



Research Article

Estimation of the Fractal Dimension of Thyroid Nodules as a Complementary Diagnostic Tool for Predicting Malignancy

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Abstract

Rationale and objectives

Ultrasound-guided fine-needle aspiration is the most sensitive investigation procedure in the evaluation of patients with thyroid nodules; however, despite the level of

achieved precision, it is still impossible to preoperatively discriminate between follicular adenomas and carcinomas. Thus, no current detection tool of thyroid nodule has both high sensitivity and high positive predictive value for the diagnosis of thyroid cancer. Ultrasound images provide

information that are currently missed due to visual interpretation, including the roughness of the echotexture. However, such information can be retrieved using the measurement of the fractal dimension (FD).

Materials and methods

This retrospective study was approved by the ethic committee of CHU Charleroi. According to the box-counting method, we measured the FD of the echotexture of ultrasound images of 13 benign thyroid nodules and 14 malignant thyroid nodules compared to normal thyroid tissue from 10 men and 16 women (mean age 40).

Results

The difference of the FD value between malignant nodules (median FD 2.31) and corresponding normal tissues (median FD 2.184) was significant ($p < 0.001$) while the FD values for the benign nodules (median FD 2.21) and for corresponding normal tissues (median FD 2.231) could not be distinguished ($p = 0.78$).

Conclusion

This preliminary work revealed that FD would be an additional feature to discriminate benign from malignant nodules. A larger sampling is now required to confirm the possible utilization of FD in the thyroid cancer diagnosis in clinical practice.

Keywords: Cancer; Fractal dimension; Image analysis; Thyroid nodules; Ultrasonography

1. Introduction

Thyroid cancer remains rare but its incidence increased due to the better detection of small papillary cancers [1]. Thus,

Ultrasound (US) imaging of the thyroid is increasingly performed and can detect nodules as small as 0.2 cm [2]. Sonographic features for discriminating benign and malignant nodules have been extensively studied but no single parameter satisfactorily identifies the subset of patients which diagnosis requires the Fine-Needle Aspiration Biopsy (FNAB) [3]. The Thyroid Imaging Reporting and Data System (TIRADS) is a standardized tool designed to avoid unnecessary FNAB [4]. The TIRADS implements a large number of US patterns (echogenicity, echostructure, shape, borders, calcifications, vascularization) to improve the clinical power of US to discriminate nodules. However even with such standardization, the inter-individual variability among radiologists and the use of different US devices impairs the reproducibility of the conclusions [5,6]. Similarly, ultrasound elastography which analyses the stiffness of the nodules could discriminate malignant from benign lesions but this technique requires an additional procedure and lacks reproducibility [7]. Papillary and follicular thyroid carcinomas are well-differentiated thyroid carcinomas and represent about 95% of all thyroid cancers. While US discrimination between benign and malign nodules has been reported in the case of papillary carcinoma, the sonographic features of follicular adenoma and follicular carcinoma are very similar and as a consequence, follicular carcinoma diagnosis using US is still challenging [8].

Fractal analysis has already many applications in the field of medicine; one of them is the analysis of anatomic structures such as vascular or bronchial trees [9] or the haemodynamic effects of several types of diseases [10,11]. A fractal structure is characterized by a Fractal Dimension (FD) allowing for a quantitative assessment of parameters such as heterogeneity, irregularity or complexity. Several

image analysis techniques have been published in order to characterize pathological tissues such as abnormal liver tissue or endobronchial nodes [12,13]. Hereby, we computed the FD of ultrasound images in order to determine if differences between normal tissue, benign and malignant thyroid nodules could be evidenced. The image requirements to draw accurate results are also investigated.

2. Material and Methods

2.1. Clinical data

All US thyroid images were retrospectively reviewed with approval of the ethic committee from CHU Charleroi (OM008) under Eudract B325201526259. As a retrospective study, there was no need to obtain informed consent. US examinations were performed by 4 different experienced radiologists, using Siemens ACUSON Antares, Philips iU22 and Philips EPIQ 5G ultrasound systems, with 5 to 12 MHz multifrequency probes. The images corresponded to 2 group of patients. The first group of 13 patients with thyroid follicular carcinoma underwent a total thyroidectomy at the CHU Vésale from July 2009 to September 2013 (Table 1). There were 7 females and 6 males; the median age was 39.6 (from 10 to 69 years) and 1 patient had 2 malignant nodules. FNAB was performed in 10 cases but cancer was never diagnosed preoperatively. Definitive histopathology was reviewed by one experienced endocrine pathologist. The second group of 11 patients underwent a thyroid lobectomy for a single benign unilateral nodule between November 2010 and July 2014 (Table 2). There were 8 females and 3 males; the median age was 41.2 (from 17 to 54 years). Two supplementary benign nodules were identified in the contralateral lobe of the thyroid of 2 patients from the first group operated for

malignant nodule (patients n° 1 and 4, see Table 1). FNAB was performed preoperatively for the 11 single nodules.

2.2. Image analyses

Original native images, issued from the database, were recorded in Tagged Image File Format (TIFF). Due to technical limitations of Matlab algorithms, images were converted to JPEG format with minimum compression. Sizes of all images are displayed in table 2. When multiple images were available, selection was performed as follow. Images where the zone of interest was partly masked by annotations were excluded. The image showing the largest view of the zone of interest was selected for further analysis. The algorithm used for the measure of the FD (see Supplemental Material) was based on the Matlab software programming language and the Image Processing Toolbox (<http://nl.mathworks.com/>). The original image was converted to gray-scale and cropped to restrict the analysis to the relevant zone. The FD was calculated using the box-counting method (14): the principle is to cover an image J with a grid whose mesh size is hereby name r , to count the number N of boxes which are covering the object and repeat the calculation by shrinking the size (r) of the boxes. The FD of an image is defined as $D = \lim_{r \rightarrow 0} \log(Nr) / \log(1/r)$. The image normalization to 256 gray levels determined the “height” of the image, seen as a fractal embedded in a 3D space (Figure 1). The quantity Nr is thus the number of boxes needed to cover such a fractal surface.

Patient	Sex	Age	Size of nodule (mm)	US characteristics	FNA	Histology	pTN	Image size in pixel (LxH)		Fractal dimension	
					B*	**		Normal	Malignant	Normal	Malignant
								tissue image	nodule image	tissue image	nodule image
1	F	42	9	Hypoechogenous, irregular,	NC	FMI	pT1aNx	18928	11662	2.2121	2.3138
				microcalcifications				(112x169)	(119x98)		
2	M	69	30	Hypoechogenous, peripheral and central	FP	FMI	pT2Nx	47872	21546	2.1374	2.3354
				vascularization				(272x176)	(189x114)		
3	M	50	40	Hypoechogenous, heterogeneous,	FP	FMI	pT2Nx	17914	63054	2.1729	2.2693
				microcalcifications				(169x106)	(226x279)		
4	M	46	20	Solid, hypervascularization	NA	FMI	pT2Nx	13578	15125	2.2312	2.5543
								(146x93)	(121x125)		
5	M	43	45	Hypoechogenous, heterogeneous,	FP	FMI	pT3Nx	17423 (133x131)	64240 (292x220)	2.1654	2.4343
				calcifications, peripheral and central vascularization							
6	F	37	13	Hypoechogenous, regular, peripheral	FP	FMI	pT1Nx	21777	12519	2.3309	2.3515
				vascularization				(183x119)	(117x107)		
7	F	34	20	Heterogeneous, hypervascularization	NA	FMI	pT2Nx	19043	34138	2.07	2.2561
								(139x137)	(202x169)		
8	F	10	30	Hypoechogenous, regular, peripheral	FP	FMI	pT2Nx	10416	24570	2.1951	2.3913
				vascularization				(112x93)	(195x126)		
9	F	36	15	Hypoechogenous, heterogeneous,	FP	PFP	pT1bNx	13231	10670	2.0884	2.233
				peripheral and central vascularization				(131x101)	(110x97)		

10	F	30	30	Hypoechoogenous, heterogeneous, calcifications, peripheral and central	FP	FMI	pT2Nx	22446 (258x87)	37000 (200x185)	2.2539	2.2602
				vascularization							
11	F	14	20	Hyperechogenous, central	C	PFP	pT2Nx	13365	14868	2.1168	2.3065
				vascularization							
				Isoechoogenous, irregular, peripheral				(135x99)	(126x118)		
			9	vascularization	C	PFP		13365	28305		2.1512
								(135x99)	(185x153)		
12	M	64	40	Hypoechoogenous, heterogeneous, peripheral and central	NA	FC	pT3Nx	12610	103488	2.245	2.3356
				vascularization				(130x97)	(336x308)		
13	M	40	20	Hypoechoogenous, peripheral and central	NA	FMI	pT1Nx	15876	11770	2.2326	2.2704
				vascularization				(189x84)	(110x107)		
<p>*NC, not conclusive; FP, Follicular proliferation; NA, Not applicable; C, Colloid</p> <p>**FMI, Follicular minimal invasive; PFP, Papillary with follicular presentation; FC, Follicular carcinoma</p>											

Table 1: Clinical data and corresponding image information (malignant nodule group).

Patient	Sex	Age	Size of nodule (mm)	US characteristics	FNA	Histology	Image size in pixel (LxH)		Fractal dimension	
					B *	*	Normal	Malignant	Normal	Benign
							tissue image	nodule image	tissue image	nodule image
1	F	42	13	Hypoechogenous, peripheral	NA	B	18928	18414	2.2121	2.2097
				vascularization			(112x169)	(186x99)		
4	M	46	20	Necrotic	NA	CD	13578	10340	2.2312	2.3643
							(146x93)	(110x96)		
14	F	17	30	Heterogeneous, necrosis	C	FA	16383	23973	2.103	2.162
							(129x127)	(183x131)		
15	M	45	34	Hypoechogenous, calcifications, regular,	FP	FA	14525	25020	2.2762	2.2446
				peripheral and central vascularization			(175x83)	(180x139)		
16	M	38	35	Hypoechogenous, peripheral and central	FP	MiA	22168	13184	2.0299	2.2564
				vascularization			(163x136)	(128x103)		
17	F	39	56	Iso -and hypoechogenous, peripheral and central vascularization	C	C	19795 (185x107)	54264 (228x238)	2.4482	2.3938
18	F	42	17	Hypoechogenous, peripheral	FP	MaA	23405	20880	2.0574	2.0094
				vascularization			(155x151)	(144x145)		
19	F	40	30	Hypoechogenous, heterogeneous,	SFP	MG	17907	18492	2.3262	2.2106
				microcalcifications, peripheral and central vascularization			(141x127)	(134x138)		
20	F	53	15	Irregular, peripheral and central vascularization	C	MiA	28392	22576	2.0939	2.1246
							(169x168)	(166x136)		
21	F	41	50	Hypoechogenous, calcifications,	FP	MiA	15908	67599	2.3007	2.2058
				peripheral and central vascularization			(97x164)	(261x259)		

22	F	44	35	Hypo, hetero, calcific, periph and central vascul	C	C	27029	16124	2.2701	2.1305
							(179x151)	(139x116)		
23	M	28	25	Hypoechogenous, peripheral and central	FP	MiA	26352	26316	2.1251	2.2136
				vascularization			(183x144)	(204x129)		
24	F	54	31	Isoechogenous, peripheral	C	C	22125	13433	2.2576	2.2104
				vascularization			(177x125)	(133x101)		
<p>*NA, Not applicable; C, Colloid; FP, Follicular proliferation; SFP, Stigmata of follicular proliferation</p> <p>**B, Benign; CD, Cystic degeneration; FA, Follicular adenoma; MiA, Microfollicular adenoma; MaA, Macrofollicular adenoma; MG, Multinodular goiter; C, Colloid</p>										

Table 2: Clinical data and corresponding image information (benign nodule group).

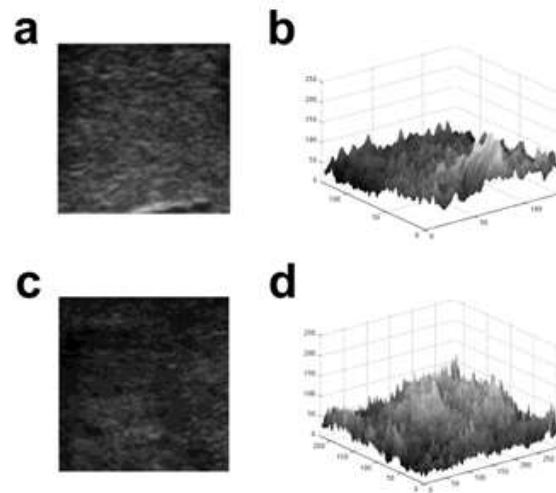


Figure 1: Conversion of 2D US image into 3D surface Lothair, et al.

Images of benign (a) and malignant nodules (c) were converted into 3D surface using gray values of pixels (b and d respectively) for fractal analysis.

2.3. Data analyses

Statistical analyses of differences of FD between normal thyroid tissue and benign nodules on the one hand and normal thyroid tissue and malignant nodules on the other hand were performed with the Wilcoxon signed rank test.

3. Results

3.1. Algorithm design and validation on reference images

We have developed dedicated algorithm which approximated the FD of a given image using the box-counting method. We benchmarked the algorithm on

synthetic images whose FD is explicitly computable, namely the Sierpinski triangle ($\log 3 / \log 2 = 1.585$), the Sierpinski carpet ($\log 8 / \log 3 = 1.8928$) and the dragon curve ($\log 2 / \log \sqrt{2} = 2$) and on the D03 texture image from the Brodatz album which estimated FD ranged from 2.60 to 2.69 [15] (Figure 2). The FD values of the Sierpinski triangle, the Sierpinski carpet and the dragon curve measured by the algorithm strictly corresponded to the theoretical values (Figure 3). The FD value of 2.66 measured for the D03 Brodatz image was within the previously published range [15] (Figure 3).

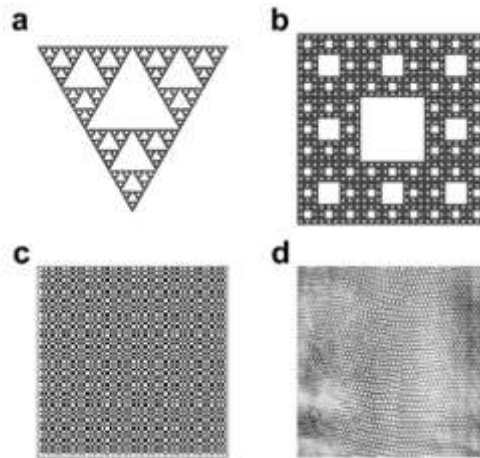


Figure 2: Figures selected to validate the algorithm Lothaire, et al.

(a) The Sierpinski triangle was built starting from a full equilateral triangle, divided into 4 equals smaller triangles and then, removing the “central one”. Iterating this process yields a structure whose theoretical FD is 1.585. (b) The Sierpinski carpet was obtained by dividing a square into 9 smaller squares and then removing the “central one”. The structure obtained by iterating the previous construction will have a theoretical FD of 1.89. (c) The Dragon curve is a space-filling curve with a theoretical FD of 2.0. (d) The grayscale texture D03 which belongs to the standard Brodatz texture album has a FD varying from 2.60 till 2.69 [15].

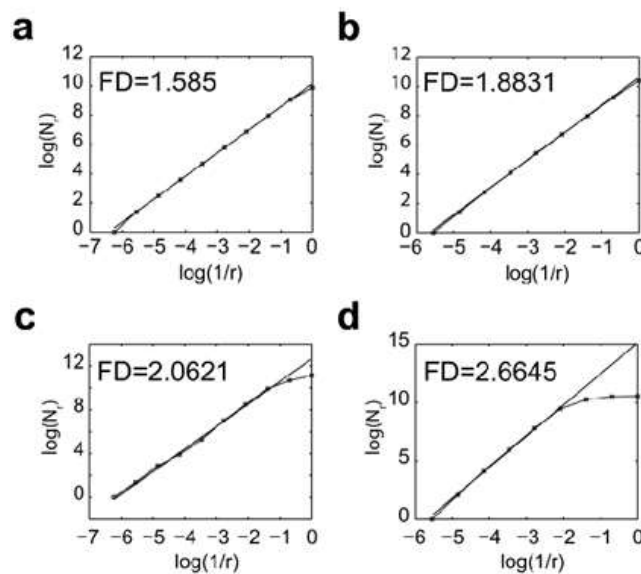


Figure 3: Measurement of the FD of reference images using the algorithm Lothaire, et al.

The FD values of the Sierpinski triangle (a), the Sierpinski carpet (b), the Dragon curve (c) and the Brodatz D03 texture (d) were calculated using the box counting method. The number of boxes (N) required to cover the whole image is plotted against the reduction factor (r) of the box sizes between each iteration of the analysis. The linear best fit of the $\log(N) = f(\log(1/r))$ curve whose slope corresponds to the FD is represented.

3.2. Algorithm validation according to the size of images

When assayed on the Brodatz D03 texture image using different resolutions, the algorithm gave reproducible and reliable values of the FD of the image (Figure 4a). This suggested that the reduction of the resolution did not affect the result of the computed FD. We also observed that reducing the image size altered the accuracy of the FD measure which reached a plateau when image surface was greater than 10 000 pixels² (Figure 4a). When using the

same image with different H/L ratio, we observed that a minimum height of 80 pixels was required for accurate FD measurement (Figure 4b). Image size limitations were confirmed on US images of normal tissue (Figure 5a), benign nodule (Figure 5b) and a malignant nodule (Figure 5c) at different sizes. The threshold value for the size of the image required to limit FD variability to 5% started at 7 000 pixels² for the normal tissue and 10 000 pixels² for both nodules (Figure 5d).

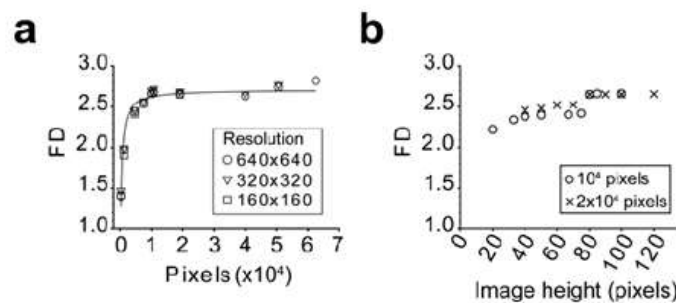


Figure 4: Assessment of the method limits using the Brodatz D03 texture image Lothaire, et al.

The importance of the image size (a) and the height over length ratio (b) was evaluated. The image was iteratively and symmetrically fractionated in smaller parts and the FD of each fragment was calculated using the algorithm. The mean FD is plotted against the fragment image size (a) or image height (b). In panel A, the Brodatz D03 texture was analyzed using different starting resolution as indicated. In panel B, image fragments from the 640x640 image were analyzed as indicated.

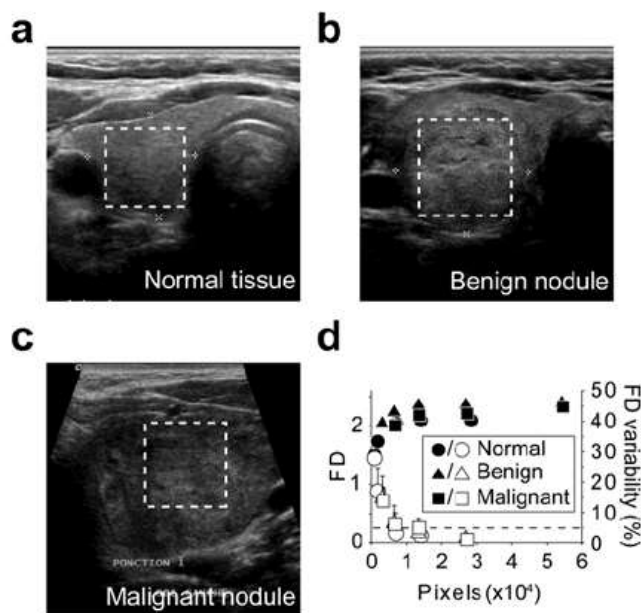


Figure 5: Assessment of the method using the US images Lothaire, et al.

FD was calculated using images of normal thyroid tissue (a), benign nodule (b) and malignant nodule (c). The boxed regions within the full size US (a,b,c) indicate the areas selected for FD calculation (d). The so-obtained images (a : 169x168; b : 228x238; c : 125x128) were iteratively and symmetrically fractionated and the FD of each fragment was calculated using the algorithm. The mean FD is plotted (solid symbols) against the fragment image size (d). The standard deviations of the FD are indicated. Open symbols represent the mean delta between the FD of the fragments and the FD of the full size area (last solid symbol). The error bar on open symbols correspond to the maximum delta. The dashed line represents the 5% variability level.

3.3. FD calculation of thyroid US images

The FD of the images of 13 benign thyroid nodules, 14 malignant thyroid nodules and the neighbouring normal thyroid tissues was calculated using the algorithm (Tables 1&2). The median FD of images corresponding to benign nodules was 2.2146 (2.146/2.251) and, the median FD of malignant nodules, 2.310 (2.259/2.361). The median FD of the corresponding normal thyroid tissues were 2.231 (2.098/2.288 [25%/75%]) and 2.184 (2.117/2.235 [25%/75%]) respectively. While the FD of benign nodules was not statistically different from the FD of the

corresponding normal tissue ($p=0.78$; Figure 6a), the FD of malignant nodules was statistically different from normal tissue ($p<0.001$; Figure 6b).

The Delta FD calculated as the FD of the nodules minus the FD the corresponding normal tissue is presented in figure 6c. While the Delta FD of all the malignant nodules of the present study were strictly positive, the Delta FD of the benign nodules were evenly distributed around the zero value (Figure 6c).

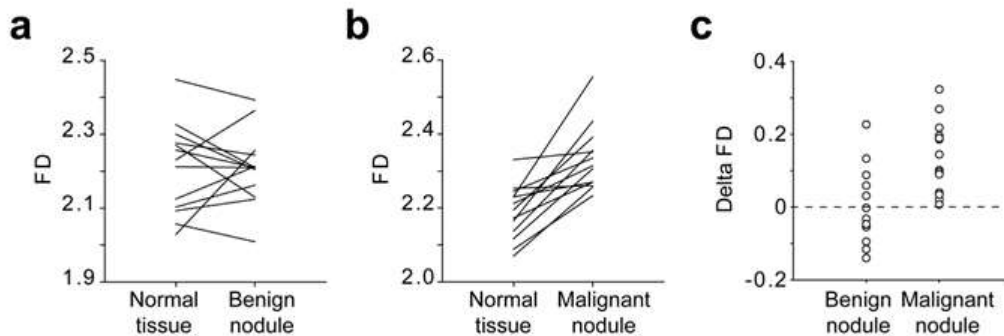


Figure 6: Comparison of the FD of normal thyroid tissue, benign nodule and malignant nodule Lothaire et al.

US images from patients with benign nodules (a; n=13) and malignant nodules (b; n=14) were analysed using the algorithm. The FD of each nodule was compared to the FD of the adjacent normal tissue. The Delta FD between the FD of the nodules and the FD of the corresponding normal tissue was calculated as follow $\Delta FD = FD_{\text{nodule}} - FD_{\text{normal}}$ and plotted in panel c.

4. Discussion

A thyroid US is recommended in the assessment of any suspected thyroid nodule detected by palpation or another imaging modality (computed tomography, magnetic resonance imaging, 18F- fluorodeoxyglucose positron emission tomography, technetium Tc 99m sestamibi scan) [16-18]. Echogenicity of homogeneous normal thyroid parenchyma appears increased in relation to the adjacent muscles but the echotexture of a nodule may be homogeneous or heterogeneous and is not a helpful finding in distinguishing malignant nodules from benign nodules [19]. Thus, no differences between the US features (size and echogenicity) of benign and malignant nodules have been reported to date [20]. Although the majority of papillary carcinoma are currently diagnosed by US and cytological findings of FNAB, the preoperative discrimination between benign and malignant follicular tumour is still difficult [21]. As it is the less frequent of the differentiated thyroid carcinomas, the sample size of the

present retrospective study was restricted to 13 benign and 14 malignant nodules only.

Using the simple and cost-effective thyroid US, we made use of the fractal dimension of the US images in order to discriminate benign and malignant nodules using the objective measure of the FD. Other techniques have previously been used in order to improve the discriminatory power of the US. Shao and col. [22] suggested that the combination of ultrasonic scores and elasticity scores could be an alternative to obtain higher sensitivity and specificity in the diagnosis of malignant thyroid nodules. However, the results rely on the observer's experience. Similarly, Acoustic Radiation Force Impulse (ARFI), a newer ultrasound elastography technique that evaluates the tissue stiffness qualitatively and quantitatively, seems to be helpful to predict malignant thyroid lesions but has many limitations due to technical factors [23,24]. Unfortunately, only a minority of follicular carcinomas are included in

these studies. Here, because echographic examinations were performed on standard US devices and by different radiologists, the images selected for the studies were unlikely to be observer-dependent and the procedure could be easily applied in any care center.

Our analysis pointed at the importance of the size of the images and the existence of a threshold value for the size of the image as a whole and for the length of each side, threshold beyond which the value of the measured FD was stable and close to the known FD value in the case of the reference images. Using the algorithm, the threshold varied between images, being around 7 000 pixels² for homogeneous images (normal thyroid tissue) and 10 000 pixels² for heterogeneous images (benign and malignant nodules). The minimal values of surface and length reported here are easily achievable in clinical practice using regular US devices. In this study, we reported the increased FD value of malignant thyroid nodules compared to normal tissue, while benign nodules and normal tissue could not be distinguished using this parameter. We postulated that the grayscale levels of each pixel would bring supplementary information and therefore should not be discarded. Therefore, we chose to convert the 2D US image to the 3D object that includes information about each pixel gray level. The main advantage of such a procedure is the lack of preliminary transformation of the image on contrary to previous reports that focused on objects boundaries [12,25]. Our strategy has proven accurate on reference images. Finally, our observation is in accordance to the fact that the rougher the appearance of the image, the larger the FD value, which fitted with the qualitative examination of the US images.

Nevertheless, since FD is not able to completely capture the complexity of a image, two different objects may have an identical FD. Therefore inter-sample comparison was not meaningful and the comparison of normal and pathologic tissues is mandatory for an accurate evaluation of the malignancy of the nodule. The Delta FD between nodule and normal tissue is a promising candidate for diagnostic purpose. Thus, in the present study, only benign nodules showed a negative Delta FD and we could have identified 61% of the studied benign nodules using this threshold. The preliminary results of this study showed that FD could be an additional discriminating feature between benign and malignant thyroid nodules. Further work will implement these first results on a broad scale by evaluating the algorithm on a larger database of native thyroid US images and correlating our findings with the known US patterns

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