**Case Report**

# The Prevalence of Coexistance Thyroid Carcinoma and Thyroid Nodules in Hyperthyroid Patients at San Juan City Hospital

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## Abstract

Hyperfunctional thyroid nodules are rarely associated with thyroid cancer, for this reason are rarely biopsied. Although multiple theories have been proposed, the relationship is still uncertain. After performing a MEDLINE literature search, we found in multiple retrospectives analysis, that patients with hyperthyroidism and hyperfunctional nodules have an estimated malignancy prevalence of 0.3% to 16.3%. In our study forty-eight hyperthyroid cases were prospectively investigated, in order to provide information about the association between hyperthyroidism and thyroid cancer. Historical, biochemical and radiological characteristics of the case subjects and their nodules were also analyzed. We decided to biopsied all nodules irrespective of their sonographic characteristics. The biopsy samples were cytologically asses (by the BETHESDA classification) and we found 77% of benign nodules, 2% of nodules presented with atypia of undetermined significance or follicular lesion of undetermined significance, 8.3% were malignant nodules, and 10.4% were nondiagnostic or unsatifactory. All patients with a cytological diagnosis of malignant underwent surgery. Thyroid malignancy (micro- or macrocarcinoma) diagnosed pre-operatively in 4 cases by US-guided FNAB were confirmed histologically after surgery. Papillary thyroid carcinoma was identified in 2 patients (4.17%), and Follicular thyroid carcinoma was found in 2 patients (4.17%). These data demonstrate a higher than expected incidental cancer rate in hyperthyroid patients compared with euthyroid subjects with nodular goiter. Our purpose is to stress the point that, although hyperfunctioning thyroid nodules are rarely described as malignant in the literature, FNAB should not be restricted to cold nodules, in view of our data and others published reports.

## INTRODUCTION

The concomitance of thyroid cancer in patients with hyperthyroidism is well described; although multiple theories have been proposed, the relationship is still uncertain (1).

Typically, hyperfunctioning thyroid nodules have been known to be exclusively benign lesions (such as an adenoma) (1-6). Most of the major guidelines for cancers and thyroid nodules, generally recommended the avoidance of fine-needle aspiration (FNA), in those patients who presented with a hot nodule by a thyroid scan and low thyroid-stimulating hormone (TSH) levels. However, in our routine clinical practice we have found the unexpected occurrence of patients with coexisting hyperfunctional nodules and thyroid malignancies. Therefore, the former concept that hyperfunctioning nodules may safely rule out thyroid cancers may not be applied to patients with hyperfunctioning thyroid nodules as easily as current guidelines suggest.

After performing a MEDLINE literature search, using the terms, "thyroid cancer, hyperthyroidism, and hyperfunctional nodules" we found in multiple retrospectives analysis, that patients with hyperthyroidism and hyperfunctional nodules have an estimated of 0.3% to 16.3% prevalence of malignancy (2).

The purpose of this study is to dispute the point that, although hyperfunctioning thyroid nodules are rarely described as malignant in the literature, FNAB should not be restricted to cold nodules, in view of our data and others published reports.

## PATIENTS AND METHODS

### Patients

We performed a prospective study in patients with an establish diagnosis of Hyperthyroidism (TSH levels < 0.4 μIU/mL, with elevated free T4 and free T3 and TSI), without history of thyroid surgery or previous radiodine therapy from the outpatient clinics of the endocrinology and metabolism department at San Juan City Hospital from the years January 2011 through December 2013; to provide information about the association between hyperthyroidism and thyroid cancer. Historical, biochemical and radiological characteristics of the subjects and their nodules were also analyzed. Finally; 55 patients (F:M=45:10 ) mean age of 47.3 (age range 29-61 years) constitute our study population.

### Pathologic Examination

Cytopathologic results were obtained by FNA biopsy, guided by ultrasonography, performed in our institution by the endocrinology staff. Fine Needle Aspiration biopsy (FNAB) were obtained in fifty-five patients, and malignancy was confirmed in 6 of them. The cytological material obtained was smeared on slides immediately after aspiration, and processed using May-Grunwald Giemsa and Papanicolau stains.

Cytopathological analysis was performed by two experienced pathologists using the Bethesda classification for cytologic analysis (7).

## Image Analysis

The ultrasonographic images were reviewed during the FNA biopsy procedure in consensus with the endocrinologists staff. A nuclear medicine specialist determined the hyperfunctionality of the thyroid nodules, based on the thyroid scans imaging.

Referring to the Korean Society of Thyroid Radiology (KSThR) recommendations and Korean Thyroid Association (KTA) guidelines, American Association of Clinical Endocrinologists (AACE), and the American Thyroid Association (ATA) Guidelines Taskforce (1, 9); thyroid nodules depicted on ultrasonography were categorized into a three-tiered classification of probably benign, indeterminate, and suspicious malignant nodules. The nodules were then classified as less than 5 mm, 5 mm to 1 cm, or larger than 1 cm, in maximal dimension.

## RESULTS

### Ultrasonographic and Pathologic Results of Hyperfucntioning Nodules

Fifty-five patients were found to have 63 hyperfunctional nodules on thyroid scans. The ultrasonographic and pathologic results of the hyperfunctioning nodules are shown in **(fig 1. Table1)**.

Fifty-three of the 63 hyperfunctional nodules (84%) had indications for FNAB, based on the guidelines. However; we decided to biopsied all 63 nodules. On cytological examination, of the 63 hyperfunctioning nodules, 49 (74.5%) were reported as benign, 2 (3.2%) as atypia of unknown clinical significance (AUCS), 3(4.8%) as follicular lesion of undertemined significance (FLUS), and 3 (4.8%) as non-diagnostic. Six hyperfunctional nodules suspicious for malignancy were all confirmed to be a thyroid cancer by histological pathology report obtained after surgery. Of importance is to notice that 1/14 (7.1%) suspicious for malignancy in nodules less than 1cm, malignancy was confirmed. Likewise, in probably benign nodules less than 1cm again one malignancy was also seen 1/5 (20%).

**Fig1.Table1).** *Ultrasonographic-Pathological Results of Hyperfunctioning Thyroid Nodules in the 55 Patients*

| **Ultrasonographic Classifications** | **Size** | **Hyperfunctional Nodule (n= 63)**<br>**Number Of Nodules Histologic Diagnosis** | **Cytologic Category** | |
|---|---|---|---|---|
| **Suspicious malignant (n=31, 49.2%)** | ≤ 5 mm | 0 | N/A | N/A |
| | >5 mm- ≤ 1cm | 14 | Benign (9)<br>Non Diagnostic (2)<br>FLUS (1)<br>Malignancy (1)<br>AUCS (1) | N/A<br>N/A<br>N/A<br>PTC |
| | > 1cm | 17 | Benign (13)<br>Malignancy (3)<br>AUCS (1) | N/A<br>PTC (2)<br>FTC (1) |
| **Indeterminate (n = 15, 23.8%)** | ≤1cm | 5 | Benign (4)<br>Non Diagnostic (1) | N/A<br>N/A |
| | > 1cm | 10 | Benign (9)<br>FLUS (1) | N/A<br>N/A |
| **Probably Benign (n = 17, 27%)** | ≤ 1cm | 5 | Benign (4)<br>Malignancy (1) | N/A<br>FTC |
| | > 1cm | 12 | Benign (10)<br>Malignancy (1)<br>FLUS (1) | N/A<br>FTC<br>N/A |

Numbers in parentheses are numbers of nodules showing individual cytologic or histologic results.

AUCS: atypia of undetermined clinical significance,

FLUS: follicular lesion of undeterminated significance,

N/A: not applicable,

PTC: papillary thyroid cancer,

FTC: follicular thyroid cancer.

## Thyroid Cancer in Patients with Hyperfunctional Nodules

**(fig2.Table2)**. Describes the ultrasonographic-pathologic features of thyroid cancers that occurred in patients with hyperfunctioning nodules. Of the 55 patients who underwent FNAB guided by ultrasonography, 6 (9.5%; all females; mean age, 44 years; range 29-58 years) were proven to have thyroid malignancies, and confirm by surgery, of which all were functioning nodules (3 follicular thyroid cancers, and 3 papillary thyroid cancers). A 10.9% minimal cancer risk was estimated.

All the 6 cases where thyroid cancer was identified, were classified as suspicious nodules (4/6, 66.7%), and probably benign (2/6, 33.3%), by ultrasound description. Although statistical significance was not attained, the size of the hyperfunctional cancers suspicious for malignancy (mean, 1.3 cm; range 0.8-1.8 cm) was larger than that of probably benign (mean, 1.1 cm; range 0.9-1.2) as seen in Table 2. None of the patients with thyroid cancer present with metastasis.

**(fig2. Table2).** *Clinical-Ultrasonographic-Pathological Results of 6 Patients with Thyroid Cancer*

| Age | Sex | **TSH (µg/L)** | Number of Thyroid Cancer | **Pathology of Thyroid Cancer** | **Correlation with Thyroid scan** | **Ultrasonographic Classification** | Size | Metastasis |
|---|---|---|---|---|---|---|---|---|
| **58** | F | <0.001 | 1 | PTC | Hyperfunctional | Suspicious malignancy | 1.8 | None |
| **47** | F | <0.001 | 1 | FTC | Hyperfunctional | Suspicious malignancy | 0.8 | None |
| **29** | F | <0.001 | 1 | PTC | Hyperfunctional | Probably benign | 0.9 | None |
| **40** | F | <0.005 | 1 | FTC | Hyperfunctional | Suspicious malignancy | 1.3 | None |
| **47** | F | <0.001 | 1 | FTC | Hyperfunctional | Probably benign | 1.2 | None |
| **41** | F | <0.001 | 1 | PTC | Hyperfunctional | Suspicious malignancy | 1.4 | None |

PTC: papillary thyroid cancer,

FTC: follicular thyroid cancer

## DISCUSSION

In a recent article published by our senior author (10), he described a case of a female patient with the diagnosis of Grave's disease and a palpable thyroid nodule shown to be hyperfunctional (hot) by a thyroid scan imaging. An ultrasound guided FNAB of the hot nodule showed a PTC, this drive us to undergo a prospective study to investigate the incidence of malignancy on hyperfunctional nodules in hyperthyroid patients.

Different current guidelines state that if a lesion shows indeterminate cytology such as FLUS or AUCS, the detection of a hyperfunctional nodule on thyroid scans may prove its benignancy (1-3,5,6). However, in our present study we demonstrate that thyroid cancer indeed developed in hyperthyroid patients with hyperfunctioning nodules with an estimated minimal cancer risk of 10.9%. This cancer risk is much higher than the results of various case series reported. We therefore suggest that patients with hyperfunctional nodules and hyperthyroidism may not be exempt from thyroid cancer.

In our series most of the cythopatological results of the hyperfunctional nodules were compatible with benign features. According to the literature, the most common hyperfunctioning cancer is PTC, followed by follicular variant papillary thyroid cancer and conventional FTC, but in our study both FTC and PTC were equally encountered. Is important to remark that, by sonographic imaging, 4 of the 6 patients were found with malignancy and had a suspicious malignant nodule, while 2 of the same 6 patients presented with probably benign nodule. Therefore, we believe that we cannot overlook the possibility of thyroid cancer in patients with hyperfunctional nodules.

According to the ATA guidelines, using > 1cm in size criteria as the indication for FNAB (7) 14 out of 31 (45%) of our patients would probably be screened out. Likewise two of our patients, one with a suspicious nodule (1cm) by sonography and another with a probably benign nodule (<1cm), both were positive for thyroid cancer (PTC, FTC); and according to above guidelines, probably will be left without a proper diagnosis. These results demonstrate that it is important to evaluate the hyperfunctioning nodule in patients with hyperthyroidism using high resolution ultrasonography, because this can provide both information of multiplicity and detailed characteristics of thyroid nodules that cannot be evaluated through a thyroid scan due to the limited resolution.

One limitation in our study is the small number of subjects included, however the strength of this report is the prospective nature of the case series.

In conclusion, patients with hyperfunctioning thyroid nodules and hyperthyroidism may not be exempt from thyroid malignancy, as thyroid cancer can develop in hyperfunctional nodules both with malignant and benign characteristics by sonogram at a non-negligible rate, and thus, in order to screen out thyroid cancer, thyroid ultrasonography should be performed in patients with hyperfunctioning thyroid nodules. FNAB should not be restricted to cold nodules.

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