

# Clinical relevance of non-palpable thyroid nodules as assessed by ultrasound-guided fine needle aspiration biopsy

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**ABSTRACT.** It is known from autopsy data that thyroid nodules are far more common than can be detected by palpation alone. With the wide use of modern non-invasive imaging many non-palpable thyroid nodules are discovered but the proper approach to these nodules is still debatable. In a retrospective study, we reviewed the data from 186 US-guided FNA biopsies (US-FNAB) performed between May 1995 and March 1997 at the Sapir Medical Center, Israel, a iodine-sufficient urban area. Sixty-one of the 186 US-FNAB of the thyroid were performed in non-palpable nodules. The mean size of these nodules was  $2.4 \pm 1.0$  cm (mean $\pm$ SD) ranging from 1.1-5.5 cm. Description of the nodule consistency was available in 53 cases; 42/53 were

solid and 11/53 were solid-cystic. FNAB was diagnostic in 46 patients and non-diagnostic in 15. Forty-three of the diagnostic cytology reports were benign, one revealed papillary carcinoma, one had suspicious findings and the third was suspicious for a follicular neoplasm. The last two patients were referred to surgery and a follicular adenoma was found in both. Among the 61 non-palpable thyroid nodules, only one was papillary carcinoma, a prevalence of 1.6%. The other two patients referred to surgery had benign lesions. We found a low prevalence of malignancy in relatively large non-palpable thyroid nodules.

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## INTRODUCTION

The frequent use of various sensitive imaging modalities has made it possible to detect many non-palpable thyroid nodules. The proper management of these nodules has been debated over recent years (1, 2).

It is generally agreed that nodules greater than 1 cm can be palpated, especially when they are favorably situated. It is more difficult to palpate a nodule on the posterior, rather than on the anterior surface (3). Another important factor is the shape of the patient's neck, with short and fat necks making physical examination more difficult. Wiest *et al.* (4) compared physical examination vs high-resolution thyroid US in the detection of thyroid nodules. They detected 249 nodules on high resolution US but only 53 (21%) were found on physical exami-

nation. As nodule size increased, physical examination improved the detection of nodules, but still 50.2% of nodules larger than 2 cm were missed by palpation alone. Rago *et al.* (5) found thyroid nodules in 5.6% of healthy patients in an area of borderline iodine sufficiency, with 30% of nodules increasing in size or number during a 3 yr follow-up. In a non-irradiated thyroid gland there is less than a 10% chance that a nodule found by physical examination is malignant.

The rate of malignancy in a non-palpable thyroid nodule has been examined in recent years (6, 7). Leenhardt *et al.* (6) biopsied 450 non-palpable thyroid nodules, diagnosing 20 carcinomas (4.4%), 8 of them in nodules measuring less than 1 cm. In spite of the fact these microscopic carcinomas may metastasize early and that it is not possible to predict their biological behavior, the vast majority of these microcarcinomas have an indolent course as shown by their high frequency in autopsies of individuals dying from unrelated illnesses (8, 9).

Whether non-palpable or difficult to palpate nodules carry the same malignancy rate as palpable ones or represent a more benign form of thyroid

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nodularity is not clear. We therefore examined the rate of malignancy in non-palpable thyroid nodules greater than 1 cm in our population.

## PATIENTS AND METHODS

We examined the files of all patients who underwent US-guided FNAB of the thyroid at the Sapir Medical Center, Kfar Saba, Israel, between May 1995 and March 1997, a iodine sufficient urban area. Files were found by searching for the computer code of the procedure. On the whole, 186 files were examined. Cases were included in the study if the nodule was recorded as non-palpable by an endocrinologist, otolaryngologist or a surgeon. Findings recorded by family doctors, other specialists or residents were not considered. A nodule was defined as non-palpable if the physician could not feel a discrete nodule, whether or not the gland was completely normal on palpation or enlarged. Data were extracted from the files concerning demographic information, the method by which the nodule was found, a history of head and neck radiation therapy, family history, relevant laboratory tests (TSH levels, FT<sub>4</sub>, TT<sub>3</sub> and titer of microsomal antibodies), US description of the nodule, radioactive scanning results with <sup>99m</sup>Tc-pertechnetate, the cytological diagnosis of the FNAB and histologic diagnosis if the patient underwent surgery. It is our policy not to biopsy non-palpable thyroid nodules smaller than 1 cm in low risk patients.

US guided FNAB was performed with a 22-gauge needle with a 7-MHz linear array probe with a biopsy guide. Suction technique was applied.

In a partially cystic nodule, sampling was done in the solid portion of the nodule without removal of fluid; in multi-nodular goiters the dominant nodule was biopsied.

Smears were fixed immediately in 95% ethanol and stained by the method of Papanicolaou. FNAB was considered adequate if there were at least 6 groups of well-visualized epithelial cells. Inadequate smears were comprised predominantly by blood with scant or no colloid and few follicular cells. The cytologic diagnoses of the nodules were classified into the following groups: benign, malignant, suspicious of malignancy, suspected follicular neoplasm and inadequate.

## RESULTS

### Patients

Information was obtained on 61 patients who had non-palpable nodules larger than 1 cm and were referred for US-guided FNAB.

There were 54 women and 7 men, with a mean age of 55.7±16.6 yr (mean±SD) and a range of 18-84 yr. Three patients were exposed to head and neck radiation therapy in the past, two for *tinea capitis* and one for facial leishmaniasis.

In 42 patients there was a record of the initial method by which the nodule was discovered. In 33 patients a thyroid US was done because a primary physician suspected a nodule or goiter on physical examination, hyperthyroidism, abnormal thyroid

scan, surveillance after thyroid surgery, neck pain or sensation of choking; in 9 patients the nodule was an incidental finding while the patient underwent carotid artery Doppler examination, ultrasound of the parathyroids or cervical CT (Table 1). Ten patients had thyroid surgery in the past, one for papillary carcinoma and the remaining 9 for benign disease.

### Physical exam and laboratory data

On physical exam 28 (46%) of the patients had a normal thyroid and 33 (54%) had a diffuse goiter. In none of the patients was a discrete thyroid nodule felt.

TSH levels were obtained in 49 patients and if suppressed FT<sub>4</sub> and TT<sub>3</sub> levels were also measured. Forty-one patients were euthyroid, 4 had elevated TSH levels and 4 had suppressed TSH levels with normal FT<sub>4</sub> and TT<sub>3</sub>.

### Thyroid scan

A thyroid scan using <sup>99m</sup>Tc-pertechnetate was obtained in 31 patients. Ten (32%) had a scan compatible with a multi-nodular goiter, 8 (26%) had a cold area, 2 (6.5%) had a hot area and 11 (35.5%) had normal thyroid scans.

### Ultrasonographic data

There was a record of US findings in 59 patients. Single nodules were reported in 29 (49%), 2 nodules in 10 (17%) and more than two nodules in 20 patients (34%). The size of the nodules ranged between 1.1-5.5 cm, with a mean of 2.4±1 cm (mean

Table 1 - Indication for the US or CT that revealed the non-palpable thyroid nodule.

Purpose of study	No. of patients
US done for suspected thyroid disease	33
Goiter	13
*G.P. suspected a nodule	2
Follow-up after thyroid surgery	2
Abnormal thyroid laboratory tests	6
Neck pain or choking sensation	3
Abnormal thyroid scan	5
Miscellaneous	2
<i>Incidentally found thyroid nodules</i>	9
Ultrasonographic studies	
Parathyroids	1
Doppler of carotid arteries	2
Computerized tomography-cervical CT	6

\*General physician suspected a thyroid nodule but examination by experienced specialists failed to detect the nodule.

±SD). Forty-two of the nodules (79%) were solid and 11 (21%) were solid-cystic (mixed).

#### Cytopathological data

FNAB was diagnostic in 46 patients and non-diagnostic in 15 (25%).

Forty-three of the diagnostic cytology reports were benign. Of the remaining three, one revealed papillary carcinoma, the second suspicious findings (atypical cells) and the third was a suspected follicular neoplasm.

Our cytopathological studies of 61 US guided FNAB of non-palpable thyroid nodules found only one carcinoma, a prevalence of 1.6%. The other two patients referred to surgery had benign follicular adenomas. There was no statistically significant difference between the size of the nodules that had diagnostic and non-diagnostic results. The mean size of the nodules with diagnostic results was  $2.5 \pm 0.9$  cm (mean±SD) while that of the nodules that yielded non-diagnostic results was  $2.2 \pm 1.2$  cm (mean±SD) (NS). In 53 patients there was an US description of the nodule. Among the 40 nodules that yielded diagnostic results there were 31 solid nodules (77.5%) and 9 cystic-solid nodules (22.5%). In the 13 nodules that yielded non-diagnostic results FNAB there were 11 solid nodules (85%) and 2 cystic-solid nodules (15%). There was no statistically significant difference between the groups with regard to nodule consistency ( $p=0.74$ ).

The size and consistency of the nodules in the diagnostic and non-diagnostic FNAB groups were not different. There were a few more cystic-solid nodules in the group with diagnostic results compared with the non-diagnostic results, although not statistically significant. The patients with non-diagnostic FNABs were followed clinically, ultrasonographically and were re-biopsied, but none agreed to an open biopsy of the nodule.

#### DISCUSSION

The wide use of modern non-invasive imaging methods has brought to clinical attention a large number of thyroid nodules that cannot be detected by palpation. This is not surprising in view of the high prevalence of thyroid nodules in the population (1). We are on the verge of an increase in this epidemic since endocrinologists themselves are using US more frequently to manage patients with goiter and nodular thyroid disease (10). Whether incidentally found nodules carry the same risk of malignancy as palpable ones is not clear. Khurana et al. (11) performed US guided FNAB in 48 non-palpable thyroid nodules, finding a malignancy rate

of 4.2% compared to 12.7% in the palpable thyroid nodules. All the non-palpable thyroid nodules measured less than 1.5 cm in Khurana's series. Based on the prevalence of occult thyroid carcinoma in the population and the benign course of the disease (12) it is not clear whether finding and treating these carcinomas is warranted. In our clinic, we follow ultrasonographically non-palpable thyroid nodules measuring less than 1 cm in low risk patients. In our population the mean size of the non-palpable thyroid nodules was  $2.4 \pm 1$  cm (mean±SD), ranging from 1.0-5.5 cm. It is interesting that experienced specialists were not able to palpate these relatively large nodules. In a few patients the difficulty in palpation could be attributed to the presence of short necks or obesity in the patients but in the great majority the thyroid gland was normal or enlarged but no discrete nodule was felt. Hagag et al. (7) performed US guided FNAB in non-palpable thyroid nodules greater than 1 cm in 108 patients. The average nodular size was  $1.90 \pm 0.75$  cm (mean±SD). They found 8 malignant nodules, 7 primary thyroid carcinomas and one metastatic nodule. The malignancy rate in palpable thyroid nodules was 10.5%, similar to that found in the non-palpable nodules (7.4%). Leenhardt et al. (6) biopsied 450 non-palpable thyroid nodules, finding among 94 surgically treated cases 20 carcinomas, 8 infracentimetric and 12 centimetric or supracentimetric. The greatest prevalence of malignancy in non-palpable thyroid nodules was found by Takashima et al. (13); of 133 non-palpable thyroid nodules in 105 patients who were biopsied there were 22 carcinomas among the 24 patients referred to surgery. The high rate of malignancy found in this series may in part be explained by the fact that only nodules suspicious for malignancy were referred to FNAB.

Many experts advise follow up for small (<1.5 cm) incidentally found thyroid nodules in low risk patients (1, 14). Whether the same approach can be extrapolated to larger non-palpable thyroid nodules is less clear.

In our study we found only one malignant cytology result in 61 non-palpable thyroid nodules. The other two patients referred to surgery because of atypical cytology and suspected follicular tumor, had follicular adenomas.

In 15 patients the FNAB was not diagnostic. Small nodules, mixed consistency (cystic-solid) and operator experience are important factors in the rate of non-diagnostic results. In our series the size and consistency of the thyroid nodules yielding diagnostic and non-diagnostic results were similar. It is our policy to refer such patients for excisional biop-

sy if consecutive FNA biopsies yield non-diagnostic results. In a recent published series by Tambouret *et al.* (15), there were 44 non-diagnostic results out of 290 US guided FNAB; 14/44 patients were referred for excisional biopsy and benign findings were obtained in all.

Ultrasonography and color flow-doppler (CFD) have been extensively investigated as tools to differentiate between malignant and benign thyroid nodules (16, 17). Nodules that are hypoechoic, lack the halo sign, have irregular margins, contain microcalcifications and have intranodular vascular spots are considered more suspicious for malignancy. Unfortunately the specificity and sensitivity of these tests are lower than FNA-B. Papini *et al.* (17) recommended byopsying hypoechoic nodules with irregular margins, intranodular vascular spots or microcalcifications, identifying 87% of the malignant nodules. Since the non-palpable thyroid nodules evaluated by Papini *et al.* were smaller than 1.5 cm it is not clear if the same approach can be recommended for larger non-palpable thyroid nodules. We found a low prevalence of malignancy (1.6%) in our population of non-selected patients harboring relatively large non-palpable thyroid nodules. US guided FNAB was performed in all thyroid nodules greater than 1 cm without risk stratification.

It is possible that discrete non-palpable thyroid nodules that cannot be distinguished from normal thyroid tissue by physical examination carry a better prognosis than hard and/or symptomatic thyroid nodules. Studies are needed correlating pathologic results with US appearance in order to identify nodules with higher risk of malignancy. We recommend biopsying non-palpable thyroid nodules that are larger than 1 cm, but patients can be informed of the lower risk of malignancy of these nodules.

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