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PhD THESIS

THE ROLE OF ELASTOGRAPHY METHODS IN PREDICTING MALIGNANCY IN THYROID NODULES

A B S T R A C T

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GENERAL PART

The prevalence of nodular goiter is increasing, being highly dependent on the method of screening. Thyroid cancer prevalence is also rising, but it still remains one of the cancers with relatively low risk of death. The increase is in direct relation with an improved imaging ability to early detect very small lesions, but also with a real increase in the incidence of thyroid malignancies. The clinical challenge resides in establishing an accurate diagnosis in order to correctly identify cases that need referral to surgery versus active follow up, respectively to select the moment of fine-needle aspiration (FNA) biopsy.

High resolution US represents the first line morphological evaluation for thyroid disease in general, and for thyroid nodules in particular. Its role in differentiating cancerous nodules from non-malignant ones is crucial. Good diagnostic accuracies were described for classifications that associate multiple US criteria of high risk, describing the concept of the thyroid imaging reporting and data systems (TI-RADS). Newer technologies, such as elastography and three-dimensional (3D) Color Doppler may improve the diagnostic performance of US. Strain elastography (SE), as well as shear wave elastography (SWE), have demonstrated good outcomes in predicting the malignancy risk of thyroid nodules, considering increased stiffness, as a criterion of suspicion, which so far brought superior results for SE.

FNA represents the next step in evaluating suspicious lesions, selected according to the risk stratification evaluation by anamnestic, clinical and especially US characteristics, therefore risk stratification is one of the main topics in the world of thyroidology. Its main limitation refers to indeterminate cytology (according to Bethesda classification: categories III and IV), which represents the so-called grey area of the FNA results and need further investigation in order to clarify the final attitude.

SPECIFIC PART

1. GENERAL OBJECTIVES

In the context of up to 50% prevalence of thyroid nodules in US-screened populations, the correct identification of those that are at risk of malignancy represents the clinical priority. The present thesis is composed of multiple studies that are gradually and consecutively meant to reach the final scope: ***to assess the best imaging method for describing thyroid lesions and predicting the malignancy risk.***

Our research objectives were:

1. To evaluate the need of a complete and precise US evaluation of all thyroid nodules in order to provide a better selection of nodules that truly have surgical indication;
2. To identify the performance of the most commonly used risk-stratification scores (TI-RADS);
3. To assess the impact of additional US applications as parameters in the TI-RADS;
4. To investigate whether the general findings regarding the use of elastography in the evaluation of thyroid nodules also apply to the subgroup of indeterminate cytology (Bethesda III and IV);
5. To evaluate which type of elastography, SE or SWE, performs better in the evaluation of thyroid nodules.

2. PREAMBLE: THE PRESURGICAL STRATIFICATION OF THYROID NODULES - IS IT REALLY NEEDED?

2.1. AIMS OF THE RESEARCH

Minimizing unneeded thyroid surgeries could have a positive impact on hospitalization costs, but also on surgical complications and iatrogenic hypothyroidism. The objective of the present study was to retrospectively assess the number of cases which had a complete clinical and imaging thyroid evaluation and to estimate the need for precise presurgical risk stratification, in order to reduce the number of unneeded surgeries.

2.2. MATERIALS AND METHODS

Subjects and data collection

This study was performed retrospectively and consisted of an analysis of 1036 thyroid surgeries: unilateral lobectomies, total thyroidectomies and also redo surgeries for completion thyroidectomy. The surgical interventions were performed on adult patients, between January 1st 2018 and December 31st 2019 (two years) and represented all thyroid interventions performed in this period in the three Departments of Surgery (1st, 2nd and 3rd Surgery Clinic) from Timisoara County Hospital "Pius Brinzeu", Romania, incorporating more than 120 beds. The 9 redo interventions were performed due to malignant pathology report findings or recurrence of nodular goiter following initial lobectomy. For the final number of 1027 operated subjects, the patient information was collected retrospectively from the hospital records and included personal history, the clinical diagnosis, the laboratory evaluation confirming the surgical indication, the extent of the surgical intervention and the details from the pathology report. The majority of patients were females: 928 (90.36%) and only 99 were males (9.64%), with a mean age of 53.8 ± 13 years.

Analysis of the surgical indication and final diagnosis

The presurgical diagnosis was established by various clinicians in Western Romania, who performed more or less the specific investigations. Data from the US evaluation was not available in all cases, thus only the admission diagnosis was considered for comparison with the final pathology report.

2.3. RESULTS

The vast diagnosis of nodular goiter was assigned pre-surgery in 674 (65%) of the patients. A prior FNA biopsy was present in only 121 (18%) of the analyzed cases. The pathology report showed 689 (67%) benign findings, 299 (29%) thyroid cancers and 39 (4%) borderline lesions (non-invasive follicular thyroid neoplasm with papillary-like features: NIFTP). A higher prevalence of thyroid malignancy was noticed in men. In the female group, young women showed a lower prevalence of cancer compared to older ones. The distribution of cancers included an important percentage of papillary (133; 39%) and micropapillary (140; 41%) thyroid cancers; borderline cancers were well-represented (39; 12%), but only 8 follicular thyroid cancers, 4 medullary cancers, 2 anaplastic thyroid cancers and 2 thyroid lymphomas were detected.

Regarding the indication for the extent of surgery, in the lobectomy group 22.8% of the cases were cancers, while 65% of the total thyroidectomies proved to be benign. Discordances between the clinical diagnosis and the pathology report were detected in 475 of the cases (46.2%).

2.4. DISCUSSIONS

Studies reporting thyroidectomies performed in some European countries show similar results to ours in terms of overtreatment and suboptimal presurgical evaluation, although presurgical ultrasound evaluation and risk stratification show excellent accuracy for US methods. A postoperative diagnosis of cancer was established in only 17% of the cases operated in one year in France. In a very large cohort from Germany with benign goiter, a clear overtreatment was found in cases that underwent surgery for the exclusion of

malignancy, only 12.2% having prior FNA. In our analysis, out of the total 892 cases with NG, only 218 (24.4%) presented a well-defined indication for surgery, counting compression, suspect/malignant cytology result or hyperthyroidism. In 110 cases, the pathology report showed that chronic autoimmune thyroiditis (CAT) was misdiagnosed, clinically or on US evaluation, as nodular goiter. Establishing the appropriate extent of surgery from the beginning is attributed to the clinician's priorities. Undoubtedly, the lobectomies in our group of study exceeded guideline indications (unilateral nodule and proven benign FNA cytology, or isolated micropapillary carcinoma with low-risk US characteristics). Cancer was detected in 41/180 (22.8%) lobectomy cases, which led to redo surgery in 18 high-risk/multifocal lesions in the lobectomy group, cases that could have benefitted from initial total thyroidectomy with a correct preoperative assessment.

2.5. CONCLUSIONS

In our group, it was estimated that surgery could have been avoided, with correct presurgical risk stratification algorithms, in up to 46% (473/1027) of the cases. Nevertheless, the important percentage of detected thyroid cancers supports the current radical surgical attitude, given the lack of uniform and precise presurgical diagnosis.

3. STUDY I: THE DIAGNOSTIC PERFORMANCE OF STRAIN ELASTOGRAPHY AND 4D DOPPLER AS ADDITIONAL PARAMETERS TO THE TI-RADS

3.1. AIMS OF THE RESEARCH

Our research aimed to compare four important TI-RADS, as well as to evaluate the contribution of elastography and of real-time 3D Color Doppler assessment of vascularity in estimating the risk of malignancy. We also investigated the performance of stratification scores that include these parameters.

3.2. MATERIALS AND METHODS

Subjects and data collection

The study was a prospective study conducted on 133 thyroid nodules evaluated in the US department of "Dr. D" Medical Center Timisoara, between January 2017 and May 2018. The inclusion criteria comprised all the cases with mostly or completely solid thyroid nodules that were evaluated in the US department in the inclusion period and had a complete US report with conventional US, SE and 2D SWE, and a pathology report completed by May 2018.

US evaluations

The US evaluations were performed in all cases using a Hitachi Preirus, a linear multifrequency probe (5–18 MHz) and a linear volumetric probe (5–13 MHz) (B-mode US, strain elastography and volumetric Color Doppler assessment) on 314 nodules; 133 of them had a pathology report and were finally included in the study. A comprehensive characterization of the US appearance of all nodules was made and the presence of US-detectable lymph nodes was also noted. The nodules were classified using four different scoring systems: the European (EU) TI-RADS, the 2016 American College of Radiology (ACR) TI-RADS, the Horvath TI-RADS and the French TI-RADS and results were compared with the golden standard for diagnosis: the histopathological record.

The qualitative SE evaluation was performed in all patients based on the color-map-acquired images translated into the 4-category Asteria score and the semi-quantitative evaluation represented by the strain ratio (SR). The features of interest of the 3D Doppler images included the integrity of the capsule (altered or intact) and vascularization inside the

nodule (increased or normal). Lesions with moderate to high perinodular vascularization were considered in our study as criteria suggestive of malignancy. We proposed an algorithm for the US classification of thyroid nodules, based on B-mode (2B) US, elastography and volumetric Color Doppler evaluations, adapted from the French TI-RADS, and we compared its performance with the four above-mentioned TI-RADSs.

3.3. RESULTS

The analysis of the pathology reports showed thyroid cancer (including borderline tumors) in 26.3% of the cases. Significant differences were detected between the benign and malignant group in terms of the SR ($p < 0.0001$), which was the most prevalent US risk feature in the group of histology confirmed cancers. The EU- and ACR TI-RADS, with overall similar results (accuracy of 42.8% and 45.8%), generated a great number of high-risk lesions. Horvath TI-RADS had an improved overall accuracy (66.9%, AUROC 0.75). The French TI-RADS (2B+SE) sorted more appropriately the nodules (accuracy 84.9%, AUROC 0.907). Thyroid cancer was described in 88.1% of the category-5 nodules. Our algorithm (2B+SE+4D) generated a slight improvement for the calculated risk, increasing sensitivity, but decreasing the accuracy (80.4%; AUROC 0.913). Good positive correlations were found between the predictor variables: elastography (SR), volumetric Doppler and the French score (0.505, 0.650, 0.553) and the histopathological exam. Consecutively, the binomial logistic linear regression was employed and the only variable which was a very good predictor was the SR ($p < 0.001$). The “taller-than-wide” shape was a good predictor of malignancy ($p = 0.12$). A generalized relation between our improved score (2B+SE+3D) and the histopathology report revealed very good performance ($p < 0.001$) with similar results for the French TIRADS ($p < 0.001$).

3.4. DISCUSSIONS

The number of current ultrasound assessment scores is considerable, as clinical research intends to improve the current strategies. We included in the study the ones that are more often employed in our region. Our results were good for all systems. Our team found the Horvath model more complicated to apply, as described also by other authors. While the expected risk of the highly-suspicious category was higher than 80%, we determined a calculated risk of only 55.17%. The EU-TIRADS was the most simply-structured and time-efficient algorithm, with similar calculated risk to the expected risk, but considerably wide risk intervals. Good sensitivity (97.14%) was reported, but a great number of false negatives, with modest specificity (23.46%) and NPV (31.19%). The ACR TI-RADS demonstrated comparable diagnostic quality. Based on our statistical analysis, it can be confirmed that SR is a significant predictor for thyroid cancer, both independently and as part of a combined algorithm of US evaluation. Our innovative approach included 3D Doppler vascularity in the score; the parameter showed very good performance, but its inclusion in the score did not significantly improve the risk-assessment strategy. Out of the five algorithms included in our comparison, the French TI-RADS performed the best in terms of diagnostic quality.

3.5. CONCLUSIONS

All imaging scoring systems performed well in detecting high-risk nodules, thus clinicians should select the one they understand and feel comfortable to use in everyday practice in supporting the therapeutical decision. Although elastography is currently not largely used in the US evaluation of thyroid nodules, our results support that it represents the most beneficial additional tool to the classic US evaluation and encourage its use, when it is available. 3D Doppler was also a performing predictor of thyroid cancer, but a definite conclusion concerning its use in detecting malignancy cannot be drawn yet. Advanced US techniques definitely add valuable information to the classic grayscale evaluation of thyroid nodules and do improve the current algorithms.

4. STUDY II: THE VALUE OF ELASTOGRAPHY AND VOLUMETRIC DOPPLER IN THE DIAGNOSIS OF INDETERMINATE CYTOLOGY CASES

4.1. AIMS OF THE RESEARCH

The final evaluation recommended in diagnosing thyroid nodules is FNA, but indeterminate cytology (Bethesda categories III and IV) is observed in about 15%–25% of the results and has divergent recommendations: follow-up or surgery. The aim of the present research is to investigate the benefit of multimodal US evaluation in clarifying the management approach in this cytology category.

4.2. MATERIALS AND METHODS

Subjects and US evaluation

This prospective study was performed between January and December 2019 in the US Unit of “Dr. D” Medical Center, Timisoara, Romania. FNA was performed in 218 selected patients with solid thyroid nodules; indeterminate results were detected in 64 of them, which were included in the study analysis. Prior to FNA, all nodules were evaluated using combined advanced US technologies: conventional US, SE and 3D Doppler, conducted as described in Chapter 3.

4.3. RESULTS

Thyroid cancer was identified in 16 of the cases (25%), mostly papillary carcinomas (15/16) and 5 cases (7.8%) were classified as borderline neoplasia (NIFTPs). B-mode US evaluation had an accuracy of 64%, qualitative SE had an accuracy of 82.81% and the combination of the two had 85.9% accuracy. Most cancers (16/21) displayed increased stiffness. 3D Doppler showed an accuracy of 84.3% in detecting thyroid cancer. The vast majority of malignant nodules showed important 3D vascularization pattern (15/21). The best accuracy (90.2%) was determined for the score including all three US evaluations.

4.4. DISCUSSIONS

Our results confirm the great value that SE brings to the risk assessment, even when considered on its own. 3D Doppler is also useful when available. Moreover, both assessments show very good NPV (92.68% and 82.85%, respectively), reconfirming and endorsing the recommendation of active follow-up in cases with Bethesda III and IV FNA cytology with low-risk US pattern, as outlined in previous research studies.

4.5. CONCLUSIONS

Our results suggest that incorporating SE and volumetric Doppler information alongside the classical sonographic features in the risk evaluation of intermediate cytology cases adds diagnostic confidence and narrows the number of unclear cases, with respect to treatment recommendations. Highly suspicious US features identified in B-mode US, in qualitative SE, and/or in 3D Doppler assessment do increase the risk of malignancy.

5. STUDY III: THE VALUE OF 2D SWE EVALUATION IN THE RISK ASSESSMENT OF THYROID NODULES AND IN COMPARISON TO SE

5.1. AIMS OF THE RESEARCH

The results of the preceding studies reconfirmed the evidence offered by SE in detecting high-risk thyroid nodules. Nevertheless, SWE techniques still need to gain confidence in thyroid imaging. The main objective of this study was to evaluate the diagnostic value of SWE and to provide a head-to-head comparison of SE and 2D-SWE techniques in predicting the risk of malignancy of thyroid nodules.

5.2. MATERIALS AND METHODS

Subjects and US evaluation

This prospective study included 437 consecutive patients with mostly solid thyroid nodules evaluated by means of US, between the 1st June and the 31st December 2020. FNA was indicated in 115 patients and in 90 of them it was performed and analyzed during the enrollment period.

Conventional US of the neck, followed by elastography examination with 2 different techniques: SE and 2D-SWE, were performed in all patients, in a maximum interval of 6 weeks (before FNA). The US evaluation and SE were performed on a Hitachi machine, as described in Chapter 3. The 2D-SWE evaluation was performed in all cases on an Aixplorer Mach 30 machine (SuperSonic Imagine) using a high-resolution linear US probe (5–18 MHz). The mean of the 5 measurements was considered in the analysis for the mean (Mean SWE) and maximum (Max SWE) elasticity index (kPa) and the nodule-to-parenchyma Q-Box ratio was determined.

5.3. RESULTS

FNA was performed in all 94 nodules, 58 of which were consecutively treated surgically (42 FNA results included in Bethesda categories III-VI and 14 due to compressive symptoms). Out of the 94 focal lesions, 29 proved to be malignant. All malignancies in our study group were differentiated variants. Significant differences were identified between the median values of benign and malignant nodules in all five parameters quantifying tissue elasticity: the Mean SWE, Max SWE, the Q-Box ratio, the qualitative SE evaluation (Asteria score) and the strain ratio.

2D SWE in the evaluation of the Malignancy Risk of Thyroid Nodules

The SWE parameters performed as follows: for an optimal cut-off value >30.5 kPa, the Mean SWE predicts malignancy with a sensitivity of 79.3%, specificity of 95.38%, NPV of 91.2% and PPV of 88.5% (AUROC: 0.912); for the Max SWE, a value above 40.3 kPa has sensitivity of 86.2% and specificity of 81.5% (AUROC 0.877); for a cut-off value of 2.8, the Q-Box ratio also represents a good parameter, with very good specificity of 92.3% (AUROC 0.851) in detecting thyroid malignancy. The algorithm we proposed in this study (TIRADS+SWE), had a sensitivity of 79.3%, specificity of 76.9% and AUROC of 0.816, compared to similar sensitivity but lower specificity and AUROC of 0.610 obtained in the study for the ACR TIRADS.

A head-to-head comparison of elastography techniques: SE versus 2D SWE in diagnosing thyroid nodules

The SE parameters also showed very good diagnostic performance. The SR performed somewhat better: for a cut-off value of >3.9 it predicts the disease with a sensitivity of 82.7%, specificity of 92.3%, AUROC=0.905. Following the main aim of this research, elastography parameters were compared. For the comparison of the two methods, we included the parameters that tested best for each type of evaluation: the Mean SWE for SWE and the SR for SE. The two parameters are comparable in terms of diagnostic accuracy (90.4% for Mean SWE versus 89.3% for the strain ratio) and both proved excellent

results in terms of ROC curve statistics (AUROC 0.912 for Mean SWE and 0.905 for SR). Five thyroid cancers were missed by SE and six malignancies by the SWE evaluation. SE generated five false positives and SWE, three.

5.4. DISCUSSIONS

Most of the literature data provide a comparison between SE and SWE in different populations. This study intended to detect any discrepancies between the diagnostic potential of the two methods and any significant differences between the two types of evaluation, by providing a consecutive evaluation of both methods, in the same population. Meta-analyses that compared the methods revealed similar diagnostic quality for SE and SWE in differentiating malignant and benign thyroid nodules, slightly superior for SE, but evaluations were performed in different populations and results in smaller studies usually reveal comparable results for the two methods. Moreover, as the elastography evaluation of thyroid nodules is not standardized yet, it should be acknowledged that when comparing two or more studies using the same method, the protocols that were used might slightly differ.

Our findings are encouraging for both techniques. Although SWE tested slightly better, the differences were not statistically significant in terms of the AUROC: 0.912 for the Mean SWE and 0.905 for SR ($p=0.0952$). A considerable advantage of SWE refers to its superiority when it comes to the evaluation of nodules that coexist with autoimmune thyroid disease, while SE is described to have lower feasibility in this setting. Our team described that nodules in the proximity of the trachea, particularly located on the isthmus, associate more artifacts on the SWE evaluation. For this location, SE seems to perform better. The experience of the operator is essential for both methods, particularly in the case of strain elastography. The strength of this study regards the comparison of the two main elastography techniques in the same population. Our findings showed strong agreement between SE and SWE evaluation. A considerable limitation of this study was that most of the malignant nodules were PTCs, thus the differences in SWE parameters between different malignancies could not be estimated.

5.5. CONCLUSIONS

By providing a head-to-head evaluation of the two methods, our study confirms that both elastography techniques have excellent diagnostic quality with similar overall results, slightly better for SWE. They both do improve the diagnostic confidence of thyroid US imaging, providing an accurate selection of the nodules for FNA.

FINAL CONCLUSIONS

1. The Presurgical Stratification of Thyroid Nodules - Is It Really Needed?

The results we obtained demonstrate that it is imperative to perform a complete and multidisciplinary presurgical evaluation in all cases of thyroid nodules, in order to identify and select more precisely the cases that truly benefit from FNA or thyroid surgery and to determine from the start which type of surgery favors every patient individually: total thyroidectomy or lobectomy. The final goal is to minimize hospital costs, reduce the number of reoperations, have fewer postsurgical potential complications and avoid the surgeries that are unnecessary.

2. Strain Elastography and 3D Doppler as Additional Tools to the TI-RADS

Our results reconfirm that all imaging classifications provide good selection for the nodules that are at risk; still, they can be improved. SE essentially improved the risk-stratification scores in the present study. Increased stiffness was detected in 80% of the

malignant nodules and in only 12% of the benign. Our results confirm the significant additional value that strain elastography measurements bring, supporting its inclusion in the standard evaluation, when it is available. 3D Doppler also revealed very good predictions of malignancy. We designed an innovative US score including both SE and 3D Doppler, which showed an overall accuracy similar to the French score (US + SE).

3. The Value of Elastography and 3D Doppler in Indeterminate Thyroid Cytology

Given the excellent results of elastography and 3D Doppler in diagnosing thyroid malignancy, we confirmed their role also in the particular category of indeterminate cytology. Our results demonstrate that adding volumetric Doppler and elasticity information alongside the conventional sonographic characteristics enhances diagnostic confidence in the evaluation of indeterminate cytology cases and narrows down the number of uncertain cases, with respect to the recommendations of treatment.

4. SWE Evaluation in the Risk Stratification of Thyroid Nodules

Our investigation confirms excellent diagnostic value also for 2D-SWE in detecting high risk TN. A cut-off value of 30.5 kPa for the employed technique predicts malignancy with very good accuracy. When integrated in a combined US score, SWE substantially boosts the diagnostic performance and the algorithm specificity, compared to standard US risk-stratification.

5. Comparison of Elastography Methods: Strain versus 2D Shear-Wave Elastography Evaluation in the Risk Assessment of Thyroid Nodules

Our results reassess the power of both SE and 2D SWE elastography techniques in enhancing the diagnostic performance of classic US, by providing a pertinent, head-to-head comparison of the two techniques. They both displayed excellent diagnostic quality, in particular when considering the Mean value in the case of 2D SWE and the SR for SE. The diagnostic value was overall similar for both methods, slightly better for SWE.

In conclusion, our research demonstrated that, regardless of the technique, elastography is a promising instrument for the assessment of thyroid nodules and the detection of thyroid malignancy. It does improve the diagnostic confidence in thyroid imaging and helps achieve the final objective: an accurate selection of the nodules that are at risk and need further management from the ones that are at low risk and benefit from follow-up and decreasing the number of unnecessary FNAs and surgeries.