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Original research

Conventional ultrasound integrated with elastosonography and B-flow imaging in the diagnosis of thyroid nodular lesions

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ABSTRACT

The purpose of this study was to evaluate the sonographic features of thyroid nodules suspicious for malignancy with standard examination in B-mode and Color Doppler associated with modern techniques such as ultrasound RTE (Real Time Elastosonography) and BFI (B-flow imaging) in correlation with the results of the sonographically guided fine-needle aspiration to establish their role in predicting the risk of malignancy.

Between November 2012 and January 2014, 354 consecutive patients (age range, 18–73 years; mean age ± SD, 41.2 ± 9.2 years; 90 male and 264 female) with 493 suspected nodules (maximum diameter > 9 mm) were enrolled in this prospective study.

Sonographic, elastosonographic and BFI examinations were performed with a commercially available real-time ultrasound system, and all patients also underwent a cytologic evaluation. Patients with suspicious or malignant cytologic features underwent surgery.

On histologic examination, 71 of 493 nodules were malignant (62 papillary thyroid carcinoma, 1 Hürthle cell carcinoma, and 8 follicular carcinoma). All sonographic characteristics, which were potential predictors of thyroid malignancy (microcalcifications, hypoechogenicity, absence of a halo, and a predominantly solid composition), were found in different percentages in both histologically verified malignant and benign nodules. For BFI, pattern 3 (≥4 signs and distance > 2 mm) was the most predictive factor for malignancy (specificity, 99.6%; sensitivity, 65.2%), whereas pattern 2 (≥4 signs and distance < 2 mm) was a positive factor because it was detected only in benign lesions. For the RTE, scores 1–2 were detected in 68% of benign nodules, while scores 3–4 in 94% of malignant nodules.

Our results indicate that Elastosonography and BFI can overcome the limits of the traditional B-mode and color Doppler sonographic features in the diagnosis of thyroid nodules. This techniques provides maximum specificity levels both in the case of benign nodules and in the case of malignant nodules.

1. Introduction

Thyroid nodules are the most common endocrine cancer, affecting more than 50% of women over 50 years of age. Screening studies based on general population identify clinically palpable nodules in approximately 5% of adults, while ultrasound and autopsy studies have demonstrated nodules in more than 50% of women and 20% of men over the age of 50, [1]. Thyroid cancer, which usually presents as a nodule, is increasing in incidence faster than any other cancer, however, it is thought that this increase is due to an improvement in the incidence of technical study of the thyroid as well as the use of screening policies on population [2]. However, only less than 5% of all nodules identified, regardless of their size, both by palpation is discovered purely incidental, direct the investigation appears malicious.

The primary challenge in the evaluation of thyroid nodules is reliably identify the majority of benign nodules that do not require, therefore, surgical removal, avoiding the risk of not identifying malignant nodules (or pre – malignant) and thus losing the possibility of a treatment early surgical effectively also because

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standard chemotherapies have systemic toxicities and limited efficacy in the case of thyroid cancer as well as of other more common solid tumors [3].

The number of FNA procedures continues to grow at a rapid pace and may be partly responsible for the increasing incidence of cancer diagnosis [4–8]. With the increasing use of imaging technologies that identify thyroid nodules, including the use of ultrasound as screening tool in the general population, the cost and morbidity of the evaluation of thyroid nodules is likely to become a problem for the public health expenditure, therefore, a convenient and effective strategy for the evaluation of these nodules is an important objective for current and future applications in clinical practice [9–12].

For the study of nodular thyroid disease recourse is the use of ultrasound, not only understood as a morphological study in B-mode, in which we evaluate the structural characteristics of nodulation, but also with the use of new techniques such as ultrasound Color Doppler, for the evaluation of the vascularity of the B-flow imaging, which as we will see below is able to give us important information on the nature of the nodule, and finally with the use of recent elastosonography. The integrated ultrasound examination, then, will, once identified a nodule, to tell if that nodulation can be considered benign, suspicious for malignancy or frankly malignant. However, beyond this end, ultrasound also has the role of responding to the questions of the surgeon who later proceed to intervention, we must determine whether the individual is suspected of nodulation or less, the characteristics of malignancy, but the seat even if there is an involvement of lymph nodes, stations latero- cervical superficial and deep, because this element must be to affect the type and extent of surgery.

2. Methods

Between November 2012 and January 2014, 354 consecutive patients (age range, 18–73 years; mean age ± SD, 41.2 ± 9.2 years; 90 male and 264 female) with 493 suspected nodules (maximum diameter >9 mm) were enrolled in this prospective study. The patients' main characteristics were palpable and nonpalpable thyroid nodules.

After the sonographic examinations, we selected 343 patients with 493 suspected nodules to execute an FNA cytologic evaluation according to selection criteria of the 2005 ultrasound consensus conference statement of the Society of Radiologists in Ultrasound [14]. Thyroid hormone serum levels, thyroid-stimulating hormone levels, and calcitonin levels were normal in all patients. The study was conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients. Methods Sonographic, Color Doppler (CD), and BFI examinations were performed with a LOGIQ 9 system (GE Healthcare, Chalfont St Giles, England), a commercially available real-time sonography system, equipped with 5- to 14-MHz (M12L) and 2.5- to 7-MHz (7L) linear array transducers. All examinations were performed by 2 blinded radiologists separately, and all data analysis was performed by another investigator. When results of the examiners were discordant, agreement was found by a conjoint review of clips from the sonographic examinations.

The following sonographic characteristics were recorded for each nodule: size, parenchymal composition, echogenicity, presence or absence of a halo, margin characteristics, and presence or absence of microcalcifications. As to the size, 3 orthogonal dimensions were measured. The echogenicity of each nodule was determined by comparing the solid portion of the nodule to the surrounding thyroid parenchyma. Echogenicity was rated as hyperechoic when more echogenic, isoechoic when similar, or hypoechoic when less echogenic than the thyroid tissue [6]. Hyperechoic spots (calcifications or colloidal crystals) were assessed by taking into account the surrounding thyroid tissue. [5],14 In this study, CFD analysis was performed at 7.5 MHz (M12L) and 6 MHz (7L) to evaluate the presence of marked intranodular blood flow.15 B-flow imaging was performed at 10 MHz (M12L) and 7 MHz (7L) with the BFI capability at the level of the nodule. The pulse repetition interval was set at 3. The BFI gain was not fixed and was adjusted to allow better visualization of the signs. This technique focuses on high flow with suppression of the tissue signal. B-flow images were used to evaluate the presence, appearance, intensity, and distribution of the signs (grouped or scattered within the nodule).

For the classification, the single scan in which the greatest number of signs was visible was selected, and quantification of signs was assessed for each scan. In case of 4 or more signs, the minimum distance among them was measured. The distances were manually measured with the cursor on the image with the highest number of twinkling signs. The sign distribution in a single scan (the maximum number of signs inside the nodule evaluated in a single scan) followed 4 patterns, which were classified as follows: pattern 0, absence of signs; pattern 1, fewer than 4 signs; pattern 2, 4 or more signs and a distance of less than 2 mm; and pattern 3, 4 or more signs and a distance of greater than 2 mm.

Later was carried out the study elastosonography of suspicious nodules. Elastosonography is a technique that evaluates the degree of compressibility of a tissue, and then evaluates mechanical properties of tissues. The deformation of the structures was achieved with the mechanical compression given by the probe. During the exam, the system calculates the levels of tissue deformation and displays them as green and gray on the side of the image. The bar indicates an appropriate (green) or inadequate (gray) tissue deformation in order to obtain a good quality of elastosonographic evaluation. The display mode “dual” allows you to view the elastosonographic image and the corresponding B-mode image, at the same time. In our experience, the box of interest is selected to include the nodule and part of the surrounding parenchyma; sampling was carried out before entering a region of interest (ROI) on the nodule in question and a second ROI above the adjacent parenchyma. In our study, the images obtained were classified into four scales of stiffness to decrease the degree of elasticity:

- 1: nodule evenly colored in light green.
- 2: the central part of the nodule in the periphery in green and blue.
- 3: nodule colored with a mixture of green and red.
- 4: nodule completely colored in blue.

Nodules with a score of 1 and 2 were classified as probably benign nodules while scoring 3 and 4 as probably malignant. This classification was compared with the cytological diagnosis in order to evaluate the sensitivity and specificity of the RTE. In addition to evaluation based on the color, the value of ratio distortion (SR; M1/M2) was quantified for each nodule, SR was calculated by the average value of stiffness measured in ROI − 1 corresponding to the nodule and indicated by M1 and average value for the ROI 2, located at the level of the surrounding parenchyma and indicated with M2. A value of SR C 3:28 was considered indicative of malignancy.

The same ultrasound techniques were then applied to the study of the lateral cervical lymph node stations to assess and describe the lymph node involvement in cases of thyroid malignancy. Even in this case after a morphological evaluation based on the structural characteristics of the lymph node and that is: the round shape (ratio of short axis to long axis of >0.5), the absence of hyperechoic hilum, abnormal echogenicity, presence of calcifications, the variation in sense of cystic and/or abnormal vascularity, with loss of hilar vascularity, Color Doppler evaluation, we passed the evaluation in B-flow where they were evaluated in the same way the presence or absence of signals, indicative of the presence of microcalcifications lymph node that correlate with metastatic papillary thyroid carcinoma and finally was also associated with the elastosonographic evaluation lymph nodes whose degree of rigidity, evaluated against adiposity surrounding, elastosonography classified into four categories.

After the sonographic features were assessed, patients underwent a cytologic evaluation, and findings were recorded by a radiologist. Sonographically guided FNA was simultaneously performed by two radiologists. The physicians were extremely experienced in performance of sonographically guided FNA with 27- and 22-gauge needles; the technique used has been described in the literature. Three or 4 smears were prepared; the first was air dried and immediately stained with Diff-Quik (Baxter Scientific, McGraw Park, IL), which is a May-Grünwald-Giemsa modified stain that allows staining of smears in less than 1 min. The other smears were fixed in absolute alcohol for a subsequent Papanicolaou test or immunostains The Diff-Quik smears were immediately evaluated by a cytopathologist to assess the adequacy of the samples. Inadequate smears were immediately repeated. Cytologically benign cases were enrolled for a clinical and sonographic follow-up to control the dimensions and sonographic features of the nodules. Patients with suspicious or malignant cytologic features underwent surgery with an additional intraoperative frozen section examination, which confirmed the cytologic diagnosis. To improve accuracy levels, cytospray fixation of frozen intraoperative sections was used, and comparative observation of cytologic imprints was performed. All of the patients underwent a total thyroidectomy with cervical node exploration. Ipsilateral central neck lymph node dissection was performed in patients with suspicious nodal enlargement. Removal of lateral neck nodes was performed in cases of confirmed nodal metastases at the frozen section examination. Surgical samples were cut before fixation for macroscopic examination. Histologic evaluation was performed on multiple 5-mm slices of the whole thyroid gland to estimate the tumor dimensions and to rule out malignant and multifocal lesions. Specimens were then routinely processed; tumors were diagnosed and staged on the basis of their size, nodal involvement, and distant metastasis (TNM) according to the current classification criteria. A statistical evaluation was performed with the χ^2 test and the predictivity test.

After, we examined for preoperative sonographic evaluation with gray-scale ultrasonography (US), color Doppler US, BFI-TS and elastosonography. 157 patients with suspicious metastatic cervical LN at US examination underwent FNAB for cytology and thyroglobulin determination in the aspirate fluid. Only 109 patients (38 men, 71 women; mean age 54 years range, 25–77 years) with at least one metastatic LN were included in our study. All these patients underwent surgery, and the final diagnosis was based on the results of histologic examination of the resected specimens.

3. Results

The specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) of the different sonographic features of malignancy are summarized in Table 1. The following sonographic features were taken into account: absence of a halo or irregular margins, microcalcifications, hypoechogenicity, and intranodular vascularization (Table 1).

Among each single sonographic pattern, the presence of microcalcifications was the most predictive factor of malignancy (Table 1; $P < .001$; specificity, 96%; sensitivity, 35%). Absent halo signs or irregular margins were found in 31 of 71 malignant lesions and also in 118 of 422 benign nodules (not statistically significant). Hypoechogenicity was found in 46 of 71 malignant lesions and in 203 of 422 benign nodules (not statistically significant). Intranodular color Doppler flow CFD was also one of the most predictive factors of malignancy (Table 1; $P < .001$; specificity, 80%; sensitivity, 57%). B-Flow Imaging Evaluation Pattern 3 was the most predictive factor of malignancy ($P < .001$; specificity, 99%; sensitivity, 66%; PPV, 95%; NPV, 91%). On histologic evaluation, 45 of 47 nodules (96%) showing this pattern resulted in PTC, whereas 2 of 47 nodules (4%) resulted in benign lesions. When present, pattern 2 was a positive factor because it was detected only in benign lesions, with a PPV of 0. Pattern 1 was present in 6 of 71 tumors and in 50 of 422 benign lesions (not statistically significant). Pattern 0 had low sensitivity (26%) and specificity (48%). Fifty-one of 62 PTC nodules were positive for the BFI twinkling sign; 46 showed pattern 3, and 5 were characterized as pattern 1. Only 11 of 62 PTC nodules did not show the sign (pattern 0). The other 9 malignant nodules with pattern 0 showed different histologic types .

Table 1
Sensitivity, Specificity of US standard.

	Specificity (%)	Sensitivity (%)	PPV (%)	NPV (%)
Irregular margins or absence of halo	73	43	21	87
Microcalcifications	96	35	52	91
Hypoechogenicity	53	64	17	90
Intranodular color Doppler flow	80	57	31	92

Elastosonography with evaluation of the color map yielded the following:

Scores 1–2 were detected in 68% of benign nodules, while scores 3–4 in 94% of malignant nodules. The distribution of the SS (stiffness score) according to the cytological categories of diagnosis. SS values were higher in nodules with a diagnosis of malignancy than in benign nodules. The qualitative RTE analysis based on the SS had a 94% sensitivity, 68% specificity, 32% PPV (Table 2).

A total of 773 LNs were analyzed. Of these, 341 were metastatic while the remaining 432 were benign, as evaluated by histopathology. The diagnostic performance of each ultrasound finding evaluated in this study is shown in Table. Most ultrasound features had high specificity and positive predictive value (PPV) but low sensitivity and negative predictive value (NPV). The sonographic characteristic with high specificity and sensitivity were the BFI-TS and elastosonography. The BFI-TS was positive in all LNs with microcalcifications at US examination (121 LNs) and in 192 LNs (all metastatic) in which microcalcifications were not evident at US. Two LNs positive at the BFI-TS and with calcifications at US was found to be a tuberculous nodes after treatment with intranodal macrocalcifications at histological examination. Strain index greater than 1.5 was the best criterion in discrimination of metastatic lymph nodes with 98.5% specificity, 84% sensitivity, and 93% accuracy. We used a 5-pattern color scoring system based on distribution and percentage of stiff areas in the cervical lymph nodes. The elastosonographic cut-off line for reactive versus metastatic lymph nodes was set between patterns 2 and 3 while patterns 3–5 were considered metastatic.

Table 2
Sensitivity, Specificity and PPV in detecting malignant nodules.

	Sensitivity (%)	Specificity (%)	PPV (%)
US	75	94	94
FNAB	98	28	59
B-Flow (pattern 3)	99	66	95
RTE	94	68	32

Sensitivity, specificity and accuracy of B-mode sonography were 98%, 59% and 84% respectively; 83%, 100% and 89% for elastosonography; and 92%, 94% and 93% for the combined evaluation. The integrated use of elastosonography, B-flow and gray-scale sonography has the potential to improve the diagnosis of metastatic enlarged cervical lymph nodes.

4. Discussion

The prevalence of nodular thyroid disease, detectable by ultrasound, is estimated at around 50%. However, only about 5% of the nodules reveal malignant cyto histological diagnosis [11]. Therefore, the differential diagnosis of nodules is crucial to allow the early diagnosis of cancers and ensure appropriate treatment. In thyroid cancer, there is no hint of a remodeling of the Ca^{2+} toolkit, that has been observed in other malignancies, including renal cellular carcinoma [13,14], and prostate cancer [15], mielofibrosis [16], and has been put forward as alternative target for selective molecular therapies.

Currently, thyroid ultrasound is the first-line examination for the identification and follow-up of nodules since it makes it possible to formulate a suspicion of malignancy and select the nodules to be subjected to FNAC [1,17–19]. Cytological evaluation is considered the most accurate diagnostic technique. However, it has two limitations: nondiagnostic results due to inadequate cytology sampling and the presence of follicular proliferation or Hartle cells. FNAC is also reserved for nodules with a maximum diameter exceeding 10 mm. Smaller nodules are not subjected to FNAC unless they show suspicious ultrasonographic features and flow. In the case of follicular proliferation or in the presence of Hartle cells, cytology does not differentiate adenoma from carcinoma, as the differential diagnosis is based on the presence of capsular or vascular invasion, which can only be evaluated histologically after thyroidectomy [20–23]. B-flow and elastosonography allows for noninvasive, real-time tissue characterization which provides additional information to B-mode and power Doppler ultrasound. Although sonographic and Doppler features are the criteria taken into consideration for FNAC performance and allow an accurate identification and follow-up of thyroid nodules, they do not contribute significantly to their characterization, which requires cytological evaluation. On this basis, our study compared the information provided by B-flow and RTE in addiction at ultrasound with the cytological diagnosis achieved by FNAC in on a cohort of patients with a sonographic diagnosis of thyroid nodules [24–27]. RTE technique made it possible to evaluate the mechanical–elastic properties of tissues, and in particular the stiffness of the nodules analyzed. Stiffness was analyzed in terms of color map (SS) and by comparison with the stiffness of the surrounding healthy parenchyma, by calculating the deformation ratio (SR). The results obtained proved to be superior to those of conventional ultrasound. It should be emphasized that Score 1 was found in benign lesions only, with 98% NPV. This finding, if confirmed in a larger study, may exclude immediate recourse to FNAC, which would be reserved for nodules showing a change in size or morphology over time. With regard to the calculation of the SR, the significant values reported in recent studies were not reached [28,29] in discriminating benign from malignant forms. In agreement with the research published to date, our study confirmed that the benefits of RTE are many:

- it is easy to perform, fast, accurate and reproducible;
- it provides a qualitative assessment of tissue elasticity in real time;
- it provides a semiquantitative evaluation of the SR;
- it increases the sensitivity, specificity and NPV of conventional ultrasound in the diagnosis of thyroid cancer;
- it can potentially help to select patients requiring invasive diagnosis, thus lowering the costs for further investigations.

Fine punctuate calcifications on sonography are generally accepted as the most reliable indicators of malignancy because they are related to PBs on microscopy.

Psammoma bodies are microcalcified concentric laminated structures commonly found in neoplasms such as meningioma, papillary carcinoma of the ovary, and PTC [24,25]. The coalescence of a number of PBs determines the formation of larger calcifications [24,25]. Psammoma bodies represent the remnants of necrotic papillae; their diagnostic value [26,27] is greater if they are localized within the cores of papillae and not in the neoplastic follicles [26,30]. Up to now, the BFI technique has been used to evaluate carotid artery stenosis and other vessel diseases [31,32]; our study showed the importance of using this technique also during sonographic diagnosis of thyroid nodules. Among echographic parameters, BFI twinkling sign pattern 3 had the highest degree of sensitivity and specificity in the diagnosis of PTC; its PPV (96%) was considerably higher than that of other B-mode and CFD features. The most recent consensus statement by the Society of Radiologists in Ultrasound stated that the presence of microcalcifications within the nodule raises the likelihood of malignancy, showing the highest specificity but very low sensitivity [14]. In agreement with the literature, our study showed that, in comparison to conventional sonographic and CFD features, the sonographic detection of microcalcifications and PBs had the highest specificity level (95%) in the diagnosis of thyroid cancer but low sensitivity (36%). The low sensitivity of B-mode sonography for detection of microcalcifications and PBs is due to its limited resolution power in relation to the PB dimensions. The sensitivity of BFI twinkling sign pattern 3 for detection of PBs was considerably higher than that of B-mode imaging (65% versus 36%). Taking into account PTC only, whose main characteristic is the presence of PBs, the sensitivity was even higher (73%). In our opinion, pattern 3 does not reach 100% sensitivity levels for diagnosis of PTC for the following reasons: (1) some PTC nodules have no PBs (or their number is extremely limited); and (2) PBs go through a phase in which the calcium component is poor or completely absent. The BFI twinkling sign might lead to identification of PB groupings whose dimensions are considerably lower than those identified by the B-mode sonography. In our opinion, these results were achieved by means of total inactivation of the 2-dimensional signal, which allowed a relative increase of the signal produced by the aggregation of small PBs. Because of the rough interface of sparse reflectors, PBs might cause an irregular refraction of the ultrasound beam, simulating movement, as well as a twinkling sign, which originates from urinary stones in the color Doppler mode [30,33,34]. When compared to a B-mode examination, specificity levels increase slightly (99% versus 95%), due to the fact that the BFI twinkling sign allows discrimination between the hyperechoic spots produced by microcalcifications and the ones produced by other factors (colloidal crystals without the typical comet tail and multiple tissue or vascular interfaces). In our study, only 1 case proved to be positive for the BFI twinkling sign with pattern 3 and to have negative FNA cytologic evaluation results. A follow-up will be conducted for the following reasons: (1) a sampling mistake during FNA cytologic evaluation might have taken place; and (2) microcarcinoma might have developed on a benign nodule. In an analysis of our results, of 144 nodules with BFI twinkling sign pattern 2, none was PTC or non-PTC cancer (PPV = 0). We think that in these cases, the sign was produced by the crystallized colloid, which with its multiple interfaces, might have produced multiple twinkling signs very close to each other. Our hypothesis was supported by detection of abundant colloid on the FNA cytologic evaluation in 83% of the nodules. If these results are confirmed, pattern 2 might be considered a clear sign of benignity in the analyzed lesions. In conclusion, our data support the use of the BFI technique as well as the characterization of different twinkling sign patterns for accurate evaluation of thyroid nodules. This technique increases the sensitivity, specificity, PPV, and NPV levels but up to now has been used only for evaluation of vascular structures; therefore, its potentialities need to be clearly established. Further longitudinal studies are necessary to confirm our results for detection of thyroid carcinoma. The BFI sign will play a key role in diagnosis and in the standardization of sonographic examinations of thyroid nodules, providing maximum specificity levels both in the case of benign nodules with pattern 2 and in the case of malignant nodules with pattern 3. We think that this new technique can overcome the limits of traditional diagnostic sonography, for which research has primarily focused on B-mode and color Doppler parameters, which do not have a high degree of sensitivity and specificity at the same time.

For the study of cervical lymph nodes neck US is highly sensitive for the diagnosis of metastatic LNs. The specificity reported varies from 85% to 90% [35]. A variety of diagnostic criteria have been reported to be useful for the distinction between benign and metastatic LNs. Lymph node shape has been used as a diagnostic criterion of metastatic LNs. Metastatic lymph nodes often appeared as round lesions, whereas benign nodes are usually flat or oval [36]. In the present study, LN shape had an excellent specificity (90.8%) but low sensitivity (52%). Initial or partial metastatic LN involvement does not result in an alteration of the shape. Of note, LNs of the parotid and submandibular regions are often round in normal individuals [37]. The presence of a hyperechoic hilum of the nodes is usually considered a strong diagnostic criterion for benign LNs [38]. It has been reported that 84%–92% of benign nodes but less than 5% of metastatic nodes have a hyperechoic hilum [39]. The absence of a fatty hilum is often seen in normal individuals, especially in young subjects and in LNs located in level V [40]. In our study, metastatic LNs with visible hilum and partial involvement were at I–II level, whereas the LN metastases at low level showed in 99.5% the absence of hyperechoic hilum. The absence of the hilum had high sensitivity (91.9%) but low specificity (58.8%). Differently, abnormal LN echogenicity had both high sensitivity and specificity (resp., 81.9% and 85%). In our experience, echogenicity was normal in 54 metastatic LNs (18%). Calcification was a specific sign but not sensitive criterion. Calcification in metastatic LNs is characteristic of PTC but generally rare. In our study, nodal calcifications were detected in only 93 of the 298 metastatic LNs. Similarly, cystic appearance had a very high specificity (100%) and a low sensitivity (21.1%). All LNs with hyperechoic punctuations or a cystic appearance in a patient with PTC should be considered as malignant. Assessment of nodal vascularity at color Doppler US is another diagnostic criterion for metastatic LNs. It has been noted that benign LNs tend to show hilar vascularity or to appear avascular. In contrast, metastatic nodes tend to have peripheral or mixed (both peripheral and hilar) vascularity. In our study, color Doppler US vascularity had intermediate specificity (68.6%) but low sensitivity (47.6%).These findings could reflect the high differentiation of PTC and the reduced tendency to neoangiogenesis.

The BFI-TS had a higher specificity and sensitivity (resp.,99.7% and 80.9%) than conventional US features. Given its high specificity (99.7%), BFI-TS identifies better suspicious LNs that should be reevaluated by surgery or US-guided FNAC. Therefore, the presence of BFI in addition to conventional US increases the diagnostic specificity for suspicious LNs. The techniques have several limits; namely, they can be affected by the pulsatility of the main neck vessel and by the deep places of examined LNs. These limits could explain the missed detection of 57 LNs (19%) that were metastatic at histological examination. The other limit is the presence of nonmetastatic LN calcifications; in fact, the BFI-TS was false-positive only in one LN with calcifications deriving from tuberculosis. Overall, our results indicate that this technique can be applied to studies of cervical nodes in patients with PTC and that its sensitivity and specificity is higher than those of traditional US diagnostic techniques.

Ethical approval

Ethical approval was requested and obtained from the “Azienda Universitaria SUN” ethical committee.

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Author contribution

Alfonso Reginelli: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also partecipated substantially in the drafting and editing of the manuscript.

Fabrizio Urraro: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also partecipated substantially in the drafting and co-editing of the manuscript.

Graziella Di Grezia: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Giuseppina Napolitano: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Nicola Maggialetti: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Salvatore Cappabianca: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Luca Brunese: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also partecipated substantially editing of the manuscript.

Ettore Squillaci: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Conflicts of interest

All Authors have no conflict of interests.

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