Male sex, single nodularity and young age are associated with the risk of finding a papillary thyroid cancer on fine-needle aspiration cytology in a large series of patients with nodular thyroid disease.


Abbreviated title: Risk of malignancy of papillary thyroid cancer at FNA

Key terms: Thyroid, Fine-needle aspiration, cytology, papillary thyroid cancer, nodular thyroid disease.

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Abstract

**Objective**: the risk of papillary thyroid carcinoma (PTC) at fine needle aspiration (FNA) cytology was evaluated in 34120 patients.

**Results**: false positive and false negative rates of FNA cytology were 1.2% and 1.8% in comparison with histology in 3406 nodules from 3004 patients who underwent surgery.

PTC (901 cases) was more frequent in solitary nodule (SN 446/13549, 3.3%) than in multinodular goiter (MNG) (411/19923, 2%; $\chi_2^2= 48.8, p<0.0001$) and in males (209/6382, 3.3%) than in females (648/26945, 2.40%; $\chi_2^2= 15.58; p<0.0001$). PTC prevalence in Graves’ disease (GD) (13/286, 4.5%) and Hashimoto’s thyroiditis (HT) (31/508, 6.1%) was higher than in SN, this difference being significant in HT ($\chi_2^2= 8.7; p=0.003$), but not in GD ($\chi_2^2= 1.6; p=0.2$).

Using the multiple logistic regression analysis, independent risk predictors of PTC were younger age (OR= 0.97, confidence interval (CI) 0.964-0.974, p<0.0001), male gender (OR= 1.44, CI 1.231-1.683, p<0.0001) and SN vs MNG (OR= 0.63; CI 0.547-0.717, p<0.0001). The individual risk predictivity was highly improved by including in the prediction model serum TSH, measured at FNA in 11919 patients.

**Conclusion**: a cytology suspicious or indicative of PTC was associate with younger age, male gender and solitary vs multiple nodularity. These clinical parameters, together with serum TSH, may allow to formulate an algorithm which could be usefully applied to predict the risk of PTC in individual patients when cytology does not give a diagnostic result.
Introduction.

Thyroid nodular disease is quite common, especially in iodine deficient areas (1,2). Clinically overt thyroid cancer accounts for approximately 1% of all new malignant disease, although the annual incidence is reported to be rising (3, 4). The risk that a thyroid nodule either solitary or in the context of multinodular goiter, may harbour a cancer is quite low when clinically evident thyroid cancers are considered. However it is higher when cancers are incidentally detected on histology in patients operated on for compressive symptoms or hyperthyroidism (5, 6). Cytological examination of samples obtained by fine needle aspiration (FNA) cytology was proven in the last few decades to be an accurate method for differentiating benign from malignant thyroid nodules. Its routine use has decreased surgical intervention by 25 % and has increased the yield of cancer in surgical specimens from 15% to more than 30% (5, 6). Thyroid ultrasonography (US) is useful to define the characters associated with malignancy and to select in multinodular goiter those nodules which require FNA (5-8). FNA has been found to have a high diagnostic accuracy (8-11). However, in the largest series FNA results are nondiagnostic or indeterminate in 20-25% of cases and false positive or false negative in 5% (10, 12,13). In few patients a history of neck irradiation, nodule hardness or fixity to adjacent structures, the presence of cervical adenopathy strongly suggest malignancy. But in the large majority of patients the physician is left with more general clinical features such as sex, age, solitary or multiple nodularity, the importance of which is reported in the literature with discrepant results (8, 14, 16).

In this study we have retrospectively reviewed the clinical records of a large series of patients submitted to FNA between 1997 and 2004 in our Institution. The diagnostic performance of FNA cytology was validated comparing FNA results with histology in a subgroup of patients who underwent surgery. By this analysis we could confirm the great accuracy of FNA in predicting malignancy. This allowed us to analyze the relationship between cytology and several clinical features in the entire cytological series, with the aim to establish the parameters that before surgery may help to predict malignancy in nodular thyroid disease. Our results indicate that male sex, single nodularity and age are independent variables associated with the risk of suspected papillary cancer in nodular thyroid disease.
Subjects and Methods

Thyroid function tests

Serum free thyroxine (FT4) and free triiodothyronine (FT3) were measured by RIA (FT4 Liso-Phase, normal values 7-17 pg/mL; FT3 Liso-Phase kit, normal values 2.7-5.7 pg/mL, Technogenetics, s.r.l., Milan, Italy). Antibodies to thyroglobulin (AbTg) and thyroperoxidase (AbTPO) were measured by an immunoenzymometric assay (AIA-Pack TgAb, and TPOAb, Tosoh, Tokyo, Japan) and expressed as U/mL. Normal values are <30 U/mL for AbTg and <10 U/mL for AbTPO. TSH receptor antibodies (TRAb, normal value= <2 UI /L) were measured by a first generation TRAk assay (Brahams, Berlin, Germany).

Serum thyroid stimulating hormone (TSH) was measured by a sensitive immunoradiometric assay (Delphia. Pharmacia, Turku, Finland normal values 0.4-3.4 µU/ mL). Serum calcitonin was measured by an immunoradiometric assay (CIS BIO International, France, normal values <10 ng/mL).

Patients

34266 patients (27826 F: mean age 48 ± 23; range 13-76 yr; 6440 M: mean age 50 ± 17, range 13-80 yr) were submitted to FNA between 1997 and 2004 in the Department of Endocrinology, University of Pisa. The diagnosis, established on clinical, echographic and laboratory criteria was: multinodular goiter (MNG, n=19923): enlarged thyroid with multiple nodules at US and thyroid scintiscan; solitary nodule (SN, n = 13549): single nodule in an enlarged thyroid or isolate nodule in a thyroid of normal volume; nodular Graves’ disease (GD, n=286) and nodular Hashimoto’s thyroiditis (HT, n=508). The diagnosis of nodular GD was made according to usual standard criteria including active or treated hyperthyroidism, goiter with diffuse hypoechoic “thyroiditis” pattern at ultrasound, ophthalmopathy and positive serum anti-TSH receptor antibodies (TRAb) and/or TgAb or TPOAb. Patients were defined as affected by nodular HT if they had a diffuse hypoechoic “thyroiditis” pattern at ultrasound and high levels of TgAb and/or TPOAb. FNA was performed in all nodules cold at scintiscan either solitary or in multinodular goiter when they were greater than 1 cm, and in those less than 1 cm in the presence of clinical and/or echographic signs suspicious for malignancy.

Thyroid surgery was advised in all patients with a cytological result suspicious or indicative of carcinoma and in most of those with an indeterminate cytology. Surgery was also advised for patients carrying nodules with benign or non diagnostic cytology when they had large nodules with compressive symptoms, or nodules
displaying clinical or US signs suspicious of malignancy. Comparison between cytological and histological findings was feasible in 3406 nodules from 3004 patients, which had undoubtedly been localized by the pathologist based on clinical and sonographic pre-operative findings.

*Fine needle aspiration and cytology*

Fine needle aspiration (FNA) was performed under echo guidance by skilled endocrinologists, using a 23 gauge needle attached to a 10 mL syringe with or without aspiration and without local anaesthesia. Multiple passes were usually done in different parts of the nodule. In cystic or mixed lesions the fluid was aspirated completely and the sediment examined. The aspiration was repeated if the material was judged as insufficient macroscopically or at an immediate microscopic examination without staining. According to the guidelines of the Papanicolaou Society (17), the sample was considered adequate in the presence of at least five or six well-defined and well-preserved groups of follicular epithelial cells, each group containing at least 10 cells (16). Cytological results were reported according to the British Thyroid Association (18): 1. non diagnostic; 2. non-neoplastic (benign or negative for malignancy); 3. follicular; 4. suspicious of malignancy; 5. indicative of malignancy. The cytopathologists had clinical information about the patient.

*Histopathologic diagnosis*

Formalin-fixed and paraffin-embedded tumor tissue, including normal parenchyma obtained from the contralateral thyroid lobe of each case, were stained by hematoxylin and eosin. The histological diagnosis was made blindly by two independent pathologists who were not aware of the cytology result and according to the World Health Organization guidelines (19). When the diagnosis was discordant, agreement was found by joint re-examination of each case. Nodules or goiters with an occasional histological finding of a microcarcinomas less than 1 cm were classified as benign lesions.

*Statistical analysis*

Parametric tests were used for statistical evaluation. Results obtained in different groups of subjects were compared using the \( \chi^2 \) test and Student’s t-test for paired data. Predictivity was assessed using the Galen and Gambino test (20). For the multivariate analysis the binary logistic regression was used. Analysis of the influence of the serum TSH on the risk of papillary thyroid cancer was confined to a subgroup of 11919
patients as detailed under Results. A formula could then be proposed to predict the probability of malignancy in an individual patient through binary logistic regression analysis using the serum TSH concentration as a continuous variable. The Cox-Snell $R^2$ and Nagelkerke $R^2$ were used to quantify the goodness of fit of logistic regression, since they provide an analogy to $R^2$ in linear regression. The Nagelkerke $R^2$ adapts the Cox-Snell index so that it varies from 0 to 1 as $R^2$ in linear regression.

Results

Overall results of FNA cytology and comparison with histology

Table 1 reports the overall results of FNA cytology in 47775 nodules from 34266 patients. 74.7% of nodules were benign, 5.7% were indeterminate, 2.4% were indicative or suspicious for carcinoma while 17.1% were non-diagnostic. Accuracy of cytology was assessed comparing the FNA results with histology in patients submitted to thyroidectomy. Table 2 reports the comparative results of cytology and histology in 3406 nodules from 3004 patients who underwent thyroidectomy at the Department of Surgery and had histological examination at the Department of Pathology of the University of Pisa. All nodules with a cytology indicative of carcinoma (n=504) were confirmed to be malignant on histology, whereas 11 out of 391 nodules with an FNA suspicious for malignancy were benign on histology: 8 patients had a nodular goiter, 3 of whom had extensive necrotic features; 2 had Hashimoto’s thyroiditis, 1 with a 2 mm papillary carcinoma and 1 had Graves’ disease with a pseudopapillary organization on cytology. Overall, 884/895 (98.8%) nodules with a cytology indicative or suspicious of thyroid carcinoma were malignant on histology. Out of 1295 nodules with benign cytology, 1271 (98.2%) were confirmed to be benign hyperplastic nodules or adenomas, while 24/1295 (1.8%) were malignant on histology: twenty-three were papillary thyroid carcinomas (19 follicular variant, 4 classic variant) and 1 was a minimally invasive follicular carcinoma. The reasons for thyroidectomy in these 24 patients (13 with single/isolate nodule, 11 with multinodular goiter) were the size of the nodule/s in 18, clinical/echographic patterns suspicious of malignancy in 5 and toxic multinodular goiter in 1.

Out of 969 nodules with indeterminate cytology 283 (29.3%) were malignant on histology: 240 were papillary thyroid carcinomas (164 follicular, 66 classic, 2 oxyphilic and 8 tall cell variant), 28 were minimally invasive follicular carcinomas, 10 poorly differentiated thyroid carcinomas and 5 Hurthle cell carcinomas.
70.7% (686/969) of the nodules with indeterminate cytology were benign: 159 hyperplastic nodules, 520 adenomas and 7 benign nodules in HT.

Out of 247 nodules with non-diagnostic cytology who underwent thyroidectomy due to the size of the nodule(s) or for clinical/US signs suggestive of malignancy, 82 (33%) were malignant (63 papillary thyroid carcinomas, 12 medullary carcinomas, 3 follicular carcinomas, 2 Hurthle cell carcinomas and 2 poorly differentiated carcinomas), while 165 (67%) were benign on histology (Table 2). When indeterminate results at cytology were considered as negative for neoplasm, the FNA cytology in our series of patients demonstrated a sensitivity of 69%, a specificity of 99% and an accuracy of 88%. If indeterminate results were included among the positive results for neoplasm, the sensitivity raised to 92%, while specificity was 67% and accuracy 76%.

Foci of papillary carcinoma were occasionally found at histology in 222 out of 3004 patients, and were not included among malignant lesions.

Clinical parameters associated with the risk of papillary thyroid carcinoma on FNA.

Taking into account the high diagnostic performance of our FNA cytology, we reviewed the clinical features associated with the risk of papillary thyroid carcinoma in this large series of patients with nodular thyroid disease. We assigned patients to one diagnostic class defined according to the cytological result: 1. non diagnostic (7126 patients), 2. benign nodular thyroid disease (BNTD, 23,587 patients), 3. indeterminate (2506 patients), 4. suspicious or indicative of carcinoma (Ca, 1047 patients)) (Table 3). Patients with MNG were assigned to one of the diagnostic classes following these criteria: BNTD if all nodules were diagnostic for benign lesions, Ca if they had at least one nodule with this cytology, indeterminate if they had at least one nodule with this cytology and none with carcinoma, non diagnostic if they had one or more nodules with this cytology and none with carcinoma or indeterminate cytology. In the Ca group 901 patients had a cytology suspicious or indicative of papillary thyroid carcinoma (PAP) and 146 other types of neoplasia (53 medullary carcinoma, 26 poorly differentiated ca, 1 Hurthle cell ca and 66 lymphoma or metastasis of non-thyroidal neoplasia).

To establish the risk factors for PAP on cytology, various clinical parameters of patients with PAP (n=901) were reviewed in comparison with all the others diagnostic class taken together (n=33 219)
PAP was significantly more frequent in SN (446/13549, 3.3%) than in MNG (411/19923, 2 %, \( \chi^2=48.8 \ p<0.0001 \)), and was significantly higher in males (209/6382; 3.27%) than in females (648/26945, 2.40%) (\( \chi^2=15.58 \ p<0.0001 \)), both in SN (males: 111/2820, 3.9%, females: 335/10644, 3.1% (\( \chi^2=4.3 \ p=0.03 \)) and in MNG (males: 98/3562, 2.7 %, females: 313/16301, 1.9% % (\( \chi^2=9.96 \ p=0.001 \)) (Fig. 1).

The prevalence of PAP in patients with nodular GD (13/286, 4.5%), and HT (31/508, 6.1%) was higher than that found in SN. This higher prevalence was statistically significant in HT (\( \chi^2=8.7 \ p=0.003 \)) but not in GD (\( \chi^2=1.6 \ p=0.2 \)). The frequency of PAP was higher in males vs females both in GD (4/55, 7.3% vs 9/231, 3.9%; \( \chi^2=1.16 \ p=0.27 \)) and in HT (4/48 8.3% vs 27/460 5.8 %; \( \chi^2=0.46 \ p=0.49 \) (Fig. 1).

The age distribution of PAP showed a higher prevalence in younger patients (\( \chi^2=197; \ p<0.0001 \), Fig. 2). Accordingly, the mean age of patients with PAP (43 ± 14) was significantly lower than that of patients with BNTN (48.8 ± 15.7), both in males and females (\( \chi^2= \ p<0.0001 \)).

To determine which factors could be considered independent risk predictors of PAP on cytology, a multiple logistic regression analysis simultaneously analyzing gender, age, and type of nodularity (solitary and multinodular) was applied. To perform this analysis patients with Graves’ disease and Hashimoto’s thyroiditis were included in the category of solitary thyroid nodule. PAP cytology was inversely related to age (Odds Ratio, OR= 0.97; 95% confidence interval 0.964-0.974, \( p<0.0001 \)); and was positively associated with the male gender (OR= 1.440; CI 1.231-1.683, \( p<0.0001 \)) and with SN vs MNG (OR= 0.626; CI 0.547-0.717, \( p<0.0001 \)).

**Risk of papillary thyroid carcinoma on FNA according to clinical parameters and TSH level**

It was recently reported that TSH levels are positively associated with the risk of PAP (21, 22). We have also shown this association in 10182 patients with non-autoimmune nodular thyroid disease who were not taking methimazole or L-thyroxine (24). These 10182 patients are also included in the present series of patients together with a further 1737 who satisfied the same conditions. TSH (mean =0.76 µU/mL, SD=0.93, median=0.5 µU/mL, range=0.005-9.9 µU/mL) had a skewed distribution, 5493/11919 (46.1%) patients had serum TSH concentrations below the normal range (0.4 µU/mL), with normal serum FT4 and FT3; 6256 (52.5%) patients had serum TSH levels within the normal range; 170 (1.4%) patients had serum TSH levels slightly higher than normal, ranging from 3.5 µU/mL to 9.9 µU/mL. Although the patients of the last group
probably had Hashimoto’ thyroiditis, they did not meet sufficient clinical criteria for this diagnosis and were then included among those with non autoimmune nodular thyroid disease. Thus in 11919 patients we were able to calculate the risk of PAP taking into account both the clinical parameters and the TSH levels. The formula used to calculate the probability of cancer (P) was as follows: P= 1/ (1+exp^−x), x representing  a score based on patient age, gender, type of nodularity and serum TSH: x=-1.195-0.032 (age) + 0.43 (gender)-0.704 (type of goiter) + 0.234 (TSH concentration). The age was expressed in years, the type of goiter was coded as 1 for solitary nodules and 2 for multinodular goiter; the patient gender was coded as 1 for females and 2 for males; TSH concentration was expressed in µU/mL. Although TSH had a skewed distribution, this did not influence our regression model as long as serum concentrations were below 10 µU/mL. This formula can be applied to calculate the risk for individual patients. Table 4 reports the risk calculated for some clinical settings.

The validity of the prediction model was evaluated through Nagelkerke R^2. This was 0.012 when only clinical parameters were included and raised to 0.064 when considering also TSH level. Thus, the risk predictivity was highly improved by including serum TSH in the prediction model.

Discussion

Cytological examination of FNA samples is a pivotal diagnostic tool for assessing malignancy in thyroid nodules. In large published series, FNA cytology sensitivity varies from 65 to 98% (mean 83%) and specificity varies from 72 to 100 % (mean 92%) depending on the criteria used for definition of malignancy (25-28). In this study we retrospectively reviewed the performance of FNA cytology in 3406 nodules from 3.004 patients submitted to thyroidectomy, whose cytological and histological examination was performed within the same institutions. The results of cytology in a large series of 34266 patients submitted to FNA cytology, and the relationship between clinical features and a cytology suggestive or indicative of papillary thyroid cancer was also examined.

In our experience FNA cytology showed a performance similar to the best series published, the sensitivity being 92 %, the specificity 67 % and the accuracy 76%, when indeterminate results were considered as positive for neoplasm. The pattern of indeterminate (follicular) lesion is a major diagnostic pitfall of cytology in nodular thyroid disease. In the present paper 2506 patients had an indeterminate cytology and 969 underwent
surgery and a pathological exam in our Institution. 283 (29.3%) of the follicular nodules were malignant on histology, mostly being follicular variant of papillary carcinomas. These data confirm our previous data obtained in smaller series of patients (29). Because of the high rate of carcinomas in nodules with indeterminate cytology, most authors include these lesions among those suspicious for malignancy. When indeterminate results were considered as negative for neoplasm, the FNA cytology in our series of patients demonstrated a sensitivity of 69%, a specificity of 99% and an accuracy of 88%.

A false-negative cytological result was found in 24/1295 patients (1.8%), in whom surgery was advised for the size of the nodule (18 cases), the presence of suspicious clinical / US findings (5 cases) and for toxic multinodular goiter (1 case). 23 cases were papillary thyroid carcinoma (19 follicular variant and 4 classic variant) and 1 case was a minimally invasive follicular carcinoma. A very low rate of false positive results was found. In only 11 cases out of 895 (1.2%) the final histology was benign nodular disease despite a cytology suggestive of malignancy. It is important to stress that these cases were included among the 391 smears interpreted as suggestive of malignancy (class IV), while none of the 504 patients in whom the cytology was interpreted as indicative of malignancy (class V) resulted negative on histology.

Non-diagnostic results which account for 10 to 30% of the results of cytology (4, 12) are also a major limitation of FNA. A non-diagnostic cytology is caused in most cases by the cystic, hemorrhagic or mixed solid and liquid composition of the nodule. About 5-10% of patients with solid nodules will have a persistently non-diagnostic cytology. A rate of malignancy of 2 to 9% of these nodules is reported (12). In our series the non-diagnostic results was found in 8236 (17%) cases. 247 patients underwent surgery: 82 (33%) of them were malignant on histology, a considerably high rate reflecting the selection based on the presence of suspicious clinical and/or US findings.

In agreement with the data in the literature (4, 8-12) our results confirm that 20-25% of patients will have at least 1 nodule with a non-diagnostic or indeterminate cytology and therefore stress the importance of clinical considerations in the decision-making process in patients with nodular thyroid disease. For this reason we were interested in identifying the risk factors associated to malignancy in the large series of patients submitted to FNA.
Patients with thyroid autoimmune diseases were considered separately, as associations with papillary thyroid cancer have been reported for both Graves’ disease and Hashimoto’s thyroiditis (30-40).

In our study we found that the frequency of papillary thyroid cancer in Graves’ disease was not significantly different to that found in non autoimmune nodular thyroid disease. The number of patients included in our study however may be too small to draw final conclusions on this matter. At variance, we found a cytology indicative of cancer in 31/508 (6.1%) patients with Hashimoto’s thyroiditis, a prevalence that was slightly but significantly higher than that found in non autoimmune thyroid nodular disease. These data suggest that a positive association between clinically overt Hashimoto’s thyroiditis and papillary thyroid carcinoma may exist.

In patients with non-autoimmune nodular thyroid disease we compared clinical features of patients with a FNA cytology of benign nodular lesion (n=23052) with those with a cytology suggestive or indicative of papillary thyroid cancer (n=857). Patients with papillary thyroid cancer were found to be younger (43 vs 48.8 yr, p<0.0001), in agreement with Mittendorf (41), but in contrast to other reported series where thyroid cancer is more common in older patients. Belfiore et al (42) found a lower proportion of malignancy in 31-40 year old patients, the risk of cancer being increased about twofold in patients younger than 20 and almost six-fold in those older than 70 (43, 44).

Male sex, in agreement with most authors (4, 43-45) conferred a higher risk of cancer in our series of patients submitted to FNA, although the absolute number of cancers detected were 3-fold in females vs males. These data have to take into account that the majority of patients included in this paper come from an area of mild iodine deficiency where the prevalence of nodular goiter is much higher in females (45). In male gender the prevalence of multinodular goiter due to mild iodine deficiency is less frequent than in females and it is conceivable that nodular thyroid disease is more often linked to the presence neoplastic thyroid disease. In agreement with this consideration is the fact that in our large series of patients in both genders, papillary thyroid carcinoma was more frequent in SN than in MNG, the last phenotype being more closely linked to iodine deficiency. This result is in agreement with some authors (45) while others (42, 44) reported no difference in cancer prevalence between patients with solitary thyroid nodule with respect to those with multiple nodular goiter. Our data confirm that, as reported in a recent consensus on management of the patients with thyroid
nodule, FNA should be performed in most solitary nodules larger than 1cm, while in multinodular goiter only nodules with clinical or ultrasonographic signs suggestive of malignancy should be submitted to FNA (14-16).

Using the multiple logistic regression we analyzed which factors could be considered independent risk predictors of papillary thyroid cancer in patients with non-autoimmune nodular thyroid disease. Expected values were obtained by fitting a multivariate logistic regression to the observed value. A highly significant inverse relationship was observed between the risk of papillary thyroid carcinoma and age. Male gender and type of goiter (solitary nodule vs multinodular goiter) were also independent risk predictors of papillary carcinoma.

It was recently been reported in the literature (21) that the risk of thyroid malignancy rises in parallel with the serum TSH concentration at presentation. We have recently confirmed this data in a series of 10,182 patients in whom serum TSH was measured and who were not taking L-thyroxine and methimazole (24) at the moment in which FNA was performed. In the series of patients included in this work 1737 more patients satisfied this criteria. In a total of 11919 patients we could therefore combine clinical features with spontaneous TSH level to calculate an integrated formula of papillary cancer risk. The risk predictivity was highly improved by including the TSH level together with the clinical parameters in the prediction model. Although autonomously functioning nodules were not submitted to FNA, the possibility exists that part of the relationship between TSH and papillary thyroid cancer in this study is driven by multinodular goiters with autonomous areas, especially since most patients were from areas of moderate iodine deficiency.

A limitation of this study is that the size of the nodules and their ultrasound features were not included among the variables that were analyzed. This was due to the difficulty of collecting standardized ultrasound data from the high number of subjects included in this retrospective series. There is therefore a possibility that some of the predictive parameters that we have identified in this study may not remain in the statistical model as significant variables when considering ultrasound features.

In conclusion, the data presented in this paper show a high accuracy of FNA cytology, with the major publications in this field. A cytology suspicious or indicative of papillary thyroid carcinoma was inversely related to age, was more frequent in males and in solitary nodule with respect to females and multinodular goiter. These clinical parameters, together with serum TSH, may serve to construct an algorithm that may be
usefully applied to predict the risk of papillary thyroid carcinoma in individual patients when cytology does not give a diagnostic result.

**Declaration of interest:** we declare that there is no conflict of interest that could preclude as prejudicing the impartiality of the research reported.

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References


Table 1 Clinical vs cytological diagnosis in 47775 thyroid nodules from 34266 patients.

<table>
<thead>
<tr>
<th>Clinical diagnosis (n. of patients)</th>
<th>N. of nodules</th>
<th>Non-diagnostic (%)</th>
<th>Benign (%)</th>
<th>Indeterminate (%)</th>
<th>Suspicious/Indicative of cancer (%)</th>
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<tr>
<td>MNG (n.= 19923)</td>
<td>33402</td>
<td>13.6</td>
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<td>25.6</td>
<td>60.8</td>
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<td>Graves’ disease (n.=286)</td>
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<td>23.3</td>
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<td>Autoimmune thyroditis (n.=508)</td>
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<td>21.4</td>
<td>73.9</td>
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<td>47775</td>
<td>17.1</td>
<td>74.7</td>
<td>5.7</td>
<td>1147 (2.4)</td>
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Table 2 Cytological results of FNA vs histology in 3406 nodules from 3004 patients submitted to surgery.

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<th>FNAC diagnosis</th>
<th>Surgery n.</th>
<th>Final histology</th>
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<tr>
<td></td>
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<td>BN n. (%)</td>
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<td>Carcinoma</td>
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<td>Benign</td>
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<td>Indeterminate</td>
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<td>Total</td>
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Table 3 Clinical diagnosis and diagnostic classes according to the cytological results in 34266 patients.

<table>
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<th>Clinical diagnosis (n. of patients)</th>
<th>Non-diagnostic</th>
<th>BNTD</th>
<th>Indeterminate</th>
<th>Total n.</th>
<th>PAP n. (%)</th>
<th>Other Ca</th>
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<tr>
<td>MNG (n.= 19923)</td>
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<td>1186</td>
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<td>411 (2)</td>
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<td>SN (n.= 13549)</td>
<td>3475</td>
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**Table 4** Probability of malignancy at FNA in 6 index patients, as assessed by the formula reported in the result section.

<table>
<thead>
<tr>
<th>n</th>
<th>sex</th>
<th>Age (yr)</th>
<th>Type of nodularity</th>
<th>TSH (µU/mL)</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>16</td>
<td>Solitary Nodule</td>
<td>4</td>
<td>35.1</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>54</td>
<td>Solitary Nodule</td>
<td>8</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>36</td>
<td>Solitary Nodule</td>
<td>2</td>
<td>15.2</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>75</td>
<td>Solitary Nodule</td>
<td>6</td>
<td>11.5</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>38</td>
<td>Multinodular goiter</td>
<td>1.9</td>
<td>7.5</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>40</td>
<td>Multinodular goiter</td>
<td>0.5</td>
<td>3.4</td>
</tr>
</tbody>
</table>
Legend of Figures

Fig. 1
Prevalence of papillary thyroid carcinoma on cytology (PAP %) in relation to clinical diagnosis and sex. MNG= multinodular goiter, SN= solitary nodule; HT= Hashimoto’s thyroiditis; GD: Graves’ disease.

Black columns: males
White columns: females

Fig. 2
Age distribution on cytology of papillary thyroid carcinoma (PAP) on benign nodular thyroid disease (BNTN).
Squares: solitary nodules; triangles: multinodular goiter (MNG).
Fig. 1

- **MNG**: N=3562
- **SN**: N=2820
- **HT**: N=48
- **GD**: N=55

Bar chart showing the comparison between males (M) and females (F) for different categories.
Fig. 2

The graph shows the percentage of PAP/BTNTN over different age groups. The age groups are categorized as follows:

- <20: No = 267
- 21-30: No = 1571
- 31-40: No = 2992
- 41-50: No = 6627
- 51-60: No = 6036
- 61-70: No = 3288
- >71: No = 1167

The graph includes two lines:
- Solid line for SN
- Dashed line for MNG

The data indicates a decrease in PAP/BTNTN percentage as age increases from <20 to >71.