

Should we determine the significance of “follicular lesion of undetermined significance”

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Abstract: Aim: Thyroid fine-needle aspiration biopsy (TFNAB) is the gold standard methodology for the evaluation of thyroid nodule. Nevertheless, diagnosis of TFNAB specimens is sometimes interpreted as “follicular lesion of undetermined significance”: This indeterminate diagnosis is given upon TFNAB despite the presence of sufficient cellular material available for cytopathological analysis. Furthermore, this indeterminate diagnosis constitutes a grey zone between benign lesion and malignancy. As a result, it becomes difficult to determine the type of surgical intervention that needs to be performed on the patient and the technique that will be used. In this study, we aim to correlate the diagnosis of “follicular lesion of undetermined significance” with clinical and postoperative evaluations. Methods: A total of 147 patients, who were diagnosed as “follicular lesion of undetermined significance” following initial TFNAB, were included in this retrospective study. These patients were evaluated according to whether they underwent a second TFNAB or thyroidectomy pathology following initial diagnosis of “follicular lesion of undetermined significance”. Results: Results were generated by evaluating the reports of the second TFNAB and 15 of 147 patients were followed. Histopathological examination of specimens derived from 132 patients following surgery revealed the following diagnosis: (i) hyperplasia in 67 patients, (ii) nodular lesion belonging to Hashimoto’s thyroiditis in 34 patients, (iii) papillary carcinoma in 28 patients, (iv) follicular carcinoma in two patients, and (v) anaplastic carcinoma in one patient. Conclusion: Based on this retrospective study and on examination of the available literature concerning the treatment options and follow-up of patients initially diagnosed as “follicular lesion of undetermined significance” (FLUS or Atypia of undetermined significance) upon TFNAB, we conclude that it is important to keep in mind the elevated rates of malignancy that potentially develop from these undetermined lesions. This document is a “live” template. The various components of your paper [title, text, heads, etc.] are already defined on the style sheet, as illustrated by the portions given in this document.

Keywords: Atypia of Undetermined Significance, FLUS, Follicular Lesion of Undetermined Significance, TFNAB, Thyroid Cancer

1. Introduction

Thyroid fine-needle aspiration biopsy (TFNAB) is the most frequency used, the safest, the simplest and the most cost-effective method to evaluate the presence of thyroid nodule(s) in patients(1). The Bethesda 2007 Thyroid Cytology Classification system is considered as the basis for the evaluation of aspirates(1); According to this system, the “atypia of undetermined significance or follicular lesion of undetermined significance” or FLUS group, is given the category V, a recommended diagnostic category which is given to cases that are neither convincingly benign (category II) nor sufficiently atypical for diagnosis of

suspicious for malignancy (category III) (1). The aim of this retrospective study was to (i) focus on patients diagnosed with “follicular lesion of undetermined significance” following initial TFNAB, i.e. patients for whom standardization is not possible in terms of specific surgical treatment, and (ii) within this specific patient group, examine the type of treatment(s) that was recommended and the incidence of malignancy.

2. Patients and Methods

A total of 147 patients, for whom (i) nodular goiter diagnosis was established between 2006 and 2011, (ii)

TFNAB was performed, and (iii) “follicular lesion of undetermined significance” was reported, were included in this study. The BSRTC includes 9 well-described criteria for FLUS: (i) microfollicular architecture, but sparse cellularity, (ii) predominant oncocyctic cells and low cellularity, (iii) predominant oncocyctic cells and goiter or Hashimoto thyroiditis, (iv) cytological atypia suggesting papillary carcinoma, (v) cytological atypia, (vi) cytological atypia due to technical artifact, (vii) atypical “cyst lining cells,” (viii) abnormal lymphocytic population, and (ix) other (1). In our center FLUS incidence varies %4-9. 2 patients which the cytological findings are not convincingly benign and described as follicular lesion with cellular atypia/cellular atypia before FLUS description in Bethesda system included the study with the diagnose of FLUS in the light of responsible pathologists’ opinions after re-evaluation. FNAB was performed all nodules which was bigger than 1 cm in thyroid ultrasonography in multinodular patients, and the specific nodule which was diagnosed as FLUS followed and included this study.

Retrospective analysis was performed by examining the patient files. The age of patients included in the study ranged between 24 and 71, with an average age of patients of 46.4 ± 12.5 yrs. A total of 118 patients (80.2%) were women and 29 patients (19.7%) were men. Of the 147 patients included in the study, 24 patients (16.3%) had solitary thyroid nodule and 123 (83.6%) patients had multinodular goiter; 105 (71.4%) patients were euthyroid, 6 (4.0%) patients were hyperthyroid, and 36 (24.4%) patients had hypothyroidism. All patients underwent thyroid scintigraphy and cold nodule was found in 98 patients (66.6%), warm nodule was found in 41 patients (27.8%), and hot nodule was found in 8 patients (5.4%).

A total of 96 patients (65.3%) were immediately operated, and a TFNAB was performed on 51 of these patients (34.6%) for the second time. The operation was performed without second TFNAB if patients had any of the following conditions: old age and male sex, a painless nodule which grows fast, a nodule which appeared recently, thyroid cancer family history, previous radiotherapy directed at the head and shoulder, a firm palpable nodule, aphonia which improves later, and/or neck lymphadenopathy.

All patients underwent thyroidectomy except the patients who had benign nodules according to second TFNAB results and two patients with low risk.

Unilateral total thyroidectomy+isthmectomy was performed on 51 patients (34.6%) and bilateral total thyroidectomy was performed on 26 of them (65.3%). The study has approved by local ethical comitee and has been ran in compliation with Helsinki Declaration principles.

The SPSS statistic program for Windows 11.5 package (SPSS Inc., Chicago, US) was used to generate statistical analysis of data gathered from patient files. While determining statistics were shown as average \pm standard deviation, minimum and maximum for continuous variables, frequency distribution was given by calculating the number of patients and the % values for nominal variables.

3. Results

A total of 96 patients were operated after the first TFNAB was reported as “follicular lesion of undetermined significance”; of these 96 patients, 51 patients underwent a second TFNAB. From these 51 patients who underwent a second TFNAB, 31 patients had follicular neoplasia, 13 patients had benign lesions, five patients had suspicion of malignancy, and two patients had papillary thyroid carcinoma. The results are summarized in Table 1.

Table 1. Procedures after initial diagnosis

	n (%)	Column1	Column2
Procedure		Row1	Row1
Operation	96 (65,3%)	Row2	Row2
2 nd FNAB	51 (34,7%)	Row3	Row3
2 nd FNAB Cytology		Row4	Row4
Follicular neoplasia	31 (60,8%)	Row5	Row5
Benign	13 (25,5%)	Row6	Row6
Suspicion of malignancy	5 (9,8%)	Row7	Row7
Papillary carcinoma	2 (3,9%)		
Procedure after 2 nd FNAB			
Operation	36 (70,6%)		
Follow-up	15 (29,4%)		
Thyroidectomy Pathology			
Hyperplastic Nodule	67 (50,8%)		
Hashimato Thyroiditis	34 (25,8%)		
Papillary Carcinoma	28 (21,2%)		
Follicular Carcinoma	2 (1,5%)		
Anaplastic Carcinoma	1 (0,8%)		

Following the results of the second TFNAB, 36 patients underwent surgery and 15 patients were closely followed. Thus, based on the evaluation of the results presented in Table 1, 15 of the 147 patients for whom “follicular lesion of undetermined significance” was reported based on initial TFNAB, were closely followed, and 132 patients underwent surgery (Table 1).

After the surgery, histopathological examination of the specimens derived from the 132 patients revealed the following diagnosis: (i) hyperplastic nodule in 67 patients, (ii) nodular organism belonging to Hashimoto’s thyroiditis in 34 patients, (iii) papillary thyroid carcinoma in 28 patients, (iv) follicular thyroid carcinoma in two patients, and (v) anaplastic thyroid carcinoma in one patient. These results are summarized in Figure 1.

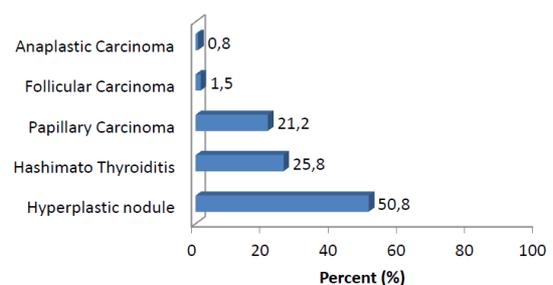


Figure 1. Pathology of thyroidectomy specimens

4. Discussion

Thyroid fine-needle aspiration biopsy (TFNAB) is a gold standard methodology for the evaluation and optional treatment of thyroid nodules (1). Based on the fact that the material content of some aspirates is insufficient for providing a clear determination of neoplastic lesion during cytological diagnosis, it is of great importance to establish the proper usage terminology (1).

At the same time, some TFNAB materials cannot provide a clear diagnosis: For this reason there are categories established by the Bethesda 2007 Thyroid Cytology Classification system, such as “suspicious for malignancy”, “suspicious for follicular neoplasia” and “follicular lesion of undetermined significance”, that allow for classification of borderline lesions during TFNAB diagnosis (2). One of the most significant categories is the “follicular lesion of undetermined significance” group. Although this group has a low malignancy risk compared to the “suspicious for malignancy” group in terms of the incidence of malignancy, it is suggested that “follicular lesion of undetermined significance” should not be used in TFNAB reports because it is deemed to be subjective in terms of diagnosis, and extremely heterogenic in content (1). Yet, in TFNAB reports in which the use of “follicular lesion of undetermined significance” is permitted, rates of “follicular lesion of undetermined significance” vary between 9.9% and 14% (3-4). These elevated reporting ratings for “follicular lesion of undetermined significance” are the result of subjective views, presence of papillary microcarcinoma or Hashimoto’s thyroiditis, or specimens which are poorly prepared.

In this respect, it is of great importance that the clinician who will evaluate the TFNAB report has all information available concerning the types of technical facilities of the center (5-7). In our study, the rate of Hashimoto’s thyroiditis following initial “follicular lesion of undetermined significance” diagnosis is 25.8%, thus supporting this proposition.

Consequently, when a nodule is reported as “follicular lesion of undetermined significance” based on initial TFNAB evaluation, the main difficulty is the evaluation of the potential for malignancy of this nodule. In addition to the fact that TFNAB reports provide different rates for “follicular lesion of undetermined significance” depending on the center which performs the diagnosis, there are further studies that report malignancy frequency rates to reach between 6% and 17%, and even up to 27% (1,3,8,9). In our study this rate is 21% and is therefore an elevated rate. Because of this, it is extremely important that a surgeon should evaluate “follicular lesion of undetermined significance” patients in terms of potential for malignancy. In a study performed by Jo and colleagues, rates of applying a second TFNAB is unpredictably so low on the patients initially diagnosed with “follicular lesion of undetermined significance”, due to high rates of malignancy that is said it is observed that the surgeons more likely opt for

thyroidectomy (1). In our study, the results observed corroborate the findings of Jo and colleagues: the option of a second TFNAB is selected by only just 51 (34.7%); of 147 patients initially diagnosed with “follicular lesion of undetermined significance”, and the option for immediate surgery was selected for 65.3% patients based on concern. Moreover, in some studies it is especially important that diagnostic-aimed surgery is considered in that situation (1, 10).

However, as far as the diagnosis of “follicular lesion of undetermined significance” and related problems, there is so far no consensus in the literature in is topic: There are numerous discussions and suggestions in the literature about supplementary methods which will help a clinician for diagnosis. On the other hand, we propose to include herein some methods that appear to be the most adequate in terms of practicability, based on their cost-effectiveness and simplicity: Singh and colleagues (11) recently suggested that the “follicular lesion of undetermined significance” category may be itself subdivided into subgroups, such as “suboptimal papillary carcinoma”, “atypia, not otherwise specified” and “atypia, Hurtle cell neoplasm”; In this way, the authors argue that this so far heterogeneous category can be potentially narrowed or perhaps be removed.

Several research articles suggest that in cases in which the initial TFNAB report diagnosis is “follicular lesion of undetermined significance”, it is more effective to perform a core biopsy instead of a second TFNAB(12); Furthermore, the study of Chaves et al suggests that a joined protocol, which combines TFNAB results with clinic-derived radiological data, would be most effective (13). In order to overcome these discrepancies in terms of choice of methodology, there are additional studies that suggest that analysis at a molecular level provides almost the same results as with a second TFNAB (2,14). A view that has recently gained momentum is a consensus approach mentioned by Jing and colleagues (15). In this approach, after the specimens which initially present as “follicular lesion of undetermined significance”, are evaluated by a different team of pathology specialists, a consensus decision is then provided. In the same study, reevaluation of the specimens initially reported as “follicular lesion of undetermined significance” with this method, revealed the following: (i) 52% of patients are reclassified as benign lesion, (ii) 20% of patients are reclassified as follicular neoplasia, (iii) 2% of patients are reclassified as papillary carcinoma, (iv) 4% of patients are reclassified as non-diagnostic, and (v) 22% of patients remain in the “follicular lesion of undetermined significance” category. A correlation rate of 89.2% is observed following clinical and histopathologic analysis of these patients. The results of our study suggest the weakness of this correlation is remarkable after second TFNAB and thyroidectomy.

5. Conclusion

Based on the information above, we suggest that surgeons

should keep high alignite rate in mind until this improvement is provided is important with increasing studies about correlating FNAB results of FLUS group extremely undetermined and subjective in nature with clinic as far as possible suggest.

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