation (4D) respectively, real-time elastography, using a linear multifrequency probe and a linear volumetric probe (Hitachi Prerius Machine, Hitachi Inc, Japan). All the nodules were classified using a risk stratification model comprising seven conventional US characteristics, two 4 D characteristics and a color map RTE aspect. The results were compared with the pathology results, considered the golden standard diagnosis.

Results: The prevalence of malignant nodules was 21.83% (57 cases). Conventional risk classification generated: 106 low-risk cases, 113 intermediate-risk and 42 high-risk cases. Our proposed risk classification changes the conventional risk classification with a risk upgrade in 27 cases and with a risk downgrade in 69 cases. The diagnostic quality of the combined risk stratification model was better, considering a low-risk category predictive for benignancy and a high category predictive for malignancy: Sensitivity: 80.88% versus 49.01%, respectively, Specificity: 91.22% versus 54.38. The diagnostic power differences were observed regardless of the nodule size.

Conclusion: Advanced ultrasound techniques did add diagnostic value in the presurgical risk assessment of the thyroid nodules.

Keywords: strain elastography, volumetric Doppler, complex ultrasound thyroid evaluation, risk stratification

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Introduction

The prevalence of thyroid nodular pathology in the general population is high,¹ increasing with age² gender-dependent,³ lifestyle^{4,5} and iodine intake influenced.⁶⁻⁸ There is also a significant increase in thyroid cancer prevalence⁹ not only related to better diagnosis techniques,¹⁰ data in the literature describing a real increase per se.¹¹ The increase initially explained by the diagnosis of a more subclinical form of the disease,¹² is described to be similar in small (less than 1 cm) intermediate (2–4 cm) and even bigger than 4 cm nodules.¹³ This true increase was recently found in the United States population¹³ and is valid for papillary thyroid carcinoma variant.¹⁴ No significant change in the prevalence of the follicular variant, neither in medullar or anaplastic thyroid cancer was reported.^{9,13}

Fine-needle aspiration cytology (FNAC) is considered to be the most cost-effective preoperative diagnostic tool^{15,16} but the indications for FNAC have changed comparatively with the previous guidelines,^{17,18} according to the ultrasound (US) characteristics suggestive for malignancy (taller than wider irregular margins, marked hypoechoic texture, micro and macro-calcifications, spiculated margins, extracapsular invasion). From the universal referral of all nodules bigger than 1 cm to FNAC,^{15,16} the current US risk stratification recommendations use a different size threshold in recommending FNAC: nodular diameter bigger than 1.5–2 cm if low risk versus diameter bigger than 1cm in high-risk cases.^{17,18} The problem is that there is not a complete overlap of the risk categories as identified by the American Thyroid Association (ATA) and the American Association of Clinical Endocrinology (AACE) guidelines. Also, the nodular size threshold required for FNAC recommendation is different in the two major guidelines: in the case of very low-risk nodules: 2.5 cm (AACE), respectively, of 2 cm (ATA), for low-risk nodules: 2 cm if proven growth (AACE) or just 1.5 cm (ATA); in the case of intermediate-risk nodules – size 2 cm (AACE) or 1 cm (ATA). The only category where the same threshold size is recommended is the high-risk category, in which all nodules bigger than 1 cm need further evaluation with FNAC. In addition, in order to simplify the risk stratification different Thyroid reporting and Data System (TI-RADS) models have emerged^{19–21} with good sensitivity and specificity, but with different recommendations regarding the moment of referral to FNAC according to risk and size.

Russ et al²² found that adding strain elastography findings in the TI-RADS model increases the sensitivity (96.7% versus 92.5%) but decreases the specificity (61% versus 44.7%). Our group previously demonstrated that adding quantitative strain elastography as the 6th parameter in the TI-RADS model, an excellent diagnostic quality (AUROC = 0.9567), could be obtained.²³ High stiffness is currently considered a high-risk feature.^{17,18,24}

It is known that FNAC is considered unclear in the Bethesda 3 and 4 diagnostic categories and in these situations the recommended management is divers: follow-up, lobectomy thyroidectomy or completion with molecular assays.^{17,18} In these cases, US pattern has to be taken into consideration.²⁵

The aim of our study is to evaluate the efficacy of a multimodal ultrasound risk stratification model in the preoperative selection of the thyroid nodules. In order to avoid confounding factors due to the limited diagnostic

availability and value of FNAC, we included in the analysis only nodules with proven pathology diagnostics after surgical resection.

Patients and Methods

This prospective study was performed in accordance with the Ethical Guidelines of the Helsinki Declaration and was approved by the Ethics Committee of our Center, No 78/15.01.2016. Written informed consent was obtained from all patients prior to inclusion.

Patients

The study group included patients with a solid nodular goiter examined in our Ultrasound evaluation Unit between January 2016 and June 2018. In this period, we identified 564 patients with a nodular goiter; 261 of them were operated till the end of the enrolment period. For each case, a pathology report was obtained and was considered the golden standard for further analysis. The exclusion criterion was the absence of a pathology report. The ultrasound evaluation, comprising conventional grayscale, SE and tri-dimensional CD, was performed prior to surgery by one operator with more than 10 years' experience in conventional US and 5 years in elastography, less than 2 months before surgery. In cases with a multinodular goiter, the nodule with a high risk on ultrasound evaluation according to our criteria was considered for statistical analysis. FNAC was not performed in all cases due to lack of acceptance, 51 cases, or no need in multinodularity associated with compression or autonomy, 34 cases. Rapid growth, uninodular lesion with autonomy, intermediate and high-risk ultrasound patterns were the indication FNAC.

Because FNAC was not performed in all cases, it was not included in the final analysis of the present study.

Table 1 is presenting the proposed risk classification in our study.

Ultrasound Evaluation

All ultrasound evaluations were performed using the Hitachi Preirus (Hitachi Medical Corporation, Tokyo, Japan) machine with a 5–18 MHz linear multifrequency probe and a 5–13MHz linear volumetric probe. SE was performed using mild external pressure.²⁶ Images obtained with inadequate external pressure were not used in the final analysis. The color map types (ES) were interpreted following the Asteria criteria:²⁶ ES 1 (complete green) and 2 color map (predominant green) – soft lesions, ES 3

Table 1 Proposed Risk Classification Model

Technique	Low Risk	Intermediate Risk	High Risk
US	Oval Mild hypo echoic No risk sign	Hypo echoic Sub capsular position Inhomogeneity	Taller than wide Sub capsular Intense hypo echoic Calcification Suspect lymph nodes
SE	ES 1 +2	ES 3	ES 4
V	Intact thyroid capsule No vascularization		Altered thyroid capsule Intranodular increased vascularization

Abbreviations: US, conventional ultrasound; SE, Real-Time Elastography; V, Volumetric Real-time three-dimensional ultrasound.

(mixed green + blue images) intermediate lesion and ES 4 (complete blue lesion) – high stiffness lesion.

Volumetric Doppler evaluation offers a tri-dimensional image of the scanned region, with the nodule in the center of the image, the rotational scanning, in all three axis, if needed, in order to evaluate the degree of vascularization spreading from the surrounding thyroid parenchyma into the nodular lesion.^{27,28} A significant difference in 3D Doppler evaluation is seen in cases with similar 2D CD pattern images. **Figures 1** and **2** present differences (2b versus 1b) observed in volumetric Doppler images, compared with the similar monoplane CD pattern (1a and 2a).

For this reason, we used volumetric Doppler evaluation instead of monoplane Doppler evaluation.

Slices of 0.2 mm, in each X, Y and Z plane, represent the second type of obtained images. In cases with abundant vascularization, the volumetric view was completed, as previously described²⁸ with the biplane combined views, observing all the planes from one border to the opposite border of the nodule.

The following findings of the nodules and thyroid gland were evaluated: conventional US patterns: shape, ecogenicity, homogeneity, margins, position, presence of calcification and of suspect lymph nodes;²⁹ SE - color map

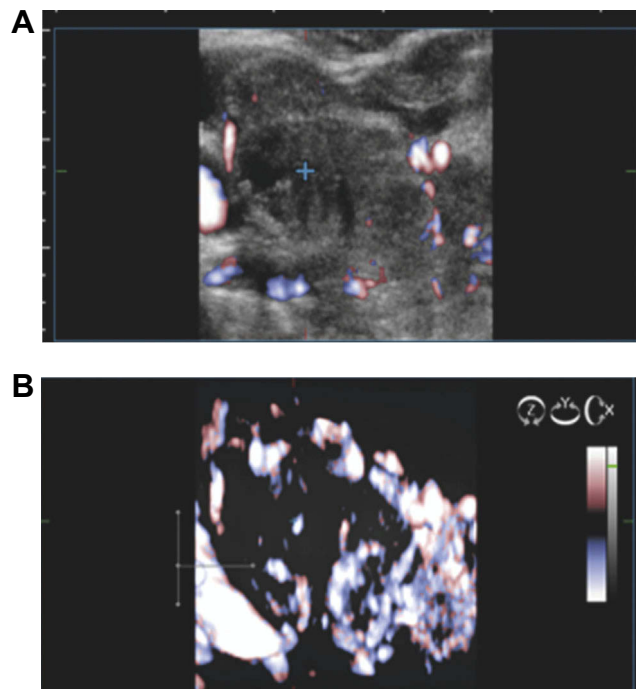


Figure 1 (A) Low intra- and peri-nodular vascularisation pattern observed on 2D examination. **(B)** Low intra- and peri-nodular vascularisation observed on 3D examination (same thyroid nodule).

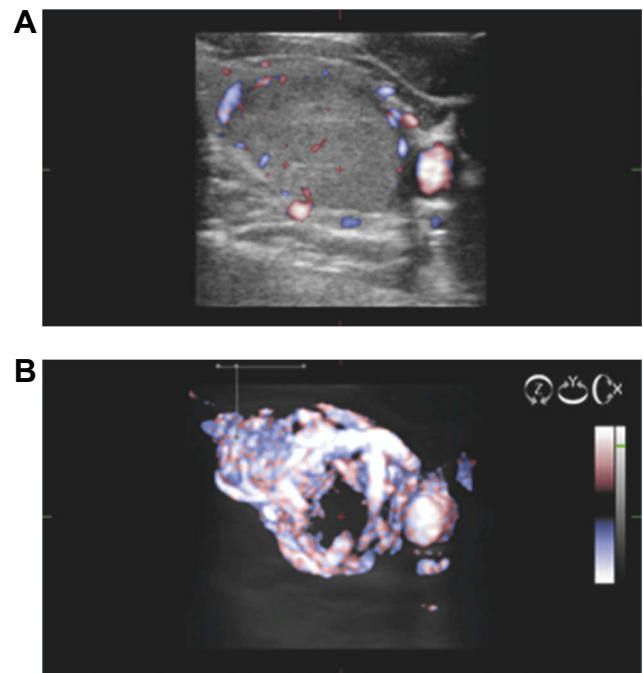


Figure 2 (A) Low intra- and peri-nodular vascularisation observed in 2D examination. **(B)** Increased intra- and peri-nodular vascularisation observed in 3D examination (same nodule).

code, ES 1–4; volumetric evaluation: capsule integrity and perinodular/intranodular vascularization.

As detailed in Table 1 we classified the nodules as low, intermediate and high-risk for malignancy.

Surgical Intervention

The surgeon of our team performed unilateral lobectomy or total thyroidectomy. The surgical treatment was recommended due to the presence of laterocervical level VI or III lymph nodes with noninflammatory observed on ultrasound associated to high-risk thyroidal nodules, in 34 cases, intermediate and positive FNAC result (Bethesda III, IV, V, and VI) in 109 cases, compression-only effects in 32 cases, functional autonomy (defined by suppressed TSH levels in the absence of thyroid hormone therapy) in 15 cases, rapid growth in 20 cases, cosmetic reasons in 17 cases, respectively, multinodularity associated with compression or autonomy in 34 cases.

Pathology Examination

Thyroid pathology specialists, in the Pathology Department, made the pathology diagnosis. Immunohistochemical evaluation, HBME, CH-19, K067 and TTF reactions were performed, if needed.

Statistical Analysis

Data were collected and analyzed using SPSS v.17 statistical software package (SPSS Inc, Chicago, IL, USA). Clinical and laboratory characteristics of the patients

were expressed as a mean, standard deviation (SD), median, and range. Prior to analysis, variables were tested for normality using the Shapiro–Wilk test for homogeneity of variances with Levene’s test. Sensitivity, specificity, positive and negative predictive values, and likelihood ratio were calculated for each risk category, using pathology reports as the golden standard. In cases with multinodular goiter, we used, in the statistical analysis, only the characteristics of the diagnostic nodule, the nodule considered as conclusive for the diagnosis in the pathology report.

Results

From the total of 261 analyzed patients, we analyzed 261 nodules. The final pathology diagnostic was: thyroid cancer in 57 cases (21.83%): papillary carcinoma 45 cases, follicular carcinoma 5 cases, Hurthle cell carcinoma 3 cases, 2 borderline malignancy cases and 2 medullary carcinoma patients.

The risk stratifications of the 261 evaluated thyroid nodules, according to different ultrasound characteristics, are presented in Table 2.

We used a stepwise evaluation of the nodules. After initial grayscale evaluations, when considering the elastographic and volumetric characteristics, we reassess the risk category. Risk upgrade was made in 9.19% of cases, from low to intermediate risk 4 cases and from intermediate to high risk, another 20 cases. Risk downgrade was made in 26.81% of cases, from intermediate to

Table 2 Low Intermediate and High-Risk Categories, According to the Conventional, Conventional + Elastography Respectively Conventional + Elastography + Volumetric Characteristics

Risk US Technique	Low Risk			Intermediate Risk			High Risk			Total Cases
	BN	CA	T	BN	CA	T	BN	CA	T	
US (no of cases)	100	6	106	93	20	113	11	31	42	261
US (%of cases)										100%
US +SE (No of cases)	165	3	168	33	9	42	6	45	51	261
US +SE (%of cases)										100%
US+SE+V (No of cases)	165	2	167	33	3	36	6	52	58	261
US+SE+V (%of cases)										100%

Abbreviations: BN, confirmed benignity (pathology report); CA, confirmed malignancy (pathology report); T, Total number of cases in the category, US, conventional ultrasound; SE, Real-Time Elastography; V, Volumetric Real-time three-dimensional ultrasound.

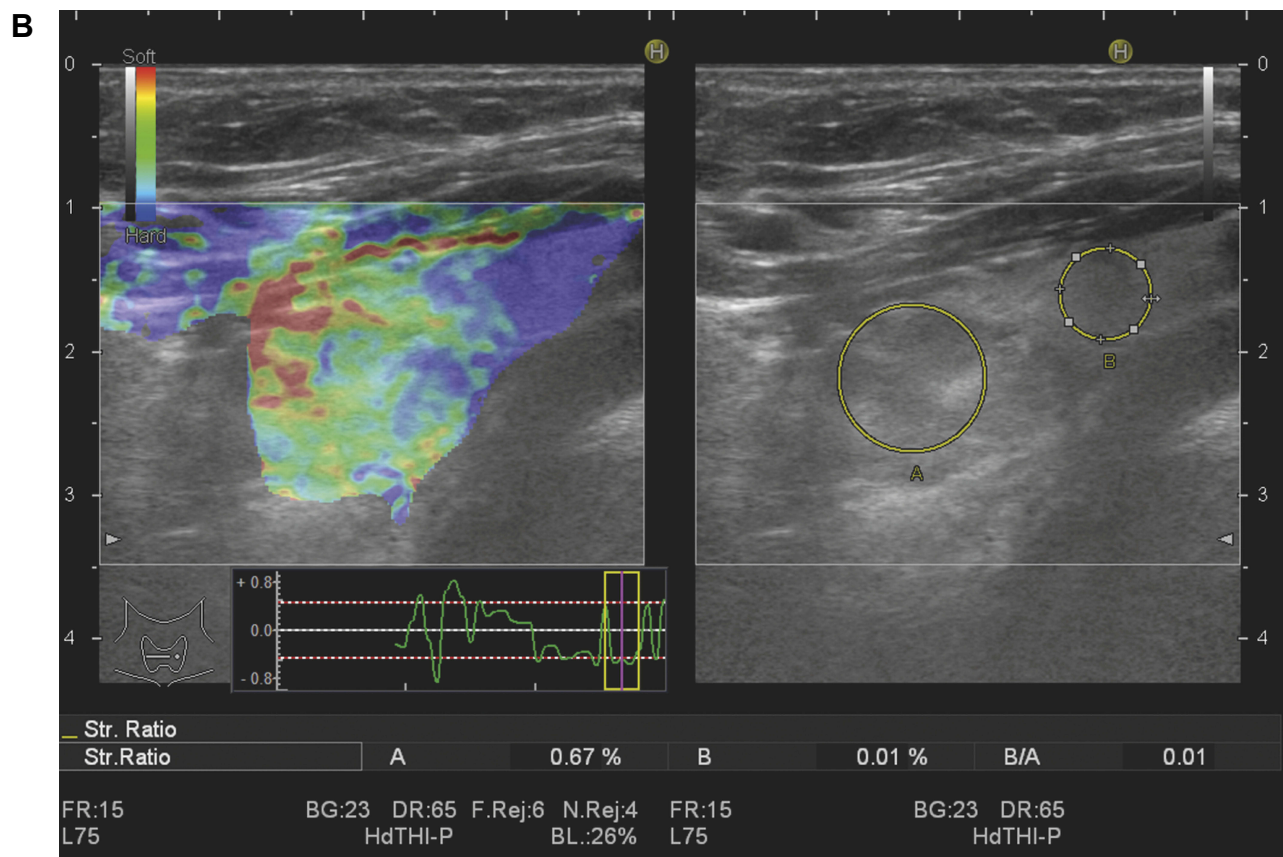
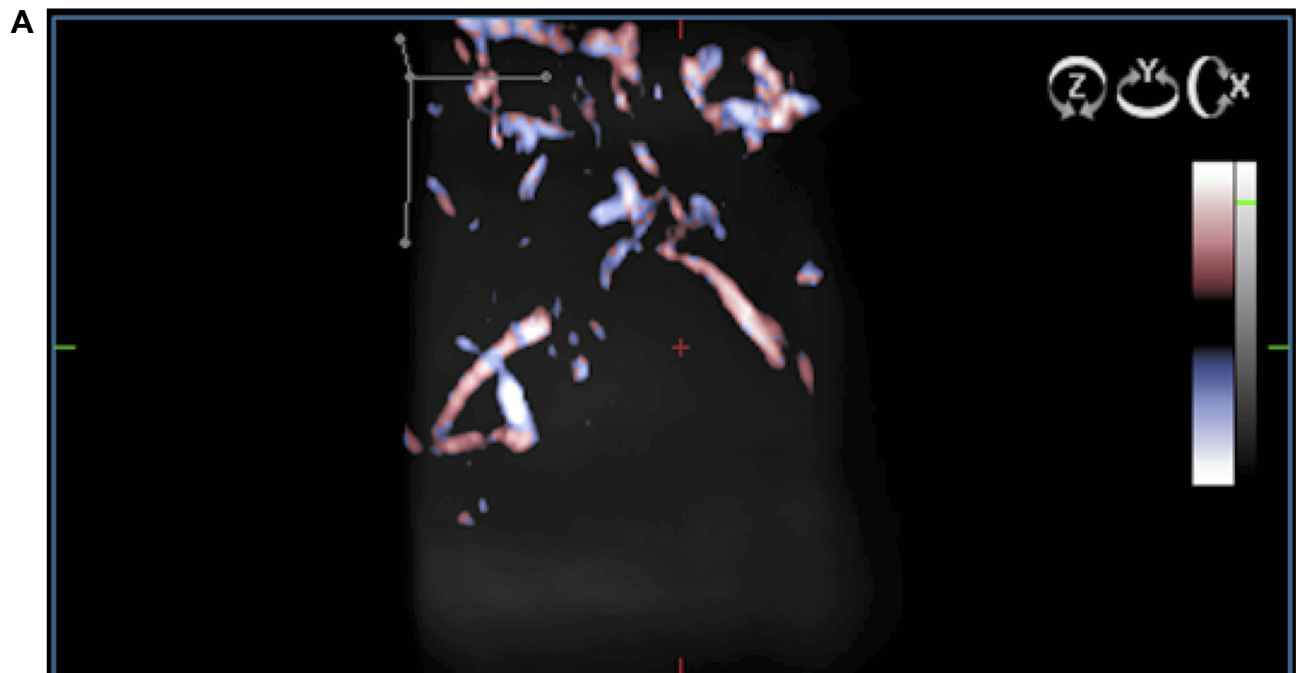


Figure 3 2B Intermediate risk nodule with normal volumetric aspect (**B**) and normal stiffness (**A**) (ES color map 1 and 2 code) is reconsidered as a low-risk lesion.

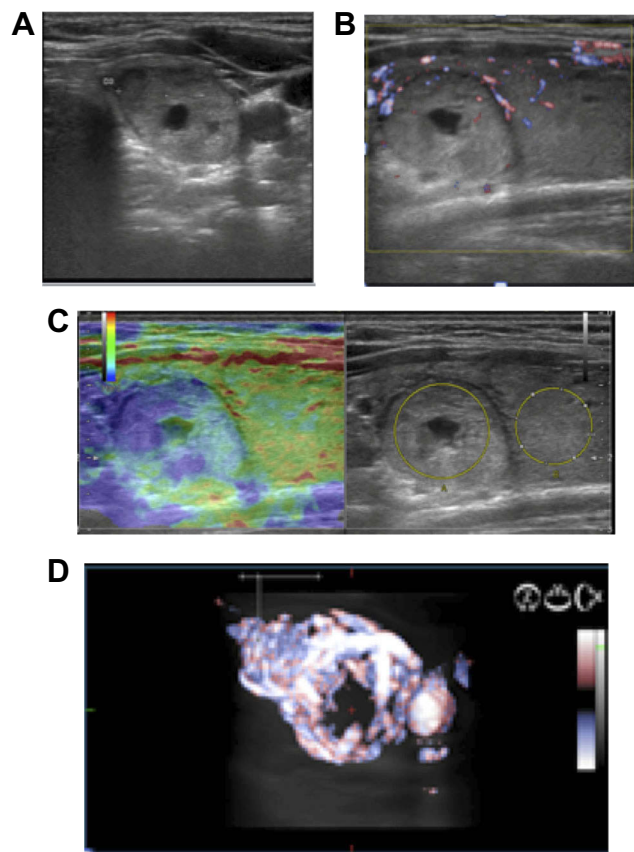


Figure 4 Low-risk nodules (A) with increased stiffness (B) and increased vascularization in volumetric evaluation (C) versus color Doppler (D) were reconsidered as intermediate risk lesions.

low risk in 65 cases, respectively, 5 cases where downgraded from the high-risk category.

Figure 3 presents a case of risk downgrade because of low stiffness and low vascularization in volumetric Doppler.

Figure 4 presents a case with a risk upgrade, from a low-grade lesion, because of an increased US stiffness and increased vascularization (volumetric evaluation). The same upgrade is described in Figure 5, but from an intermediate grade lesion, because of an increased US stiffness

and increased vascularization (volumetric evaluation). The risk upgrade was considered even in the presence of only one high-risk characteristic, increased volumetric vascularization, despite the normal stiffness and the intermediate-risk category, according to the conventional US characteristics, as seen in Figure 6.

We analyzed the sensibility, specificity and accuracy, in differentiating benign versus malignant lesions, of the conventional only US risk stratification, respectively, conventional + ES and volumetric Doppler characteristics. The results are presented in Table 3. We did consider low-risk nodules as a predictor for benign lesions. Since intermediate-risk category is a gray zone of predictive diagnostic, when evaluating the prediction of malignancy, we performed 2 separate analyses: considering just the high-risk nodules as suggestive for malignancy and considering intermediate and high-risk nodules suggestive for malignancy.

The diagnostic power of this modified risk stratification was also studied in respect to the size of the nodule. The sensitivity and specificity of low risk (suggestive for benign lesions) and intermediate + high-risk cases (suggestive for malignant lesions) for all types of ultrasound evaluations are listed according to the size of the nodules in Table 4. Sensibility, specificity and accuracy were considered in nodules lower than 2 cm, between 2 and 4 cm, respectively, higher than 4 cm in the highest diameter.

Discussions

In our study, we evaluated the combined integrated ultrasound model in the stratification risk thyroid nodules. We combined conventional ultrasound recommended parameters^{17-20,30} with high stiffness^{18,22,23} on elastography and alteration in the thyroid capsule integrity or increased intranodular vascularization observed on the real-time tri-dimensional technique.^{27,28}

Our study is emerging because of the general recommendation of diagnostic risk stratification, in order to reduce the

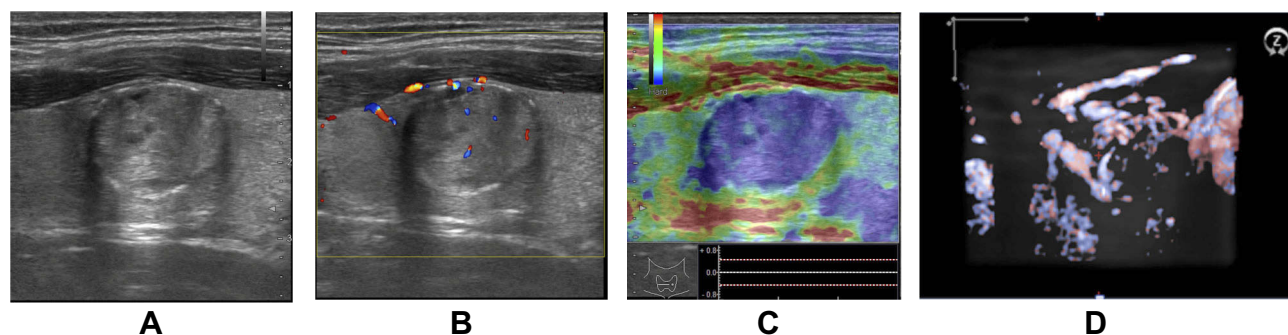


Figure 5 Intermediate risk case (A) with increased stiffness (C) was reconsidered as high risk, regardless of color Doppler (B) or volumetric aspect (D).

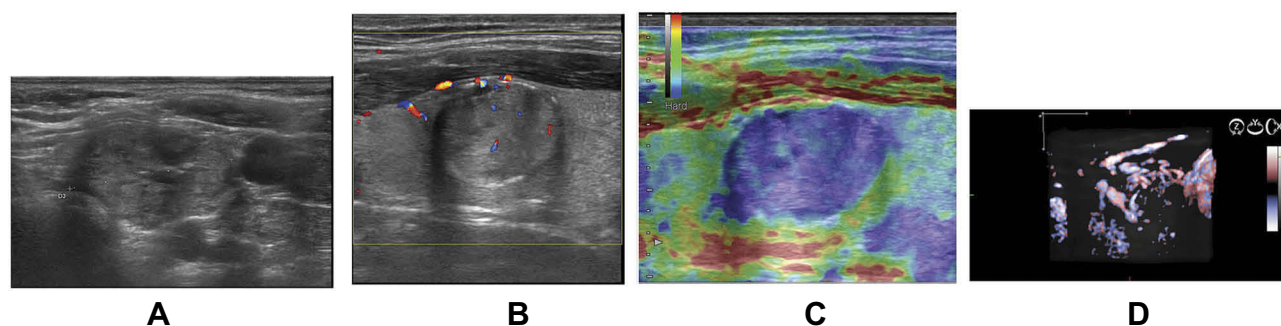


Figure 6 Intermediate risk case (A) was reconsidered as high risk, in the presence of high-risk volumetric characteristics (B) despite intermediate stiffness (C).

number of unnecessary FNAC and surgeries.^{17–19} An accurate presurgical diagnostic is mandatory for the surgeon, in order to choose the best surgical technique and to control de invasiveness of the surgery.^{31,32}

The results are convincing: better sensitivity, specificity and accuracy in combined models US+SE+V and US+SE better than US evaluation alone: increasing sensitivity in case of soft nodules, and soft nodules with no alteration in volumetric evaluation in detection of benign lesions: 49.01%-80.88%-80.88%, with an important increase also of the specificity when integrating information: 89.47%-94.7%-66.49%. Our results were similar to other integrated thyroid nodule models,²² describing a 98.8 positive predictive value for the combined ultrasound risk stratification model, meaning the rate of mistake equals 0.02, in the presence of benign

characteristics in all used ultrasound techniques (grayscale, elastography and volumetric evaluation).

The calculated risk for malignancy was different for the 3 used models, with a lower malignancy risk in the low-risk category in the 2B+RTE+volumetric model (1.19%) versus 5.6% in the conventional 2 B model, borderline risk in the intermediate group (8.33% versus 17.69%), with a suggestive risk in the high-risk group (89.65% versus 73.80%). The results are explained by downgrading the risk category, using mainly the elastography details. The same combined approach was used by other authors, with better stratification results^{33,34} due to the decrease of false-positive results. Higher stiffness increased the risk.^{17,18,34} The increase in sensitivity is consistent, independent of the nodule size. Even if combined diagnostic quality seems better in small nodules, the improvement of the multimodal ultrasound is observed regardless of the nodular size. In the literature, the results regarding nodular size impact on ultrasound diagnostic qualities are still controversial: some report the TIRADS is better in small size nodules (<1 cm) and ATA criteria better in nodules bigger than 2 cm.³⁵ Others do state than there is no difference in US risk patterns in nodules bigger or smaller than 3 cm,³⁶ although there is a slightly higher malignancy risk in nodules smaller than 2 cm.³⁶ Also, in nodules with a high suspicion US pattern, there was no significant association between the malignancy risk and nodule size.³⁶ Other studies do show an increase in the malignancy risk as the size of the nodule increases^{37–40} with the threshold of 2 cm³⁷ or of 3–4 cm^{39,40} predictive for malignancy, but others described the opposite, with differences regarding the size.^{41,42}

The impact of the size might be associated with the histological type of cancer, since PTC do show high-risk ultrasound characteristics and non-PTC cancer show intermediate to low risk characteristics.³⁶ In our study, the 2 B model classified 27/

Table 3 Comparison of Diagnostic Quality (Sensitivity, Specificity, Accuracy) for Risk Category Assessment by Means of US Only, US +SE and US+SE+V Models

Risk Category by Ultrasound Evaluation	Correct Diagnostic	Se (%)	Sp (%)	Acc (%)
Low Risk				
US	100/204	49.01	89.47	57.85
US+SE	165/204	80.88	94.70	83.90
US+SE+V	165/204	80.88	96.49	84.29
High Risk				
US	31/57	54.38	94.60	90.03
US+SE	45/57	78.94	97.05	93.10
US+SE+V	52/57	91.22	97.05	98.08
Intermediate + High Risk				
US	51/57	91.71	49.01	57.85
US+SE	54/57	94.73	80.88	83.90
US+SE+V	55/57	96.43	80.88	91.18

Note: Final pathology report 204 benign cases, 57 malignant cases.

Abbreviations: Se, sensitivity; Sp, specificity; Acc, accuracy; SE, Real-Time Elastography; V, Volumetric Real-time three-dimensional ultrasound.

Table 4 Diagnostic Values of Different Risk Stratification Models According to the Nodule Diameter

Diameter		< 2 cm		2–4 cm		> 4 cm		T
Cases (No)		158		69		34		261
CA (No)		26		24		7		57
CA (%)		16.45%		34.7%		20.56		21.83
Technique		Se (%)	Sp (%)	Se (%)	Sp (%)	Se (%)	Sp (%)	
US	L	59.09	96.15	26.66	79.16	37.03	100	
	I+H	57.69	99.24	50.00	84.44	57.14	74.01	
US+SE	L	94.96	96.5	51.11	91.66	45.94	100	
	I+H	80.76	99.24	79.16	95.55	71.40	88.8	
US+SE+V	L	94.6	96.5	51.11	95.88	45.94	100	
	I+H	92.30	99.24	91.66	95.55	85.71	88.80	

Abbreviations: CA, Cancer; Se, sensitivity; Sp, specificity; SE, Real-Time Elastography; V, Volumetric Real-time three-dimensional ultrasound; T, Total number of cases, L – Low, I, Intermediate, H, High.

45 PTC (58.69%) as high risk and 16/45 (28.07%) as intermediate risk, compared with the complex combined model that considered 44/45 PTC (97.77%) as high-risk lesions.

All 3 Hurthle cell carcinomas were considered as high risk, both in the simple and complex ultrasound model. In the group of FTC cases, the 2 B model considered only 3 cases low risk (60%) and 2 cases intermediate risk (40%), compared with the complex model that assigned 1 case as a high risk (20%), with the others as a low and intermediate risk. Even this complex model is nonperforming in the imagistic diagnostic of FTCs because of low stiffness observed in FTC.⁴³

Because of the great discrepancy of cases in the intermediary risk category, between 5% and 80%^{22,44–46} and because of the decrease in specificity, as seen in Table 3, we did consider only low risk as a clear indicator for benignancy and high risk as a consistent indicator for malignancy.

Volumetric evaluation did not increase the number of the correct classified benign nodules (164/204) benign; in high-risk nodules, volumetric evaluation did add further identified cases.

Using this stratification, the overall sensitivity of the combined method was higher using RTE added information (80.88% versus 49.01%) or RTE + 4D information (80.88% versus 49.01%) with an increase also in specificity, better for added V+SE versus SE only extra information (91.22–78.44 compared with 54.38%).

The retrospective analysis of the study group suggests that in the presence of complex low-risk characteristics, the cancer probability is very low. Nonperforming FNAC in these cases

would have overlooked 2 cancer cases (3.5%). The intermediate-risk category remains the gray zone of thyroid ultrasound evaluation – no general recommendations can be made for this special category.

In our study, we observed that using elastography and the volumetric information increased stiffness or thyroid capsule rupture, did upgrade the risk category in the high-risk class. Observation of low stiffness can decrease the risk category of the nodule. This risk reassignment did decrease the intermediary risk category by 68.14%. Similar approaches are described for RTE^{29,30,33} or volumetric²⁷ alone. Accordingly, publications using combined conventional, strain elastography and volumetric Doppler evaluation are few in the literature.

There are several limitations to our study. The number of cases smaller than 2 cm, and higher than 2 cm or 4 cm is not equal. The size distribution in our study group does not necessarily overlap the distribution in the general population, so a clear conclusion of the cancer prevalence according to size cannot be made in our cohort. Populational studies are needed in order to answer the question about nodule size prevalence. The costs of volumetric evaluations can be limited if using pre-existing compatible ultrasound platforms. We could not evaluate the economic ratio of cost benefits, of the method, considering the ultrasound machine cost versus the hospitalization cost for each identified and treated thyroid cancer case. To our knowledge, we are the first to incorporate volumetric evaluation besides elastography and conventional ultrasonography, in a risk stratification model for

thyroid evaluation: increased intranodular vascular branching, alteration of the capsule integrity and high stiffness in elastography do upgrade the risk category.

Conclusion

Our proposed risk stratification model, not described before, combines elastographic results and volumetric Doppler characteristics with conventional grayscale characteristics. The model adds diagnostic value in the preoperative evaluation of thyroid nodules. Reevaluating the risk category does reduce the intermediate-risk case. In cases with a low risk, in all US used techniques, FNAC can be avoided, regardless of the nodule size. The proposed stepwise US+SE+V evaluation, with a reconsideration of the risk category, increases the diagnostic confidence of solid thyroid nodules.

Abbreviations

2B, conventional ultrasound; RTE, real-time elastography; V, volumetric Doppler; Se, Sensitivity; Sp, Specificity; Acc, Accuracy; FNAC, Fine-needle aspiration cytology; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma.

Author Contributions

DS, IS and VI performed the process of patients' diagnostic and evaluation. IM conceived the study and performed the statistical analysis, while DN_a and DN_e participated in the design of the study and helped to draft the manuscript. VF performed the surgeries. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Funding

“This research was funded by a research grant: grant number: SMIS 45997/21.01.2014- “Cresterea calitatii actului medical prin valorificarea potentialului IT” funder: Guvernul Romaniei, Ministerul Comunicatiilor si societatii informatiionale, axa POS CCE.

Disclosure

The authors report no conflicts of interest in this work.

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