CLINICAL STUDY

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

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Abstract

Objective: To evaluate the risk of papillary thyroid carcinoma (PTC) at fine-needle aspiration (FNA) cytology in 34 120 patients.

Results: False positive and false negative rates of FNA cytology were 1.2 and 1.8% in comparison with the histology in 3406 nodules from 3004 patients who underwent surgery. PTC (901 cases) was more frequent in solitary nodule (SN; 446/13 549, 3.3%) than in multinodular goiter (MNG; 411/19 923, 2%, $\chi^2 = 48.8$; $P < 0.0001$), and in males (209/6382, 3.3%) than in females (648/26 945, 2.40%, $\chi^2 = 15.58$; $P < 0.0001$). 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 ($\chi^2 = 8.7$; $P = 0.003$), but not in GD ($\chi^2 = 1.6$; $P = 0.2$).

Using the multiple logistic regression analysis, independent risk predictors of PTC were determined, which were younger age (odds ratio (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 versus MNG (OR = 0.63, CI 0.547–0.717; $P < 0.0001$). The individual risk predictivity was highly improved by including serum TSH in the prediction model, which was measured at FNA in 11 919 patients.

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

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Introduction

Thyroid nodular disease is quite common, especially in iodine-deficient areas (1, 2). Clinically overt thyroid cancer accounts for ∼1% of all new malignant diseases, 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 (MNG) may harbor a cancer is quite low when clinically evident thyroid cancers are considered. However, it is higher when cancers are incidentally detected based on the 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 MNG 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 the cases, and false positive or false negative in 5% of the cases (10, 12, 13). In few patients, a history of neck irradiation, nodule hardness or fixity to adjacent structures, and 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, and solitary or multiple nodularity, the importance of which is reported in the literature with discrepant results (8, 14, 15).

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 by comparing FNA results with the 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 of establishing 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 (FT_4) and free triiodothyronine (FT_3) were measured by RIA (FT_4 Liso-Phase, normal values 7–17 pg/ml; FT_3 Liso-Phase kit, normal values 2.7–5.7 pg/ml, Technogenetics, s.r.l., Milan, Italy). Antibodies to thyroglobulin (TgAb) and thyroperoxidase (TPOAb) 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 TgAb and <10 U/ml for TPOAb. TSH receptor antibodies (TRAbs, normal value ≤ 2 UI/l) were measured by a first-generation TRAk assay (Brahms, Berlin, Germany).

Serum TSH was measured by a sensitive IRMA (Delphia, Pharmacia, Turku, Finland; normal values 0.4–3.4 μU/ml). Serum calcitonin was measured by an IRMA (CIS BIO International, Gif-sur-Yvette, France; normal values <10 ng/ml).

Patients

A total of 34 266 patients (27 826 F: mean age 48 ± 23, range 13–76 years; 6440 M: mean age 50 ± 17, range 13–80 years) 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 as follows: MNG ($n=19 923$): enlarged thyroid with multiple nodules at US and thyroid scintiscan; solitary nodule (SN, $n=13 549$): single nodule in an enlarged thyroid or isolated 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 the usual standard criteria including active or treated hyperthyroidism, goiter with a diffuse hypoechoic 'thyroiditis' pattern at ultrasound, ophthalmopathy,

and positive serum anti-TRAbs and/or TgAbs or TPOAbs. Patients were defined as affected by nodular HT if they had a diffuse hypoechoic 'thyroiditis' pattern at ultrasound and high levels of TgAbs and/or TPOAbs. FNA was performed in all nodules cold at scintiscan either solitary or in MNG when they were >1 cm, and in those <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 nondiagnostic 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 the clinical and sonographic preoperative findings.

FNA and cytology

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 anesthesia. Multiple passes were usually done in different parts of the nodule. In cystic or mixed lesions, the fluid was aspirated completely, and the sediment was 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 [16], the sample was considered adequate in the presence of at least five or six well-defined and well-preserved groups of follicular epithelial cells, with each group containing at least ten cells [15]. Cytological results were reported according to the British Thyroid Association [17] as follows: i) nondiagnostic; ii) nonneoplastic (benign or negative for malignancy); iii) follicular; iv) suspicious of malignancy; and v) indicative of malignancy. The cytopathologists had clinical information about the patient.

Histopathological diagnosis

Formalin-fixed and paraffin-embedded tumor tissues, including normal parenchyma obtained from the contralateral thyroid lobe of each case, were stained with hematoxylin and eosin. The histological diagnosis was made blindly by two independent pathologists who were not aware of the cytological result and according to the World Health Organization Guidelines [18]. 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 microcarcinoma of <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 χ^2 test and Student's *t*-test for paired data. Predictivity was assessed using the Galen and Gambino test (19). 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 11 919 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 47 775 nodules from 34 266 patients. In total, 74.7% of the nodules were benign, 5.7% were indeterminate, and 2.4% were indicative or suspicious of carcinoma, while 17.1% were nondiagnostic. Accuracy of cytology was assessed by comparing the FNA results with the 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 underwent a 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 based on the histology, whereas 11 of 391 nodules with an FNA suspicious for malignancy were benign based on the histology: eight patients had a nodular goiter, three of whom had extensive necrotic features; two had HT,

one with a 2-mm papillary carcinoma; and one had GD with a pseudopapillary organization based on the cytology. Overall, 884/895 (98.8%) nodules with a cytology indicative or suspicious of thyroid carcinoma were malignant based on the histology. 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 based on the histology: 23 were papillary thyroid carcinomas (PTC; 19 follicular variants and 4 classic variants) and 1 was a minimally invasive follicular carcinoma. The reasons for thyroidectomy in these 24 patients (13 with single/isolated nodule and 11 with MNG) were the size of the nodule(s) in 18, clinical/echographic patterns suspicious of malignancy in 5, and toxic MNG in 1.

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

Of 247 nodules with nondiagnostic cytology, which were obtained from patients who underwent thyroidectomy due to the size of the nodule(s) or for clinical/US signs suggestive of malignancy, 82 (33%) were malignant (63 PTCs, 12 medullary carcinomas, 3 follicular carcinomas, 2 Hurthle cell carcinomas, and 2 poorly differentiated carcinomas), while 165 (67%) were benign based on the 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 rose to 92%, while specificity was 67% and accuracy was 76%.

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

Table 1 Clinical versus cytological diagnosis in 47 775 thyroid nodules from 34 266 patients.

Clinical diagnosis (number of patients)	Cytological diagnosis				
	Number of nodules	Nondiagnostic (%)	Benign (%)	Indeterminate (%)	Suspicious/indicative of Ca number (%)
MNG ($n=19\,923$)	33 402	13.6	80.4	4.2	569 (1.7)
SN ($n=13\,549$)	13 549	25.6	60.8	9.6	531 (3.9)
Graves' disease ($n=286$)	286	23.3	71.3	2.5	13 (4.5)
Autoimmune thyroiditis ($n=508$)	508	21.4	73.9	1.6	32 (6.2)
Total ($n=34\,266$)	47 775	17.1	74.7	5.7	1147 (2.4)

Table 2 Cytological results of fine-needle aspiration (FNA) versus histology in 3406 nodules from 3004 patients submitted to surgery.

| FNAC diagnosis | Surgery numbers | Final histology | |
| | | BNTD | Ca |
		n (%)	*n* (%)
Carcinoma			
Suspicious	391	11	380
Indicative	504	0	504
Total	895	11 (1.2)	884 (98.8)
Benign	1295	1271 (98.2)	24 (1.8)
Indeterminate	969	686 (70.7)	283 (29.3)
Nondiagnostic	247	165 (67)	82 (33)
Total	3406	2132	1274

Clinical parameters associated with the risk of PTC on FNA

Taking into account the high diagnostic performance of our FNA cytology, we reviewed the clinical features associated with the risk of PTC in this large series of patients with nodular thyroid disease. We assigned patients to one of the diagnostic classes defined according to the cytological result as follows: i) nondiagnostic (7126 patients), ii) benign nodular thyroid disease (BNTD, 23 587 patients), iii) indeterminate (2506 patients), iv) suspicious or indicative of carcinoma (Ca, 1047 patients; Table 3). Patients with MNG were assigned to one of the diagnostic classes according to the following 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; and nondiagnostic, 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 PTC and 146 had other types of neoplasia (53 medullary carcinomas, 26 poorly differentiated carcinomas, 1 Hurthle cell carcinoma, and 66 lymphomas or metastasis of nonthyroidal neoplasia).

To establish the risk factors for PTC based on the cytology, various clinical parameters of the patients with PTC ($n=901$) were reviewed in comparison with all the other diagnostic classes taken together ($n=33$ 219).

PTC was significantly more frequent in SN (446/13 549, 3.3%) than in MNG (411/19 923, 2%, $\chi^2=48.8$; $P<0.0001$), and was significantly higher in males (209/6.382, 3.27%) than in females (648/26 945, 2.40%, $\chi^2=15.58$; $P<0.0001$), both in SN (males: 111/2820, 3.9%; females: 335/10 644, 3.1%, $\chi^2=4.3$; $P=0.03$) and in MNG (males: 98/3562, 2.7%; females: 313/16 301, 1.9%, $\chi^2=9.96$; $P=0.001$) (Fig. 1).

The prevalence of PTC in patients with nodular GD (13/286, 4.5%) and nodular 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 PTC was higher in males than in 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 PTC showed a higher prevalence in younger patients ($\chi^2=197$; $P<0.0001$, Fig. 2). Accordingly, the mean age of patients with PTC (43 ± 14) was significantly lower than that of patients with BNTD (48.8 ± 15.7) in both males and females ($\chi^2=P<0.0001$).

To determine which factors could be considered as independent risk predictors of PTC based on the 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 GD and HT were included in the category of solitary thyroid nodule. PTC cytology was inversely related to age (odds ratio, OR=0.97; 95% confidence interval (CI) 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 versus MNG (OR=0.626; CI 0.547–0.717, $P<0.0001$).

Risk of PTC on FNA according to clinical parameters and TSH levels

It was recently reported that TSH levels are positively associated with the risk of PTC (20–22). We have also shown this association in 10 182 patients with nonautoimmune nodular thyroid disease who were not taking methimazole or L-T$_4$ (23). These 10 182

Table 3 Clinical diagnosis and diagnostic classes according to the cytological results in 34 266 patients.

| Clinical diagnosis (number of patients) | Diagnostic classes according to cytology | | | | | |
| | Nondiagnostic | BNTD | Indeterminate | Ca | | |
				Total *n*	PTC *n* (%)	Other Ca
MNG ($n=19$ 923)	3453	14 813	1186	471	411 (2)	60
SN ($n=13$ 549)	3475	8239	1.304	531	446 (3.3)	85
Graves' disease ($n=286$)	80	186	7	13	13 (4.5)	0
Autoimmune thyroiditis ($n=508$)	118	349	9	32	31 (6.1)	1
Total ($n=34$ 266)	7126	23 587	2506	1047	901	146

The prevalence of PTC in each clinical diagnostic group is reported in parenthesis.
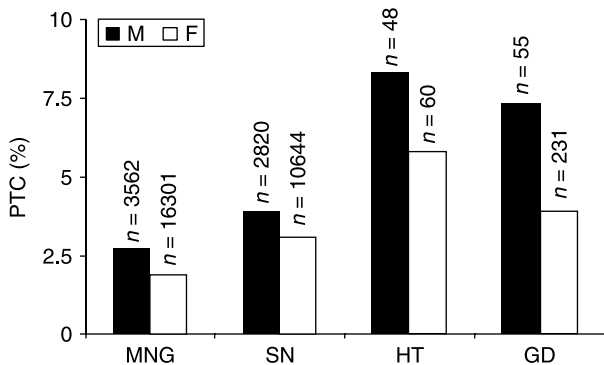
Figure 1 Prevalence of papillary thyroid carcinoma (PTC %) based on the cytology in relation to clinical diagnosis and sex. MNG, multinodular goiter; SN, solitary nodule; HT, Hashimoto's thyroiditis; GD, Graves' disease. Black columns, males; white columns, females.

Table 4 Probability of malignancy at fine-needle aspiration in six index patients, as assessed by the formula reported in the Results section.

No.	Sex	Age (years)	Type of nodularity	TSH (μU/ml)	Risk (%)
1	Male	16	Solitary nodule	4	35.1
2	Female	54	Solitary nodule	8	21
3	Male	36	Solitary nodule	2	15.2
4	Male	75	Solitary nodule	6	11.5
5	Male	38	Multinodular goiter	1.9	7.5
6	Female	40	Multinodular goiter	0.5	3.4

patients are also included in the present series of patients together with an additional 1737 patients who satisfied the same conditions. TSH (mean $= 0.76$ μU/ml, S.D. $= 0.93$, median $= 0.5$ μU/ml, range $= 0.005$– 9.9 μU/ml) had a skewed distribution. Of 11 919 patients, 5493 (46.1%) patients had serum TSH concentrations below the normal range (0.4 μU/ml), with normal serum FT_4 and FT_3; 6256 (52.5%) patients had serum TSH levels within the normal range; and 170 (1.4%) patients had serum TSH levels slightly higher than the normal range, ranging from 3.5 to 9.9 μU/ml. Although the patients of the last group probably had HT, they did not meet sufficient clinical criteria for this diagnosis, and were then included among those with nonautoimmune nodular thyroid disease. Thus, in 11 919 patients, we were able to calculate the risk of PTC by 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 (years), gender (1 for females and 2 for males), type of nodularity (1 for solitary and 2 for multinodular goiter), and serum TSH (expressed in
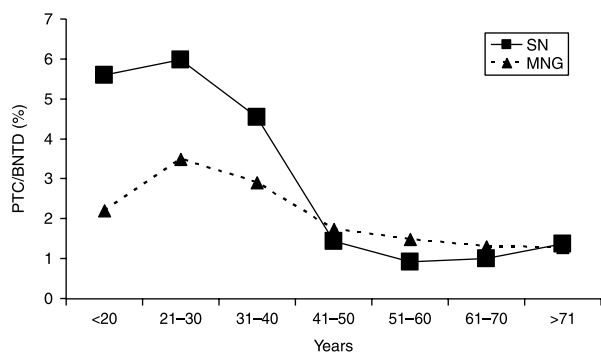
1/4 U/ml): $x = -1.195 - 0.032\,(\text{age}) + 0.43\,(\text{gender}) - 0.704\,(\text{type of goiter}) + 0.234\,(\text{TSH concentration})$. The age was expressed in years, the type of goiter was coded as 1 for SNs and as 2 for MNG, the patient gender was coded as 1 for females and as 2 for males; and 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 rose to 0.064 when considering TSH level also. 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 a 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 the definition of malignancy (24–27). In this study, we retrospectively reviewed the performance of FNA cytology in 3406 nodules from 3004 patients submitted to thyroidectomy, whose cytological and histological examinations were performed within the same institutions. The results of the cytological examination in a large series of 34 266 patients submitted to FNA cytology, and the relationship between clinical features and a cytology suggestive or indicative of papillary thyroid cancer were also examined.

In our experience, FNA cytology showed a performance that was similar to that observed in the best series published, with 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 cytological examination in nodular thyroid disease. In the present paper, 2506 patients had an indeterminate cytology, and 969

Figure 2 Ratio between papillary thyroid carcinoma (PTC) and benign nodular thyroid disease (BNTD) on cytology according to age in patients with solitary nodules (SN) or multinodular goiter (MNG).

underwent surgery and a pathological examination in our institution. In total, 283 (29.3%) of the follicular nodules were malignant based on the histology, mostly being follicular variants of papillary carcinomas. These data confirm our previous data obtained in smaller series of patients (28). 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 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 due to the size of the nodule (18 cases), the presence of suspicious clinical/US findings (5 cases), and toxic MNG (1 case). Twenty-three cases were PTCs (19 follicular variants and 4 classic variants) and one case was a minimally invasive follicular carcinoma. A very low rate of false positive results was found. In only 11 of 895 (1.2%) cases, the final histology indicated 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 based on the histology.

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

In agreement with the data given in the literature (4, 8–12), our results confirm that 20–25% of the patients will have at least one nodule with a nondiagnostic 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 with 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 GD and HT (29–39).

In our study, we found that the frequency of papillary thyroid cancer in GD was not significantly different from that found in nonautoimmune nodular thyroid disease.

However, the number of patients included in our study 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 HT, a prevalence that was slightly but significantly higher than that found in nonautoimmune thyroid nodular disease. These data suggest that a positive association between clinically overt HT and PTC may exist.

In patients with nonautoimmune nodular thyroid disease, we compared the clinical features of patients with an FNA cytology of benign nodular lesion ($n = 23\,052$) 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 years, $P < 0.0001$) in agreement with Mittendorf (40), but in contrast to other reported series where thyroid cancer is more common in older patients. Belfiore *et al*. (2) 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 years and almost sixfold in those older than 70 years (41, 42).

Male sex, in agreement with most authors (4, 41–43), conferred a higher risk of cancer in our series of patients submitted to FNA, although the absolute number of cancers detected was threefold in females that in males. These data have to take into account that the majority of the patients included in this paper come from an area of mild iodine deficiency where the prevalence of nodular goiter is much higher in females (43). In males, the prevalence of MNG 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 of neoplastic thyroid disease. In agreement with this consideration is the fact that in our large series of patients of both genders, PTC 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 (43), while others (2, 42) 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 SNs larger than 1 cm, while in MNG, only nodules with clinical or ultrasonographic signs suggestive of malignancy should be submitted to FNA (14, 15, 44).

Using the multiple logistic regression, we analyzed which factors could be considered as independent risk predictors of papillary thyroid cancer in patients with nonautoimmune 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 PTC and age. Male gender and type of goiter (SN versus MNG) were also independent risk predictors of papillary carcinoma.

Recently, it has been reported in the literature (20) that the risk of thyroid malignancy rises in parallel with the serum TSH concentration at presentation. We have recently confirmed these data in a series of 10 182 patients in whom serum TSH was measured and who were not taking L-T$_4$ and methimazole (23) during the time FNA was performed. In the series of patients included in this work, 1737 patients satisfied these criteria. In a total of 11 919 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 MNGs 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 in collecting standardized ultrasound data from the high number of subjects included in this retrospective series. Therefore, there is 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 PTC was inversely related to age, and was more frequent in males and in SN with respect to females and MNG. These clinical parameters, together with serum TSH, may serve to construct an algorithm that may be usefully applied to predict the risk of PTC in individual patients when cytology does not give a diagnostic result.

Declaration of interest

Funding

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