

# The challenge for an accurate pre-operative diagnosis of echographically detected solid thyroid nodules with indeterminate cytological results

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## RESUMO

**Objetivo:** Avaliar a possibilidade de diagnóstico pré-operatório de nódulos da tiróide (de diâmetro superior a 10 mm) usando ultra-sonografia da glândula tiróide e citologia de punção aspirativa por agulha fina guiada pela ultra-sonografia.

**Casística e Métodos:** Nódulos tiróideos (maiores que 10 mm) foram classificados ultra-sonograficamente em graus de I a IV e scores numéricos de 1 a 4, de acordo com a crescente possibilidade de malignidade. O exame citológico, subsequentemente, classificou os nódulos como benigno (score 1) indeterminado (score 2) suspeito (score 3) e maligno (score 6). Somando-se os scores obtidos nas duas metodologias obtém-se um índice considerado benigno (índice combinado 2-4), duvidoso (índice combinado 5) suspeito para malignidade (índice combinado 6) e elevada probabilidade de malignidade (índice combinado 7 a 10). Cirurgia da Tiróide foi realizada em 274 pacientes, dos quais 64 apresentavam índice de 2-4; destes, apenas 2 pacientes (3,1%) apresentaram comprovação histológica de carcinoma. Em pacientes com índice 5 (n= 51), 11,8% apresentaram carcinoma de tiróide e, em 61 pacientes com índice 6, (n= 31), 51% tiveram diagnóstico confirmado de malignidade. O índice combinado de 7-10 (n= 98) apresentou 99% de pacientes com carcinoma de tiróide.

**Conclusões:** O índice combinado apresentou sensibilidade de 94,1% e especificidade de 77,5%. A acurácia desta metodologia foi de 85,8%. Concluímos que o índice combinado pode ser útil no diagnóstico pré-cirúrgico do nódulo tireóideo, mormente se associado com outras metodologias como a ecografia com Doppler colorido, nível elevado de TSH sérico, análise de expressão de galectina-3 e imagens por FDG/PET.

## PALAVRAS-CHAVE

Nódulo tireóideo; Carcinoma de Tiróide; Ultra-sonografia Cervical; Citologia da Tiróide; FDG-PET; Galectina-3; TSH sérico.

## SUMMARY

**Purpose:** To evaluate the pre-operative assessment of thyroid nodules using ultrasound studies and cytology of nodular aspirates.

**Subjects and methods:** 2.468 patients with thyroid nodules were examined from 1999 to 2005. All patients were clinically examined and submitted to ultrasonography followed by fine-needle aspiration biopsy (FNAB) and cytology.

Results: Nodules larger than 10mm were classified ultrasonographically in a four-tier system and received a score number (1-4) according to criteria of possible malignancy. Cytological examinations were conducted, independently, by two cytologists and classified as benign (score 1), indeterminate (score 2), suspicious (score 3) and malignant (score 6). Combining both scores an index was generated that would indicate a higher probability of malignancy [(benign (2-4), doubtful (5), suspicious (6) and malignant (7-10)]. Thyroid surgery was performed in 274 patients. Of those 115 patients had a score of 2-5 and only 8 had histological diagnosis of thyroid cancer (6.9%). For patients with score 5 (n= 51) 11.5% had a malignant lesion and 61 patients with score 6 had 51% of confirmed thyroid cancer. A combined score of 7-10 (n= 98) had 99% of histological confirmation of malignancy.

Conclusions: The index score had a sensitivity of 94.1% and specificity of 77.5%. The overall accuracy was 85.8%. Therefore we concluded that this methodology may improve the pre-operative diagnosis of thyroid cancer in nodules larger than 10mm. Association with other methods such as color Doppler echography, serum TSH concentration, galectin-3 expression analysis, <sup>99m</sup>Tc-depreotide scintigraphy and FDG/PET scan would be useful to avoid the higher costs of thyroid surgical procedures.

#### KEY-WORDS

Thyroid nodules; Thyroid cancer; Thyroid echography; Thyroid cytology; Serum TSH; FDG-PET scan; Galectin-3; <sup>99m</sup>Tc-depreotide.

## INTRODUCTION

Thyroid nodules are a common clinical finding being more frequently found in women, the elderly population and those exposed to past period of iodine deficiency. With the more widespread use of high-resolution ultra-sound as a relatively low cost imaging of the thyroid gland, the prevalence of nodules of randomly selected individuals is estimated to be 19-67%<sup>1-4</sup>. The clinical importance of thyroid nodules rests with the need to exclude thyroid cancer that occurs in about 10% depending on age, gender, radiation exposure history, family incidence of thyroid cancer and possibly iodine intake<sup>1</sup>. Papillary and Follicular thyroid cancer (and variants) comprises the vast majority (90%) of all thyroid malignancies<sup>4-6</sup> and due to more efficient and adequate diagnostic tools, the yearly incidence is increasing<sup>6,7</sup>. Controversy exists regarding the most cost-effective approach in the diagnostic evaluation of a thyroid nodule<sup>5-7</sup>. In this paper we present an approach to pre-surgical evaluation of the thyroid nodule using an index based on ultra-sonographic and cytological studies that will enhance the ability of the attending physician to recommend thyroid surgery for selected cases. Furthermore, the value of FDG-PET imaging method was recently investigated in patients that had an indeterminate cytological

diagnosis in fine needle aspiration biopsies and may prove to be a useful tool to pre-operative diagnosis of thyroid nodules.

## PATIENTS AND METHODS

We have examined 2,468 consecutive patients with thyroid nodular disease from 1999 to 2005. All patients were submitted to ultrasonographic examination (with an ALOKA SSD 500, Aloka Co, Tokyo, Japan) equipped with a 7.5 MHz linear probe. Ultrasound guided fine needle aspiration biopsy (USG-FNAB) was performed in all nodules with a diameter larger than 10 mm.

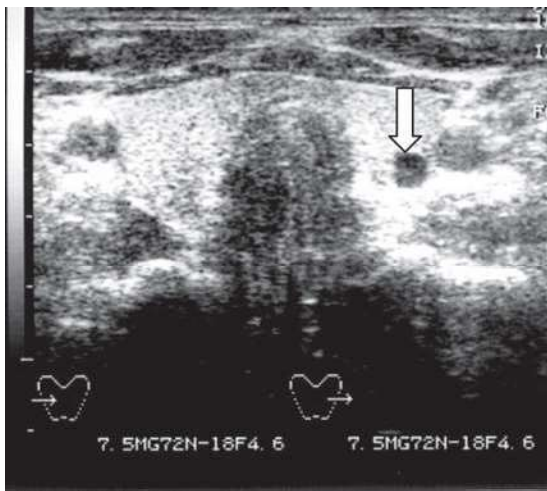
## ULTRA-SONOGRAPHIC CLASSIFICATION OF THE NODULES (Figure 1)

Each nodule was classified in a fourtier system (grades I, II, III and IV) and each grade received a score number<sup>1-4</sup>, according to criteria previously reported<sup>8</sup>.

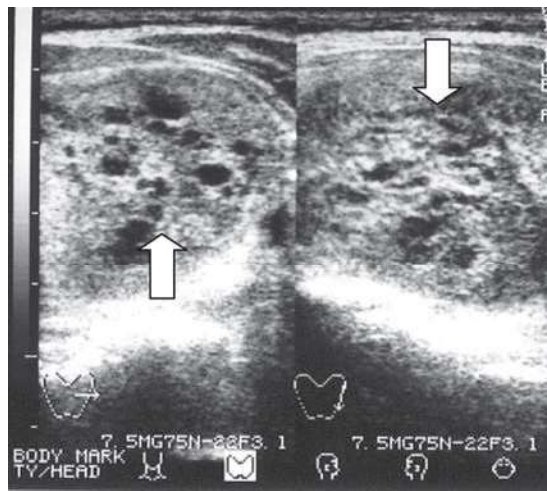
**Grade I** (score=1) small round and anechoic image that is suggestive of a thyroid cyst.

**Grade II** (score=2) multiple isoechoic or hyper echoic solid nodules with or without cystic change and coarse calcification are suggestive of adenomatous goiter. A single complex nodule

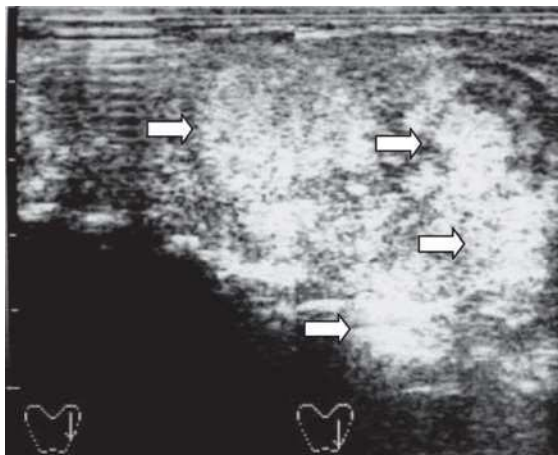
FIGURE 1: Ultra-sonographic classification of nodules. From top left, clockwise: grade I, a small round anechoic image (thyroid cyst); grade II, a complex nodule (like a sponge); grade II, multiple echonormal nodules; grade III, a hypochoic solid nodule with regular border; grade III, cystic mass with solid projection from the cyst wall; and grade IV, a hypochoic solid nodule with irregular border and micro calcifications.



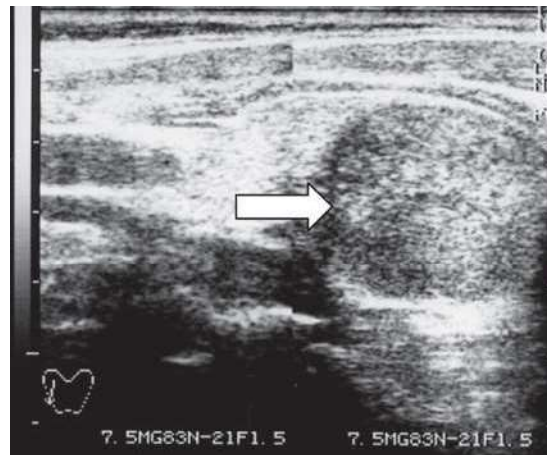
Grade I – Thyroid cyst  
Transverse scan ↓



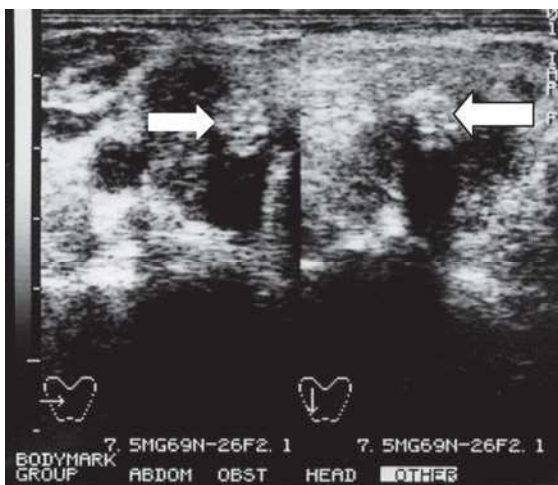
Grade II – Complex nodule  
Transverse ↑ and longitudinal scan ↓



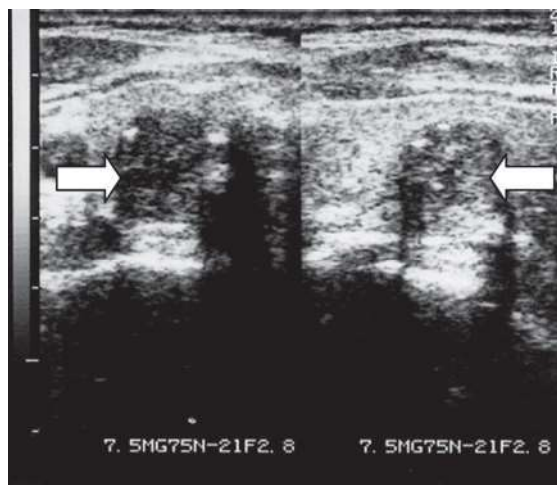
Grade II – Multiples echonormal nodules →  
Transverse scan



Grade III – Hypochoic nodule →  
Longitudinal scan



Grade III – Cystic mass with solid projection  
from the cyst wall  
Transverse → and longitudinal scan ←



Grade IV – Hypochoic mass with irregular  
margin and microcalcifications.  
Transverse → and longitudinal scan ←

(with cystic areas like a sponge) with the remainder of the gland with normal echo graphic texture could be a follicular adenoma.

**Grade III** (score=3) a single isoechoic nodule or a hypo echoic solid nodule with regular border may be a thyroid neoplasm. A cystic nodule with a solid projection from the cyst wall may represent a papillary carcinoma.

**Grade IV** (score=4) hypo echoic solid nodule with an irregular border with micro calcifications is considered suspicious for papillary carcinoma.

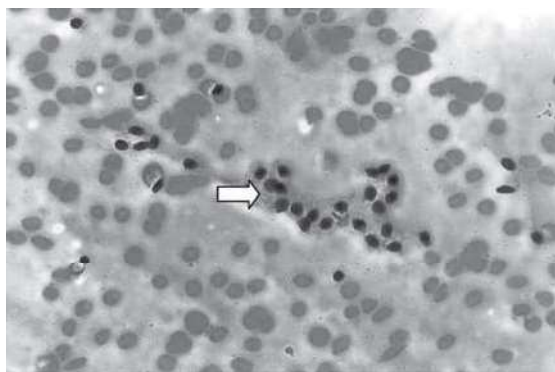
### CYTOLOGICAL CLASSIFICATION OF USG-FNAB (Figure 2)

Ultra-sound guided fine needle aspiration biopsy (USG-FNAB) was performed using a 22 G

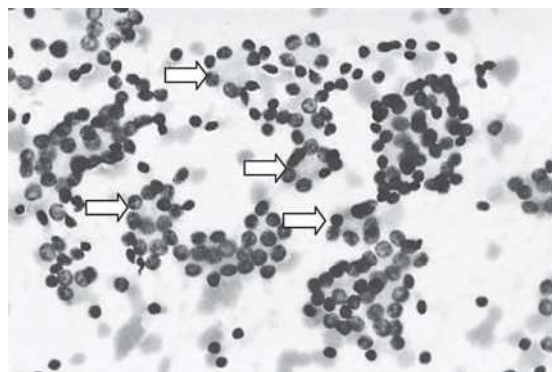
needle and a 10 mL syringe. The aspirates were fixed in 96° alcohol and stained with haematoxylin-eosin. Cytological examinations were conducted, independently, by two experienced cytologists and classified as follows:

- **Benign pattern grade I** (score = 1): epithelial cells are distributed in cohesive clusters. The nuclei are round or oval with dense and homogeneous chromatin. The cytoplasm is scanty and slightly eosinophilic but some oncocytic cell change may be present. Abundant colloid may be seen. This pattern is suggestive of nodular goiter.
- **Indeterminate grade II** (score = 2): epithelial cells distributed in solid clusters or in micro follicular arrangements. The nuclei are round or oval with homogeneous chromatin. The cytoplasm is scanty or

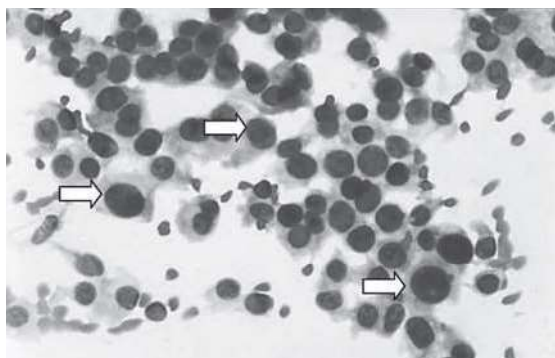
FIGURE 2: Cytological classification of aspirates of thyroid nodules. From top left, clockwise: grade I, follicular cells with dense and homogeneous chromatin and abundant colloid; grade II, micro follicular pattern with nuclei with homogenous chromatin and scanty colloid; grade III, suspicious pattern with nuclear enlargement, prominent nucleoli, granular chromatin and absent colloid; and grade IV, malignant pattern represented by papillary carcinoma with enlarged and irregular nuclei, powdery chromatin and pseudo inclusions.



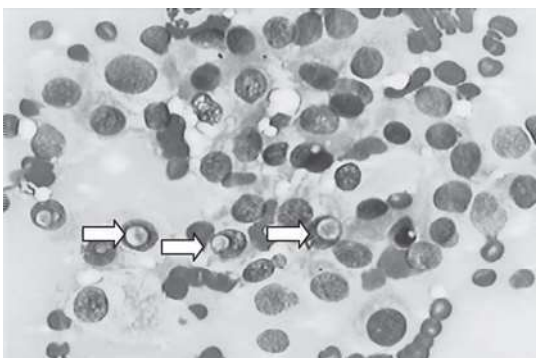
**Grade I** – Follicular cells arranged in monolayer sheets with abundant colloid



**Grade II** – Microfollicular pattern



**Grade III** – Nuclear enlargement with granular chromatin and moderate degrees of pleomorphism



**Grade IV** – Papillary carcinoma: The nuclei are typically enlarged and irregular with dusty to powdery chromatin and nuclear pseudo-inclusions

slightly eosinophilic. Colloid is absent or scanty. This pattern can be found in adenomatous goiter or in follicular neoplasm.

- *Suspicious pattern grade III* (score=3): epithelial cells distributed in solid clusters or in follicular arrangements. The nuclei are round or oval with nuclear enlargement, granular chromatin and prominent nucleoli. The cytoplasm is slightly eosinophilic or may be large, deeply eosinophilic and granular characteristic of oncocyctic cell change. Colloid is absent or scanty. This pattern is suspicious of neoplasm.
- *Malignant pattern grade IV* (score=6):
  - a) Papillary pattern – the epithelial cells are seen in a papillary arrangement. Round or oval nuclei are seen with nuclear pseudo inclusions and/or nuclear grooves.
  - b) Medullary pattern – the aspirates are typically hyper cellular with non-cohesive cells. The cells are variable in shape with round, oval or spindle shapes. The nuclei are often eccentric with a plasmocytoid appearance. Amyloid is rarely seen.
  - c) Anaplastic pattern – small, giant multinucleated and spindle cells are the predominant types in this pattern. The nuclei are usually large, bizarre, single or multiple and coarsely clumped with prominent nucleoli. Atypical mitosis may be present.
  - d) Malignant lymphoma - monomorphic lymphoid cells (frequently associated with Hashimoto’s thyroiditis).

Combining the scores of both ultra-sonographic and cytological classification, we propose an index that would indicate, progressively, a higher probability of the presence of malignancy. Thus an index of 2-4 is considered as a benign lesion, an index of 5 as doubtful, an index of 6 as suspicious for malignancy and index 7-10 with a high probability for thyroid cancer<sup>8</sup>.

### PRE-OPERATIVE ASSESSMENT OF THYROID NODULES WITH FDG-PET SCAN

FDG-PET is well established in diagnosis, follow-up and treatment monitoring of several malignancies. Recently, the value of FDG-PET was investigated not only for the follow-up of <sup>131</sup>I-Whole Body Scan negative patients but also for the pre-operative assessment of hypoechogenic/hypo functioning solid thyroid nodules<sup>9-16</sup>. In most centers, FDG-PET is performed after the patient has fasted overnight and presents with a blood glucose less than 140 mg/dL. Sixty to ninety minutes after the intravenous injection of 200-500 MBq, FDG (depending on the PET system, 2D, 3D acquisition) emission scanning is started. Transmission scanning is performed either before FDG injection (cold transmission) or after FDG injection (hot transmission).

Computerized Tomography transmission is available in combined PET/CT machines, where morphology and metabolism are imaged during one investigation. Recent reports<sup>14-16</sup> have indicated increased FDG-PET uptake in malignant nodules. Those can be separated from benign ones using a variable standardized uptake value (SUV) cut off.

TABELA 1 – Comparative studies of the echographic four-tier system and the cytological findings

Echographic Classification (n)	Cytology (USG-FNAB)*			
	Benign	Indeterminated	Suspicious	Malignant
Grade I & II (1039)	902 (87.0)	96 (9.2)	37 (3.6)	4 (0.4)
Grade III (1276)	743 (59.0)	272 (21.3)	176 (13.8)	85 (6.7)
Grade IV (153)	38 (24.8)	7 (4.6)	20 (13.1)	88 (57.0)
2468	1683	375	233	177

\*Number of nodules examined and respective percentage (%) within the echographic pattern.

## RESULTS

### PREVALENCE OF THYROID CANCER IN THE STUDY POPULATION

#### Echographic studies and USG-FNAB (cytology)

A total of 2,468 patients were referred to the Thyroid Unit for diagnostic ultra-sound and possible USG-FNAB from

1999 to 2005. All patients had a nodule larger than 10 mm in diameter. There were 198 (8.02%) males and 2270 (91.98%) females. No patients reported exposure to childhood head or neck irradiations and no patients had a familial history of medullar carcinoma and multiple endocrine neoplasia.

From the total cohort of 2,468 patients, 274 were submitted to thyroid surgery. Of those, 115 patients with lower combined scores 2-5 were thyroidectomized by recommendation of their private physicians. Only eight patients had a thyroid cancer confirmed in subsequent histological examination. As seen in Table 2, in patients with scores 2-4 (n=64), a benign lesion was present in about 97% of the examined nodules.

TABELA 2 – Thyroid cancer prevalence in patients with thyroid nodules that were submitted to thyroid surgery (n = 274)

Combined echographic and cytological scores (index score)	Number of patients		Malignancy confirmed (%)
	Total	Thyroid cancer	
2-4	64	2	3.1
5	51	6	11.8
6	61	31	50.8
7-10	98	97	99.0

Sensitivity 94.1%; Specificity 77.5%; Positive predictive value 80.5%; Negative predictive value 93.0%; Accuracy 85.8%

For patients with score 5 (n= 51), 11.7% had a malignant lesion (Table 2). Sixty-one patients with score 6 had close to 51% of malignant nodules whereas patients with a combined score of 7-10 had 99% histological confirmation of thyroid cancer.

Thus, the index score had a sensitivity of 94.1% and specificity of 77.5% to predict the pre-operative diagnosis of thyroid cancer. Furthermore, the positive predictive value of the combined score was 80.5% and the negative predictive value was 93.0%. Thus, accuracy of this numeric score for pre-surgery diagnosis was 85.8%.

As mentioned before from the 2,468 studied patients, 274 were submitted to surgery and 136 had a confirmed diagnosis of thyroid cancer after surgery (5.6%). The mean age of patients with thyroid cancer was 46.2±6.9 yr (mean±SD) compared with 40.1±10.3 yr in those without cancer (NS). The types of thyroid cancer included 101 cases of papillary carcinoma, 22 of follicular carcinoma and 13 of medullar carcinoma.

An association with thyroid cancer was detected in certain sonographic characteristics. In particular, the more cystic a nodule was (score 1) the lower the likelihood of malignancy. Hypoechoic nodules had a higher rate of thyroid cancer (score 3) than nodules that were isoechoic or hyper echoic. The presence of coarse or rim calcifications increased the risk of cancer and punctate micro calcifications resulted in a 3-fold incidence of malignancy (score 4).

## DISCUSSION

The aim of this paper was to evaluate the capacity of pre-operative analysis of thyroid nodules using echographic studies associated with cytological evaluation to diagnosis the presence of thyroid malignancy. Furthermore, we added to our pre-operative diagnosis the new methodology of <sup>18</sup>F-Fluorodeoxyglucose-position emission tomography (FDG-PET) imaging that is claimed to be able to separate malignant nodules from benign ones using a standardized uptake value (SUV).

Population studies suggest that about 3-8% of asymptomatic adults have thyroid nodules<sup>1,5-7</sup> and this prevalence increases substantially with age<sup>1</sup>. Following ultra-sound examination, more than half of adults after age of 50 may have a thyroid nodule<sup>1,17</sup>. USG-FNAB is the method of choice for determining the risk of malignancy<sup>2,4</sup>. Also a number of studies have also assessed various sonographics characteristics as prediction of thyroid cancer including hypoechogenicity, solid composition, and absence of halo, irregular margins and the presence of micro calcifications<sup>17</sup>. In our institution, we perform a large number of USG-FNAB for nodules larger than 10 mm and the cytological results are expressed by a score number that when in association with the sonographic score number will result in an index score that might be helpful for the pre-operative diagnosis of thyroid cancer.

As indicated in Figure 1, sonographic features alone do not reliably separate benign from malignant thyroid nodule. As recently reported by Frates et al<sup>17</sup>, the more cystic a nodule is, the lower the likelihood of cancer. Hypoechoic nodules had a higher rate of malignancy than isoechoic or hyper echoic nodules. The pre-

sence of coarse or rim calcifications increased the likelihood of cancer almost two-fold, when compared with the malignancy rate for nodules without calcification. Punctate micro-calcifications increased the likelihood almost three-fold. Well-defined or poorly defined nodule's margins were not significantly associated with presence of thyroid cancer<sup>17</sup>.

To assess how the likelihood of malignancy as indicated by sonographic characteristics, we combined both the results of ultra-sonographic appearance with the cytological diagnosis after USG-FNAB. As shown in Table 1, in our cohort of 2,468 nodules, grade III and IV sonographic patterns were detected in 1,429 nodules. Of these, 261/1,276 grade III nodules (20.4%) were cytologically classified as suspicious (13.7%) or malignant (6.7%), whereas 70.5% sonographically grade IV nodules (n=153) were cytologically diagnosed as malignant (n=88) or suspicious (n=20). In Table 2, it is shown the combined echographic and cytologic scores (index score) for patients that subsequently were submitted to total thyroidectomy.

A total of 274 patients were submitted to thyroid surgery. Usually, patients with low scores (2-4) are not routinely indicated for surgery unless compressive symptoms and recent growth are present. However, 64/274 patients (23.3%) were operated on the advice of their respective family-practice doctors and malignancy was confirmed histologically in only 2 patients (3.1%). Patients with a combined score of 5 could be advised to follow a period of observation with or without L-T4 suppressive therapy. However, 51/279 (18.4%) were operated and 11.7% (6/51) harbored thyroid malignancy. For higher scores such as index 6 patients, it was found 50.8% of malignancy in the nodules (31/61) whereas nodules with index scores of over 7 had 99% incidence of thyroid cancer. Thus, sensitivity of the combined sonographic features and cytological results index scores was 94.1% and specificity 77.5% with a positive predictive value of 80.5% and a negative predictive value of 93.0%. Accuracy of his numeric score was 85.9%.

We may conclude that the sonographic studies of a nodule larger than 10 mm associated with USG-FNAB resulting in a cytological diagnosis will conduct to a better pre-operative diagnosis tool for thyroid nodules as compared

to each method individually. However, we were not able to secure a firm indication for score 5 nodules although about 11% of those could be thyroid cancer. Moreover, nodules with an index score of 6 had a fifty percent chance of being associated with thyroid cancer and in this particular group, our tendency is to indicate thyroid surgery. Finally, for nodules score of 7 and more, it will be candidates for mandatory thyroid surgery.

As seen in Table 1, about 15% of cytological results were classified as indeterminate and therefore not conclusive. The decision for indicating thyroid surgery is thus difficult unless sonographic characteristics suggestive of malignancy are present. However, recent data<sup>17</sup> confirm that sonography cannot be used to confidently exclude malignancy based on its negative predictive value. Several studies have identified a role for color Doppler in the evaluation of thyroid nodules. Nodules with prominent central flow have an increased risk of malignancy<sup>18-20</sup>. Thus color Doppler sonographic studies may be helpful to select nodules that will be submitted to thyroid surgery.

Another predictor of malignancy in thyroid nodules may be the presence of increasing serum levels of TSH at presentation. Regression analysis revealed significantly increased adjusted odds ratios for serum TSH greater than 5.5 mU/L as compared with TSH < 0.4 mU/L for the presence of malignancy, principally in males, younger patients and those with clinically solitary nodules<sup>21</sup>. Thus, serum TSH levels may serve as an adjunct to USG-FNAB in predicting risk of malignancy in solitary nodules.

An alternative to the diagnosis of thyroid malignancy in selected thyroid nodules with indeterminate FNA cytology was proposed by Carpi et al<sup>22</sup>. They introduced a strategy for improving the diagnosis of follicular lesions which is based on large needle aspiration biopsy and galectin-3 expression analysis. Eighty-five thyroid specimens were obtained by large needle (20-gauge needles) aspiration biopsy from thyroid nodules with indeterminate follicular cytology. Aspirate material was processed as a tissue micro-biopsy to obtain cells blocks for morphological evaluation and galectin-3 expression analysis (purified monoclonal antibody to galectin-3). Among 85 nodules tested, 14 galectin-3 positive tissues were discovered

pre-operatively (final histology after surgery, 11 thyroid cancers and 3 follicular adenomas). Galectin-3-negative cases were 71 and final histology indicated 70 benign proliferations and one follicular carcinoma. Sensitivity, specificity and diagnostic accuracy of these integrated morphologic and phenotypic diagnostic approaches were 91.6, 97.2 and 95.3%. This methodology can potentially reduce unnecessary thyroid surgery more even so when associated with the results of echographic studies with color Doppler.

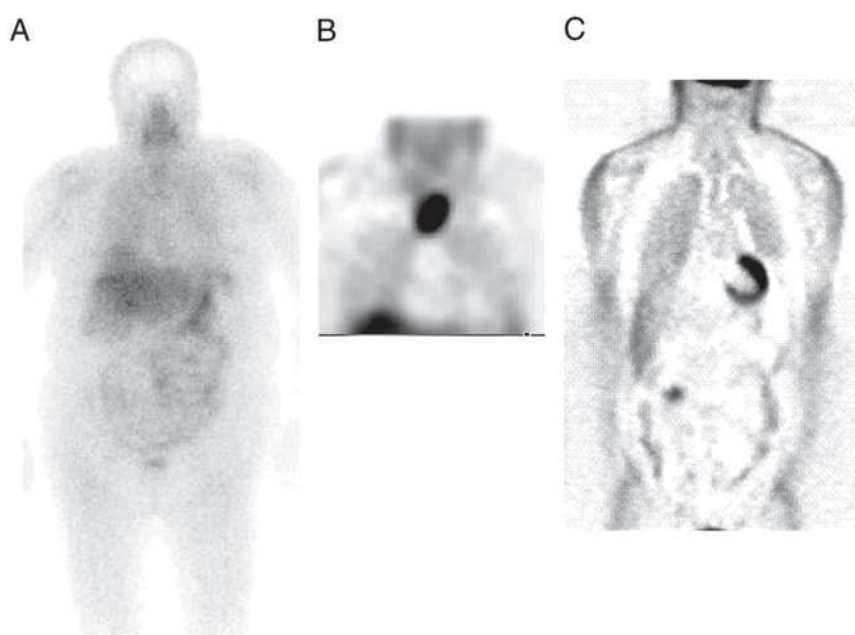
Lee and co-workers<sup>23</sup> used thallium-201 scan in evaluating thyroid nodules with indeterminate cytological diagnosis. Fifty one nodules were examined and forty were benign and eleven harbored thyroid malignancy. Papillary carcinoma was diagnosed histologically in 6 patients and follicular carcinoma in 5 patients. All malignant lesions had a grade 3 thallium uptake whereas only one patient with a benign nodule exhibited a grade 3 uptake. Thus sensitivity was 100%, specificity 75% and accuracy 80%. They concluded that the dual-phase thallium-201 scan may be useful for detecting malignancy in the pre-operative stage.

Rodrigues and co-workers<sup>24</sup> compared the results of <sup>99m</sup>Tc-Depreotide scintigraphy versus <sup>18</sup>F-FDG-PET in the diagnosis of radioiodine-negative thyroid cancer. As papillary and follicular cancer was found to express somatostatin receptors (SSTRs) the tracer <sup>99m</sup>Tc-depreotide binds with high affinity to SSTRs. This technique may prove to be useful to distinguish follicular adenomas from follicular cancer nodules. The results obtained by the authors have indicated a potential value of <sup>99m</sup>Tc-depreotide scintigra-

phy for the diagnosis of thyroid cancer in the setting of detectable serum thyroglobulin and negative radioiodine scan as well as negative <sup>18</sup>F-FDG-PET scan (Figure 3).

Recently, the value of FDG-PET was investigated not only for the follow-up of thyroid cancer patients but also for pre-operative assessment of hypoechogenic/hypo functioning nodules. An early study of 5 patients by Joensuu et al<sup>11</sup> indicated a clearly increased FDG-PET uptake in one patient with anaplastic thyroid cancer and one with Hürthle cell carcinoma. In contrast with this study, Uematsu and co workers<sup>12</sup> demonstrated in eleven patients that all malignants nodules could be separated from benign ones using a standardized uptake value of FDG-PET higher than 5. Kresnik et al<sup>13</sup> studied 43 patients (11 papillary TC, 3 follicular TC, 2 anaplastic cancer, 11 microfollicular adenomas, 10 oxiphillic adenomas, 2 macro follicular adenomas and 4 goiters). All patients with TC and oncocytic adenomas had increased FDG uptake. Using a SUV threshold of 2 for differentiating benign from malignant nodules, sensitivity and specificity was 100% and 63%, respectively. More recently, Mitchell et al<sup>14</sup> used FNAB and FDG-PET before surgery and docu-

FIGURE 3: <sup>99m</sup>Tc-depreotide scan in (A) total body anterior view (B) coronal SPECT slice showing increased activity at a loco regional recurrence in a radioiodine-negative patient with follicular carcinoma, serum thyroglobulin of 30 ng/mL and (C). Negative FDG-PET scan (reproduced with permission of the "The Endocrine Society", J Clin Endocrinol & Metabolism 91:3997-4000, 2006)





mented that nine of 15 malignant lesions were FDG positive (sensitivity 60%) and thirty of 33 benign lesions were FDG negative (specificity 91%). The authors concluded that FDG-PET has a relatively high negative predictive value (83%) for malignancy.

Lind & Kohlfurst in a recent review<sup>15</sup> reported that in a subgroup of 24 patients with cytological diagnosis of follicular proliferation FDG-PET was able to differentiate between follicular adenoma and follicular carcinoma. Thus, in case of indeterminate cytology, FDG-PET seems to be the method of choice to decide whether thyroid surgery or, alternatively, wait and watch strategy should be recommended.

In conclusion, the use of an index score based on echographic studies of thyroid nodules and the results of USG-FNAB cytology may improve our pre-operative diagnosis of thyroid cancer in nodules larger than 10 mm. Color Doppler echography may add to the sensitivity of the index score. Elevated serum TSH concentration ( $> 5.5 \mu\text{U/mL}$ ) was shown to be an independent predictor of thyroid malignancy. Large needle aspiration biopsy derived cell blocks and galectin-3 expression analysis led to a better pre-operative selection of patients with follicular thyroid proliferation cytological diagnosis. The potential value of  $^{99\text{m}}\text{Tc}$ -depreotide scintigraphy has been shown recently, to distinguish follicular cancer with radioiodine-negative scans. Finally, FDG-PET scan is a promising methodology to decide on thyroid surgery of nodules with indetermined cytology. Most of the unnecessary surgery for benign thyroid nodules may be avoided when those methods are employed with a consistent reduction of hospitalization and social costs to the Health systems of many countries.

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