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Cyto-Histological Correlation of the "Follicular Lesion of Undetermined Significance" Category According to the Bethesda Classification System of Thyroid Aspirative Cytology

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Resumo

Os nódulos tiroideus são uma entidade comum, sendo a sua maioria benignos. As neoplasias malignas da tiróide apresentam-se, contudo, como nódulos em 95% dos casos. A citologia aspirativa por agulha fina é fundamental para o estudo dos nódulos tiroideus, pois reduz cirurgias nos pacientes com lesões benignas e tria adequadamente pacientes com nódulos malignos ou potencialmente malignos para intervenção cirúrgica.

A nomenclatura de Bethesda é uma proposta internacional de classificação dos achados citopatológicos. Uma das suas categorias, a "lesão folicular de significado indeterminado" é utilizada quando os achados citomorfológicos não são nem convincentemente benignos nem suficientes para uma interpretação de malignidade. Nódulos com esta classificação revelam-se um desafio em termos de manejo clínico.

Vários estudos têm sido feitos para determinar que patologias estão na origem de uma lesão folicular de significado indeterminado. Neste estudo é feita uma correlação cito-histológica dos casos de lesão folicular de significado indeterminado submetidos a cirurgia, utilizando dados do Instituto Português de Oncologia Francisco Gentil de Lisboa, do Hospital da Luz e do Hospital Beatriz Ângelo.

Os hospitais consultados tinham 5267 relatórios de citologias tiroideias entre 1 de Janeiro de 2012 e 31 de Dezembro de 2013 e 310 foram de classificados como "lesão folicular de significado indeterminado". Cento e um casos foram submetidos a cirurgia e o relatório anátomo-patológico foi consultado. Cada diagnóstico histológico foi anotado individualmente e como muitos casos tinham mais do que uma patologia um único diagnóstico dominante foi considerado para o estudo estatístico. Quatro grupos foram criados de acordo com um diagnóstico dominante: neoplasia maligna, neoplasia benigna, inflamação e hiperplasia. Um quinto grupo foi criado para doenças com potencial maligno incerto e para micro carcinomas. Uma vez que a inflamação pode ser um estímulo para a malignidade, todos diagnóstico histológico associados a inflamação foram inventariados.

As neoplasias malignas foram o diagnóstico dominante em 28 casos, correspondendo a 27.72% de todos os casos. As neoplasias benignas foram o diagnóstico dominante em 25 casos e a inflamação em 10 dos casos. A hiperplasia foi considerada como diagnóstico dominante em 30 dos casos, sendo este o maior grupo. Os micro carcinomas e os tumores com potencial maligno incerto perfizeram 8 casos no total. A inflamação estava presente em 22 casos.

Na população estudada revelou-se que a maioria dos casos de lesão folicular de significado indeterminado tinham o diagnóstico histológico de hiperplasia. As neoplasias malignas tiveram uma frequência de 27.72%, maior que o esperado. O total de casos de neoplasias benignas e malignas corresponderam a mais de metade de todos os casos e a citologia aspirativa de agulha fina deveria ter triado adequadamente estes casos.

A inflamação coexistiu com neoplasias malignas e benignas e com micro carcinomas e os casos do grupo da Inflamação estavam associados a hiperplasia. Com estes achados, é pertinente questionar a influência da inflamação na lesão folicular de significado indeterminado.

Palavras-chave: CAAF, Correlação, Lesão Folicular de Significado Indeterminado, Nódulo, Tiróide.

Abstract

Thyroid nodules are a common entity, the majority being benign. Thyroid malignancies, however, present themselves as nodules in 95% of the cases. "*Fine needle aspiration plays an essential role in the evaluation of the euthyroid patient with a thyroid nodule*". The Bethesda System for Reporting Thyroid Cytopathology is an international classification of cytologic findings that links to clinical management. Its follicular lesion of undetermined significance category is employed when "*cytomorphologic findings are neither convincingly benign nor sufficient for interpretation of neoplasia/malignancy*". This category proves a challenge in the management of these nodules.

Several studies are ongoing to determine the diseases underlying a follicular lesion of undetermined significance category report. In this study a correlation between this cytological cathegory and a histological diagnosis is made using data from Portuguese hospitals. The percentage of this cytological cathegory and those who underwent surgery was calculated. The post surgical histological diagnosis was noted and their relative percentage calculated.

The consulted hospitals had 5267 thyroid cytology reports and 310 were reported as follicular lesion of undetermined significance. A hundred and one underwent surgery and the histological report was consulted. Each histological diagnosis was noted individually and because many cases had more than one histological diagnosis a single dominant disease was considered for statistical study.

Four groups where created according to the dominant diagnosis: malignant neoplasia, benign neoplasia, inflammation and hyperplasia. A fifth group was created for diseases that had an uncertain malignant potential and for micro carcinomas. Since inflammation can be a stimulus to malignant disease, all histological diagnosis associated with inflammation where noted.

The malignant neoplasia group had 28 cases, the benign neoplasia group had 25 cases, the inflammation group had 10 cases and the hyperplasia group had 30 cases. Micro carcinomas and tumors with uncertain malignant potential had 8 cases in total. Inflammation was present in 22 cases.

This study has found that most cases associated with FLUS are hyperplasic in origin. Malignancies where higher than expected, being the predominant disease in 27.72% of all cases. The total cases of benign and malignant neoplasias combined far outnumber the remainder cases and FNAC should appropriately triage surgical cases. Inflammation coexisted with malignant and benign neoplasias and with microcarcinomas and cases in the inflammatory group had some form of hyperplasia. With these findings it is pertinent to question the influence of inflammation in a FLUS diagnosis.

Key-words: FNAC, Follicular Lesion of Undetermined Significance, Correlation, Thyroid, Nodule.

Index

Figure List

Tables List

Acronyms

FLUS	Follicular lesion of undetermined significance
FNA	Fine needle aspiration
FNAC	Fine needle aspiration cytology
FTUMP	Follicular tumor with uncertain malignant potential
HBA	*Hospital Beatriz Ângelo*
HCTUMP	Hürthle cell tumor with uncertain malignant potential
HL	*Hospital da Luz*
IPOFGL	*Instituto Portugês de Oncologia Francisco Gentil de Lisboa*
PCCV	Papillary carcinoma classic variant
PCFV	Papillary carcinoma follicular variant
PCOV	Papillary carcinoma oncocytic variant

Introduction and Objectives

Thyroid nodules are a common entity, the majority being benign. Thyroid malignancies, however, present themselves as nodules in 95% of the cases[1]. According to *Direcção Geral da Saúde*[2] the prevalence of palpable thyroid nodules is 3 to 7%, the prevalence of ecographic detected nodules is 20 to 76% and, of these nodules, 5 to 15% are malignant. Similar data was reported in the USA[3].

"*Fine needle aspiration (FNA) plays an essential role in the evaluation of the euthyroid patient with a thyroid nodule: it reduces unnecessary surgery for patients with benign nodules and appropriately triages patients with malignant nodules for timely clinical intervention*"[4]. The Bethesda System for Reporting Thyroid Cytopathology is an international classification of cytologic findings that links to clinical management. Its diagnostic categories and risk for malignancy are shown in the following table 1[5]:

Diagnostic category	Risk of malignancy (%)
Non diagnostic	-
Benign	0 - 3
Follicular Lesion of Undetermined Significance	~5 - 15
Follicular Neoplasm	15 - 30
Suspicious for Malignancy	60 - 75
Malignant	97 - 99

The FLUS diagnostic category is employed when "*cytomorphologic findings are neither convincingly benign nor sufficient for interpretation of neoplasia/malignancy*"[6]. This category proves a challenge in the management of these nodules.

Several studies are ongoing to determine the diseases underlying a FLUS report. According to Gardner and Shoback[7], 10 to 15% of all cytologies are classified as FLUS and of these cases 15% are malignant. Jing et al[8] found that 5.8% of the FNAs investigated had a FLUS diagnosis and, within the FLUS cases, 6% were malignant. According to "*The Bethesda System for Reporting Thyroid Cytopathology*"[9] FLUS is reported in 3 to 18% of all thyroid FNAs, the risk of malignancy in these cases is between 5 to 15% and the recommended frequency of FLUS report should be 7%.

Objectives: In this study a correlation between FLUS cytology and a histological diagnosis was made using data from Portuguese hospitals. The percentage of FLUS diagnosis and those who underwent surgery was calculated. The post surgical histological diagnosis wias noted and their relative percentage calculated.

Materials and Methods

In this study, pathology databases from *IPOFGL*, *HL* and *HBA* were consulted from January 1st 2012 to December 31st 2013. A correlation between the histological diagnosis and the cytology report was made. For a correct comparison, the location and ultrasound characteristics of the punctured lesion were considered.

The percentage of FLUS was calculated as well as the percentage of FLUS with surgery. The youngest and oldest ages were noted and the mean age and mode were calculated. The female:male ratio was calculated as well.

Each histological diagnosis was noted individually and because many cases had more than one histological diagnosis a single dominant disease was considered for statistical study. For the selection of the dominant disease a hierarchy was followed. Malignant neoplasia was considered the most important pathologic process, followed by benign neoplasia, inflammation and hyperplasia. Cases of micro carcinomas and tumors with uncertain malignancy were considered separately. Since inflammation can be a stimulus to malignant disease[10], all histological diagnosis associated with inflammation where noted.

Results

Patients were predominantly female and most at the 6th decade. Female:male ratio was 3.39. This data encompasses with other series and it is described in the literature[1].

Table 2: Age description.

Age			
Min.	**Max.**	**Mean age**	**Mode**
18y	86y	50.92y	56y

Table 3: Gender description.

Gender		
Male	**Female**	**F:M Ratio**
23	78	3.39:1

From January 1st 2012 to December 31st 2013 these hospitals had 5267 thyroid cytology reports and 310 were reported as FLUS. A hundred and one underwent surgery and the histological report was consulted.

Table 4: FLUS relative percentages.

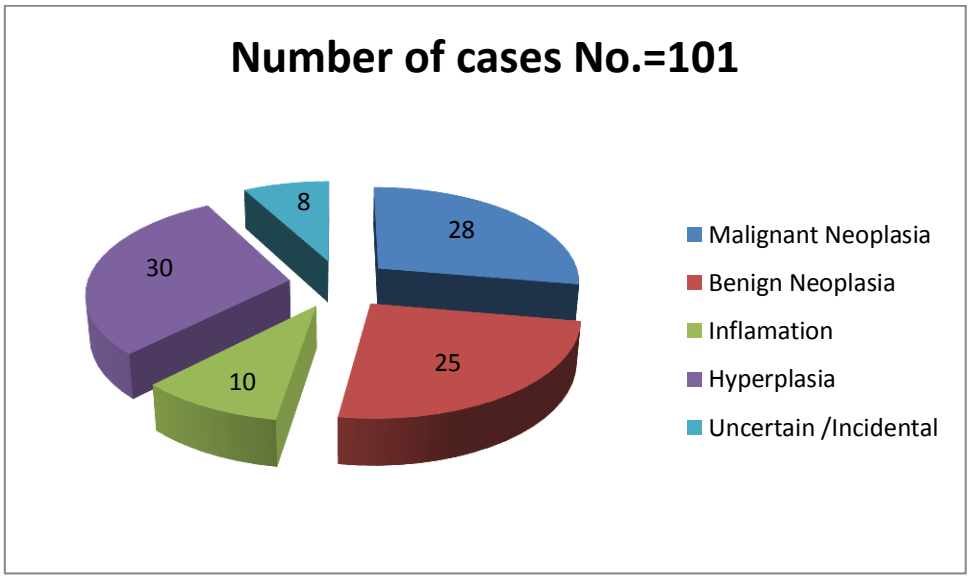
FLUS Cases (%)	
FLUS/Total	**FLUS w/ surgery/Total FLUS**
5.89 (310/5267)	32.58 (101/310)

Table 5 describes the main diagnosis found on thyroid specimens with FLUS cytology and the chart depicts the grouped entities.

Table 5: Description of histological diagnoses found on thyroid specimens with FLUS cytology.

Diagnosis
Adenomatous Nodule
Follicular Adenoma/Hürthle cell Adenoma
Follicular Carcinoma
FTUMP/ HCFTUMP
Graves' disease
Hyperplasic nodule/ Multinodular Goiter
Lymphocytic Thyroiditis
Medullary Carcinoma
Micro Follicular Carcinoma
Micro Papillary Carcinoma
Micro PCFV
PCCV
PCFV
PCOV
Parathyroid Adenoma

Four groups where created according to the dominant histological diagnosis: malignant neoplasia, benign neoplasia, inflammation and hyperplasia. A fifth group was created for diseases that had an uncertain malignant potential and for micro carcinomas.



Graphic 1: Cases grouped by dominant pathology found on thyroid specimens with FLUS cytology.

Table 6: Dominant pathology with the histological diagnosis and relative percentage.

Pathology	%	Diagnosis	No. of cases	% in Group	% in Total
Malignant Neoplasia	27,72	PCFV	19	67,86	18,81
		PCCV	5	17,86	4,95
		Follicular Carcinoma	2	7,14	1,98
		Medullary Carcinoma	1	3,57	0,99
		PCOV	1	3,57	0,99
Benign Neoplasia	24,75	Follicular Adenoma	17	68	16,83
		Hürthle cell Adenoma	7	28	6,93
		Parathyroid Adenoma	1	4	0,99
Inflamation	9,9	Lymphocytic Thyroiditis	10	100	9,9
Hyperplasia	29,7	Multinodular Goiter	24	80	23,76
		Adenomatous nodule	6	20	5,94
		Hyperplasic nodule	4	13,33	3,96
		Hürthle cell metaplasia	3	10	2,97
		Graves disease	2	6,67	1,98
Uncertain and Incidental	7,92	Micro Papillary Carcinoma	4	50	3,96
		FTUMP	1	12,5	0,99
		HCFTUMP	1	12,5	0,99
		Micro Follicular Carcinoma	1	12,5	0,99
		Micro PCFV	1	12,5	0,99

Diseases that coexisted with inflammation are depicted in table 7.

Table 7: Entities coexisting with inflammation.

No.cases	Associated Diseases	No.
22	Multinodular Goiter	11
	Follicular Adenoma	6
	Hürthle cell Adenoma	2
	Adenomatous nodule	2
	PCFV	2
	Hyperplasic Nodule	1
	Graves' Disease	1
	Micro Follicular Carcinoma	1
	Micro Papillary Carcinoma	1
	PCCV	1

As we can see in table 6, malignant neoplasia was the dominant diagnosis in 27.72% of all cases. The most common malignancy was the follicular variant of papillary carcinoma, corresponding to 67.86% of this group. The second most common malignancy was the classic variant of papillary carcinoma (17.86%), followed by follicular carcinoma (7.14%). The oncocytic variant of papillary carcinoma and the medullary carcinoma corresponded to 3.57%, each, of this group.

Benign neoplasias where the dominant diagnosis in 24.75% of all cases. Follicular adenoma was the most common corresponding to 68% of this group, followed by Hürthle cell adenoma (28%) and by one case of parathyroid adenoma (4%).

Cases that had inflammation and hyperplasia, the inflammation was considered the main diagnosis. Lymphocytic thyroiditis represented the only inflammatory disease.

Hyperplasia was the dominant diagnosis in 29.7% of all cases, being this the group with more cases. Since each case had more than one form of hyperplasia each one was considered individually. The most recurring histological diagnosis were multinodular goiter, hyperplasic nodules and adenomatous nodules. Hürthle cell metaplasia and Graves’ disease were also reported.

A separated group was created for micro carcinomas and tumors with uncertain malignant potential. Micro papillary carcinoma was the most common, followed by micro follicular carcinoma and a micro papillary carcinoma follicular variant. The uncertain cases were the follicular tumor with uncertain malignant potential and the Hürthle cell follicular tumour with uncertain malignant potential.

Similarly to the group of hyperplasia, more than one diagnosis was found accompanied by inflammation, so each diagnosis was considered individually. The diseases found were multinodular goiter, adenomatous/hiperplasic nodules, follicular/Hürthle cell adenomas, PCFV, Graves’ disease, micro follicular carcinoma, micro papillary carcinoma and PCCV.

Discussion

This study has found that 5.89% of all cytologies were classified as FLUS. This value is in accordance to the recommendations of "*The Bethesda System for Reporting Thyroid Cytopathology*"[9]. Approximately one third of the patients were treated surgically in the consulted hospitals, however it is unknown what course of treatment was followed in the other two thirds.

The statistical studies of age and sex were based on the population submitted to surgical treatment and not on the total population with a FLUS cytology report. In this population the minimum age was 18 years and the maximum was 86 years of age, with a mean age of 50.92 years and a mode of 56 years. Again these statistics have to be interpreted in light of a population treated surgically since age is a major consideration for a surgical approach. There are more females than males in the population studied. In a total of 101 patients, 78 where females and 23 males with a sex ratio of 3.39 females to 1 male. The incidence of thyroid nodules is higher in females and this can explain the higher amount of females in this study[1].

Both benign and malignant diseases were diagnosed in thyroid specimens with a FLUS cytological report, as can be seen in table 5.

In this study 27.72% of the cases where malignant, a higher percentage than expected[(7-9)]. This can be attributed to the fact that the FLUS cases where not revised and repetition of FNAC was not taken in consideration. Most malignancies in this group had follicular characteristics, with the exception of PCCV cases, that were not expected in a FLUS setting. Again this high percentage can be explained by not considering the cases where FNAC was repeated and wielded a different cytological report. On the other hand, if clinical and image criteria favoured maligancy patients would underwent surgery without repeating.

Benign neoplasias where the third most frequent diagnosis found on this study, with a percentage of 24.75. Lesions with a follicular architecture were the most common finding. Parathyroid adenomas can be confused with thyroid nodules in FNAC since many morphologic features overlap[11].

Neoplasias, benign and malignant, correspond to 52.47% of all cases. Since FNAC should triage the surgical cases[4] the presence of neoplasias in more than half of all cases raise the question if cytlogical criteria have been well aplied.

The cases of hyperplasia were the most common in this study with a percentage of 29.7%.

The group of micro carcinomas and tumors of uncertain malignant potential had 8 cases in total. Six of the cases were micro carcinomas, incidental findings not correlated with

punctured nodules. Two were follicular tumors of uncertain malignant potential, with histological criteria.

Inflammation was present in cases of all groups. In the 101 cases, 22 had inflammation (21.78%) and in 10 cases it was considered the main diagnosis (9.9%), although there was some form of hyperplasia. The malignant neoplasias accompanied by inflammation were 2 cases of PCFV and 1 case of PCCV. In the group of uncertain and incidental diagnosis 2 cases had inflammation, a micro carcinoma papillary carcinoma and a micro follicular carcinoma. Since 21.78% of all cases had inflammation associated, it is pertinent to question the influence of inflammation in FLUS.

Conclusion

In this study the frequency of FLUS diagnosis is in accordance to the recommendations of “The Bethesda System for Reporting Thyroid Cytopathology”.

Although being a surgically treated population, patients in this study were predominantly female and most at the 6th decade.

Most cases associated with a FLUS diagnosis are hyperplasic, being the predominant diagnosis in 29.7% of all cases.

Malignancies where higher than expected, being the predominant disease in 27.72% of all cases. Since this study is limited by not considering FNAC repetition more investigations are necessary. The total cases of benign and malignant neoplasias combined far outnumber the remainder cases and FNAC should appropriately triage surgical cases, which means that better application of cytological criteria should be applied to ensure a correct diagnosis prior to surgery.

Inflammation coexisted with malignant and benign neoplasias and with microcarcinomas and also, cases in the inflammatory group had some form of hyperplasia. With these findings it is pertinent to question the influence of inflammation in a FLUS diagnosis.

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Appendix

Table depicting age, sex and associated case, with all histological diagnosis.

Sex	Age	Histological Diagnosis
F	65	Multinodular Goiter
M	29	PCFV
F	48	Follicular Adenoma
F	47	PCFV
F	34	Follicular Carcinoma
F	80	Hürthle Cell Adenoma
M	55	Multinodular Goiter and Lymphocytic Thyroiditis
F	72	Multinodular Goiter and Graves disease
F	59	Multinodular Goiter with Hyperplasic nodule
M	60	Multinodular Goiter with Hyperplasic Nodule
F	51	Multinodular Goiter and Follicular Adenoma
F	45	PCFV
F	40	Folicular Adenoma and Lymphocytic Thyroiditis
M	33	Multinodular Goiter
F	69	PCFV and Lymphocytic Thyroiditis
F	68	PCCV
F	33	Follicular Adenoma
F	74	Multinodular Goiter with Hyperplasic nodule and lymphocytic thyroiditis
F	75	Hürthle cell Adenoma and Lymphocytic Thyroiditis
F	44	PCFV and Lymphocytic Thyroiditis
F	25	PCFV
F	22	PCFV and Multinodular Goiter
F	82	Hürthle cell Adenoma
M	56	Multinodular Goiter and Lymphocytic Thyroiditis
F	66	Multinodular Goiter and Lymphocytic Thyroiditis
M	26	PCCV
F	36	PCFV and Multinodular Goiter
M	40	PCFV
M	49	PCFV
F	63	PCFV and Multinodular Goiter
F	86	Multinodular Goiter
F	22	PCFV
F	37	PCOV
F	56	PCCV, Multinodular Goiter, Lymphocytic Thyroiditis, Follicular Adenoma
F	68	PCFV

F	60	Multinodular Goiter
F	44	Follicular Adenoma
F	53	PCFV
F	38	Multinodular Goiter and Lymphocytic Thyroiditis
M	55	Follicular Adenoma
F	37	Graves disease and Lymphocytic thyroiditis
M	49	Hyperplasic nodule
F	40	Multinodular Goiter
F	46	Follicular Adenoma
F	45	Follicular Carcinoma
F	56	Follicular Adenoma
F	51	Multinodular Goiter and Lymphocytic Thyroiditis
F	45	Multinodular Goiter
F	45	Multinodular Goiter and Hürthle cell Adenoma
F	32	PCFV
F	56	Hürthle cell Adenoma
F	41	Follicular Adenoma
F	56	Follicular Adenoma
F	40	Multinodular Goiter
F	62	Hürthle cell Adenoma and Multinodular Goiter and Lymphocytic Thyroiditis
M	62	Multinodular Goiter
F	39	PCFV
F	39	PCCV
M	51	Follicular Adenoma
F	36	Hyperpastic nodule
F	54	Multinodular Goiter and Hürthle cell Adenoma
M	65	Follicular Adenoma and Lymphocytic Thyroiditis
M	37	PCCV
F	36	PCFV
F	18	Hyperplasic nodule and Lymphocytic Thyroiditis
F	62	Multinodular Goiter
F	69	Multinodular Goiter
F	69	Multinodular Goiter
F	41	Multinodular Goiter
F	53	Follicular tumour with uncertain malignant potential
M	76	Graves disease
F	57	Multinodular Goiter
F	50	Follicular Adenoma and Lymphocytic Thyroiditis
F	55	Multinodular and Hyperplasic nodule
F	56	PCFV
F	61	Hyperpastic nodule
M	32	Follicular Adenoma and Lymphocytic Thyroiditis
F	53	Multinodular Goiter with Hyperplasic nodule

F	55	Multinodular Goiter with Hyperpastic nodule
F	42	Multinodular Goiter
M	38	Multinodular Goiter
M	59	Multinodular Goiter and Lymphocytic Thyroiditis
F	34	Multinodular Goiter and Lynfocitic Thyroiditis
F	71	Multinodular Goiter and Lynfocitic Thyroiditis
M	52	Follicular Adenoma
F	66	Parathyroid Adenoma
M	32	Follicular Adenoma and Lynfocytic Thyroiditis
F	65	Multinodular Goiter
F	68	Multinodular Goiter
F	56	Hürthle cell follicular tumour with uncertain malignant potential
F	57	Hyperplastic Nodule and Hurtle Cell Metaplasia
F	66	Hyperpastic nodule
F	30	Multinodular Goiter Oncocytic Transformation
M	38	Follicular Adenoma
F	79	Multinodular Goiter and Lynphocytic Thyroiditis
F	54	Multinodular Goiter
F	40	Hürthle cell Adenoma
M	35	Hyperpastic nodule
M	54	PCFV
F	65	Multinodular Goiter
F	50	Multinodular Goiter