

Assessment of malignancy rate in thyroid nodules according to the Bethesda system of fine-needle aspiration

Report from a tertiary center in the Southwestern region of Saudi Arabia

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ABSTRACT

الأهداف : دراسة معدلات الأورام السرطانية في كل فئة من الفئات التشخيصية للفحص الخلوي للغدة الدرقية باستخدام نظام بيتيسدا .

الطريقة : أجريت هذه الدراسة الوصفية الاسترجاعية في قسم علم الأمراض، مستشفى عسير المركزي بالمنطقة الجنوبية الغربية، عسير، المملكة العربية السعودية خلال الفترة من أكتوبر 1998م إلى أبريل 2007م. وقد شملت الدراسة جميع الغدد الدرقية التي خضعت للفحص الخلوي قبل الجراحة بواسطة ارتشاف الإبرة الرفيعة والتي خضعت للفحص النسيجي المجهرى بعد العملية الجراحية. تم إعادة تصنيف جميع التشخيصات الخلوية باستخدام نظام بيتيسدا لتشمل الفئات التالية: فئة غيرتشخيصية (العينة غير كافية)، وفئة الأورام الحميدة، وفئة التغيرات الخلوية ذات الأهمية غير المعروفة، وفئة الأورام الدرقية الحويصلية، وفئة اشتباه الورم السرطاني، وفئة الأورام السرطانية. تم تحديد معدلات الأورام السرطانية في كل فئة بناءً على التشخيص النهائي حسب الفحص المجهرى للأنسجة المرضية لكل من هذه الفئات التشخيصية الخلوية .

النتائج : شملت هذه الدراسة 323 حالة. لقد تم إعادة تصنيف جميع التشخيصات الخلوية باستخدام نظام بيتيسدا وأظهرت النتائج الفئات التالية: عدم التشخيص (العينة غير كافية) في 6.2% من الحالات، وأورام حميدة في 57.3%، وفئة التغيرات الخلوية ذات الأهمية غير المعروفة في 13.6%، وفئة الأورام الدرقية الحويصلية في 16.1%، وفئة اشتباه الورم السرطاني في 1.5%، وفئة الأورام السرطانية في 5.3%. لقد كانت المعدلات المناظرة للأورام السرطانية بعد الفحص المجهرى للأنسجة المرضية لكل فئة على النحو التالي: 35% في فئة عدم التشخيص (العينة غير كافية)، و10.3% في فئة الأورام الحميدة، و15.9% في فئة التغيرات الخلوية ذات الأهمية غير المعروفة، و32.7% في فئة الأورام الدرقية الحويصلية، و60% في فئة اشتباه الورم السرطاني، و94% في فئة الأورام السرطانية.

خاتمة : أظهرت هذه الدراسة بأن استخدام نظام بيتيسدا المعياري للفئات الخلوية لارتشاف الإبرة الرفيعة في تشخيص أمراض الغدة الدرقية قد يؤدي إلى تعزيز التواصل بين الجراحين وأطباء علم الأمراض، ويساعد في معرفة نسبة الأورام السرطانية في كل فئة من فئات الفحص الخلوي، ويسهل إتباع نهج أكثر اتساقاً لعلاج المرضى .

Objectives: To determine the rates of malignancy of thyroid nodules in each standard cytologic diagnostic category of the Bethesda system.

Methods: In a retrospective cohort study from October 1998 to April 2007 at the Department of Pathology, Aseer Central Hospital, Southwestern region of Saudi Arabia, all cases of thyroid nodules that underwent preoperative cytologic examination by fine-needle aspiration (FNA) and concurrent postoperative histopathologic examination were included. All FNA diagnoses were reclassified using the thyroid FNA Bethesda reporting system, including non-diagnostic (insufficient), benign, atypical follicular lesion of undetermined significance (AFLUS), neoplasm, suspicious of malignancy, and malignant groups. The rate of malignancy based on final histopathologic evaluation was analyzed for each of these cytologic groups.

Results: A total of 323 thyroid fine needle aspiration cytology (FNAC) diagnoses were reclassified into non-diagnostic 6.2%, benign 57.3%, AFLUS 13.6%, follicular and Hürthle cell neoplasms 16.1%, suspicious of malignancy 1.5%, and malignant 5.3% groups. The corresponding rate of malignancy on histopathologic examination was as follows: 35% in the non-diagnostic group, 10.3% in the benign group, 15.9% in AFLUS group, 32.7% in follicular and Hürthle cell neoplasms, 60% in the suspicious of malignancy group, and 94% in the malignant group.

Conclusion: Applying a standard terminology reporting system for thyroid FNA may enhance the communication between pathologists and clinicians, assists them to find out the rate of malignancy in each cytologic group, and facilitating a more consistent approach for patients' management.

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Thyroid nodules can be identified in 4-8% of adults by clinical examination.^{1,2} The preoperative algorithmic approach for evaluation of thyroid nodules involves the assessment of the patients' risk factors (such as radiation exposure, low-iodine diet, and family history of thyroid cancer), physical examination, and running a panel of ancillary techniques such as thyroid function tests, imaging studies, and fine needle aspiration cytology (FNAC).³ Fine needle aspiration cytology is considered a useful simple preoperative test for triaging patients with palpable thyroid nodules. The ultimate goal is to differentiate between malignant and benign lesions. Most of the thyroid nodules turned out to be benign and approximately 5-10% are anticipated to be malignant.^{4,5} This distinction is not only important to avoid unnecessary surgery, but also to plan the appropriate surgical approach. Reporting of thyroid fine-needle aspiration (FNA) using a standard terminology is not yet widely implemented. Diagnostic terminology varies from institution to another; however, using a standardized nomenclature for reporting thyroid FNA cytology can enhance the communication and common understanding between pathologists and clinicians and better correlation with histopathology. The purpose of this study is to categorize thyroid lesions by FNA using the thyroid FNA classification of Bethesda system⁶ including: non-diagnostic, benign, atypical follicular lesion of undetermined significance (AFLUS), follicular/Hürthle cell neoplasm, suspicious of malignancy, and malignant categories; and to determine the rate of malignancy in each cytologic category by correlating the results with histopathologic diagnoses on the resected specimens. Infrequent studies⁷ described the malignancy frequency in each cytological group according to the standardized 6-tier Bethesda reporting system. Similar study at the national level does not exist.

Methods. This is a retrospective cohort study of all FNAC of the thyroid were reviewed and categorized using the Bethesda reporting system.⁶ The study was performed at Aseer Central Hospital, Abha, Saudi Arabia during October 1998 to April 2007. The review process was performed by 3 pathologists (2 cytopathologists and one histopathologist). These categories include non-diagnostic (unsatisfactory), benign, AFLUS, follicular/Hürthle cell neoplasm, suspicious for malignancy and malignant category. The interpretations of FNAC cases were recorded by at least 3 pathologists who were blinded to the final histopathologic results. Cases using descriptive cytologic diagnoses were located by consensus into the best overall group. Thyroid FNA performed in our institution used Papanicolaou stained smears. The final corresponding histopathologic diagnoses were

then compared. Cases of FNAC with no corresponding histopathology were excluded. Only cases with preoperative FNA cytologic material and postoperative histologic diagnosis were included in the present study. Cases in which FNA was performed in other hospitals in which the cytologic material was not available for review were also excluded. The histopathologic sections were stained using the standard Hematoxylin-Eosin staining method of 4 micron-thick paraffin-embedded sections. The cytomorphologic diagnostic criteria used in non-diagnostic or unsatisfactory category applied for cases in which the smear consists predominately of blood, absent or insufficient follicular epithelium, or cases with extensive air-drying artifact or thick smear with obscuring cellularity. Benign was used for cases having features of conditions such as thyroiditis (Figure 1a), colloid nodule (Figure 1b), and hemorrhagic colloid nodule, AFLUS category for cases that having cytomorphologic findings are not convincing benign, and at the same time insufficient to be categorized as follicular/Hürthle cell neoplasms or suspicious of malignancy. Neoplasm (follicular neoplasm) was used for cases having moderate to high cellularity with microfollicular cytoarchitecture and absent or scant colloid; however, if the cytoplasm was oncocytic, it is classified as a Hürthle cell neoplasm (Figure 1c).

Suspicious of malignancy was applied to cases that have cytologic features suggestive of papillary carcinoma, lymphoma, or anaplastic carcinoma, with some limitation such as cystic degeneration of the aspirated lesion or low-cellularity of the aspirated cytologic material; and the malignant category for cases that have smears with adequate and optimum quantity and quality of aspirated thyroid lesion allowing definitive cytologic diagnosis such as papillary carcinoma (Figure 1d), medullary or anaplastic carcinoma. Occult incidental microscopic papillary carcinomas (OIMPC) (≤ 1 cm) detected by histopathologic examination of the resected specimens were not considered in this group as applied in previous studies.⁷ Fine-needle aspiration was performed in our institution by different specialties, including, general surgery, ENT, internal medicine, radiology, and pathology.

Data were coded, validated and analyzed using SPSS® for Windows (Version 13.0). Frequency and percentage were used to present the data of cytologic diagnoses and malignancy by histopathology. We calculated 95% confidence interval (CI) of the present rate. We used Pearson Chi-square test as a test of significant at 5% level to compare the malignancy rates of the current study with the corresponding rates of other published studies.

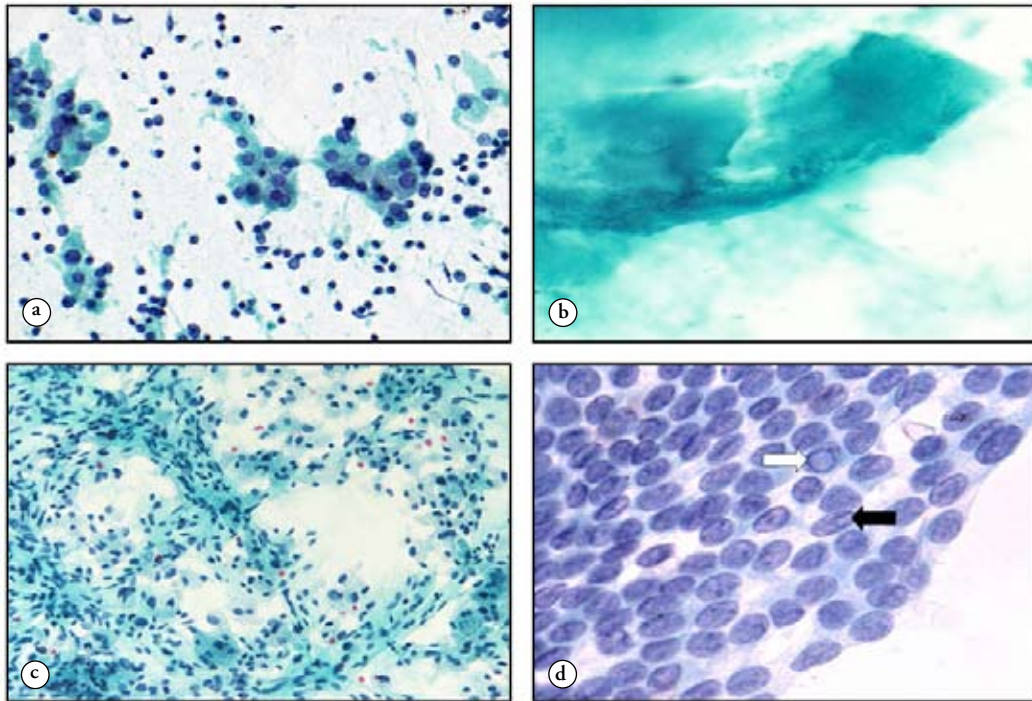


Figure 1 - A picture of a) Lymphocytic thyroiditis showing a background of lymphocytes admixed with small clusters of follicular cells with oncocytic change (Papanicolaou stain, original magnification x 200). b) Colloid nodule with a fragment of inspissated colloidal material in a background of watery colloid (Papanicolaou stain, original magnification x 400). c) Hurthle cell neoplasm showing microfollicles with Hurthle features and prominent transgressing blood vessels (Papanicolaou stain, original magnification x 200). d) Papillary carcinoma showing monolayered sheet of follicular cells with nuclear grooves (black arrow), and nuclear pseudoinclusion (white arrow).

Results. The present study included 323 thyroid FNA diagnoses (Table 1). Diagnoses rendered on these specimens were distributed as follows: 20 non-diagnostic (6.2%), 185 benign (57.3%), 44 AFLUS (13.6%), 52 follicular/Hürthle cell neoplasms (16.1%), 5 suspicious of malignancy (1.5%), and 17 malignant (5.3%). Further evaluation of these cases by histopathologic examination showed 17 malignant cases and 53 cases of OIMPC. The benign cases on histopathologic examination of the surgically resected thyroid tissue were 253 cases representing 78.3%. The rates of malignancy for each FNA diagnostic category as proven on histopathologic examination were as follows: non-diagnostic 35% (7/20); benign 10.3% (19/185); AFLUS 15.9% (7/44); follicular/Hürthle cell neoplasms 32.7% (17/52); suspicious of malignancy 60% (3/5); and malignant 94% (16/17). On histopathologic subtyping, 17 malignant cases shows invasive papillary carcinoma (n=11), Hürthle cell carcinoma (n=3), and follicular carcinoma (n=3). If we combined benign and malignant diagnoses by cytology and histopathology, we found a false-positive rate of FNA of 5.9% (1/17), and a false-negative rate of 54.3% (19/35).

Discussion. As per the guidelines established by the American Thyroid Association, FNAC is recommended

Table 1 - Frequency of cytologic diagnoses and rates of malignancy on thyroid resection for fine needle aspiration diagnostic categories (N=323).

Diagnostic FNAC category*	Frequency		Rate of malignancy by histology	
	n	(%)	n	(%)
Non-diagnostic (insufficient)	20	(6.2)	7/20	(35.0)
Benign	185	(57.3)	19/185	(10.3)
Atypical follicular lesion of undetermined significance	44	(13.6)	7/44	(15.9)
Follicular/Hürthle cell neoplasm	52	(16.1)	17/52	(32.7)
Suspicious of malignancy	5	(1.5)	3/5	(60.0)
Malignant	17	(5.3)	16/17	(94.0)

*Based on Bethesda system for reporting thyroid fine needle aspiration.⁶
FNAC - fine needle aspiration cytology

to be used as part of the initial diagnostic work up for thyroid nodule prior to both ultrasound and scintigraphy due to its diagnostic usefulness and cost-effectiveness.⁸ Fine needle aspiration cytology has been demonstrated in many reports to reduce the percentage of unnecessary thyroidectomies; therefore, FNAC can play an important role in patient management. On the other hand, FNAC can have potential limitations and diagnostic pitfalls particularly for small thyroid nodules or cystic lesions. Fine needle aspiration was

Table 2 - Percentages of fine-needle aspiration diagnoses among published series with *p*-values.

Diagnostic FNAC category ^a	Present study		Yassa et al ²¹		Jo et al ⁷		Nayar & Ivanovi ²⁰		Yang et al ¹⁹	
	%	95% CI	%	<i>P</i> -value	%	<i>P</i> -value	%	<i>P</i> -value	%	<i>P</i> -value
Non-diagnostic (insufficient)	6.2	3.8-9.5	7	0.650	18.6*	0.001	5	0.304	10.4*	0.015
Benign	57.3	51.8-62.6	66*	0.001	59.0	0.551	64*	0.001	64.6*	0.008
Atypical follicular lesion of undetermined significance	13.6	10.2-17.7	24*	0.001	17.0	0.120	6*	0.001	19.2*	0.013
Follicular/Hürthle cell	16.1	12.4-22.4	28*	0.001	25.4*	0.001	14	0.292	32.2*	0.001
Suspicious of malignancy	1.5	0.6-3.4	9*	0.001	2.3	0.381	2	0.569	2.6	0.247
Malignant	5.3	3.2-8.1	5	0.831	7.0	0.236	5	0.837	7.6	0.882

^aBased on Bethesda system for reporting thyroid FNA.⁶ *Significantly different from the present study (*p*<0.05), CI - 95% confidence interval

introduced in 1960 in Sweden as a useful technique to categorize thyroid nodules.^{9,10} Use of non-standardized terminology has led to variable practices among pathologists, surgeons, and other clinicians. In 2007, NCI proposed a standardized nomenclature for thyroid FNAC, known as Bethesda System for Reporting Thyroid Cytology,¹¹ which included the following categories: non-diagnostic (unsatisfactory), benign; AFLUS; follicular neoplasm/suspicious of a follicular neoplasm, including Hürthle cell type; suspicious of malignancy; and malignant. Increased utilization of ultrasound has led to recognition of more non-palpable thyroid nodules up to 10-41%.¹²⁻¹⁸ The main ultimate goal of performing FNAC for patients presenting with thyroid nodules is to determine whether the lesion is benign or malignant. Patients with cytologic diagnoses suggesting malignancy and/or neoplasia are treated surgically, while patients with cytologic diagnoses suggesting benign can be followed up clinically. The diagnostic yield of thyroid FNA varies from one institution to another. This variation is due to several factors, which include, but are not limited to the followings: i) The method of acquisition of the lesional tissue by FNA, whether under ultrasound guidance or not, experience in smearing and preparation of the cytology slides, ii) Experience of cytology technologists, iii) Interpretation of the cytologic material, particularly for uncertain categories such as follicular lesions, iv) Reporting method of FNA results.

We recognized that the cytologic classification of thyroid nodules in our institution according to the standardized nomenclature of Bethesda system yielded some significantly different results for the distribution of FNAC diagnoses among the other published studies^{7,19,20} (Table 2).

The rate of malignancy in the non-diagnostic group in our study was 35%. This was higher than that reported in other series.^{19,21} Inadequacy is an inherent limitation in diagnostic cytopathology due to sampling error, especially for multiple nodules or cystic lesions, but it can be minimized by targeted FNAC under ultrasound

guidance. This higher rate in our study could be related to non-use of ultrasound guidance during thyroid aspiration particularly, for the non-palpable thyroid nodules. In fact, thyroid aspirations in our institution were performed by different specialties such as surgery, ENT, internal medicine services and by residents with different levels of training. Fine-needle aspiration is a special technique requiring certain skills in acquisition of the aspirated material and proper handling of the cytologic material post-aspiration. It is important for the treating physician or surgeon when receiving a thyroid cytologic report indicating insufficient material to prompt for repetition of FNAC to rule out malignancy. We recommend that all thyroid FNAC to be carried out with the presence of a well-trained cytopathologist/cyrotechnologist who can ensure the proper handling of the aspirated cytologic material and perform on-site assessment for the adequacy of the specimen. For the benign group, the malignancy rate was also higher (10.3%), and this is attributed also to the fact that FNA is performed in our institution by different specialties including general surgery, ENT, endocrinologists and others without ultrasound guidance for small thyroid nodules; this could result into a sampling of a non-lesional tissue or a perilesional tissue; furthermore, no on-site assessment of the aspirated material is not routinely carried out during the study.

The high false positive and high false-negative rates in our current study could be attributed to the low number of cases involved, high number of OIMPC, and also to the fact that lesional tissue may not be adequately represented by FNA technique in our institution. The rate of malignancy in AFLUS and follicular/Hürthle neoplasm in our study was 15.9% and 32.7%, respectively. These 2 categories are heterogenous, and their diagnostic criteria are subjective to inter-observer and intra-observer variability. This can explain the wide range of rate in other studies.^{19,20,21} namely, Nayar et al²⁰ reported a rate of 18% in AFLUS group, while Yang et al¹⁹ reported a lower rate of 3.2%. The malignancy rate in suspicious group was 60% and

in the malignant groups was 94% in the present study, which was comparable to what was reported in other studies^{7,20} in which the malignancy rate was 53-70% for the “suspicious of malignancy” group, and 97-98% for the “malignant” group in the published studies.^{7,20} The implication of these findings is to investigate and compare the malignancy rate in each Bethesda standard group in other national medical institutions, practically for the unsatisfactory and AFLUS groups.

There are some limitations in the present study, which include the relatively low number of the patients involved, absence of on-site assessment of adequacy, which could explain the higher frequency of cases in non-inadequate (unsatisfactory) group, and the type of cytology practice in which the fine aspiration is performed by various specialties in different levels of training.

In conclusion, although thyroid cytology is a useful preoperative technique for triage of thyroid nodules, it is associated with inherent diagnostic limitations, particularly for the indeterminate group. It is recommended to repeat the non-diagnostic (insufficient) group with on-site assessment to ensure the adequacy of the aspirated cytologic material and to rule out malignancy.

Standardized terminology for reporting thyroid fine-needle aspiration by Bethesda has recently been proposed. Using this reporting system can enhance the communications between pathologists and clinicians, and may facilitate a more consistent approach for patients' management.

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