

# Thyroid Fine-needle Aspiration: Histologic Correlation of the Diagnostic Categories of the Bethesda System with Emphasis on “Atypia of Undetermined Significance”: A 5-year Single-institution Experience

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## ABSTRACT

**Aim:** The aim of this study is to correlate the thyroid cytology diagnosis with the final histologic diagnosis, which is considered by us as the gold standard diagnostic test.

**Materials and methods:** We studied all the thyroid cytopathology cases performed over the last 5 years at King Salman Military Hospital. We found a total of 1,048 thyroid fine-needle aspiration (FNA) cases, of which 318 cases had a follow-up histologic data. The cases are reported according to the Bethesda system for reporting thyroid cytopathology (BSRTC). The rate of malignancy is calculated for each diagnostic category (DC) as the proportion of malignant cases from the cases with histologic diagnosis. The false-positive cases are defined as the cases diagnosed in FNA as DC V or VI (suspicious for malignancy or malignant) and the following thyroid surgery showed a benign histology. The false-negative cases are those diagnosed in FNA as DC II (benign) and the following thyroid surgery showed a malignant diagnosis.

**Results:** The percentage of false-positive cases for DC V (suspicious for malignancy) is 22.5%, while it is 2.38% for DC VI (malignant). The false-negative cases are those diagnosed in FNA as DC II (benign) and the following thyroid surgery showed a malignant diagnosis (8.7%). However, after reviewing the false-negative cases, eight cases were reclassified retrospectively, as “nondiagnostic”. The malignancy rate for our “atypia of undetermined significance (AUS)” cases is estimated to be between 21% and 35%.

**Keywords:** Atypia of undetermined significance, Fine-needle aspiration, The Bethesda system for reporting thyroid cytopathology.

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## BACKGROUND

Fine-needle aspiration (FNA) of the thyroid gland is currently the most accurate and cost-effective way of examining thyroid nodules. It has successfully reduced unnecessary surgical interventions and their complication. For poorly palpated nodules, posterior nodules or nodules with cystic components, ultrasound-guided FNA is strongly recommended, as these scenarios have a higher rate of nondiagnostic or false-negative results (2015 American Thyroid Association guidelines, strong recommendation, high-quality evidence).<sup>1</sup>

The benign FNA result normally indicates no immediate further diagnostic modalities and serial ultrasound to be continued. However, the surgeon should rely on clinical judgment in patients with negative FNA if there are “warning signs”, such as rapid tumor growth, very firm nodules, fixation of nodule to adjacent structures, paralysis of vocal cords, regional lymphadenopathy, age less than 20 or greater than 70, history of head or neck irradiation, nodule greater than 4 cm or that is partially cystic, or family history of thyroid cancer or multiple endocrine neoplasia (MEN) II syndromes.<sup>2</sup>

The Bethesda system for reporting thyroid cytology (BSRTC), the standard reporting system for thyroid FNA cytology, consists of six DCs that aimed at achieving uniformity in the diagnostic terms used among pathologist and to associate each of these categories with a certain risk of malignancy and recommended management.<sup>3</sup> Listed are the usual recommended treatment:<sup>3</sup>

- Diagnostic category I: Nondiagnostic, repeat under ultrasound guidance.

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- Diagnostic category II: Benign, follow-up.
- Diagnostic category III: AUS, repeat FNA.
- Diagnostic category IV: Follicular neoplasm/suspicious for follicular neoplasm, lobectomy.
- Diagnostic category V: Suspicious for malignancy; near total thyroidectomy or lobectomy.
- Diagnostic category VI: Malignant, total thyroidectomy.

Table 1 shows the estimated risk of malignancy in each of the DCs of the BTRTC, from Ali and Cibas.<sup>3</sup>

The BSRTC has been shown on meta-analysis to be a reliable reporting system.<sup>4</sup>

One of the BSRTC categories, AUS or “follicular lesion of undetermined significance (FLUS)” is applied when the cells (follicular, lymphoid, or others) show architectural or cytologic atypia that is not sufficient to be classified as suspicious for follicular neoplasm, suspicious for malignancy or malignant, and the atypia is more than what would be seen in benign lesions. The most common scenarios where this term is applied are listed in the Bethesda System for Reporting thyroid Cytopathology textbook<sup>3</sup> and the reader is referred to the textbook for those criteria.

The FNA diagnosis of “AUS” is usually accompanied by a recommendation to repeat the FNA. It has been recommended to be strict in assigning this category to cases and to limit the rate of this diagnosis to 7% of the thyroid FNAs, to prevent the misuse of this category.<sup>5</sup>

**MATERIALS AND METHODS**

We looked into the thyroid FNA cases performed at our institution over the last 5 years (January 2012 until March 2018) (Table 2). We correlated the FNA diagnosis with the final tissue diagnosis

**Table 1:** Implied risk of malignancy in each of the diagnostic categories of the Bethesda system for reporting thyroid cytopathology, from Ali and Cibas<sup>3</sup>

Diagnostic category	Cytologic diagnosis	Risk of malignancy (%)
II	Benign	0–3
III	Atypia of undetermined significance	5–15
IV	Follicular neoplasm/suspicious for follicular neoplasm	15–30
V	Suspicious for malignancy	60–75
VI	Malignant	97–99

**Table 2:** The fine-needle aspiration cases according to the diagnostic terminology of the Bethesda system for reporting thyroid cytopathology

Diagnostic category	Number of cases (%)
Nondiagnostic or unsatisfactory (I)	111 (10.5)
Benign (II)	764 (72.9)
Atypia of undetermined significance (AUS) (III)	58 (5.5)
Follicular neoplasm (FN) or suspicious for a follicular neoplasm (IV)	30 (2.86)
Suspicious for malignancy (SUSP) (V)	38 (3.6)
Malignant (VI)	47 (4.48)
Total	1048

**Table 3:** All fine-needle aspiration cases with histologic follow-up

Diagnostic category	Total number of cases	Number of cases with follow-up surgery (%)	Number of cases with benign histology (%)	Number of cases with malignant histology (%)
Nondiagnostic or unsatisfactory (I)	111	23 (0.7)	13 (56.52)	10 (45.8)
Benign (II)	764	183 (18%)	167(91.26)	16 (8.7)*
Atypia of undetermined significance (AUS) (III)	58	20 (34.4)	13 (65%)	7 (35%)
Follicular neoplasm (FN) or suspicious for a follicular neoplasm (IV)	30	19 (63.3)	14 (73.6)	5 (26.3)
Suspicious for malignancy (SUSP) (V)	38	31 (81.58)	7 (22.5)	24 (77.4)
Malignant (VI)	47	42 (89.3)	1 (2.38)	41 (97.6)
Total	1048	318 (30.3)	215 (67.6)	103 (32.4)

\*In retrospect, eight cases should have been called “nondiagnostic”, according to the BSRTC, since these cases contained either macrophages only or very few thyrocytes; therefore, the “actual” malignancy risk is 4.9%

(thyroidectomies, partial or total) or metastasis, if present. We considered the histology to be the “gold standard” test.

We considered papillary microcarcinomas as incidental findings, and we assumed that they were not accountable for any of those categories (III, IV, V, and VI). Although theoretically these small lesions might be aspirated.

The malignancy rate for a given category is defined as the number of malignant cases divided by the total number of cases within that category, which underwent surgery (i.e., the percentage of cases that are true positive confirmed to be malignant by histology) (Table 3).

**RESULTS**

We looked into our electronic thyroid cytopathology reports for the last 5 years (January 2012 to March 2018). A total of 1,048 FNA took place in that period at King Salman Armed Forces Hospital, Tabuk, Saudi Arabia.

Table 2 shows the FNA diagnosis of thyroid lesions according to the BSRTC.

Table 3 shows the cases that underwent subsequent thyroid surgery. The number and percentage of benign and malignant diagnoses proved by histology is provided for each of the DCs.

The false-positive cases are those diagnosed using FNA as DCs V or VI (suspicious for malignancy or malignant) and those following thyroid surgery showed benign histology. The false-positive rate for DC V (suspicious for malignancy) is 22.5%, while it is 2.38% for DC VI (malignant). The one false-positive case that was called malignant in cytology is subsequently proved to be multinodular goiter with atypical Hurthle cells, accounting for overcalling the lesion on cytology.

The false-negative cases are those diagnosed using FNA as DC II (benign) and those following thyroid surgery showed a malignant diagnosis (8.7%). However, since eight cases, when retrospectively reviewed, were reclassified as nondiagnostic, the false-negative is 4.9%.

**Diagnostic Category I: Nondiagnostic**

A total of 111 cases were reported as nondiagnostic. Twenty-three cases of which underwent thyroid surgery, 13 of which are benign and 10 thyroidectomies showed malignant papillary thyroid carcinoma [(PTC) follicular variant  $n = 5$ , classic = 4, and cystic = 1]. Additionally, one case showed malignant PTC on repeat cytology, making the malignancy rate (45.8%). Twelve cases showed “consistent with a benign follicular nodule” on repeat FNA. If we consider these cases as true benign, the malignancy risk would be

30.55%. In both cases, we found the malignancy risk of the thyroids with nondiagnostic FNA to be high. This is likely due to the method we followed. Our method depends on the cases that have histologic follow-up as the "gold standard". However, the cases that are selected for surgery are likely not representative of all the patients with nondiagnostic aspirate, since those who underwent surgery have other risk factors or "red flags" for malignancy. Espinosa De Ycaza et al. found that the risk of malignancy in patient with nondiagnostic aspirate is 3%.<sup>6</sup> However, the method used in the latter paper is different from our method, hence partially explaining the difference in the rates.

### Diagnostic Category II: Benign

Of the 764 cases, 183 underwent some form of thyroid surgery, 167 of those thyroidectomies showed benign diseases, and 16 showed malignancies (malignancy risk 8.7%). In retrospect, eight cases should have been called nondiagnostic, according to the BSRTC, since these cases contained either macrophages only or very few thyrocytes; therefore, the "actual" malignancy risk is 4.9%.

### Diagnostic Category III: AUS

In all, 58 cases (5.5%) were reported as AUS. Of these, 20 patients (34.4%) underwent thyroid surgery. Of the cases that underwent surgery, seven (35%) proved to be malignant, five of which are EFVPTC and two are oncocyctic (Hurthle cell) variant. Four other thyroids showed papillary microcarcinoma and the remaining nine cases proved benign on excision (multinodular goiter ( $n = 8$ ) and Hashimoto's thyroiditis ( $n = 1$ )).

The four cases of papillary microcarcinoma are assumed to be incidental findings and not accountable for the AUS diagnosis.

In 2007, a conference in Bethesda, Maryland, created the core that later formed into the BSRTC.

The first edition of the BSRTC was published in 2010. However, the diagnostic terminology, especially the term atypia of undetermined significance took some time before getting popular to the general pathologists. Hence, the low rate of our AUS diagnosis. In fact, the majority of our AUS cases (47 cases) are diagnosed in the period between 2015 and 2018.

### Diagnostic Category IV: Follicular Neoplasm/Suspicious for Follicular Neoplasm

Of the 30 cases diagnosed as "follicular neoplasm/suspicious for follicular neoplasm", 19 had subsequent thyroid surgeries (total thyroidectomies  $n = 11$  and hemithyroidectomies  $n = 8$ ). Nine of these cases (47.3%) are neoplastic (five are malignant PTC (26.3%) and four are follicular adenomas). Seven cases showed multinodular goiter and three cases showed Hashimoto's thyroiditis.

It is noteworthy that we have not had any cases of follicular carcinoma over the last 5 years. Most of the malignant follicular patterned lesions are follicular variant of papillary carcinoma, a point to consider when evaluating FNA cases within DC IV.

### Diagnostic Category V: Suspicious for Malignancy

Of the 38 cases of "suspicious for malignancy", 31 underwent subsequent thyroidectomy (the rest likely had the surgery in other hospitals). Among those, 23 (74.19%) proved malignant. The malignant cases are PTC ( $n = 20$ ), medullary carcinoma ( $n = 1$ ), and poorly differentiated (insular) carcinoma ( $n = 1$ ). One of those cases finally was called noninvasive follicular thyroid tumor with papillary-like nuclear feature (NIFTP).<sup>7</sup> Although considered nonmalignant, we included this with the "truly positive cases" since the cytologic

diagnosis is solely dependent on the papillary nuclear features and NIFTP is a surgical diagnosis, i.e., the diagnosis depends on establishing a noninvasive pattern after resection with sampling the entire tumor perimeter and demonstrating lack of invasive and aggressive characteristics.<sup>7</sup>

Eight cases proved benign on surgical resection, the most common benign diagnoses were "Hashimoto's thyroiditis" ( $n = 4$ ), follicular adenoma ( $n = 2$ ), multinodular goiter ( $n = 1$ ), and one peculiar case of neck soft tissue nodular fasciitis clinically mimicking a thyroid nodule.

### Diagnostic Category VI: Malignant

In all, 47 FNA specimens were reported as "malignant", 5 were not followed by subsequent surgery (likely they had the surgery in other hospitals), 42 had tissue diagnosis (40 total thyroidectomies, 1 partial thyroidectomy due to suspicion of lymphoma, and 1 had brain metastasis). The overwhelming majority of the cases proved PTC ( $n = 38$ , 95% of the cases). Two had poorly differentiated (insular) carcinoma and one proved multinodular goiter with Hurthle cell nodule (the latter is the only false-positive case, 2.38%). Therefore, the total number of true malignant cases is 41 (97.6%) of 42 diagnosed "malignant FNA".

### The AUS Category: Discussion

The rate of malignancy in thyroid nodules diagnosed as AUS is hard to estimate, since not all the patients would have surgery. Different reports had different rates of malignancy. In a large study from Memorial Sloan-Kettering Cancer Center, Ho et al. found that of the 350 (64.7%) nodules with AUS cytopathology who had an immediate surgery, the rate of malignancy was 38.6%.<sup>8</sup> They estimated that the risk of malignancy for an AUS/FLUS nodule is between 26.6% and 37.8%, surpassing the initially described 5–15% risk.<sup>3</sup> The suggestion was based on their findings, given that the AUS diagnosis is not being overused and also stressing the fact that their patient cohort might be different from other cohorts, that these patients may indeed require surgery.

VanderLaan et al. had 331 cases with an initial diagnosis of AUS by FNA; and of those, 240 (72.5%) were benign and 91 (27.5%) were malignant. Eighty-nine percent of all the malignant cases are PTC.<sup>9</sup>

Alqahtani et al. found 54 malignant nodules out of a total of 115 of patients with AUS. No significant correlation was found between the ultrasound findings and the final diagnosis of nodules with AUS.<sup>10</sup>

Layfield et al. identified malignancy in 36 cases out of the total 127 cases of AUS that underwent surgical exploration (28.3%).<sup>11</sup> The malignancy risk found by Gucon et al. is 15.7%.<sup>12</sup>

According to Chandra et al., of the total 63 cases of AUS that underwent surgery, 18 were found to be malignant with an overall malignancy rate of 28.5%.<sup>13</sup>

Our results showed of the 20 cases of operated AUS, 7 (35%) were malignant, and the majority are EFVPTC. If we consider the repeated FNA for these lesions diagnosed as "benign" as a final outcome, the malignancy rate would be reduced to 21.4%.

### CONCLUSION

In conclusion, the DC AUS is associated with a risk of malignancy that is in excess with the originally described rate of 5–15%,<sup>3</sup> and it seems from the literature review that the risk of malignancy is comparable to that of DC IV, justifying a subsequent surgery.

It is still not clear how the recent nomenclature change of a portion of the EFVPTC to NIFTP<sup>7</sup> will affect the rate of malignancy for each DC of the BSRTC. It is estimated that for the indeterminate categories (i.e., AUS/FLUS, FN/SFN, and suspicious for PTC), the rate of malignancy will be lowered.<sup>14</sup>

Additionally, for the last 5 years, not a single case of follicular carcinoma was diagnosed in our center, and most of the follicular patterned lesions are follicular variant of PTC, a point for the pathologist to consider when assigning cases to DC IV: Follicular neoplasm/suspicious for follicular neoplasm, and looking close to the nuclear features, can lead to the correct diagnosis.

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